PROTOCOL APPROVAL PAGE

The principal investigator is responsible for ensuring that all study site personnel, including sub-investigators and other staff members conduct this study according to this protocol, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki, and the pertinent individual country laws/regulations and to comply with its obligations, subject to ethical and safety considerations during and after study completion. The principal investigator also agrees not to disclose the information contained in this protocol or any results obtained from this study without written authorization.

Investigational Material:	RSV Recombinant F Nanoparticle Vaccine (*Sf9* cells with recombinant Baculovirus expression) with aluminum
Reference Material:	Formulation buffer (placebo)
Protocol:	RSV-M-301
Date of Issue:	12 October 2018
Prepared By:	[redacted]

I have read and approve the protocol specified above and agree on its content:

Novavax Representatives:

Electronically signed

[redacted] _____ _____
Date

Electronically signed

[redacted] _____ _____
Date

Clinical Study Site:

_____ _____
Print Name – Principal Investigator Date

_____
Signature

A PHASE 3, RANDOMIZED, OBSERVER-BLIND, PLACEBO-CONTROLLED, GROUP-SEQUENTIAL 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

Investigational Material:	Respiratory Syncytial Virus (RSV) Recombinant F Nanoparticle Vaccine (*Spodoptera frugiperda* [*Sf9*] cells with recombinant Baculovirus expression) with aluminum phosphate adjuvant (herein referred to as aluminum)
Reference Material:	Formulation buffer (placebo)
Protocol Number:	RSV-M-301
Short Title:	A Study to Evaluate the Efficacy of Maternal Immunization with RSV F Vaccine in Preventing RSV Lower Respiratory Tract Infection in Young Infants
Sponsor:	Novavax, Inc. (Novavax) 20 Firstfield Road Gaithersburg, MD 20878 USA
Responsible Clinical Operations Manager:	[redacted] Novavax, Inc. Office: [redacted] Mobile: [redacted] Email: [redacted]
Version – Date:	10.1 – 12 October 2018
Prior Version(s):	10.0 – 02 October 2018 9.0 – 21 July 2017 8.0 – 23 August 2016 7.0 – 15 July 2016 6.0 – 09 May 2016 5.0 – 09 February 2016 4.0 – 08 January 2016 3.0 – 09 July 2015 2.0 – 11 June 2015 1.0 – 20 April 2015

PROTOCOL CHANGE HISTORY

Protocol Version 10.1, 12 October 2018 (revised from 10.0, 02 October 2018)

The following is a summary of the changes made to this version of the protocol.

Location of Change	Change/Modification in Version 10.1
Protocol Title on Title page and Synopsis	• The title of the study has been reverted to the original title from Version 9.0 by the addition of "group-sequential". Version 10.1 is otherwise identical to Version 10. **Rationale**: Protocol RSV-M-301 was originally designed as a group-sequential study and all subjects were enrolled under prior versions of the protocol (Version 9 or earlier) in which the study design was specified as group-sequential. Version 10 of the protocol removed the group sequential study design as the Sponsor decided that the first analysis with the ~4600 subjects enrolled to date would be the final analysis. The rationale to stop the study and conduct the final analysis is that the minimum required safety database of at least 3000 active subjects has been met and the Sponsor believes the trial has adequate power to make a statistically sound conclusion based on the aggregate number of blinded primary endpoint cases accrued and the projected placebo attack rate of 3-4%. To ensure continued traceability between the current protocol and the numerous study-related documents which include the protocol title, "group-sequential" will be retained in the protocol title.

Protocol Version 10.0, 02 October 2018 (revised from 9.0, 21 July 2017)

The following is a summary of the changes made to this version of the protocol.

Note: A complete tabular summary of changes made to previous versions of the protocol has been provided in Appendix 5.

Location of Change	Change/Modification in Version 10.0
Study Title	• The title of the study has been updated by the removal of "group-sequential". **Rationale**: As a group-sequential design with multiple interim analyses is no longer planned, the reference to the phrase has been deleted from the study title.
Section 1.7, Synopsis	• The sentence, "Two recent reports of prospective studies have confirmed the existence of a symptomatic RSV disease burden in mothers [Hause 2018, Madhi 2018].", has been added and referenced. **Rationale:** This statement updates the current knowledge of the burden of RSV illness in pregnancy based on recent publications.

Location of Change	Change/Modification in Version 10.0
Section 2.1, Synopsis	• The words "through the first" have been added before the enumeration of the 120, 150, and 180 day intervals. • The sentence "Success will be demonstrated under the primary hypothesis that the event ratio (RSV F Vaccine/Placebo is ≤ 0.70 (i.e., vaccine efficacy is ≥ 30%" has been modified to: "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 (lower bound of a 95% confidence interval for later time points) for the estimate of vaccine efficacy which equals or exceeds target values agreed with regulatory authorities." **Rationale:** The words "through the first" were added to clarify that the successive 120, 150, and 180 day analyses are intended to span the entire intervals from delivery through the specified days. This is a clarification and not a change to the intended analysis. The sentence concerning the success criteria for the primary objective has been modified to reflect the Type 1 error rate agreed with the US-FDA. The target values to be exceeded vary from jurisdiction to jurisdiction and have now been specified in Section 10.4.3.
Section 2.2, Synopsis	• "in infants" has been added to the closed bullet sentence "to determine the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence **in infants** of". **Rationale:** These words were added to clarify the precise subject population being referenced in the objective. • The two open bullet objectives: "RSV LRTI with severe hypoxemia (SpO_2 < 92% at sea level or < 87% at altitudes > 1800 meters) or the need for high flow nasal cannula, or mechanical ventilatory support" and "RSV LRTI leading to hospitalization" have been modified as (shown in **bold**): 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 **through** 120, 150, and 180 days of life.

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	and 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. **Rationale:** The wording of these two important secondary endpoints was altered to: a) provide more specific enumeration of methodologies used for respiratory support in infants that are more advanced than simple oxygen supplementation by standard flow-rate nasal cannula and imply greater compromise and b) to clarify that, as in the case of the primary endpoint, successive analyses consider the intervals from delivery through 90, 120, 150, and 180 days of life, inclusive. • The following sentence has been <u>added</u>: "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%." **Rationale:** The above sentence has been added to clarify the population to be used to support the analysis of the secondary endpoints. This is a clarification, not a change of the protocol. • The following open bullet secondary objective has been <u>recategorized as exploratory</u>: "RSV LRTI resulting in death" **Rationale:** This endpoint has been downgraded to exploratory status, based on the very low incidence rate of RSV-related death in populations with access to adequate supportive care – which precludes statistically robust conclusions. • The following two secondary objectives have been <u>recategorized as exploratory</u>: "To determine the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of all RSV LRTI 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." and "To determine the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence of healthcare interventions associated

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	with wheezing through the first year of life in infants of maternal RSV F vaccinees as compared to placebo recipients." **Rationale:** The first of these objectives was downgraded to exploratory status because the endpoint, while potentially medically meaningful is very heterogeneous and unsupported by any objective measure other than documentation of RSV recovery from the nasopharynx. The second was downgraded to exploratory status because of the uncertain reliability of parental reports of wheezing as a driver for medical intervention.
Section 2.3, Synopsis	• The following exploratory objectives have been <u>added</u>: o 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. o 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. o 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. o 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

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	records for infants undergoing hospitalization for a respiratory serious adverse event. o 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. o To describe the efficacy of maternal immunization with the RSV F vaccine in reducing the incidence in infants of all RSV LRTI. o 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. • The following note has also been added "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." **Rationale:** The first three of these objectives mirror the primary and two secondary objectives, but allow for the inclusion of data derived from the adequately documented medical observations of non-study medical personnel, using pulse oximeters and/or diagnostic tests not supplied by the sponsor but in use within local clinics and/or hospitals. While these do not have the standardization or validation of the protocol-mandated primary or secondary efficacy endpoint parameters, they allow for the inclusion of many observations concerning infants transported directly to hospital for the evaluation and treatment of medically-important respiratory illnesses, as well as infants first evaluated at the clinical sites, who then subsequently deteriorated and fulfilled the endpoint criteria while inaccessible to the investigators in hospitals or emergency departments. This broader definition allows for capture of RSV LRTI cases which may have evaded direct observation by site personnel. The fourth new exploratory objective has been added to capture medically-significant RSV LRTI characterized by hypoxemia or a level of tachypnea approximately 10 breaths per minute lower than that used to define the primary endpoint. This lower level of tachypnea is specified by the WHO Handbook for Integrated Management of Childhood Illness, and may represent illness of sufficient severity to trigger (potentially inappropriate) therapy and/or consideration of hospitalization; thus imposing a healthcare resources burden. Three of these exploratory objectives have been shifted from the secondary objective list for the reasons listed above under Section 2.2.
Section 3.1, Synopsis	• The first paragraph of the study design description has been <u>modified</u> as follows:

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	The total number of enrolled maternal subjects has been updated from approximately 8,618 to approximately 4,600. The following sentence has been <u>added</u>: "Randomization will be configured to provide approximately 3,000 exposures to the active test article." The following sentence has been <u>deleted</u>: "Although the trial is projected to enroll an estimated 8,618 third-trimester pregnant subjects, numbers may be smaller based on the operation of the group-sequential design (see details in Section 3.2), the incidence rate of the primary clinical endpoint events, and the efficacy of the intervention." **Rationale:** It has been determined to terminate the trial at a total enrollment of approximately 4,600 pregnant women because the accrual rate of primary endpoints renders a statistically robust conclusion concerning the primary endpoint likely, which is congruent with the provisions of Section 6.6. In addition, the enrolled number of approximately 4,600 pregnant women, in conjunction with the 1:1 randomization in season one and 2:1 subsequently, is sufficient to yield ≥ 3,000 pregnant women in the active treatment group, thereby providing a safety database sufficient to observe, with 95% confidence, at least one instance of a unique vaccine-related event. Because the protocol will no longer follow a group-sequential design, mention of the operation of such a design is deleted. • Table 1 has been <u>updated</u> to provide approximate number of subjects in treatment groups, i.e., Group A ~ 1,562 (originally 2,930) and Group B ~ 3,038 (originally 5,688). **Rationale:** Table 1 has been modified the approximate number of subjects to be included in the two treatment groups based on the new final enrollment target and the randomization scheme. • The last sentence "A Data and Safety Monitoring Board (DSMB) will supervise enrollment and monitoring of subject safety throughout the trial" has been <u>extended to include the following</u>: "A Data and Safety Monitoring Board (DSMB) will supervise enrollment and monitor subject safety throughout the trial (see Section 8.10**). In order to ensure that mothers and infants are not placed at risk with scant possibility of success, repeated futility analyses will be performed twice per year during the period of the study**. 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 is not consistent with a predefined 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

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	30 September, comprising a Northern hemisphere season and the following Southern hemisphere season); and subject to constraint (applied by the 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. **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 LRTI in infants from delivery through the first 90 days of life. If successful outcomes are obtained through 90 days of life, then additional analyses for efficacy will be performed in a closed hierarchical sequence considering data from delivery 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 10.4.2). Only endpoints validated by CEAC review will be used for the efficacy analyses. Section 10.4.3 provides details of the futility and efficacy analyses**." **Rationale:** The above additions to the final paragraph of Section 3.1 replace closely similar or identical text in the prior Section 3.2 of protocol version 9.0, which described the operation of the group-sequential design and has now been deleted. The added text describes the rationale for repeated futility analyses (which have occurred throughout the life of the trial), the timing of those analyses as driven by the seasonality of RSV disease, and the planned DSMB response to a determination of futility. The section concludes with a general description of the primary efficacy analysis concerning medically-significant RSV LRTI from delivery through 90 days of life, followed by a closed hierarchical sequence of tests through 120, 150, and 180 days of life. This description is unchanged from the prior Section 3.2. In addition, reference is made to the introduction of a Clinical Endpoint Adjudication Committee (CEAC), a group of pediatricians who will examine the data content, and temporal sequencing of that content, of each primary, secondary, and infant RSV illness exploratory endpoint to ensure that these fulfill the relevant definitions in a clinically reasonable temporal sequence.
Section 3.2, Synopsis	• The section "Group Sequential Design Strategy" has been deleted in its entirety. **Rationale:** As a group-sequential design with multiple interim analyses is no longer planned, the prior Section 3.2 has been deleted *in toto.* Information that remains relevant concerning the DSMB, futility analysis strategy, and overarching efficacy analysis plan are incorporated into Section 3.1 (see above). Note that this change alters the subsection numbering within Section 3, with the description of endpoints (prior Section 3.3) now forming Section 3.2.

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Section 3.2.1, Synopsis	• The language to describe the primary efficacy endpoint has been clarified from "incidence of medically-significant RSV LRTI" to "**Percentages of infants with** medically-significant RSV LRTI through 90, 120, 150, and 180 days of life." **Rationale:** The description of all efficacy endpoints has been amended to more specifically state that the endpoints are in fact Percentages of subjects with a given clinical disease state. These counts will be used to calculate incidence rates and perform statistical contrasts. This is a change for clarity and consistency only, it does not affect the execution of the trial or the efficacy analyses. • The following sentences have been <u>deleted</u>: "The primary analysis will consider term infants (≥ 37 weeks of gestation at delivery) of mothers who received test article ≥ 2 weeks prior to delivery. Analyses at 120, 150, and 180 days of life will be performed dependent on successful outcomes at the prior, shorter intervals." "Note that, where it appears as a component of secondary or exploratory endpoints, the term "RSV LRTI" will be defined by the first two major bullet points above, with the additional characteristic specified in that particular endpoint, e.g., hospitalization." **Rationale:** The first sentence, specifying the primary analysis population, has been relocated to the primary objective description (Section 2.1). The second sentence has been removed as unnecessary; all conditions required for any given endpoint are now described within the endpoint. Neither of these changes affect the execution of the trial or the efficacy analyses. • The following sentences have been <u>added</u>: "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 10.4.2) 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."

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	Rationale: The first sentence above specifies the exact source of the data supporting the primary endpoint events. This sentence is a clarification and represents no change in the execution or analysis of the trial. The second sentence indicates that the primary endpoint events will be subject to review and validation by an independent, blinded committee of pediatricians prior to inclusion in the primary efficacy analysis. This Clinical Endpoint Adjudication Committee has been added to ensure that temporally or clinically implausible events are not included in the analyses.
Section 3.2.2, Synopsis	• The two secondary efficacy endpoints have been <u>modified</u> as follows: Percentages of infants with 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) 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: o RSV infection as confirmed by detection of the RSV genome by RT-PCR, AND o 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 o 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). – and 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:

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	○ 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. • **Rationale:** The endpoints described correspond to the secondary objectives. The description of the endpoints has been modified for clarity to utilize the terminology of "Percentages" and include all of the elements necessary for each endpoint. The endpoint relating to severe hypoxemia has been modified to provide specific enumeration of methodologies used for respiratory support in infants that are more advanced than simple oxygen supplementation by standard flow-rate nasal cannula and imply greater compromise. The endpoint relating to hospitalization is unchanged in content. • The following sentences have been <u>added</u>: "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 PAP, intubation, or mechanical 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 10.4.2) 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." **Rationale:** As above for the primary endpoints, the first sentence above specifies the exact source of the data supporting the secondary endpoint events. This sentence is a clarification and represents no change in the execution or analysis of the trial. The second sentence indicates that the secondary endpoint events will be subject to review and validation by an independent, blinded committee of pediatricians prior to inclusion in the secondary efficacy analysis. This Clinical Endpoint Adjudication Committee has been added to ensure that temporally or clinically implausible events are not included in the analyses.

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	• The following original secondary endpoints have been removed as secondary endpoints and placed under exploratory endpoints: "Incidence of RSV LRTI resulting in death in infants through 90 days of life," "Incidence of RSV LRTI (all severities) in infants through 90 days of life. "Incidence of healthcare interventions associated with wheezing through the first year of life." **Rationale:** In parallel with changes in the secondary objectives, these three endpoints have been downgraded to exploratory endpoints.
Section 3.2.3	• "seroconversion rate, SCR [maternal subjects only]" has been added to the first bullet of the immunogenicity endpoints. • It has been specified that micronuetralization titers "may be generated for a subset of the population". The following sentence has been added: "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." **Rationale:** These changes correct the omission of the term "seroconversion rate" from prior versions (the analyses were planned and were represented as "2- and 4-fold rises) and provide an expectation for the schedule of completion of microneutralization.
Section 3.2.4	• The language used to describe the safety endpoints has been changed from "counts and percentages" to "percentages" for all safety endpoints. **Rationale:** To be more specific in describing how the safety endpoints will be described.
Section 3.2.5, Synopsis	• The following seven exploratory endpoints have been <u>added</u>: o 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. o 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

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	(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. o 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. o 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. o 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. o 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. o Counts and incidence rates of infant healthcare interventions associated with wheezing through the first year of life. **Rationale:** In parallel with the first three new exploratory objectives, these changes to the exploratory endpoints mirror the primary and secondary endpoints, but allow for the inclusion of data derived from the adequately documented medical observations of non-study medical personnel, using pulse oximeters and/or diagnostic tests not supplied by the sponsor but in use within local clinics and/or

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	hospitals. While these do not have the standardization or validation of the protocol-mandated primary or secondary efficacy endpoint parameters, they allow for the inclusion of many observations concerning infants transported directly to hospital for the evaluation and treatment of medically-important respiratory illnesses, as well as infants first evaluated at the clinical sites, who then subsequently deteriorated and fulfilled the endpoint criteria while inaccessible to the investigators. This broader definition allows for capture of RSV LRTI cases which may have evaded direct observation by site personnel. The fourth new exploratory endpoint parallels the fourth new exploratory efficacy objective and is intended to evaluate efficacy against RSV LRTI characterized by hypoxemia or tachypnea consistent with the WHO Handbook for Integrated Management of Childhood Illness. The fifth, sixth, and seventh new exploratory endpoints represent three prior secondary endpoints moved to exploratory status in parallel with the related objectives. In addition, the fifth and sixth new exploratory endpoints permit the use of well-documented medical record data in the ascertainment of RSV LRTI. o The following text has been <u>added</u>: "A Clinical Endpoint Adjudication Committee (CEAC) composed of expert pediatricians (see Section 10.4.2) 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." **Rationale:** This summary paragraph indicates the introduction of a committee of expert pediatricians to adjudicate all endpoint cases involving RSV disease in infant subjects to ensure that these endpoints fulfill the requisite criteria and are temporally and clinically plausible before their use in efficacy analyses. • The endpoint: "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)", has been modified by the additional of the text in bold. **Rationale:** To clarify the source of data for the referenced endpoint.
Section 3.3	• The second sentence of Section 3.3 has been <u>modified</u> to delete mention of the group-sequential design as a determinant of study duration. **Rationale:** As the trial will no longer be governed by a group-sequential design, this reference is now irrelevant. The estimated total duration remains

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	approximately four years, considering completed safety follow-up on the last infant born.
Section 3.5	• The first sentence of Section 3.5 has been modified to specify a total enrollment of **approximately 4,600 women and their infants**. **Rationale:** With the decision to terminate enrollment and delete the group-sequential design, the final enrollment target of approximately 4,600 pregnant women can be specified; the additional specification of their infants is a clarification.
Section 7.2	• The first sentence of this section has been modified to indicate that immunologic testing will be performed on subjects' sera "at protocol-specified time-points." In addition, the following sentence has been added: "Completion of microneutralization testing may be staged, due to its cumbersome nature, and results may be reported in addenda to the primary clinical study report." **Rationale:** Sera that are collected outside protocol-defined windows may not be contributory to the overall analysis of immunogenicity and may not undergo testing. Micronuetralization testing requires substantially greater time and technician/supervisor hours per assay than anti-F IgG or PCA ELISA, and may therefore impede progress to the initial report of study results. Therefore, the option to complete microneutralization testing in a staged manner with reporting in addenda to the final study report is provided.
Section 8.6	• The following sentence has been added to the end of the first paragraph. "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)." **Rationale:** The sentence provides clarity on how the GA at birth will be determined.
Section 8.10	• The phrase "or for demonstration of efficacy" has been deleted. • The sentence "the DSMB may elect, based on a vote of the members, to meet less frequently (e.g. quarterly), after the first year of the study" has been added. **Rationale:** The changes have been applied to provide clarity on the functioning of the data and safety monitoring board (DSMB).
Section 10.1	• A separate definition of the infant safety population has been added to distinguish it from the maternal safety population. The infant safety population (Safety-I) has been defined as all infants born live to maternal subjects who received any test article. • "and post-partum, respectively" has been added to the intent-to-treat efficacy population definition. • Phrases "post-treatment" and "and have no major protocol deviations affecting the primary efficacy outcomes as determined and documented by Novavax

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	prior to database lock and unblinding" have been added to the definition of the per-protocol efficacy population for maternal subjects. • Phrases "between birth and Day 180 after delivery" and "and e) have no major protocol deviations affecting the primary efficacy outcomes as determined and documented by Novavax prior to database lock and unblinding" have been added to the definition of the per-protocol population for infant subjects. **Rationale:** These additions are intended to add clarity to the population definitions; they do not alter the underlying analysis plan.
Section 10.4.1.2, Synopsis	• The definition of symptomatic RSV infection in maternal subjects has been modified with the addition of the text in bold. 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. **Rationale**: To clarify the source of data for the referenced endpoint.
Section 10.4.1.1	• The definition of RSV LRTI with severe hypoxemia has been changed from "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" to "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 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)." **Rationale:** This altered definition reflects the specific enumeration of respiratory support modalities in the secondary and exploratory endpoints.
Section 10.4.2	• This section has been <u>added</u> to present information about the CEAC. The following text has been added: "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 infant 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

Location of Change	Change/Modification in Version 10.0
	CEAC with regard to each endpoint event will be final and binding on the sponsor." **Rationale:** This paragraph describes the projected membership and operations of the Clinical Endpoint Adjudication Committee (CEAC) of expert pediatricians which has been empaneled to adjudicate all endpoint cases involving RSV disease in infant subjects. The goal of this is to ensure that these endpoints fulfill the requisite criteria and are temporally and clinically plausible before their use in efficacy analyses.
Section 10.4.3	• The section has been updated to reflect aforementioned changes to the study objectives and endpoints and the decision to eliminate the group-sequential design strategy. The section has been updated to include the following new text: "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 2-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 report as Appedix 1 in the SAP. 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

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	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 ≤ 0% and H_0: VE < 30%. Rejection of the first null hypothesis, H_0: VE ≤ 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. The null hypothesis, H_0: VE ≤ 0%, using the 1-sided Type I error rate (i.e., lower bound of 2-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 will 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.” **Rationale:** This text introduces the plan to eliminate the group-sequential design, convert the primary analysis to a frequentist approach, avoid Type 1 error inflation due to the decision to stop the study early at ~4600 maternal subjects, and summarizes the three different analytical uses of the primary efficacy data. The section then continues as originally worded to describe the Bayesian methods already used in the futility and informational analyses to date.

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Section 10.5	• The phases "(2- and 4-fold seroconversion rates [SCR])" have been added to numbered items 1 and 2. **Rationale:** To be consistence within the document.
Section 10.6	• The phrase "Counts and percentages" for the assessment of safety endpoints has been replaced with "percentages" **Rationale:** To provide precision on how the safety endpoints will be described.
Section 10.7	• The following text has been added: "The relative risk (RR) and its 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. 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." **Rationale**: The original text has been modified and new text has been added to better describe the analyses regarding the updated proposed exploratory objectives of the study.
Section 10.8	• The original text has been deleted entirely and replaced with the following: "This study is designed to enroll approximately 4,600 total 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

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	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%." **Rationale:** Because of the conversion from a Bayesian analysis of a group-sequential design to a single final analysis based on frequentist methodology, the prior Bayesian simulation-based summary of operating characteristics for implementation of the group-sequential design have been replaced by a frequentist power calculation for a range of placebo attack rates consistent with the literature and a panel of potential vaccine efficacies and considering the single target enrollment and known randomization ratio.
Section 10.9	• It has been clarified that "interim" analyses refer to futility and informational analyses.
Section 10.10.1	• The original text has been deleted entirely and replaced with the following: "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 when all live-born infants of all enrolled pregnant mothers have completed 180 days of follow-up after delivery, a final Day 180 Unblinded Analysis of Efficacy, Immunogenicity, and 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 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 of these data are monitored, all applicable queries are resolved, and the database is locked. The data 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

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	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 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 ≥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. 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." **Rationale:** In parallel with Sections 10.4.3 and 10.8, this text outlines the temporal sequence of futility analyses, the implementation of an informational analysis, and the plan to trigger a single final efficacy analysis when all live-born infants of enrolled mothers have completed Day+180 follow-up.
Section 10.10.3	• The following text has been deleted: "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." **Rationale:** To avoid redundancy.
Section 12	• The following 3 references have been added: o Hause AM, Avadhanula V, Maccato ML, et al. A cross-sectional surveillance study of the frequency and etiology of acute respiratory illness among pregnant women. J Infect Dis 2018; 218:528-35. o Madhi SA, Cutland CL, Downs S, et al. Burden of respiratory syncytial virus infection in South African human immunodeficiency virus (HIV)-infected and HIV-uninfected pregnant and postpartum women: a longitudinal cohort study. Clin Infect Dis 2018; 66(11):1658-65.

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	o Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159(7):702-6.
General	Minor changes have been made to improve the readability of the document.

TABLE OF CONTENTS

LIST OF TABLES

GLOSSARY OF ABBREVIATIONS

Abbreviation or Term	Definition
AD	After Delivery
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
ASQ	Ages and Stages Questionnaire
AST	Aspartate Aminotransferase
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
bpm	Breaths per Minute
BUN	Blood Urea Nitrogen
C	Celsius or Caesarean
CBC	Complete Blood Count
CBER	Center for Biologics Evaluation and Research
CD	Compact Disc
CEAC	Clinical Endpoint Adjudication Committee
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CPE	Cytopathic Effect
CQA	Clinical Quality Assurance
CRO	Contract Research Organization
CSR	Clinical Study Report
CVS	Chorionic Villus Sampling
DSMB	Data and Safety Monitoring Board
EC	Exclusion Criterion
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDD	Estimated Date of Delivery
EDD-E	Estimated Date of the Earliest Delivery
EDD-L	Estimated Date of the Latest Delivery

Abbreviation or Term	Definition
ELISA	Enzyme-linked Immunosorbent Assay
EU	ELISA Unit
FDA	Food and Drug Administration
FI-RSV	Formalin Inactivated-Respiratory Syncytial Virus
FOC	Frontal Occipital Head Circumference
GA	Gestational Age
GBS	Group B Streptococcus
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMC	Geometric Mean Concentration
GMEU	Geometric Mean ELISA Unit
GMFR	Geometric Mean Fold-rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GP	General Practitioner
GSD	Group Sequential Design
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
IBG	Independent Biostatistical Group
IC	Inclusion Criterion
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IM	Intramuscular
IRB	Institutional Review Board
ISP	Instituto de Salud Pública de Chile
ITT	Intent-to-treat
IVF	*In vitro* Fertilization
IWRS	Interactive Web Randomization System
kg	Kilogram

Abbreviation or Term	Definition
L	Liter
LMP	Last Menstrual Period
LRTI	Lower Respiratory Tract Infection
M	Molar Concentration
MAE	Medically-attended Event
MCC	Medicines Control Council
MedDRA	Medical Dictionary for Regulatory Activities
MEDSAFE	Medicines and Medical Devices Safety Authority
MFNAESI	Maternal/Fetal/Neonatal Adverse Event of Special Interest
µg	Microgram
µM	Micromolar
mg	Milligram
mL	Milliliter
mM	Millimolar
MN	Microneutralization; an assay
MS	Maternal Serum
NaCl	Sodium Chloride
ng	Nanogram
NOAEL	No-Observed-Adverse-Effect-Level
OD	Optical Density
PCA	Palivizumab-Competitive Antibody
PCP	Primary Care Physician
PP	Per Protocol
PPS	Predictive Probability of Success
PT	Preferred Term
RBC	Red Blood Cell
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
Sf9	*Spodoptera frugiperda* — Insect Cells
SMS	Short Message Service (i.e., text messaging)

Abbreviation or Term	Definition
SNMC	Significant New Medical Condition
SOC	System Organ Class
SpO_2	Peripheral Oxygen Saturation
SRR	Seroresponse Rate
Tdap	Tetanus, Diphtheria, Acellular Pertussis; a vaccine
TGA	Therapeutic Goods Administration
TGS	Toxicity Grading Scale
Th2	T Helper Cell Type 2
TIV	Trivalent Influenza Vaccine
TMB	3, 3'5, 5-tetramethyl-benzidine
TMF	Trial Master File
US	United States
WBC	White Blood Cell
WHO	World Health Organization
yo	Years of Age

CLINICAL PROTOCOL SYNOPSIS

NAME OF COMPANY Novavax, Inc.	**INDIVIDUAL STUDY TABLE SYNOPSIS**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF ACTIVE INGREDIENT RSV Recombinant F Nanoparticle Vaccine		

Protocol Number: RSV-M-301

Protocol Title: A Phase 3, Randomized, Observer-Blind, Placebo-Controlled, Group-Sequential 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

Clinical Development Program: Maternal Immunization for Prevention of RSV Lower Respiratory Tract Infection (LRTI) in Infants

Sponsor: Novavax, Inc., 20 Firstfield Road, Gaithersburg MD 20878 USA

Investigational Material: RSV Recombinant F Nanoparticle Vaccine (*Spodoptera frugiperda* [Sf9] cells with recombinant Baculovirus expression) with aluminum

Reference Material: Formulation buffer (placebo)

Regimen and Dosing: Maternal subjects will receive a single 0.5 mL intramuscular (IM) injection with the assigned test article, either a 120 µg dose of RSV F protein adsorbed to a 0.4 mg dose of aluminum as the phosphate salt (herein referred to as RSV F vaccine) or placebo, on Study Day 0.

Phase of Development: Phase 3

Rationale:

The goal of this clinical development program is to establish efficacy of the RSV F vaccine in 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]. Two recent reports of prospective studies have confirmed the existence of a symptomatic RSV disease burden in mothers [Hause 2018, Madhi 2018].

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 immunoglobulin G (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 of infants 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 with binding activity to the antigenic sites I and IV 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. Please refer to the Investigator's Brochure (IB) for current updates and new findings pertaining to the RSV F vaccine.

Study Definitions:

Infant Subjects

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).
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.

Maternal Subjects

Symptomatic RSV Infection:	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.

Study Objectives:

***Primary*:**

The primary objective of this study is:

- 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 (lower bound of a 95% confidence interval for later time points) for the estimate of vaccine efficacy which equals or exceeds target values agreed with regulatory authorities.

Secondary:

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 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 through 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.

Exploratory:

The exploratory objectives of this study are:

- 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 (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) 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 [SpO_2] < 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.

Study Endpoints:

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 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 10.4.2) 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.

Secondary Efficacy Endpoints *(In Infant Subjects)**:***

- Percentages of infants with 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) 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 10.4.2) 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.

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 correlates 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, 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

Safety Endpoints:

In 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.

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:
    - 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.

Exploratory/Informational Endpoints *(In Maternal and Infant Subjects as Stated)**:***

- 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 10.4.2) 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.

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.

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 three months prior to peak RSV season as shown in Treatment Assignments. After the first global season of enrollment, the randomization scheme will be changed 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. Please refer to the **Study Operations Manual** for further details.

Treatment Assignments

Treatment Group	Target Maternal Subjects/Group[1]	Test Article	Dosing Volume	Vaccination Day
A	~ 1562	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 (see Infant Subject Study **Visit**). It is anticipated that a percentage of the randomized maternal subjects and their delivered infant 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, either the RSV F vaccine or placebo (see Treatment Assignments table). The procedures to be performed in the study are described in detail in this protocol and are summarized in the Maternal Subject Study Visit and Infant Subject Study Visit Procedures sections. Maternal subjects will be monitored for typical vaccine reactogenicity, clinical laboratory impacts, and specified adverse pregnancy outcomes, as well as general AEs and SAEs. In addition, because the maternal illness and obstetrical risk burden due to RSV is largely unknown, the occurrence of RSV disease in maternal subjects will be monitored before and after delivery.

Vaccine impacts on markers of infant development and well-being at birth will be monitored, as will growth and development through the first year of life. Infant blood samples will be taken to assess the decay half-life of maternally-derived RSV antibodies. Symptomatic infant and maternal RSV infections will be monitored through the first RSV season using both active and passive surveillance mechanisms; and will be etiologically-confirmed using RSV RT-PCR. Infant RSV infections will be characterized based on their symptomatology, associated degree of hypoxemia as measured by pulse oximetry, respiratory rate as measured by observation for 1 minute, and required medical interventions.

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.

A Data and Safety Monitoring Board (DSMB) will supervise enrollment and monitor subject safety throughout the trial (see Section 8.10). In order to ensure that mothers and infants are not placed at risk with scant possibility of success, repeated futility analyses will be performed twice per year during the period of the study. 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 is not consistent with a predefined 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 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.

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 LRTI in infants from delivery through the first 90 days of life. If successful outcomes are obtained through 90 days of life, then additional analyses for efficacy will be performed in a closed hierarchical sequence considering data from delivery 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 10.4.2). Only endpoints validated by the CEAC review will be used for the efficacy analyses. Section 10.4.3 provides details of the futility and efficacy analyses. (see Section 8.10).

Eligibility Criteria:

Inclusion:

Pregnant women must meet all of the following criteria to be eligible for participation in the study:

1) ≥ 18 and ≤ 40 years-of-age (which connotes a lower limit of 18 years and 0 days and an upper limit of 40 years and 0 days).
2) Singleton pregnancy of 28 to $36^{0/7}$ weeks gestation on the day of planned vaccination. Documentation of gestational age will be based on one of the following composite criteria *(Note: The investigator should use the earliest ultrasound data available to establish the study-specific gestational age dating)*:
   (a) Gestational Age Dating Based on First Trimester Data (data obtained ≤ $13^{6/7}$ weeks):

   The date of the first day of the reported last menstrual period (LMP) may be used to establish the gestational age if corroborated by a first trimester ultrasound. If the gestational age estimation derived using the LMP and the first trimester ultrasound are discrepant by > 7 days, the ultrasound will be used to establish the gestational age.

   If LMP is uncertain or unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

   (b) Gestational Age Dating Based on Early Second Trimester Data (data obtained $14^{0/7}$ to $21^{6/7}$):

   The date of the first day of the reported LMP may be used to establish the gestational age if corroborated by an early second trimester ultrasound (that estimates the gestational age between $14^{0/7}$ and $21^{6/7}$ weeks). If the gestational age estimation derived using the LMP and the early second trimester ultrasound are discrepant by > 10 days, the ultrasound will be used to establish the gestational age.

   If LMP is uncertain of unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

   (c) Gestational Age Dating Based on Later Second Trimester Data (data obtained $22^{0/7}$ to $27^{6/7}$ weeks by LMP):

   The date of the first day of the reported LMP may be used to establish the gestational age if corroborated by a later second trimester ultrasound (that estimates the gestational age between $22^{0/7}$ to $27^{6/7}$ weeks). If the gestational age estimation derived using the LMP and the later

second trimester ultrasound are discrepant by > 14 days, the ultrasound will be used to establish the gestational age.

If LMP is uncertain or unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

(d) Gestational Age Dating When the LMP is Uncertain or Unknown AND No Prior First or Second Trimester Ultrasound Has Been Performed:

An ultrasound performed at screening within the second trimester ($\leq 27^{6/7}$ weeks) will be used to establish the gestational age dating.

3) Documentation of a second or third trimester (between $18^{0/7}$ weeks and prior to randomization) ultrasound with no major fetal anomalies identified.

4) Good general maternal health as demonstrated by:

- Medical history (including history of clinically significant adverse reactions to prior vaccines and allergies).
- Physical examination including at least vital signs (blood pressure, pulse, respirations, and axillary body temperature); weight; height; examination of the HEENT, cardiovascular, pulmonary, gastrointestinal (abdominal), musculoskeletal, lymphatic, and dermatologic organ systems; and documentation of fetal heart tones. Note that abnormal vital signs may be repeated at the investigator's discretion since these measures may be labile. Vital signs should be assessed in the context of normal values for the third trimester of pregnancy (see the **Study Operations Manual**).
- Clinical laboratory parameters that include:
  - For the first year of study conduct in any country, normal/clinically insignificant blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), hemoglobin, white blood count, and platelet count. Note that normal ranges for clinical laboratory parameters will be based on reference ranges appropriate for the third trimester of pregnancy, specified in the toxicity grading scale (TGS) provided in the **Study Operations Manual**) and should be referenced to assess for any abnormalities. This testing should be performed by the central laboratory.
  - For all subjects, serologic exclusion of infection with hepatitis B (HBV) and C (HCV) viruses, syphilis, and HIV as documented by testing (performed at the central or local laboratory) at screening or by medical records during the current pregnancy.

5) Able to understand, and both willing and physically able to comply with study procedures. This includes anticipation of reasonable geographic proximity to the study clinic and adequate transportation to comply with scheduled and unscheduled study follow-up visits.

6) Able and willing to provide written informed consent for themselves and infant.

Exclusion:

Pregnant women will be excluded if there is historical, physical examination, or laboratory evidence of any of the following:

1) Symptomatic cardiac or pulmonary disease requiring chronic drug therapy, including hypertension and asthma. Asthma will be exclusionary if the subject is receiving chronic systemic

glucocorticoids at any dose or inhaled glucocorticoids at any dose > 500 µg per day of beclamethasone or fluticasone, or > 800 µg per day of budesonide.

2) Pregnancy complications (in the current pregnancy) such as preterm labor, hypertension (blood pressure [BP] > 140/90 in the presence of proteinuria or BP > 150/100 with or without proteinuria) or currently on an antihypertensive therapy, or pre-eclampsia, or evidence of intrauterine growth restriction.
3) Grade 2 or higher clinical laboratory or vital sign abnormality. Exclusion of subjects with grade 1 abnormalities will be based on the subject's prior medical history and the investigator's clinical judgment that the abnormality is indicative of a meaningful physiologic event.
4) Receipt of any licensed vaccine (e.g., Tdap, inactivated influenza vaccine) within 14 days of study vaccination.
5) Received any RSV vaccine at any time.
6) Body mass index (BMI) of ≥ 40, at the time of the screening visit.
7) Hemoglobinopathy (even if asymptomatic) or blood dyscrasias.
8) Hepatic or renal dysfunction.
9) Established diagnosis of seizure disorder, regardless of therapy.
10) Known, active auto-immune disease or immunodeficiency syndrome.
11) Endocrine disorders, including (but not limited to) untreated hyperthyroidism, untreated hypothyroidism (unless due to auto-immune disease), and glucose intolerance (e.g., diabetes mellitus type 1 or 2) antedating pregnancy, or occurring during pregnancy and requiring interventions other than diet for control.
12) History of major gynecologic or major abdominal surgery, including bariatric surgery (previous Caesarean section is not an exclusion).
13) Known HIV, syphilis, HBV, or HCV infection, as assessed by serologic tests conducted during the current pregnancy or as a procedure during the screening period of the study.
14) Primary genital Herpes simplex (HSV) infection during the current pregnancy.
15) Current alcohol or drug abuse based on the investigator's knowledge of present or recent (within the last 2 years) use/abuse of alcohol or illegal or non-prescription drugs.
16) Documentation that current pregnancy results from *in vitro* fertilization (IVF).
17) Documentation that current pregnancy results from rape or incest.
18) Documentation that the infant will be a ward of the state or be released for adoption.
19) History/presence of deep venous thrombosis or thromboembolism, or the use of anticoagulants during pregnancy (the use of low-dose aspirin as prophylaxis [e.g., for the prevention of morbidity and mortality from preeclampsia] is acceptable in dosages consistent with local standards of care).
20) Red blood cell allo-immunization.
21) Prior stillbirth or neonatal death, or multiple (≥ 3) spontaneous abortions.
22) Prior preterm delivery ≤ 34 weeks gestation or having ongoing intervention (medical/surgical) in current pregnancy to prevent preterm birth.
23) Greater than five (5) prior deliveries.

24) Previous infant with a known genetic disorder or major congenital anomaly.

25) Receipt of investigational drugs or immune globulins (with the exception of prophylactic anti-Rho D immune globulin) within six (6) months prior to the administration of the study vaccine.

26) Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study vaccine. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted except for the limit established in exclusion criterion #1.

27) Neuro-psychiatric illness, including a history of severe post-partum depression, deemed likely to interfere with protocol compliance, safety reporting, or receipt of pre-natal care; or requiring treatment with psychotropic drugs (excluding treatment for depression and anxiety).

28) Any other physical, psychiatric or social condition which may, in the investigator's opinion, increase the risks of study participation to the maternal subject or the fetus/infant; or may lead to the collection of incomplete or inaccurate safety data.

29) Acute disease within 72 hours of the day of the planned vaccination (defined as the presence of a moderate or severe illness with or without fever, or an axillary body temperature > 38.0°C).

30) History of a serious adverse reaction (e.g., anaphylaxis) to any prior vaccine.

Maternal Subject Study Visit Procedures:

Up to Two (2) Months Prior to Study Start – Pre-Screening

Obstetrical investigators may, at their discretion, introduce the concept of participation in a third-trimester RSV vaccine trial to women who they regard as potentially fulfilling the inclusion/exclusion criteria. If required by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) having authority, interested women may be asked to provide informed consent in order for the investigator to collect information regarding their general health history, obstetrical history, and results of screening testing performed for the current pregnancy. The screening consent will be for collection of existing data only, and will not provide for any invasive procedure (including phlebotomy). Screening consent may be withdrawn at any time, and will not bind the prospective subject to enroll in the clinical trial or the investigator to offer enrollment.

Day -28 to 0 – Screening (up to four weeks before the planned day of vaccination)

Healthy pregnant subjects, who are considered to be at low-risk of obstetrical complications, ≥ 18 to ≤ 40 years of age (18 years and 0 days to 40 years and 0 days), have provided written Informed Consent for themselves and their infants to participate in the main study, and are able to comply with study requirements, will have the following procedures performed:

- Review of medical history, including history of clinically significant adverse reactions to prior vaccines and allergies.
- Review of the parameters by which the gestational age dating of the current pregnancy was established, to include the LMP (if known), physical examination, and the results of a first-or second-trimester ultrasound.
- Performance of a second trimester (≤ $27^{6/7}$ weeks) ultrasound (if not previously done) that establishes gestational age dating.
- Performance of a second or third trimester ultrasound (if not previously done) that confirms there are no major fetal anomalies.

- Review of obstetrical history to include the following outcomes of previous pregnancies: length of gestation, birth weight, length of labor, type of delivery, fetal/neonatal outcomes, complications of pregnancy, including history of fetal losses and elective abortions.
- Review of surgical history including prior gynecologic, abdominal, or uterine surgery.
- Document results of any Group B streptococcus (GBS) screening (urine or recto-vaginal swab as applicable), or other infectious disease screening (i.e., for syphilis, gonorrhea, Herpes simplex, chlamydia, HBV, HCV, and HIV).
- Administration of a licensed vaccine recommended during pregnancy, if indicated. Note: This dose should be administered at least 14 days before or at least 14 days after the Day 0 vaccination.
- Document current smoking, alcohol, and recreational drug use.
- Document results of gestational diabetes screen.
- Vital signs (blood pressure, pulse, respirations, and axillary body temperature. (*Note that repeat testing may be performed for subjects with any abnormality*), height, and weight.
- Physical examination including the following body systems: HEENT, cardiovascular, pulmonary, gastrointestinal (abdominal), musculoskeletal, lymphatic, and dermatologic; and confirmation of fetal heart tones.
- Blood draw:
  - For RSV baseline serology (20 mL)
  - For subjects participating in the first year of any country: Clinical laboratory assessments (10 mL) for select serum chemistry (i.e., blood urea nitrogen, creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin) and hematology (i.e., hemoglobin, white blood cell [WBC], and platelet counts) parameters as applicable by central laboratory testing; AND HIV, syphilis, HBV, and HCV antigen tests/serologies as required by central or local laboratory testing (i.e., if screening results are not available in prior data collected during the course of the current pregnancy). *Since results of the clinical laboratory testing are needed to confirm subject eligibility, it is recommended this phlebotomy be performed at least two days before the planned Day 0 vaccination.*
  - For subjects participating in all other years in any country: HIV, syphilis, HBV, and HCV antigen tests/serologies (10 mL, as required) by central or local laboratory if screening results are not available in prior data collected during the course of the current pregnancy.
- Medication history, including concomitant medications.
- Query for any AE experienced since informed consent was obtained.

Note that further procedures may be performed at the Investigator's discretion in order to adequately screen subjects against eligibility criteria and/or to confirm medical history. Potential subjects who meet all inclusion criteria and none of the exclusion criteria (see Eligibility Criteria) may be enrolled.

Day 0 – Vaccination (gestational week 28 to $36^{0/7}$)

All subjects who have vital signs taken, fetal heart tones checked, and eligibility reconfirmed will be randomized to a treatment group and infant serology cohort. Information concerning the occurrence of any AE (and SAE specifically) experienced by the subject since informed consent was obtained

will be collected. Subjects will then receive a single IM injection in the deltoid with the assigned study treatment, followed by monitoring in the clinic for approximately 30-60 minutes post vaccination for the occurrence of any local injection site and systemic reactions. Prior to completion of this visit, subject locator information and the delivery center to be utilized will be verified. Vital signs and a fetal heart tone check will be performed approximately 30 minutes (permissive range: 30 - 60 minutes) post-vaccination.

A diary will be distributed to subjects before release from the clinic. Starting on vaccination day and for 6 days thereafter (Day 0 to Day 6 inclusive), subjects will record their oral temperature using a supplied oral thermometer, and any adverse event experienced in their diary, daily. The following local and systemic reactions will be solicited by diary: injection site (local) events – pain, bruising (ecchymosis), redness (erythema), and swelling (edema); systemic events – oral temperature (collected as a continuous variable), chills, muscle pain or aching remote from the injection site (myalgia), joint pain or aching (arthralgia), diarrhea, nausea, vomiting, headache, and fatigue. Subjects will also be asked to record any concomitant medications taken, and to document any unscheduled physician visit or hospitalization associated with an adverse even through to Day 6 (inclusive). Subjects will be instructed to notify the study staff promptly using the 24-hour telephone contact number(s) provided in the diary in the event of any severe (grade 3) solicited or unsolicited AE, new obstetrical complications, or symptoms suggestive of an RSV infection. A separate Study Identification Card will also be issued that indicates the maternal subject is part of an investigational vaccine trial and provides the contact number(s) of obstetrical investigator's study staff. The identification card will also include a list of the clinical signs and symptoms of an RSV infection in adults and infants. In the event the maternal subject experiences symptoms suggestive of an RSV infection, she will be instructed to contact study staff promptly and, if warranted, may be asked to provide a sampling of upper respiratory secretions for detection of respiratory viruses. (Please refer to the RSV Surveillance section for further details.) The next visit will be scheduled before subjects are released from the clinic.

Day 7 (+ 2 days) – In-clinic or Home Follow-up Visit

Subjects will return to the clinic or participate in a home visit for vital sign collection, to review and return their symptom diaries, and to report any unsolicited AEs, MAEs, SNMCs, and SAEs they have experienced and concomitant medications taken for these events. Subjects will also be queried regarding symptoms suggestive of an RSV infection (see Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects table) and, in the event onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses. In addition to normal obstetrical follow-up, including confirmation of fetal heart tones, a physical exam may also be performed to evaluate any adverse event reported. Before release from the clinic, a replacement Study Identification Card will be offered to subjects, if needed, along with a memory aid for them to record any medical events experienced in between extended clinic visits. *(Note that the memory aid is considered a tool that subjects may or may not choose to use, and as such is NOT considered a source document and WILL NOT be collected.)* The next visit will also be scheduled before subjects are released from the clinic.

Day 14 (± 2 days) – In-clinic or Home Follow-up Visit

Subjects will return to the clinic or participate in a home visit for vital sign collection and to report any unsolicited AEs, MAEs, SNMCs, and SAEs they have experienced and concomitant medications taken for these events. Subjects will also be queried regarding symptoms suggestive of an RSV infection (see Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects table) and, in the event onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses. In addition to normal obstetrical follow-up, including confirmation of fetal heart tones, a physical exam may also be performed to evaluate any

adverse event reported. A blood sample will be obtained for RSV serology (20 mL) and (if applicable) clinical laboratory safety (10 mL). If a subject has delivered prior to the Day 14 visit, then the visit will be considered closed and no missed visit protocol deviation will be captured. The single exception is the blood draw for the clinical safety laboratory assessment [which only applies to subjects enrolled in the first year of study conduct in any country] that should be obtained at the Delivery visit.

Before subjects are released from the clinic, a replacement Study Identification Card will be offered to subjects, if needed, and the next visit will be scheduled. Subjects will also be reminded to contact the site to report the onset of labor, any severe or serious AE, any obstetrical complication, or symptom(s) suggestive of an RSV infection. The next visit will also be scheduled before subjects are released from the clinic.

Day 28 (± 2 days) – Telephone/Short Message Service (SMS) Contact, In-clinic, or Home Visit Safety Follow-up

Subjects who have not yet delivered will have a safety follow-up performed as either a telephone/SMS contact visit using an IRB/IEC-approved script (if applicable), an in-clinic visit, or a home visit. At this visit, whether conducted in in-clinic or at a home visit, study staff will assess the general health of the subject and query for any severe unsolicited AE, SAE, SNMC, MAE, clinical symptoms or signs of a suspected RSV illness, or any new obstetrical complication occurring since the last visit, and any concomitant medications taken for these events. Subjects participating in this visit via telephone or SMS and who report any severe or serious adverse event or symptoms suggestive of an RSV infection, may be asked to return to the clinic or schedule a home visit for evaluation of the event(s) to assess any effect(s) it may have on the pregnancy, and to potentially undergo a sampling of upper respiratory secretions for detection of respiratory viruses if symptom onset is within seven (7) days. The same procedures will be performed for subjects participating in this follow-up as an in-clinic or home visit, with the addition that a replacement Study Identification Card will be offered to all subjects (if needed) at the completion of this visit.

Delivery (D) – Hospital Follow-up Visit

Subjects will be counselled to notify the obstetrician of the start of labor and will go to the registered hospital or delivery center for delivery. A venous blood sample (20 mL) for RSV serology should be obtained from the mother any time after hospital admission and optimally up to 12 hours post-delivery, which in extenuating circumstances (such as a delivery on a holiday or weekend), may be obtained up to 72 hours post-delivery. For applicable subjects (i.e., those enrolled in the first year of study conduct in any country) who deliver prior to the Day 14 visit, a venous blood sample (10 mL) for the clinical safety laboratory assessment should also be obtained. A cord blood sample (at least 5 mL) for RSV serology should be obtained by the obstetrician or designee immediately at the time of delivery. If cord blood is not obtained, then this information should be conveyed to the study staff responsible for the infant, so that infant sera may be collected in lieu of the cord blood (see Infant Subject Study Visit at the Delivery Day visit for details). The obstetrician or designee will also collect vital sign data at admission from the subject's medical chart and record all unsolicited adverse events experienced, and concomitant medications taken by, or administered to, the subject since the last visit. *(Note that routine medications for the management of labor and delivery do not need to be recorded.)* In addition, study staff will document the presence of perinatal management (including antibiotic therapy and any medical or surgical interventions for cause) and of any GBS screening result and treatment. Study staff will inform the infant's primary healthcare provider/pediatrician of the child's anticipated participation in the study before or immediately after delivery. A replacement Study Identification Card will be offered to all maternal subjects (as needed), and subjects will be reminded to contact study staff if symptoms suggestive of an RSV infection are experienced.

D+35 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visit

Maternal subjects will return to the clinic or will be evaluated by study staff at a home visit at approximately 35 days post-delivery for vital sign collection and to report any unsolicited AEs, MAEs, SNMCs, and SAEs that may have occurred since the last visit, and concomitant medications taken for these events. A physical exam may also be performed at the investigator's discretion to evaluate any adverse event reported. Maternal subjects will also be queried regarding symptoms suggestive of RSV infection and, in the event symptom onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses. A replacement Study Identification Card will be offered to all subjects, as needed. A blood sample (20 mL) will be obtained for RSV serology.

D+180 (± 14 days) – In-clinic or Home Post-delivery Follow-up Visit

Maternal subjects will return to the clinic or will be evaluated by study staff at a home visit at approximately 180 days post-delivery for vital sign collection, pregnancy testing, and to report any unsolicited AEs, MAEs, SNMCs, and SAEs that may have occurred since the last visit, and concomitant medications taken for these events. A physical exam may also be performed at the investigator's discretion to evaluate any adverse event reported. Maternal subjects will also be queried regarding symptoms suggestive of RSV infection and, in the event symptom onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses. A blood sample (20 mL) will be obtained for RSV serology. This visit will mark the end of study participation for the maternal subject. However, maternal subjects with ongoing respiratory episodes at the D+180 visit will be contacted weekly by telephone and followed until symptoms for that episode have resolved or have returned to baseline. In addition, maternal subjects with a positive pregnancy result will be followed for safety through the time of delivery to determine the outcome of this pregnancy.

Unscheduled Visits

Maternal subjects will be encouraged to notify the investigator if any severe (grade 3) local or systemic solicited AE occurs during the 7-day post-immunization period, or if any severe, serious, or otherwise concerning AE occurs at any time following vaccination. If symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected. Note the RSV Surveillance visits are not considered unscheduled visits.

Time and Events Schedule - Maternal Subject:

Maternal Subject Study Procedures									
Study Day:	**-28 to 0**	**0**	**0-6**	**7**[1]	**14**[1]	**28**[1]	**Delivery**	**D+35**[1]	**D+180**[1]
Window (days):	**--**	**--**	**--**	**+2**	**±2**	**±2**	**--**	**±7**	**±14**
Approximate Week of Gestation:	**24-36$^{0/7}$**	**28-36$^{0/7}$**	**28-36**	**29-37**	**30-38**	**32-40**	**--**	**--**	**--**
Informed consent	x								
Medical history	x								
Physical exam	x								
Vital signs	x	x[5]		x	x		x[10]	x	x
Physical exam, if indicated		x		x	x		x	x	x
Ultrasound	x[2]								
Clinical safety phlebotomy	x[3]				x[3]		x[11]		
Confirm eligibility		x							
Injection with recommended licensed vaccine	x[6]								
Injection with RSV F vaccine or placebo		x							
Diary card completed			x						
Diary card reviewed and collected				x					
Distribution of Study Identification Card[9]		x		x	x	x	x	x	
Memory aid distribution				x					
RSV serology phlebotomy	x				x		x[7]	x	x
Cord blood							x[8]		
RSV surveillance		←			Continuous				→
AEs, MAEs, SNMCs, and SAEs query	x	x		x	x	x	x	x	x
Concomitant medications		x		x	x	x	x	x	x
Document perinatal management & GBS screening/treatment results	x						x		

[1] Performed as a telephone/SMS contact visit (Day 28 only) using an IRB/IEC-approved script, if applicable, or as an in-clinic or home visit (Day 7, Day 14, D+35, and D+180) to monitor for safety. Depending on responses, maternal subjects participating via telephone or SMS contact or home visit, may be asked to return to the clinic or to schedule a home visit for further evaluation.

[2] May be performed if subject does not have a prior second or third-trimester ultrasound that indicates there are no fetal anomalies.

[3] To be performed at least two days prior to the planned Day 0 vaccination and on Day 14 in all subjects enrolled in the first year of study conduct in any country for select serum chemistry (ALT, AST, total bilirubin, ALP, creatinine, and BUN) and hematology (hemoglobin, platelet count, and WBC count) assessments.

[4] To be performed as required by the central or local laboratory if screening results are not available in prior data collected during the course of the current pregnancy.

[5] To be performed before and 30 minutes after vaccine administration.
[6] Must be administered at least 14 days before or at least 14 days after the Day 0 vaccination, if applicable.
[7] The blood draw will be performed at any time from admission to the hospital up to 12 hours post-delivery for most deliveries, but may be obtained up to 72 hours post-delivery in extenuating circumstances such as a the occurrence of a delivery on a holiday or weekend.
[8] Obstetrical investigator or designee should inform the investigator to the infant (or designee) of the collection status of the cord blood sample.
[9] The Study Identification Card will be distributed at the Day 0 visit; a replacement card will be offered at all follow-up visits.
[10] Limit collection to clinically significant vital sign data at hospital admission.
[11] Performed only for applicable subjects (i.e., those enrolled in the first year of study conduct in any country) who deliver prior to the Day 14 visit.

Infant Subject Study Visit Procedures:

Delivery (D) – Hospital Follow-up Visit

All procedures, including routine vaccinations that are considered standard of care for the newborn infant may be performed at any study visit which coincides with the usual timing for such procedures. Before any study-specific procedures are performed, informed consent for the infant subject and release of medical records will be reviewed with the maternal subject (i.e., the mother will not be re-consented) or will be obtained from the other parent or guardian if not already captured under the institution's policy. If cord blood is not obtained at the time of delivery (see delivery procedures for maternal subjects), an infant blood draw will be obtained within 72 hours of birth. *(Note that cord blood is markedly preferred and all efforts should be directed to obtaining this specimen. A phlebotomy/heel stick within 72 hours is a fall back procedure only. The volume of a postpartum phlebotomy/heel stick must be accounted for within the phlebotomy limits as per the investigator's institution [whereas a cord blood sample need not]).* The investigator (or trained designee) will collect results of the physical exam, weight, length, frontal-occipital circumference (FOC), and APGAR measurements performed following birth and used to assess the overall health of the infant. The results of questions pertaining to the exposure of the infant to certain environments or behaviors, such as the mode of infant feeding (e.g., exclusively breastfed, exclusively formula fed, breast milk and supplemented with formula, expressed breast milk, wet nurse, receiving solids), if a smoker or one or more children < 5 years of age will reside in the same household, and whether the infant or another child in the household (< 5 years of age) will be/is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week, will also be documented.

Parents and/or guardians will be issued a Study Identification Card for their infant that indicates he/she is part of an investigational vaccine trial and provides the contact number of the investigator and study staff responsible for study-related follow-up of the infant. The Study Identification Card will also include details of the signs and symptoms of RSV infection in adults and infants. If the infant subject develops an "RSV-suspect illness" characterized by the symptoms listed in the Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects table, parents/guardians are to contact the study site, but will be instructed to seek appropriate medical care for the infant first. This is especially important in instances when the initial evaluating physician providing care to the infant is not affiliated with the study.

D+14 (± 3 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 14 days post-delivery, all infants will participate in a study visit at home or in-clinic for evaluation of any AEs, MAEs, SNMCs, or SAEs experienced since delivery and concomitant medications taken for these events. The parent or guardian of the infant will also be asked to report any healthcare provider-confirmed episodes of wheezing; and the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or

another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week. A physical exam may be performed to evaluate any adverse events as needed. Symptoms suggestive of an RSV infection will be sought and, if onset has been within seven (7) days, a sampling of upper respiratory secretions for detection of respiratory viruses will be performed. A blood sample will be obtained from infants in phlebotomy **Cohort 1** for RSV serology.

All procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit. Prior to release from the clinic, study staff will schedule the next visit and remind the parent or guardian to contact the study staff directly if the infant develops symptoms suggestive of an RSV infection (see RSV Surveillance section). A replacement Study Identification Card will be offered to the parent/guardian of the infant before discharge, if needed.

D+35 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 35 days after birth, all infants will participate in a study visit at home or in-clinic for evaluation of any AE, MAE, SNMCs, or SAE experienced since the last delivery; to record concomitant medications administered for these events; to report any healthcare provider-confirmed episodes of wheezing; symptoms of RSV-suspected illness will be sought and, if onset has been within seven (7) days, a sampling of upper respiratory secretions for detection of respiratory viruses will be performed; and to report the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week. Infants will have a physical exam performed; weight, length, and FOC measurements will also be recorded. A blood sample will be obtained from infants in phlebotomy **Cohort 2** for RSV serology.

All procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit. Prior to release from the clinic, study staff will schedule the next visit and remind the parent or guardian to contact the study staff directly if the infant develops a suspect illness (see RSV Surveillance section). A replacement Study Identification Card will be offered to the parent/guardian of the infant before dismissal, if needed.

D+60 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 60 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 3**. Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit, may be performed at this visit.

D+90 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 90 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 1**. Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit, may be performed at this visit.

D+120 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 120 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 2**. Note that all

procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit, may be performed at this visit.

D+180 (± 14 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 180 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with three exceptions: 1) the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 3**, 2) infant subjects will complete the first of two developmental tests and 3) most activities associated with active RSV surveillance will conclude, with the exception that infant subjects with ongoing respiratory episodes will be followed weekly until symptoms of that episode have resolved or have returned to baseline. Parents/guardians of infant subjects will also be reminded to contact the site promptly to report any severe, serious, or otherwise concerning AE in the infant. Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

D+252 (± 14 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 252 days after birth, all infants will participate in a study visit at home or in-clinic for evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since the last visit and to record concomitant medications administered for these events; to report any healthcare provider-confirmed episodes of wheezing; and to report the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week. A physical exam may be performed to evaluate any adverse events as needed; weight, length, and FOC measurements will be recorded. All procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit, may be performed at this visit. Parents/guardians of infant subjects will also be reminded to contact the site promptly to report any severe, serious, or otherwise concerning AE in the infant. A replacement Study Identification Card will then be offered to the parent/guardian of the infant before dismissal, if needed.

D+364 (± 14 days) – In-clinic or Home Post-delivery Follow-up Visit

At approximately 364 days after birth, all infants will participate in a study visit at home or in-clinic for evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since the last visit; to record concomitant medications taken for these events; to report any healthcare provider-confirmed episodes of wheezing; and to report the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week. Infants will have a physical exam performed, and weight, length, and FOC measurements will be recorded. Developmental testing will be performed for all infant subjects. Note that parents/guardians of infant subjects with a positive screen detected at both 6 and 12 months of age (as this is an AE), or first appearing at 12 months of age, will be offered repeat Ages and Stages Questionnaire (ASQ)-3 screening at 15 and 18 months of age as a follow-up procedure. Novavax will collect this information as safety data. In addition, appropriate referrals for diagnostic pediatric developmental testing (according to local standards of care) will also be advised for infants with a positive screen identified. All procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit, may be performed at this visit.

Parents/guardians may also be asked to consent to additional infant follow-up for future respiratory disease such as severe LRTI syndromes or recurrent wheezing. Such follow-up, if requested, will be voluntary and will be the subject of a separate future protocol and consent document.

Completion of this visit will mark the end of study participation for the infant subject.

Unscheduled Visits

Parents/guardians will be encouraged to report, or ask the infant's primary healthcare provider/pediatrician to report at any time, any other type of severe, serious, or otherwise concerning AE. If symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected.

Note the RSV surveillance visits discussed in the RSV Surveillance section below are not considered unscheduled visits prior to D+180. Symptoms suggestive of an RSV-suspect illness reported during passive surveillance, but after D+180, will be captured as AEs and *not* on the RSV Surveillance page.

Time and Events Schedule - Infant Subject:

Infant Subject Study Procedures									
Visits: **Study Day:** **Window:**	**1** **Delivery** **--**	**2** **D+14** **±3 days**	**3** **D+35** **±1 week**	**4** **D+60** **±1 week**	**5** **D+90** **±1 week**	**6** **D+120** **±1 week**	**7** **D+180** **±2 weeks**	**8** **D+252** **±2 weeks**	**9** **D+364** **±2 weeks**
Informed consent	x								
Physical exam	x		x	x	x	x	x		x
Physical exam, if indicated		x						x	
Gestational age, APGAR scores	x								
Weight, length, FOC	x		x	x	x	x	x	x	x
Phlebotomy, Cohort 1	x[1]	x			x				
Phlebotomy, Cohort 2	x[1]		x			x			
Phlebotomy, Cohort 3	x[1]			x			x		

Time and Events Schedule - Infant Subject (Cont.):

Infant Subject Study Procedures									
Visits: **Study Day:** **Window:**	**1** **Delivery** **--**	**2** **D+14** **±3 days**	**3** **D+35** **±1 week**	**4** **D+60** **±1 week**	**5** **D+90** **±1 week**	**6** **D+120** **±1 week**	**7** **D+180** **±2 weeks**	**8** **D+252** **±2 weeks**	**9** **D+364** **±2 weeks**
RSV surveillance	← Continuous →								
Distribution of Study Identification Card[2]	x	x	x	x	x	x			
Query for smokers and children < 5 years of age in the household; mode of infant feeding; whether infant or another child (< 5 years of age) in the household is cared for outside the home	x	x	x	x	x	x	x	x	x
AEs, MAEs, SNMCs, and SAEs		x	x	x	x	x	x	x	x

Query for healthcare-provider confirmed wheezing		x	x	x	x	x	x	x	x
Concomitant medication		x	x	x	x	x	x	x	x
Performance of all routine baby-wellness procedures/ vaccinations[3]	x	x	x	x	x	x	x	x	x
Developmental testing							x		x[4]

Note: Study visits after Visit #1 may be performed as in-clinic or home visits to facilitate infant subject follow-up.

[1] An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery, but is permissive up to 72 hours post-delivery.

[2] The Study Identification Card will be given to the parent/guardian of the infant subject at the delivery visit; a replacement card will be offered at all follow-up visits, as needed.

[3] Performed at the Investigator's discretion.

[4] Infant subjects with a positive screen detected at both 6 and 12 months of age, or first appearing at 12 months of age, will be offered repeat developmental testing at 15 and 18 months of age as a follow-up procedure.

RSV Surveillance – Active and Passive:

Active and Passive Components of Surveillance

RSV surveillance will comprise both active and passive components. All queries for RSV-suspect illnesses will be made using an IRB/IEC-approved script, if applicable.

- Active Surveillance (applicable to all subjects through the D+180 visit):
  - Study staff will contact the maternal subject and a parent/guardian of the infant subject (via telephone call or SMS) on a once weekly interval through the D+180 visit to query for an RSV-suspect illness. Newly-discovered RSV-suspect illnesses as assessed by the presence of "trigger symptoms" (see Table Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects) will precipitate a home or clinic visit for evaluation (see Section *Clinical Study Site Response to Reports of Initial Trigger Symptoms*).
  - Study staff will re-evaluate (at home or in the clinic) all *infant* subjects with RSV-suspect illnesses between 2 to 3 days after any initial RSV surveillance visit to ascertain worsening in the illness. This re-evaluation will include the same procedures outlined in Section *Clinical Study Site Response to Reports of Initial Trigger Symptoms*.
- Passive Surveillance (applicable at any time during the study):
  - If the maternal subject develops any symptom suggestive of an RSV-suspect illness, or shows signs of worsening of a previously-evaluated RSV-suspect illness, she should contact the study site directly within 3 days of the onset/worsening of symptoms.
  - If an infant develops symptoms of an RSV-suspect illness while on study, or shows signs of worsening of a previously-evaluated RSV-suspect illness, parents or guardians should contact study staff directly within 3 days of the onset/worsening of symptoms.
  - Any newly-discovered RSV-suspect illnesses as assessed by the presence of "trigger symptoms" (see Table Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects) will precipitate a home or clinic visit for evaluation (see Section *Clinical Study Site Response to Reports of Initial Trigger Symptoms*).

- Study staff will re-evaluate (at home or in the clinic) all *infant* subjects with RSV-suspect illnesses between 2 and 3 days after any initial RSV surveillance visit to ascertain worsening in the illness. This re-evaluation will include the same procedures outlined in Section *Clinical Study Site Response to Reports of Initial Trigger Symptoms*.
- If the initial evaluation of the maternal or infant subject for an RSV-suspect illness is performed by a healthcare provider, not affiliated with the study (e.g., in an urgent care clinic, emergency room, or other outpatient clinic), he/she should notify the study staff of the maternal or infant subject's status as per the information provided on the Study Identification Card.
- Note: symptoms suggestive of an RSV-suspect illness reported during passive surveillance but after D+180 will be captured as AEs and not on the RSV Surveillance Page.

Please refer to the **Study Operations Manual** for additional details regarding the procedures performed during the RSV Surveillance.

Trigger Symptoms for RSV-suspected Illness

Surveillance for RSV will be based on the occurrence of "RSV-suspected illnesses" characterized by one or more of the following **Trigger Symptoms** in infant and maternal subjects (shown below) that persist for a period of ≥ 24 hours, either in a continuous or intermittent manner, and are assessed as "atypical" (by the maternal subject herself, or a parent or other routine caregiver for the infant) in nature.

Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects

Symptoms in Infant Subjects	Symptoms in Maternal Subjects
• Cough • Stuffy nose or runny nose • Trouble breathing or fast breathing when resting • Trouble feeding or not feeding well • Less active than normal when awake • Sleeps more than normal • More crying or more fussy than normal • Wheezing (whistling noise when breathing)	• Cough • Stuffy nose or runny nose • Shortness of breath • Sore throat • Fever • New or increasing wheezing • New or increasing sputum production

Note: It is not intended that these triggers for reporting be specific, or diagnostic of RSV, or LRTI; rather the goal is to capture acute respiratory illnesses generally. Physician (or qualified clinical designee) evaluation, (including an assessment of the infant's oxygen saturation level via pulse oximetry readings and respiratory rate by observation for 1 minute at the time of presentation of the acute illness) will capture those features which characterize LRTI, tachypnea, and hypoxemia or severe hypoxemia: molecular diagnosis by reverse transcription-polymerase chain reaction (RT-PCR) will detect RSV. These symptoms are intended to be a sensitive, rather than specific, trigger for further evaluation.

Clinical Study Site Response to Reports of Initial Trigger Symptoms

In response to a report via active or passive surveillance of *Initial Trigger Symptoms*, the study site staff will:

- Arrange for an in-clinic or home visit as soon as possible, but not later than 7 days after symptom onset, for evaluation by the study physician/qualified clinical designee of the subject (infant or mother) displaying the symptom/s and/or findings in the Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects table.

- Arrange for an in-clinic or home visit by a study physician/qualified clinical designee for evaluation as soon as possible within 7 days of symptom(s) onset for maternal or infant subjects who received care for trigger symptoms at a non-study, affiliated medical facility. Note that this visit would only be applicable to subjects who are receiving outpatient care or have been released from inpatient care.

Procedures to Occur During the Visit

Specific for Symptomatic Infants:

- Measure the respiratory rate on room air (if possible) for all *symptomatic infants*. The measurement should be performed first, on a calm, infant, and should be performed by observation only (i.e., without stethoscope auscultation) for a full, timed one minute period.
  - If the result is ≥ 60 bpm in an infant 0 to 59 days age or ≥ 50 bpm in an infant ≥ 60 days of age, a second timed one minute count should be obtained.
  - If a second count is obtained, the lower of the two observations should be recorded.
- Measure the SpO_2 via pulse oximetry (using study-specific pulse oximeter), for all symptomatic infants, which is to be performed when the infant is calm and not crying, and before administration of oxygen supplementation. The lowest stable SpO_2 observed during a one minute measure should be recorded. *Note that the oxygen should not be removed to measure SpO_2 in infants already receiving oxygen supplementation at the time of assessment.* Please refer to the Pulse Oximeter Manual for more details.

For All Symptomatic Subjects (Maternal and Infant):

- Review and confirm the history of respiratory illness, including the approximate date of first symptom onset.
- Perform an examination of the symptomatic infant subject to ascertain, by observation or auscultation, the presence of the LRTI manifestations listed in the Clinical Signs/Symptoms to be Clinically Evaluated during an RSV-suspected Illness table.
- Collect a respiratory specimen from the symptomatic subject for detection of respiratory viruses.
  - Symptomatic maternal subjects will have a nasal and throat specimen collected. The nasal secretion will be collected by mid-turbinate swabbing.
  - Symptomatic infant subjects will have a mid-turbinate nasal swab collected.
  - RT-PCR testing for RSV and other viruses by the study laboratory will be for the purposes of this protocol, and not for clinical care.
  - Respiratory specimens collected from the maternal and infant subject during an RSV surveillance visit may be split so that samples are provided for this protocol and for a qualified local laboratory supporting clinical care if the attending physician would ordinarily regard testing for bacterial and/or viral pathogens as warranted.
- Collect vital signs other than respiratory rate (heart rate, blood pressure [if available for the infant], and axillary body temperature) for the *symptomatic* subject.
- Ascertain any medically-attended visit by the subject in response to the respiratory illness.
- Ascertain any new concomitant medications resulting from the respiratory illness.
- Notify the infant's primary healthcare provider of the RSV surveillance visit and outcome, as necessary.

Clinical Signs/Symptoms to be Clinically Evaluated during an RSV-suspected Illness

Infant Subjects	**Maternal Subjects**

• Cough
• Nasal flaring
• Difficulty breathing, manifesting in at least one of the following clinical signs or symptoms:
  ○ Lower chest wall indrawing
  ○ Subcostal retractions Abnormal breath sounds, inclusive of:
  • Stridor
  • Rales
  • Rhonchi
  • Wheezing
  • Crackles/crepitations
  ○ Observed apnea
	• Cough
	• Nasal congestion
	• Fever
	• Runny nose
	• Sore throat
	• Dyspnea
	• New or increasing wheezing
	• New or increasing sputum production

Follow-up of RSV-suspect Illnesses

Following the evaluation of an RSV-suspect illness outlined in Section Clinical Study Site Response to Reports of Initial Trigger Symptoms, the clinical site:

- For *symptomatic infant* subjects, schedule a follow-up visit in 2 to 3 days to ascertain whether the illness is worsening.
  - The follow-up visit will include the same procedures outlined in Section Clinical Study Site Response to Reports of Initial Trigger Symptoms.
  - Parents/guardians will be strongly encouraged to report any worsening after the follow-up visit, including hospitalizations, which may trigger any number of additional follow-up visits at the investigator's discretion.
  - In the event than an infant is hospitalized, site staff are encouraged to perform a follow-up visit in-hospital, if permissible under local administrative and ethical review procedures.
- For *symptomatic maternal* subjects, and for *symptomatic infant* subjects after the first follow-up visit described above, a weekly contact by telephone/SMS will be performed to ascertain respiratory symptom status through to the D+180 visit, and to monitor the status of RSV-suspect illnesses until symptoms have resolved, or have returned to baseline if after the D+180 visit.
- In the event new and/or worsening symptoms are reported during active or passive follow-up, an in-clinic or home RSV surveillance visit may be scheduled at the investigator's discretion for an evaluation to occur as soon as possible; a re-evaluation as per Section Clinical Study Site Response to Reports of Initial Trigger Symptoms may be performed.
  - At the investigator's discretion, collection of ONE more respiratory specimen for pathogen detection for infant subjects who have developed qualitatively different or quantitatively worse symptoms. *Note that no more than 3 respiratory specimens should be collected from an infant within the same episode*.

- If the new or worsening symptom in the maternal subject is associated with a respiratory episode for which a specimen has already been obtained, the investigator may exercise his/her judgement as the utility of an additional swab.

Definitions and Rules for RSV Surveillance

- If possible, study staff should collect symptom data for any RSV-suspected illness for maternal and infant subject pairs during the same weekly telephone call or SMS contact. In the event the maternal and infant subject pair have independent clinic visits for assessment of an RSV-suspected illness within a given surveillance period, the subsequent weekly telephone or SMS contact for the next surveillance period can be resynchronized based on the earlier of the two contacts. For example, if a maternal subject had a clinic visit to evaluate an illness on Monday of surveillance week (SW)-1, this would trigger the next contact for the following Monday of SW-2. If the infant subject of the same mother had a clinic visit to evaluate an illness on Thursday of SW1, his/her next weekly contact could be rescheduled to coincide with the maternal subject contact on Monday of SW-2. (The intent of this provision is to relieve the need for mother/infant pairs to make multiple follow-up visits in a one-week period.)
- A new respiratory illness will be deemed to occur any time a one week (7 day) interval elapses during which the subject is free of respiratory symptoms. When a subject is determined to have a new respiratory illness, the subject should be evaluated at an in-clinic or home visit by study staff for this new episode.
- A medically-attended visit will be deemed to have occurred whenever the subject or a parent/guardian of the infant subject precipitates a visit or home encounter with a physician or other healthcare provider for the purpose of evaluation or treatment of a respiratory illness. *Note that at-home and in-clinic visits undertaken specifically to fulfill the requirements of this protocol, for illnesses which would not otherwise cause the parent/guardian to present the infant for care, are NOT "medically-attended visits," with the exception noted immediately below.*
- In the event that the investigator is also the subject's primary care physician (PCP)/general practitioner (GP), any RSV surveillance visit will be counted as a "medically-attended visit."
- Note that the intent of the evaluation of subjects with *Trigger Symptoms* is fulfillment of the objectives of this protocol. The investigator or study site staff should use their best professional judgment to ensure that subjects receive prompt medical care appropriate to their clinical condition, if necessary either by referring the subject to their usual physician or medical care facility, or providing care if the investigator is the subject's primary physician or if the case is emergent. The collection of the study data to support the primary and secondary efficacy endpoints are key objectives of this trial, but when necessary, appropriate medical care should supersede this goal.
- Respiratory events captured as efficacy endpoints will NOT be recorded in the AE electronic case report form (eCRF) or AE eSource page, with the exception of those that fulfill the definition of an SAE. The full particulars of the SAE(s) will also be captured in the SAE report form.
- Respiratory events ongoing at the 6 months post-delivery visit (D+180) will be followed by study staff at weekly intervals until symptoms resolve or return to baseline.

Laboratory Analyses:

Information regarding the central and local laboratories that will perform clinical laboratory safety testing, RSV serology testing, and genotyping of respiratory specimens is provided in the **Study Operations Manual**.

Statistical Methods:

General:

The analysis populations will include the following:

- Safety Populations
  - Maternal Safety Population (Safety-M) - defined as all maternal subjects who receive any test article. The Safety-M Population will be analyzed as actually treated.
  - Infant Safety Population (Safety-I) – defined as all infants born live to maternal subjects who received any test article. The Safety-I Population will be analyzed as actually treated.
- Intent-to-treat (ITT) Populations
  - 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 for both the mother and the infant 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 for both the mother and the infant. The ITT-IMM Population will be analyzed as randomized.
- 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 and 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 $\geq$ 37 weeks gestational age at birth, b) are born to maternal subjects who received a study injection as randomized and $\geq$ 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.
- 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 (up to 72 hours post-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.

Demographic parameters and other baseline characteristics (e.g., age, age group, gender, race, ethnicity, etc.) will be summarized by treatment group and serology cohort (as applicable) for all maternal and infant subjects (separately) in the Safety Population, as well as the number and description of protocol deviations. Summary statistics at birth for infant length, weight, FOC, APGAR scores, and gestational age will be provided by treatment groups. In addition, a listing will be prepared linking, by mother/infant pair, maternal demographic characteristics, maternal treatment, and infant length, weight, FOC, APGAR scores, and gestational age at birth.

Analyses of the 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 2-sided 97.52% 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 report as Appendix 1 in the SAP.

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 ≤ 0% and H_0: VE < 30%. Rejection of the first null hypothesis, H_0: VE ≤ 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 π_v and n_v, respectively, are the probability of an RSV event and the total number of subjects in the vaccine group and π_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 π_v and π_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 π_v and π_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 π_v and π_p
2. Calculating the event ratio, $r = \pi_v / \pi_p$ under each pair-wise sample from the posterior of π_v and π_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, time to the first medically-significant RSV LRTI event will be analyzed by treatment group using Kaplan-Meier methods. 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 regarding the sensitivity analyses will be described in the SAP.

The null hypothesis, H_0: VE $\leq$ 0%, using the 1-sided Type I error rate (i.e., lower bound of 2-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 will 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.

Analyses of Safety and Immunogenicity Objectives:

All safety endpoints will be summarized overall and by treatment group for maternal subjects and infant subjects based on Percentages of subjects experiencing an adverse event. Clinical laboratory data summaries for maternal subjects will include (by parameter and treatment group) toxicity grade shift summaries; absolute means and standard deviations with minima and maxima values, and tabulations of changes from baseline.

For infant subjects, summary statistics will be provided for infant length, weight, FOC, 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 above normal, normal, at-risk at 6 or 12 months, and at-risk at both 6 and 12 months.

Immunogenicity analyses will be descriptive and include tabulations by treatment group for maternal subjects and infant subjects based on anti-F IgG, PCA, and RSV/A and RSV/B MN. The transplacental transfer of anti-F IgG, PCA, and RSV/A and RSV/B MN antibodies will be examined; first order modeling of their decay in infants will be performed for half-life estimations.

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 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 ≤ 0% (i.e., the RR ≤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.

Sample Size Calculations:

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%. The table below 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%.

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%
	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 H_0: Vaccine Efficacy < 30% using one-sided Type I error rate of 0.0124.

1 INTRODUCTION

1.1 Respiratory Syncytial Virus (RSV) Background

Respiratory syncytial virus (RSV) is the leading viral cause of severe lower respiratory tract disease in infants and young children worldwide. The World Health Organization (WHO) has estimated that the global annual burden of infections and mortality due to human RSV are 64 million and 160,000, respectively [WHO 2009]. In industrialized countries, nearly all children have been infected with RSV by 2 years of age. Most infected children present with mild upper respiratory tract symptoms, but a subset develops severe lower respiratory tract disease characterized by tachypnea, hyperinflation, crackles, and expiratory wheezing (i.e., bronchiolitis and pneumonia). The most severe disease occurs within the first 2 to 8 months of life, particularly in infants born prematurely and infants with underlying chronic lung and congenital heart diseases.

Immunity to RSV remains incomplete and frequent reinfections occur throughout life, with the frail elderly, immunocompromised, and those with underlying cardiopulmonary disorders being among the most susceptible to severe disease in the adult population. It is estimated that between 11,000 to 17,000 elderly adults die of RSV infection or its complications annually in the US, with approximately ten-fold more admitted to the hospital with respiratory symptoms [Walsh 2012]. Actual attack rates may be higher still, as an RSV diagnosis is often not made in adults unless highly sensitive molecular diagnostic tests (i.e., RT-PCR) are performed. Acute respiratory illness due to RSV has been documented in previously healthy immunocompetent adults as well (e.g., military recruits), although the clinical severity of infection or subsequent re-infection is typically diminished [O'Shea 2007].

RSV is a pleomorphic virus belonging to the *Paramyxoviridae* family, and comprises two major subtypes, A and B, that co-circulate. The two major surface glycoproteins of RSV, F and G, are the primary targets of neutralizing antibodies, which are associated with protection [Graham 2011] The F protein mediates fusion of the viral envelope with the plasma membrane and syncytium formation, while the G protein is essential for viral attachment. There is a high degree of genetic and antigenic homology in the F proteins across RSV/A and B viruses, and among individual isolates, whereas the G protein is much more variable [Johnson 1987]. Immunization with vaccinia virus containing the F gene protected animals against homologous and heterologous subtype A and B viral challenge; whereas, animals immunized with the G gene expressed in the same system were only protected against the homologous virus [Olmsted 1986, Stott 1987]. These data demonstrate the ability of anti-F neutralizing antibodies to generate immunity across RSV/A and B subtypes.

1.2 Summary of RSV Disease in Various Geographies

1.2.1 High-resource Countries in the Northern and Southern Hemispheres

Data from the United States (US) and Australia suggest that 1.7 to 2.6% of infants are hospitalized for RSV infection before 1 year of age [Hall 2009, Iwane 2004, Ranmuthugala 2011]. Annually in the US, RSV infection is associated with an estimated 57,527 hospitalizations and 2.1 million outpatient visits among children < 5 years of age

[Centers for Disease Control and Prevention (update May 05 2015), Hall 2009]. In the US, Native American children are at increased risk for RSV infection. In 2000-2001, the rate of RSV hospitalization among Native American children <1 year of age in the southwest US was 48 per 1000, nearly double the rate of similarly aged children in the general US population (27 per 1000) [Holman 2004]. Among Native American infants in the southwest US, 11% of healthy babies were hospitalized with RSV in their first year of life. [O'Brien 2015] The elevated risk of admission - roughly six-fold that of infants in the general US population - is probably related to socioeconomic and geographic conditions [Bockova 2002].

In the United Kingdom (UK), over the winter seasons from 1989 to 2000, the average annual RSV-associated mortality in infants 1 to 12 months of age was 8.4 per 100,000 population [Fleming 2005]. The clinical manifestations and morbidity of RSV are similar among infants and young children worldwide, regardless of the country of residence. However, the majority of deaths due to RSV still occur in developing countries, where burden and risk factors for life-threatening illness remain the greatest. In fact, mortality rates due to RSV are difficult to ascertain in many settings, because children in developing countries, where 99% of fatal cases occur [Nair 2010], often die at home [Moisi 2011].

1.2.2 Argentina

Lower respiratory tract infections, in which RSV is a frequent pathogen in children under 2 years of age [Marguet 2009], are the second leading cause of death in children under 5 years of age in Argentina [Marconi 2010]. A recent publication by Ferolla and coworkers confirmed the incidence of severe RSV infections as a major burden of respiratory illness among young children in Argentina [Ferolla 2013], in agreement with similar studies [Moisi 2011, Nair 2010], and stressed the central role of RSV on hospital admissions among children younger than 2 years. Specifically, this study revealed that over 60% of the respiratory infections in 1,293 hospitalized children in Buenos Aires within a catchment population of over 360,000 children, were due to RSV. Almost 20% of these children had life-threatening disease (as assessed by oxygen saturations below 87%), a finding that helps explain the high mortality rates associated with RSV in many underdeveloped areas of the world, where access to care is suboptimal. The mortality rate attributable to RSV was estimated to be 7% in this study sample. The gravity of the RSV disease burden in Argentinean children is exemplified by noting that in the Buenos Aires metropolitan area, the burden of RSV illness in 2011 outweighed that of 2009 H1N1 influenza A virus during the pandemic year: 14-fold in hospitalizations and 4-fold in virus-confirmed deaths [Libster 2010].

1.2.3 South Africa

Acute respiratory tract infections due to RSV in South Africa remain a predominant cause of morbidity and mortality in young children [Tempia 2014]. A recent surveillance study in South Africa by Moyes et al., revealed that acute respiratory tract infections, in which RSV is a frequent pathogen, are the cause of approximately 8% of all deaths in children under the age of 5 years [Moyes 2013]. Results from this study confirm the findings of similar studies [Madhi 2006, Moisi 2011, Nair 2010], stressing the central role of RSV on hospital admissions among children younger than 2 years. The published hospital-based incidence of RSV infection in South Africa is estimated at 3 to 18%, with a mortality rate between 12% and 43% in

hospitalized cases [Moisi 2011]. An additional challenge in South Africa is that although a seasonal peak in RSV cases is established, with the majority of cases occurring in the winter (February-July), a low–level circulation of the virus has been identified outside of the epidemic period [Moisi 2011].

1.2.4 India, Southern Asia, and the Philippines

As in other geographies, acute lower respiratory tract infections are a major cause of mortality and hospitalization of young children throughout the region, accounting for an average of approximately 29% of hospitalizations for acute lower respiratory illness (ALRI) in children 0 to 11 months of age in studies from India, Southeast Asia, and the Philippines [Shi 2017]. Estimates of RSV-associated illness incidence rates for India, Bangladesh, Vietnam, Cambodia, and the Philippines are relatively consistent, and range from 35.3 to 59.8 events per 1,000 children per year [Shi 2017]. In multiple studies from India, respiratory syncytial virus is the dominant viral pathogen detected in children under 1 year of age who are hospitalized for lower respiratory tract infections, where it appears in cases of both bronchiolitis and bronchopneumonia, but especially the former [Chattopadhya 1992, Mishra 2016, Singh 2014, Kamigaki 2017] estimated incidence rates for severe acute respiratory disease associated with RSV ranged from 44.0 to 64.4 events per year per 1,000 children < 6 months old, estimates which outstripped the impact of influenza virus in this same age group by 2 to 8-fold.

1.3 Therapeutic and Prophylactic Agents Against RSV

To date, the therapeutic and prophylactic agents for use against RSV are limited. Ribavirin, a synthetic nucleoside analog with antiviral activity against both DNA and RNA viruses, is recommended for hospitalized children and select adults with severe RSV disease, but is difficult to administer and of limited benefit unless given early after symptom onset. Two immunoglobulin preparations have been indicated for prophylaxis of RSV infection: one, a polyclonal human anti-RSV IgG (RSV-IVIG, Respigam [Groothuis 1995, 1993]), was discontinued in 2004; and the other, a humanized monoclonal antibody (palivizumab, Synagis® [MedImmune, Gaithersburg MD]) therapy, is currently approved for use in high-risk infants in the US and worldwide. Palivizumab binds to a neutralizing epitope on the RSV F protein at amino acids 254-278, termed antigenic site II [Johnson 1997]. Although the clinical benefits of palivizumab have been demonstrated, the monthly administration and high expense make this product less-than-ideal for use except in premature infants at highest risk.

Vaccination is considered a potentially cost-effective approach to limit RSV infection in infants, elderly adults, and other high-risk populations, but safety remains a major concern in the field of RSV vaccine development. In the 1960s, a formalin-inactivated RSV (FI-RSV) vaccine produced by Pfizer (i.e., Lot 100 vaccine), although immunogenic, unexpectedly caused exacerbation of pulmonary disease in children who subsequently acquired an RSV infection [Kim 1969]. This vaccine-enhanced disease phenotype has been attributed in part to an imbalanced T helper cell type 2 biased T cell response [Waris 1996]. Other studies have suggested disease exacerbation was due to the development of anti-F antibodies deficient in fusion-inhibiting and virus-neutralizing activity post-vaccination [Murphy 1988]. Although the precise mechanisms underlying these findings remain open to debate [Blanco 2010], the phenomenon of vaccine-enhanced RSV disease has been limited to RSV-naïve infants

immunized with FI-RSV. Vaccine-enhanced disease has not been observed either with passive antibody prophylaxis (monoclonal or polyclonal) in animal models or humans or in clinical trials of various F protein-targeted vaccines in adults or older RSV-seropositive children [Groothuis 1998, Munoz 2003, Piedra 2003a].

1.4 Maternal Immunization

RSV disease is rare in the first two weeks of life, but rapidly appears thereafter, presumably due to waning of the maternally-derived, RSV-specific antibodies. The example of palivizumab demonstrates that passively-acquired serum antibody alone, if of sufficient titer and appropriate specificity, is protective in infants. Passive immunization mediated through placental transfer of maternally-derived antibodies elicited by RSV F vaccination of pregnant mothers is an attractive strategy to raise or boost anti-F neutralizing titers in infants to "protective" levels that persist over the vulnerable first months of infancy.

Maternal immunization has been successfully implemented by WHO to address neonatal tetanus and early estimates are that incidence of that disease has been reduced by 92% since the program's inception [Khan 2013]; and influenza immunization of pregnant women has been shown to have efficacy against influenza disease in both the woman and her infant and to lack adverse impacts on either the course of the pregnancy or the neonate [Pasternak 2012, Richards 2013, Steinhoff 2012, Zaman 2008]. A recent published report in an *in vivo* mouse model provides further evidence that maternally-derived antibodies in the offspring of pregnant females immunized with FI-RSV are safe and have protective activity. The pups display a marked reduction in lung viral loads after RSV challenge, relative to controls pups of unimmunized pregnant females, and show no histopathological characteristics of vaccine-enhanced disease [Kwon 2014].

In humans, maternal immunoglobulin G (IgG) antibodies are transplacentally transferred to the fetus by active transcytosis facilitated by IgG Fc receptors expressed on the placenta. Indeed, the active transport of IgG antibodies can result in enhanced antibody concentrations in cord blood that accumulate to substantial excess of maternal levels in some instances [Gendrel 1990]. Accordingly, it is a reasonable expectation that raising anti-F neutralizing titers in a pregnant woman will increase titers in infants [Simister 2003], and that such an increase will reduce the risks of serious RSV disease in the first months of life.

1.5 RSV F Vaccine

Novavax' response to the unmet need for RSV prophylaxis is the development of an RSV F vaccine, based on a purified, recombinant near full-length RSV fusion (F) glycoprotein. The RSV F is produced using the baculovirus/*Spodoptera frugiperda* (*Sf9*) insect cell system, and assembles into trimers, which further associate via hydrophobic interactions into nanoparticles resembling the previously-described 40 nm protein-protein micelles of isolated RSV F protein [Calder 2000]. The purified F protein is adsorbed to aluminum phosphate and contains 120 µg of RSV F protein and 0.4 mg of aluminum per 0.5 mL injection. The vaccine contains no viable viruses.

1.6 Safety and Immunogenicity of RSV F Vaccine in Animals and Humans

A detailed review of the nonclinical and clinical experience with the RSV F vaccine is provided in the Investigator's Brochure (IB). A brief summary is provided here.

1.6.1 Nonclinical Experience

Results from a Good Laboratory Practice (GLP) three repeat-dose toxicology study in New Zealand White rabbits indicated the No-Observed-Adverse-Effect-Level (NOAEL) of the RSV F vaccine was ≥ 30 µg (irrespective of adjuvantation with aluminum), a dose that is approximately 2.5 to 4.2-fold in excess (on a weight-adjusted basis) of a 120 µg antigen dose (the highest proposed human exposure) in a 50 kg human. The single relevant finding observed in vaccinated animals was the presence of inflammatory lesions at the injection site, which were consistent with immune system activation in response to the vaccine. The reduction in incidence and severity of such lesions at the recovery time-point suggested that these events are reversible following cessation of treatment.

A GLP-compliant reproductive toxicity study in New Zealand White rabbits evaluated the impact of four (4) doses of RSV F vaccine (120 µg) formulated with aluminum phosphate (0.8 mg Al content) in contrast to a saline placebo. Two doses were administered intramuscularly at a 21-day interval prior to mating, and two further doses at approximate Days 7 and 21 of gestation. F0 does were evaluated for mortality, clinical signs, body weight and food consumption, and mating performance. Half of the F0 animals were sacrificed and underwent caesarean delivery on approximately Day 29 of gestation for ovarian and uterine examinations, and fetal examinations. The balance of F0 animals were allowed to deliver naturally. The F1 kits were assessed for mortality, clinical signs, weight gain and food consumption, reflex and physical development, and an observational battery of behavioral assessments.

There was no RSV F vaccine-related effect on mortality or clinical signs in the F0 does, or overall impact on mean weights or weight gain before mating, during gestation, or during lactation. Mating occurred in 100% of control animals and 98% of vaccine-treated animals, and pregnancy occurred in 98 and 94%, respectively. One doe in each of the control and treatment groups aborted. In general, there were no clear effects on ovarian/uterine or litter observations. The percentage of pre-implantation losses was slightly, but significantly higher in the vaccine group, but there were no significant differences in litter sizes or counts of live fetuses. There were non-statistically significant increases in the number of litters with reversible delays in skeletal development (incomplete ossification of the sterna or pubes) in the active vaccine group, but these occurred in the smallest fetuses of pregnant animals with episodes of body weight loss, an association known in the literature. Pre-weaning and post-weaning mortality, clinical signs, weight gain, food consumption, and a functional observational battery assessing behaviors in post-weaning animals showed no impact of RSV F vaccine treatment on the F1 kits. Immune responses to the vaccine in the F0 does, and placental transfer of RSV F-specific maternal antibodies to the fetuses, were documented. It was concluded by the study director that RSV F vaccine treatment had no apparent adverse F0

maternal effects on mating or fertility and reproduction, and no adverse effects on postnatal growth and development of F1 kits of either sex.

In nonclinical studies of immunogenicity, the aluminum-adjuvanted vaccine has proven to be immunologically active in all animal models tested (including mice, cotton rats, rabbits, guinea pigs, and baboons) and generally superior to unadjuvanted RSV F protein, as indicated by RSV neutralizing and anti-F IgG antibody titers, and also the induction of antibodies capable of both competing with palivizumab for its binding site on the F protein and binding to an antigenic site II linear peptide. When challenged with intranasal RSV, F protein-immunized mice and cotton rats were protected from infection (as evidenced by reduced viral replication in lung homogenates), and failed to exhibit any evidence of the enhanced pulmonary disease which can be elicited in animals vaccinated with FI-RSV and subsequently challenged. In addition, passive transfer of sera from cotton rats immunized with RSV F vaccine was able to protect naïve cotton rats against RSV challenge in a manner similar to passive palivizumab treatment, indicating that a cellular immune response was not required to mediate at least short-term protection. Both rabbits and guinea pigs, the latter having placental architecture similar to humans, demonstrate vigorous anti-F immune responses after immunization during pregnancy and transplacental transfer of vaccine-induced antibodies to their pups. Preliminary data in baboon infants of vaccinated mothers indicate that these offspring acquire antibodies to RSV F protein *in utero* and show clinically relevant protection against RSV challenge, as demonstrated by improved activity levels, reduced tachypnea, and reduced work of breathing relative to infants of unimmunized mothers.

1.6.2 Clinical Experience

Novavax' clinical experience with the RSV F vaccine in young adults and children is based upon accumulated data in five randomized, blinded and placebo-controlled clinical trials which are complete to date. These completed trials include 1,069 subjects exposed to active vaccine, of which 1,022 were healthy young adults ≤ 49 years of age, and 973 were young women of child-bearing age. Additional active vaccine recipients in completed trials include 22 pregnant women between 18 and 40 years of age and 25 children, 2 to 5 years of age. In addition, Novavax has treated a total of approximately 6,879 adults 60 years of age and over with a different formulation of the RSV F nanoparticle vaccine. This older adult population has a different baseline co-morbidity status than healthy young adults, and a different immunogenicity and reactogenicity profile than young adults; therefore it will not be detailed further. However, the older adult population has revealed no unusual safety concerns.

Overall, the completed trials in young adults and children have shown that all RSV F vaccine formulations tested have produced an acceptable safety profile and were well-tolerated, with no significant dose-related toxicities observed. There have been no deaths, serious adverse events deemed related to the RSV F vaccine by the Sponsor, or subject withdrawals due to an AE reported in any of these completed studies. The majority of complaints have been mild to moderate solicited injection site events of tenderness/pain and systemic events of headache, muscle pain, and fatigue, which have resolved without sequelae during study conduct. The active vaccine reactogenicity profile was clearly differentiable from placebo in all studies, but did not demonstrate either a strong dose-related increase in the frequency or severity of

symptoms or increased reactogenicity after a second dose. The frequency of reports of fever in the first seven days after vaccine doses exceeds that in the first seven days after placebo by approximately 1%. A small increase in injection site complaints of pain, swelling, and redness, and muscle pain and joint pain was attributable to the addition of aluminum adjuvant. A review of the clinical laboratory assessments did not indicate any systematic toxicity to the renal or hepatobiliary systems, or to the bone marrow or circulating formed elements of the blood.

The predominant local reactogenicity profile observed across studies in adjuvanted vaccine recipients included mild to moderate injection site pain/tenderness reported in approximately 70% of all aluminum-adjuvanted vaccine recipients versus approximately 20% of placebo recipients. Swelling, redness, and bruising at the injection site occurred at substantially lower rates by comparison, reported by 10 to 20% of adjuvanted vaccine recipients compared to 1 to 3% of placebo recipients. Injection site reactogenicity did not increase notably in frequency or severity among subjects who received a second dose. Additionally, 10% of subjects may report residual mild injection site discomfort lasting outside the 7-day active solicitation interval.

Systemic reactogenicity reports were generally mild to moderate in severity. The predominant systemic complaints in adjuvanted vaccine and placebo recipients alike were muscle pain (33 and 16%, respectively), headache (36 and 32%), fatigue (30 and 26%); followed by less frequent reports of nausea (17 and 19%), chills (12 and 10%), joint pain (12 versus 7%), diarrhea (12% in both active and placebo), vomiting (3 and 5%), and fever (2 and 1%). Unsolicited adverse event reports of cough, oropharyngeal pain, nasal congestion, upper respiratory tract infection, anemia, nasopharyngitis, pharyngitis, contusion, decreased hemoglobin, rhinorrhea, toothache, rhinitis, viral infection, and pain in extremity were commonly reported (>1 to 10% of subjects) in adjuvanted vaccine recipients. For comparison, all except the nasopharyngitis, rhinitis, contusion, and pain in extremity were also commonly reported in placebo recipients.

Considering the 22 pregnant women who received RSV F vaccine in the third trimester (concurrently with 28 who received placebo), a review of safety data showed the RSV F Vaccine candidate was well-tolerated with no significant risks to overall health identified. Four maternal subjects reported a total of 5 serious adverse events (SAEs), but none of the SAEs were considered related to treatment and all were judged by the investigator as moderate in severity. No maternal deaths or subject withdrawals due to an adverse event (AE) were reported. Medical treatment for AEs (ie, medically-attended events or MAEs) was sought by similar proportions of placebo and active vaccine recipients. Most MAEs were related to labor and delivery, including labor pain (54.5% active and 46.4% placebo), obstructed labor (31.8% and 39.3%, respectively), postpartum hemorrhage (22.7% and 28.6%, respectively), and afterbirth pain (13.6 and 21.4%, respectively).

More active vaccinees among the pregnant women reported solicited AEs typical of intramuscular vaccine reactogenicity as compared to placebo recipients (68 vs 36%, respectively). This difference was primarily driven by pain at injection site (59% vs 0%, respectively). The local pain was entirely mild or moderate in severity and transient; all events resolved within the 7-day solicited period in the active group. The incidence of solicited systemic AEs was similar in the active and placebo groups (27% vs 36%, respectively) with

headache identified as the most commonly reported event among both groups (18 and 25%, respectively). None of the active vaccine recipients reported instances of fever. None of the solicited AEs were severe.

There was no difference in the incidence rates of unsolicited AEs through 6 months after delivery between the placebo and active vaccine groups, or the proportion that were deemed related to the treatment (11 and 9%, respectively), or severe (14% each). None of the severe AEs were considered related to treatment. The most commonly reported unsolicited AEs among placebo and active subjects (> 10% of subjects) pertained to labor and delivery events, hemorrhoids, observed decreased respiratory rate, hypotension, and perineal injury. Lastly, administration of the vaccine was not clearly associated with any systemic toxicity pertaining to renal or hepatic injury, ability to regulate glucose systemically, or abnormal changes in hematological parameters such as hemoglobin, white blood cells, or platelet counts.

Considering the infants born to mothers treated with vaccine or placebo, there was no evidence that administration of the RSV F vaccine to pregnant women posed any safety risk to their infants that was apparent in this limited data set. No clear differences were noted in the pattern of adverse events reported among infants born to mothers that received the RSV F vaccine as compared to infants of mothers that received placebo. The subject incidence rates of unsolicited AE reports in infants were comparable in both groups (93% placebo vs 91% active). Gastroesophageal reflux disease, upper respiratory tract infection, acute otitis media, and vomiting were the most commonly (> 10%) reported unsolicited events in the placebo group. Upper respiratory tract infection, acute otitis, acute, contusions, eczema, gastroesophageal reflux disease, conjunctivitis, decreased appetite, and dry skin were the most commonly reported unsolicited events in the active group. All events reported in infants in the active group were deemed mild or moderate in severity by the investigator (compared with 3 severe events reported in the placebo group), and none were considered related to treatment in either group. The proportions of infant subjects who reported MAEs were similar in both groups (89% placebo vs 82% active) with no systematic association or trend within a particular class of AEs noted in infants in the active group. No deaths were reported among the infants in the study. A total of 19 SAEs were reported in 11 infant subjects, which included 8 infants (14 SAEs) in the placebo group and 3 infants (5 SAEs) in the active vaccine group. All SAEs reported were considered unrelated to the test article administered to the maternal subject, and only a single event term (failure to thrive in two infants of placebo recipients) was reported more than once.

Health outcomes in both groups of delivered infants were also unremarkable, as mean gestational age (~39 weeks), weights (~3.4 kg), heights (~51 cm), FOC (~34 cm), and 1 and 5 minute APGAR scores (~8-9) were all comparable. All changes in length, weight, FOC, and Bayley III developmental screening results for both groups of infants through Day 365 post-delivery were considered by investigators as within normal limits in both groups. Two infants born to mothers that received the RSV F Vaccine had RSV infections at 49 and 87 days post-delivery during the 1st RSV season; a third infant was diagnosed with RSV at 359 days post-delivery, which was during the infant's 2nd RSV season. In addition, in the placebo group, one maternal subject and one infant subject at 33 days post-delivery had RSV disease. Importantly, none of the RSV disease in any subject was identified as severe or serious or required

hospitalization and thus no findings of enhanced RSV disease or severe RSV disease were present.

1.7 Study Rationale

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]. Two recent reports of prospective studies have confirmed the existence of a symptomatic RSV disease burden in mothers [Hause 2018, Madhi 2018].

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 with binding activity to the antigenic sites I and IV 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. Please refer to the Investigator's Brochure (IB) for current updates and new findings pertaining to the RSV F vaccine.

1.8 Risk

The most relevant studies to inform the risk of the RSV F vaccine in young pregnant women are derived from clinical observations made in 973 female subjects of child-bearing potential (the intended study population for this protocol), who were exposed to the RSV F antigen at doses up to 120 µg, alone or with up to a 1.2 mg dose of aluminum per injection, and from observations made in the 22 RSV F vaccine exposures of third-trimester pregnant women and their infants.

Overall, results have indicated the vaccines were not associated with persistent (based on a six-month post-second dose and one year post-first dose safety follow-ups) reactogenicity; and most short-term reactogenicity events were mild or moderate in severity. Most symptoms were transient, resolved without sequelae during study conduct, and did not require medical intervention. Adjuvanted-RSV F vaccine recipients were two to three times more likely to experience a mild solicited adverse event at the injection site relative to their counterparts receiving unadjuvanted vaccines or placebo, with pain/tenderness at the injection site observed as the most frequent local complaint. Up to 10% of adjuvanted vaccine recipients may have mild local discomfort at the injection site that persists beyond 7 days. Headache, muscle pain, and fatigue were the most frequently reported systemic solicited adverse events, followed by reports of nausea, chills, joint pain, diarrhea, vomiting, and fever, which all occurred at lower frequencies. Of the solicited systemic events reported, only muscle pain and joint pain occurred at notably higher rates in adjuvanted vaccinees than placebo recipients. The vaccine-attributable rate of fever in the 7 days after immunization among adjuvanted vaccine recipients has been 1 to 2%. Unsolicited adverse events experienced by >1% of adjuvanted RSV F vaccine recipients included cough, oropharyngeal pain, nasal congestion, upper respiratory tract infection, anemia, nasopharyngitis, pharyngitis, contusion, decreased hemoglobin, rhinorrhea, toothache, rhinitis, viral infection, and pain in extremity. In general, these events were reported at similar incidence rates by placebo recipients. SAEs have been infrequent, generally comprise common intercurrent illnesses or events that were presaged by prior medical history, and have been assessed by investigators as unrelated to the experimental vaccines.

Results obtained in RSV F vaccine-treated pregnant women suggested the vaccine did not appear to pose any increased safety risk to the general health of the woman, to the health and progression of the pregnancy, or to the infant. Pregnancy and labor and delivery complications noted were unremarkable in terms of the frequency, or severity of events and approximately equally distributed between in active vaccinees and placebo recipients. Infants of actively-immunized women achieved normal marks for all growth and development measures at birth through two months of age.

Because of the limited clinical trial subject numbers, it is not yet possible to evaluate whether the adverse events described here are, or are not, causally-related to the RSV F vaccine (with or without adjuvant), and other adverse effects may exist which have not yet been detected. In common with all vaccines produced in cell culture or other systems, the RSV F vaccine contains residual non-vaccine proteins derived from the production system, and sensitization to these may theoretically occur. Safety monitoring for hypersensitivity and/or allergic reactions has been conducted routinely during study conduct through clinical evaluations and direct observations up to 30 minutes post-immunization. While the occurrence of immediate hypersensitivity is possible with the parenteral administration of any vaccine, whether licensed or in development, no such reactions have been observed in the clinical studies conducted with the RSV F vaccine to date. As clinical data become available with increased exposure, it is possible that this profile may change.

As discussed in Section 1.2.4, a formalin-inactivated RSV vaccine trial conducted in the 1960s in very young children largely without prior RSV immunity led to an increase in the severity of subsequent RSV infections. The exact basis of this result has never been completely clarified. However, clinical trials of several RSV vaccines containing F protein, with or without other components, and performed in adults and older children, have never resulted in this complication. With a mean exposure within the RSV transmission season of 54.5 days among infants of actively-immunized women in the RSV-M-203 trial, there were no safety signals suggestive of enhanced RSV disease in the infants of actively immunized mothers in the phase II trial. While that trial represents a small experience, the signal of enhanced disease noted in the Kim (1969) experience was so large that the currently available dataset is inconsistent with a finding of similar, or substantially smaller, magnitude.

This study is the second to evaluate the RSV F vaccine in third-trimester pregnant women. Currently, there may be adverse effects that may exist that cannot be predicted to occur. Thus, the safety of maternal and infant subjects is being carefully monitored throughout the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- 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 (lower bound of a 95% confidence interval for later time points) for the estimate of vaccine efficacy which equals or exceeds target values agreed with regulatory authorities.

2.2 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 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 through 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.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- 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 (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) 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 [SpO_2] < 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.

3 STUDY DESIGN

3.1 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.

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 three months prior to peak RSV season as shown in Table 1. After the first global season of enrollment, the randomization scheme will be changed 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. Please refer to the **Study Operations Manual** for further details.

Table 1: Treatment Assignments

Treatment Group	Target Maternal Subjects/Group[1]	Test Article	Dosing Volume	Vaccination Day
A	~ 1562	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 (see Appendix 1). It is anticipated that a percentage of the randomized maternal subjects and their delivered infant 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 intramuscular (IM) injection on Day 0 with the assigned test article, either the RSV F vaccine or placebo (see Table 1). The procedures to be performed in the study are described in detail in Section 6.1 of this protocol. Maternal subjects will be monitored for typical vaccine reactogenicity, clinical laboratory impacts, and specified adverse pregnancy outcomes, as well as general AEs and SAEs. In addition, because the maternal illness and obstetrical risk burden due to RSV is largely unknown, the occurrence of RSV disease in maternal subjects will be monitored before and after delivery. Vaccine impacts on markers of infant development and well-being at birth will be monitored, as will growth and development through the first year of life. Infant blood samples will be taken to assess the decay half-life of maternally-derived RSV antibodies. Symptomatic infant and maternal RSV infections will be monitored through the first RSV season using both active and passive surveillance mechanisms; and will be etiologically-confirmed using RSV RT-PCR. Infant RSV infections will be characterized based on their symptomatology, associated degree of hypoxemia as measured by pulse oximetry, respiratory rate as measured by observation for 1 minute, and required medical interventions.

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.

A Data and Safety Monitoring Board (DSMB) will supervise enrollment and monitor subject safety throughout the trial (see Section 8.10). In order to ensure that mothers and infants are not placed at risk with scant possibility of success, repeated futility analyses will be performed twice per year during the period of the study. 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 is not consistent with a predefined 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 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.

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 LRTI in infants from delivery through the first 90 days of life. If successful outcomes are obtained through 90 days of life, then additional analyses for efficacy will be performed in a closed hierarchical sequence considering data from delivery 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 10.4.2).

Only endpoints validated by the CEAC review will be used for the efficacy analyses. Section 10.4.3 provides details of the futility and efficacy analyses.

3.2 Study Endpoints

3.2.1 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 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 10.4.2) 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.

3.2.2 Secondary Efficacy Endpoints *(In Infant Subjects)*

- Percentages of infants with 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) 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 10.4.2) 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.

3.2.3 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 correlates 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, 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.

3.2.4 Safety Endpoints

3.2.4.1 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.

3.2.4.2 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:
  - 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.

3.2.5 Exploratory Endpoints (In Maternal and Infant Subjects as Stated)

- 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 (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) 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 [SpO_2] < 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 10.4.2) 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.

3.3 Study Duration

The approximate maximum duration of the maternal subject's participation in the study conduct is nine months. The maximum duration of the infant subject's participation in the study conduct is approximately one year. The duration of the entire study is estimated to be approximately four years.

3.4 Study Population

Maternal subjects for the study will be healthy (as determined by physical examination, medical history, and clinical laboratory parameters), third-trimester pregnant subjects deemed to be at low-risk for obstetrical complications, between the ages of ≥ 18 to ≤ 40 years, who meet all of the inclusion criteria and none of the exclusion criteria (see Section 5).

3.5 Randomization Scheme

The sample size for this trial will be approximately 4,600 third-trimester pregnant subjects in the Northern and Southern hemispheres and their infants. 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. 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 (see Appendix 1).

3.6 Randomization and Blinding Procedure

Maternal subject randomization will be conducted using an Interactive Web Randomization System (IWRS). The system will ensure proper distribution of maternal subjects across group assignments. Stratification will be based on study site and age (18 to < 29 years and 29 to 40 years), in order to distribute the proportion of such subjects in each age group equally across treatment groups. At maternal randomization, the infant of that mother-infant pair will also be randomized to one of three phlebotomy cohorts.

Preparation and administration of the RSV F vaccine and placebo will be performed by an unblinded vaccine administrator(s), with masking of the syringe content. Administration of the RSV F vaccine and placebo will be performed by designated site personnel.

Maternal subjects and the main study team clinical staff will remain blinded as to treatment assignment for the duration of the study unless emergency unblinding is necessary. Refer to Section 3.7 for information regarding the process for emergency unblinding. However,

assignment with regard to the infant's phlebotomy cohort will be transmitted immediately to site personnel.

All treatment assignments, vaccine and placebo storage and accountability, and/or dosing related matters, will be monitored by a designated "unblinded monitor." Any deviations will be discussed, documented and resolved by the unblinded monitor and the unblinded site personnel. The unblinded monitor will be responsible for escalating issues to the clinical project team in a blinded manner. The Clinical Supplies Manager at Novavax will be responsible for determining whether the team will be unblinded in order to adequately resolve issues. Any unblinding of the project team will be clearly documented in the Trial Master File (TMF). No reports from the unblinded monitor will be released to the TMF until database lock for the final analysis and official declaration of unblinding is given by Novavax.

3.7 Procedure for Unblinding Individual Subject Treatment Assignments

In the event of a medical emergency, when knowledge of the maternal subject's treatment assignment may influence her or her infant's clinical care, the investigator or designee may request that the blind be broken for the maternal subject-infant subject pair experiencing the emergency. If feasible, the investigator is asked to notify the Medical Monitor or designee prior to unblinding; however, the investigator may unblind without consulting the Medical Monitor, if it is deemed to be in the best interest of the subject. The investigator will be expected to provide a rationale for the necessity of unblinding, based on a meaningful change to the maternal or infant subject's immediate and short-term medical care which will result from knowledge of the treatment assignment. Novavax also retains the right to initiate the unblinding of treatment allocation for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to the test article and that potentially require expedited reporting to regulatory authorities.

If unblinding is deemed necessary, the unblinded vaccine administrator will utilize information from IWRS to obtain treatment details for the maternal subject-infant subject pair. The date and time of breaking the blind as well as the reason must be documented and placed in the **Study Pharmacy Manual** by unblinded staff. The investigator should not otherwise divulge the treatment assignment of the maternal subject-infant subject pair to site staff, and should provide the information only to those individuals involved in the direct care of the subject. The date and reasons for breaking the blind must be submitted to the Medical Monitor within 24 hours. Additional instructions for unblinding will be contained in the **Study Operations Manual** and the **Study Pharmacy Manual**.

If treatment assignment of a maternal subject-infant subject pair is unblinded, both subjects should remain in the study and continue the protocol-specified follow-up evaluations if possible.

4 TEST ARTICLES

4.1 Overview of Product and Manufacturing Process for Clinical Trial Material

The RSV F vaccine candidate is based on a purified, recombinant near full-length RSV F glycoprotein that self-assembles into protein-protein nanoparticle structures of approximately 30 to 60 nm. The baculovirus/Sf9 insect cell system was used to clone and express the recombinant human RSV F gene. In the vaccine construct, one of two subtilisin-like protease cleavage sites in the RSV F sequence is deleted, as well as approximately half of the fusion domain, to mitigate toxicity of the protein to the expression system. In *Sf9* insect cells, recombinant F is produced as a precursor (F0) that is modified by N-linked glycans and, like the native F fusion protein, assembles into homo-oligomers as trimers [Collins 1991]. The F0 precursor is processed into F2 and F1 chains that remain predominantly covalently linked by disulfide bond(s) in the product.

4.1.1 Production and Purification of RSV F Protein

The recombinant human RSV F gene was cloned via *Escherichia coli* (*E. coli*) into a FlashBac GOLD expression vector baculovirus DNA with v-acth and chitinase genes deleted (Oxford Expression Technologies). The F gene is under transcriptional control of the baculovirus *Autographa californica* multiple nuclear polyhedrosis virus (AcMNPV) polyhedrin promoter at the 5' end and includes a poly (A) sequence at the 3' end. A single recombinant baculovirus expressing the F gene was identified, plaque-purified, and amplified for use in the manufacture of the bulk RSV F antigen.

Manufacture of the RSV F protein antigen is initiated by infecting Sf9 cells in exponential growth with baculovirus containing the RSV F gene. After infection, cells are collected by centrifugation, washed with sterile buffer, and then lysed in the presence of detergent to release membrane-bound RSV F protein. Leupeptin hemi-sulfate salt is added to the lysis buffer to protect the RSV F protein from cellular proteases, which are also inactivated by low pH treatment. The supernatant containing the RSV F protein is separated from cell debris by filtration before it is purified on an anion exchange column. The flow-through fraction is first nanofiltered through a virus removal filter and then loaded on an affinity chromatography column, which binds the RSV F protein. After washing, the RSV F protein is eluted from the column with buffer containing methyl-α-D-mannopyranoside (MMP) and Polysorbate (PS)-80, and exposed to a second low pH treatment. Eluted fractions are further purified with a cation exchange chromatography step that removes MMP and transfers the product into a sodium phosphate buffer with sodium chloride and PS-80. The product is then filtered through a sterilizing filter (0.20 μm) to produce the bulk drug substance that is clear and colorless, and contains no preservatives. The bulk drug substance is stored at -70°C until it is adsorbed onto aluminum phosphate and filled as drug product.

4.1.2 Aluminum Adjuvant

The aluminum phosphate salt is supplied as a sterile suspension in unbuffered isotonic saline (4.8 mg/mL of aluminum as a phosphate salt in 0.15 M NaCl without buffer) by Brenntag Biosector (Frederikssund, Denmark).

4.1.3 Final Drug Product

The F protein content in the purified drug substance is determined by an F protein-specific binding ELISA. To produce the adjuvanted vaccine, the bulk RSV F protein and aluminum phosphate are diluted to a specified concentration and then combined to yield a final concentration of 240 µg/mL RSV F and 0.8 mg/mL aluminum, in a final buffer of 18 mM sodium phosphate, pH 6.2, with 0.15 M NaCl, 0.8% histidine, 0.03% PS-80. The RSV F vaccine is filled into single-use glass vials. The final product appears as a white opalescent suspension. No antibiotics or preservatives are present.

4.1.4 Formulation Buffer Placebo

The placebo treatment is comprised of 22 mM sodium phosphate, pH 6.2, with 150 mM NaCl, 1.0% histidine, and 0.03% PS-80; is manufactured by Althea Technologies (San Diego, California); and is supplied in single-use 2 mL glass vials.

4.2 Investigational Product Packaging, Storage, and Handling

The RSV F vaccine and placebo will be packaged in a validated shipping container for distribution to the investigational sites under refrigerated conditions. The investigational product will be labeled with the following information: manufacturer's name and address, product name, manufacture date, storage requirements (2 - 8°C), directions for use, and any other investigational product labeling appropriate to the jurisdiction in which the trial is conducted.

The RSV F vaccine and placebo will be stored at 2 - 8°C in a temperature monitored refrigerator. Access to this refrigerator will be limited to designated site personnel.

Additional information on the packaging, storage, and handling procedures for the RSV F vaccine and placebo is provided in the **Study Pharmacy Manual**.

4.3 Compliance and Drug Accountability

It is the responsibility of the investigator at each site to ensure that all test articles (RSV F vaccine and placebo) received at the site are inventoried and tracked throughout the study and the result recorded on the product accountability form maintained in the **Study Pharmacy Manual**.

All quantities of the test articles must be reconciled at the termination of the study and a written explanation provided for any discrepancies. Unless specific written instructions to the contrary are provided by Novavax (or designee), all unused vials containing the RSV F vaccine and placebo, and packaging materials, will be inventoried and maintained at the clinical site until further notice by Novavax or (designee). The site is not permitted to return or destroy used or unused test articles or packaging materials unless specifically authorized by Novavax (or designee) in writing.

5 SELECTION OF STUDY SUBJECTS

5.1 Inclusion Criteria

Pregnant women must meet all of the following to be eligible for participation in the study:

1) ≥ 18 and ≤ 40 years-of-age (which connotes a lower limit of 18 years and 0 days and an upper limit of 40 years and 0 days).

2) Singleton pregnancy of 28 to $36^{0/7}$ weeks gestation on the day of planned vaccination. Documentation of gestational age will be based on <u>one</u> of the following composite criteria (*Note: The investigator should use the earliest ultrasound data available to establish the study-specific gestational age dating)*:

   (a) Gestational Age Dating Based on First Trimester Data (data obtained ≤ $13^{6/7}$ weeks):

   The date of the first day of the reported last menstrual period (LMP) may be used to establish the gestational age if corroborated by a first trimester ultrasound. If the gestational age estimation derived using the LMP and the first trimester ultrasound are discrepant by > 7 days, the ultrasound will be used to establish the gestational age.

   If LMP is uncertain or unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

   (b) Gestational Age Dating Based on Early Second Trimester Data (data obtained $14^{0/7}$ to $21^{6/7}$ weeks):

   The date of the first day of the reported LMP may be used to establish the gestational age if corroborated by an early second trimester ultrasound (that estimates the gestational age between $14^{0/7}$ and $21^{6/7}$ weeks). If the gestational age estimation derived using the LMP and the early second trimester ultrasound are discrepant by > 10 days, the ultrasound will be used to establish the gestational age.

   If LMP is uncertain of unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

   (c) Gestational Age Dating Based on Later Second Trimester Data (data obtained $22^{0/7}$ to $27^{6/7}$ weeks)

   The date of the first day of the reported LMP may be used to establish the gestational age if corroborated by a later second trimester ultrasound (that estimates the gestational age between $22^{0/7}$ to $27^{6/7}$ weeks). If the gestational age estimation derived using the LMP and the later second trimester ultrasound are discrepant by > 14 days, the ultrasound will be used to establish the gestational age.

   If LMP is uncertain or unknown, the ultrasound-established gestational age estimation will be used to establish the gestational age of the pregnancy.

(d) Gestational Age Dating When the LMP is Uncertain or Unknown AND No Prior First or Second Trimester Ultrasound Has Been Performed:

An ultrasound performed at screening, within the second trimester ($\leq 27^{6/7}$ weeks) will be used to establish the gestational age.

3) Documentation of a second or third (between $18^{0/7}$ weeks and prior to randomization) trimester ultrasound with no major fetal anomalies identified.

4) Good general maternal health as demonstrated by:

- Medical history (including history of clinically significant adverse reactions to prior vaccines and allergies).
- Physical examination including at least vital signs (blood pressure, pulse, respirations, and axillary body temperature); weight; height; examination of the HEENT, cardiovascular, pulmonary, gastrointestinal (abdominal), musculoskeletal, lymphatic, and dermatologic organ systems; and documentation of fetal heart tones. Note that abnormal vital signs may be repeated at the investigator's discretion since these measures may be labile. Vital signs should be assessed in the context of normal values for the third trimester of pregnancy (see the **Study Operations Manual**).
- Clinical laboratory parameters that include:
  - For the first year of study conduct in any country, normal/clinically insignificant blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), hemoglobin, white blood count, and platelet count. Note that normal ranges for clinical laboratory parameters will be based on reference ranges appropriate for the third trimester of pregnancy, specified in the toxicity grading scale (TGS, provided in the **Study Operations Manual**) and should be referenced to assess for any abnormalities. This testing should be performed by the central laboratory.
  - For all subjects, serologic exclusion of infection with hepatitis B (HBV) and C (HCV) viruses, syphilis and HIV as documented by testing (performed at the central or local laboratory) at screening or by medical records during the current pregnancy.

5) Able to understand, and both willing and physically able to comply with study procedures. This includes anticipation of reasonable geographic proximity to the study clinic and adequate transportation to comply with scheduled and unscheduled study follow-up visits.

6) Able and willing to provide written informed consent for themselves and infant.

5.2 Exclusion Criteria

Pregnant women will be excluded if there is historical, physical examination, or laboratory evidence of any of the following:

1) Symptomatic cardiac or pulmonary disease requiring chronic drug therapy, including hypertension and asthma. Asthma will be exclusionary if the subject is receiving chronic

systemic glucocorticoids at any dose or inhaled glucocorticoids at any dose > 500 μg per day of beclamethasone or fluticasone, or > 800 μg per day of budesonide.

2) Pregnancy complications (in the current pregnancy) such as preterm labor, hypertension (blood pressure [BP] > 140/90 in the presence of proteinuria or BP > 150/100 with or without proteinuria) or currently on an antihypertensive therapy or pre-eclampsia; or evidence of intrauterine growth restriction.

3) Grade 2 or higher clinical laboratory or vital sign abnormality. Exclusion of subjects with grade 1 abnormalities will be based on the subject's prior medical history and the investigator's clinical judgment that the abnormality is indicative of a meaningful physiologic event.

4) Receipt of any licensed vaccine (e.g., Tdap, inactivated influenza vaccine) within 14 days of study vaccination.

5) Received any RSV vaccine at any time.

6) Body mass index (BMI) of ≥ 40, at the time of the screening visit.

7) Hemoglobinopathy (even if asymptomatic) or blood dyscrasias.

8) Hepatic or renal dysfunction.

9) Established diagnosis of seizure disorder, regardless of therapy.

10) Known, active auto-immune disease or immunodeficiency syndrome.

11) Endocrine disorders, including (but not limited to) untreated hyperthyroidism, untreated hypothyroidism (unless due to auto-immune disease), and glucose intolerance (e.g., diabetes mellitus type 1 or 2) antedating pregnancy, or occurring during pregnancy and requiring interventions other than diet for control.

12) History of major gynecologic or major abdominal surgery, including bariatric surgery (previous Caesarean section is not an exclusion).

13) Known HIV, syphilis, HBV, or HCV infection, as assessed by serologic tests conducted during the current pregnancy or as a procedure during the screening period of the study.

14) Primary genital Herpes simplex virus (HSV) infection during the current pregnancy.

15) Current alcohol or drug abuse based on the investigator's knowledge of present or recent (within the last 2 years) use/abuse of alcohol or illegal or non-prescription drugs.

16) Documentation that the current pregnancy results from *in vitro* fertilization (IVF).

17) Documentation that the current pregnancy results from rape or incest.

18) Documentation that the infant will be a ward of the state or be released for adoption.

19) History/presence of deep venous thrombosis or thromboembolism, or the use of anticoagulants during pregnancy (use of low-dose aspirin as prophylaxis [e.g., for the prevention of morbidity and mortality from preeclampsia] is acceptable in dosages consistent with local standards of care).

20) Red blood cell allo-immunization.

21) Prior stillbirth or neonatal death, or multiple (≥ 3) spontaneous abortions.

22) Prior preterm delivery ≤ 34 weeks gestation or having ongoing intervention (medical/surgical) in current pregnancy to prevent preterm birth.

23) Greater than five (5) prior deliveries.

24) Previous infant with a known genetic disorder or major congenital anomaly.

25) Receipt of investigational drugs or immune globulins (with the exception of prophylactic anti-Rho D immune globulin) within six (6) months prior to the administration of the study vaccine.

26) Chronic administration (defined as more than 14 continuous days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the study vaccine. An immunosuppressant dose of glucocorticoid will be defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted except for the limit established in exclusion criterion #1.

27) Neuro-psychiatric illness, including a history of severe post-partum depression, deemed likely to interfere with protocol compliance, safety reporting, or receipt of pre-natal care; or requiring treatment with psychotropic drugs (excluding treatment for depression and anxiety).

28) Any other physical, psychiatric or social condition which may, in the investigator's opinion, increase the risks of study participation to the maternal subject or the fetus/infant; or may lead to the collection of incomplete or inaccurate safety data.

29) Acute disease within 72 hours of the day of the planned vaccination (defined as the presence of a moderate or severe illness with or without fever, or an axillary body temperature > 38.0°C).

30) History of a serious adverse reaction (e.g., anaphylaxis) to any prior vaccine.

6 STUDY ASSESSMENTS AND PROCEDURES

A study schematic flowchart is provided in Appendix 1 for maternal and infant subjects, separately. A detailed description of procedures performed at each in-clinic visit is described in this section.

6.1 Study Visit Procedures

This study contemplates a two-staged design with study procedures for maternal subjects provided in Section 6.1.1, and infant subjects in Section 6.1.2. Study visits were designed to coincide approximately with pregnancy, postpartum, and baby wellness visits.

6.1.1 Maternal Subject Study Visit Procedures

6.1.1.1 Up to Two (2) Months Prior to Study Start – Pre-Screening

Obstetrical investigators may, at their discretion, introduce the concept of participation in a third-trimester RSV vaccine trial to women who they regard as potentially fulfilling the inclusion/exclusion criteria. If required by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) having authority, interested women may be asked to provide informed consent in order for the investigator to collect information regarding their general health history, obstetrical history, and results of screening testing performed for the current pregnancy. The screening consent will be for collection of existing data only, and will not provide for any invasive procedure (including phlebotomy). Screening consent may be withdrawn at any time, and will not bind the prospective subject to enroll in the clinical trial or the investigator to offer enrollment.

6.1.1.2 Day -28 to 0 – Screening (up to four weeks before the planned day of vaccination)

The healthy pregnant subjects, who are considered to be at low-risk of obstetrical complications, ≥ 18 to ≤ 40 years of age (18 years and 0 days to 40 years and 0 days), have provided written Informed Consent for themselves and their infants to participate in the main study, and are able to comply with study requirements, will have the following procedures performed:

- Review of medical history, including history of clinically significant adverse reactions to prior vaccines and allergies.
- Review of the parameters by which the gestational age dating of the current pregnancy was established, to include the LMP (if known), physical examination, and the results of a first or second trimester ultrasound.
- Performance of a second trimester ($\leq 27^{6/7}$ weeks) ultrasound (if not previously done) that establishes gestational age dating.
- Performance of a second or third trimester ultrasound (if not previously done) that confirms there are no major fetal anomalies.
- Review of obstetrical history to include the following outcomes of previous pregnancies: length of gestation, birth weight, length of labor, type of delivery,

fetal/neonatal outcomes, complications of pregnancy, including history of fetal losses and elective abortions.

- Review of surgical history including prior gynecologic, abdominal, or uterine surgery.
- Document results of any Group B streptococcus (GBS) screening (urine or recto-vaginal swab as applicable), or other infectious disease screening (i.e., for syphilis, gonorrhea, Herpes simplex, chlamydia, HBV, HCV, and HIV).
- Administration of a licensed vaccine recommended during pregnancy, if indicated. *Note: This dose should be administered at least 14 days before or at least 14 days after the Day 0 vaccination.*
- Document current smoking, alcohol, and recreational drug use.
- Document results of gestational diabetes screen.
- Vital signs (blood pressure, pulse, respirations, and axillary body temperature [*Note that repeat testing may be performed for subjects with any abnormality*]), height, and weight;
- Physical examination including the following body systems: HEENT, cardiovascular, pulmonary, gastrointestinal (abdominal), musculoskeletal, lymphatic, and dermatologic; and confirmation of fetal heart tones.
- Blood draw:
  - For RSV baseline serology (20 mL).
  - <u>For subjects participating in the first year in any country:</u> Clinical laboratory assessments (10 mL) for select serum chemistry (i.e., blood urea nitrogen, creatinine, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin) and hematology (i.e., hemoglobin, white blood cell [WBC], and platelet counts) parameters by central laboratory testing; and HIV, syphilis, HBV, and HCV antigen tests/serologies as required by central or local laboratory testing (i.e., if screening results are not available in prior data collected during the course of the current pregnancy). Since results of the clinical laboratory testing are needed to confirm subject eligibility, it is recommended this phlebotomy be performed <u>at least two days</u> before the planned Day 0 vaccination.
  - <u>For subjects participating in all other years in any country:</u> HIV, syphilis, HBV, and HCV antigen tests/serologies (10 mL, as required) by central or local laboratory if screening results are not available in prior data collected during the course of the current pregnancy.
- Medication history, including concomitant medications.
- Query for any AE experienced since informed consent was obtained.

Note that further procedures may be performed at the investigator's discretion in order to adequately screen subjects against eligibility criteria and/or to confirm medical history. Potential subjects who meet all inclusion criteria and none of the exclusion criteria (see Section 5) may be enrolled.

6.1.1.3 Day 0 – Vaccination (gestational week 28 to $36^{0/7}$)

On Day 0, all subjects who have vital signs taken, fetal heart tones checked, and eligibility re-confirmed will be randomized to a treatment group and infant serology cohort. The following procedures will then be performed:

- Query for any AE (and SAE specifically) experienced by the subject since informed consent was obtained.
- Alcohol swab or cleanse the area of vaccination (following the local standard of care), followed by IM injection into the deltoid with the designated study treatment.
- Monitoring for any AEs for approximately 30-60 minutes following vaccination.
- Vital sign (heart rate, blood pressure, respiratory rate, and axillary body temperature) and a fetal heart tone check performed at approximately 30 minutes (range 30-60 minutes) post-vaccination.
- Distribution of the subject diary and oral thermometer for documentation of any AEs (solicited and unsolicited), oral temperature and concomitant medications taken; and documentation of any unscheduled physician visit or hospitalization associated with an adverse event, occurring from the time of discharge through to Day 6 (inclusive). Diaries will provide a telephone number for 24-hour contact to the study staff in the event of concerns, solicited or unsolicited AEs, new obstetrical complications, or symptoms suggestive of an RSV infection.
- Issuance of a Study Identification Card that indicates the maternal subject is part of an investigational vaccine trial and provides the contact number(s) of the obstetrical investigator's study staff. The identification card will also include a list of the clinical signs and symptoms of an RSV infection in adults and infants.
- Instruction for subjects to inform the study site promptly of any severe (grade 3) solicited or unsolicited AE, obstetrical complication, or symptoms suggestive of an RSV infection.
- Verify subject locator information and the delivery center to be utilized.
- Schedule the next visit.

6.1.1.4 Day 7 (+ 2 days) – In-clinic or Home Follow-up Visit

In addition to normal obstetrical follow-up including confirmation of fetal heart tones, all subjects will return to the clinic or will be evaluated by study staff at a home visit on Day 7 for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and axillary body temperature).
- Review and collection of subject diary.
- Query for any unsolicited AEs, MAEs, SNMCs, and SAEs occurring since the last study visit, and any concomitant medications taken for these events. *A physical exam may also be performed to evaluate any adverse event reported.* Subjects will also be queried regarding symptoms suggestive of RSV infection and, in the event onset is within seven

(7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses (see **RSV Illness Surveillance** procedures in Section 6.2).

- Reminder for subjects to contact the site promptly to report any severe or serious AE or obstetrical complication, or symptom(s) suggestive of an RSV infection.
- Distribution of a memory aid for subjects to record any medical events experienced in between clinic visits. (Note that the memory aid is considered a tool that subjects may or may not choose to use, and as such is NOT considered a source document and WILL NOT be collected.) A replacement Study Identification Card will also be provided to all subjects, as needed.
- Schedule the next visit.

6.1.1.5 Day 14 (± 2 days) – In-clinic or Home Follow-up Visit

In addition to normal obstetrical follow-up including confirmation of fetal heart tones, all subjects will return to the clinic or will be evaluated by study staff at a home visit on Day 14 for the procedures listed below.

- Vital sign collection (heart rate, blood pressure, respiratory rate, and axillary body temperature).
- Query for any unsolicited AEs, MAEs, SNMCs, and SAEs occurring since the last study visit, and any concomitant medications taken for these events. *A physical exam may also be performed to evaluate any adverse event reported.* Subjects will also be queried regarding symptoms suggestive of RSV infection and, in the event onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses (see **RSV Illness Surveillance** procedures in Section 6.2).
- Blood draw (10 mL) for post-vaccination clinical safety laboratory assessments (if applicable) and (20 mL) RSV serology. Subjects will be reminded to contact the site to report any severe or serious AE, obstetrical complication, or symptoms suggestive of an RSV infection.
- A replacement Study Identification Card will be offered to all subjects, as needed.
- Schedule the Day 28 visit.

If a subject delivers prior to the Day 14 visit, the procedures discussed above will not be performed and no missed Day 14 visit protocol deviation will be captured. The single exception is the blood draw for the clinical safety laboratory assessment [which only applies to subjects enrolled in the first year of study conduct in any country] that should be obtained at the Delivery visit.

6.1.1.6 Day 28 (± 2 days) – Telephone/SMS Contact, In-clinic or Home Visit Safety Follow-up

Subjects who have not yet delivered will have a safety follow-up performed as a telephone/SMS contact visit using an IRB/IEC-approved script (if applicable), an in-clinic visit, or a home visit. At this visit, whether conducted in-clinic or at home, study staff will assess the general health of the subject and query for any severe unsolicited AEs, SAEs, MAEs, SNMCs, clinical symptoms or signs of a suspected RSV illness, or any new obstetrical complications occurring

since the last visit, and any concomitant medications taken for these events. Subjects participating in this visit via telephone or SMS and who report any severe or serious adverse event or symptoms suggestive of an RSV infection, may be asked to return to the clinic or to schedule a home visit for evaluation of the event(s) to assess any effect(s) it may have on the pregnancy, and to potentially undergo a sampling of upper respiratory secretions for detection of respiratory viruses if symptom onset is within seven (7) days (see **RSV Illness Surveillance** procedures in Section 6.2). The same procedures will be performed for subjects participating in this follow-up as an in-clinic or home visit with the exception that a replacement Study Identification Card will be offered to all subjects, if needed.

6.1.1.7 Delivery (D) – Hospital Follow-up Visit

Subjects will be counselled to notify the obstetrician of the start of labor and will go to the registered hospital or delivery center for delivery where the following procedures will be performed:

- For applicable subjects (i.e., those enrolled in the first year of study conduct in any country) who deliver prior to the Day 14 visit, collection of a venous blood sample (10 mL) for the clinical safety laboratory assessment.
- Collection of a venous blood sample (20 mL) for RSV serology at any time from admission to the hospital and optimally up to 12 hours post-delivery. Note: In extenuating circumstances such as a delivery on a holiday or weekend, the venous blood sample may be obtained up to 72 hours post-delivery.
- Collection of a cord blood sample (at least 5 mL) by the obstetrician or designee immediately upon delivery. If cord blood is not obtained, then this information should be conveyed to the study staff responsible for the infant, so that infant sera may be collected in lieu of cord blood (see Section 6.1.2, Infant Study Procedures at the Delivery Day visit for details).
- Record vital sign data at admission from the subject's medical chart.
- Query for all unsolicited AEs experienced and concomitant medications taken by, or administered to, the subject since the last clinic visit. *(Note: Routine medications for the management of labor and delivery do not need to be recorded.)*
- Documentation of perinatal management including antibiotic therapy and any medical or surgical interventions for cause.
- Documentation of any GBS screening result and treatment.
- Study staff notification of the infant's primary healthcare provider of the child's anticipated participation in the study before or immediately after delivery.
- Reminder of subjects to contact the site promptly to report any symptoms suggestive of an RSV infection.
- Distribution of a replacement Study Identification Card to all subjects, as needed.

6.1.1.8 D+35 (± 7 days) – In-clinic or Home Post-delivery Follow-up Visits

Maternal subjects will return to the clinic or will be evaluated by study staff at a home visit on approximately 35 days post-delivery for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and axillary body temperature).
- Query for any unsolicited AEs (including MAEs, SNMCs, and SAEs) experienced and concomitant medications taken for these events since the last visit. *Note that a physical exam may also be performed at the investigator's discretion to evaluate any adverse event reported.* Maternal subjects will also be queried regarding symptoms suggestive of RSV infection and, if symptom onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses if specific events are present (see **RSV Illness Surveillance** procedures in Section 6.2).
- Blood draw (20 mL) for post-vaccination RSV serology.
- Reminder of subjects to contact the site promptly to report any symptoms suggestive of an RSV infection and replacement of the Study Identification Card to all subjects, as needed.
- Schedule the Day 180 visit.

6.1.1.9 D+180 (± 14 days) – In-clinic or Home Post-delivery Follow-up Visit

Maternal subjects will return to the clinic or will be evaluated by study staff at a home visit on approximately 180 days post-delivery for the following procedures:

- Vital sign collection (heart rate, blood pressure, respiratory rate, and axillary body temperature).
- Pregnancy testing. Note that a positive result will trigger additional follow-up to monitor the outcome of this pregnancy.
- Query for any unsolicited AEs (including MAEs, SNMCs, and SAEs) experienced and concomitant medications taken for these events since the last visit. *Note that a physical exam may also be performed at the investigator's discretion to evaluate any adverse event reported.* Maternal subjects will also be queried regarding symptoms suggestive of RSV infection and, if symptom onset is within seven (7) days, will undergo a sampling of upper respiratory secretions for detection of respiratory viruses if specific events are present (see **RSV Illness Surveillance** procedures in Section 6.2).
- Blood draw (20 mL) for post-vaccination RSV serology.

This visit will mark the end of study participation for the maternal subject. However, maternal subjects with ongoing respiratory episodes will be contacted weekly by telephone/SMS contact and followed until symptoms have resolved or have returned to baseline. In addition, maternal subjects with a positive pregnancy result will be followed for safety through the time of delivery to determine the outcome of this pregnancy.

6.1.1.10 Unscheduled Visits

Maternal subjects will be encouraged to notify the investigator if any severe (grade 3) local or systemic solicited AE occurs during the 7-day post-immunization period, or if any severe, serious, or otherwise concerning AE occurs at any time following vaccination. If symptoms are

presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected.

Note the RSV surveillance visits discussed in Section 6.2 are not considered unscheduled visits.

6.1.2 Infant Subject Study Visit Procedures

6.1.2.1 Visit 1: Delivery – Hospital Follow-up Visit

All procedures, including routine vaccinations that are considered standard of care for the newborn infant may be performed at any study visit which coincides with the usual timing for such procedures. Before any of the following study-specific procedures are performed, informed consent for the infant subject and release of medical records will be reviewed with the maternal subject (i.e., mothers will not be re-consented) or will be obtained from the other parent or guardian if not captured under the institution's policy.

- If cord blood is not collected at the time of delivery (see delivery procedures for maternal subjects in Section 6.1.1.7), a blood sample from the infant (2 mL by venipuncture preferred; 1 mL by heel stick acceptable) should be obtained within 72 hours of birth for RSV serology. *(Note: Cord blood is markedly preferred and all efforts should be directed to obtaining this specimen. A phlebotomy/heel stick within 72 hours is a fall back procedure only. The volume of a postpartum phlebotomy/heel stick must be accounted for within the phlebotomy limits as per the investigator's institution, whereas a cord blood sample need not.)*
- The investigator or a trained designee will perform the following procedures: collection of results from the physical exam, weight, length, frontal-occipital circumference (FOC), and APGAR measurements performed following birth and used to assess the overall health of the infant; and documentation of the mode of infant feeding (e.g., exclusively breastfed, exclusively formula fed, breast milk and supplemented with formula, expressed breast milk, wet nurse, receiving solids), if a smoker or one or more children < 5 years of age will reside in the same household, and whether the infant or another child in the household (< 5 years of age) will be/is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week.
- Issue a Study Identification Card to parents and/or guardians of each infant that indicates that he/she is part of an investigational vaccine trial and provides the contact number to the investigator and study staff responsible for the study-related follow-up of the infant, along with a list of the signs and symptoms of RSV infection in adults and infants.
- Provide instruction to parents and/or guardians to contact the study staff promptly if the infant develops an "RSV-suspect illness" listed in Section 6.2.2, but to seek appropriate medical care for the infant first. This is especially important in instances when the initial evaluating physician providing care to the infant is not affiliated with the study.

6.1.2.2 Visit 2: D+14 (± 3 days) – In-clinic or Home Follow-up Visit

On approximately 14 days post-delivery, all infants will participate in a study visit at home or in-clinic and the following procedures will be performed:

- Query and evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since delivery and concomitant medications taken for these events. *Note that a physical exam may be performed to evaluate any adverse events as needed.* Symptoms of RSV-suspect illness will be sought and, if onset has been within seven (7) days, a sampling of upper respiratory secretions for detection of respiratory viruses will be performed.
- Collection of all healthcare provider-confirmed episodes of wheezing experienced by the infant since the last visit.
- Documentation of the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week.
- A blood sample (1 to 2 mL) will be obtained from infants in phlebotomy **Cohort 1** for RSV serology by venipuncture or heel stick and the method used will be documented.
- Prior to release from the clinic, parent(s) and/or guardians will be reminded to contact the study staff promptly if the infant develops a suspect illness (see RSV Illness Surveillance procedures in Section 6.2). The Study Identification Card will also be offered to the parent/guardian, if needed.
- Schedule the next visit.

Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.3 Visit 3: D+35 (± 7 days) – In-clinic or Home Follow-up Visit

At approximately 35 days after birth, all infants will participate in a study visit at home or in-clinic and the following procedures will be performed:

- Query and evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since birth and concomitant medications taken for these events. *Note that a physical exam may be performed to evaluate any adverse events as needed.* Symptoms of an RSV-suspected illness will be sought and, if onset has been within seven (7) days, a sampling of upper respiratory secretions for detection of respiratory viruses will be performed.
- Documentation of the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week.
- Collection of all healthcare provider-confirmed episodes of wheezing experienced by the infant since the last visit.
- Physical exam and collection of weight, length, and FOC measurements.
- A blood sample (1 to 2 mL) will be obtained from infants in phlebotomy **Cohort 2** for RSV serology by venipuncture or heel stick and method used will be documented.
- Prior to release from the clinic, parent(s) and/or guardians will be reminded to contact the study staff directly if the infant develops a suspect illness (see RSV Illness

Surveillance procedures in Section 6.2). The Study Identification Card will also be offered to the parent/guardian, if needed.

- Schedule the next visit.

Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.4 Visit 4: D+60 (± 7 days) – In-clinic or Home Follow-up Visit

At approximately 60 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 3**. Note also that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.5 Visit 5: D+90 (± 7 days) – In-clinic or Home Follow-up Visit

At approximately 90 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 1**. Note also that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.6 Visit 6: D+120 (± 7 days) – In-clinic or Home Follow-up Visit

At approximately 120 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures performed at the D+35 post-delivery visit, with the exception that the blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 2**. Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.7 Visit 7: D+180 (± 14 days) – In-clinic or Home Follow-up Visit

At approximately 180 days after birth, all infants will participate in a study visit at home or in-clinic for the same procedures that were performed at the D+35 post-delivery visit, with three exceptions:

- The blood sample for RSV serology will only be obtained from infants in phlebotomy **Cohort 3.**
- Infant subjects will complete the first of two developmental tests.
- Most activities associated with active RSV surveillance will conclude at this visit, except for the weekly follow-up of infant subjects with respiratory episodes that are ongoing.

Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit. In addition, parents/guardians of infant subjects will be reminded to contact the site promptly to report any severe, serious, or otherwise concerning AE.

6.1.2.8 Visit 8: D+252 (± 14 days) – In-clinic or Home Follow-up Visit

At approximately 252 days after birth, all infants will participate in a study visit at home or in-clinic and the following procedures will be performed:

- Query and evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since the last visit and to record concomitant medications administered for these events, and reports of any healthcare provider-confirmed episodes of wheezing. *Note that a physical exam may be performed to evaluate any adverse events as needed.*
- Documentation of the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week.
- Collection of weight, length, and FOC measurements.
- The Study Identification Card will also be offered to the parent/guardian, if needed.
- Reminder for parents/guardians of infant subjects to contact the site promptly to report any severe, serious, or otherwise concerning AE.
- Schedule the next visit.

Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.9 Visit 9: D+364 (±14 days) – In-clinic or Home Follow-up Visit

At approximately 364 days after birth, all infants will participate in a study visit at home or in-clinic and the following procedures will be performed:

- Query and evaluation of any AEs, MAEs, SNMCs, and SAEs experienced since delivery and concomitant medications taken for these events, and reports of any healthcare provider-confirmed episodes of wheezing.
- Documentation of the mode of infant feeding, if a smoker or one or more children < 5 years of age reside in the same household, and whether the infant or another child in the household (< 5 years of age) is cared for in a group setting with other children (e.g., daycare) for ≥ 3 days per week.
- Physical exam and collection of weight, length, and FOC measurements.
- Developmental testing for all infant subjects. Parents/guardians of infant subjects with a positive screen detected at both 6 and 12 months of age (as this is an AE), or first appearing at 12 months of age, will be offered repeat Ages and Stages Questionnaire (ASQ)-3 screening at 15 and 18 months of age as a follow-up procedure. Novavax will collect this information as safety data. In addition, appropriate referrals for diagnostic pediatric developmental testing (according to local standards of care) will also be advised for infants with a positive screen identified.
- Parents/guardians may be asked to consent to additional infant follow-up for future respiratory disease such as severe LRTI syndromes or recurrent wheezing. Such follow-

up, if requested, will be voluntary and will be the subject of a separate future protocol and consent document.

Completion of this visit will mark the end of study participation for the infant subject. Note that all procedures, including routine vaccinations that are considered standard of care for a corresponding baby-wellness visit may be performed at this visit.

6.1.2.10 Unscheduled Visits

Parents/guardians will be encouraged to report, or ask the infant's primary healthcare provider/pediatrician to report at any time, any other type of severe, serious, or otherwise concerning AE. If symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected.

Note the RSV surveillance visits discussed in Section 6.2 are not considered unscheduled visits prior to D+180. Symptoms suggestive of an RSV-suspect illness reported during passive surveillance but after D+180, will be captured as AEs and *not* on the RSV Surveillance page.

6.2 RSV Surveillance: Active and Passive

6.2.1 Active and Passive Components of Surveillance

RSV surveillance will comprise both active and passive components. All queries for RSV-suspect illnesses will be made using an IRB/IEC-approved script, if applicable.

- Active Surveillance (applicable to all subjects through the D+180 visit):
  - Study staff will contact the maternal subject and a parent/guardian of the infant subject via telephone call or SMS on a once weekly interval through the D+180 visit to query for an RSV-suspect illness. Newly-discovered RSV-suspect illnesses as assessed by the presence of "trigger symptoms" (see Section 6.2.2 and Table 2) will precipitate a home or clinic visit for evaluation (see Section 6.2.3).
  - Study staff will re-evaluate (at home or in the clinic) all *infant* subjects with RSV-suspect illnesses between 2 and 3 days after any initial RSV surveillance visit to ascertain worsening in the illness. This re-evaluation will include the same procedures outlined in Section 6.2.3.
- Passive Surveillance (applicable at any time during the study):
  - If the maternal subject develops any symptom suggestive of an RSV-suspect illness, or shows signs of worsening of a previously-evaluated RSV-suspect illness, she should contact the study site directly within 3 days of the onset/worsening of symptoms.
  - If an infant develops symptoms of an RSV-suspect illness while on study, or shows signs of worsening of a previously-evaluated RSV-suspect illness, parents or guardians should contact study staff directly within 3 days of the onset/worsening of symptoms.
  - Any newly-discovered RSV-suspect illnesses as assessed by the presence of "trigger symptoms" (see Section 6.2.2 and Table 2) will precipitate a home or clinic visit for evaluation (see Section 6.2.3).

- Study staff will re-evaluate (at home or in the clinic) all *infant* subjects with RSV-suspect illnesses between 2 and 3 days after any initial RSV surveillance visit to ascertain worsening in the illness. This re-evaluation will include the same procedures outlined in Section 6.2.3.
- If the initial evaluation of the maternal or infant subject for an RSV-suspect illness is performed by a healthcare provider, not affiliated with the study (e.g., in an urgent care clinic, emergency room, or other outpatient clinic), he/she should notify the study staff of the maternal or infant subject's status as per the information provided on the Study Identification Card.
- Note: symptoms suggestive of an RSV-suspect illness reported during passive surveillance but after D+180 will be captured as AEs and *not* on the RSV Surveillance page.

Please refer to the **Study Operations Manual** for additional details regarding the procedures performed during the RSV Surveillance.

6.2.2 Trigger Symptoms for RSV-suspected Illness

Surveillance for RSV will be based on the occurrence of "RSV-suspected illness" characterized by one or more of the following **Trigger Symptoms** in infant and maternal subjects (Table 2) that persist for a period of ≥ 24 hours, either in a continuous or intermittent manner, and are assessed as "atypical" (by the maternal subject herself, or a parent or other routine caregiver for the infant) in nature.

Table 2: Signs and (Trigger) Symptoms of RSV-suspected Illness in Infant and Maternal Subjects

Symptoms in Infant Subjects	Symptoms in Maternal Subjects
• Cough	• Cough
• Stuffy nose or runny nose	• Stuffy nose or runny nose
• Trouble breathing or fast breathing when resting	• Shortness of breath
• Trouble feeding or not feeding well	• Sore throat
• Less active than normal when awake	• Fever
• Sleeps more than normal	• New or increasing wheezing
• More crying or more fussy than normal	• New or increasing sputum production
• Wheezing (whistling noise when breathing)	

Note: It is not intended that these triggers for reporting be specific, or diagnostic of RSV, or LRTI; rather the goal is to capture acute respiratory illnesses generally. Physician (or qualified clinical designee) evaluation, (including an assessment of the infant's oxygen saturation level via pulse oximetry readings and respiratory rate by observation for 1 minute at the time of presentation of the acute illness) will capture those features which characterize LRTI, tachypnea, and hypoxemia or severe hypoxemia; molecular diagnosis by reverse transcription-polymerase chain reaction (RT-PCR) will detect RSV. These symptoms are intended to be a sensitive, rather than specific, trigger for further evaluation.

6.2.3 Clinical Study Site Response to Reports of Initial Trigger Symptoms

In response to a report via active or passive surveillance of **Initial Trigger Symptoms**, the study site staff will:

- Arrange for an in-clinic or home visit as soon as possible, but not later than 7 days after symptom onset, for evaluation by the study physician/qualified clinical designee of the subject (infant or mother) displaying the symptom/s and/or findings listed in Table 2.
- Arrange for an in-clinic or home visit by a study physician/qualified clinical designee for evaluation as soon as possible within 7 days of symptom(s) onset for maternal or infant subjects who received care for trigger symptoms at a non-study, affiliated medical facility. *Note that this visit would only be applicable to subjects who are receiving outpatient care or have been released from inpatient care.*

Procedures to Occur During the Visit:

- *Specific for Symptomatic Infants:*Measure the respiratory rate on room air (if possible) for all *symptomatic* infants. This measurement should be performed first, on a calm infant, and should be performed by observation only (i.e., without stethoscope auscultation) for a full, timed one minute period.
  - If the result is ≥ 60 bpm in an infant 0 to 59 days of age or ≥ 50 bpm in an infant ≥ 60 days of age, a second timed one minute count should be obtained.
  - If a second count is obtained, the lower of the two observations should be recorded.
- Measure the SpO_2 via pulse oximetry (using study-specific pulse oximeter) for all *symptomatic* infants, which is to be performed when the infant is calm and not crying, and before administration of oxygen supplementation. The lowest stable SpO_2 observed during a one minute measure should be recorded. *Note that the oxygen **should not** be removed to measure SpO_2 in infants already receiving oxygen supplementation at the time of assessment.* Please refer to the **Pulse Oximeter Manual** for more details.

For all Symptomatic Subjects (Maternal and Infant):

- Review and confirm the history of respiratory illness, including the approximate date of first symptom onset.
- Perform an examination of the *symptomatic* infant subject to ascertain, by observation or auscultation, the presence of the LRTI manifestations listed in Table 3 below.
- Collect a respiratory specimen from the *symptomatic* subject for detection of respiratory viruses.
  - Symptomatic maternal subjects will have a nasal and throat specimen collected. The nasal secretion will be collected by mid-turbinate swabbing.
  - Symptomatic infant subjects will have a mid-turbinate nasal swab collected.
  - RT-PCR testing for RSV and other viruses by the study laboratory will be for the purposes of this protocol, and not for clinical care.
  - Respiratory specimens collected from the maternal and infant subject during an RSV surveillance visit may be split so that samples are provided for this protocol and for

a qualified local laboratory supporting clinical care if the attending physician would ordinarily regard testing for bacterial and/or viral pathogens as warranted.

- Collect vital signs other than respiratory rate (heart rate, blood pressure [if available for the infant], and axillary body temperature) for the *symptomatic* subject.
- Ascertain any medically-attended visit by the subject in response to the respiratory illness.
- Ascertain any new concomitant medications resulting from the respiratory illness.
- Notify the infant's primary healthcare provider of the RSV surveillance visit and outcome, as necessary.

Table 3: Clinical Signs/Symptoms to be Clinically Evaluated during an RSV-suspected Illness

Infant Subjects	Maternal Subjects

• Cough
• Nasal flaring
• Difficulty breathing, manifesting in at least one of the following clinical signs or symptoms:
  ○ Lower chest wall indrawing
  ○ Subcostal retractions
  ○ Abnormal breath sounds, inclusive of:
  • Stridor,
  • Rales,
  • Rhonchi,
  • Wheezing,
  • Crackles/crepitations
  ○ Observed apnea
	• Cough
	• Nasal congestion
	• Fever
	• Runny nose
	• Sore throat
	• Dyspnea
	• New or increasing wheezing
	• New or increasing sputum production

6.2.4 Follow-up of RSV-Suspect Illnesses

Following the evaluation of an RSV-suspect illness outlined in Section 6.2.3, the clinical site will:

- For *symptomatic infant* subjects, schedule a follow-up visit in 2 to 3 days to ascertain whether the illness is worsening.
  - The follow-up visit will include the same procedures outlined in 6.2.3.
  - Parents/guardians will be strongly encouraged to report any worsening after the follow-up visit, including hospitalizations, which may trigger any number of additional follow-up visits at the investigator's discretion.
  - In the event that an infant is hospitalized, site staff are encouraged to perform a follow-up visit in-hospital, if permissible under local administrative and ethical review procedures.
- For *symptomatic maternal* subjects, and for *symptomatic infant* subjects after the first follow-up visit described above, a weekly contact by telephone/SMS will be performed to ascertain respiratory symptom status through to the D+180 visit, and to monitor the

status of RSV-suspect illnesses until symptoms have resolved, or have returned to baseline if after the D+180 visit.

- In the event new and/or worsening symptoms are reported during active or passive follow-up, an in-clinic or home RSV-surveillance visit may be scheduled at the investigator's discretion for an evaluation to occur as soon as possible, and a re-evaluation as per Section 6.2.3 may be performed.
  - At the investigator's discretion, collection of ONE more respiratory specimen for pathogen detection for infant subjects who have developed qualitatively different or quantitatively worse symptoms. *Note that no more than 3 respiratory specimens should be collected from an infant within the same episode.*
  - If the new or worsening symptom in the maternal subject is associated with a respiratory episode for which a specimen has already been obtained, the investigator may exercise his/her judgement as to the utility of an additional swab.

6.2.5 Definitions and Rules for RSV Surveillance

- If possible, study staff should collect symptom data for any RSV-suspected illness for maternal and infant subject pairs during the same weekly telephone call or SMS contact. In the event the maternal and infant subject pair have independent clinic visits for assessment of an RSV-suspected illness within a given surveillance period, the subsequent weekly telephone or SMS contact for the next surveillance period can be resynchronized based on the earlier of the two contacts. For example, if a maternal subject had a clinic visit to evaluate an illness on Monday of surveillance week (SW)-1, this would trigger the next contact for the following Monday of SW-2. If the infant subject of the same mother had a clinic visit to evaluate an illness on Thursday of SW1, his/her next weekly contact could be rescheduled to coincide with the maternal subject contact on Monday of SW-2. (The intent of this provision is to relieve the need for mother/infant pairs to make multiple follow-up visits in a one-week period.)
- A new respiratory illness will be deemed to occur any time a one week (7 day) interval elapses during which the subject is free of respiratory symptoms. When a subject is determined to have a new respiratory illness, the subject should be evaluated at an in-clinic or home visit by study staff for this new episode (as described in Section 6.2.3).
- A medically-attended visit will be deemed to have occurred whenever the subject or a parent/guardian of the infant subject precipitates a visit or home encounter with a physician or other healthcare provider for the purpose of evaluation or treatment of a respiratory illness. *Note that at-home or in-clinic visits undertaken specifically to fulfill the requirements of this protocol, for illnesses which would not otherwise cause the parent/guardian to present the infant for care, are NOT "medically-attended visits," with the exception noted immediately below.*
- In the event that the investigator is also the subject's primary care physician (PCP)/general practitioner (GP), any RSV surveillance visit will be counted as a "medically-attended visit."
- Note that the intent of the evaluation of subjects with *Trigger Symptoms* is fulfillment of the objectives of this protocol. The investigator or study site staff should use their

best professional judgment to ensure that subjects receive prompt medical care appropriate to their clinical condition, if necessary either by referring the subject to their usual physician or medical care facility, or providing care if the investigator is the subject's primary physician or if the case is emergent. The collection of the study data to support the primary and secondary efficacy endpoints are key objectives of this trial, but when necessary, appropriate medical care should supersede this goal.

- Respiratory events captured as efficacy endpoints will NOT be recorded in the AE electronic case report form (eCRF) or AE eSource page, with the exception of those that fulfill the definition of an SAE. Full particulars of the SAE(s) will also be captured in the SAE report form.
- Respiratory events ongoing at the 6 months post-delivery visit (D+180) will be followed by study staff at weekly intervals until symptoms resolve or return to baseline.

6.3 Concomitant Therapy

Maternal and infant subjects may receive all concomitant medications and procedures deemed necessary to provide adequate healthcare during the study, with the exception of those specified in the exclusion criteria. Routine medical standards of care are permitted, including vaccines needed for emergent indications (e.g., tetanus booster in response to a penetrating injury and palivizumab prophylaxis during RSV season of infants born prior to 35 weeks). Routine vaccination is permitted at all times for the infant (e.g., well-baby vaccinations).

Concomitant medications, procedures, and hospitalizations will be recorded throughout the study including the period from the day Informed Consent Form (ICF) is signed through the end of study follow-up. All new or changed concomitant medications taken through the entire study period for both maternal and infant subjects will be recorded (excluding routine medications administered for the management of labor and delivery). The investigator will document whether the concomitant medication was provided for either a solicited systemic or an injection site adverse event.

6.4 Declining Study Treatments or Procedures

The maternal subject and parents/guardians of the infant subject have the right to decline study treatment or other study procedures for themselves or their infants for any reason at any time during the study. If a maternal subject declines study procedures subsequent to receipt of a treatment dose or if a parent/guardian of the infant declines study procedures at any time during the study, it should be recorded as a protocol deviation and the reason should be clearly documented in the source document. The maternal subject and/or parent/guardian of the infant will be asked to complete all other study procedures for herself and infant, as applicable. If the maternal subject or parent/guardian of the infant does not wish for herself or the infant to remain in the study, either can choose to withdraw consent and discontinue at any time as outlined in Section 6.5.

The investigator may, at his/her discretion, restrict a maternal or infant subject from receiving a specific study procedure if he or she consider it to be in the maternal or infant subject's best interest to do so, but can suggest that both 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.

6.5 Premature Discontinuation from Study

Pregnant subjects who provide consent but are found to be ineligible on screening will be informed of the reason for ineligibility and may be provided with local medical referral by the investigator as appropriate, but will receive no further study follow-up.

Maternal and infant subject participation in the study is strictly voluntary. Maternal subjects and/or parents/guardians of infants have the right to withdraw themselves and/or the infant from the study at any time and for any reason, without penalty. The investigator may, at his/her discretion, discontinue subjects from the study if he/she considers it to be in the participants' best interest to do so, or if the maternal subject or the infant's parent or guardian is not willing or able to comply with the study requirements. Novavax will be notified immediately by the investigator if a subject prematurely ends study participation. The reason for early discontinuation will be clearly documented in the electronic Case Report Form (eCRF) or eSource. A withdrawal due to an AE will initiate additional reporting requirements as outlined in Section 8.7.

In the event of early termination, investigators will make every reasonable effort to perform study completion procedures. Study completion procedures will include a query for any MAEs, SNMCs, or SAEs occurring since the last study visit, and any concomitant medications taken to treat these events, as well as:

- For maternal subjects: a blood draw for serology testing (20 mL) at any time and for clinical laboratory safety assessments (10 mL) in applicable subjects (i.e., those subjects with safety labs performed at screening) if before the Day 14 visit.
- For infant subjects: a blood draw for serology testing (1 to 2 mL by venipuncture or heel stick with documentation of the method used, but not within two weeks of a prior phlebotomy) if prior to the:
  - Day 90 visit for **Cohort 1** subjects,
  - Day 120 visit for **Cohort 2** subjects, and
  - Day 180 visit for **Cohort 3** subjects.

Additionally any SNMC or SAE that continues beyond the duration of the study is to be followed to resolution or until the event becomes stable. Maternal and infant subjects who terminate from the study early will not be replaced.

6.6 Study Termination

Novavax reserves the right to terminate the study at any time for any reason. When the study is terminated (either prematurely or as scheduled), the investigator will notify the IRB/IEC for the study, and other authorities as required by local regulatory requirements.

The scheduled end of the study will be the completion of the last post-delivery Day 364 follow-up visit with the last infant enrolled in the study.

7 LABORATORY REQUIREMENTS

Appendix 3 specifies the maximum amount of blood that will be drawn from maternal (120 mL) and infant (from 3 to 6 mL, depending on the collection method) subjects, and from the cord blood at delivery (a minimum of 5 mL) for clinical safety and/or immunogenicity laboratory procedures to be completed throughout the study. This amount may increase for maternal subjects if repeat laboratory safety assessments are performed (see Section 8.2.3 for more details).

Specific information regarding the central or local laboratories that will perform clinical laboratory safety testing, RSV serology testing, and genotyping of respiratory specimens is provided in the **Study Operations Manual**.

7.1 Clinical Laboratory Testing

The following laboratory tests will be performed by a qualified central laboratory (unless otherwise stated) designated by Novavax on blood samples collected from maternal subjects enrolled in the first year of study conduct in any country at the screening visit (Days -28 to 0) and on Day 14 (unless the subject delivers prior to this visit at which time the blood sample will be obtained at delivery):

- Serum chemistry – alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), creatinine, and blood urea nitrogen (BUN).
- Hematology – hemoglobin, platelet count, and white blood cell (WBC) count.

Additional clinical laboratory antigen tests/serologies for HIV, syphilis, HBV, and HCV detection will be performed by a central or local laboratory at the screening visit, if results are not available in prior data collected during the course of the current pregnancy.

A urine pregnancy test will be administered to all maternal subjects at the D+180 visit; a positive result will trigger additional follow-up to determine the outcome of the pregnancy.

7.2 Assessments of Immunogenicity

Anti-F IgG antibody levels in EU, PCA concentrations, and neutralizing antibody titers to RSV/A and RSV/B will be determined at protocol-specified time points for all subjects. Completion of microneutralization testing may be staged, due to its cumbersome nature, and results may be reported in addenda to the primary clinical study report. Serological immunogenicity parameters will include GMEU, geometric mean concentration (GMC), or GMT (as appropriate); GMFR, SCR, and SRR by treatment group for most analyses. Comparisons across groups will be performed as described in the statistical analysis plan and briefly in Section 10.5. Blood samples from maternal subjects will be drawn for RSV serology testing at screening (Day -28 to 0) and on Day 14 prior to delivery, at delivery, and on Days 35 and 180 post-delivery. Blood samples from infant subjects will be drawn for RSV serology testing at post-delivery study Days 14 and 90 for Cohort 1 infants, on Days 35 and 120 for Cohort 2 infants, and on Days 60 and 180 for Cohort 3 infants. Infant subjects may also have blood drawn within 72 hours of birth if cord blood is not collected at delivery.

7.2.1 Anti-F IgG ELISA

For the anti-F IgG ELISA, 96-well microtiter plates are coated overnight with the RSV F antigen, then blocked with an irrelevant protein to reduce non-specific binding. Serial dilutions of subject sera are added starting minimally at 1:10. Serial three-fold dilutions of an anti-F IgG reference standard as well as negative and positive controls are also included. After incubation, wells are washed extensively and an anti-human IgG peroxidase conjugated antibody is added to detect the presence of anti-RSV F IgG specific antibodies in the wells. Following secondary antibody incubation and extensive washing, substrate is added to the plates, color is allowed to develop, and the plate is read at an optical density (OD) of 450 nm with subtraction at 630 nm to account for background. A four-parameter logistic (4-PL) curve fit is applied to the reference standard and the reported titer is determined from the mean calculated from serial dilutions, interpolated from the reference standard concentrations. A full description of the validated method can be found in Novavax standard operating procedure (SOP) numbered P_SOP_00659.

7.2.2 Palivizumab-Competitive Antibody (PCA) ELISA

In the PCA ELISA, 96-well microtiter plates are coated overnight with the RSV F antigen, then blocked with an irrelevant protein to reduce non-specific binding. Serial dilutions of test sera, diluted minimally at 1:4, are incubated with a fixed amount of biotin-labeled palivizumab in the RSV F-coated plates. Reference standards as well as negative and positive controls are also included. After incubation to reach binding equilibrium, the plates are washed and then incubated with avidin-conjugated horseradish peroxidase. After additional washing, substrate is added to the plates, color is allowed to develop, and the plate is read at OD_{450} with subtraction at 630 nm to account for background. Palivizumab-like antibodies in the test serum are quantitated based on OD values corresponding to 50% binding of unlabeled palivizumab. The final concentration is obtained by linear interpolation/extrapolation of the reference curve adjusted by dilution factor using a 4-PL curve fit analysis. The binding of biotinylated palivizumab to the antigen on the plate reflects the competition of palivizumab-like antibodies from human serum. A full description of the validated method can be found in Novavax SOP numbered P_SOP_01066.

7.2.3 RSV/A and B Microneutralization (MN)

Tests for serum neutralizing antibodies against a minimum of one RSV/A and B group viruses are performed using a MN assay developed by P.A. Piedra and colleagues at the Baylor College of Medicine. This assay is well-controlled and has been extensively tested for over 20 years, in both seroepidemiology and vaccine studies, and has been used to estimate potential protective titers [Piedra 2003b]. The RSV/A and B MN assay is qualified.

In brief, RSV/A and RSV/B stocks are prepared in HEp-2 monolayers, divided into aliquots, and stored at -70ºC as previously described [Piedra 2003b, Suara 1996]. Duplicate serial two-fold dilutions of sera are added to a constant virus inoculum in a 96-well microtiter plate. HEp-2 cells are then added to each well and plates are incubated for 6 to 7 days. Positive (no test serum) and negative (no virus) controls are included. Multiple standard control sera with established titers across the dynamic range of the assay are included in each assay run, and their titers must conform to pre-specified acceptance criteria in order for results of that run to be

valid. The viral cytopathic effect (CPE), defined as tissue destruction, is determined visually after the cells are fixed with formalin and stained with crystal violet. The neutralizing antibody titer is defined as the reciprocal of the serum dilution at which > 50% reduction in viral CPE was observed.

7.3 Detection of RSV and Other Pathogens by RT-PCR

A respiratory specimen will be collected as soon as possible after onset of illness in maternal or infant subjects with an RSV-suspected illness that is accompanied with the symptoms listed in Table 2. The specimen will be processed and subjected to a commercially available multiplex RT-PCR for identification of a range of common viral pathogens in addition to RSV. Instructions on how to obtain the respiratory specimen are provided in the **Study Operations Manual**. *Note that the testing described in this section will be for research purposes and the protocol does not contemplate use of these data for clinical care; which will be the responsibility of the subjects' primary physicians and their local laboratory services.*

7.4 Retention and Use of Archived Specimens

Serum specimens may be archived by Novavax or its contractors for a period not to exceed 25 years. The archived sera, which will not contain information that can identify a subject, may be used for repetition of the assays listed above (Section 7.2) using different RSV antigens, or for other exploratory assays of RSV immunity in development. Archived sera may also be used for clinical laboratory testing for safety if needed to evaluate an adverse event, provided that a) sample storage falls within conditions previously validated by the clinical laboratory to yield interpretable results (or an appropriate control strategy can be used to evaluate potential storage impacts), and b) such testing will not include either assays to detect HIV infection, or any genetic testing. Archived samples may also be used to create positive or negative panels for quality control or for assay development related to other infectious diseases (excluding HIV), in which case they will be anonymized. The above uses will be outlined in the Informed Consent document.

8 ASSESSMENT OF SAFETY

The safety assessments performed in this study will include a seven-day solicited AE profile in the vaccinated maternal subject, as well as an extended unsolicited AE profile through six (6) months after delivery. Additionally, vaccine safety will include measures that assess for potential pregnancy/labor and delivery complications for the maternal subject, and for potential safety concerns for the infant exposed to anti-F antibodies *in utero* via transplacental immunization. The infant's health status will be assessed for any adverse events including physical and/or developmental impairments, as well as increased severity of RSV illness upon natural exposure. Because safety outcomes are different based on the subject population (i.e., maternal subjects vs. infant subjects) under evaluation, AE assessments specific to the maternal or infant subject are indicated in this section.

8.1 Adverse Events

Adverse events (AEs) 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 or due to a procedure performed in the trial 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.

Data concerning ALL adverse events will be collected at all scheduled visits for the entire study period for maternal subjects (i.e., from the time informed consent is obtained though post-delivery study Day 180) and through one year of life for infant subjects.

- In addition to the scheduled visits, maternal subjects will be encouraged to return to the clinic or notify the investigator if any severe (grade 3) local or systemic solicited AE occurs during the 7-day post-immunization period, or if a severe AE, a serious AE, or any other AE worrisome to the subject occurs at any time following vaccination.
- Parents/guardians will also be encouraged to report, or ask the infant's primary healthcare provider/pediatrician to report at any time, any other type of severe, serious, or otherwise concerning AE.
- If at a scheduled or unscheduled visit, symptoms are presented that would require a physical exam to adequately assess potential AEs, the exam should be performed and vital signs collected.

Adverse events will be recorded as observed by the investigator, designated personnel, or as provided by the maternal subject on the diary card or during a face-to-face visit with the maternal subject or the infant's parent/guardian. Full details of the AE (i.e., nature, date of onset and recovery as well as an assessment of severity, relationship to study agent, seriousness, treatment and outcome) will be recorded in the source documentation and captured in the eCRF

or entered into the eSource directly, and will generally require the investigator(s) causality assessment, except as discussed in subsequent sections.

8.2 Maternal Adverse Events

8.2.1 Solicited Adverse Events Collected by Subject Diary

Maternal subjects will be provided with a diary for the documentation of solicited and unsolicited AEs, daily recording of their oral temperature, and concomitant medications and procedures starting on vaccination day and for six days following vaccination (i.e., from Day 0 to Day 6, inclusive, or 7 days total). A series of local injection site and systemic reactions that are reasonably likely to occur in vaccine programs (Table 4) will be solicited daily in the diary and standardized severity grades offered to the subject. A standard tool for the measurement of visible local reactions will be provided (see example provided in Appendix 4) as will a digital oral thermometer. Maternal subjects will also be asked to record any physician visits or hospitalizations, and any unsolicited AEs experienced during Day 0 through Day 6. In addition to reporting grade 3 solicited adverse events in the diary card, subjects should be encouraged to contact the Investigator by telephone if these occur. The investigator may request an *ad hoc* clinic visit at his/her judgment, and should enter any grade 3 solicited adverse events reported by telephone in the solicited AE eCRF or AE eSource Page promptly, even if the balance of diary data is not yet available.

Table 4: Listing of Diary Solicited Events

Injection Site (Local) Events	Systemic Events	
Pain	Body temperature (oral)	Nausea
Bruising	Chills	Vomiting
Redness	Muscle pain	Headache
Swelling	Joint pain	Fatigue
	Diarrhea	

Note: All events listed will be solicited by diary for seven days following vaccination (i.e., from Day 0 to Day 6, inclusive) and will be categorized as solicited events. Events reported outside this window will be categorized and reported as unsolicited AEs.

Standard severity grading definitions will be provided in the diary. Grading of visible, measurable injection site reactions will be based on the Food and Drug Administration (FDA) Guidance for Industry, Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). Definitions are summarized in Table 6. Body temperature (for assessment of fever) during pregnancy will be collected as a continuous variable and graded by the investigator based on third-trimester values published in Sheffield et al. [2013] (see Table 7) and also provided in the Toxicity Grading Scale (TGS) located in the **Study Operations Manual**.

Investigators will not be required to assess causality of solicited adverse events specifically named in the diary if onset is during the solicitation period (these will be presumed to be treatment-related). Adverse events consistent with the solicited adverse events listed in the diary, but with onset after the solicitation period (i.e., post-Day 6), will be captured as unsolicited AEs and are subject to all procedures for unsolicited AE data.

Solicited AEs, collected from the subject diary, which continue after the collection period (i.e., post-Day 6) will be followed to resolution. The continuing, solicited AE will be captured by verbatim term, on the AE eCRF or AE eSource page. Investigators will be required to assess severity of the continuing solicited adverse event(s) starting from the day after the last diary entry until resolution.

8.2.2 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 or eSource page promptly, even if the balance of diary data is not yet available.

All unsolicited AEs occurring in maternal subjects will be assessed for severity (as defined in Section 8.8) and for causality (as discussed in Section 8.9), and will be documented in the source documents and captured in the eCRFs or entered into the eSource directly.

8.2.3 Clinical Laboratory Findings as Adverse Events

Clinical laboratory parameters will be tabulated in study reports by grades using the Toxicity Grading Scale (TGS) provided in the **Study Operations Manual**, which is based on third-trimester values published in Sheffield *et al.* [2013]. Note that normal ranges for these parameters are based on reference ranges appropriate for women in the third trimester of a pregnancy.

Laboratory values that show an increase in the toxicity grade relative to baseline values in the same subject, and *attain* at least grade 2 (e.g., normal or grade 1 to grade 2 or higher) will be reported as AEs (along with the severity grade). Repeat testing will be conducted as defined below until the laboratory parameter returns to baseline, becomes stable, or an explanatory diagnosis is available:

- Grade 2 events - weekly, from the time the investigator becomes aware of the abnormal laboratory parameter.
- Grade 3 events - every 72 hours from the time the investigator becomes aware of the abnormal laboratory parameter.

The investigator may also elect to report less severe abnormalities as AEs (e.g., grade 1 events), at his/her discretion, if the abnormality is of sufficient concern to trigger, or should have triggered, a diagnostic evaluation (including repeat testing).

8.2.4 Vital Sign Abnormalities as Adverse Events

Severity grades for vital signs are provided in the TGS located in the **Study Operations Manual**. These ranges are adopted directly from the third-trimester values in Sheffield *et al.* [2013], and are summarized in Table 7 for fever. The toxicity grade range for a fetal heart tone abnormality is also provided in Table 7. For the purposes of reporting vital sign abnormalities as AEs, those values that show an increase in the toxicity grade relative to the baseline values (in the same subject) and *attain* at least a grade 2 (e.g., normal or grade 1 to grade 2, or grade 2 to grade 3) must be reported as an AE. Investigators may report lesser abnormalities as AEs if indicated based on clinical judgment. Abnormal vital signs may be repeated at the investigator's discretion, and because these measures are highly labile, they should only be reported as AEs when the investigator believes there is a meaningful physiologic change. An exception is made for the fetal heart tones measure, which may be repeated, but should also be reported as an AE if an abnormality is consistently observed (i.e., present on more than one observation) with repeat testing.

8.3 Infant Subject Safety Assessments

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), MAE, or SNMC (as defined in Section 8.4). All unsolicited AEs will be assessed for severity (as defined in Section 8.8) and for causality (as discussed in Section 8.9), and will be documented in the source documents and captured in the eCRFs or entered into the eSource directly. Severity for all unsolicited events, including those for which numerical values may be available (e.g., vital signs or clinical laboratory parameters) will be based on interference with daily-activities and/or whether medical intervention/therapy is required, according to the investigator's medical judgment.

Events that meet the threshold for SAEs (as discussed in Section 8.5), will be designated as such, and are associated with enhanced reporting requirements (see Section 8.7).

8.3.1 Ages and Stages Questionnaire

The Ages & Stages Questionnaires®, Third Edition (ASQ-3™) consists of a brief (10-15 minute) parent questionnaire that is then scored by health professionals. It is designed as a screening tool to pinpoint developmental progress in children between the ages of one month to 5 ½ years. One of the strengths of the ASQ is that it employs a parent-centric approach, although assistance by site staff is permissible (http://agesandstages.com/). Developmental assessments will be performed at 6 and 12 months (assessment for infants born prematurely may use age-appropriate adjusted scoring) of age for all infant subjects. For purposes of reporting the developmental screening as AEs, only abnormalities observed at both 6 and 12 months of age will be reported as an AE. Parents/guardians of infant subjects with a positive screen detected at both 6 and 12 months of age, or first appearing at 12 months of age, will be offered repeat ASQ screening of their infant at 15 and 18 months of age as a follow-up procedure. In addition, appropriate referrals for diagnostic pediatric developmental testing

(according to the local standards of care) will also be advised for infants with a positive screen identified.

As a guidance, *and solely for the purposes of consistency within this protocol*, it is suggested that investigators report ASQ abnormalities which persist at 6 and 12 months in a given infant as an AE that is "moderate" in severity. If diagnostic developmental testing is undertaken, the event should be further classified as a medically-attended event (MAE, see Section 8.4). If diagnostic evaluation, during the trial or afterward, leads to the diagnosis of a persistent developmental disability, the event then also becomes a serious adverse event (SAE, see Section 8.5) and should be reported as such.

8.4 Medically-Attended Events and Significant New Medical Conditions

Medically-attended events (MAEs) are adverse events which result in an unscheduled visit to a healthcare provider (e.g., physician, midwife, or other provider as per local standards of care) due to symptomatic illness or injury. These may include office visits, clinic visits, home consultations, emergency room evaluations for non-life-threatening events, and hospitalizations.

Significant new medical conditions (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. For example, while new diagnoses of presbyopia or tinea versicolor are chronic conditions, they are not SNMCs because no significant change in health status is implied. Similarly, adverse events which are isolated, treatable events that resolve and do not require chronic therapy are also not SNMCs (examples could include an uncomplicated acute urinary tract infection or a simple fracture resolved with conservative treatment and with no residual disability). In contrast, new diagnoses of rheumatoid arthritis or coronary artery disease are SNMCs because they imply a long-term change in health status and require ongoing medical management.

The eCRF/eSource will provide a field in which the investigator may designate AEs as MAEs, SNMCs, or both. Because of the significance of the designation for the subject's health, long-term medical management, and for evaluation of vaccine safety, SNMCs are expected to be substantiated diagnoses, not isolated symptoms which might or might not be an SNMC, and the Investigator should record sufficient data in the source document to support the diagnosis.

Full details of MAEs and SNMCs (i.e., nature, date of onset and recovery (if applicable) as well as an assessment of severity, relationship to study agent, seriousness, treatment, and outcome) will be recorded in the source documentation and captured in the eCRF or entered into the eSource directly, and will require the Investigator(s) causality assessment.

8.5 Serious Adverse Events

An 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.
  - 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), or
- 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in in-patient hospitalization. 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.

The eCRF or eSource will provide a field for designating an AE as an SAE. SAEs are associated with enhanced reporting requirements (see Section 8.7).

8.6 Maternal/Fetal/Neonatal Adverse Events of Special Interest

Table 5 summarizes and defines a series of maternal, fetal, and 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 above 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). Investigators should strive to collect the same level of data as for any SAE, and are encouraged to use the exact terms in Table 5 to report events meeting these definitions (see Table 5 footer for exceptions for reporting of neonatal and infant death). Note that the SAE eCRF/eSource will provide a field for designating an SAE report as a Maternal/Fetal/Neonatal Adverse Event of Special Interest (MFNAESI). Some MFNAESIs are open to interpretation as to which subject should be recorded as sustaining the event. Table 5 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 GA at birth, the study defined EDD and the birth date will be used to determine the

gestational age (GA) at birth for the summary of the preterm birth categories (Very preterm and Moderate to late preterm).

Table 5: 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: • Antepartum • 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: • Very preterm: 28 to < 32 weeks gestation • 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. Pre-Eclampsia: A hypertensive disorder of pregnancy with: • 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 proteinuria (≥ 300 mg of urinary protein / 24 hours; or protein/ creatinine ratio ≥ 0.3, dipstick reading of 1+), or • In the absence of proteinuria, new-onset hypertension with the new onset of any of the following: o Thrombocytopenia (platelet count <100,000/ μL), 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), o Impaired liver function, o Pulmonary edema, o Cerebral or visual symptoms. Eclampsia: All components of Pre-Eclampsia, with convulsions.	Mother
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: • Very early neonatal death: < 24 hours • Early neonatal death: birth to < 7 days • Late neonatal death: 7 to < 28 days	Infant

Table 5: Maternal/Fetal/Neonatal Adverse Events of Special Interest

Term	Definition	Reported as an Event In
Infant Death*:	A post-neonatal death that occurs between 28 days and 1 year of life.	Infant
Low Birth Weight:	Subcategorized as: • Low birth weight: < 2,500 grams • Very low birth weight: < 1,500 grams • Extremely low birth weight: < 1,000 grams	Infant
Intrauterine Growth Restriction or Retardation (IUGR):	A fetus whose estimated weight is below the 10th percentile for gestational age and whose abdominal circumference is below the 2.5 percentile.	Infant
Small for Gestational Age (SGA):	Defined as a birth weight < 10% for infants of the same gestational age and gender, in the 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: • Due to hypoxic insult (intrapartum), • Due to another cause.	Infant
Hypoxic-Ischemic Encephalopathy:	A syndrome of abnormal neurological behavior in the neonate, which is frequently associated with multi-system dysfunction and follows severe injury before or during delivery associated with hypoxic and/or ischemic event.	Infant
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.

8.7 Safety Reporting Requirements and Timelines for SAEs and Certain Other Events

Any SAE must be reported (using the SAE Report Form) to Novavax Product Safety within 24 hours of the investigator's first knowledge of the event, regardless of the presumed relationship to the investigational product. The investigator or qualified designee must complete the SAE Report Form, sign, and transmit the completed form to Novavax Product Safety.

Initial reports of SAEs may be reported via fax or e-mail. Initial reports via telephone **must** be supported by transmission of documentation (paper or electronic) signed (physically or electronically) by the investigator or a qualified sub-investigator **within 24 hours** of notification. When additional follow-up information becomes available, a written follow-up SAE report (depending on the qualified event) must be completed, signed by the investigator or a qualified sub-investigator and transmitted as soon as possible. The investigator is responsible

for obtaining detailed information to support all SAE reports, including records of inpatient and outpatient care, laboratory reports, and autopsy or medical examiner reports.

The following events must be reported to the Medical Monitor **within 24 hours** of the investigator's first knowledge of the event:

- Any withdrawal of consent after dosing due to an AE.
- Any SAE.
- Any pregnancy occurring after the birth of the planned child enrolled in the current study AND before the maternal subject has completed the Day 180 post-delivery visit (Note however that such pregnancies will not be captured as an AE).
- Overdose (of a test article as specified in the protocol with or without an AE).
- Inadvertent or accidental exposure to the test article with or without an AE.
- Medication error (includes the administration of an incorrect treatment, an expired test article, a test article that has deviated from its required storage or refrigeration requirements, or any test article prior to documentation of informed consent).

Novavax or its designee will be responsible for notifications of SAEs and other qualifying events that are considered by the Sponsor to be unexpected and related to study agent as expedited (e.g., 7- or 15-Day) reports to the relevant regulatory authorities and to all participating investigators. In addition, Novavax or its designee will follow all applicable local and national regulatory requirements regarding safety reporting, including reporting to Ethics Committees (in jurisdictions where this is a sponsor responsibility). Each investigator must also comply with the applicable local and national regulatory requirements related to the reporting of SAEs to the IRBs/IECs responsible for reviewing the trial at their site, as well as the regulatory authority(ies) (where applicable).

The contact information for the study's Medical Monitor is provided during site training and is specified in the **Study Operations Manual**.

8.8 Severity

All AEs experienced by maternal and infant subjects will be assigned severity according to the TGS provided in the **Study Operations Manual**.

8.8.1 Maternal Subjects

Maternal subjects will be able to indicate severity for any AEs experienced and record this in their diary according to the same scale. For quick reference, an abbreviated grading scale is provided in Table 6 for visible and non-visible local AEs and for systemic AEs for which severity is based on interference with daily activities and not numeric ranges, and in Table 7 for adverse events of nausea, vomiting, diarrhea, fever, and fetal heart tones.

The severity of visually-evaluated local AEs will be a function of size. During the diary period, maternal subjects will monitor the size of visible local AEs at the injection site using the Subject Measurement Tool (Appendix 4) which has concentric circles that correspond to the diameters

specified in Table 6. For the purposes of reporting during the solicitation period (i.e., Days 0 to 6), the maternal subjects' observations will form the primary data. During clinic visits, investigators may measure any persistent local AEs with a ruler, documenting the size of the reaction at its widest diameter and use the numeric scale provided in Table 6 to assess for severity.

Non-visible local AEs (e.g., pain), solicited systemic AEs (except for those listed in Table 7), and unsolicited AEs will be assigned a severity based primarily on interference with daily activities (Table 6). Medical care-seeking is typically absent for grade 1 (mild) and often present for grade 3 (severe) events, but is not the primary determinant, since individuals behave differently in this regard.

Severity of clinical laboratory and vital sign abnormalities (including oral or axillary body temperature, which is captured as a continuous variable) will be graded based on established ranges provided in the TGS, located in **Study Operations Manual**.

Table 6: Severity Grade Definitions for Adverse Events, Maternal Subjects

Severity Grade	Definitions for Local Adverse Events (primarily used for Solicited AEs)		Definitions for Systemic Adverse Events (used for Solicited and Unsolicited AEs)
	Visual Local AE Size Grading Description	**Non-Visual Local AE Grading Description**	**Systemic AE Description (Interference with Daily Activities)**
0 – Normal	Reaction size (greatest single diameter) < 2.5 cm	No noticeable symptom	No noticeable symptom or finding
1 – Mild	Reaction size (greatest single diameter) 2.5 to 5.0 cm	Discomfort or tenderness noticeable, but does not interfere with normal daily activities	Mild symptoms or diagnostic observations; Intervention not indicated; No interference with normal activity
2 – Moderate	Reaction size (greatest single diameter) >5.0 to 10.0 cm	Moderate discomfort or tenderness on firm pressure; Causes some limitation of normal daily activities	Moderate symptoms or diagnostic observations; Some interference with normal activity, not requiring medical intervention
3 – Severe	Reaction size (greatest single diameter) >10.0 cm	Severe pain at rest, pain (including tenderness) immobilizes the injected limb and prevents normal daily activities	Severe symptoms, significantly disrupts or prevents normal daily activities; Generally requires medical attention/intervention

Note: Vital sign and laboratory abnormalities reported as unsolicited AEs should represent increases of at least one severity grade over prior observations and *attain at least a grade 2 severity* as per the Toxicity Grading Scale provided in the **Study Operations Manual**.

Table 7: Severity Grade Definitions for Solicited Gastrointestinal Adverse Events, Fever, and Fetal Heart Tones, Maternal Subjects

Severity Grade	Nausea	Vomiting	Diarrhea	Fever	Fetal Heart Tones[1]
0 – Normal	No noticeable symptom	No noticeable symptom	No noticeable symptom	< 38.0˚C	120 to 160 beats/min
1 – Mild	No interference with activity, or 1 – 2 episodes/ 24 hour period	No interference with activity, or 1 – 2 episodes/ 24 hour period	1 – 3 unformed (loose) stools/24 hour period	38.0 to 38.4˚C	--
2 – Moderate	Some interference with activity, or > 2 episodes/ 24 hour period	Some interference with activity, or > 2 episodes/ 24 hour period	4 – 5 unformed (loose) stools/24 hour period	38.5 to 38.9˚C	--
3 – Severe	Prevents daily activity, or requires intravenous hydration	Prevents daily activity, or requires intravenous hydration	≥ 6 loose stools/24 hour period, or requires intravenous hydration	> 38.9˚C	< 120 beats/min or > 160 beats/min

[1], Fetal heart tone abnormalities may be repeated at the investigator's discretion as these measures are highly labile. Severe abnormalities (i.e., < 120 beats/min or > 160 beats/min) should be reported as AEs and should warrant additional evaluation and monitoring.

8.8.2 Infant Subjects

The investigator is to use his/her best medical judgment to assign severity for adverse events occurring in infants based on interference with daily-activities and/or whether medical intervention/therapy is required (Table 8). This will involve assessment of activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, sleeping, etc.) for infants. In addition, medical care-seeking is typically absent for grade 1 (mild) and often present for grade 3 (severe) events.

Table 8: Severity Grade Definitions for Adverse Events Occurring in Infant Subjects

AE Category	1 – Mild	2 – Moderate	3 - Severe
Unsolicited Events	No interference with normal activities; Transient or mild discomfort; No medical intervention/therapy required	Some limitation of normal daily activities; No or minimal medical intervention/therapy required; May require monitoring	Prevents normal daily activities; Medical intervention/therapy required

8.9 Relationship (Causality)

The relationship of all unsolicited AEs to the test article must be assessed and documented by the investigator or a qualified sub-investigator, and classified according to the categories shown in Table 9. The investigator should use his/her best medical judgment to consider whether the temporal sequencing of treatment and event, the existence (or lack thereof) of a biologically plausible mechanism (which is consistent with the temporal sequence), and the existence (or lack thereof) of likely alternative explanations support the causality assessment given. *(Note that Investigators will not be required to assess causality for solicited AEs reported during the solicitation period as these are presumed to be treatment-related.)*

Table 9: Definition of Relationship for Adverse Events

Relationship	Relationship Description
Unrelated / Unlikely	• May or may not follow a reasonable temporal sequence from administration of the test article; • No plausible mechanism based on known or suspected actions of the test article or product class; • Readily explained by known characteristics of the maternal or infant subject's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject.
Possibly	• Follows a reasonable temporal sequence from administration of the test article; • Based on known or suspected actions of the test article or product class, a plausible mechanism could exist; • May be reasonably explained by known characteristics of the maternal or infant subject's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject; *but the Investigator deems this less likely than test article effect*.
Probably	• Follows a reasonable temporal sequence from administration of the test article; • Based on known or suspected actions of the test article or product class, a plausible mechanism could exist; • Cannot be reasonably explained by known characteristics of the maternal or infant subject's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject.
Definitely	• Follows a reasonable temporal sequence from administration of the test article; • Consistent with known actions of the test article or product class; • Cannot be reasonably explained by known characteristics of the maternal or infant subject's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject. • May be confirmed by re-challenge (if applicable).

8.10 Data and Safety Monitoring Board (DSMB)

A Data and Safety Monitoring Board (DSMB) will be assembled for this study to perform ongoing assessments of the risks of vaccination in pregnant women through delivery, and in the delivered infant through the first year of life. In addition, the DSMB will review all recommendations from the unblinded statistician to stop enrollment in the trial for futility. The DSMB will consist of at least five clinicians to include not less than two obstetricians (at least one with expertise in high-risk obstetrics or maternal-fetal medicine), and not less than two pediatricians (at least one neonatologist), and the unblinded DSMB statistician. These individuals will not be employees of the Sponsor; and will operate under a charter agreed prior to study start which will define responsibilities and authority (including authority to halt enrollment or require changes in safety assessments), frequency of meetings, triggers of *ad hoc* meetings, access to data and treatment codes, and communication pathways. The Novavax Sr. Director of Pharmacovigilance and Product Safety, or designee, will serve as the sponsor's liaison to the Project Manager of the DSMB. The Study Physician will serve as the medical liaison to the DSMB and will be responsible for all presentations to the DSMB during the open sessions of the DSMB meetings.

In general, the DSMB will meet not less than monthly during periods of active maternal enrollment and every two months outside these periods, or as required by triggering safety events to be identified by the DSMB Charter. The DSMB may elect, based on a vote of the members, to meet less frequently (e.g., quarterly), after the first year of the study.

9 DATA MANAGEMENT

9.1 Recording and Collection of Data

Novavax will provide sites with template source documents for the recording and collection of maternal and infant subject data. Data will be entered into an electronic data capture (EDC) system by site staff. All EDC entries will be completed as soon as possible after each visit for maternal and infant subjects.

Corrections to data in the EDC or eSource system will be documented in the electronic audit trail that is compliant to US-FDA regulations (21 Code of Federal Regulations [CFR] Part 11) or equivalent. The investigator will review data resident in the EDC or eSource system and indicate by electronic signature that, to his/her knowledge, the data are complete and accurate. If further changes are made after this, the investigator will need to again sign the *Investigator Signature Page* electronically. Designated source documents will be signed and dated by the appropriate study personnel. The investigator must agree to ensure completion and maintenance of source documents for each subject participating in the study.

9.2 Data Quality Assurance

All trial data will be entered by clinical study site staff with study-specific EDC or eSource training into a computerized data management system. Statistical analyses of data will only be performed after all clinical monitoring and data queries have been resolved.

9.2.1 Monitoring

Novavax, as the Sponsor of this study, is responsible for ensuring the proper conduct of the study, in accordance with the Declaration of Helsinki (Amended Fortaleza, Brazil, 2013) and Good Clinical Practices (GCP) including, but not limited to, protocol adherence and the validity of the data recorded in the database. For the purposes of this study, Novavax may transfer responsibility for the clinical monitoring to Independent clinical monitors who may monitor on-site or remotely. Novavax and/or independent clinical monitors are responsible for ensuring that the site(s) prepare complete, accurate, legible and well-organized clinical study data. On-site monitoring inspections will be routinely performed in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely. In addition, clinical monitors will provide ongoing support to ensure the investigator's continued understanding of all applicable regulations concerning the clinical evaluation of the investigational vaccine, and the proper execution of the protocol, as well as the investigator's reporting responsibilities.

The clinical study sites will be monitored periodically for database accuracy and completeness, adherence to the protocol, regulatory compliance, safety reporting, clinical trial material accountability, and the maintenance of comprehensive source documents. Where applicable, the database will be checked against applicable source documents to verify completeness and accuracy. When data entry has been completed by the appropriate study staff, source document verified and monitored by Novavax and/or contract research organization (CRO)

representatives, and reviewed by the investigator, the investigator should sign and date the *Investigator Signature Page*.

9.2.2 Audit and Inspection

Novavax Clinical Quality Assurance (CQA) will develop a Quality Assurance plan to ensure the integrity of the conduct of the clinical study. CQA visits may be performed pre-study, during the study and post-study by Novavax CQA or other personnel authorized by Novavax. Regulatory authorities reserve the right to audit study sites following submission of data in regulatory applications. By signing this protocol, the investigator acknowledges that these inspection procedures may take place and agrees to provide access to the required subject records and other study documentation. Further, the investigator agrees to inform Novavax and the IRB/IEC immediately of any scheduled or unscheduled inspection by regulatory authorities.

9.3 Adherence to and Changes to the Protocol

Any change or addition to this protocol will only be made when a protocol amendment has been written, approved, and signed by Novavax and the investigator before the change or addition can be considered effective, unless immediate implementation of a change is necessary to ensure the safety of subjects. This amendment must also be submitted to the IRB/IEC for approval and, when necessary, regulatory authority approval before implementation. Protocol amendments may affect consent forms of current and future subjects. Novavax will clearly specify when a protocol amendment includes safety, procedural, and/or efficacy information that will require specific Informed Consent text changes.

9.4 Retention of Records

It is the responsibility of the investigators and study staff to maintain a comprehensive and centralized filing system of all study-related documentation, which is suitable for inspection at any time by Novavax, its designees, and regulatory agencies. These should minimally include:

- Subject files including the completed eCRFs/eSource (based on output from clinical database) on compact disc (CD), supporting source documentation, and the Informed Consent and any other subject information.
- Study files (essential documents and regulatory files) including the protocol with all amendments, the Investigator's Brochure, safety and protocol deviations meeting IRB/IEC reportable criteria, copies of all regulatory documentation, and all correspondence with the IRB/IEC, regulatory authority, and Novavax.
- Pharmacy files including all investigational vaccine shipment, receipt, storage, dispensing, and accountability records, and pharmacy-related correspondence.

In addition to the eCRF/eSource, the investigator will maintain adequate records that fully document the progress of the trial. Copies of these trial records and related documents must be kept on file by the investigator for a period of no less than 15 years (or longer if mandated by relevant local regulations). ALL DOCUMENTATION AND MATERIAL PROVIDED BY NOVAVAX OR A NOVAVAX REPRESENTATIVE FOR THIS TRIAL (CASE REPORT FORMS, PROTOCOL, ETC.) ARE TO BE RETAINED IN A SECURE PLACE AND TREATED AS CONFIDENTIAL MATERIAL.

10 STATISTICAL CONSIDERATIONS

The planned statistical analyses for this study are briefly outlined below. A detailed statistical analysis plan (SAP) will be created and finalized in tandem to the protocol.

10.1 Subject Populations

The following subject populations will be used in all analyses:

- Safety Populations
  - Maternal Safety Population (Safety-M) - defined as all maternal subjects who receive any test article. The Safety-M Population will be analyzed as actually treated.
  - Infant Safety Population (Safety-I) – defined as all infants born live to maternal subjects who received any test article. The Safety-I Population will be analyzed as actually treated.
- Intent-to-treat (ITT) Populations
  - 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 for both the mother and the infant 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 for both the mother and the infant. The ITT-IMM Population will be analyzed as randomized.
- 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 and 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 $\geq$ 37 weeks gestational age at birth, b) are born to maternal subjects who received a study injection as randomized and $\geq$ 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.

- 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 (up to 72 hours post-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.

10.2 General

All analysis populations will be defined and full descriptions of each population will be provided. 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% CIs for the immunogenicity endpoints), and the categorical variables will be presented by frequency distributions (percentages) for the non-immunogenicity endpoints, and percentages and their 95% confidence intervals for the immunogenicity endpoints.

10.3 Demographics and Protocol Compliance

Demographic parameters and other baseline characteristics (e.g., age, age group, gender, race, ethnicity, etc.) will be summarized by treatment group and serology cohort (as applicable) for all maternal and infant subjects (separately) in the Safety Population, as well as the number and description of protocol deviations. Summary statistics at birth for infant length, weight, FOC, APGAR scores, and gestational age will be provided by treatment groups. In addition, a listing will be prepared linking, by mother/infant pair, maternal demographic characteristics, maternal treatment, and infant length, weight, FOC, APGAR scores, and gestational age at birth.

10.4 Efficacy Analyses

10.4.1 Study Definitions for Efficacy Determination

10.4.1.1 Infant Subjects

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).
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.

10.4.1.2 Maternal Subjects

Symptomatic RSV Infection:	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.

10.4.2 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 infant 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.

10.4.3 Analysis of Primary and Secondary 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 2-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 approach, 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 report as Appendix 1 in the SAP.

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 π_v and n_v, respectively, are the probability of an RSV event and the total number of subjects in the vaccine group and π_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 π_v and π_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 π_v and π_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:

3. Sampling 10 million independent values from the posteriors of π_v and π_p
4. Calculating the event ratio, $r = \pi_v / \pi_p$ under each pair-wise sample from the posterior of π_v and π_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, time to the first medically-significant RSV LRTI event will be analyzed by treatment group using Kaplan-Meier methods. 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 regarding the sensitivity analyses will be described in the SAP.

The null hypothesis, H_0: VE $\leq 0\%$, using the 1-sided Type I error rate (i.e., lower bound of 2-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 will 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 Immunogenicity Analyses

Immunologic analyses will be conducted using the ITT and PP Populations, with primary conclusions drawn from the PP Population. The primary variable of interest for assessment of immune response to the RSV F vaccine will be anti-F IgG EU and PCA concentration, and testing by these methodologies will have the highest priority. The secondary variables will be RSV/A and B MN titers, which will be determined on all blood samples, but with priority testing assigned to samples collected at the following time-points: at delivery for the maternal subject, and at delivery, D+14, D+35, D+60, D+90, D+120, and D+180 for the infant subject.

The following immunogenicity outcome measures and their 95% CI will be summarized by treatment group. Immunogenicity analyses will be descriptive and include tabulations by treatment group.

Maternal Subjects:

1) GMEU or GMC, GMFR, proportion of subjects with $\geq$ 2-fold and $\geq$ 4-fold increases in EU/concentration from baseline (2- and 4-fold seroconversion rates [SCR]); and SRR of anti-RSV F IgG and PCA at baseline, post-immunization on Day 14, at delivery, and postpartum on Days 35 and 180.

2) GMT, GMFR, proportion of subjects with ≥ 2-fold and ≥ 4-fold increases in titer from baseline (2- and 4-fold seroconversion rates {SCR]); and SRR of RSV/A and B MN titers at baseline and delivery.
3) GMFR Transplacental Transfer Proportion, the anti-RSV F IgG GMEU, PCA GMC, and RSV/A and B MN GMT of the within-maternal-infant pair ratios for cord blood over maternal serum (MS) at delivery ($GMFR_{Cord/MS}$).

Infant Subjects:

1) GMEU, GMC, or GMT; and SRR of anti-RSV F IgG, PCA, and RSV/A and B MN antibodies in cord blood and on D+14, D+35, D+60, D+90, D+120, and D+180.
2) GMFR of anti-RSV F IgG GMEU, PCA GMC, and RSV/A and B MN GMT within-subject ratios after delivery (D) on D+14, D+35, D+60, D+90, D+120, and D+180 over cord blood value at delivery ($GMFR_{AD/Cord}$).
3) Exploratory modeling of anti-RSV F antibody decay in infants using first order models and infant data.

10.6 Safety Analyses

The primary variable for evaluation of the safety profile will be the number and percentage (95% CI) of maternal subjects with solicited and unsolicited AEs recorded post-vaccination and the number and percentage (95% CI) of infants with unsolicited AEs occurring since birth. Safety analyses will be performed using the Safety Population as defined in Section 10.1.

Safety will be summarized overall and by treatment group for maternal subjects based on Percentages of subjects with:

- Solicited seven day reactogenicity events by severity;
- Clinical laboratory safety abnormalities by severity;
- Caesarean, vaginal, and instrument-assisted vaginal modes of delivery;
- Specified third-trimester pregnancy 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 through 180 days post-delivery.

Clinical laboratory data summaries will include (by parameter and treatment group) toxicity grade shift summaries; absolute means and standard deviations with minima and maxima values, and tabulations of changes from baseline.

Safety analyses for infant subjects will be summarized overall and by treatment group, and will be based on percentages of infants with:

- 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, 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 above normal, normal, at-risk at 6 or 12 months, and at-risk at both 6 and 12 months.

10.7 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 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.

10.8 Sample Size and Power

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 10 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 10: 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%
	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%

Table 10: 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]
0.06	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 H_0: Vaccine Efficacy < 30% using one-sided Type I error rate of 0.0124.

10.9 Interim (Futility and Informational) Analyses and Data and Safety Monitoring Board Responsibilities

10.9.1 Blinding and Interim Analyses

The 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.

10.9.2 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.

10.9.3 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 statistician(s) performing these analyses for provision to the DSMB. Two unblinded statisticians will be involved in the study: the DSMB statistician and the 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 endpoint.

- **Access to study randomization:** the DSMB statistician will be unblinded to treatment assignment for all subjects enrolled at the end of each season to allow the estimation of the number of cases of medically-significant RSV LRTI in the database. Unblinded report tables will be sent to the IBG statistician to support the futility and informational analyses. In addition, unblinded safety tables may also be prepared by the DSMB statistician if requested by the DSMB. The treatment assignments (randomization schedule) of the subjects involved will be provided by the 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 statistician and to the DSMB via 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.
- **The IBG and the DSMB:** Following the 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 decision is reached based on these analyses, the IBG will inform the DSMB PM, who will then inform the Sponsor Contact.
- **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.

10.10 Plan for Analyses and Reporting of Data

10.10.1 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 when all live-born infants of all enrolled pregnant mothers have completed 180 days of follow-up after delivery, a final Day 180 Unblinded Analysis of Efficacy, Immunogenicity, and 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 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 of these data are monitored, all applicable queries are resolved, and the database is locked. The data 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 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.

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.

10.10.2 Informational Analysis

The Sponsor may trigger the performance of an informational analysis of efficacy as defined in the SAP. This analysis will be performed by the DSMB biostatistician and the IBG in a manner entirely analogous to the analyses for efficacy and futility, and will address a success criterion to be specified in the SAP. The DSMB will communicate the results of the analysis to the Sponsor only in terms of fulfillment or non-fulfillment of the target criterion.

10.10.3 Final Clinical Study Report (CSR)

The final CSR will include all efficacy, immunogenicity, and safety data (inclusive of clinical assessments and concomitant medications) through the infant subject's post-delivery study 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.

10.11 Computer Methods

Statistical analyses will be performed using SAS® version 9.3 or higher under a Windows operating system.

11 LEGAL AND ETHICAL REQUIREMENTS

11.1 Compliance with Regulatory Requirements

This study will be conducted in accordance with the protocol, the Declaration of Helsinki (1964) (amended Fortaleza, Brazil, 2013); International Conference on Harmonization (ICH) GCP Guidelines; and all applicable regulatory requirements in the region(s) the study is conducted, including the relevant national or local regulatory body having jurisdiction.

11.2 Institutional Review Board/Independent Ethics Committee

This study will be conducted under the auspices of a properly constituted IRB/IEC, as defined by US regulatory requirements, and in accordance with the Declaration of Helsinki (1964) (amended Fortaleza, Brazil, 2013). This committee will review and approve all aspects of the study, including the protocol and Informed Consent Forms (ICFs) to be used, any and all advertising or informational materials, and any modifications made to the protocol and ICFs, prior to, or during the study. Prior to initiation of clinical activity, investigators will provide Novavax with a copy of the communication from the IRB/IEC to each investigator indicating approval of the protocol and ICF(s). All changes to the protocol or Informed Consent Form must be reviewed and approved prior to implementation, except where necessary to eliminate apparent immediate hazards to human subjects.

If applicable, the investigators will be responsible for obtaining annual IRB/IEC renewal throughout the duration of the study. Copies of the investigators' annual reports to the IRB/IEC and copies of the IRB's/IEC's continuance of approval must be furnished to Novavax.

11.3 Informed Consent

The investigators or designated site study staff members will be responsible for obtaining written Informed Consent (and any applicable local or state regulatory documentation), signed and dated by each maternal subject and parent/guardian of each infant, prior to his/her participation in the study, including procedures performed at screening. Informed Consent will be obtained from each maternal subject and parent/guardian of each infant after a full explanation of the purpose of the study, the risks and discomforts involved, potential benefits, etc., have been provided by the investigators, both verbally and in writing. The original signed copy of the ICF must be maintained in the institution's records, and is subject to inspection by a representative of Novavax and/or regulatory agencies. The subject and parent/guardian of each infant will also be given a copy of the signed consent form.

11.4 Required Site Documentation

The following documents must be provided to Novavax or its designee prior to the start of the study:

- Any country-specific administrative form(s) (e.g., Executed Form FDA 1572)
- Current Curriculum Vitae and medical licenses (as applicable) for the principal investigator and all sub-investigators,
- Financial Disclosure Forms from the principal investigator and all sub-investigators,

- Signed protocol and amendments (if any),
- Copy of correspondence from the IRB/IEC indicating approval of the protocol and ICFs, signed by the IRB/IEC chairperson or designee, and containing the name and address of the IRB/IEC,
- Membership roster of the IRB/IEC, listing names and occupations. If an investigator participating in this study is an IRB/IEC member, documentation should be provided of his/her abstention from voting on this protocol,
- ICFs that were reviewed and approved by the IRB/IEC, or a revised document if changes were requested by the committee with the IRB/IEC stamp and date, and
- Reference ranges for all safety tests required in the protocol and documentation of laboratory licensure if the study site's local clinical laboratory will be used.

11.5 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties, other than those cited below, is prohibited. Confidentiality of maternal and infant subjects will be further ensured by utilizing a subject identification code and subject initials. Relevant national and local jurisdictions governing privacy rules and protection of human subjects will be followed in this study.

In compliance with regulatory guidelines regarding the monitoring of clinical studies, and in fulfillment of the investigator's obligations to Novavax, it is required that data generated as a result of the study be available for inspection, on request, by personnel from Novavax, CRO monitors representing Novavax, and/or regulatory agencies. These shall include all study relevant documentation, including medical histories to verify eligibility, laboratory test results to verify transcription accuracy, treatment and diagnostic reports, and admission/discharge summaries for hospital admissions occurring while the subject is on-study.

As part of the required content of the Informed Consent, the maternal subject or other parent/guardian of the infant subject must be informed that their records will be reviewed by Novavax and/or regulatory agencies. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the maternal subject or other parent/guardian of the infant subject in writing before the subject is entered into the study.

11.6 Disclosure of Information

Information concerning the RSV F vaccine, patent application processes, scientific data or other pertinent information, is confidential and remains the property of Novavax. The investigator may use this information for the purposes of the study only. It is understood by the investigator that Novavax will use information developed in this clinical study in connection with the development of the investigational vaccine and therefore may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Novavax.

Please refer to the clinical trial agreement for contractual terms regarding presentation and publication of trial results.

12 REFERENCES

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Appendix 1 – RSV-M-301 Study Procedures Schedule

Maternal Subject Study Procedures

Study Day:	**-28 to 0**	**0**	**0-6**	**7**[1]	**14**[1]	**28**[1]	**Delivery**	**D+35**[1]	**D+180**[1]
Window (days):	**--**	**--**	**--**	**+2**	**±2**	**±2**	**--**	**±7**	**±14**
Approximate Week of Gestation:	**24-36**$^{0/7}$	**28-36**$^{0/7}$	**28-36**	**29-37**	**30-38**	**32-40**	**--**	**--**	**--**
Informed consent	x								
Medical history	x								
Physical exam	x								
Vital signs	x	x[5]		x	x		x[10]	x	x
Physical exam, if indicated		x		x	x		x	x	x
Ultrasound	x[2]								
Clinical safety phlebotomy	x[3]				x[3]		x[11]		
HIV, syphilis, HBV, and HCV testing (if applicable)	x[4]								
Pregnancy test									x
Fetal heart tones	x	x[5]		x	x				
Confirm eligibility		x							
Injection with recommended licensed vaccine dose	x[6]								
Injection with RSV F vaccine or placebo		x							
Diary card completed			x						
Diary card reviewed and collected				x					
Distribution of Study Identification Card[9]		x		x	x	x	x	x	
Memory aid distribution				x					
RSV serology phlebotomy	x				x		x[7]	x	x
Cord blood							x[8]		
RSV surveillance		← Continuous →							

Maternal Subject Study Procedures

Study Day:	-28 to 0	0	0-6	7[1]	14[1]	28[1]	Delivery	D+35[1]	D+180[1]
Window (days):	--	--	--	+2	±2	±2	--	±7	±14
Approximate Week of Gestation:	24-36$^{0/7}$	28-36$^{0/7}$	28-36	29-37	30-38	32-40	--	--	--
AEs, MAEs, SNMCs, and SAEs query	x	x		x	x	x	x	x	x
Concomitant medications		x		x	x	x	x	x	x
Document perinatal management & GBS screening/treatment results	x						x		

[1] Performed as a telephone or SMS contact visit (Day 28 only) using an IRB/IEC-approved script, if applicable, or as an in-clinic or home visit (Day 7, Day 14, D+35, and D+180) to monitor for safety. Depending on responses, maternal subjects participating via telephone or SMS contact or home visit, may be asked to return to the clinic or to schedule a home visit for further evaluation.

[2] May be performed if subject does not have a prior second or third-trimester ultrasound that indicates there are no fetal anomalies.

[3] To be performed at least two days prior to the planned Day 0 vaccination and on Day 14 in all subjects enrolled in the first year of study conduct in any country for serum chemistry (ALT, AST, total bilirubin, ALP, creatinine, and BUN) and hematology (hemoglobin, platelet count, and WBC count) assessments.

[4] To be performed as required by the central or local laboratory if screening results are not available in prior data collected during the course of the current pregnancy.

[5] To be performed before and 30 minutes after vaccine administration.

[6] Must be administered at least 14 days before or at least 14 days after the Day 0 vaccination, if applicable.

[7] The blood draw will be performed at any time from admission to the hospital up to 12 hours post-delivery for most deliveries, but may be obtained up to 72 hours post-delivery in extenuating circumstances such as a the occurrence of a delivery on a holiday or weekend.

[8] Obstetrical investigator or designee should inform the investigator to the infant (or designee) of the collection status of the cord blood sample.

[9] The Study Identification Card will be distributed at the Day 0 visit; a replacement card will be offered at all follow-up visits.

[10] Limit collection to clinically significant vital sign data at hospital admission.

[11] Performed only for applicable subjects (i.e., those enrolled in the first year of study conduct in any country) who deliver prior to the Day 14 visit.

Infant Subject Study Procedures

Visits: Study Day: Window:	1 Delivery NA	2 D+14 ±3 days	3 D+35 ±1 week	4 D+60 ±1 week	5 D+90 ±1 week	6 D+120 ±1 week	7 D+180 ±2 weeks	8 D+252 ±2 weeks	9 D+364 ±2 weeks
Informed consent	x								
Physical exam	x		x	x	x	x	x		x
Physical exam, if indicated		x						x	
Gestational age, APGAR scores	x								
Weight, length, FOC	x		x	x	x	x	x	x	**x**
Phlebotomy, Cohort 1	x[1]	x			x				
Phlebotomy, Cohort 2	x[1]		x			x			
Phlebotomy, Cohort 3	x[1]			x			x		
Distribution of Study Identification Card[2]	x	x	x	x	x	x	x	x	x
RSV surveillance	←			Continuous			→		
Query for smokers and children < 5 years of age in the household; mode of infant feeding; whether infant or another child (< 5 years of age) in the household is cared for outside the home	x	x	x	x	x	x	x	x	x
AEs, MAEs, SNMCs, and SAEs		x	x	x	x	x	x	x	x
Query for healthcare- provider confirmed wheezing		x	x	x	x	x	x	x	x
Performance of all routine baby-wellness procedures/vaccinations[3]	x	x	x	x	x	x	x	x	x
Concomitant medication		x	x	x	x	x	x	x	x
Developmental testing							x		x[4]

Infant Subject Study Procedures

Visits:	1	2	3	4	5	6	7	8	9
Study Day:	Delivery	D+14	D+35	D+60	D+90	D+120	D+180	D+252	D+364
Window:	NA	±3 days	±1 week	±1 week	±1 week	±1 week	±2 weeks	±2 weeks	±2 weeks

Note: Study visits after Visit #1 may be performed as in-clinic or home visits to facilitate infant subject follow-up.

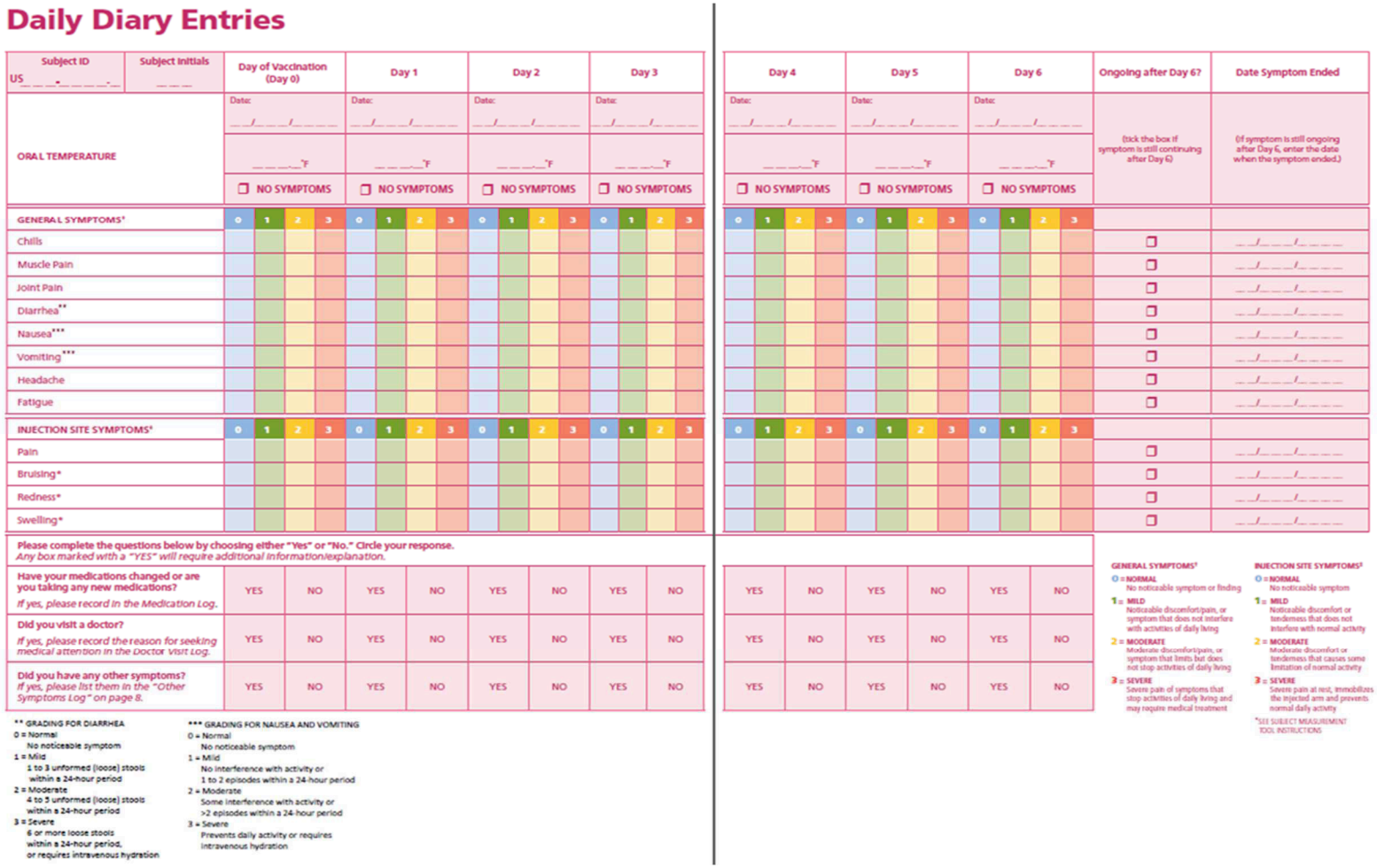
[1] An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery, but is permissive up to 72 hours post-delivery.

[2] The Study Identification Card will be given to the parent/guardian of the infant subject at the delivery visit; a replacement card will be offered at all follow-up visits, as needed.

[3] Performed at the Investigator's discretion.

[4] Infant subjects with a positive screen detected at both 6 and 12 months of age, or first appearing at 12 months of age, will be offered repeat developmental testing at 15 and 18 months of age as a follow-up procedure.

Appendix 2 – RSV-M-301 Draft Subject Diary (for Maternal Subjects Only)



Daily Diary Entries

Subject ID US __ __ - __ __ __ __ - __ __	Subject Initials __ __ __	Day of Vaccination (Day 0)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Ongoing after Day 6?	Date Symptom Ended
ORAL TEMPERATURE		Date: __/__/__	Date: __/__/__	Date: __/__/__	Date: __/__/__	Date: __/__/__	Date: __/__/__	Date: __/__/__	(tick the box if symptom is still continuing after Day 6)	(If symptom is still ongoing after Day 6, enter the date when the symptom ended.)
		__ __ __.__°F	__ __ __.__°F	__ __ __.__°F	__ __ __.__°F	__ __ __.__°F	__ __ __.__°F	__ __ __.__°F		
		❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS	❒ NO SYMPTOMS		
GENERAL SYMPTOMS*		0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3		
Chills									❒	__/__/__
Muscle Pain									❒	__/__/__
Joint Pain									❒	__/__/__
Diarrhea**									❒	__/__/__
Nausea***									❒	__/__/__
Vomiting***									❒	__/__/__
Headache									❒	__/__/__
Fatigue									❒	__/__/__
INJECTION SITE SYMPTOMS*		0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3	0 1 2 3		
Pain									❒	__/__/__
Bruising*									❒	__/__/__
Redness*									❒	__/__/__
Swelling*									❒	__/__/__

Please complete the questions below by choosing either "Yes" or "No." Circle your response.
Any box marked with a "YES" will require additional information/explanation.

Have your medications changed or are you taking any new medications? *If yes, please record in the Medication Log.*	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
Did you visit a doctor? *If yes, please record the reason for seeking medical attention in the Doctor Visit Log.*	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
Did you have any other symptoms? *If yes, please list them in the "Other Symptoms Log" on page 8.*	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO

** GRADING FOR DIARRHEA
0 = Normal
No noticeable symptom
1 = Mild
1 to 3 unformed (loose) stools within a 24-hour period
2 = Moderate
4 to 5 unformed (loose) stools within a 24-hour period
3 = Severe
6 or more loose stools within a 24-hour period, or requires intravenous hydration

*** GRADING FOR NAUSEA AND VOMITING
0 = Normal
No noticeable symptom
1 = Mild
No interference with activity or 1 to 2 episodes within a 24-hour period
2 = Moderate
Some interference with activity or >2 episodes within a 24-hour period
3 = Severe
Prevents daily activity or requires intravenous hydration

GENERAL SYMPTOMS*
0 = NORMAL
No noticeable symptom or finding
1 = MILD
Noticeable discomfort/pain, or symptom that does not interfere with activities of daily living
2 = MODERATE
Moderate discomfort/pain, or symptom that limits but does not stop activities of daily living
3 = SEVERE
Severe pain of symptoms that stop activities of daily living and may require medical treatment

INJECTION SITE SYMPTOMS*
0 = NORMAL
No noticeable symptom
1 = MILD
Noticeable discomfort or tenderness that does not interfere with normal activity
2 = MODERATE
Moderate discomfort or tenderness that causes some limitation of normal activity
3 = SEVERE
Severe pain at rest, immobilizes the injected arm and prevents normal daily activity

*SEE SUBJECT MEASUREMENT TOOL INSTRUCTIONS

A subject diary will be provided to all maternal subjects to record solicited and unsolicited adverse events experienced, concomitant medications used, and any medical visits/procedures sought, within the first seven days following vaccination. The above is a sample excerpt from such a diary. It is provided for informational purposes only and may differ from the actual diary issued to subjects.

Appendix 3 – RSV-M-301 Blood Draw Schedule *(for Maternal and Infant Subjects)*

Maternal Subjects Blood Draw Schedule

Study Visit Day		Amount of Blood Drawn for Clinical Laboratory Safety	Amount of Blood Drawn for Immunogenicity Assessments	Total Drawn at Visit
Day -28 to 0		10 mL[1]	20 mL	30 mL[1]
Day 14 (±2 days)		10 mL	20 mL	30 mL
Delivery - Maternal		--	20 mL	20 mL
Delivery – Cord Blood		--	at least 5 mL	at least 5 mL
Post-delivery Day 35 (±7 days)		--	20 mL	20 mL
Post-delivery Day 180 (±14 days)		--	20 mL	20 mL
Totals	**Venous**	20 mL[1]	100 mL	120 mL[1]
	Cord Blood	--	at least 5 mL	at least 5 mL

Note: The blue shaded row indicates the blood volume collected from the umbilical cord at delivery.

[1] Limited to those subjects participating in the first year of study conduct in any country or subjects that require a phlebotomy to document results of HIV, syphilis, HBV, and HCV antigen tests/serologies.

Infant Subjects Blood Draw Schedule

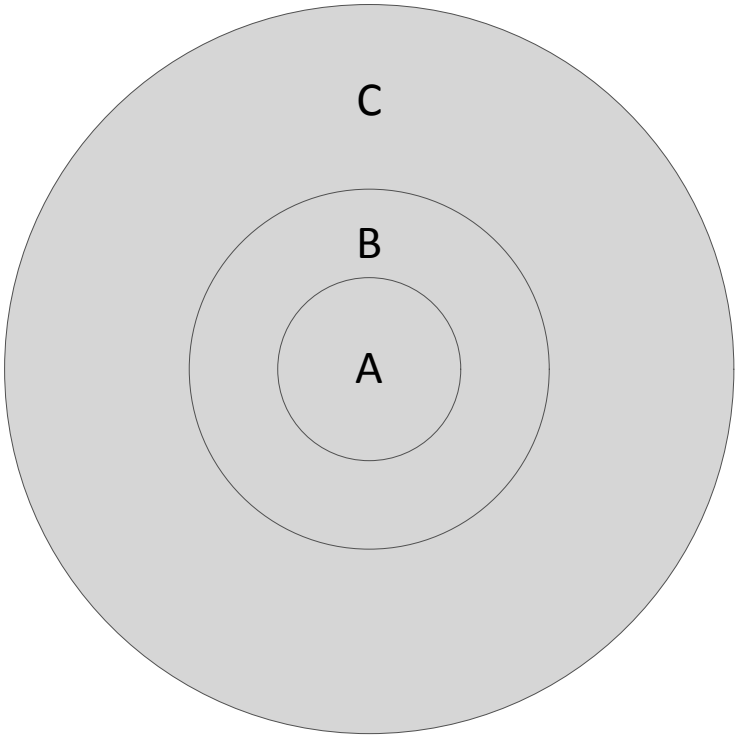
Delivery (D) Study Visit Day		Amount of Blood Drawn for Immunogenicity Assessments
Visit 1: Delivery[1] (+72 hours of birth)		1mL (heel stick) or 2 mL (venipuncture)
Visit 2: D+14 (±3 days)		1mL (heel stick) or 2 mL (venipuncture)
Visit 3: D+35 (±7 days)		1mL (heel stick) or 2 mL (venipuncture)
Visit 4: D+60 (±7 days)		1mL (heel stick) or 2 mL (venipuncture)
Visit 5: D+90 (±7 days)		1mL (heel stick) or 2 mL (venipuncture)
Visit 6: D+120 (±7 days)		1mL (heel stick) or 2 mL (venipuncture)
Visit 7: D+180 (±14 days)		1mL (heel stick) or 2 mL (venipuncture)
Cohort Totals	**1**	3 to 6 mL[1]
	2	3 to 6 mL[1]
	3	3 to 6 mL[1]

Note: The orange shaded rows indicate the blood volume collected from Cohort 1 infants. The blue shaded rows indicate the blood volume collected from Cohort 2 infants. The green shaded rows indicate the blood volume collected from Cohort 3 infants.

[1] Includes collection of 1 or 2 mL of blood that may be taken within 24 hours of birth if cord blood is not obtained at delivery.

Appendix 4 – RSV-M-301 Subject Measurement Tool

(Do not use this page in clinic, as it may not be to exact scale)



The Subject Measurement Tool consists of a transparent set of concentric circles with diameters that correspond to the ranges in the toxicity grading scale (2.5, 5, and 10 cm in diameter). Maternal subjects are instructed to overlay the template over the injection site for any reaction that can be visually observed (e.g., redness, swelling, bruising). An assessment of severity is then made by determining the circle that best describes the size of the reaction: reactions that are smaller than Circle A (2.5 cm) are considered grade 0; reactions larger than Circle A but equal to or smaller than Circle B (5 cm) are considered grade 1; reactions larger than Circle B but equal to or smaller than Circle C (10 cm) are considered grade 2; reactions larger than Circle C are considered grade 3. The table below summarizes the severity grading for visible injection site reactions based on size.

Definition of Severity Grading for Visible Local Adverse Events

Severity Grade	Injection Site Grading Description
0 - Normal	Reaction size fits inside Circle A
1 - Mild	Reaction size larger than Circle A, but fits inside Circle B
2 - Moderate	Reaction size larger than Circle B, but fits inside Circle C
3 - Severe	Reaction size larger than Circle C

Appendix 5 – RSV-M-301 Protocol Change History

Following is a complete tabular summary of changes made to previous versions of the protocol.

Protocol Version 9.0, 21 July 2017 (revised from 8.0, 23 August 2016)

The following is a summary of the changes made to this version of the protocol.

Location of Change	Change/Modification in Version 9.0
Protocol Change History	To enhance section readability, only the protocol change history pertaining to Version 9.0 has been retained in this section. Protocol change histories pertaining to previous protocol amendments have been provided in Appendix 5 of the protocol.
Section 1.2.1	A brief description of RSV epidemiology among the United States Native American pediatric population has been provided.
Section 1.2.4	The section has been added to provide a brief discussion of RSV in children in India, Southeast Asia, and the Philippines.
Section 1.6.2	The summary of clinical experience has been updated to provide safety experience from the now-completed phase II trial in 50 pregnant women.
Section 1.8	Minor updates have been made to the section to reflect discussion of the most current safety data from relevant clinical trials.
Synopsis, Section 2.1	The primary efficacy objective in infants has been changed to indicate the assessment of efficacy against the updated endpoint of medically-significant RSV LRTI. The updated objective is presented below: *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 at 120, 150, and 180 days of life.* Justification: Several recent publications have shown that the presence of tachypnea (based on WHO definitions) is an independent predictor of hospitalization of infants with RSV acute respiratory disease (Atwell et al. J Infect. Dis. [2016]; Modjarrad et al. Vaccine [2016]). Infants with severe disease may maintain their oxygenation through rapid breathing, becoming hypoxemic only when they tire and decompensate. A threshold value for tachypnea 10 breaths per minute higher than the WHO definition (which is ≥ 60 bpm for infants 0 to 59 days of age and ≥ 50 bpm for infants ≥ 60 days of age) has thus been added to the medically-significant RSV LRTI definition.

Location of Change	Change/Modification in Version 9.0
Synopsis, Sections 2.3, 3.3.3	The 2nd exploratory objective has been updated to include tachypnea. The changed objective is as follows: *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.* The 2nd corresponding endpoint to the above-stated objective has also been updated to include tachypnea. The changed endpoint is as follows: *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).*
Synopsis, Table 1	Target subject enrollment has been updated to 2,930 for placebo group and 5,688 for RSV F Vaccine group to reflect the randomization switch to 2:1 (Active / Placebo) after global year 1
Synopsis, Section 3.1	The description of the study design has been updated to remove the projected number of RSV seasons that the trial could span. The sentence "continuing for up to 4 consecutive RSV seasons in each hemisphere" has been removed. The word "inclusive" has been removed when specifying the target age range for study maternal subjects, ie, 18 to 40 years of age. Justification: The study duration is now specified in terms of enrollment rather than time, to allow adjustment of duration if needed based on enrollment rate. The removal of "inclusive" is intended to clarify the intended inclusion of women 18 to 40 years and zero (0) days, the upper breakpoint co-inciding with identified cut-offs for higher risk rates in pregnancy.
Synopsis, Section 3.2	The description of the group-sequential design strategy has been updated to reflect the updated primary objective of efficacy. Details of the proposed formal interim analyses for efficacy to evaluate success in the primary objective have been added, which will now occur: *after 1) approximately 4,600 total mother-infant pairs, including at least 3,000 cumulative actively-immunized mother- infant pairs, have completed at least 6 months of post-partum follow-up; and 2) if necessary, after an additional 2,000 mother-infant pairs have completed at least 6 months of post-partum follow-up.*
Synopsis, Section 3.3.1	The primary efficacy endpoint in infant subjects has been changed to accommodate the updated definition of medically-significant RSV LRTI. The changed endpoint is as follows: o *The presence of RSV infection confirmed by detection of RSV genome by RT-PCR on respiratory secretions (obtained within the continuous illness episode which fulfills the other criteria listed below); AND*

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	○ *At least one manifestation of LRTI from among the following: cough, nasal flaring, lower chest wall indrawing, subcostal retraction, 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 bpm in infants 0 to 59 days of age and ≥ 60 bpm in infants ≥ 60 days of age).*
Section 3.4	It has been specified that the duration of the entire study is estimated to be *approximately* four years, but will be determined by the operation of the group-sequential design and the actual enrollment rates.
Synopsis, Section 5.1	Inclusion criterion defining the age at which subjects are eligible to enroll (ie, ≥ 18 and ≤ 40 years-of-age) has been qualified with the following statement: *connotes a lower limit of 18 years and 0 days and an upper limit of 40 years and 0 days*
Synopsis, Section 6.1.2.10	It has been clarified that active surveillance for RSV-suspect illnesses will cease after D+180, and that respiratory illnesses passively reported by parents/guardians after this time point will be captured as AEs.
Synopsis, Section 6.2	RSV surveillance rules have been updated with the following: *The language describing the window for the study staff to re-evaluate all infant subjects with RSV-suspect illnesses has been modified from "24 to 48 hours" to "between 2 and 3 days" of any initial RSV surveillance visit.* The following additional rules have been added: *Newly-discovered RSV-suspect illnesses as assessed by the presence of "trigger symptoms" will precipitate a home or clinic visit for evaluation.* *Study staff will re-evaluate (at home or in the clinic) all infant subjects with RSV-suspect illnesses between 2 and 3 days after any initial RSV surveillance visit to ascertain worsening in the illness. This re-evaluation will include the same procedures outlined in Section 6.2.3 of the protocol.* It has been specified that RSV-suspect illness reported during passive surveillance but after D+180 days will be captured as AEs and not on the RSV Surveillance page. It has been clarified that whenever symptoms of a new respiratory illness emerge, or ongoing symptoms worsen, for both infant and maternal subjects, study staff should be contacted within 3 days of symptom onset/worsening. Justification: It has been noted over the first two years of the study that a number of cases of medically-significant RSV LRTI are being evaluated by study sites without fulfilling the primary endpoint definitions, but then are being admitted to

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	hospital 2-3 days later – at which time study assessments are not completed. In order to rectify this situation, a follow-up evaluation of subjects who present with RSV-suspect illnesses will be added, and parents will further be encouraged to report worsening illnesses to the study sites.
Synopsis, Section 6.2.3	Additional procedures have been outlined for the study staff to increase efficiency and completeness in capturing study endpoints, including tachypnea, during RSV surveillance. The study staff are instructed to perform the following procedures during a surveillance visit, specifically for symptomatic infants: *Measure the respiratory rate on room air (if possible) for all symptomatic infants. The measurement should be performed first, on a calm, infant, and should be performed by observation only (i.e., without stethoscope auscultation) for a full, timed one minute period.* – *If the result is ≥ 60 bpm in an infant 0 to 59 days age or ≥ 50 bpm in an infant ≥ 60 days of age, a second timed one minute count should be obtained.* – *If a second count is obtained, the lower of the two observations should be recorded.* *Measure the SpO_2 via pulse oximetry (using study-specific pulse oximeter) for all symptomatic infants, which is to be performed when the infant is calm and not crying, and before administration of oxygen supplementation. The lowest stable SpO_2 observed during a one minute measure should be recorded.* The study staff will perform the following additional procedures for all symptomatic subjects (including maternal and infant): *Review and confirm the history of respiratory illness, including the approximate date of first symptom onset.* *Perform an examination of the symptomatic infant subject to ascertain, by observation or auscultation, the presence of the LRTI manifestations listed in Table 3 of the protocol.* *Collect vital signs other than respiratory rate (heart rate, blood pressure [if available for the infant], and axillary body temperature) for the symptomatic subject.* In addition, the section specifies collection of a mid-turbinate swab for RSV detection by RT-PCR and completion of vital signs. The section has been reorganized to maintain relevance to RSV illness trigger symptoms; and also to conform to new instructional materials concerning the evaluation which will be distributed to site staff. Guidelines pertaining to follow up of subjects with RSV suspect illness have been presented in a new section numbered 6.2.4.
Table 3	The table has been re-organized to conform more closely to Section 6.2.3, although specifying collection of the same observations, save for tachypnea. Measurement of tachypnea has been removed from Table 3, which describes features of LRTI, and is now captured within the body text of Section 6.2.3; consistent with the revised role of tachypnea in the primary endpoint case definition.

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Synopsis, Section 6.2.4	This section has been added to provide additional direction for the study staff for follow-up of RSV-suspect illness among subjects. Specifically, the following have been added: *For symptomatic infant subjects, schedule a follow-up visit in 2 to 3 days to ascertain whether the illness is worsening.* • *The follow-up visit will include the same procedures outlined in Section 6.2.3.* • *Parents/guardians will be strongly encouraged to report any worsening after the follow-up visit, including hospitalizations, which may trigger any number of additional follow-up visits at the investigator's discretion.* • *In the event than an infant is hospitalized, site staff are encouraged to perform a follow-up visit in-hospital, if permissible under local adiministrative and ethical review procedures.* *For symptomatic maternal subjects, and for symptomatic infant subjects after the first follow-up visit described above, a weekly contact by telephone/SMS will be performed to ascertain respiratory symptom status through to the D+180 visit, and to monitor the status of RSV-suspect illnesses until symptoms have resolved, or have returned to baseline if after the D+180 visit.* *In the event new and/or worsening symptoms are reported during active or passive follow-up, an in-clinic or home RSV-surveillance visit may be scheduled at the investigator's discretion for an evaluation to occur as soon as possible and a re-evaluation as per Section 6.2.3, may be performed.* *At the investigator's discretion, collection of ONE more respiratory specimen for pathogen detection for infant subjects who have developed qualitatively different or quantitatively worse symptoms. Note that no more than 3 respiratory specimens should be collected from an infant within the same episode.* *If the new or worsening symptom in the maternal subject is associated with a respiratory episode for which a specimen has already been obtained, the investigator may exercise his/her judgement as the utility of an additional swab.*
Section 7.3	It has been specified that a respiratory specimen will be collected as soon as possible after onset of illness among subjects.
Section 8.3.1	The following guidance regarding the safety reporting of ASQ abnormalities has been added: *As a guidance, and solely for the purposes of consistency within this protocol, it is suggested that investigators report ASQ abnormalities which persist at 6 and 12 months in a given infant as an AE that is "moderate" in severity. If diagnostic developmental testing is undertaken, the event should be further classified as a medically-attended event (MAE, see 8.4). If diagnostic evaluation, during the trial or afterward, leads to the diagnosis of a persistent developmental disability, the*

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	event then also becomes a serious adverse event (SAE, see Section 8.5) as should be reported as such. It has been specified that assessment for infants born prematurely may use age-appropriate adjusted scoring.
Section 8.6	It has been clarified that neonatal and infant deaths should be reported whenever possible as the underlying medical condition which resulted in death, with death captured as the outcome of the SAE to allow the capture of more granular information about the incidence of specific diagnostic entities leading to death, and prevent confusion with SIDS in analysis.
Section 8.7	It has been specified that any pregnancy occurring after the birth of the planned child enrolled in the current study AND before the maternal subject has completed the Day 180 post-delivery visit will not be captured as an AE.
Section 8.10	It has been clarified that the DSMB will consist of at least five clinicians to include not less than 2 obstetricians (with at least one with expertise in high-risk obstetrics or maternal-fetal medicine) and not less than 2 pediatricians (at least one neonatologist), and the unblinded DBMB statistician.
Synopsis, Section 10.1	When defining the intent-to-treat efficacy and intent-to-treat immunogenicity study populations, the statements "subjects will be analyzed according to treatment as actually receive" have been deleted.
Synopsis, Section 10.4.1	Study definition for RSV LRTI has been changed throughout the protocol by omission of "tachypnea at rest" and of the "presence of an acute RSV infection of the lower airways and/or lungs manifesting as one or more of cough, nasal flaring, or difficulty breathing." The updated definition of RSV LRTI is presented below: *Confirmed RSV LRTI will feature a 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.* "RSV LRTI with hypoxemia" has been replaced with "medically-significant RSV-LRTI," which now is defined by the presence of medically-significant respiratory compromise as evidenced by either hypoxemia or tachypnea. The new definition of medically-significant RSV-LRTI is presented below: *An RSV LRTI episode with EITHER a resting peripheral oxygen saturation (SpO_2) < 95% at sea level or < 92% at altitudes > 1800 meters by pulse oximetry on room air OR tachypnea defined as ≥ 70 breaths per minute [bpm] in an infant 0 to 59 days of age, or ≥ 60 bpm in infant ≥ 60 days of age.*

Location of Change	Change/Modification in Version 9.0
Synopsis, Section 10.4.2	Statistical considerations have been updated to reflect changes in study efficacy objective and endpoints and to present the stipulations for stopping the trial for success after the conductance of formal interim analyses. Specifically, the following statistical criteria have been provided: *The trial may stop for success after one of two formal interim analyses occurring:* – *After 3,000 cumulative actively-immunized maternal subjects immunized with investigational vaccine (approximately 4,600 total maternal subjects in both study arms) and their infants have completed at least 6 months of post-partum follow-up, or* – *After approximately 2,000 additional maternal subjects and their infants (approximately 6,600 maternal-infant pairs total) have completed at least 6 months of post-partum follow-up.* *Alternatively, the trial may achieve success after a final analysis undertaken when the projected total of approximately 8,618 maternal subjects and their infants have completed at least 6 months of post-partum follow up.* *The interim and final analyses for determination of success in the primary objective will utilize data through the first 90 days of life of the infant subjects and will be based on the posterior probability of success. Should success be declared, the sequential analyses of the co-primary endpoints concerning efficacy through 120, 150, and 180 days, as well as all secondary and exploratory analyses, will be performed on the final dataset.* *In view of differing global regulatory requirements, the final analysis (whenever this occurs) will be carried out sequentially while maintaining Type I Error rate at no more than 1-sided 2.5% level, to address primary hypotheses concerning the posterior probability that the event ratio, $r = \pi v / \pi p$, is less than 1.0, and based on success in that test, the posterior probability that the event ratio, $r = \pi v / \pi p$, is less than or equal to 0.70.* Text has been updated to indicate that only up to 2 interim analyses are contemplated, not three. Additional specifications for sensitivity analyses have been provided, as described below. *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 record). Further details regarding the sensitivity analyses will be described in the statistical analysis plan.*
Section 10.6	Text has been corrected to reflect that all unsolicited AEs for maternal subjects through 180 days post-delivery by severity and relatedness, will be captured.

Location of Change	Change/Modification in Version 9.0
Synopsis, Section 10.8	The estimated enrollment projections per global season used for the simulation scenarios have been updated, as shown below: *Estimated enrollment projections per global season used for the simulation scenarios and operating characteristics were 174 (20 in Northern Hemisphere and 154 in Southern Hemisphere) in global season 1 and 1,304 (210 in Northern Hemisphere and 1094 in Southern Hemisphere); 2,735 (1,220 in Northern Hemisphere and 1,515 in Southern Hemisphere); 3,025 (1,510 in Northern Hemisphere and 1,515 in Southern Hemisphere); and 3,025 (1,500 in Northern Hemisphere and 1,515 in Southern Hemisphere) in subsequent seasons 2, 3, 4, and 5, respectively. The Southern Hemisphere enrollment estimate for the global season 5 was used for the operating characteristics determination for lower than projected enrollment rates.* An updated table with simulation scenarios and operating characteristics needed to satisfy the study efficacy objective, has been provided.
Section 10.10.1	It has been specified that the sequence of formal interim analyses for efficacy will be conditioned by the US FDA requirement that not less than 3,000 actively-immunized maternal subjects and their infants (approximately 4,600 mother-infant pairs in total) be included in the first formal interim. Further specifications have been provided for the conduct of formal interim analyses.
Section 10.10.2	The section has been inserted to indicate that the Sponsor may trigger the performance of an informational analysis of efficacy as defined in the SAP. This analysis will be performed by the DSMB biostatistician and the IBG in a manner entirely analogous to the analyses for efficacy and futility, and will address a success criterion to be specified in the SAP. The DSMB will communicate the results of the analysis to the Sponsor only in terms of fulfillment or non-fulfillment of the target criterion.
General	Minor changes have been made to improve the readability of the document.

Protocol Version 8.0, 23 August 2016 (revised from 7.0, 15 July 2016)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 8.0
Synopsis (Study Design); Section 3.1	Further clarified the permissive timing of maternal subject enrollment and immunization, and how this will be consistently determined for each maternal subject based on their estimated date of delivery and in consideration of the historic average onset and end date of increased RSV transmission at each study site. The reader is referred to the Study Operations Manual for further details.
Section 3.8	Clarified the procedures for unblinding of subject treatment assignment in the event of a medical emergency. The revised text now states, "If feasible, the investigator is asked to notify the Medical Monitor or designee prior to unblinding; however, the investigator may unblind without consulting the Medical Monitor, if it is deemed to be in the best interest of the subject."
Synopsis (Inclusion Criteria); Section 5.1	Inclusion criterion #2 now contains the gestational age dating composite criteria, which was formerly presented in IC#3 in the prior protocol versions. IC#2 sub-bullets (a) through (d), which already reflected current guidelines established by the American College of Obstetricians and Gynecologist (ACOG) for gestational age dating [Committee on Obstetric Practice 2014], were modified to provide further clarity. The requirement to enroll and immunize maternal subjects with an estimated date of delivery between approximately six (6) weeks before and approximately four (4) weeks after the historic average date of onset of increased RSV transmission at the clinical site was removed as an inclusion criterion.
Synopsis (Exclusion Criteria); Section 5.2	Removed the text, "including known sickle trait or thalassemias" from exclusion criterion (EC)#7. Modified EC#20 to include anyone with red blood cell allo-immunization, not just untreated.
Sections 7.2.1 and 7.2.2	The assay descriptions for anti-F IgG and PCA ELISA have been reworded for clarity. The Standard Operating Procedure (SOP) providing details on the assays has been referenced.
Section 8.7	The safety reporting requirements have been amended to ensure compliance with the European Directive 2001/20/EC. Specifically the updated text clarifies that Novavax or its designee will report serious adverse events (SAEs) to regulatory authorities and investigators, as well as to Ethics Committees in jurisdictions where this is a sponsor responsibility.

Location of Change	Change/Modification in Version 8.0
Sections 10.10.1 and 11.1	Cited the regulatory authorities in Chile and New Zealand where the study is also being conducted.

Protocol Version 7.0, 15 July 2016 (revised from 6.0, 09 May 2016)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 7.0
Synopsis (Maternal Study Visit); Section 6.1.1.2 and Appendix 1	Although stated in Exclusion Criterion #4, the administration of any licensed vaccine recommended for pregnancy to occur within 14 days of the Day 0 vaccination (i.e., at least 14 days before or 14 days after) was emphasized in the sections referenced in order to remove ambiguity.
Synopsis (Maternal Study Visit); Sections 6.1.1.2 Appendix 1	Changed the screening visit window for subjects from "-28 to -2" to "-28 to 0" days relative to the planned Day 0 vaccination to accommodate study sites in countries participating beyond their first year of study conduct. Separately described the testing that will be performed for subjects participating in the first year in any country vs those participating in all other years in any country as it pertains to clinical safety labs and HIV, syphilis, HBV, and HCV antigen tests/serologies.
Synopsis (Maternal and Infant Study Visit, RSV Surveillance); Sections 6.1, 6.2, and 7.3	The window for clinician evaluation and respiratory specimen collection of maternal and infant subjects with symptoms of RSV-suspected illness was extended from 5 to 7 days to broaden the window for data collection of any respiratory illness.
Synopsis (Maternal Study Visit); Sections 6.1.1.6 Appendix 1	Telephone contact for the Day 28 safety follow-up will encompass short message service (SMS), commonly termed "text messaging."
Synopsis (Infant Study Visit); Section 6.1.2 ; Appendix 1	Specified that all procedures, including routine vaccinations, that are considered standard of care for a corresponding baby-wellness visit may be performed at any study visit, if applicable.
Synopsis (Infant Study Visit); Sections 6.1.2.9 and 8.3.1; Appendix 1	Infant subjects with a positive screen detected at both 6 and 12 months of age, or first appearing at 12 months of age, will be offered repeat developmental testing at 15 and 18 months of age as a follow-up procedure. Novavax will collect this information as safety data in the main study, rather than in a separate follow-on protocol.

Location of Change	Change/Modification in Version 7.0
Synopsis (RSV Surveillance); Section 6.2	As part of passive RSV surveillance, symptomatic maternal subjects and parents/guardians of symptomatic infant subjects should contact the study site directly within 3 days of the onset of symptoms (rather than 5 days) to allow time to schedule and conduct the in-person evaluation.
Synopsis (RSV Surveillance); Section 6.2.3	Clarified that the evaluation of maternal and infant subjects with RSV-suspected illness will occur within 7 days of symptom/s onset.
Synopsis (RSV Surveillance); Section 6.2.2	Added "New or increasing wheezing" and "New or increasing sputum production" to the list of trigger symptoms for symptomatic maternal subjects with an RSV-suspected illness.
Section 6.5	Clarified that study completion procedures for maternal subjects who discontinue from the study prematurely, will include clinical laboratory safety assessments for those subjects with safety labs performed as screening only.
Sections 9.1 and 9.2; General	Clarified that template source documents will be used for Global Year 1, and the electronic source documentation (eSource System) for all subsequent years (i.e., Global Years 2, 3, and 4). Clarified that remote monitoring may be performed by independent clinical monitors designated by Novavax. The term "eSource" or "eSource system" was generally included wherever "eCRF" was referenced.
Section 9.4	Briefly updated the study files that will be maintained in the centralized filing system.
Synopsis and Section 10.4.1	Definition provided for a symptomatic RSV infection in maternal subjects.
Synopsis; Appendix 1	The gestational weeks for all visits occurring after Day 0 were updated to reflect the broadening of the gestational age for vaccination (28 to 36 weeks) approved in the prior protocol amendment.
General	Minor edits to correct typographical errors were made to the document.

Protocol Version 6.0, 09 May 2016 (revised from 5.0, 09 February 2016)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 6.0
Synopsis (Study Rationale, Inclusion Criteria); Sections 1.7 and 5.1, and Appendix 1	Results from the first-in-pregnant women study (RSV-M-203) with the RSV F vaccine were summarized. The gestational age for immunization of pregnant women in the third trimester with the RSV F vaccine was widened at the lower end of the third trimester, from 31 weeks to 28 weeks; a justification for this change was provided.
Synopsis (Study Objectives, Primary and Exploratory); Sections 2.1 and 2.3	Clarified that primary efficacy objective will be based on the first episode of RSV lower respiratory tract infection (LRTI) with hypoxemia experienced for infants with multiple RSV episodes. Exploratory objectives will all be descriptive in nature. The first exploratory objective was clarified to state that vaccine efficacy against <u>all</u> symptomatic RSV respiratory tract infections will be described in maternal subjects. The second exploratory objective will now describe the incidence of, and vaccine efficacy against, all-cause LRTI in infant subjects, with and without hypoxemia or severe hypoxemia.
Synopsis (Study Endpoints); Section 10.5	Any subgroup analysis for an efficacy endpoint will now consider all infants of mothers who received test article < 2 weeks prior to delivery and all infants of mothers who received any test article The geometric mean ratio (GMR) will not be derived/calculated for any immunological assay. The Percentages of infant subjects with all-cause LRTI, with or without hypoxemia or severe hypoxemia will now be presented based on the updated to the exploratory objective.
Synopsis (Study Design, Group Sequential Design, Inclusion Criteria); Sections 3.1, 3.2, and 5.1	The sample size was revised from 8,255 to 8,618 total subjects to reflect the minimum requirement of 3,000 actively-treated maternal subjects and their infants for the safety database. This change impacts how the group sequential design and interim analyses will be handled and the study operations that will be triggered based on scenarios when futility, or vaccine efficacy, or neither is observed. The timing for maternal subject enrollment and study inclusion was clarified (see inclusion criterion #8) and now considers the projected date of delivery and the historical average onset of RSV transmission at each clinical study site. RSV onset date will be a best estimate based on site, local, state/provincial, or national data as available. After the first global season of enrollment, the randomization scheme will be changed to a 2:1 (active / placebo) ratio to enable more

Location of Change	Change/Modification in Version 6.0
	efficient accrual of the safety database. The Data and Safety Monitoring Board (DSMB) will continue their supervision and monitoring of subject safety in the same manner.
Section 4.1.1	Updated the description for the manufacture (production and purification) of the RSV F protein to reflect current processes.
Synopsis (Exclusion Criteria); Section 5.2	Added the term "active" to further clarify exclusion criterion #10.
Synopsis (Eligibility, Maternal Study Visit Procedures); Sections 5.1, 6.1.1.2, and 7.1	Screening for hepatitis B (HBV) and C (HCV) viruses, syphilis, and HIV can be performed using the central or local laboratory if undocumented (based on medical records) in the current pregnancy.
Synopsis (Maternal Study Visit Procedures); Section 6.1.1.9	Specified that maternal subjects with a positive pregnancy result at the D+180 visit will be followed for safety through the time of delivery to determine the outcome of this pregnancy.
Synopsis (Maternal and Infant Study Visit Procedures); Sections 6.1.1.10 and 6.1.2.10	Clarified that RSV surveillance visits are not considered unscheduled visits.
Synopsis (Infant Study Visit Procedures); Sections 6.1.2 and 6.1.2.6, and Appendix 1 and 3	Added text to allow for procedures and vaccinations associated with a baby-wellness visit to be performed at any infant post-partum study visit, if applicable. The Day 112 visit was changed to Day 120 to accommodate the 4-month old baby wellness visit that is routine in most countries.
Synopsis (RSV Surveillance); Section 6.2	Clarified that all procedures associated with the RSV surveillance visits are performed only on symptomatic subjects. As not all regions of the world routinely assess for blood pressure in the infant, this procedure can be omitted if not the standard of care. Mid-turbinate swabbing will be collected for all symptomatic subjects with a report of trigger symptoms evaluated at an RSV surveillance visit. Additionally, a throat swab will be collected for maternal subjects.
Section 7.3	Clarified that respiratory specimens will be processed and subjected to a commercially available multiplex RT-PCR for identification of a range of common viral pathogens in addition to RSV.
Section 8.6	Text describing how SAEs are reported was revised to align with Novavax standard operating procedures.

Location of Change	Change/Modification in Version 6.0
Section 8.8.1 and Table 7	Clarified that abnormal fetal heart tone measures may be repeated, but any consistent abnormality (i.e., < 120 beats/min or > 160 beats/min and present on more than one observation) should be reported as an AE and assessed against the toxicity grading scale.
Section 9.1	Novavax will provide sites with template source documents for the recording and collection of maternal and infant subject data since electronic source technology can now be used.
Synopsis (Statistical Methods); Section 10.1	The various maternal and infant subject populations to be used in the immunogenicity and efficacy analyses were all redefined.
Synopsis (Statistical Methods); Section 10.2	Removed text that indicated symptomatic respiratory tract infections not associated with RSV will be summarized as safety data since this is no longer valid.
Synopsis (Statistical Methods); Sections 10.4.2 and 10.7	Updated the statistical methods that will be used to analyze the primary and secondary efficacy objectives. Updated to clarify the prior distribution is defined as *Beta*(1,1) for both treatment arms. Revised the statistical method and the criterion for the futility analyses from the predictive probability of success against the relative risk of 0.7 to the posterior probability against the relative risk of 0.6. This change was made to improve the computational property and the interpretability and consistency of the rule with failure. The following sentence was added as clarification for the exploratory analyses: "All exploratory efficacy analyses will be conducted using the hypothesis based on the posterior probability that the event ratio, $r = \pi v / \pi p$, is ≤ 1.00." The following sentence was added as clarification for the data sets to be used for the interim analyses: "All interim analyses of efficacy data including futility analyses will include infant subjects who are at least 90 days old at the time of the data cutoff date." The following sentence was added as clarification for the data sets to be used for the secondary and exploratory efficacy analyses: "If the study is stopped early for efficacy at an interim analysis, all secondary and exploratory efficacy analyses will be performed on the final data containing all subjects enrolled and their follow-up."
Synopsis (Statistical Methods); Sections 3.3.3 and 10.5	The immunogenicity analyses will now include the proportion of maternal subjects with 2-fold and 4-fold increases in antibody levels from baseline and the seroresponse rate (SRR) based on anti-RSV F IgG, palivizumab-competitive antibody (PCA), and RSV/A and B microneutralization (MN) levels. The time-points at which the analyses will be performed was also specified.

Location of Change	Change/Modification in Version 6.0
Synopsis (Sample Size); Section 10.8 and Table 11	Updated the revised sample size and power calculations using new simulations that reflect the minimum requirement for a 3,000 maternal and infant RSV F vaccine exposures in the safety database in order to declare efficacy, the change in the number of interim analyses and conduct of the group sequential design, new projected enrollment estimates, and changes to the simulation scenarios and operating characteristics table.
Section 10.10.1	The requirement to have at least 3,000 total maternal subjects enrollments into the active treatment arm and at least 6 months of post-partum follow-up for their infants in order to perform an interim efficacy analysis was restated.
General	Clarified that maternal subjects will record their oral temperature daily in the diary. For all other assessments of body temperature in maternal and infant subjects, the axillary temperature will be collected. Minor edits and revisions for clarity and readability were made to the document.

Protocol Version 5.0, 09 February 2016 (revised from 4.0, 08 January 2016)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 5.0
Synopsis (Inclusion/Exclusion Criteria); Sections 5.1 and 5.2	Specified that "clinically significant" adverse reactions to prior vaccines would be collected on the medical history (Inclusion Criterion [IC] #5). Clarification regarding what constitutes alcohol and drug abuse was provided in Exclusion Criterion [EC] #15. EC#19 further clarified the use of low-dose aspirin. The term "serious" was added to the description of adverse reactions to a vaccine that would exclude a subject from participation in this study (EC #30).
Synopsis (Maternal Subject Study Procedures); Sections 6.1.1.4, 6.1.1.5, 6.1.1.9, and 7.1; Appendix 1	The Day 7 and 14 visits can also be conducted as home visits. Pregnancy testing will be administered to all subjects at the D+180 visit; subjects with a positive result will be followed to determine the outcome of this pregnancy in a separate study.
Section 6.1.1.3	In addition to alcohol swabbing, vaccination procedures now include "cleansing of the area of vaccination" to accommodate local standards of care.
Synopsis (Maternal Subject Study Procedures); Sections	For applicable subjects (i.e., those enrolled in the first year of study conduct in any country) who deliver prior to the Day 14 visit, the

Location of Change	Change/Modification in Version 5.0
6.1.1.5, 6.1.1.7, and 7.1; Appendix 1	clinical safety laboratory assessment will be performed at the Delivery visit.
Synopsis (Maternal Subject Study Procedures); Sections 6.1.1.6 and 6.2.1; Appendix 1	Institutional Review Board/Independent Ethics Committee approval of telephone scripts is now designated "if applicable" as this is not a requirement in all countries where the study is being conducted.
Synopsis (Infant Subject Study Procedures); Section 6.1.3; Appendix 1	Every infant study visit will query to determine if other children < 5 years of age reside in the same household as the infant subject.
Synopsis (RSV Surveillance); Section 6.2.3	The collection methods for sampling of upper respiratory secretions were expanded to include nasopharyngeal swab, mid-turbinate swab, or nasopharyngeal aspirate for maternal and infant subjects. The method(s) selected should now be based on accustomed local practice and site expertise. The option to use RT-PCR test results performed by the local laboratory on respiratory specimens as an endpoint for this trial is still under consideration. Thus, the following sentence was removed: "Conversely, local laboratory results, while informative to the clinician, will not be included as an endpoint for this trial." The following guidance was provided to investigators to address when symptomatic maternal and infant subjects should be evaluated for an RSV-suspect illness: "…Trigger Symptoms in infant and maternal subjects that persist for a period of ≥ 24 hours, either in a continuous or intermittent manner, and are assessed as 'atypical' (by the maternal subject herself, or a parent or other routine caregiver for the infant) in nature."

Protocol Version 4.0, 08 January 2016 (revised from 3.0, 09 July 2015)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 4.0
Title Page	A short protocol title was added.
Synopsis (Group-Sequential Design); Section 3.2	The role of the independent biostatistics group (IBG), the data and safety monitoring board (DMSB) statistician, and the DSMB project manager in the execution of the group-sequential design was clarified.
Synopsis (Safety Endpoint); Sections 3.3.4.2 and 10.6	Chorioamnionitis was added to the list of labor and delivery complications.
Section 3.7	All syringes containing the assigned test article will be masked by the unblinded vaccine administrator in order to obscure any differences in the appearance of the vaccine and placebo to subjects and blinded study staff.
Synopsis (Inclusion Criteria); Section 5.1	Clarified that the earliest ultrasound performed will establish the gestation age dating of the pregnancy in cases where multiple ultrasounds may be available.

Location of Change	Change/Modification in Version 4.0
Synopsis (Exclusion Criteria); Sections 5.2 and 7.1	"Known syphilis infection" was added to exclusion criterion (EC) #13. Clinical testing for syphilis detection will now be performed at the screening visit, if results are not available in prior data collected during the course of the current pregnancy. The "Planned receipt of > 1 dose of any licensed vaccine, such as tetanus, diphtheria, pertussis (whole cell or acellular) vaccine or tetanus toxoid (TT), hepatitis B vaccine, or influenza vaccine, after the screening visit" was removed because it was addressed in EC#4. History of severe post-partum depression was added to EC#27.
Synopsis (Maternal and Infant Study Visits and Time and Events Tables); Section 6.1and Appendix 1	Maternal subjects and parents/guardians of infant subjects will have the option of completing postpartum study visits in-clinic or at home to enhance compliance and subject safety follow-up.
Synopsis (Screening Visit); Section 6.1.1.2	Clarified the study procedures to state maternal subjects will be queried for any AE experienced since informed consent was obtained beginning at the screening visit (Day -28 to -2).
Synopsis (Maternal and Infant Unscheduled Visits); Sections 6.1.2 and 6.1.4	Clarified when maternal and infant subjects may participate in an unscheduled visit and the study procedures that may be performed.
Synopsis (Infant Subject Study D+180 Visit and Safety Endpoints, Time and Events Table); Sections 3.3.4.1, 6.1.3.7, 6.1.3.9, and 8.3.1, Appendix 1	A new section for the "Ages & Stages Questionnaires®, Third Edition (ASQ-3™)" was created. Parents/guardians of infant subjects with a positive screen detected at both 6 and 12 months of age (as this is an AE), or first appearing at 12 months of age, will be offered repeat Ages and Stages Questionnaire (ASQ)-3 screening at 15 and 18 months of age in a follow-on study. In addition, appropriate referrals for diagnostic pediatric developmental testing (according to local standards of care) will also be advised for these infants. The ASQ-3 screening will be performed on all infant subjects.
Synopsis (RSV Surveillance); Section 6.2	Content was reorganized and clarified to harmonize with operational activities and to be consistent with supplemental study documents (e.g., Study Identification Card, electronic case report forms). A "Definitions and Rules for RSV Surveillance" section was also added. Clarified that maternal and infant subjects with ongoing respiratory episodes at the D+180 visit will be followed weekly until symptoms have resolved or have returned to baseline.
Section 8.2.3	The toxicity grades used to assess for severity of clinical laboratory parameters will be based on third-trimester values published in Sheffield *et al.* [2013]. Normal ranges for these parameters will also be based on reference ranges appropriate for women in the third trimester of a pregnancy as described in Sheffield *et al.*
Sections 8.2.4 and 8.8.1	A toxicity grading scale to assess for severity of an abnormal fetal heart tone value was developed and provided in Table 7.

Location of Change	Change/Modification in Version 4.0
Section 8.4	In addition to being serious adverse events, hospitalizations will now be categorized as medically-attended events.
Section 8.6, Table 5	The term "Intrauterine Growth Restriction or Retardation (IUGR)" will now be captured as a separate entity, distinct from "Small for Gestation Age (SGA)" as a Maternal/Fetal/Neonatal Adverse Event of Special Interest.
Section 8.7	The procedure for SAE reporting was revised to be compliant with Novavax internal standard operating procedures.
Section 8.8.2	Severity for all unsolicited events reported in infant subjects will be based on whether medical intervention/therapy is required (as applicable) in addition to interference with daily-activities.
Synopsis (Statistical Methods); Section 10.1 and 10.4.1	Minor improvements to the descriptions of the intent-to-treat (ITT) and modified-ITT Populations were made. Definitions for RSV season and RSV episode were deleted from the study definitions list in the protocol as these terms are more relevant to the statistical analysis.
General	The term "SaO_2" was replaced with "SpO_2" as the peripheral capillary oxygen content or saturation of the blood will be measured by pulse oximetry. Oral temperature was routinely replaced with body temperature in order to accommodate the various modes of temperature collection at the different study sites. Minor edits and revisions for clarity and readability were made to the document.

Protocol Version 3.0, 09 July 2015 (revised from 2.0, 11 June 2015)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 3.0
Synopsis (Inclusion and Exclusion Criteria), Section 5	Text regarding the methodology for gestational age dating was further refined in Inclusion Criterion (IC)#3; while IC#4 will now only serve to exclude major fetal anomalies. The physical exam will no longer include a gynecologic exam (IC#5). Fetal growth abnormalities identified by ultrasound are now included in Exclusion Criterion (EC)#2, as part of a pregnancy complication. Subjects who have received any RSV vaccine (EC#6), have an acute disease within 72 hours of the day of vaccination (EC #29), or have had an adverse reactions to any prior vaccine (EC#31), will now be excluded. Minor updates were made to EC#2, #4, #12, #17, and #20.
Synopsis (Study Endpoints), Sections 3.3.4.1, 3.3.4.2, 3.3.5, 10.4.2, 10.6, 10.7	The term "proportions" was changed to "percentages" throughout the document as this more accurately reflects how relevant safety and exploratory analyses will be calculated.

Location of Change	Change/Modification in Version 3.0
Synopsis (Pre-screening Maternal Study Procedures), Sections 6.1.1.1	Clarified that depending on the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) having authority, informed consent to "pre-screen" and identify pregnant women to contact for the main study may or may not be required in order for investigators to collect medical information on these individuals.
Synopsis (Study Procedures Schedule), Sections 6.1.1.3, 6.1.2.1, 6.2, Appendix 1	Study Identification Cards will be issued to the maternal subject on study Day 0 and at delivery and to a parent/guardian of the infant at delivery. Replacement cards will be available throughout the study, if lost or misplaced. The identification cards will indicate the maternal and infant subjects are part of an investigational vaccine trial, provide the contact number(s) of the obstetrical or pediatric investigator's study staff, and list the clinical signs and symptoms of an RSV infection in adults and infants. The Study Identification Cards will replace the RSV informational pamphlet.
Synopsis (RSV Suspect Illness Surveillance), Sections 6.2, 6.2.1	Active RSV surveillance will consist of weekly phone calls to the maternal subject and the parent/guardian of the infant subject during RSV season, which is defined by local epidemiological surveillance data. The relevant subject population to which each *Trigger Symptom* should be assessed was assigned.
Section 1.2.1	The number of hospitalizations and outpatient visits due to RSV among children <5 years of age was updated with new information from the Centers for Disease Control and Prevention (CDC).
General	The 120µg dose of the RSV F protein adsorbed to a 0.4mg dose of aluminum as the phosphate salt was referenced consistently through the protocol as the RSV F vaccine.
General	Minor edits and revisions for clarity and readability were made to the document.

Protocol Version 2.0, 11 June 2015 (revised from 1.0, 20 April 2015)

The following is a summary of the changes made to this protocol.

Location of Change	Change/Modification in Version 2.0
Synopsis, Section 3.1 (Study Design), Section 10.8 (Sample Size)	The planned number of third-trimester pregnant maternal subjects to be enrolled into the study was increased from 7,805 to 8,255 (4,128 active vaccinees and 4,127 placebos) to reflect the proposed increase in enrollment in the first year (i.e., from 1,250 to 1,700).
Synopsis, Sections 1.7, Appendix 1 (Maternal Study Procedures Schedule)	The upper limit of the gestational age window for maternal immunization of third-trimester pregnant subjects was increased by 1 week to $36^{0/7}$ weeks gestation.
Synopsis (Group Sequential Design Strategy), Sections 3.2 and 10.10.1	The calendar dates at which interim analyses will be performed to assess for futility and success at the conclusion of RSV seasons in the Northern and Southern hemispheres were specified. Justification for selection of these dates and the minimum amount of infant subject

Location of Change	Change/Modification in Version 2.0
	data required for each analysis (i.e., at least 3 months of post-natal follow-up) was also provided.
Synopsis and Section 5.1	The sentence "Ultrasound performed at ≤31 weeks estimated gestational age is acceptable" was removed. If the last menstrual period is unknown or uncertain, and no prior first or second trimester ultrasound has been performed, then an ultrasound performed at screening within the second trimester, will be used to establish gestational age dating.
Synopsis and Section 10.4.1, Table 2	The definition of RSV lower respiratory tract infection (LRTI) was further refined. Poor feeding/failure to feed, lethargy, and irritability were removed from the list of clinical signs/symptoms to be sought for RSV-suspect illness.
Synopsis and Section 10.5	The omission of the SCR analysis for anti-F IgG was corrected. The geometric mean ratio (GMR) of cord blood over maternal serum ($GMR_{Cord/MS}$) and of infant sera over cord blood ($GMR_{AD/Cord}$) was added as an additional means to assess for transplacental transfer of maternal antibodies.
Synopsis and Section 10.8, Table 8	Table 8 (Simulation Scenarios and Operating Characteristics) was revised to provide placebo RSV event rates of 0.07% and to adjust the mean sample size to conclude efficacy and the mean sample size to conclude efficacy and safety (based on 3,000 subjects) for each true event ratio based on varying placebo event rates. The cumulative probability of stopping for success by global season was also revised based on the new simulation scenarios.
Section 6.5	Clarification was provided regarding how subjects with any SNMC or SAE that continues beyond the duration of the study are to be followed.
Section 10.10.1	An interim evaluation of immunogenicity and transplacental antibody transfer will be performed by the DSMB statistician for the first global season analysis. Details of this analysis and the limited communication plan to ensure appropriate protection of the study blind will be provided in the statistical analysis plan (SAP), the DSMB charter, and the written communication plan.
General	Minor edits and revisions for clarity and readability were made to the document.

Signature Page

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