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# A Phase 3, Randomized, Observer-Blind, Placebo-Controlled Study to Determine the Immunogenicity and Safety of a Respiratory Syncytial Virus (RSV) F Nanoparticle Vaccine with Aluminum in Healthy Third-trimester Pregnant Women; and Safety and Efficacy of Maternally Transferred Antibodies in Preventing RSV Disease in their Infants

**Novavax Protocol Number: RSV-M-301**

## STATISTICAL ANALYSIS PLAN (SAP) for Unblinded and Final Analyses of Efficacy, Safety, and Immunogenicity Data

| | |
|---|---|
| **SAP Version and Date:** | Version 6.1 – 07 February 2019 |
| **Investigational Products:** | Respiratory Syncytial Virus (RSV) Recombinant F Nanoparticle Vaccine (*Spodoptera frugiperda* [Sf9] cells with recombinant Baculovirus expression) and aluminum phosphate adjuvant (herein referred to as aluminum); and isotonic saline (placebo) |

## APPROVAL SIGNATURE PAGE

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☐ Original Statistical Analysis Plan

☒ Amended Statistical Analysis Plan

SAP Originated By: _____ _____
Project Statistician Date

**Signatures below indicate the SAP has been reviewed and approved by the following personnel:**

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Date

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Statistician Lead _____
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## LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| APGAR | Appearance, Pulse, Grimace, Activity, Respiration; an assessment used to measure the health of a newborn child |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| BUN | Blood Urea Nitrogen |
| C | Celsius |
| CBC | Complete Blood Count |
| CBER | Center for Biologics Evaluation and Research |
| CI | Confidence Interval |
| CSR | Clinical Study Report |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EOS | End of Study |
| EU | ELISA Unit |
| FOC | Frontal-Occipital Head Circumference |
| GA | Gestational Age |
| GLP | Good Laboratory Practice |
| GMEU | Geometric Mean ELISA Unit |
| GMFR | Geometric Mean Fold-Rise |
| GMR | Geometric Mean Ratio |
| GMT | Geometric Mean Titer |
| IB | Investigator's Brochure |
| IBG | Independent Biostatistics Group |
| ICH | International Conference on Harmonization |
| IgG | Immunoglobulin G |
| IM | Intramuscular |
| ITT | Intent-to-Treat |
| ITT-EFF | Intent-to-Treat Efficacy |
| ITT-EFF-I | Intent-to-Treat Efficacy for Infant Subjects |
| ITT-EFF-M | Intent-to-Treat Efficacy for Maternal Subjects |
| ITT-IMM-I | Intent-to-Treat Immunogenicity for Infant Subjects |

| Abbreviation or Term | Definition |
|---|---|
| ITT-IMM-M | Intent-to-Treat Immunogenicity for Maternal Subjects |
| IWRS | Interactive Web Randomization System |
| kg | Kilogram |
| LBCI | Lower Bound of Confidence Interval |
| LLOQ | Lower Limit of Quantitation |
| MAE | Medically-Attended Event |
| MedDRA | Medical Dictionary for Regulatory Activities |
| µg | Microgram |
| µM | Micromolar |
| mg | Milligram |
| mL | Milliliter |
| mM | Millimolar |
| MN | Microneutralization Assay |
| PP | Per Protocol |
| PP-EFF | Per Protocol Efficacy |
| PP-EFF-I | Per Protocol Efficacy for Infant Subjects |
| PP-EFF-M | Per Protocol Efficacy for Maternal Subjects |
| PP-IMM | Per Protocol Immunogenicity |
| PP-IMM-I | Per Protocol Immunogenicity for Infant Subjects |
| PP-IMM-M | Per Protocol Immunogenicity for Maternal Subjects |
| PT | Preferred Term |
| RBC | Red Blood Cells |
| RSV | Respiratory Syncytial Virus |
| SAE | Serious Adverse Event |
| SCR | Seroconversion Rate |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SRR | Seroresponse Rate |
| TGS | Toxicity Grading Scale |
| ULoQ | Upper Limit of Quantitation |
| US | United States |
| vv | Vaccinia Virus |
| WBC | White Blood Cell Count |
| WHO | World Health Organization |

# 1. INTRODUCTION

The goal of this clinical development program is to establish efficacy of the RSV F vaccine by providing protection against RSV disease in infants during the first three to six months of life via active immunization of pregnant women in the third trimester of pregnancy. Passive immunization of infants will be achieved through transplacental transfer of maternal IgG antibodies from the pregnant mother who has received the RSV F vaccine in the third trimester of her pregnancy. Maternally derived, transplacentally-mediated immunity is a physiologic, effective, and established means for protecting infants against infectious diseases during the first months of life. Active Fc-gamma receptor mediated transport of maternal IgG begins early in gestation, but reaches significant levels at 28 weeks gestational age [Palmeira 2012]. By ≥ 36 weeks gestational age, antibody levels in the fetus are generally in excess of levels found in the mother [Lindsey 2013]. Maternal immunization programs addressing tetanus, pertussis, and influenza have all shown benefits to infants. Albeit less well-recognized than influenza, anecdotal observations suggest that significant RSV disease may also occur in pregnant women themselves and thus an additional benefit to the mother may also be obtained by immunization with an RSV vaccine [Wheeler 2015].

For this global clinical trial of the RSV F vaccine in pregnant women, a 120 µg dose of RSV F protein with 0.4 mg aluminum as the phosphate salt, administered as a single injection, was selected based on a previous study of women of child-bearing age, where this formulation and regimen were well-tolerated and produced the highest peak anti-F antibody responses at 14 days post-vaccination when evaluated against other vaccine formulations and regimens. This rapid response reflects the fact that all adults are immunologically primed to RSV. The RSV F vaccine in general has been shown to elicit high levels of antibodies to the neutralizing RSV F protein antigenic site II epitope based on competition with the globally licensed, proven-efficacious monoclonal antibody palivizumab, as well as assays of direct binding of IgG to the antigenic site II linear peptide encompassing amino acid residues 254 - 278. Levels of these antibodies may exceed the trough levels of palivizumab associated with clinical protection by 10-fold. This, in turn suggests that, with active placental transfer and possible concentration of these antibodies, infant protection extending through at least 3 to 6 months of life might be feasible.

Data from the first-in-pregnant women study (RSV-M-203, N = 50) with the RSV F vaccine conducted in the United States (US) showed the vaccine was well-tolerated, posing no significant safety risk to pregnant women or their infants that was apparent in this limited dataset; and was immunogenic, eliciting antibody responses that were analogous in kinetics and magnitude to levels observed in non-pregnant women of childbearing age. Results indicated the antibody profile achieved with a single dose of the RSV F vaccine in pregnant subjects immunized at 33 to 35 weeks gestation was robust, with substantial responses measurable by 14 days post-vaccination; and diverse, eliciting antibodies which compete with monoclonal antibodies specific for the antigenic sites I, IV, and VIII neutralizing epitopes on the F protein in addition to antigenic site II. Transplacental transfer of maternal antibodies with specificity to the RSV F protein in delivered infants averaged 90 to 100% of the actively-treated matched mother, but averaged 110 to 120% when immunization preceded delivery by ≥ 30 days. This supports immunization of pregnant women between 28 to 36 weeks gestation in this study, as

widening the window for vaccination to include women at the beginning of the third trimester is not expected to result in increased safety risk to the woman or fetus [Madhi 2014, Munoz 2014], and may increase the potential for higher vaccine-specific antibody titers in the delivered infant due to extended transplacental transfer [Abu Raya 2014, Eberhardt 2016, Naidu 2016].

The objectives of the Phase 2 trial were to establish an initial maternal safety database in pregnancy, assess the amplitude of transplacental transfer of vaccine-induced antibodies in humans, estimate the decay half-life of such antibodies in infants, and detect any signal suggestive of "vaccine-enhanced disease" in infants over their first RSV transmission season.

# 2. STUDY DESIGN

This is a randomized, observer-blind, placebo-controlled trial enrolling up to approximately 4,600 third-trimester pregnant women in the Northern and Southern hemispheres. Randomization will be configured to provide approximately 3,000 exposures to the active test article.

The primary analysis of the trial is an evaluation of the superior efficacy of the RSV F vaccine relative to the placebo in reducing the rate of medically-significant RSV lower respiratory tract infection (LRTI) with EITHER hypoxemia (peripheral oxygen saturation [$SpO_2$] < 95% at sea level or < 92% at altitudes > 1800 meters) OR tachypnea (≥ 70 bpm for infants 0 to 59 days of age or ≥ 60 bpm for infants ≥ 60 days of age) in infants through the first 90 days of life. If a successful outcome is obtained through 90 days of life, then additional analyses for efficacy will be performed in a closed hierarchical sequence considering data through 120, 150, and 180 days of life (with each sequential analysis being enabled by a significant result at the preceding shorter interval). Multiple secondary and exploratory efficacy analyses will also address other infant and maternal RSV disease outcomes. All primary and secondary efficacy endpoints, as well as exploratory efficacy endpoints in infants concerning RSV-associated illness, will be reviewed and validated by an independent Clinical Endpoint Adjudication Committee (CEAC) prior to unblinding (see Section 10.2). Only endpoints validated by CEAC review will be used for the efficacy analyses.

Due to the seasonal nature of RSV disease and the occurrence of RSV seasons in a roughly sequential manner across the Northern and Southern hemispheres, futility analyses for detecting situations in which the existing efficacy data are not consistent with a pre-defined minimal clinical benefit, will occur at the approximate end of each Northern hemisphere season (data as of approximately 30 May) and each global RSV season (data as of approximately 30 September), comprising a Northern hemisphere season and the following Southern hemisphere season); and subject to constraint (applied by the data and safety monitoring board [DSMB] statistician) that at least 10 cases will have accrued in the active treatment arm. A determination of futility at any futility analysis, will lead to a DSMB recommendation to terminate the trial, and stop further enrollment.

Healthy women in the third trimester of a singleton uncomplicated pregnancy, at low risk of obstetrical complications, and ≥ 18 to ≤ 40 years of age (lower limit of 18 years and 0 days and an upper limit of 40 years and 0 days) will be enrolled and randomized initially in a 1:1 ratio, into one of two treatment groups, active or placebo, over approximately the 3 months prior to peak RSV season, as shown in Table 1. After the first global season of enrollment, the randomization scheme will be changed from a 1:1 (active:placebo) ratio to a 2:1 (active : placebo) ratio to enable more efficient accrual of the safety database. Due to the importance of infant RSV exposure in order to demonstrate efficacy of the maternal immunization strategy, investigators will be instructed to base maternal enrollment on a projected date of delivery for each maternal subject. The estimated date of the earliest delivery (EDD-E) will be approximately 6 weeks prior to the historic average onset date of increased RSV transmission at each study site. The estimated date of the latest delivery (EDD-L) will be calculated based

on the historic average end date of RSV transmission at each study site, such that participating infants are likely to have a minimum 3 month exposure to RSV transmission. The Sponsor will assist and provide guidance to each site in determining the EDD-E and EDD-L using best available site-specific, local, state/provincial, or national surveillance data to the extent available. The trial will begin with enrollment of women in the Northern hemisphere, followed by enrollment in the Southern hemisphere for the first global RSV season.

**Table 1: Treatment Assignments**

| Treatment Group | Target Maternal Subjects/Group[1] | Test Article | Dosing Volume | Vaccination Day |
|---|---|---|---|---|
| A | ~1562 | Saline placebo | 0.5 mL | Day 0 |
| B | ~3038 | RSV F vaccine | | |

[1] The target number of subjects that may be enrolled over multiple global RSV seasons, based on a 1:1 randomization for the first season and 2:1 (active / placebo) randomization for all subsequent seasons.

Randomization of maternal subjects will be done at the site level and will be stratified by age (i.e., 18 to < 29 years and 29 to ≤ 40 years). No specific proportion in either age group will be sought, rather the intent of stratification will be to distribute the proportion of maternal subjects presenting for enrollment in each age group equally across the two treatment arms. In addition, infant subjects born to randomized maternal subjects will be prospectively and randomly assigned to one of three postpartum phlebotomy cohorts, which will differ only in the timing of blood sampling.

It is anticipated that a percentage of the randomized maternal subjects and their delivered infants may not complete the study; subjects (maternal and infant) who withdraw or are discontinued will not be replaced.

All maternal subjects will receive a single IM injection on Day 0 with the assigned test article, the RSV F vaccine or saline placebo (see Table 1). For each maternal subject, study participation will span approximately nine (9) months from the first dose, ending six (6) months post-delivery. Study follow-up for infant subjects who are consented will span approximately one (1) year post-delivery (Refer to the Appendix 1 of study protocol). The DSMB will supervise enrollment and monitor subject safety throughout the trial.

## 2.1. Interim (Futility and Informational) Analyses and Data and Safety Monitoring Board (DSMB)

### 2.1.1. Blinding and Interim Analyses

This SAP, the study RSV-M-301 DSMB charter, and the Communication Plan will serve to establish a written procedure for the careful handling of all interim safety and efficacy data to maintain the confidentiality of the interim data and sustained blinding of the study team.

### 2.1.2. Maintaining Sponsor Study Blind

The Novavax study biostatistician, as well as all Novavax project team members, will remain blinded to treatment assignment during the preparation and presentation of all futility analyses and the informational analysis prepared in support of the DSMB review. No Novavax project team members will have access to unblinded summary tables.

### 2.1.3. Unblinded Personnel

As described in US 21 CFR 314.126, unblinded interim data and the results of comparative interim analyses should not be accessible by anyone other than DSMB members or unblinded statistician(s) performing these analyses for provision to the DSMB.

Two unblinded statisticians will be involved in the study: the DSMB statistician and the independent biostatistics group (IBG) statistician. These statisticians are external to Novavax and will be responsible for preparation of routine safety data tabulations for the DSMB and for conduct of the futility and informational analyses of the primary efficacy endpoint.

- **Access to study randomization:** The DSMB statistician will be unblinded to treatment assignment for subjects enrolled at the end of each season to allow the estimation of the number of cases meeting the primary endpoint definition, medically-significant RSV LRTI in the data set for the analysis. An unblinded summary table of the results will be sent to the IBG statistician to support the futility and informational analyses. In addition, unblinded safety tables will also be prepared by the DSMB statistician for DSMB consumption in accordance with the DSMB SAP. The DSMB may also request *ad hoc* tabulations of safety information. The treatment assignments (randomization schedule) of the subjects involved will be provided by IWRS vendor directly to the DSMB statistician via secure FTP site or via download through SAS® on-demand.
- **Access to unblinded analyses:** Unblinded tables (for medically-significant RSV LRTI cases) and listings (safety) prepared by the DSMB statistician will be provided directly to the IBG and to the DSMB via a secure FTP site. Further dissemination and review of the unblinded tables and listings prepared by the DSMB statistician will be limited to members of the DSMB (as indicated in the DSMB Charter) and to the IBG statistician.
- **IBG and the DSMB:** Following the scheduled analyses for futility, informational, and/or efficacy, the IBG will provide the DSMB with a summary of the analyses and recommendations. If a protocol-defined stopping rule is fulfilled based on these analyses, the IBG will inform the DSMB PM. After review of the data and analyses leading to fulfillment of the pre-specified thresholds by the IBG and DSMB, the DSMB PM will then inform the Sponsor Contact of the DSMB recommendation.
- **Sponsor Biostatistician:** The Sponsor Biostatistician will be unblinded following success or futility, after all data from all enrolled mother-infant pairs through the infant D+180 visit and the maternal postpartum Day 180 visit are completed, all queries are resolved, and the database is locked. The Sponsor Biostatistician will perform the final analysis after all data through the infant D+364 visit are completed, all queries are resolved, all immunogenicity testing are completed, and the database is locked.

# 3. SCOPE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) provides a detailed outline of efficacy, safety, and immunogenicity analyses to be performed in accordance with Study Protocol RSV-M-301 Version 10.0, dated 02 October 2018, and will address the analysis presentation of the unblinded and final review of all data for the completed study.

This SAP addresses analyses of the final unblinded analysis of efficacy data and the safety and immunogenicity data through D+180 for maternal and infant subjects and the final safety analysis through the infant D+364 visit. A separate Adaptive Design Report generated by the IBG that includes additional description of the design along with details of the statistical models and simulation results for operating characteristics including robustness assessments are included in APPENDIX 1.

# 4. OBJECTIVE AND ENDPOINT

## 4.1. Study Objectives

### 4.1.1. Primary Objectives

- To determine the efficacy of maternal immunization with the RSV F vaccine against medically-significant RSV lower respiratory tract infection (LRTI) with EITHER hypoxemia (peripheral oxygen saturation [$SpO_2$] < 95% at sea level or < 92% at altitudes > 1800 meters) OR tachypnea (≥ 70 bpm for infants 0 to 59 days of age or ≥ 60 bpm for infants ≥ 60 days of age) through the first 90 days of life in infants of maternal RSV F vaccinees as compared to placebo recipients. In the event that efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy through the first 120, 150, and 180 days of life.

The primary efficacy objective will be evaluated in term infants (≥ 37 weeks gestational age at delivery) born to maternal subjects who received a study injection ≥ 2 weeks (14 days) prior to delivery. Infants with multiple RSV episodes will be counted only once, using data from the first episode of medically-significant RSV LRTI. Success under the primary hypothesis will be achieved by demonstration of a lower bound of a two-sided 97.52% confidence interval for the Day 90 analysis (two-sided 95% confidence interval for later time points) for the estimate of vaccine efficacy which equals or exceeds target values agreed with regulatory authorities.

### 4.1.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants of:
  - RSV LRTI with EITHER severe hypoxemia ($SpO_2$ < 92% at sea level or < 87% at altitudes > 1800 meters) or the documented use of oxygen by high flow nasal cannula OR a requirement for continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO), through the first 90 days of life in infants of maternal RSV F vaccinees as compared to placebo recipients. In the event that efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy at 120, 150, and 180 days of life.
  - RSV LRTI leading to hospitalization through the first 90 days of life in infants of maternal RSV F vaccinees as compared to placebo recipients. In the event that efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy through 120, 150, and 180 days of life.

The two secondary efficacy objectives will be evaluated in term infants (≥ 37 weeks gestational age at delivery) born to maternal subjects who received a study injection ≥ 2 weeks (14 days) prior to delivery. Infants with multiple RSV episodes meeting a given criterion will be counted

only once, using data from the first episode. Success under the secondary efficacy hypotheses will be achieved by demonstration of a lower bound of a two-sided 95% confidence interval for the estimate of vaccine efficacy which exceeds 0%.

- To describe the immunologic responses to the RSV F vaccine in healthy maternal subjects, in the third trimester of pregnancies deemed to be at low risk of obstetrical complications, through delivery and six months thereafter.
- To describe the transplacental transfer of maternal antibodies specific for RSV and its F protein based on the ratio of levels in maternal and cord blood at delivery.
- To estimate the rate of decay of RSV and F protein-specific antibodies in infants through the first six months of life.
- To develop an immune correlate of risk of the RSV LRTI syndromes in infants based on anti-F protein antibody and/or palivizumab-competitive antibody levels measured in the infant and/or cord blood.
- To develop an immune correlate of risk of the RSV LRTI syndromes in infants based on anti-F protein antibody and/or palivizumab-competitive antibody levels measured in maternal subjects at delivery.
- To describe the safety of third-trimester maternal immunization with the RSV F vaccine in infants of vaccinated maternal subjects through their first year of life, which will include at least one RSV season.
- To describe the safety of the RSV F vaccine in healthy maternal subjects, in the third trimester of pregnancies deemed to be at low risk of obstetrical complications, through delivery and six months thereafter.

### 4.1.3. Exploratory Objectives

- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants of medically-significant RSV LRTI defined as per the primary objective but with the inclusion of data concerning documentation of RSV infection, LRTI symptoms and signs, hypoxemia and/or tachypnea obtained from the observations of the clinical site staff OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of RSV LRTI with EITHER severe hypoxemia (SpO2 < 92% at sea level or < 87% at altitudes > 1800 meters) OR the documented use of oxygen by high flow nasal cannula OR continuous positive airway pressure (CPAP) OR bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO) defined as per the first secondary objective but with the inclusion of data concerning documentation of RSV infection, LRTI symptoms and signs, and hypoxemia obtained from the observations of the clinical site staff OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.

- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of RSV LRTI requiring hospitalization defined as per the second secondary objective but with the inclusion of data concerning documentation of RSV infection, LRTI symptoms and signs obtained from the observations of the clinical site staff OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants of RSV LRTI associated with EITHER hypoxemia (peripheral oxygen saturation [SpO2] < 95% at sea level or < 92% at altitudes > 1800 meters) OR tachypnea (≥ 60 bpm for infants 0 to 59 days of age or ≥ 50 bpm for infants ≥ 60 days of age [WHO Handbook, Integrated Management of Childhood Illness criteria for tachypnea]) with the inclusion of data concerning documentation of RSV infection, LRTI symptoms and signs, hypoxemia and/or tachypnea obtained from the observations of the clinical site staff OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants with RSV LRTI resulting in death. Evidence of RSV infection and LRTI may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants of all RSV LRTI.

For all of the above exploratory analyses infants, if efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy through 120, 150, and 180 days of life.

- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of healthcare interventions associated with wheezing through the first year of life in infants of maternal RSV F vaccinees as compared to placebo recipients.
- To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of all symptomatic RSV respiratory tract infections detected by active/passive surveillance in maternal subjects from immunization through six months after delivery.
- To describe the incidence of all-cause LRTI, with and without tachypnea, hypoxemia, or severe hypoxemia, in infant subjects as detected by active and passive surveillance from vaccination through six months after delivery, and the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of these endpoints.
- To describe the epidemiology of non-RSV respiratory viruses detected by RT-PCR in infant and maternal subjects presenting with respiratory symptoms, through six months after delivery.

## 4.2. Study Endpoints

### 4.2.1. Primary Efficacy Endpoint *(*In Infant Subjects*)*

- Percentages of infants with medically-significant RSV LRTI from delivery through 90, 120, 150, and 180 days of life, as defined by:
  - The presence of RSV infection confirmed by detection of the RSV genome by RT-PCR on respiratory secretions (obtained within the continuous illness episode which fulfills the other criteria listed below); AND
  - At least one manifestation of lower respiratory tract infection (LRTI) from among the following: cough, nasal flaring, lower chest wall indrawing, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles/crepitations, or observed apnea; AND
  - Evidence of medical significance as defined by the presence of:
    - EITHER hypoxemia (peripheral oxygen saturation [$SpO_2$] < 95% at sea level or < 92% at altitudes > 1800 meters) OR
    - Tachypnea (≥ 70 breaths per minute [bpm] in infants 0 to 59 days of age and ≥ 60 bpm in infants ≥ 60 days of age).

Data elements supporting the three (3) criteria for a primary endpoint case will be present within the start and stop dates of a continuous illness episode and derived from clinical observations (LRTI signs and symptoms and respiratory rates) made by qualified clinical trial site staff, pulse oximetry performed by site personnel using a Masimo RAD-5 pulse oximeter supplied by the sponsor, and RSV detection based on study-specified RT-PCR performed by the validated GenMark eSensor assay in place at the central laboratory (Marshfield Clinic Research Institute, Marshfield, Wisconsin).

A Clinical Endpoint Adjudication Committee (CEAC) composed of expert pediatricians (see Section 10.2) will carry out a blinded review of all potential primary endpoint cases to determine if they fulfill the primary endpoint criteria in a temporally plausible relationship consistent with RSV disease as observed in clinical practice. Only CEAC-confirmed cases will be used for the primary endpoint.

### 4.2.2. Secondary Efficacy Endpoints (In Infant Subjects)

- Percentages of infants with RSV LRTI with severe hypoxemia ($SpO_2$ < 92% at sea level or < 87% at altitudes > 1800 meters) OR the documented use of oxygen by high flow nasal cannula OR a requirement for continuous positive airway pressure (CPAP) OR bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO) from delivery through 90, 120, 150, and 180 days of life. An event is considered RSV LRTI with severe hypoxemia if all parameters outlined below are present during a continuous symptomatic illness episode:

  - RSV infection as confirmed by detection of the RSV genome by RT-PCR, AND
  - At least one manifestation of lower respiratory tract infection (LRTI) from among the following: cough, nasal flaring, lower chest wall indrawing, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles/crepitations, or observed apnea, AND
  - Evidence of severe hypoxemia or the requirement for respiratory support as defined by the presence of:
    - EITHER severe hypoxemia (peripheral oxygen saturation [$SpO_2$] < 92% at sea level or < 87% at altitudes > 1800 meters) OR
    - The documented use of oxygen by high flow nasal cannula OR continuous positive airway pressure (CPAP) OR bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO).
- Percentages of infants with RSV LRTI with hospitalization from delivery through 90, 120, 150, and 180 days of life. An event is considered RSV LRTI hospitalization if all parameters outlined below are present during a continuous symptomatic illness episode:
  - RSV infection as confirmed by detection of the RSV genome by RT-PCR, AND
  - At least one manifestation of lower respiratory tract infection (LRTI) from among the following: cough, nasal flaring, lower chest wall indrawing, subcostal retractions, stridor, rales, rhonchi, wheezing, crackles/crepitations, or observed apnea, AND
  - Documented hospitalization.

  Data elements supporting the criteria for secondary endpoint cases will be present within the start and stop dates of a continuous illness episode and derived from clinical observations (LRTI signs and symptoms and respiratory rates) made by qualified clinical trial site staff, pulse oximetry performed by site personnel using a Masimo RAD-5 pulse oximeter supplied by the sponsor, and RSV detection based on study-specified RT-PCR performed by the validated GenMark eSensor assay in place at the central laboratory (Marshfield Clinic Research Institute, Marshfield, Wisconsin). Evidence of hospitalization and/or in-hospital use of high-flow nasal cannula, CPAP, BiPAP, bubble CPAP, intubation, or mechanical/manual ventilation or ECMO will be supported by hospital records obtained by the clinical site staff.

  A Clinical Endpoint Adjudication Committee (CEAC) composed of expert pediatricians (see Section 10.2) will carry out a blinded review of all potential secondary endpoint cases to determine if they fulfill the relevant endpoint criteria in a temporally plausible relationship consistent with RSV disease as observed in clinical practice. Only CEAC-confirmed cases will be used for secondary endpoints.

### 4.2.3. Exploratory Efficacy Endpoints in Infant and Maternal Subjects

- Percentages of infants with medically-significant RSV LRTI from delivery through 90, 120, 150 and 180 days of life defined as per the primary efficacy endpoint with the exception that evidence of RSV infection, LRTI, hypoxemia, and/or tachypnea may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and

diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.

- Percentages of infants with RSV LRTI with EITHER severe hypoxemia (SpO2 < 92% at sea level or < 87% at altitudes > 1800 meters) OR the documented use of oxygen by high flow nasal cannula OR continuous positive airway pressure (CPAP) OR bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO) from delivery through 90, 120, 150, and 180 days of life defined as per the corresponding secondary efficacy endpoint with the exception that evidence of RSV infection, LRTI, severe hypoxemia, and/or respiratory support may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- Percentages of infants with RSV LRTI requiring hospitalization from delivery through 90, 120, 150, and 180 days of life defined as per the corresponding secondary efficacy endpoint with the exception that evidence of RSV infection and LRTI may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- Percentages of infants with RSV LRTI associated with EITHER hypoxemia (peripheral oxygen saturation [SpO2] < 95% at sea level or < 92% at altitudes > 1800 meters) OR tachypnea (≥ 60 bpm for infants 0 to 59 days of age or ≥ 50 bpm for infants ≥ 60 days of age [WHO Handbook, Integrated Management of Childhood Illness criteria for tachypnea]) from delivery through 90, 120, 150, and 180 days of life. Data concerning documentation of RSV infection, LRTI symptoms and signs, hypoxemia and/or tachypnea may be obtained from the observations of the clinical site staff OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- Percentages of infants with RSV LRTI resulting in death from delivery through 90, 120, 150, and 180 days of life. Evidence of RSV infection and LRTI may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- Percentages of infants with RSV LRTI (all severities) from delivery through 90, 120, 150, and 180 days of life. Evidence of RSV infection and LRTI may be based on either or both of the observations of the clinical site staff using sponsor-supplied devices and diagnostic tests OR review and abstraction of medical records for infants undergoing hospitalization for a respiratory serious adverse event.
- Counts and incidence rates of infant healthcare interventions associated with wheezing through the first year of life.
- Percentages of maternal subjects with RSV-related respiratory illness as observed by the clinical study staff and detected by active and passive surveillance from vaccination through six months after delivery, overall and by pathogen(s).

- Percentages of infant subjects with all-cause LRTI, with or without tachypnea, hypoxemia, or severe hypoxemia, as detected by active and passive surveillance from vaccination through six months after delivery, overall and by pathogen(s).
- Percentages of infant and maternal subjects with non-RSV respiratory viruses, overall and by pathogen(s), through six months after delivery.

A Clinical Endpoint Adjudication Committee (CEAC) composed of expert pediatricians (see Section 10.2) will carry out a blinded review of all potential exploratory endpoint cases involving RSV LRTI in infants to determine if they fulfill the relevant endpoint criteria in a temporally plausible relationship consistent with RSV disease as observed in clinical practice. Only CEAC-confirmed cases will be used for exploratory endpoints.

#### 4.2.3.1. Data Sources for Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be supported by any combination of data derived from the following sources of data:

- The observations of RSV genome detection by RT-PCR via the validated assay at the central laboratory (Marshfield Clinic Research Institute, Marshfield, Wisconsin), the verification of RSV LRTI symptoms and signs and respiratory rates per qualified site staff, and pulse oximetry using a Masimo Rad-5 pulse oximeter provided by the sponsor, AND

- Documented healthcare records available to the site personnel which capture clinical observations of respiratory rate and LRTI symptoms and signs, oxygen saturation using non-sponsor provided pulse oximeters, and locally performed RT-PCR detection of RSV genome and any oxygen interventions utilized to support hypoxemic infants. These data will be derived from records of hospitalizations or emergency room observations. The above information will be recorded in an eCRF and monitored against source documentation. Wherever possible, the name, model, and manufacturer of pulse oximeters and RSV diagnostic tests will be collected.

### 4.2.4. Immunogenicity Endpoints (In Maternal and Infant Subjects as Stated)

- Serum immunoglobulin G (IgG) antibody concentrations specific for the F protein antigen measured by enzyme-linked immunosorbent assay (ELISA) and serum concentrations of antibodies competitive with palivizumab for binding to the RSV F protein. Derived/calculated endpoints based on these data will include geometric mean concentrations as ELISA Units (GMEU) or µg/mL as appropriate, geometric mean fold-rise (GMFR), proportion of subjects with ≥ 2-fold and ≥ 4-fold increases in concentration from baseline (seroconversion rate, SCR [maternal subjects only]), and seroresponse rate (SRR). Analyses will be used to evaluate:
  - Immunogenicity through six months post-delivery in maternal subjects.
  - Transplacental transfer of maternal antibodies specific for RSV described as a ratio of levels in maternal and cord blood at delivery.

- Infant RSV-specific antibody decay during the first six months of life relative to cord blood levels.
- Immune correlate of risk of RSV LRTI in infants based on anti-RSV F protein IgG or palivizumab-competitive antibody responses in the infant and/or cord blood, and maternal subjects at delivery.

- Serum microneutralization (MN) titers against RSV/A and B in maternal and infant subjects at select time-points may be generated for a subset of the population using the derived/calculated endpoints previously referenced, but based on geometric mean titer (GMT). An external laboratory, whose personnel are blinded to study treatment, will perform RSV/A and B MN testing during study conduct and after Day 180 unblinding. Final MN results, because of their time-consuming nature, may be provided as one or more sequential addenda to the main study report.

## 4.3. Safety Endpoints

### 4.3.1. In All Infant Subjects

- Percentages of term (≥ 37 weeks gestational age), healthy infants appropriate for gestational age (as determined by ultrasound gestational age assessment), APGAR scores, length, birth weight, frontal-occipital head circumference (FOC), and physical examination at birth.
- Percentages of infants with AEs and SAEs (with special attention to congenital anomalies, respiratory failure other than RSV-associated hospitalization; neonatal death; infant death; sudden infant death syndrome; asphyxia; neonatal or hypoxic-ischemic encephalopathy; or other adverse events or complications of adverse events that necessitate hospitalization) during the neonatal period and through the first year of life.
- Percentages of infants with unsolicited adverse events (including abnormalities detected in routine metabolic screening blood and neonatal hearing tests), unscheduled medical visits for adverse events, and serious adverse events through the first year of life.
- Percentages of infants with developmental delay, as measured by the outcome of testing using a validated developmental scale at six months and at one year, in infants of RSV F vaccinees as compared to placebo.

### 4.3.2. In Maternal Subjects

- Percentages of subjects with solicited injection site and systemic reactogenicity within seven days of vaccination.
- Percentages of subjects with unsolicited (local and systemic) adverse events (AEs), unscheduled medically-attended adverse events (MAEs), significant new medical conditions (SNMCs), and serious adverse events (SAEs) through delivery and six (6) months thereafter.
- Clinical safety laboratory assessments of select serum chemistry and hematology parameters through delivery.

- Percentages of subjects with Caesarean, vaginal, or instrument-assisted vaginal modes of delivery.
- Percentages of subjects with post-immunization onset of specific complications of third-trimester pregnancy and delivery including (but not necessarily limited to):
    - Pregnancy complications:
        - Stillbirth,
        - Preterm birth (moderate to late preterm: 32 to < 37 weeks of gestation; very preterm: 28 to < 32 weeks of gestation),
        - Preterm premature rupture of membranes,
        - Placental abruption,
        - Hypertensive disorders of pregnancy including: gestational hypertension, pre-eclampsia/eclampsia,
        - Third-trimester hemorrhage, and
        - Gestational diabetes.
    - Labor and delivery complications:
        - Emergency Caesarean (C)-section for maternal or fetal indications,
        - Postpartum hemorrhage,
        - Chorioamnionitis, and
        - Maternal fever or infection.

# 5. ANALYSIS POPULATIONS

The subject populations to be evaluated and used for presentation and analysis of the data are defined in Sections 5.1 to 5.3. Unless otherwise specified, all maternal subjects and/or infants will be presented in treatment groups based on actual treatment received (RSV F Vaccine or Placebo).

## 5.1. Safety Population

- The maternal Safety Population (Safety-M) includes all maternal subjects who receive any test article. The infant Safety Population (Safety-I) includes all infants born live to maternal subjects who received any test article. The Safety Populations will be used for all safety analyses and will be analyzed based on treatment actually received (i.e., as randomized, unless conclusive documentation exists to confirm the mis-dosing of a subject AND the identity of the treatment actually received).

## 5.2. Intent-to-Treat Population

- Intent-to-treat Efficacy (ITT-EFF) Population – defined as all maternal subjects (ITT-EFF-M) and their infants (ITT-EFF-I) in the Safety Population for whom at least one post-treatment and post-partum, respectively, efficacy measurement is available as evidenced by collection of surveillance observations. The ITT-EFF Population will be analyzed as randomized.
- Intent-to-treat Immunogenicity (ITT-IMM) Population – defined as all maternal subjects (ITT-IMM-M) and their infants (ITT-IMM-I) in the Safety Population for whom at least one post-treatment immunogenicity measurement is available.

## 5.3. Per-Protocol Population

### 5.3.1. Per-Protocol Efficacy (PP-EFF) Populations

- The PP-EFF Populations will be the primary analysis populations for the efficacy analyses.
- PP-EFF for Maternal Subjects (PP-EFF-M) – defined as all maternal subjects who receive the test article and regimen to which they were randomized, have at least one post-treatment encounter documented during which active and/or passive surveillance activities for RSV-suspect illness can occur, and have no major protocol deviations affecting the primary efficacy outcomes as determined and documented by Novavax prior to database lock and unblinding.
- The Per-Protocol Population for infant subjects (PP-EFF-I) – defined as all infant subjects who: a) are ≥ 37 weeks gestational age at birth, b) are born to maternal subjects who received a study injection as randomized and ≥ 2 weeks prior to delivery, c) have not received prophylactic treatment with palivizumab between birth and Day 180 after delivery, d) have at least one documented post-partum contact during which active and/or passive surveillance activities for RSV-suspect illness can occur, and e) have no major protocol

deviations affecting the primary efficacy outcomes as determined and documented by Novavax prior to database lock and unblinding.

### 5.3.2. Per-Protocol Immunogenicity (PP-IMM) Populations

- The PP-IMM Populations will be the primary analysis populations for the immunogenicity analyses.
- PP-IMM for Maternal Subjects (PP-IMM-M) – defined as all maternal subjects who receive the test article and regimen to which they were randomized, provide baseline and delivery (within 72 hours of delivery) serology data, and have no major protocol deviations affecting the primary immunogenicity outcomes as determined and documented by Novavax prior to database lock and unblinding.
- PP-IMM for Infant Subjects (PP-IMM-I) – defined as all infant subjects who: a) are ≥ 37 weeks gestational age at birth, b) are born to maternal subjects who received a study injection as randomized and ≥ 2 weeks prior to delivery, c) have provided a cord blood specimen (or infant blood sample by venipuncture or heel stick within 72 hours of delivery as an acceptable substitute), d) have not received prophylactic treatment with palivizumab between birth and Day 180 after delivery, and e) have no major protocol deviations affecting the primary immunogenicity outcomes as determined and documented by Novavax prior to database lock and unblinding.

### 5.3.3. Protocol Deviations

Subjects with major protocol deviations may be excluded from the PP analysis population. Protocol deviations that meet the threshold of "major" will be determined prior to unblinding, at the Sponsor's discretion. The Sponsor or designee will be responsible for producing a final deviation file prior to database lock. This file will provide a description of each protocol deviation and will clearly identify whether or not a deviation warrants exclusion from the PP analysis population. All protocol deviations will be presented in a data listing, with a flag to indicate if a deviation was considered major and resulted in the exclusion of the subject from the PP analysis population.

#### 5.3.3.1. Major Protocol Deviations Assessment

Prior to unblinding, the Novavax Clinical Development personnel will assess protocol deviations and create a consensus final protocol deviations assessment file. Protocol deviations deemed to have a likely effect on the primary efficacy or immunogenicity outcomes, or demonstrating an important failure of Good Clinical Practice, will exclude those subjects from one or both of the PP analysis populations. In general, the following will be deemed "major:"

- Failure to obtain completely executed and documented informed consent for both mother and infant.
- Failure to receive, or document receipt of, all study treatments as randomized and within the protocol-specified window.

- Failure to provide a sample from the maternal subject for serologic analysis at baseline and at delivery, and a cord blood (or acceptable alternative) and at least one later anti-RSV F serology time-point from the infant within the protocol-specified window. "Failure to provide a sample" will be interpreted based on the protocol visit windows, i.e., provision of one or more sample(s) outside the windows may constitute grounds for a deviation if deemed significant by the medical lead.
- Receipt of any non-protocol vaccine, within 14 days of study test article administration.
- Receipt of any immunosuppressive medication before delivery.

Other deviations deemed likely by the Sponsor to degrade the immune response to the test article, or to indicate a serious departure from Good Clinical Practice, may be exclusionary from the PP population, but must be documented before unblinding for the D+180 analysis.

# 6. SUBJECT DISPOSITION

The number of maternal subjects consented, randomized, and vaccinated will be presented by treatment group according to the test article received (Placebo or RSV F vaccine) at Day 0 for all subjects. Infant subjects will also be presented according to the test article received by the maternal subjects in all tables and listings.

The number (percentage) of maternal subjects who have completed the study through delivery and through D+180, and the number of infants who completed the study through D+180 and D+364 of life will be presented by treatment group for all subjects in the Safety Population. The number of maternal subjects who discontinue the study prior to delivery and between delivery and D+180 will be presented. Similarly, the number of infant subjects who discontinue the study prior to D+180 and D+364 of life, and the reason for discontinuation (e.g., withdrawal of consent, loss to follow-up, death, etc.) will be presented. Study completion status of the maternal subjects through delivery and D+180, and infant subjects through D+180 and D+364 of life will be determined based on delivery visit date for the maternal subject and the D+180 study visit date for the infant subject. Study completion status through D+364 will be determined based on the D+364 End of Study (EOS) electronic case report form (eCRF).

A listing of all subjects in the Safety Population who are discontinued will be presented by treatment group, reason for discontinuation, and day of last study contact. Day of last study contact for the maternal subjects is the date of study discontinuation (as recorded on the Study Day 180 post-delivery/eCRF) minus Day 0 vaccination date. The date of last study contact for the infant will be calculated as follows: date of study discontinuation (as recorded post-delivery on the Study Day 364/EOS eCRF) minus the delivery date. Infants of maternal subjects who discontinue prior to delivery will be deemed to have discontinued at the same time as the maternal subjects; tabulation of infant subjects discontinued in this manner will not be performed as no post-natal data exists for these infants.

A listing of all subjects in the Safety Population with one or more protocol deviations recorded through D+180 for mothers/infants, and updated at the end of the study, will be provided and will include: treatment group, study day associated with the deviation (as provided on the protocol deviation log if available), and protocol deviation category (as described below). All deviations from protocol procedures, evaluations, and visits will be documented throughout the course of the study. The following categories of protocol deviations are to be recorded on a per-subject basis:

**Maternal Subject Deviation Categories:**

- Diary Compliance
- Inclusion Criteria
- Missed Visit
- Randomization Error
- Excluded Concomitant Medication or Procedure
- RSV Surveillance Specimen Collection Not Done
- Exclusion Criteria
- Informed Consent
- Out of Window Visit
- Study Procedure Not Done
- Vaccination Error
- Other

**Infant Subject Deviation Categories:**

- Informed Consent
- Missed Visit
- Out of Window Visit
- Randomization Error
- Study Procedure Not Done
- Other
- RSV Surveillance Specimen Collection Not Done

# 7. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and other baseline characteristics (age at Day 0 vaccination, gender [for infants], ethnicity, race, height [cm], weight [kg]) will be summarized by treatment group and serology cohort (as applicable) for all maternal and infant subjects (separately) in the Safety Population. Descriptive statistics (number of subjects [N], mean, median, minimum and maximum values) will be presented for weight (kg), and height (cm) measurements recorded at Study Day 0. No statistical testing will be performed on these data.

Age (years) at the Day 0 vaccination will be calculated as the closest lower integer result of (date of Study Day 0 vaccination – date of birth) / 365.25, and will be presented as a continuous variable, using descriptive statistics. Age will also be summarized as a categorical variable (e.g., 18 to < 29 years and 29 to ≤ 40 years). Gender of infants will be summarized as a categorical variable (e.g., "Male", "Female"). Ethnicity will be summarized as number and percentage of subjects according to predefined categories (i.e., Hispanic or Latino, not Hispanic or Latino) listed in the eCRF. Race will also be summarized as number and percentage of subjects according to predefined categories (i.e., American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White).

Continuous variables will be presented by summary statistics (e.g., mean and standard deviation for the non-immunogenicity endpoints, and geometric means and their 95% confidence intervals for the immunogenicity endpoints); APGAR scores and other infant health outcomes at delivery may additionally be summarized as medians and interquartile ranges. Categorical variables will be presented by frequency distributions (frequency percentages for the non-immunogenicity endpoints, and percentages and their 95% confidence intervals for the immunogenicity endpoints).

Medical history and physical examination diagnoses/abnormalities will be coded using MedDRA version 16.1. Baseline medical history and physical examination findings recorded on Day 0 (prior to vaccination) will be summarized separately, by body system, treatment group, and for all maternal subjects in the Safety Population. Within each body system, the number and percentage of subjects with at least one abnormality in that body system will be presented, respectively. Multiple abnormalities within a given body system for a subject will be counted once within that respective body system.

# 8. EXTENT OF EXPOSURE

## 8.1. Study Vaccine

Subject vaccination exposure will be summarized as the number and percentage of maternal subjects who received the study vaccine at Day 0. The number of maternal subjects vaccinated at Day 0 will be presented by treatment group and for all subjects. The number of maternal subjects vaccinated by location (right or left deltoid) will be presented in subject data listings.

## 8.2. Concomitant Medication

The assessment of concomitant medication use by subjects during the study will coincide with the collection period of adverse events for each vaccination; per the protocol, concomitant medication includes prescription and non-prescription drugs or other treatments, and any vaccine other than study vaccines. Concomitant medications recorded on the Concomitant Medications eCRF will be summarized by WHO-DRUG DDE (Enhanced) B2 format September 1, 2013. The number (percentage) of subjects who record one or more concomitant medications will be presented by treatment group for all subjects in the Safety Population. Multiple occurrences of medication usage for a subject will be counted only once within an ATC term and standardized medication name. The presentation of concomitant medications will include all medications recorded on the Concomitant Medications eCRF, including medications with a missing or partial start date or a start date prior to Study Day 0 vaccination. A separate listing of treatment-emergent new concomitant medications will be presented.

# 9. INTERIM (FUTILITY AND INFORMATIONAL) ANALYSES

An IBG will perform the futility and informational analyses (see Section 14.1 for details on the informational analysis) based on a summary table provided by the DSMB statistician. All futility and informational analyses of efficacy data will include all infant subjects who will be at least 90 days old at the time of the data cutoff date.

# 10. EFFICACY ANALYSES

A closed sequential testing approach will be adopted for the primary efficacy endpoints to control the Type I error rate for the study. The detailed approach is summarized in Section 16.4 (Multiple Comparisons/Multiplicity).

## 10.1. Study Definitions of Efficacy Determination

| Abbreviation or Term | Definition |
|---|---|
| **RSV LRTI:** | Confirmed RSV LRTI will feature detection of RSV in respiratory secretions by RT-PCR and at least one of the following clinical manifestations observed and documented by appropriately-trained study staff: cough, nasal flaring, lower chest wall indrawing, subcostal retractions, abnormal breath sounds (inclusive of stridor, rales, rhonchi, wheezing, and crackles/crepitations); and/or observed apnea. |
| **Medically-significant RSV LRTI:** | An RSV LRTI episode with EITHER a resting $SpO_2$ < 95% at sea level or < 92% at altitudes > 1800 meters by pulse oximetry on room air OR tachypnea defined as ≥ 70 bpm in an infant 0 to 59 days of age, or ≥ 60 bpm in an infant ≥ 60 days of age. |
| **RSV LRTI with Severe Hypoxemia:** | An RSV LRTI episode with a resting $SpO_2$ < 92% at sea level or $SpO_2$ < 87% at altitudes > 1800 meters by pulse oximetry on room air OR documented use of oxygen by high flow nasal cannula OR a requirement for continuous positive airway pressure (CPAP) OR bilevel positive airway pressure (BiPAP) OR Bubble CPAP OR bag-mask ventilation OR intubation with subsequent mechanical (or manual) ventilation OR extracorporeal membrane oxygenation (ECMO). |
| **RSV Season:** | The period spanning the onset/remission of increased confirmed RSV infections in the community based on local surveillance data. |
| **RSV Episode:** | The interval between the onset of respiratory symptoms (start date) and the episode stop date with confirmation of RSV infection by RT-PCR of any respiratory secretions collected within this period. |
| **Correlate of Risk:** | An immune marker statistically correlated with risk, either absolute or relative to a control population, of meeting an RSV infection clinical endpoint. |
| **Symptomatic RSV infection (maternal subjects)** | An acute, clinical study site-observed RSV infection, manifesting as one or more of cough, stuffy nose, runny nose, dyspnea, sore throat, fever, new or increasing wheezing, or new or increasing sputum production; with detection of RSV in respiratory secretions by RT-PCR. |

## 10.2. Clinical Endpoint Adjudication Committee (CEAC)

A clinical endpoint adjudication committee (CEAC) comprising an odd number of three or more clinically-experienced voting pediatricians, a non-voting chair who will oversee meetings of the CEAC, and a non-voting coordinator for administrative support will be empaneled to review all primary, secondary, and exploratory efficacy endpoints relative to infant subjects. The operations of the CEAC will be carried out according to a charter which will be collaboratively drafted by the CEAC and the sponsor, and will be adopted prior to any review CEAC activities. The CEAC will review each potential efficacy endpoint event to determine whether the protocol-specified criteria have been fulfilled in a plausible temporal relationship. All deliberations of the CEAC will be carried out in blinded manner with regard to treatment

assignment and the determination of the CEAC with regard to each endpoint event will be final and binding on the sponsor.

## 10.3. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoint will be analyzed on the ITT-EFF-I and PP-EFF-I (infant) Populations. Conclusions concerning stopping for futility, the informational analysis, or declaration of attainment of the primary efficacy endpoint at the completion of the study, will only be based on the PP-EFF-I Population. In addition, supportive analyses based on the ITT-EFF-I Population will also be performed.

The Vaccine Efficacy (VE) is defined as VE (%) = (1 – RR) x 100, where RR = Relative Risk of incidence rates between the two treatment groups (RSV F Vaccine / Placebo). The final analysis will be carried out at one-sided Type I error rate of 0.0124 (i.e., the lower bound of two-sided 97.52% confidence interval). An estimate of vaccine efficacy will be reported using a two-sided 95% confidence interval. This conservative Type I error rate was determined as a part of the original group sequential design (GSD) approach and will be retained to guard against a potential Type I error inflation resulting from the decision to stop the study at ~4,600 maternal subjects given this decision occurred after the informational analysis. Since this change was not part of the original study design at the initiation of the study, the agreement on how to implement the change with respect to Type I error rate was finalized in consultation with the US-FDA.

For the original design using the GSD, a simulation of 5,000 trials was performed under a range of scenarios (including both varying placebo rates of medically-significant RSV LRTI and endpoint event ratios in infants of active vaccinees relative to placebo recipients). A summary of the simulation results is provided in the adaptive design for reference (APPENDIX 1).

The RR and its CI will be estimated using Poisson regression with Robust error variance [Zou 2004]. The generalized linear model with unstructured correlation matrix (Robust error variances) will be used. The explanatory variables in the model will include the treatment group. The dependent variable will be the incidence rate of the endpoint of interest. The Robust error variances will be estimated using repeated statement and the subject identifier. Poisson distribution will be used with a link function logarithm.

Hypothesis testing of the primary efficacy endpoint will be carried out sequentially for $H_0$: VE $\leq$ 0% and $H_0$: VE < 30%. Rejection of the first null hypothesis, $H_0$: VE $\leq$ 0% demonstrates a statistically significant vaccine effect. Rejection of the second null hypothesis, $H_0$: VE < 30% at Type I error rate of 1-sided 0.0124 is required to meet the statistical success criterion pre-specified for the US-FDA. Should success be declared for the primary endpoint through 0 - 90 days of age, the hierarchical sequential analyses of 0 - 120, 0 - 150, and 0 - 180 days of age will be carried out using the Type I error rate of 1-sided 0.025 and the same null hypothesis.

Two types of analyses concerning the primary efficacy endpoint will be performed prior to the final analysis: recurring futility analyses approximately twice per year after the Northern and

Southern hemisphere winter virus season, and an informational analysis with approximately 1/3 of projected subjects enrolled and followed through at least 90 days.

For the futility analyses and the informational analysis, a Bayesian approach will be used and the analyses will be performed by the Independent Biostatistical Group (IBG) as originally designed. An assumption is made that the distribution of the number of events under the vaccine, $x_v$, and the number of events under placebo, $x_p$, are binomial:

$$x_v \sim Bin(\pi_v, n_v)$$
$$x_p \sim Bin(\pi_p, n_p)$$

where $\pi_v$ and $n_v$, respectively, are the probability of an RSV event and the total number of subjects in the vaccine group and $\pi_p$ and $n_p$, respectively, are the probability of an event and the total number of subjects in the placebo group.

Furthermore, we assume prior distributions for $\pi_v$ and $\pi p$ that are flat, non-informative beta distributions:

$$\pi_v \sim Beta(1,1)$$
$$\pi_p \sim Beta(1,1).$$

Futility will be demonstrated under the primary hypothesis based on the posterior probability that the event ratio, $r = \pi_v / \pi_p$, is less than or equal to 0.60.

Given $x_v$ events out of $n_v$ total subjects in the vaccine group and $x_p$ events out of $n_p$ total subjects in the placebo group, the posterior distributions of $\pi_v$ and $\pi_p$ are:

$$\pi_v | x_v \sim Beta(1+x_v, 1+(n_v - x_v))$$
$$\pi_p | x_p \sim Beta(1+x_p, 1+(n_p - x_p)).$$

Sampling from the posterior probability distribution for the event ratio is generated by:

1. Sampling 10 million independent values from the posteriors of $\pi_v$ and $\pi_p$
2. Calculating the event ratio, $r = \pi_v / \pi_p$ under each pair-wise sample from the posterior of $\pi_v$ and $\pi_p$.

Futility stopping will be based on the posterior probability of futility that the event ratio is less than or equal to 0.60 is less than or equal to 0.05. Furthermore, an additional constraint governing the ability to stop the trial early for futility requires that a minimum of 10 events be observed in the vaccine arm. All futility analyses will include all infant subjects who are 90 days old at the time of the data cutoff date.

In addition as a sensitivity analysis, time to the first medically-significant RSV LRTI event will be analyzed by treatment group using Kaplan-Meier methods taking potential differences in the length of subject follow-up into account. Sub-analyses will be performed to evaluate vaccine effects on all infections in which RSV is confirmed by RT-PCR, and also infections in which only RSV is found (i.e., no co-infections). The incidence rate of medically-significant RSV LRTI may be generated by age stratum or co-morbidities present, if sufficient event numbers are available.

Sensitivity analyses for the primary efficacy endpoint will be performed to investigate the impact of missing specimens for suspected-RSV illnesses, including RSV-negative specimens collected outside the specified collection window, and clinical assessments, including clinical signs/symptoms, respiratory rates, and pulse oximetry measurements, obtained by non-study healthcare providers (e.g., hospitalization records). Further details are presented in Section 16.8.

## 10.4. Analysis of Secondary Efficacy Objective

Analysis of secondary efficacy endpoints will be using the frequentist method. The relative risk (RR) and its two-sided 95% CI will be estimated using Poisson regression with robust error variance [Zou 2004]. A generalized linear model with unstructured correlation matrix (robust error variances) will be used. The explanatory variables in the model will include the treatment group. The dependent variable will be the incidence rate. The Robust error variances will be estimated using repeated statement and the subject identifier. Poisson distribution will be used with a link function logarithm. The vaccine efficacy and the corresponding two-sided 95% CI will be calculated.

The null hypothesis, $H_0$: VE $\leq$ 0%, using the 1-sided Type I error rate (i.e., lower bound of two-sided 95% CI) will be used for analyses of all secondary efficacy endpoints in infants. For each endpoint, in the event that efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy through 120, 150, and 180 days of life.

Additional efficacy analyses may describe the incidence of symptoms used to define RSV LRTI. Percentages of infant subjects with any RSV-confirmed respiratory illness accompanied with the following events/complaints may be presented by treatment group through six months postpartum: cough, nasal flaring, difficulty breathing, manifesting in any of the following clinical signs or symptoms as lower chest wall indrawing, subcostal retractions, abnormal breath sounds (inclusive of stridor, rales, rhonchi, wheezing, and crackles/crepitations), and/or observed apnea. Time to the first RSV-associated event referenced above will also be analyzed using Kaplan-Meier methods for each event category and by treatment group.

## 10.5. Exploratory Analyses

Exploratory analysis will be conducted by generating classical two-by-two cross tabulations of all RSV respiratory tract infection endpoints detected by active/passive surveillance in infant and maternal subjects from immunization through six months after delivery and by treatment group. The relative risk (RR) and its two-sided 95% CI will be estimated using Poisson

regression with robust error variance [Zou 2004]. A generalized linear model with unstructured correlation matrix (robust error variances) will be used. The explanatory variables in the model will include the treatment group. The dependent variable will be the incidence rate. The Robust error variances will be estimated using repeated statement and the subject identifier. Poisson distribution will be used with a link function logarithm. The vaccine efficacy, and the corresponding two-sided 95% CI will be calculated. Similar analysis will be conducted to assess the incidence of non-RSV LRTI in infant subjects as detected by active and passive surveillance from vaccination through six months after delivery. Percentages of infants and maternal subjects presenting with respiratory symptoms of non-RSV respiratory viruses detected by RT-PCR will be summarized.

All exploratory efficacy analyses will be conducted against the null hypothesis of VE $\leq$ 0% (i.e., the RR $\leq$ 1.00). For each endpoint, in the event that efficacy is shown through the first 90 days of life, a hierarchical sequence of hypothesis tests will be carried out to examine efficacy through 120, 150, and 180 days of life.

# 11. IMMUNOGENICITY ANALYSES

Immunogenicity summaries and associated statistical analyses will be based primarily on the PP immunogenicity Populations, i.e., PP-IMM-M for maternal subjects and PP-IMM-I for infant subjects with supportive results derived from the ITT Populations, i.e., ITT-IMM-M for maternal subjects and ITT-IMM-I for infant subjects. No imputation for missing data will be performed. Data will be transformed as appropriate prior to analysis. Please refer to Section 16 for the handling of lower limit of quantitation (LLOQ) for the seroconversion (SCR, definition provided below) analysis.

## 11.1. Analysis of the Secondary Objectives of Immunogenicity

The principal variables of interest for assessment of immune response to the RSV F vaccine will be anti-F IgG EUs and PCA concentrations that will be determined at all prospectively defined time-points as stated below. Additional immunogenicity variables will be RSV/A and B MN titers, which will be measured at the baseline and delivery visits for maternal subjects and at the delivery and D+14, D+35, D+60, D+90, D+120, and D+180 visits for infant subjects. For the analysis of paired immunogenicity measures, geometric mean of fold rise in post–vaccination measures compared to baseline (pre-vaccination) in maternal subjects (GMFR) and geometric mean ratio (GMR) of paired samples over time within a maternal subject, an infant subject, or a maternal and infant subject pair (GMR) will be summarized. GMC, GMEU, GMT, and GMFR/GMR will be calculated as the antilog of the mean and 95% CI of $\log_{10}$-transformed values. The values reported as below the LLOQ of the assay will be set to half of LLOQ. In addition, seroconversion rates (SCR) based on $\geq$ 2- and $\geq$ 4-fold rise thresholds and seroresponse rates (SRR) will be calculated as defined below.

The following immunogenicity outcome measures and their 95% CI will be summarized by treatment group.

### 11.1.1. Anti-F IgG ELISA (EU)

The following parameters will be analyzed for maternal subjects.

- GMEU at baseline (pre-vaccination on Day 0) and post-vaccination on Day 14, at delivery, and postpartum on Days 35 and 180 (as applicable).
- $GMFR_{Post/Pre}$ on post-vaccination Day 14, at delivery, and postpartum on Days 35 and 180 (as applicable).
- $GMR_{Cord/MS}$ on the within-maternal-infant pair for cord blood over maternal serum (MS) at delivery, e.g., GMFR Transplacental Transfer Proportion.
- Seroconversion Rate (SCR) – defined as the proportion of subjects with $\geq$ 2-fold and $\geq$ 4-fold increases in concentration from baseline, calculated as the proportion (%) of subjects in a particular treatment group with a baseline concentration < LLOQ and a post-vaccination concentration $\geq$ 2 x LLOQ and $\geq$ 4 x LLOQ, respectively, or a baseline concentration $\geq$ LLOQ and a $\geq$ 2-fold and $\geq$ 4-fold, respectively, increase in

post-vaccination concentrations. These response rates will be summarized post-vaccination on Day 14, at delivery, and postpartum on Days 35 and 180 (as applicable).

- Seroresponse rate (SRR) – defined as the proportion (%) of subjects in the RSV F treatment group with an increase in antibody level over a specific time period which is greater than the 95th percentile of antibody response in the absence of active vaccine based on the behavior of placebo recipients' sera over the same period. SRR will be analyzed by computing the ratio (post-vaccination/pre-vaccination [Day 0]) at each post-vaccination time-point on Day 14, at delivery, and postpartum on Days 35 and 180 (as applicable). At a given time-point, the 95$^{th}$ percentile of the ratios in the placebo group will be estimated. A subject in any treatment group will be identified as a responder if its ratio is greater than the estimated threshold in the placebo group at the given time-point.

The following parameters will be analyzed for infant subjects:

- GMEU of anti-F IgG in cord blood and on D+14, D+35, D+60, D+90, D+112, and D+180.
- $GMR_{AD/Cord}$ of anti-F IgG EU within-subject ratios after delivery (AD) on D+14, D+35, D+60, D+90, D+120, and D+180 over cord blood value at delivery.
- SRR for infant subjects will be analyzed at a given time-point by estimating the 95th percentile of the EU levels in the placebo group. An infant subject in any treatment group will be identified as a responder if its EU level is greater than the estimated threshold in the placebo group at the given time-point.

### 11.1.2. Palivizumab-competitive Antibody (PCA) ELISA (µg/mL)

For maternal subjects:

- The same parameters described in Section 11.1.1 will be analyzed. The GMEU for the anti-F IgG will be replaced by geometric mean concentration (GMC) in µg/mL for the PCA ELISA.

For infant subjects:

- The same parameters analyzed described in Section 11.1.1 will be analyzed. The GMEU for the anti-F IgG will be replaced by geometric mean concentration (GMC) in µg/mL for the PCA ELISA.

### 11.1.3. RSV/A and RSV/B Microneutralization (MN) Titers

For maternal and infant subjects: GMT, GMFR/GMR, and SRR, as described above and for the same time-points referenced above for the anti-F IgG ELISA. For maternal subjects only, SCR will be calculated as defined as the proportion of subjects with ≥ 2-fold and ≥ 4-fold increases in titers from baseline to post-vaccination using the same approach as anti-F IgG ELISA.

### 11.1.4. Infants Antibody Decay Modeling

To estimate the decay of antibody levels in per protocol infants (PP-IMM-I) that result from RSV F protein vaccine immunization in pregnant women, the log10 transformed antibody

levels will be used as the independent variable and the actual age of infant subjects in days at the time of sample collection as the exploratory variable in the regression analysis. The estimated slope will be used to estimate the half-life as log10(2)/slope with the corresponding 2-sided 95% confidence interval. All observed values, except for the measures reported as < LLOQ, for each time-point and infant cohort (Phlebotomy Cohort 1, Cohort 2, and Cohort 3) will be pooled to assess the persistence of anti-F IgG antibody, PCA, and/or MN levels over time. Since values reported as < LLOQ do not provide the exact time when the values crossed the LLOQ, they will be excluded from the half-life estimation. All measurements from subjects with at least two ≥ LLOQ measures will be included in the analysis. A conventional first order antibody decay model will be used for analysis. A second order or other, more complex, antibody decay model may be further developed to explain the rate of decay of antibody levels in the infants in the study, albeit the dataset may not be sufficiently rich to support more complex models.

### 11.1.5. Immune Correlate of Risk of the RSV LRTI Syndromes in Infants

Analyses will be performed to attempt to identify a correlate of risk (CoR) for the RSV LRTI syndromes in infants based on anti-F IgG and/or PCA levels measured in the infant and/or cord blood and the maternal subjects at Day 14 post-vaccination and delivery. For the purpose of this analysis, the CoR is defined as a general inverse relationship between the level of an immune response parameter before the onset of the first episode of a RSV infection and the RSV disease status. RSV immune measure(s) will be tabulated for each primary and secondary efficacy disease endpoint status for each treatment group and for the combined treatment groups. Qin et al. define a surrogate of protection (SoP) as a CoR that reliably predicts a vaccine's level of protective efficacy on the basis of differences between the vaccinated and unvaccinated groups' immunological measurement(s). Appropriate SoP validating methods as proposed in Qin et al. will be used to explore if the chosen CoR is a potential SoP [Qin 2007].

Two sets of graphs will be created for each primary and secondary efficacy disease endpoint status as screening tools to identify CoRs that are potential SoPs for further assessment.

The first set, which will comprise graphs for each endpoint and each time-point, will show cumulative distribution functions displaying the level of anti-F IgG and PCA levels for the combined treatment group and for each treatment group separately.

The second set, which will consist of receiver operating curves (ROC), will have six graphs for each endpoint, one for each marker and blood pair. If the clinicians consider the area under the ROC curve sufficiently high, the marker will be deemed a CoR. As a rule of thumb, markers with areas of 0.9 and above are considered excellent while those with areas between 0.8 and 0.9 are considered good [Pepe 2004]. Marker and blood pairs with areas under the ROC curve of at least 0.8 will be deemed candidate CoRs.

The maximum values of Youden's J Index (sensitivity + specificity -1), will be used as a first pass at selecting a cut-off value defining the level of the CoR that will be used to explore whether the CoR is a surrogate of protection. The Index assigns equal weight to sensitivity and

specificity. Different weightings may be explored if Novavax and/or external clinician experts judge equal weighting inappropriate.

Thus far, we have considered the two markers, anti-F IgG or PCA, separately. It is possible that while neither alone is an excellent CoR, some combination of the two better identifies risk, or a different immune measure (e.g., microneutralization). Exploratory analyses will be used to try to identify a function of the two markers that together constitute a CoR and/or additional immune measure(s).

# 12. SAFETY ANALYSES

Adverse events are defined as any unfavorable or unintended change in the physical, psychological, or biochemical condition of the subject. An AE temporally related to participation in the study will be documented whether or not considered related to the test article. This definition includes intercurrent illnesses and injuries, and exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the study are not considered AEs; however, these should be collected as part of the medical history. AEs will be considered treatment emergent from the date and time of the first administration of the investigational product. All safety and reactogenicity summaries will be based on the Safety Population.

## 12.1. Overall Handling of Adverse Events

The principal variable for evaluation of the safety profile for the RSV F vaccine will be the number and percentage (95% CI) of maternal subjects with solicited and unsolicited adverse events (including MAEs and SAEs) recorded post-vaccination, and the number and percentage (95% CI) of infants with unsolicited AEs occurring since birth. An overall summary will present the number and percentage of solicited adverse events in maternal subjects by verbatim term and treatment group; and unsolicited adverse events by MedDRA SOC and PT, and by treatment group for all maternal and infant subjects in the Safety Population. Laboratory values and vital signs will also be summarized (percentages) by treatment group for all maternal subjects in the Safety Population.

Solicited adverse events occurring in the first 7 days after each dose of test article will be presumed to be related; and severity will be graded by specific definitions included in the protocol and subject diary. Unsolicited adverse event summaries by relationship to study vaccine will be categorized as “not related” (including “unrelated or unlikely”) or “related” (including “possible, probable, and definite”). For multiple occurrences of an adverse event in the same subject, a subject will be counted only once, using the most severe or most related occurrence for the summarization by severity or relationship to study vaccine, respectively.

Solicited adverse events will not be coded, and will be summarized by solicited term only. All unsolicited adverse events will be coded using MedDRA version 16.1.

## 12.2. Analyses of Safety Objectives

Safety will be summarized for maternal and infant subjects separately. Safety will be summarized overall and by treatment group for maternal and infant subjects based on percentages.

Tabulations of counts and proportions of the following safety parameters, by treatment group and overall, will be produced for maternal subjects:

- Solicited seven-day reactogenicity events by severity;
- Clinical laboratory safety abnormalities by severity;
- Caesarean, vaginal, and instrument-assisted vaginal modes of delivery;
- Pre-specified third-trimester pregnancy and delivery complications (i.e., stillbirth, placental abruption, preterm birth, preterm premature rupture of membranes, hypertensive disorders of pregnancy, third-trimester hemorrhage, and gestational diabetes), and labor and delivery complications (i.e., emergency Caesarean section, postpartum hemorrhage, chorioamnionitis, and maternal fever or infection); and
- Unsolicited adverse events through 180 days post-delivery by severity and relatedness (possibly, probably, or definitely), including SAEs, MAEs, and SNMCs.

Tabulations of counts and proportions of the following safety parameters, by treatment group and overall, will be produced for infant subjects:

- Congenital anomalies; respiratory failure other than RSV-associated hospitalization; neonatal death; infant death; sudden infant death syndrome; asphyxia; neonatal or hypoxic-ischemic encephalopathy; or other adverse events or complications of adverse events that necessitate hospitalization during the neonatal period and through the first year of life;
- All other unsolicited/unspecified adverse events by severity, relatedness, and seriousness, including respiratory events that test negative for RSV by RT-PCR.

Summary statistics will also be provided for infant length, weight, FOC, 1- and 5-minute APGAR scores, and responses to environmental and behavioral queries, through one year post-delivery overall, and by treatment group. Results of developmental testing will be summarized by treatment group, and percentages of infants in the developmental testing subset above normal, normal, at-risk at 6 or 12 months, and at-risk at both 6 and 12 months.

In addition, Chi-Square tests may be used to assess association between categorical variables, and logistic-regression models may be constructed to determine the predictors of RSV LRTI in infants. The candidate covariates for these models may include infant length, weight, FOC, APGAR score, and gestational age at birth.

## 12.3. Solicited Adverse Events

Solicited AEs for maternal subjects are pre-specified in Section 8.2.1 of the protocol and include both injection site reactions (i.e., pain, bruising, redness, and swelling) and systemic events

(i.e., oral temperature [for assessment of fever], chills, muscle pain, joint pain, diarrhea, nausea, vomiting, headache, and fatigue) that are reported within seven days following the Day 0 vaccination and are solicited by diary. These events are considered related to the study vaccine and are collected using a severity rating of 0 (did not occur), or 1, 2, or 3 (mild, moderate, or severe, respectively), using the maximal severity observed for the specific symptom post-vaccination. Notable exceptions include temperature, which is collected as a continuous variable, and that uses temperature grade ranges established in the toxicity grading scale (TGS), which are applied later in the analysis, and events of injection site redness and swelling, which will be measured using a Subject Measurement Tool (see protocol, Appendix 4). The Subject Measurement Tool is a transparent acetate sheet imprinted with a set of concentric circles with diameters that correspond to TGS ranges that are also used to assign severity.

Solicited AEs will be tabulated and analyzed by the verbatim terms specified in the diary, and not MedDRA coded. Analysis will use exact diary wording (i.e., "muscle pain' rather than changing it to "myalgia"). Only solicited adverse events which record a start date within the 7-day window of the Day 0 to Day 6 post-vaccination period will be included in the tabular summary and listing of solicited events. Solicited AEs will be presented by treatment group for all maternal subjects.

Solicited AEs, collected from the subject diary, which continue after the collection period (i.e., post-vaccination Day 6) will be captured by verbatim term, on an AE electronic case report form (eCRF) page and flagged in the listing of solicited AEs.

The following summaries of solicited AEs will be presented by treatment group as part of the secondary analysis of safety:

- Summary of solicited treatment-emergent AEs by the verbatim terms specified in the diary and within the post-vaccination window (Days 0 - 6).
- A summary of all solicited AEs by severity (mild, moderate, severe), and within the post-vaccination window (Days 0 - 6).

## 12.4. Unsolicited Adverse Events

Any AEs reported by maternal subjects will be categorized as unsolicited events and Medical Dictionary for Regulatory Activities (MedDRA) coded by system organ class (SOC) and preferred term (PT). Solicited events with an onset after the solicitation period will also be classified as unsolicited AEs. Unsolicited events that occur within 7 days following vaccination should also be recorded in the subject diary. If any grade 3 unsolicited event is reported during this period, maternal subjects should be encouraged to contact the investigator by telephone. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any grade 3 unsolicited adverse event reported by telephone in the unsolicited AE eCRF promptly, even if the balance of diary data is not yet available. Continuing non-serious solicited AEs lasting beyond the 7-day diary period reported on the AE CRF to collect the symptom end date will not be summarized in the unsolicited AE tables. Solicited AEs reported on the AE CRF will be treated as solicited AEs and will be summarized in solicited AE tables only.

Any AEs reported in infants will be categorized as unsolicited events and MedDRA coded by SOC and PT. These can include, but are not limited to, abnormalities in vital signs, metabolic screening and developmental tests, neonatal hearing, congenital anomalies, respiratory failure, perinatal infections, neonatal death, complications that result in extended hospitalization; as well as any other SAE (as defined in Section 8.5 of the Protocol) or MAE or SNMC (as defined in Section 8.4 of the Protocol).

All unsolicited AEs will be assessed for severity and for causality for infants and maternal subjects.

The following summaries of unsolicited AEs will be presented for all maternal subjects in the Safety Population as part of the secondary analysis of safety:

- Overall summary of unsolicited AEs by treatment group (Day 0 post-vaccination to Day of delivery -1 and also Day 0 post-vaccination to Delivery +180).
- A summary by severity (mild, moderate, or severe), MedDRA SOC, PT, and treatment group (Day 0 post-vaccination to D+180).
- A summary by relationship to study vaccine, MedDRA SOC, PT, and treatment group (Day 0 post-vaccination to D+180).
- A summary of severe and related AEs, MedDRA SOC, PT, and treatment group (Day 0 post-vaccination to D+180).

For infants, the following summaries of unsolicited AEs will be presented:

- An overall summary of unsolicited AEs (Delivery to Delivery + 180 days and/or Delivery + 364 days).
- A summary by severity (normal, mild, moderate, or severe), MedDRA SOC, PT, and treatment group (Delivery to Delivery + 180 days and/or Delivery + 364 days).
- A summary by relationship to study vaccine, MedDRA SOC, PT, and treatment group (Delivery to Delivery + 180 days and/or Delivery_+364 days).
- A summary of severe and related AEs, SAEs, MAEs, and SNMCs, by MedDRA SOC, PT, and treatment group (Delivery to Delivery + 180 days and/or Delivery + 364 days).

## 12.5. Medically-Attended Events and Significant New Medical Conditions

These classes of events will be collected at all study visits, and if offered spontaneously by the subject at any time.

MAEs are adverse events which result in an unscheduled visit to a healthcare provider due to symptomatic illness or injury. These may include office visits, clinic visits, home consultations, or emergency room evaluations for non-life-threatening events that do not result in hospitalization (life-threatening events or hospitalizations are SAEs, see Section 8.5 of the Protocol).

SNMCs are adverse events that are new (that is, not present at baseline), clinically significant (meaning that they imply an important change in the subject's long-term health status), and typically chronic (requiring an ongoing change in the subject's medical management). This category is not meant to include minor or transient diagnoses or age-related changes.

MAEs and SNMCs will be recorded and summarized from Day 0 to Delivery + 180 days for the maternal subjects and from Delivery to Delivery + 180 days for the infants for the unblinded analysis; and from Delivery to Delivery + 364 following study completion for the final analysis, for all infants in the Safety Population. Note that MAEs and SNMCs are also included in the overall summary of AEs.

## 12.6. Maternal/Fetal/Neonatal Adverse Events of Special Interest

Table 2 summarizes and defines a series of maternal/fetal/neonatal adverse events that are of special interest in the evaluation of maternal immunization strategies. The majority of these events will fulfill one or more of the criteria listed below (Section 12.7) for SAEs. In the event that one of these events does not meet the criteria for an SAE (e.g., "Small for Gestational Age" might not), it will nonetheless be reported as an SAE using the same reporting requirements as an SAE. The majority of these terms and definitions are derived from the Brighton Collaboration Definitions of Key Terms (WHO meeting July 2014). Some maternal/fetal/neonatal AESIs are open to interpretation as to which subject should be recorded as sustaining the event. Table 2 also designates to which subject each class of event should be assigned; solely as a uniform data collection convention. Since there are multiple potential sources to determine the gestational age (GA) at birth, the study defined EDD and the birth date will be used to determine the GA at birth for the summary of the preterm birth categories (Very preterm and Moderate to late preterm).

**Table 2: Maternal/Fetal/Neonatal Adverse Events of Special Interest**

| Term | Definition | Reported as an Event In |
|---|---|---|
| Stillbirth: | Delivery of a dead fetus of > 22 weeks gestation, subcategorized as:<br>• Antepartum<br>• Intrapartum | Mother |
| Placental Abruption: | Placental separation from the uterus with bleeding (concealed or vaginal) before fetal birth, with or without maternal/fetal compromise | Mother |
| Preterm Birth: | Delivery of a live newborn child, subcategorized as:<br>• Very preterm: 28 to < 32 weeks gestation<br>• Moderate to late preterm: 32 to < 37 weeks gestation | Mother |
| Gestational Hypertension/ Pre-Eclampsia/ Eclampsia: | Gestational Hypertension: New onset elevations of blood pressure after 20 weeks of gestation, in the absence of accompanying proteinuria.<br>Pre-Eclampsia: A hypertensive disorder of pregnancy with:<br>• A blood pressure ≥ 140/ ≥ 90 on 2 occasions, at least 4 hours apart after 20 weeks of gestation, or a blood pressure ≥ 160/ ≥ 110 and the presence of | Mother |

**Table 2: Maternal/Fetal/Neonatal Adverse Events of Special Interest**

| Term | Definition | Reported as an Event In |
|---|---|---|
| | proteinuria (≥ 300 mg of urinary protein / 24 hours; or protein/ creatinine ratio ≥ 0.3, dipstick reading of 1+), or<br>• In the absence of proteinuria, new-onset hypertension with the new onset of any of the following:<br>o Thrombocytopenia (platelet count < 100,000/ μL),<br>o Renal Insufficiency (serum creatinine concentrations > 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease,<br>o Impaired liver function,<br>o Pulmonary edema,<br>o Cerebral or visual symptoms.<br>Eclampsia: All components of Pre-Eclampsia, with convulsions. | |
| Third Trimester Hemorrhage: | Any third trimester bleeding with the etiology specified and may include, but not limited to, placenta previa, vasa previa, placental abruption. | Mother |
| Neonatal Death*: | Death of a live newborn child at any time from birth to 28 days of life, regardless of gestational age based on the following subgroups:<br>• Very early neonatal death: < 24 hours<br>• Early neonatal death: birth to < 7 days<br>• Late neonatal death: 7 to < 28 days | Infant |
| Infant Death*: | A post-neonatal death that occurs between 28 days and 1 year of life. | Infant |
| Low Birth Weight: | Subcategorized as:<br>• Low birth weight: < 2,500 grams<br>• Very low birth weight: < 1,500 grams<br>• Extremely low birth weight: < 1,000 grams | Infant |
| Small for Gestational Age (SGA): | Also referred to as intrauterine growth restriction or retardation (IUGR), is defined as a birth weight < 10% for infants of the same gestational age and gender, in same population. | Infant |
| Asphyxia: | Insufficient oxygen supply to organs at birth resulting from inadequate ventilation or perfusion. | Infant |
| Neonatal Encephalopathy: | A disturbance of neurological function manifested by difficulty initiating and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures. Categories of neonatal encephalopathy include:<br>• Due to hypoxic insult (intrapartum),<br>• Due to another cause. | Infant |
| Hypoxic-Ischemic Encephalopathy: | A syndrome of abnormal neurological behavior in the neonate, which is frequently associated with multi-system | Infant |

**Table 2: Maternal/Fetal/Neonatal Adverse Events of Special Interest**

| Term | Definition | Reported as an Event In |
|---|---|---|
| | dysfunction and follows severe injury before or during delivery associated with hypoxic and/or ischemic event. | |
| Sudden Infant Death Syndrome (SIDS): | Sudden death of any child under 12 months of age which remains unexplained after excluding other causes of death. | Infant |

*Neonatal and infant deaths should be reported whenever possible as the *underlying medical condition which results in death*, with death captured as the outcome of the SAE. This allows the capture of more granular information about the incidence of specific diagnostic entities leading to death, and prevents confusion with SIDS in analysis.

## 12.7. Serious Adverse Events

A SAE is defined as an AE that results in any of the following outcomes:

- Death.
- An immediate threat to life.
- In-patient hospitalization or prolongation of an existing hospitalization subject to the following:
    - Hospitalization is defined as an actual admission, not a 24-hour stay or emergency room visit.
    - Admissions for elective surgeries, undertaken for conditions present prior to receipt of study drug and without complication, should not be considered SAEs.
    - Hospitalization for delivery represents normal obstetrical care and is not an SAE unless precipitated by an unanticipated adverse fetal or maternal event.
- A persistent or significant disability/incapacity (substantial disruption of an ability to conduct normal life functions).
- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Events which could have led to the above outcomes had they occurred with greater severity are not SAEs, but should be reported as AEs, MAEs, or SNMCs, as appropriate.

A listing of subjects with SAEs will be summarized from Day 0 to Delivery + 180 days for the maternal subjects and from Delivery to Delivery + 180 days for the infants for the unblinded analysis, and from Delivery to Delivery + 364 days for the infants following study completion for the final analysis, for all infants in the Safety Population.

## 12.8. Vital Signs

Descriptive statistics for vital signs for the maternal subjects (e.g., blood pressure, pulse, respiratory rate, and temperature) on Days 0, 7, 14, Delivery (D), D+35, and D+180 will be presented by treatment group for all maternal subjects in the Safety Population. Temperature

(fever) will be summarized by severity according to regulatory guidance, e.g., Normal ≤ 38.0ºC, Mild = 38.0 – 38.4ºC, Moderate = 38.5 – 38.9ºC, Severe > 38.9ºC.

Descriptive statistics for vital signs for the infants will be summarized by treatment group based on all the parameters assessed.

## 12.9. Laboratory Data

Descriptive statistics (mean, median, standard deviation, minimum and maximum values) for continuous laboratory parameters and/or number (percentage) for categorical laboratory parameters will be presented by treatment group. Change from pre-vaccination (Day 0) to Day 14 post-vaccination will also be presented for all continuous parameters.

All laboratory values will be presented in subject data listings, including any available drug screen parameters, and additional labs ordered by the investigator, if applicable. The following protocol-specified parameters (see protocol, Section 7) will be included in summary tables:

- Hematology
    - White Blood Cell count [w/differential] ($x10^9$/L).
    - Hemoglobin ($x10^{12}$/L).
    - Platelet count ($x10^9$/L).
- Serum Chemistry
    - Serum creatinine (µmol/L).
    - Alkaline phosphatase [ALP] (U/L).
    - Alanine aminotransferase [ALT] (U/L).
    - Aspartate aminotransferase [AST] (U/L).
    - Blood urea nitrogen [BUN] (mmol/L).
    - Total bilirubin (µmol/L).
- HIV, HCB, and HCV antigen tests/serologies as required.

A listing of subjects with laboratory values recorded as newly abnormal following study vaccination and meeting toxicity mild criteria (Grade 2) or above as specified in the TGS for the study, will be presented at Screening and Day 14 for clinical laboratory data. If the number of events warrants, a tabular summary (number and percentage of abnormal laboratory values per TGS criteria) of these data will be included. Tabular summaries by race/ethnicity, nationality or geography, or other demographic features may be created.

Toxicity grade shift summaries by treatment group will be generated for each parameter. A shift table of the change from Screening to Day 14 in toxicity grade rating time-points labeled as “Decrease by 2 grades”, “Decrease by 1 grade”, “Normal” (or “No Change”), “Increase by 1 grade”, “Increase by 2 grades”, etc., will be presented as number (percentage) of total subjects by treatment group. Each of these categories will only be presented when data are available.

Clinical laboratory abnormalities reported as adverse events will be included in the summary of adverse events. These include: 1) laboratory values that show an increase in the toxicity grade relative to baseline values in the same subjects, ***and*** attain at least Grade 2 (e.g., normal or Grade 1 to Grade 2, or Grade 2 to Grade 3) and 2) clinically significant events the Investigator has classified as an AE. A listing of laboratory values associated with adverse events will be presented, along with all associated laboratory values. AE preferred terms coded to a MedDRA SOC of 'Investigations', will be used to select the AEs in this listing in the data listings. A subset listing will be presented for all Grade 3 laboratory values.

# 13. SAMPLE SIZE CONSIDERATIONS

This study is designed to enroll approximately 4,600 total maternal subjects that include a minimum of 3,000 RSV F vaccine recipients over 4 global RSV seasons.

Assuming a medically-significant RSV LRTI incident rate of 4% in the placebo group and a vaccine efficacy of 65%, then the power of the design to claim success is 87%. Table 3 summarizes the power for different placebo attack rates and vaccine efficacies. Power calculations were performed using the normal approximation (NCSS PASS 14). An estimated PP population size of 4,218 total evaluable infant subjects (2,786 in the RSV F vaccine group and 1,432 in the placebo group to account for 1:1 and 2:1 randomization ratios in Year 1 and the subsequent years, respectively) was used for all calculations.

The target sample size of the safety and efficacy database in third-trimester pregnancy that will be required for licensure is at least 3,000 actively-immunized maternal subjects and their infants. Therefore, the final analysis for efficacy will commence only after a total of 3,000 subjects have been enrolled in the active treatment arm. If no events of a given class are observed among the 3,000 subjects receiving the RSV F vaccine, an approximation to the one-sided upper 95% confidence bound on the rate of SAE occurrence would be 0.1%.

**Table 3: Power Calculations for the Primary Efficacy Endpoint (Medically-Significant RSV LRTI Through 90 Days)**

| Placebo Event Rate | True Event Ratio | Efficacy (1-RR) | Power[1] |
|---|---|---|---|
| 0.02 | 0.5 | 50% | 17% |
| | 0.4 | 60% | 41% |
| | 0.35 | 65% | 57% |
| | 0.3 | 70% | 72% |
| | 0.2 | 80% | 92% |
| 0.03 | 0.5 | 50% | 26% |
| | 0.4 | 60% | 59% |
| | 0.35 | 65% | 76% |
| | 0.3 | 70% | 88% |
| | 0.2 | 80% | 99% |
| 0.04 | 0.5 | 50% | 34% |
| | 0.4 | 60% | 73% |
| | 0.35 | 65% | 87% |
| | 0.3 | 70% | 96% |

**Table 3: Power Calculations for the Primary Efficacy Endpoint (Medically-Significant RSV LRTI Through 90 Days)**

| Placebo Event Rate | True Event Ratio | Efficacy (1-RR) | Power[1] |
|---|---|---|---|
| | 0.2 | 80% | >99% |
| 0.05 | 0.5 | 50% | 42% |
| | 0.4 | 60% | 83% |
| | 0.35 | 65% | 94% |
| | 0.3 | 70% | 99% |
| | 0.2 | 80% | >99% |
| 0.06 | 0.5 | 50% | 50% |
| | 0.4 | 60% | 90% |
| | 0.35 | 65% | 97% |
| | 0.3 | 70% | >99% |
| | 0.2 | 80% | >99% |

[1] Estimated using normal approximation to rule out H0: Vaccine Efficacy < 30% using one-sided Type I error rate of 0.0124.

# 14. UNBLINDED AND FINAL ANALYSES

## 14.1. Unblinded Analysis of Efficacy, Immunogenicity, and Safety

The sequencing of RSV seasons in the Northern and Southern hemispheres lends a natural periodicity which will be reflected in the futility analyses. Futility analyses will be conducted based on data available 30 May (for convenience called "Northern hemisphere," although a small number of Southern hemisphere subjects may also meet the criteria for inclusion) and on approximately 30 September (for convenience called "Southern hemisphere" or "global season"); and subject to the constraint (applied by the DSMB statistician) that at least 10 cases will have accrued in the active treatment arm. The DSMB will communicate to the Sponsor after each futility analysis its recommendation that the trial is either: a) futile and should be discontinued, or b) should continue enrollment.

When futility (with no requirement for further subject enrollment) has been declared, or Day 180 post-delivery data for efficacy and immunogenicity are available on all delivered infants and maternal subjects, a final Day 180 unblinded analysis of efficacy and immunogenicity, and a preliminary analysis of safety, will be performed upon completion of the last infant D+180 visit and the last maternal postpartum Day 180 visit for all enrolled subjects. This unblinded analysis of efficacy, immunogenicity, and preliminary safety will include all available efficacy, immunogenicity, and safety (inclusive of clinical assessments and concomitant medications) data through the infant D+180 visit and the maternal postpartum Day 180 visit. Treatment codes for this analysis will only be unblinded to the Sponsor statistician after all efficacy and immunogenicity data are monitored, all applicable queries are resolved, and the database is locked without any known critical issues. Safety data will continue to be collected, monitored, and cleaned through the Day 365 visit. The efficacy and immunogenicity data through Day 180, except for the additional immunogenicity testing to be performed post unblinding (e.g., microneutralization assay testing of global season 3 and 4 samples) provided in this analysis will be considered final for the material contained therein, and will not change. In order to execute this unblinded analysis, a select group of study staff will be unblinded at Novavax. No individual unblinded at a subject treatment level will be involved in follow-up safety monitoring. Specifically, personnel at the clinical study site including, investigators and study staff, research site, and study subjects will remain blinded to subject treatment assignments until the end of study for the last infant on post-delivery study D+364.

In addition, an informational analysis of efficacy as specified in the study protocol (Section 10.10.2) may be performed when approximately 25 primary events, i.e., medically-significant RSV LRTI though the first 90 days among the PP-EFF-I population, have accrued. The success criterion is defined as the posterior probability that the event ratio is less than or equal to 1.00 (i.e., Vaccine Efficacy $\geq$ 0%) is greater than or equal to 0.90. This analysis will be performed by the DSMB biostatistician and the IBG in a manner entirely analogous to the analyses for efficacy and futility. The DSMB will communicate the results of the analysis to the Sponsor only in terms of fulfillment or non-fulfillment of the target criterion. Novavax will remain blinded and the outcome will not result in any change in the conduct of the study or the primary efficacy objectives and endpoints.

Results of the unblinded analysis of efficacy, immunogenicity, and safety through Day 180 may be presented by the Sponsor, and may be submitted to the appropriate regulatory authorities as needed.

The final CSR will include all immunogenicity data and safety data (inclusive of clinical assessments and concomitant medications) through the infant subject's D+364 visit, the scheduled end of study. The database will be locked and the final study report prepared, when all of the above data have been entered, reviewed, and all queries related to the data have been addressed.

Modifications or additions to the analyses described above will be included in the SAP. Any decisions to deviate from the planned analyses described in the protocol and in the statistical analysis plan will be described in detail in the final study report.

# 15. COMPUTER METHODS

The statistical analyses for immunogenicity will be performed using SAS® version 9.4 in a Windows environment. The statistical analyses for the primary and secondary efficacy endpoints may also be performed using R Copyright 2004, The R Foundation for Statistical Computing Version 3.2.4 (2016-03-16) or higher, ISBN 3-900051-07-0.

# 16. DATA HANDLING CONVENTIONS

All statistical analyses will be 2-tailed and assessed at the 5% significance level.

All output will be incorporated into Microsoft Word (including rtf format) or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonization (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented.

For all analyses, a two-sided p-value of $< 0.05$ (one-sided p-value $< 0.025$ where appropriate) will be considered statistically significant except for the primary efficacy endpoint, medically significant RSV LRTI through 90 day that will be evaluated using a one-sided p value of 0.0124 .

All references to analysis of GMEU/GMC/ GMT will be interpreted as analysis of the log (base 10) of EU or concentration values or of the reciprocal titers (e.g., the reciprocal titer of 1:160 is the number 160). Values recorded as below the lower limit of quantitation (LLOQ) of the assay for PCA and anti-F IgG will be set to half LLOQ for the purposes of GMEU/GMC, and GMFR analyses. For MN assays, titers will be reported in International Unit (IU) with the LLOQs of 13 for RSV/A and 8 for RSV/B. Titers below the LLOQs will also be set to half LLOQ, 6.5 IU for RSV/A and 4 IU for RSV/B.

For all data analyses and summary tabulations, categories for analysis and presentation will consist of the RSV F vaccine treatment groups. All descriptive statistical analyses will be performed using SAS statistical software Version 9.3 or higher in a Windows environment, unless otherwise noted. Medical history and AEs will be coded using the MedDRA Version 16.1.

## 16.1. Random Seeds

For efficacy analyses, random seeds will be set at 200120 with the statement set.seed(200120) in R or call streaminit(200120) in SAS when appropriate.

## 16.2. Baseline Definitions

For all analyses, baseline will be defined as the last non-missing measurement prior to the first administration of the study material. For immunogenicity analysis, baseline will be the sample drawn prior to the first vaccination, on the day of vaccination.

## 16.3. Adjustments for Covariates

No covariate adjustment will be made in the primary and secondary efficacy and immunogenicity endpoint analyses. In order to evaluate a potential effect of covariates,

subgroup analyses will be performed for factors including maternal age stratification (18-28 years of age and 29-40 years of age), the World Bank income categories (low and middle income countries and high income countries), the interval between the immunization and delivery (≤ 30 days and > 30 days), the GA at delivery (pre-term and full term), and by race/ethnicity. Additional subgroup analyses may also be performed.

## 16.4. Multiple Comparisons/Multiplicity

Analysis of the primary efficacy endpoint, medically-significant RSV LRTI in infant subjects, will be performed following a hierarchical closed procedure to control for the overall Type I error rate at 1-sided 0.025. A demonstration of vaccine efficacy though the first 90 days at a Type I error rate of 0.0124 (i.e., lower bound of two-sided 97.52% CI above the pre-specified threshold) will be required prior to testing of subsequent time-points, through 120, 150, and 180 days at Type I error rate of 0.025 (i.e., lower bound of two-sided 95% CI above the pre-specified threshold). Two sets of parallel analyses will be performed for the primary efficacy endpoint, one set for the US-FDA and the other for the ex-US global regulatory submissions (e.g., EMA and WHO) using different success criteria for the primary endpoint, $H_0$: Vaccine Efficacy < 30% for the US-FDA and $H_0$: Vaccine Efficacy ≤ 0% for the ex-US global regulatory submissions. The two sets of analyses will be the same for all other statistical approaches (i.e., methods of analysis, Type I error adjustments, and hierarchical testing approach).

Analysis of secondary and exploratory efficacy endpoints and immunogenicity endpoints will be performed without adjustment for multiple comparisons. The final interpretation of the total vaccine efficacy and the duration of protection will be based on the totality of statistical evidence including immunogenicity results and pre-specified exploratory endpoints; and the clinical importance in discussions with the regulatory agencies and scientific communities.

## 16.5. Withdrawals, Dropouts, Loss to Follow-up

The Investigator may, at his/her discretion, restrict a maternal or infant subject from receiving study treatment or other study procedures if he/she considers it to be in the maternal or infant subject's best interest to do so, but can suggest that the maternal or infant subject remain in the study to be followed for safety if the maternal subject has received a test article. In this situation, the reason for not performing the study treatment and/or procedure should also be recorded as a protocol deviation and clearly documented in the source document.

In the event of early termination, Investigators will make every reasonable effort to perform study completion procedures. Subjects (maternal and infants) who terminate from the study early will not be replaced. See Sections 6.4 to 6.6 of the protocol for more details on withdrawal of subjects.

## 16.6. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

For maternal subjects, if delivery date is missing, it will be imputed as the estimated delivery date (EDD) to establish the projected end time for their efficacy analysis.

When tabulating AE data, partial dates of AE onset will be handled as follows:

- If the day of the month is missing, the onset date will be assumed to be the date of either the first, in order to conservatively report the event as vaccine-emergent, unless the month reported clearly indicates the event would be outside the window for vaccine-emergent events, in which case no date will be imputed.
- If the onset day and month are both missing, the event onset will be coded to the day of vaccination (the birth date for infant subjects) in order to conservatively report the event as vaccine-emergent, unless it is clear by reference to the year that the event is outside the window for vaccine-emergent events.
- A completely missing onset date will be coded as the day of vaccination.

A conservative approach will be taken to assess the relationship of an AE to vaccine: if the relationship of an event is missing, it will be considered treatment-related. Missing severity for an AE will not be imputed.

When determining whether the concomitant medication was taken post-vaccination (i.e., start date is on or after the vaccination date), missing or incomplete start date will be handled as follows:

- If the start date is completely missing and the reason for use is not marked as preexisting, it will be treated as post-vaccination.
- If only the year is provided and the year is on or after the year of the vaccination and the reason for use is not marked as preexisting it will be treated as post-vaccination.
- If only the year and month are provided and the year and month are on or after the year and month of the vaccination and the reason for use is not marked as preexisting it will be treated as post-vaccination.

When tabulating concomitant medications data associated with the RSV surveillance illnesses, partial or missing dates of start and stop will be handled as follows:

- If a start date is completely missing, it will be assigned as Day 14 (start of the RSV surveillance for each subject) for maternal subjects (the birth date for infant subjects).
- If a stop date is missing, it will be assigned Day 180 post-delivery (end of the RSV surveillance for all subjects).
- If the day and month are missing for a start date, it will be assigned 01 January of the year or Day 14 for maternal subjects (the birth date for infant subjects) whichever is the latest.
- If the day and month are missing for a stop date, it will be assigned Day 180 post-delivery (end of the RSV surveillance for all subjects) or December 31 of the year whichever is the earliest.

- If the day is missing for a start date, it will be assigned the 1st day of the month or Day 14 (start of the RSV surveillance for each subject) for maternal subjects (the birth date for infant subjects) whichever the latest.
- If the day is missing for a stop date, it will be assigned the last day of the month or Day 180 post-delivery (end of the RSV surveillance for all subjects), 01 May for 2016 or December 31 of the year whichever is the earliest.

When determining preterm birth categories (Very preterm and Moderate to late preterm), if the study EDD is missing other available data (e.g. LMP or third trimester ultrasound, or GA at birth reported on the SAE narrative) will be used to determine the GA at birth.

When tabulating RSV surveillance illness episodes, onset or end date will be determined as follows:

- Parent-reported illness start date and return to normal date will be used as the start/end date for an episode.
- In the case of a missing or incomplete start date or return to normal date:
    - If start date is missing: impute the start date by the first contact date when parent reported symptoms or the first on-site visit date when site observed symptoms (whichever is earlier).
    - If return to normal date is missing: impute the return to normal date by the last contact date when parent reported symptoms or the last on-site visit date when site observed symptoms (whichever is later).
- If there is a "2~3 days after initial" visit record after the episode end date AND the record indicates site-observed symptom(s), adjust the episode end date to coincide with on-site visit date (episode will be extended).
- Each hospital stay is considered a single illness episode.
- If a parent-reported outpatient illness episode overlaps with a hospital stay, or extends to the onset of a hospital stay, or begins at the end of a hospital stay, then the episodes will be merged using the earliest of episode start or hospital admission as the start date and the latest of the hospital discharge or parent-reported episode end date as the end date.
- If 2 illness episodes occur within 7 days ($\leq$ 6 days), combine them to form a single illness episode (two episodes will be combined into one).
- Additional imputations may be performed by a Novavax medical staff if warranted in a blinded fashion.

When respiratory hospitalization admission and discharge dates for an infant subject are missing (or incomplete), they will be determined as follows:

- If the day of the month is missing:
    - The admission date will be imputed as the 1st of the month or the start date of the corresponding SAE whichever is later.
    - The discharge date will be imputed as the last of the month or the end date of the corresponding SAE whichever is earlier.
- If both the day of the month and the month are missing:
    - The admission date will be imputed as the 1st of January or the start date of the corresponding SAE whichever is later.
    - The discharge date will be imputed as the 31st of December or the end date of the corresponding SAE whichever is earlier.
- If the year is missing, the admission date or the discharge date will be imputed as the onset or the end date of the corresponding SAE, respectively.

Meeting all of the following conditions will be required to link a RSV surveillance illness episode and a concomitant medication:

- Answer to "Did subject take any medications/treatments for these symptoms?" on the RSV Surveillance CRF is marked as "Yes".
- The reason for taking the medication is marked as "Respiratory Surveillance" or "Unsolicited Adverse Event". If it is marked "Unsolicited Adverse Event", a manual review of the reported medications by clinician to confirm the link.
- Medication start date is not later than the illness end date.
- Medication stop date is on or after the illness onset date.

The following data conventions will be used for handling serology samples with respect to collection windows and missing or incomplete collection dates.

- If delivery time and dates are missing or incomplete to calculate the sample collection windows for samples at delivery, the CRF visit information will be used without applying the collection window. Cord blood samples identification will be based on the CRF visit information without applying the window and the cord blood if collected will be used for all analyses as the delivery sample.
- Delivery sample windows are defined as -24 to 72 hours from delivery for infants and -72 to 72 hours from delivery for maternal subjects.
- For each visit, one sample with the closest to the scheduled visit date will be selected for the analysis.

## 16.7. Data Handling for Incidence Calculations

- Any infant with an RSV illness fulfilling the primary, secondary, or an exploratory efficacy endpoint will be counted once in the incidence analysis using the first episode even if this endpoint has been recorded multiple times and in several days.
- Any infant with an RSV illness fulfilling the primary, secondary, or an exploratory efficacy endpoint who dies before 90 days of age will be counted as having reached the endpoint and will be included in all subsequent analyses of 0-120, 0-150, and 0-180 days of age.
- Any infant who dies for of any illness other than an RSV LRTI will be included in the non-infected group for analysis.
- Two consecutive illness episodes that are within 7 days of each other will be combined as one continuous episode for the efficacy analysis.

## 16.8. Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses for the primary efficacy endpoints will be performed to investigate the impact of missing specimens and visits for suspected medically-significant RSV LRTI. Whenever possible, supplemental data collected outside the study sites (i.e., hospitalization data within suspected RSV illness episodes) will be used for the sensitivity analysis instead of imputation. If there exists a hospital record for any components of the medically-significant RSV-LRTI endpoint definition, it will be used instead of imputations. These episodes will not be treated as missing.

In order to facilitate the assessment of other reasonable sensitivity assessments, a tipping point analysis will be performed by constructing a grid of all possible ($m_v$ +1) by ($m_p$+1) imputed outcomes for missing values by assigning imputed number of "endpoints" from 0 to $m_v$ in the vaccine group and 0 to $m_p$ in the placebo group. For each possible imputed outcome, the overall vaccine efficacy and the corresponding confidence interval will be constructed using the same statistical method used for the primary efficacy endpoint. The imputed data points in the grid will be evaluated against the $H_0$: Vaccine Efficacy $\leq$ 0%.

## 16.9. Calculation of Relative Days and Duration of Event

- Duration of an illness episode or an AE will be calculated as: End Date – Onset Date + 1. For example, for an event that starts on 01 January 2016 and ends on 10 January 2016, the duration of the event will be 10 days, calculated as (10 January 2016) – (01 January 2016) + 1.
- Relative days between the specimen collection of an illness episode and the illness onset date will be calculated as: Specimen Collection Date – Onset Date. For example, for an event that starts on 01 January 2016 and ends on 06 January 2016, the relative days between the illness specimen collection and the onset will be 5 days, calculated as (06 January 2016) – (01 January 2016).
- If two illness events are not separated by at least 7 calendar days (e.g., if an end date of an illness event is 01 January 2016, the onset date of the subsequent illness event has to be 08 January 2016 or later), the two events will be analyzed as one event per the protocol specified window.

# 17. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

Refer to the RSV-M-301 Protocol, Version 10.0, Dated 02 October 2018 for a summary of the various changes.

# 18. CHANGES TO THE SAP

## 18.1. List of Changes from Version 6.0 to Version 6.1

The following changes were made the SAP; no corresponding updates to Version 10 of Protocol RSV-M-301 were required based on these changes.

- Clarified that a time-to-event analysis for the primary efficacy endpoint will be performed as a sensitivity analysis taking potential differences in the length of subject follow-up into account. Minor wording changes to the Introduction, Study Design, and Major Protocol Deviations Assessment sections to be consistent with the protocol. (Section 10.3)
- Clarified that the analysis of SoP will be an exploratory analysis to identify a potential candidate, and that cumulative distribution functions and receiver operating characteristics curves will be used only as screening tools to identify CoRs that have potential to be validated as SoPs (Section 11.1.5).
- Clarified that the statistical significance for the primary efficacy endpoint, medically significant RSV LRTI through 90 days, will be evaluated against a one-sided p-value of 0.0124. (Section 16)
- Revised how <LLOQs are handled for MN assays. MN titers below the LLOQs will be set to half the LLOQ, i.e., 6.5 IU for RSV/A and 4 IU for RSV/B. The method for calculating SCRs was updated to use the same approach as the anti-F IgG ELISA (Sections 11.3 and 16)
- Clarified that missing delivery dates only applies to maternal subjects since no infant subjects had a missing delivery date. This provision was written for maternal subjects who withdrew early so that we can establish the projected end time for their efficacy analysis. (Section 16.6)

## 18.2. List of Changes from Version 5.0 to Version 6.0

The following changes were made the SAP; no corresponding updates to Version 10 of Protocol RSV-M-301 were required based on these changes.

- Minor wording changes to the Introduction, Study Design, and Major Protocol Deviations Assessment sections to be consistent with the protocol. (Section 1, 2, and 5.3.3.1)
- Wording changes were made to the ITT analysis population definitions to clarify that the mother does not have to have data for the infant, and vice versa. (Section 5.2)
- Updated to clarify the delivery serology sample window for the PP-IMM-M population (Section 5.3.2)
- Category of major protocol deviation involving receipt of any non-protocol vaccine was updated to reflect the current protocol (Section 5.3.3.1)
- Clarified that the protocol deviation listing does not have to be for maternal/infant pairs, but rather for all subjects. (Section 6)

- Added that APGAR scores will additionally be summarized as medians and interquartile ranges. (Section 7)
- Dictionary used to code medical history and unsolicited AEs has been updated (Section 7, 12.1, and 16)
- Dictionary used to code the concomitant medication has been updated (Section 8.2)
- Updated the analysis approach for the infant antibody decay modeling. Instead of using the target visit day for all samples, the actual age of infant subjects in days at the time of sample collection will be used as the exploratory variable in the regression analysis. Also since values reported as < LLOQ do not provide the exact time when the values crossed the LLOQ, they will be excluded from the half-life estimation. (Section 11.1.4)
- Updated how the seroconversion rates are determined (Section 11.1.3) and titers below the LLOQs are handled for the Microneutralization assays that are to be reported in International Units (Section 16)
- Updated the data cleaning plan for the final Day 180 unblinded analysis of efficacy and immunogenicity consistent with the submission provided to CBER on 16 November 2018 (SN 0187) specifying the data cleaning plan for the Day 180 unblinding. The initial plan for cleaning all efficacy, immunogenicity, and safety data for the Day 180 analysis was based on the original plan to submit the BLA with a Day 180 Clinical Study Report (CSR), with only partial Day 365 safety data available at the time of the original BLA submission (reference is made to BLA content proposal submitted in SN 0155; dated 27 April 2018). Per CBER's feedback on this proposal (reference is made to the CBER email dated 11 July 2018), a final CSR with Day 365 data for all subjects will be included in the BLA. Based on this feedback, the data cleaning plan was modified for the safety data at the time of the Day 180 efficacy unblinding. (Section 14.1)
- Added rules for determination of start and stop dates for whether concomitant medications were taken post-vaccination; for missing/incomplete suspect-illness start/stop dates; and for missing/incomplete admission and/or discharge dates for respiratory hospitalizations. (Section 16.6)
- Clarified how death will be handled in the efficacy analyses (Section 16.7)

## 18.3. List of Changes from Version 4.0 to Version 5.0

In addition to some minor clarifications and corrections, the following changes were made throughout the document to reflect the following changes in the objectives/endpoints and statistical analyses consistent with the Version 10 of Protocol RSV-M-301.

- Updated the study design to reflect the design change that the next analysis will be the final analysis without interim analyses. (Section 3)
- Removed the description of mITT populations, since they are defined the same as the ITT populations. (Section 5.2)

- Updated study objectives and the endpoints to reflect the change made to the study protocol. (Section 5)
- Updated analysis population definitions to clarify the existence of two distinct safety populations (maternal and infant) and to add the review of blinded protocol deviations in determination of the PP populations. (Section 6.3)
- Updated to reflect that there will be no interim analyses. (Section 10)
- Added a description of adjudication to be performed for hospitalizations taken for respiratory symptoms reported on RSV surveillance. (Section 11.2)
- Statistical approaches for the analyses of all efficacy endpoints were changed from the Bayesian method to a frequentist method. The Type I error rate of one-sided 0.0124 will be used for the final analysis without any interim analyses. (Sections 11.3 and 11.4)
- Updated immunogenicity endpoints to make them consistent with the study protocol and additional detail provided for the planned CoR and CoP analyses. (Section 12).
- Added how the GA at birth will be determined for the preterm birth categories (Very preterm and Moderate to late preterm). (Sections 12.6 and 16.6)
- Clarified to state that solicited AEs will not be summarized again in the unsolicited AE tables. (Section 13.4)
- Power calculations were updated based on one final analysis and the frequentist method. (Section 14)
- It has been indicated that the statistical analyses for immunogenicity will be performed using SAS® version 9.4 in a Windows environment. (Section 15)
- Some subgroup analyses have been pre-specified. (Section 16.3).
- Updated to reflect the current plan for handling the multiplicity. (Section 16.4)
- Provided additional details on imputations of EDDs; and concomitant medications associated with RSV surveillance illnesses (Section 16.6)
- Sensitivity analysis proposal for the primary efficacy endpoint was revised for the primary endpoint to simplify and reflect the switching the statistical method to a frequentist method. (Section 16.8)
- Updated Adaptive Design Report to correct randomization ratio for Seasons 2 - 4 from 1:1 to 2:1 (RSV F Vaccine : Placebo). (Appendix 1)

## 18.4. List of Changes from Version 3.0 to Version 4.0

The following changes to text were made to the RSV-M-301 SAP, Version 3.0, dated 17 May 2016.

- Updates were made to the throughout the document to reflect the changes made to the following changes made to the latest protocol amendment Version 9 (Ref: 072117_RSV-M-301_Protocol_V9.0):
    - co-primary efficacy endpoint definition
    - enrollment approach that resulted in changes to the Type I error adjustment and power calculations
    - addition of sequential testing within each co-primary efficacy endpoint
    - classification to the ITT population with respect to the treatment assignment
- Sensitivity analysis methods of the primary efficacy endpoint for missing values were updated (Section 17.8) to select one of the 3 multiple imputation methods previously proposed. Additional clarifications were made to the J2R method and the tipping point method.
- Added imputation methods for missing or incomplete data (Section 17.6).
- Added data convention for calculation of relative days and duration of event (Section 17.9)

## 18.5. List of Changes from Version 2.0 to Version 3.0

The following changes to text were made to the RSV-M-301 SAP, Version 2.0, dated 07 October 2015.

Reason for Changes/Location:

- Additional terms were added to the abbreviation list.
- The design section was updated following CBER's recommendation: i.e., the minimum requirement of 3,000 actively-treated maternal subjects and their infants for the safety database and the first interim analysis to be able to declare efficacy early. The first formal analysis for efficacy will be conducted when at least 3,000 cumulative actively-immunized maternal subjects and their infants have completed at least 6 months of post-partum follow-up have been enrolled at the close of the next hemispheric season.
- The scope section was modified due to the same reason stated in the prior bullet.
- Minor edits were made in Section 5 to correct typographical errors and to clarify analysis objectives.
- The analysis population definitions in Section 6 were clarified.
- The statistical methods for the efficacy analyses were updated (see Sections 10.3 and 10.4) with the following:
    - Addition of supportive analysis based on ITT-EFF-I after study completion.
    - Change in the statistical method used for the futility analyses.
    - Clarification of prior distribution to be used for primary endpoint.

  - Clarification of null hypothesis to be used for secondary and exploratory endpoints.
  - Clarification of the data sets to be used for the analyses.
- Minor edits were made in Section 11 due to the new immunogenicity population definitions.
- The Sample Size (Section 13) section was updated with new simulation results.
- Section 15 was updated based on CBER's recommendation on efficacy analysis.
- Changes in Sections 12 and 17 to harmonize the data handling convention for immunogenicity measures reported as below the LLOQ to be half of the LLOQ. Additional sensitivity analysis of handling < LLOQ for pre-vaccination measures in calculating GMFR added.
- Sensitivity analysis section for missing RSV PCR specimens was added (Section 16.8).
- Minor general edits were performed to harmonize the content of the protocol and the SAP and to enhance overall readability.

## 18.6. List of Changes from Version 1.0 to Version 2.0

The following changes to text were made to RSV-M-301 Statistical Analysis Plan Version 1.0, 11 June 2015.

Reason for Changes:

- The title of the version 1.0 of SAP included "DRAFT" and is now removed for version 2.0.
- The method of estimation of relative risk was not included in Version 1.0 of the SAP. It is now added.
- Clarified the communication between the IBG and the DSMB PM and the DSBM Statistician.
- A section was added for the justification of the interim evaluation of immunogenicity data and transplacental antibody transfer by the DSMB statistician.
- The term "proportions" was changed to "percentages" throughout the document as this more accurately reflects how relevant safety and exploratory analyses will be calculated.
- General edits due to changes in the protocol.
- Minor edits were made to correct typographical errors and to enhance overall readability.

Location of Changes:

- Page 1.
- Pages 12 and 14.
- Section 5.2.3.
- Sections 5.3.1, 5.3.2, 5.4, 6.3, 8.0, 11.2, 11.3, 11.4, 13.2, 15.0, and 20.

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# APPENDIX 1: MATERNAL IMMUNIZATION WITH RSV VACCINE: PIVOTAL EFFICACY TRIAL ADAPTIVE DESIGN REPORT


**Maternal Immunization with RSV Vaccine: Pivotal Efficacy Trial**
**Adaptive Design Report**

*Berry Consultants, LLC*
*July 30th 2018*

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## 1.0 Introduction

This document outlines the adaptive design for the randomized, adequate and well-controlled, confirmatory trial for demonstrating the superiority of the vaccine in preventing RSV disease in infants via ante-partum maternal immunization. The purpose of this document is to provide a description of the design along with details of the statistical models and simulation results.

This trial is a randomized study, comparing the efficacy of RSV vaccine against placebo. The primary efficacy endpoint is the RSV event rate for the infants under maternal immunization with the vaccine, relative to placebo, referred to as the *event ratio*. We define an RSV event as the occurrence of a protocol-defined medically significant RSV lower respiratory tract infection outcome for the infant, within 3 months of birth. The primary hypothesis of interest is to show super-superiority of the RSV vaccine over placebo. In particular, the primary analysis is to demonstrate that the event ratio is less than or equal to an event ratio target of 0.70.

Enrollment in the study will occur within two different geographic hemispheres per year. Enrollment will take place in the northern and southern hemispheres, prior to and during the typical RSV seasons for those hemispheres. This leads to two "hemispheric" seasons of data, which combine to provide a "global season" of data within an approximate calendar year. During enrollment of the northern hemisphere within the first year subjects will be randomized 1:1 to vaccine or placebo and 2:1 thereafter.

The maximum study size is 8,618 subjects in total across northern and southern hemispheres. However, the sample size required to demonstrate efficacy on the primary endpoint might be smaller. Therefore, an adaptive design is proposed that will allow multiple interim analyses in order to enable early demonstration of the primary efficacy endpoint. Rules are also created for futility interim analyses.


## 2.0 Statistical Modeling

Throughout we assume that the distribution of the number of events under the vaccine, $x_v$, and the number of events under placebo, $x_p$, are binomial:

$$x_v \sim Bin(\pi_v, n_v)$$
$$x_p \sim Bin(\pi_p, n_p)$$

where $\pi_v$ and $n_v$ are the probability of an RSV event and the total number of subjects in the vaccine group and $\pi_p$ and $n_p$ are the probability of an event and the total number of subjects in the placebo group.

Furthermore, we assume prior distributions for $\pi_v$ and $\pi_p$ that are flat, non-informative beta distributions:

$$\pi_v \sim Beta(1,1)$$
$$\pi_p \sim Beta(1,1).$$

### *2.1 Posterior Success and Futility Probabilities*

Success is demonstrated under the primary hypothesis based on the posterior probability that the event ratio, $r = \pi_v / \pi_p$, is less than or equal to .70.

Futility is demonstrated under the primary hypothesis based on the posterior probability that the event ratio, $r = \pi_v / \pi_p$, is less than or equal to .60.

Given $x_v$ events out of $n_v$ total patients in the vaccine group and $x_p$ events out of $n_p$ total patients in the placebo group, the posterior distributions of $\pi_v$ and $\pi_p$ are:

$$\pi_v | x_v \sim Beta(1 + x_v, 1 + (n_v - x_v))$$
$$\pi_p | x_p \sim Beta(1 + x_p, 1 + (n_p - x_p)).$$

We sample from the posterior probability distribution for the event ratio by:

1. Sampling 10 million independent values from the posteriors of $\pi_v$ and $\pi_p$
2. Calculating the event ratio, $r = \pi_v / \pi_p$ under each pair-wise sample from the posterior of $\pi_v$ and $\pi_p$.


We then report the proportion of samples from the posterior distribution that are less than or equal to 0.70 and 0.60 as the posterior probability that the event ratio is less than 0.70 and 0.60. We also report as an estimate of vaccine efficacy the posterior median event ratio, and as a 95% credible interval for the estimated vaccine efficacy the 2.5% and 97.5% quantiles from the posterior distribution.

## 3.0 Interim Analyses

The bolus of enrollment within two hemispheres creates a natural design structure. In particular, interim analyses for futility will take place after the completion of enrollment and three months post-natal follow-up of infants in each hemisphere. Interim analyses for success, however, are timed according to the number of patients enrolled and with complete primary endpoint information.

### *3.1 Success Stopping*

There are two interim analyses for early success. The first interim analysis is when 3,000 maternal subjects have been enrolled and treated with active vaccine and there has been complete post-natal follow-up of their infants. Similarly, the second interim analysis will take place when 6,600 total maternal subjects have been enrolled and there has been complete post-natal follow-up of their infants. If the trial does not stop early for success or futility, the final determination of success will be made when the trial has accrued to the maximum sample size of 8,616 and there is complete post-natal follow-up of infants.

Success is declared at any of these three analyses if the posterior probability of success as defined in Section 2.1 is greater than 0.9876. This critical value is chosen to maintain an overall one-sided type I error of .025 and is based on a Pocock-spending function with three looks at the corresponding information times.

### *3.2 Futility Stopping*

The trial may be stopped for futility after *each* hemisphere has enrolled for a season and generated data (i.e, at the end of any "hemispheric" season). Futility stopping is based on the posterior probability of futility as defined in Section 2.1. In particular, the trial will be stopped for futility if the posterior probability that the event ratio is less than or equal to 0.60 is less than or equal to 0.05. Futility stopping will be allowed only once 10 or more events have been observed among infants on the active treatment arm.


## 4.0 Simulation Scenarios and Operating Characteristics

In order to characterize and understand the performance of the design, we created simulations of the design as described in this document. In this section we provide operating characteristics across numerous simulated trials of the design in a range of scenarios.

For each scenario 5,000 trials were simulated. The range of scenarios was for 4 possible event rates under the placebo (.02, .03, .04, and .05) and 9 possible event ratios (1, .85, .7, .6, .5, .4, .35, .3, .2). Passive polyclonal and monoclonal antibody therapies in high risk infants have been associated with estimated event ratios in the range of 0.2 to 0.35; and 0.35 has been highlighted as a potential true event ratio for the product.

Table 1 provides average operating characteristics across 5,000 simulated trials under the 36 total possible simulation scenarios. In particular, for each scenario we report the following characteristics: 1) Mean total trial size, 2) Cumulative probability of stopping for success at each of the three success looks, and 3) Cumulative probability of stopping for futility after each hemisphere season.

Under a true event ratio of 0.35 the power of the above-defined adaptive design is 0.894, 0.958, 0.983, and 0.983 under placebo event rates of .02, .03, .04, and .05 respectively. Under a placebo RSV event rate of .03 and an event ratio of 0.35 the probability that a trial will stop for success after the first or second look is 0.78 and 0.92 respectively. On average the trial enrolls 4,971 total maternal subjects before stopping in this scenario.

Under a true event ratio of 1 (equal event rates under placebo and vaccine) greater than 66% of the trials are deemed futile by at least the 5$^{th}$ hemispheric season. The average trial size is 2,977, 2,182, 1,765 and 1,471 under placebo event rates of .02, .03, .04, and .05 respectively.

Under a true event ratio of 0.70 (equal to the target event ratio) the probability of a successful trial is 0.023-0.025 and approximately 40-60% of the trials are stopped early for futility. The average trial size is 6,488, 6,181, 5,787, and 5,507 under placebo event rates of .02, .03, .04, and .05 respectively.

Finally, to understand which trials end up stopping for futility or success at each interim, Table 2 summarizes the estimated event ratio for all trials stopped for success or futility at each of the interims. Results are pooled across all simulation scenarios. We show the minimum event ratio among trials that stopped for success at each of the success looks and the maximum event ratio among trials that stopped for futility at each futility look. Trials that are successful have a maximum event ratio


of 0.525 at the first success look, 0.549 at the second success look, and a maximum event ratio of 0.562 for trials that were successful at the final analysis. Trials that stop for futility at the 2nd and 3rd hemisphere have a minimum event ratio greater than 1. As the trial continues, trials that stop for futility have a minimum event ratio of at least 0.71.


**Table 1: Operating Characteristics Base Scenario**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 2% | 0.2 | 4622 | 0.994 | 0.9504 | 0.9910 | 0.9942 | 0.003 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 |
| | 0.3 | 5123 | 0.956 | 0.7510 | 0.9032 | 0.9558 | 0.008 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 0.35 | 5612 | 0.894 | 0.6056 | 0.7970 | 0.8944 | 0.008 | 0.017 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 |
| | 0.4 | 6237 | 0.757 | 0.4322 | 0.6328 | 0.7568 | 0.012 | 0.022 | 0.026 | 0.027 | 0.027 | 0.027 | 0.027 | 0.027 | 0.027 | 0.027 |
| | 0.5 | 7158 | 0.378 | 0.1758 | 0.2808 | 0.3776 | 0.023 | 0.042 | 0.056 | 0.065 | 0.070 | 0.073 | 0.074 | 0.075 | 0.075 | 0.075 |
| | 0.6 | 7253 | 0.125 | 0.0570 | 0.0928 | 0.1252 | 0.032 | 0.067 | 0.097 | 0.122 | 0.142 | 0.155 | 0.166 | 0.174 | 0.175 | 0.175 |
| | 0.7 | 6488 | 0.025 | 0.0134 | 0.0192 | 0.0250 | 0.041 | 0.092 | 0.160 | 0.220 | 0.278 | 0.327 | 0.371 | 0.404 | 0.404 | 0.404 |
| | 0.85 | 4606 | 0.002 | 0.0010 | 0.0012 | 0.0016 | 0.072 | 0.151 | 0.287 | 0.423 | 0.550 | 0.654 | 0.736 | 0.795 | 0.796 | 0.797 |
| | 1 | 2977 | 0.000 | 0.0002 | 0.0002 | 0.0002 | 0.092 | 0.191 | 0.443 | 0.659 | 0.802 | 0.896 | 0.945 | 0.974 | 0.975 | 0.975 |
| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 3% | 0.2 | 4530 | 0.995 | 0.9922 | 0.9952 | 0.9954 | 0.003 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 |
| | 0.3 | 4674 | 0.983 | 0.9050 | 0.9712 | 0.9830 | 0.008 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 0.35 | 4971 | 0.958 | 0.7844 | 0.9200 | 0.9580 | 0.012 | 0.020 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 |
| | 0.4 | 5556 | 0.891 | 0.6142 | 0.8002 | 0.8914 | 0.011 | 0.019 | 0.022 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 |
| | 0.5 | 6742 | 0.523 | 0.2636 | 0.4074 | 0.5228 | 0.025 | 0.045 | 0.057 | 0.062 | 0.066 | 0.068 | 0.069 | 0.070 | 0.070 | 0.070 |
| | 0.6 | 7029 | 0.162 | 0.0706 | 0.1184 | 0.1622 | 0.042 | 0.074 | 0.112 | 0.140 | 0.159 | 0.177 | 0.189 | 0.199 | 0.199 | 0.199 |
| | 0.7 | 6181 | 0.024 | 0.0124 | 0.0168 | 0.0242 | 0.058 | 0.107 | 0.185 | 0.250 | 0.319 | 0.377 | 0.429 | 0.471 | 0.472 | 0.473 |
| | 0.85 | 3778 | 0.001 | 0.0004 | 0.0006 | 0.0006 | 0.095 | 0.170 | 0.356 | 0.535 | 0.683 | 0.781 | 0.851 | 0.897 | 0.898 | 0.898 |
| | 1 | 2182 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.141 | 0.268 | 0.583 | 0.788 | 0.916 | 0.966 | 0.986 | 0.995 | 0.995 | 0.995 |


**Table 1: Operating Characteristics Base Scenario**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 4% | 0.2 | 4530 | 0.997 | 0.9970 | 0.9970 | 0.9970 | 0.002 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 |
| | 0.3 | 4550 | 0.989 | 0.9664 | 0.9874 | 0.9892 | 0.007 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 | 0.010 |
| | 0.35 | 4711 | 0.983 | 0.8894 | 0.9664 | 0.9826 | 0.010 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 0.4 | 5011 | 0.953 | 0.7640 | 0.9078 | 0.9530 | 0.016 | 0.023 | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 | 0.025 |
| | 0.5 | 6329 | 0.669 | 0.3642 | 0.5480 | 0.6688 | 0.025 | 0.042 | 0.051 | 0.054 | 0.056 | 0.056 | 0.056 | 0.057 | 0.057 | 0.057 |
| | 0.6 | 6911 | 0.198 | 0.0900 | 0.1464 | 0.1978 | 0.047 | 0.084 | 0.117 | 0.141 | 0.161 | 0.177 | 0.190 | 0.199 | 0.199 | 0.199 |
| | 0.7 | 5787 | 0.023 | 0.0102 | 0.0176 | 0.0230 | 0.071 | 0.123 | 0.218 | 0.299 | 0.371 | 0.436 | 0.497 | 0.542 | 0.543 | 0.543 |
| | 0.85 | 3169 | 0.000 | 0.0002 | 0.0002 | 0.0002 | 0.111 | 0.213 | 0.433 | 0.611 | 0.765 | 0.864 | 0.923 | 0.951 | 0.951 | 0.952 |
| | 1 | 1765 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.161 | 0.304 | 0.673 | 0.874 | 0.968 | 0.992 | 0.998 | 0.999 | 0.999 | 0.999 |
| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 5% | 0.2 | 4532 | 0.997 | 0.9974 | 0.9974 | 0.9974 | 0.002 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 |
| | 0.3 | 4520 | 0.991 | 0.9842 | 0.9910 | 0.9912 | 0.007 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 |
| | 0.35 | 4547 | 0.983 | 0.9524 | 0.9794 | 0.9832 | 0.013 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 |
| | 0.4 | 4782 | 0.967 | 0.8442 | 0.9452 | 0.9672 | 0.017 | 0.022 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 | 0.023 |
| | 0.5 | 6037 | 0.758 | 0.4374 | 0.6392 | 0.7582 | 0.025 | 0.041 | 0.047 | 0.049 | 0.050 | 0.050 | 0.050 | 0.051 | 0.051 | 0.051 |
| | 0.6 | 6822 | 0.241 | 0.1086 | 0.1806 | 0.2412 | 0.050 | 0.077 | 0.114 | 0.138 | 0.158 | 0.177 | 0.190 | 0.196 | 0.196 | 0.196 |
| | 0.7 | 5507 | 0.024 | 0.0110 | 0.0188 | 0.0240 | 0.076 | 0.136 | 0.241 | 0.324 | 0.410 | 0.482 | 0.545 | 0.594 | 0.596 | 0.596 |
| | 0.85 | 2749 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.126 | 0.231 | 0.482 | 0.683 | 0.835 | 0.916 | 0.956 | 0.977 | 0.977 | 0.977 |
| | 1 | 1471 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.191 | 0.360 | 0.755 | 0.930 | 0.987 | 0.998 | 1.000 | 1.000 | 1.000 | 1.000 |


| Table 2A: Max Event Ratios (Vaccine/ Placebo) for trials stopped for success at each interim. | |
|---|---|
| **Success Look** | **Max ER** |
| 1 | 0.525 |
| 2 | 0.549 |
| 3 | 0.562 |

| Table 2B: Min Event Ratios (Vaccine/ Placebo) for trials stopped for futility at each interim. | |
|---|---|
| **Futility Hemisphere** | **Min ER** |
| 2 | 1.32 |
| 3 | 1.07 |
| 4 | 0.83 |
| 5 | 0.78 |
| 6 | 0.74 |
| 7 | 0.72 |
| 8 | 0.71 |
| 9 | 0.71 |
| 10 | 0.72 |
| 11 | 0.71 |

## 5.0 Summary

The trial design described herein will provide high quality evidence for the study of efficacy of the RSV vaccine. The design has a maximum Type I error of 2.5% with a high probability of stopping early for futility if the assumed event ratio is equal to the target event ratio of 0.70. If the event ratio is .35 or less and the vaccine reduces RSV events by 65% or more compared to placebo the design offers high power and the opportunity to identify this benefit with a decreased trial size.


## 6.0 Additional Operating Characteristics

We assess the sensitivity of the operating characteristics to the scenario in which there is no futility stopping as well as the scenario in which accrual rates differ from what was expected.

### *6.1 Alternative Accrual Rates*

We simulate 5,000 trials under all previously defined simulations scenarios in Section 6.2 with varying accrual patterns given in Table 3.

**Table 3: Alternative Accrual Scenarios – Mean Accrual Per Hemisphere**

| Scenario | 1 | 2 | 3 | 4 | 5 | 6 to 12 |
|---|---|---|---|---|---|---|
| Base | 20 | 154 | 210 | 1094 | 1220 | 1512 |
| 25% Less | 15 | 115.5 | 157.5 | 820.5 | 915 | 1134 |
| 25% More | 25 | 192.5 | 262.5 | 1367.5 | 1525 | 1891 |

Operating characteristics for the slower and faster accrual scenarios are provided in Table 5 and Table 6. Under the slower and faster accrual assumptions, the Type I error (the scenario where the event ratio is 0.70) is consistent with the 2.5% level and the power of the design if the event ratio is 0.35 is at least 88%.

### *6.2 No Futility Stopping*

Under all accrual scenarios described in Table 3, we simulate 50,000 trials without the possibility of futility stopping under the null assumption that the event ratio is .70. Operating characteristics are provided in Table 4. Under our design with no futility stopping the maximum Type I error under the assumption that the event ratio is .70 is at most 2.60%.

**Table 4: Type I Error No Futility Stopping**

| Scenario | Placebo Event Rate | | | |
|---|---|---|---|---|
| | .02 | .03 | .04 | .05 |
| Base | 0.0260 | 0.0251 | 0.0246 | 0.0257 |
| 25% Less | 0.0248 | 0.0249 | 0.0254 | 0.0257 |
| 25% More | 0.0246 | 0.0247 | 0.0251 | 0.0246 |


**Table 5: Operating Characteristics for Accrual 25% Slower**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look 1 | 2 | 3 | Cumulative Probability of Futility in Hemisphere 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2% | 0.2 | 4600 | 0.994 | 0.9534 | 0.9894 | 0.9936 | 0.003 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 |
| | 0.3 | 5107 | 0.957 | 0.7404 | 0.9014 | 0.9568 | 0.007 | 0.016 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 |
| | 0.35 | 5586 | 0.889 | 0.6086 | 0.7910 | 0.8894 | 0.009 | 0.017 | 0.021 | 0.021 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 |
| | 0.4 | 6144 | 0.751 | 0.4412 | 0.6260 | 0.7506 | 0.016 | 0.028 | 0.034 | 0.036 | 0.037 | 0.037 | 0.037 | 0.037 | 0.037 | 0.037 |
| | 0.5 | 7066 | 0.386 | 0.1828 | 0.2950 | 0.3862 | 0.024 | 0.044 | 0.058 | 0.065 | 0.071 | 0.075 | 0.077 | 0.079 | 0.079 | 0.080 |
| | 0.6 | 7134 | 0.128 | 0.0560 | 0.0938 | 0.1276 | 0.029 | 0.063 | 0.099 | 0.124 | 0.142 | 0.155 | 0.165 | 0.176 | 0.183 | 0.189 |
| | 0.7 | 6367 | 0.025 | 0.0106 | 0.0176 | 0.0248 | 0.047 | 0.092 | 0.150 | 0.200 | 0.252 | 0.290 | 0.326 | 0.357 | 0.387 | 0.410 |
| | 0.85 | 4401 | 0.001 | 0.0008 | 0.0010 | 0.0010 | 0.064 | 0.132 | 0.251 | 0.366 | 0.477 | 0.575 | 0.651 | 0.714 | 0.767 | 0.802 |
| | 1 | 2774 | 0.000 | 0.0002 | 0.0002 | 0.0002 | 0.083 | 0.177 | 0.375 | 0.561 | 0.721 | 0.820 | 0.892 | 0.934 | 0.959 | 0.972 |

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look 1 | 2 | 3 | Cumulative Probability of Futility in Hemisphere 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3% | 0.2 | 4517 | 0.994 | 0.9896 | 0.9942 | 0.9942 | 0.005 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 |
| | 0.3 | 4665 | 0.983 | 0.9058 | 0.9702 | 0.9832 | 0.008 | 0.013 | 0.014 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 | 0.015 |
| | 0.35 | 4979 | 0.955 | 0.7720 | 0.9132 | 0.9552 | 0.013 | 0.021 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 |
| | 0.4 | 5465 | 0.888 | 0.6156 | 0.7980 | 0.8882 | 0.017 | 0.027 | 0.032 | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 | 0.033 |
| | 0.5 | 6731 | 0.541 | 0.2600 | 0.4194 | 0.5406 | 0.023 | 0.040 | 0.053 | 0.057 | 0.063 | 0.064 | 0.066 | 0.067 | 0.068 | 0.069 |
| | 0.6 | 7002 | 0.156 | 0.0686 | 0.1142 | 0.1556 | 0.034 | 0.070 | 0.107 | 0.131 | 0.149 | 0.163 | 0.173 | 0.184 | 0.193 | 0.200 |
| | 0.7 | 5884 | 0.024 | 0.0116 | 0.0192 | 0.0242 | 0.053 | 0.097 | 0.177 | 0.242 | 0.302 | 0.359 | 0.400 | 0.441 | 0.480 | 0.503 |
| | 0.85 | 3486 | 0.000 | 0.0004 | 0.0004 | 0.0004 | 0.083 | 0.166 | 0.329 | 0.479 | 0.609 | 0.707 | 0.781 | 0.837 | 0.877 | 0.904 |
| | 1 | 2023 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.111 | 0.217 | 0.494 | 0.701 | 0.850 | 0.932 | 0.967 | 0.986 | 0.993 | 0.998 |


**Table 5: Operating Characteristics for Accrual 25% Slower**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 4% | 0.2 | 4511 | 0.995 | 0.9944 | 0.9946 | 0.9948 | 0.003 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 | 0.005 |
| | 0.3 | 4524 | 0.983 | 0.9566 | 0.9808 | 0.9834 | 0.012 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 | 0.016 |
| | 0.35 | 4664 | 0.979 | 0.8944 | 0.9654 | 0.9792 | 0.012 | 0.017 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 | 0.019 |
| | 0.4 | 5023 | 0.942 | 0.7468 | 0.8908 | 0.9418 | 0.017 | 0.027 | 0.030 | 0.030 | 0.031 | 0.031 | 0.031 | 0.031 | 0.031 | 0.031 |
| | 0.5 | 6304 | 0.658 | 0.3416 | 0.5304 | 0.6582 | 0.030 | 0.049 | 0.059 | 0.064 | 0.066 | 0.067 | 0.068 | 0.068 | 0.068 | 0.069 |
| | 0.6 | 6860 | 0.204 | 0.0898 | 0.1448 | 0.2036 | 0.042 | 0.073 | 0.109 | 0.131 | 0.153 | 0.168 | 0.178 | 0.190 | 0.203 | 0.210 |
| | 0.7 | 5670 | 0.027 | 0.0142 | 0.0210 | 0.0270 | 0.065 | 0.112 | 0.190 | 0.257 | 0.323 | 0.379 | 0.434 | 0.476 | 0.521 | 0.553 |
| | 0.85 | 2998 | 0.000 | 0.0002 | 0.0004 | 0.0004 | 0.094 | 0.179 | 0.368 | 0.534 | 0.678 | 0.778 | 0.856 | 0.906 | 0.939 | 0.961 |
| | 1 | 1628 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.135 | 0.261 | 0.581 | 0.799 | 0.919 | 0.970 | 0.989 | 0.997 | 0.999 | 1.000 |
| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 5% | 0.2 | 4517 | 0.996 | 0.9964 | 0.9964 | 0.9964 | 0.003 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 |
| | 0.3 | 4493 | 0.988 | 0.9804 | 0.9874 | 0.9876 | 0.010 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 |
| | 0.35 | 4559 | 0.983 | 0.9390 | 0.9774 | 0.9826 | 0.011 | 0.016 | 0.017 | 0.017 | 0.017 | 0.017 | 0.017 | 0.017 | 0.017 | 0.017 |
| | 0.4 | 4765 | 0.968 | 0.8388 | 0.9436 | 0.9684 | 0.015 | 0.024 | 0.025 | 0.026 | 0.026 | 0.026 | 0.026 | 0.026 | 0.026 | 0.026 |
| | 0.5 | 5953 | 0.754 | 0.4500 | 0.6384 | 0.7536 | 0.026 | 0.045 | 0.051 | 0.053 | 0.055 | 0.055 | 0.056 | 0.056 | 0.056 | 0.056 |
| | 0.6 | 6769 | 0.240 | 0.1050 | 0.1730 | 0.2404 | 0.046 | 0.076 | 0.110 | 0.135 | 0.154 | 0.169 | 0.179 | 0.187 | 0.197 | 0.205 |
| | 0.7 | 5417 | 0.025 | 0.0132 | 0.0180 | 0.0248 | 0.065 | 0.118 | 0.203 | 0.277 | 0.354 | 0.421 | 0.472 | 0.520 | 0.569 | 0.603 |
| | 0.85 | 2478 | 0.000 | 0.0002 | 0.0004 | 0.0004 | 0.110 | 0.209 | 0.432 | 0.621 | 0.768 | 0.862 | 0.912 | 0.948 | 0.968 | 0.977 |
| | 1 | 1351 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.151 | 0.301 | 0.666 | 0.872 | 0.961 | 0.990 | 0.997 | 0.998 | 1.000 | 1.000 |


**Table 6: Operating Characteristics for Accrual 25% Faster**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 2% | 0.2 | 4634 | 0.995 | 0.9522 | 0.9906 | 0.9952 | 0.002 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 |
| | 0.3 | 5168 | 0.959 | 0.7426 | 0.9006 | 0.9592 | 0.007 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 |
| | 0.35 | 5713 | 0.882 | 0.5826 | 0.7810 | 0.8818 | 0.007 | 0.016 | 0.017 | 0.017 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 |
| | 0.4 | 6250 | 0.754 | 0.4276 | 0.6238 | 0.7536 | 0.012 | 0.024 | 0.029 | 0.030 | 0.031 | 0.031 | 0.031 | 0.031 | 0.031 | 0.031 |
| | 0.5 | 7212 | 0.376 | 0.1674 | 0.2784 | 0.3760 | 0.022 | 0.048 | 0.059 | 0.064 | 0.067 | 0.068 | 0.069 | 0.069 | 0.069 | 0.069 |
| | 0.6 | 7348 | 0.121 | 0.0510 | 0.0878 | 0.1212 | 0.036 | 0.066 | 0.101 | 0.124 | 0.142 | 0.159 | 0.166 | 0.166 | 0.166 | 0.166 |
| | 0.7 | 6579 | 0.024 | 0.0124 | 0.0188 | 0.0236 | 0.050 | 0.101 | 0.176 | 0.245 | 0.302 | 0.356 | 0.394 | 0.395 | 0.395 | 0.395 |
| | 0.85 | 4702 | 0.001 | 0.0002 | 0.0006 | 0.0006 | 0.079 | 0.156 | 0.323 | 0.486 | 0.631 | 0.735 | 0.796 | 0.797 | 0.797 | 0.797 |
| | 1 | 3128 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.110 | 0.225 | 0.512 | 0.720 | 0.867 | 0.939 | 0.968 | 0.968 | 0.969 | 0.969 |

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look | | | Cumulative Probability of Futility in Hemisphere | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 1 | 2 | 3 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| 3% | 0.2 | 4549 | 0.996 | 0.9916 | 0.9962 | 0.9964 | 0.002 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 |
| | 0.3 | 4742 | 0.990 | 0.8998 | 0.9732 | 0.9896 | 0.005 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 |
| | 0.35 | 4981 | 0.970 | 0.8042 | 0.9288 | 0.9696 | 0.010 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 | 0.014 |
| | 0.4 | 5501 | 0.903 | 0.6326 | 0.8108 | 0.9032 | 0.014 | 0.022 | 0.023 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 | 0.024 |
| | 0.5 | 6859 | 0.536 | 0.2578 | 0.4106 | 0.5358 | 0.022 | 0.040 | 0.049 | 0.051 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 | 0.054 |
| | 0.6 | 7220 | 0.155 | 0.0678 | 0.1126 | 0.1546 | 0.041 | 0.074 | 0.106 | 0.131 | 0.147 | 0.161 | 0.173 | 0.173 | 0.173 | 0.173 |
| | 0.7 | 6228 | 0.024 | 0.0110 | 0.0194 | 0.0240 | 0.063 | 0.111 | 0.207 | 0.285 | 0.364 | 0.421 | 0.472 | 0.473 | 0.474 | 0.475 |
| | 0.85 | 3913 | 0.001 | 0.0004 | 0.0008 | 0.0008 | 0.110 | 0.200 | 0.419 | 0.590 | 0.746 | 0.846 | 0.901 | 0.902 | 0.902 | 0.902 |
| | 1 | 2292 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.157 | 0.302 | 0.645 | 0.859 | 0.960 | 0.989 | 0.997 | 0.997 | 0.997 | 0.997 |


**Table 6: Operating Characteristics for Accrual 25% Faster**

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look 1 | 2 | 3 | Cumulative Probability of Futility in Hemisphere 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4% | 0.2 | 4545 | 0.998 | 0.9972 | 0.9976 | 0.9976 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 |
| | 0.3 | 4576 | 0.991 | 0.9640 | 0.9890 | 0.9910 | 0.007 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 | 0.009 |
| | 0.35 | 4720 | 0.986 | 0.8972 | 0.9714 | 0.9856 | 0.010 | 0.012 | 0.013 | 0.013 | 0.013 | 0.013 | 0.013 | 0.013 | 0.013 | 0.013 |
| | 0.4 | 5061 | 0.953 | 0.7626 | 0.9014 | 0.9530 | 0.014 | 0.021 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 | 0.022 |
| | 0.5 | 6410 | 0.672 | 0.3606 | 0.5410 | 0.6716 | 0.028 | 0.039 | 0.045 | 0.049 | 0.049 | 0.050 | 0.051 | 0.051 | 0.051 | 0.051 |
| | 0.6 | 7059 | 0.201 | 0.0914 | 0.1528 | 0.2008 | 0.051 | 0.079 | 0.113 | 0.132 | 0.150 | 0.164 | 0.174 | 0.174 | 0.174 | 0.174 |
| | 0.7 | 6047 | 0.025 | 0.0118 | 0.0190 | 0.0254 | 0.072 | 0.124 | 0.221 | 0.302 | 0.387 | 0.465 | 0.518 | 0.519 | 0.520 | 0.520 |
| | 0.85 | 3304 | 0.000 | 0.0002 | 0.0002 | 0.0004 | 0.123 | 0.226 | 0.489 | 0.687 | 0.836 | 0.920 | 0.955 | 0.955 | 0.955 | 0.955 |
| | 1 | 1825 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.195 | 0.363 | 0.755 | 0.936 | 0.987 | 0.997 | 0.999 | 0.999 | 0.999 | 0.999 |

| Control Rate | ER | MeanN | Power | Cumulative Probability of Success At Look 1 | 2 | 3 | Cumulative Probability of Futility in Hemisphere 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5% | 0.2 | 4548 | 0.999 | 0.9986 | 0.9986 | 0.9986 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |
| | 0.3 | 4541 | 0.994 | 0.9892 | 0.9944 | 0.9944 | 0.004 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 | 0.006 |
| | 0.35 | 4595 | 0.988 | 0.9464 | 0.9838 | 0.9878 | 0.010 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 |
| | 0.4 | 4823 | 0.974 | 0.8472 | 0.9484 | 0.9738 | 0.013 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 | 0.018 |
| | 0.5 | 6037 | 0.757 | 0.4304 | 0.6316 | 0.7566 | 0.031 | 0.045 | 0.052 | 0.055 | 0.056 | 0.056 | 0.056 | 0.056 | 0.056 | 0.056 |
| | 0.6 | 6974 | 0.244 | 0.1120 | 0.1820 | 0.2440 | 0.047 | 0.075 | 0.106 | 0.132 | 0.150 | 0.167 | 0.176 | 0.176 | 0.176 | 0.176 |
| | 0.7 | 5752 | 0.024 | 0.0098 | 0.0176 | 0.0240 | 0.090 | 0.146 | 0.249 | 0.341 | 0.431 | 0.511 | 0.570 | 0.570 | 0.571 | 0.571 |
| | 0.85 | 2821 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.146 | 0.267 | 0.561 | 0.761 | 0.898 | 0.957 | 0.979 | 0.979 | 0.979 | 0.979 |
| | 1 | 1576 | 0.000 | 0.0000 | 0.0000 | 0.0000 | 0.222 | 0.412 | 0.820 | 0.965 | 0.996 | 0.999 | 1.000 | 1.000 | 1.000 | 1.000 |

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