

Primary Statistical Analysis Plan for IMPAACT 2013 and CIR 313

Version 3.1

Date Finalized: January 11, 2022

**Phase I Placebo-Controlled Study of the Infectivity,
Safety and Immunogenicity of a Single Dose of a
Recombinant Live-Attenuated Respiratory Syncytial
Virus Vaccine, D46/NS2/N/ΔM2-2-HindIII, Lot RSV#011B,
Delivered as Nose Drops to RSV-Seronegative Infants 6
to 24 Months of Age**

ClinicalTrials.gov Identifier: NCT03102034

Protocol Version 1.0 (LOA #1)

This is IMPAACT 2013 SAP Version 3.1 with names of authors, names of publication writing team members and analysis timeline redacted. The Appendix includes details of the analyses that were pre-specified in the study protocol.

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Version	Changes Made	Date Finalized
1.0	Original Version	May 31, 2017
2.0	Major updates include removing information about the interim DSMB reviews and adding section 4 Definitions and section 5 Statistical Methods, as well as information about analyses for the infectivity and immunogenicity primary objectives and for the secondary objectives	March 9, 2018
3.0	Designated a secondary objective as exploratory for ct.gov submission	December 21, 2021
3.1	Corrected the ClinicalTrials.gov identifier number on the cover page	January 11, 2022

1 Introduction

This Primary Statistical Analysis Plan (SAP) describes the general statistical approaches that will be used in the primary statistical analysis of IMPAACT 2013. It will facilitate discussion of the statistical analysis components among the study team members and will provide agreement between the team and statistician regarding the analyses to be performed and presented in the primary statistical analysis report. Analyses for the primary statistical report will be initiated once the last participant has completed the last study visit, all laboratory data are available, all queries have been resolved, and the database has been frozen for analysis. This report will be used for submission of results to ClinicalTrials.gov. Results are required to be submitted within one year of the primary completion date (PCD), which is the date the last participant is examined for the purposes of data collection for the primary outcome measure. For this study, the PCD is based on the last study visit.

2 Key Updates to the SAP

SAP Version 1.0 was dated 31 May, 2017.

Updated to SAP Version 2.0 on March 9, 2018:

Major updates include removing information about the interim DSMB reviews and adding section 4 Definitions and section 5 Statistical Methods, as well as information about analyses for the infectivity and immunogenicity primary objectives and for the secondary objectives.

Updated to SAP Version 3.0 on December 21, 2021:

Designated the outcome measure for Secondary Objective 4 as exploratory in Section 6.8; also updated the title page and added a note in Section 3.1 stating that the outcome measures are in protocol Section 9.2.

Updated to SAP Version 3.1 on January 11, 2022:

Corrected the ClinicalTrials.gov identifier number on the cover page.

3 Study Schema and Objectives

DESIGN: A double-blind, randomized, placebo-controlled study design will be used to evaluate the safety and immunogenicity of the vaccine in RSV-seronegative infants and children. Seronegativity refers to RSV antibody status, which is defined as a serum RSV-neutralizing antibody titer <1:40 (as determined within 42 days prior to inoculation).

SAMPLE SIZE: Approximately 33 healthy RSV-seronegative infants and children ≥6 months (180 days) to <25 months (750 days) of age will be randomized at a ratio of 2:1 to receive vaccine or placebo, respectively.

REGIMENT: A single dose of the recombinant live-attenuated respiratory syncytial virus D46/NS2/N/ΔM2-2-HindIII, Lot RSV#011B vaccine or placebo at study entry.

N	Treatment	Dose
22	Vaccine	10 ⁵ PFU*
11	Placebo	0

*plaque forming units

Study Duration: Participants will be enrolled in the study between April 1st and October 14th (outside of RSV season) and will remain on study until they complete the post-RSV season visit between April 1st and April 30th in the calendar year following enrollment. For example, a participant enrolled on July 1st, 2017 will remain on study approximately 9-10 months (completing a final visit in April 2018) while a participant enrolled on October 14th, 2017 will remain on study approximately 6 months (also completing a final visit in April 2018).

This protocol is a companion study to CIR 313, a study being conducted by the Center for Immunization Research (CIR, Johns Hopkins, Baltimore), and the Laboratory of Infectious Diseases (LID, NIAID, NIH, Bethesda). The protocols have identical primary and secondary objectives; inoculation schedules; evaluation assays and schedules; safety monitoring and reporting.

3.1 Objectives:

Primary Objectives:

- Objective 1. Safety: To assess the frequency and severity of study product-related solicited and unsolicited adverse events (AEs), from Day 0 through midnight of the 28th day following inoculation, in vaccinated participants
- Objective 2. Safety: To assess study product-related serious adverse events (SAEs) from Day 0 through midnight on the 56th day following inoculation for vaccinated participants
- Objective 3. Infectivity: To determine the peak titer of vaccine virus shed and duration of virus shedding by each participant
- Objective 4. Infectivity: To assess the proportion of vaccinated infants infected with study vaccine

Objective 5. Immunogenicity: To characterize antibody responses (Day 56) to the study vaccine

Secondary Objectives:

- Objective 1. To characterize clinical outcomes (frequency and severity of symptomatic, medically attended respiratory and febrile illness) in the vaccine and placebo recipients who experience natural infection with wild-type (wt) RSV during the subsequent RSV season
- Objective 2. To characterize antibody responses in the vaccine and placebo recipients who experience natural infection with wt RSV during the subsequent RSV season
- Objective 3. To characterize the B cell response to vaccine and the quality and epitope specificity of RSV F specific antibody, and to characterize these responses in the vaccine and placebo recipients who experience natural infection to wt RSV during the subsequent RSV season
- Objective 4. To characterize the mucosal antibody response to vaccine

Note: The outcome measures for all objectives are specified in protocol section 9.2.

Safety Monitoring:

Infants and children enrolled in the study will be monitored for the following (see table below which is also Table 2 from the protocol document; the tables and sections it refers to are from the protocol as well):

Table 1: AE CRF Recording Requirements (Table 2 from the protocol)

Study Phase at the time of event onset	Calendar Date	AEs to record on CRFs	Concomitant Medications to record on CRFs
Days 0 through midnight of 28 th day following inoculation (Acute Phase)	ANY	<ul style="list-style-type: none"> • All SAEs • All solicited AEs that meet Appendix IV criteria • All unsolicited AEs (Grades 1 to 4), with the exception of the following conditions if not treated with prescription medication or OTC medications with antipyretic properties: diaper rashes, teething pain, and spitting up. <p>Note: SAEs and LRIs must be reported via DAIDS Adverse Experience Reporting System (DAERS; see Section 7.3.4).</p>	<p>Record these medications on CRFs regardless of whether the related event is recorded on CRFs:</p> <ul style="list-style-type: none"> • All cough and cold remedies including decongestants, cough suppressants, expectorants • All nasal sprays (except saline spray) • All antihistamines • All antipyretics • All prescription medications <p>For SAE and LRIs:</p> <ul style="list-style-type: none"> • All concomitant medications related to the recorded event
From 12:01 am on 29 th day after inoculation to midnight of the 56 th day following inoculation (Post-Acute Phase)	ANY	<ul style="list-style-type: none"> • All SAEs <p>Note: SAEs must be reported via DAERS (see Section 7.3.4).</p>	<ul style="list-style-type: none"> • All concomitant medications related to the recorded event
After Day 56 Visit and until RSV Season Surveillance Period	Up to October 31 st in year of inoculation	<ul style="list-style-type: none"> • Grade ≥3 AE or SAE that is deemed related to Pre-RSV Season Study Visit procedures. 	<ul style="list-style-type: none"> • All concomitant medications related to the recorded event
RSV Season Surveillance Period	November 1 st to March 31 st following inoculation	<ul style="list-style-type: none"> • Fever, LRI, URI, and/or otitis media that are medically attended • All SAEs <p>Note: these events do not need to meet the Appendix IV criteria. SAEs and Grade ≥3 LRIs must be reported via DAERS (see Section 7.3.4).</p>	<p>For SAE and LRIs (all grades):</p> <ul style="list-style-type: none"> • All concomitant medications related to the recorded event <p>Medications related to recorded medically attended illness should be documented in source notes.</p>
Post-RSV Season	April 1 st -April 30 th in the year after the inoculation	<ul style="list-style-type: none"> • Grade ≥3 AE or SAE that is deemed related to Post-RSV Season Study Visit procedures. 	<ul style="list-style-type: none"> • All concomitant medications related to the recorded event
Throughout study	ANY	<ul style="list-style-type: none"> • Unresolved AE or SAE with onset date during Day 0 to midnight on the 28th day after inoculation • Unresolved SAE with onset date prior to midnight on the 56th day following inoculation • Unresolved SAE with onset date during RSV Surveillance Period or related to the Pre- or Post-RSV Season Study Visit 	<ul style="list-style-type: none"> • All concomitant medications related to the recorded event

4 Definitions

4.1 Baseline

Study Day 0 is defined as the inoculation date. The values used for baseline summaries will be the last evaluation on or before the inoculation date.

4.2 Analysis Populations

Safety population: Safety analyses will be limited to infants who were inoculated.

Infectivity and immunogenicity population: The primary infectivity and immunogenicity analyses will use an as-treated approach, limited to infants who were inoculated.

5 Statistical Methods

Baseline characteristics will be summarized by treatment group but with no statistical comparisons comparing arms.

Statistical tests will not be adjusted for multiple comparisons. For data where rank order statistics are appropriate, the Wilcoxon rank sum test will be used to determine the statistical significance of differences between vaccine and placebo recipients. A 1-tailed Fisher's exact test will be used to test the hypothesis that the vaccinated group will exhibit a greater proportion of participants who develop fourfold or greater rises in RSV-neutralizing antibody titer following vaccination compared to the placebo group. The statistical tests will have a nominal significance level of 0.05.

Categorical data will be summarized using N (%), and continuous data using N, min, Q1, median, Q3, max, and mean (STD) (when appropriate). Any modifications to outcome measures after the team has seen data collected after entry will be identified as *post hoc*.

5.1 Visit and Evaluation Schedule

Study visits are conducted on Days 0, 3, 5, 7, 10, 12, 14, 17, and 28 (each with a window of ± 1 day), and on Day 56 (with a window of +7 days). Non-clinic contacts (via phone or e-mail) are conducted on all other days during the Acute Phase (each with a window of ± 1 day), and on Day 29 (with a window of +1 day). A Pre-RSV season visit takes place between October 1st and October 31st, and then weekly contacts are made during the time period between Nov 1st and March 31st. A Post-RSV season visit takes place between April 1st and April 30th.

6 Report Components

As requested by the DSMB for previous RSV studies, the data for this review will be summarized with the treatment arms pooled, so blinding will be maintained. All subjects who received inoculation (vaccine or placebo) will be included in these safety analyses.

6.1 Accrual

The following tables will be presented or described in text (based on the *status* study dataset).

- a. Table with number enrolled
- b. Table with enrollment by month
- c. Table with enrollment by site

6.2 Study status

- a. Table including number enrolled, number off treatment and still on study, and number off study with reasons for early discontinuation (based on the *pstat1* variable from the *status* study dataset)

The following tables will be restricted to only the participants who received inoculation.

6.3 Selected characteristics of participants at baseline

- a. Table showing n and % for gender, race, ethnicity (from the *status* study dataset)
- b. Table showing mean, standard deviation (SD), median, 25th-75th percentile, min, max for age (in months) at randomization

6.4 Days between randomization and inoculation

- a. Table showing the number of days between randomization and inoculation, to check if the inoculation was received as requested, within 3 days of randomization.

6.5 Safety Primary Objectives

Objective 1: Safety: To assess the frequency and severity of study product-related solicited and unsolicited adverse events (AEs), from Day 0 through midnight of the 28th day following inoculation, in vaccinated participants

Objective 2: Safety: To assess study product-related serious adverse events (SAEs) from Day 0 through midnight on the 56th day following inoculation for vaccinated participants

Notes:

1. The protocol requires grading of events according to The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, which is available on the RSC website:

http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8

with the exception of the solicited events which will be graded using a study-specific grading table (see Tables 2-4 at the end of this document).

2. The protocol does not require the collection of any laboratory evaluations, but abnormal values reported from non-study mandated blood draws will be recorded in the database. The protocol requires all adverse events and solicited events to be recorded on CRFs and reported according to Table 1 above (Table 2 in the protocol). Solicited events are: fever, acute otitis media, URI (rhinorrhea, cough without lower respiratory tract illness, hoarseness, pharyngitis), LRI (wheezing, rhonchi, rales, pneumonia, laryngotracheobronchitis (croup)).
3. Analyses will be based on events reported on the following forms: PE6833 (signs/symptoms) and PE6853 (diagnoses) (and PE6813 (hematology), PE6818 (chemistry) – if any data are reported on them) and will not explicitly include events reported as SAEs to DAIDS. Before the database is finalized, the data manager will ensure that all SAE events deemed “reportable” and included in the SDMC AR001AES table are reflected on the study CRFs. The data manager will also ensure that all events recorded on the Event Evaluation form (PE6866) are also documented on the source forms (signs/symptoms, diagnosis, hematology, or chemistry forms).
4. The adverse events with date of onset or specimen date prior to the inoculation and which are still ongoing at the time of the inoculation will be presented in a separate table, and then they will be excluded from subsequent tables summarizing adverse events.

a. Signs, symptoms and diagnoses:

The tables described in this section will be generated for the first 56 days after inoculation and then separately for the RSV Season Surveillance Period.

- i. Line listing of subjects with signs, symptoms or diagnoses **present at the time of inoculation** discussed by the team on conference calls (from the *events* study dataset): patient ID, date of receipt of study agent, days from onset of AE to inoculation, abnormality, grade, onset date and end date
- ii. Line listing of subjects with signs, symptoms or diagnoses **occurring after inoculation** discussed by the team on conference calls (from the *events* study dataset): patient ID, date of receipt of study agent, days from inoculation to onset of AE, abnormality, grade, relationship to study treatment (from *trac* study dataset), onset date and end date

- iii. Line listing of subjects with the subset of solicited and unsolicited signs, symptoms or diagnoses discussed by the team on conference calls and **which were judged to be related, possibly related, or probably related to study treatment** (from the *events* study dataset): patient ID, date of receipt of study agent, days from inoculation to onset of AE, abnormality, grade, relationship to study treatment (from *trac* study dataset), onset date and end date
- iv. Line listing of subjects with solicited and unsolicited signs, symptoms or diagnoses discussed by the team on conference calls **of grade>3** (from the *events* study dataset): patient ID, date of receipt of study agent, days from inoculation to onset of AE, abnormality, grade, relationship to study treatment (from *trac* study dataset), onset date and end date
- v. Summary table with n (%) of subjects experiencing at least one episode of a solicited and unsolicited adverse event, counting the worst (highest) grade adverse event by MedDRA System Organ Class (SOC) and Preferred Term (PT) (applying the CBAR *eventsum* macro on the study derived events dataset)
- vi. List of all serious adverse events reported to Regulatory Safety Center (RSC) and NIAID DSMB [in Appendix]
- vii. Table with number (%) of missed visits/contacts during the study (separated by acute vs RSV surveillance portion)

b. Hospitalizations (if any):

- i. List: patient ID, week, days in hospital, diagnosis

c. Concomitant Medications:

- i. Line listing of patients and the medications received during the study (using the *pe0414* dataset): patient ID, date of inoculation, drug code, drug name, start date, stop date, drug frequency, drug indication, drug unit, and drug indication.

d. Deaths (if any):

- i. List: days/weeks since inoculation, site's report of primary cause of death, site's determination of relatedness to study treatment. More detailed information on each death will be included in an Appendix.

6.6 Infectivity Primary Objectives

Objective 3. Infectivity: To determine the peak titer of vaccine virus shed and duration of virus shedding by each participant

Objective 4. Infectivity: To assess the proportion of vaccinated infants infected

Summaries will include:

- (i) the proportion of participants infected with vaccine virus;
- (ii) summaries of peak titer and of duration of virus shed.

6.7 Immunogenicity Primary Objective

Objective 5. Immunogenicity: To characterize antibody responses (Day 56) to the study vaccine

Summaries will include:

- i) summaries of antibody titers to the RSV F glycoprotein as assessed by ELISA (anti-RSV F IgG) and of the RSV neutralizing antibody for each treatment group.
- ii) the proportion of participants who develop a four-fold or greater rise in RSV neutralizing antibody titer following vaccination, at day 56;
- iii) the proportion of participants who develop a four-fold or greater rise in anti-RSV F IgG antibody titer following vaccination, at day 56;

6.8 Secondary Objectives

Objective 1. To characterize clinical outcomes (frequency and severity of symptomatic, medically attended respiratory and febrile illness) in the vaccine and placebo recipients who experience natural infection with wild-type (wt) RSV during the subsequent RSV season

Objective 2. To characterize antibody responses in the vaccine and placebo recipients who experience natural infection with wt RSV during the subsequent RSV season

Objective 3. To characterize the B cell response to vaccine and the quality and epitope specificity of RSV F specific antibody, and to characterize these responses in the vaccine and placebo recipients who experience natural infection to wt RSV during the subsequent RSV season

Objective 4. To characterize the mucosal antibody response to vaccine

NOTE: The outcome measure for Secondary Objective 4 has been changed from a secondary outcome measure to an exploratory outcome measure. Since this objective's outcome measure relies on previously untested assays to reliably quantify RSV specific mucosal antibodies from nasal wash samples, it was changed to exploratory to fit with its intended analysis type.

Summaries will include:

- i) line listing of participants with solicited and unsolicited signs, symptoms or diagnoses during the RSV surveillance discussed by the team on conference calls (from the *events* study dataset): patient ID, date of receipt of study agent, days from inoculation to onset of AE, abnormality, grade, relationship to study treatment (from *trac* study dataset), onset date and end date
- ii) summary table with n (%) of subjects experiencing at least one episode of a solicited and unsolicited adverse event, counting the worst (highest) grade adverse event by MedDRA System Organ Class (SOC) and Preferred Term (PT) (applying the CBAR *eventsum* macro on the study derived events dataset)
- iii) summaries of antibody titers to the RSV F glycoprotein as assessed by ELISA (anti-RSV F IgG) and of the RSV neutralizing antibody pre and post RSV surveillance season for each treatment group.
- iv) summaries of antibody titers to the RSV F glycoprotein as assessed by ELISA (anti-RSV F IgG) and of the RSV neutralizing antibody pre and post RSV surveillance season for the participants who reach a ≥ 4 fold increase in antibody levels (participants are presumed not exposed to RSV).
- v) the proportion of participants who develop a four-fold or greater rise in RSV neutralizing antibody titer from pre to post RSV surveillance season;
- vi) the proportion of participants who develop a four-fold or greater rise in anti-RSV F IgG antibody titer from pre to post RSV surveillance season.

Table 2: Definitions of Solicited Adverse Events (Solicited AEs) (Appendix IV from the protocol)

Event	Defined
Fever	Temporal temperatures $\geq 100.0^{\circ}\text{F}$ unconfirmed by rectal temp -or- Rectal temperature of $\geq 100.4^{\circ}\text{F}$.
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	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}	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) ^{1,2,3}	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.

**Table 3: IMPAACT 2013-specific AE Grading Table for solicited adverse events
(Table 3 from the protocol)**

Severity	Defined
Grade (0) None	Not applicable
Grade (1) Mild	No medical intervention required; may include use of over-the-counter medications managed by the caregiver for treatment of symptoms
Grade (2) Moderate	Outpatient medical intervention by a health care provider required; may include use of over-the-counter and/or prescription medications.
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

Table 4: IMPAACT 2013-specific Fever Grading* (Table 4 from the protocol)

Severity	Defined
Grade (0)	$\geq 100.0^{\circ}\text{F}$ but $< 100.4^{\circ}\text{F}$ ($\geq 37.8^{\circ}\text{C}$ but $< 38^{\circ}\text{C}$)
Grade (1)	$\geq 100.4^{\circ}\text{F}$ but $\leq 101.4^{\circ}\text{F}$ ($\geq 38^{\circ}\text{C}$ but $< 38.6^{\circ}\text{C}$)
Grade (2)	$\geq 101.5^{\circ}\text{F}$ but $\leq 102.4^{\circ}\text{F}$ ($\geq 38.6^{\circ}\text{C}$ but $\leq 39.1^{\circ}\text{C}$)
Grade (3)	$\geq 102.5^{\circ}\text{F}$ but $\leq 104.8^{\circ}\text{F}$ ($\geq 39.2^{\circ}\text{C}$ but $\leq 40.4^{\circ}\text{C}$)
Grade (4)	$\geq 104.9^{\circ}\text{F}$ ($\geq 40.5^{\circ}\text{C}$)

*Applies to any modality of temperature measurement

Appendix containing Section 9.5 from Protocol Version 1.0 dated February 14, 2017

9.5 Analyses

9.5.1 Assessment of Primary Objectives

Safety data from all study participants who have been inoculated will be summarized, including data from participants who discontinue study early or have some missed visits. In the immunogenicity analyses, those who do not provide data for the Day 56 Visit follow-up (due to early discontinuation or missed visit) will be treated as “failures”. Sensitivity analyses will be performed to check if the results are consistent with those when these participants are excluded. Participants who receive any of the disallowed treatments listed in Section 5.11 after inoculation may be excluded from the immunogenicity evaluations after the time of the treatment. These participants will, however, be included in the safety evaluations for the duration of the study. These participants will not be replaced. Details of the analyses listed below will be included in the Statistical Analysis Plan.

The frequency of solicited AEs and unsolicited AEs, along with 90% confidence intervals, during Study Days 0 to 28 and of vaccine-related SAE during Study Day 0 to the Day 56 Visit will be summarized. In addition, line listing of individual clinical solicited AEs and unsolicited AEs during Study Days 0 to 28 and vaccine-related SAE during Study Day 0 to the Day 56 Visit, graded by severity, will be prepared.

The proportion of participants with infection defined as recovery of vaccine virus from a nasal wash, as determined by culture and RT-PCR, and/or a \geq fourfold rise in serum antibody titer to RSV, will be summarized. A line listing of the individual peak titer of vaccine virus shed and duration of virus shedding in nasal washes by each individual will be prepared. In addition, the geometric mean peak titer and mean duration of virus shed will be provided, for each treatment group.

The proportion of participants that develop fourfold or greater rises in RSV-neutralizing antibody titer following vaccination will be summarized. A line listing of the individual RSV antibody titer pre- and post-vaccination will be prepared. In addition, the geometric mean and median antibody titers will be provided, for each treatment group. Line listings of individual RSV-neutralizing antibody responses as well as of antibody responses to the RSV F glycoprotein will be prepared as well.

Where appropriate, the Wilcoxon rank sum test will be used to test the hypothesis that the vaccinated group will exhibit greater peak viral titers and antibody titers following vaccination compared to the placebo group. A 1-tailed Fisher's exact test will be used to test the hypothesis that the vaccinated group will exhibit a greater proportion of participants who develop fourfold or greater rises in RSV-neutralizing antibody titer following vaccination compared to the placebo group.

These will be the only formal statistical comparisons between the vaccinated and placebo groups. These tests will be carried out at a 5% significance level.

The study results will be compared with the criteria listed in Section 1.1 to determine if this vaccine is a promising candidate for further evaluation in expanded Phase I studies or Phase II studies.

9.5.2 Assessment of Secondary Objectives

The summary of the frequency and severity of symptomatic, medically attended respiratory and febrile illness in the vaccine and placebo recipients who experience natural infection with wt RSV during the subsequent RSV season will be presented. A line listing of the individual RSV antibody titer pre- and post-RSV Season Surveillance Period will be prepared. In addition, the geometric mean and median antibody titers will be provided for each treatment group. The B cell responses to vaccine as well as the quality and epitope specificity of RSV F specific antibody will be summarized for each treatment group.