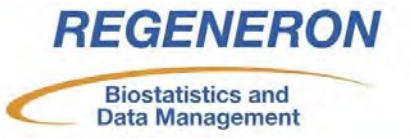

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:

A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of a Human Monoclonal Antibody, REGN2222, for the Prevention of Medically attended RSV Infection in Preterm Infants

Part B

Compound:	**REGN2222**
Protocol Number:	**REGN2222-RSV-1332**
Clinical Phase:	**Phase 3**
Sponsor:	**Regeneron Pharmaceuticals, Inc.**
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	**Original Statistical Analysis Plan / July 28, 2017**

APPROVAL PAGE

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

Study Biostatistician

See appended electronic signature page

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Study Clinical Pharmacologist

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Head of Biostatics and Data Management or designee

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[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUCinf	Area under the concentration-time curve from time 0 to infinity
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
EOS	End of study
ET	Early termination
FDA	Food and Drug Administration
GA	Gestational age
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ICF	Informed Consent Form
IM	Intramuscular
IVRS	Interactive voice response system
IWRS	Interactive web response system
LLN	Lower limit of normal
LRTI	Lower respiratory tract infection
MedDRA	Medical dictionary for regulatory activities
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PT	Preferred term
Q	Every
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RSV	Respiratory syncytial virus
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan

SAS	Statistical Analysis Software
SOC	System organ class
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for REGN2222-RSV-1332 Part B only. A separate SAP was prepared for Part A.

This plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution or data that affect planned analyses. A final plan will be issued prior to database lock of Part B.

1.1. Background/Rationale

This phase 3 study of REGN2222 is designed to evaluate the efficacy, safety, pharmacokinetics (PK), and immunogenicity of REGN2222, a new human immunoglobulin G1 (IgG1) monoclonal antibody directed against the respiratory syncytial virus (RSV) fusion glycoprotein in infants born no more than 35 weeks 6 days gestational age (GA), who are no more than 6 months of age at the time of first dose of study drug. The study has 2 parts:

Part A was an open-label PK study of REGN2222 to determine the PK in pre-term infants after a single dose to enable the selection of dosing regimens for Part B. It provided an initial evaluation of safety and tolerability in infants. A separate SAP was prepared for Part A.

Part B is a randomized, double-blind, placebo-controlled, study designed to evaluate efficacy, safety, concentrations of REGN2222 in serum, and immunogenicity of IM administration of REGN2222 in preterm infants who are not eligible or recommended for, or who do not have access to, palivizumab. Up to 1515 subjects (1010 assigned to receive REGN2222 [505 subjects in each of the 2 arms] and 505 to receive placebo) are planned to be enrolled and randomized 1:1:1 into 3 arms. The use of a placebo arm is justified because infants enrolled into the study would not receive less than standard of care for RSV prevention because only infants who are not eligible, recommended, nor is access available to receive palivizumab will be included in the study.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study in Part B is to demonstrate the efficacy of REGN2222 in preventing medically attended RSV infections (subjects with either RSV-confirmed hospitalizations or outpatient lower respiratory tract infection [LRTI]).

1.2.2. Secondary Objectives

The secondary objectives of the study in Part B are:

- To evaluate safety and tolerability of REGN2222
- To demonstrate the efficacy of REGN2222 in reducing RSV-confirmed hospitalizations, emergency room (ER), urgent care (UC), or pediatric clinic (PC) visits
- To assess serum levels of different dosing regimens of REGN2222
- To assess immunogenicity of REGN2222

1.2.3. Modifications from the Statistical Section in the Final Protocol

None.

1.2.4. Revision History for SAP Amendments

This is the first version.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a Phase 3 study that will be conducted in 2 parts.

Part A was an open-label, single cohort, multicenter, PK study.

Part B is a randomized, placebo-controlled, 3-arm, multicenter study. In Part B, the sponsor (Regeneron Pharmaceuticals, Inc.) will provide permitted windows for prophylaxis of subjects in each geographical area based on historical data on the timing and duration of the RSV season. A total of 3 treatment arms (1 dose of REGN2222 and 1 dose of placebo; 2 doses of REGN2222; and 2 doses of placebo) with a total of 1515 subjects are planned in Part B and will be randomized in a 1:1:1 ratio (505 subjects in each arm for a total of 1010 assigned to receive REGN2222 [505 subjects in each of the 2 REGN2222 arms] and 505 subjects to receive placebo). Randomization will be stratified by region (North America or rest of the world) and GA (≤31 weeks, 6 days GA or from 32 weeks, 0 days to 35 weeks, 6 days GA).

2.2. Sample Size and Power Considerations

Originally Planned Sample Size

For Part B, the sample size estimation is based on the primary efficacy endpoint of medically attended RSV infection (hospitalization or outpatient LRTI). Literature (Hall 2009, Ambrose 2014) show that the event rate in this endpoint is in the range of 12% to 22% in the studied infant populations. The Hall data is population based and the majority of infants are full-term; the Ambrose publication of data from the RSV Respiratory Events Among Preterm Infants Outcomes and Risk Tracking (REPORT) study evaluated preterm infants of 32-35 weeks gestational age and less than 6 months of chronological, whom were not receiving RSV prophylaxis. As the event rate may vary over RSV season or geographic region, a relatively conservative approach was taken to assume that event rate is 10% for the placebo group, and either dosing regimen of REGN2222 would reduce the event rate from placebo by 60% (event rate of 4%). With 505 randomized subjects per arm or a total of 1515 randomized subjects, the study would have 90% power to demonstrate a 60% or greater reduction at 2-sided significance level α=0.025. This originally planned sample size also incorporated a 5% early dropout rate. The sample size calculation was based on chi-square test with continuity correction and performed using nQuery version 7.0 (Statistical Solutions Ltd, Cork, Ireland).

Based on the originally planned sample size and event rate assumption, we anticipated approximately 90 primary endpoint events.

The blinded sample size re-estimation (as detailed in the study protocol Section 9.2.1) designed for the originally planned sample size has not been performed for this study.

Power Calculation for Reduced Sample Size

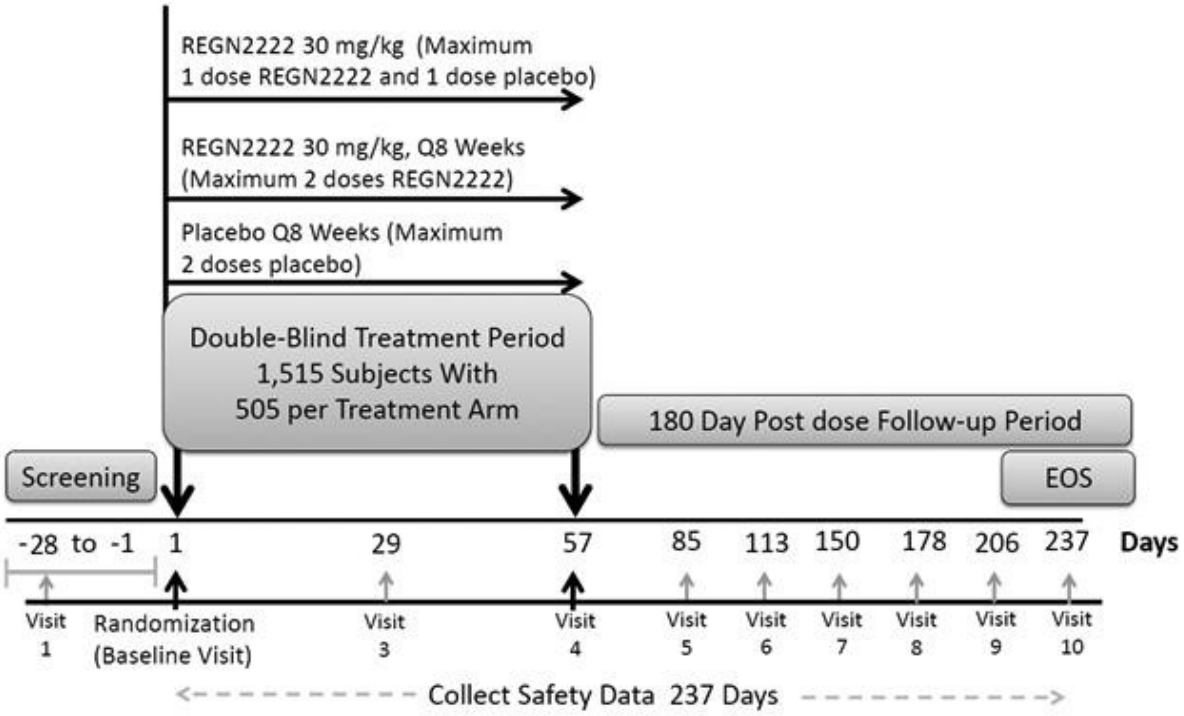
The sample size of the study has been reduced due to business considerations. The intent of this power calculation is to understand the impact of the reduced sample size on the primary efficacy analysis. Specifically, to accommodate the reduced sample size, the overall Type I error for the pairwise comparisons of each REGN2222 dose regimen to placebo will be controlled using a

pre-specified hierarchical inferential approach (2-sided α=0.05 for each statistical test; see Section 5.7.3), as opposed to the originally planned Bonferroni adjustment (2-sided α=0.025 for each pairwise treatment comparison). Therefore, assuming approximately 1200 subjects are administered study drug, the comparison of the REGN2222 2-dose regimen to placebo will have approximately 87% power to detect the previously planned 60% reduction in medically attended RSV infections with a 2-sided significance level of 0.05.

2.3. Study Plan

After the parent(s) or legal guardian(s) provide informed consent (obtained up to 28 days prior to randomization), subjects will be assessed for study eligibility for Part B at the screening visit. Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 baseline assessments and will be randomly assigned in a 1:1:1 ratio to REGN2222 30 mg/kg single dose (1 dose REGN2222 and 1 dose placebo), REGN2222 30 mg/kg Q8 weeks (2 doses of REGN2222), or placebo (2 doses of placebo). The study flow diagram for Part B is depicted in Figure 1.

Figure 1: Part B: 30 mg/kg IM (1 Dose REGN2222 and 1 Dose Placebo), 30 mg/kg IM (2 Doses of REGN2222), or Placebo IM (2 Doses of Placebo)



EOS = end of study; IM = intramuscular; Q8 = every 8
Note: The screening visit occurs from Day -28 to Day -1. Black arrows denote dosing visits. Subjects will be monitored on site for at least1 hour after each dose of REGN2222 or placebo. Grey arrows denote study visits at which dosing does not occur. Visits 8, 9, and 10 will occur via phone call. In the event an AE is reported during a phone call visit, an unscheduled onsite visit may be required to follow-up, per investigator.

In Part B, assessment of the clinical efficacy endpoints will only occur during the 150 day study period (ie, through Visit 7). Any RSV infection occurring after Day 150 visit will not be included in the efficacy evaluation. If a primary endpoint is reached during the study period, ongoing assessments for other endpoints and measurements will continue until the end of the study period. Subjects who reach the primary endpoint during the study period will not have additional study drug administered for the remainder of the RSV season because the risk of a second RSV infection is substantially (~70%) reduced for 6 months after the first infection (Ohuma 2012) and this practice is consistent with recommendations in the 2014 AAP guidelines for palivizumab. Subjects who have reached the primary endpoint will continue to be monitored for additional medically attended acute respiratory infections that may occur during the study period.

During the 150-day efficacy assessment period, data will be collected on subjects with any acute respiratory illness requiring medical attention. After enrollment of their infant into the study, parent(s) or guardian(s) taking their enrolled infant to a healthcare provider (inpatient or outpatient, including hospitalizations, ER, UC, or pediatric clinic) will be asked to contact the study staff immediately or soon after seeking medical attention for any of the following symptoms: fever, cough, earache, nasal congestion, rhinorrhea, vomiting after coughing, wheezing, or difficulty breathing (labored, rapid, or shallow).

When the parent(s) or guardian(s) takes their child for medical attention for an acute respiratory infection, they will be instructed to take a Medical Information Packet with them for the treating clinician. All infants who have a medically attended visit for a respiratory illness will be asked to have an unscheduled study visit as soon as possible or within 72 hours of discharge from the medical facility. Study site personnel will evaluate the subject during an unscheduled visit, including a history of the acute illness and nose swab collections for viral detection will occur. All nose swabs will be tested using a reverse-transcriptase polymerase chain reaction (RT-PCR) assay for RSV, which will be conducted in a central laboratory. All RSV isolates will be tested for their subtypes, specifically subtype A or subtype B. If the unscheduled study visit following a medically attended respiratory infection occurs >72 hours but <14 days of discharge from the medical facility, all procedures (as appropriate), including nose swab collection, should occur despite being outside of the 72 hour window. Unscheduled study visits for medically attended respiratory illness will be required through Day 150 even if a child has had a prior RSV-confirmed or other respiratory illness. Unscheduled study visits for medically attended respiratory illness will not be required between the day after the Day 150 visit and Day 237 (end of study) visit for the purpose of nose swab collection.

For infants who do not have an RSV RT-PCR assay for RSV infection done by the central laboratory, study site personnel will obtain and record information about all RSV RT-PCR assay done in a medical facility, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the RT-PCR is a CLIA (Clinical Laboratory Improvement Amendments) certified (or equivalent) laboratory.

All subjects will be monitored for safety until the end of the study at Day 237. Safety monitoring after Day 150 visit through Day 237 (end of study) visit will be made by telephone call, only to solicit information about concomitant medications and AEs. In order to minimize total blood samples obtained throughout the study, a sparse blood collection schedule will be implemented based on a blood collection schedule that includes up to 3 total planned blood draws for each infant for safety laboratory tests, PK, and ADA assays from first visit through Day 150 visit.

The schedules of events are provided in Appendix 11.2 .

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following populations of analysis will be used for all statistical analyses:

3.1. The Full Analysis Set (FAS)

FAS includes all randomized subjects (received a random number as assigned by the IVRS) who receive any study drug. Efficacy analyses will be based on the treatment allocated by the IVRS at randomization (as randomized).

FAS is the primary analysis set for all efficacy endpoints.

3.2. The Safety Analysis Set (SAF)

SAF includes all subjects (randomized or non-randomized) who receive any study drug. For all safety variables, subjects will be analyzed as treated. As-treated is defined as the actual number of REGN2222 doses received by a subject, ie, single dose of REGN2222, 2 doses of REGN2222, and placebo.

3.3. The Pharmacokinetic Analysis Set

The PK analysis set will contain subjects who receive at least 1 dose of the study drug (REGN2222 or placebo) and have at least 1 post-baseline non-missing concentration value.

3.4. The Anti-drug antibody (ADA) Analysis Set

The ADA analysis set will contain subjects who receive at least 1 dose of the study drug (REGN2222 or placebo) and have at least 1 post-baseline non-missing ADA result.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Chronological age at the time of first dose (weeks)
- Chronological age group
  - ≤ 3 months
  - > 3 months
- Gestational age categories (per CRF)
  - ≤ 31 weeks 6 days
  - ≥ 32 weeks 0 days and ≤ 35 weeks 6 days
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Region (North America [US and Canada], Rest of World) (per CRF)
- Baseline Weight (kg)
- Mother employed (Yes, No, or not applicable)
- Father employed (Yes, No, or not applicable)
- Guardian employed (Yes, No, or not applicable)
- Hemisphere (Northern, Southern)
- Enrollment season (2015/2016 Northern Hemisphere, 2016 Southern Hemisphere, 2016/2017 Northern Hemisphere)

In addition, the following risk factor variables assessed at screening will be summarized:

- Multiple births (Yes or No)
- Infant small for gestational age (Yes or No)
- Infant in child care (Yes or No)
- Infant expected to be in a childcare setting in their first year of life (Yes or No)
- Family history of Atopy (Yes or No)
- Family history of Asthma (Yes or No)
- Family history of Hay fever (Yes or No)
- Family history of Eczema (Yes or No)
- Smoker in the household (Yes or No)
- Number of people currently living in household
- Number of siblings
- Children, 6 yrs or younger, currently living in household (Yes or No)
- Children in household attending daycare or child care (Yes or No)

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA®) version in effect and available at the time of the database lock.

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the version of WHO Drug Dictionary (WHODD) in effect and available at the time of database lock. Note: a drug can be matched to more 1 ATC classification, ie, subjects can be counted in several categories for the same medication.

Pre-treatment medications/procedures: medications that were started prior to the first dose of the study drug or procedures performed prior to the first dose of the study drug.

Concomitant medications/procedures: medications taken (or continued to be taken) or procedures performed following the first dose of study drug through the end of the TEAE period (Section 4.7.1).

4.4. Prohibited Medication During Study

Definition of prohibited medications during the study is described in Section 5.6.1 of the study protocol.

All pre-treatment/concomitant medications will be reviewed to determine if any of them are prohibited medications on an ongoing basis throughout the study, with the final list to be finalized before database lock.

4.5. Exposure to Study Drug and Compliance Variables

Exposure to study drug variables are listed below with the associated definitions:

- The total number of study doses administered.
- The calculated actual dose (in the unit of mg/kg) of each study treatment. Actual dose is calculated as: (volume of dose × 150mg/mL) divided by body weight at dosing.
- Number of injections received for each dose.
- Length of observation period during the study is calculated as: (date of the last study visit - date of first dose of study drug) +1.

Compliance will be assessed using the following variables with the associated definitions applied to both REGN2222 and placebo:

- The compliance ratio (continuous) of actually administered dose (in the unit of mg/kg) vs. planned dose will be calculated for each dose received by a subject.

- The compliance ratio (categorical) defined above categorized into <0.8, 0.8 to <1.2, ≥1.2, ≥1.5, and ≥2.0.

4.6. Efficacy Variable

Assessment of all efficacy variables will occur during the 150-day study period (ie, through the Day 150 visit). Any RSV infection occurring after that period will not be included in the efficacy evaluation.

For a subject who discontinued study treatment early (ie, not receiving the second dose), the subject will be followed to Day 150 visit for assessment of efficacy.

4.6.1. Primary Efficacy Variable

The primary efficacy variable is the proportion of FAS subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the 150-day efficacy assessment period. The 150-day efficacy assessment period is defined as the first study drug administration through the Day 150 visit (defined as the protocol specified window which includes Study Day 155). In the event that Day 150 visit occurs beyond the protocol specified window (ie, on or after Day 156) and a respiratory AE is reported at that visit, that AE will only be considered for the primary endpoint if its start date is before Study Day 156.

A medically attended RSV infection (hereafter referred to as a primary endpoint event) is defined as an infant with a positive RSV test by RT PCR with any of the following events:

- Hospitalized (on the basis of the assessment of the admitting physician) for RSV infection.
- Outpatient visit (emergency room [ER], urgent care [UC], or pediatric clinic [PC] for either a sick or well visit) with RSV LRTI.

An RSV LRTI in an infant is defined as an RSV-proven respiratory infection (ie, positive RSV RT-PCR test) with parent(s)/guardian(s) report of cough or difficulty breathing, and with 1 of the following signs of LRTI, as assessed by a healthcare provider:

- Lower chest wall indrawing
- Hypoxemia (peripheral capillary oxygen saturation <95% breathing room air)
- Wheezing or crackles

The positive RSV RT-PCR test has to occur within a 14-day period since the start date of the adverse event (AE) corresponding to the medically attended respiratory illness (MARI), ie, the specimen collection date for RT-PCR - AE start date must be ≤ 14. If multiple medical visits are made for the same episode of RSV illness, an RSV positive test by RT-PCR at any medical visit will label that episode as being RSV positive, and it will be counted toward the primary endpoint. If there are multiple medically attended visits during an episode associated with an RSV positive test, then the most severe occurrence will be defined as the primary endpoint event, and events of decreasing severity will be defined in the following order: RSV positive hospitalization > RSV positive ER/UC LRTI > RSV positive pediatric clinic LRTI. If a subject had multiple episodes of RSV infection, the first episode will be defined as the primary endpoint.

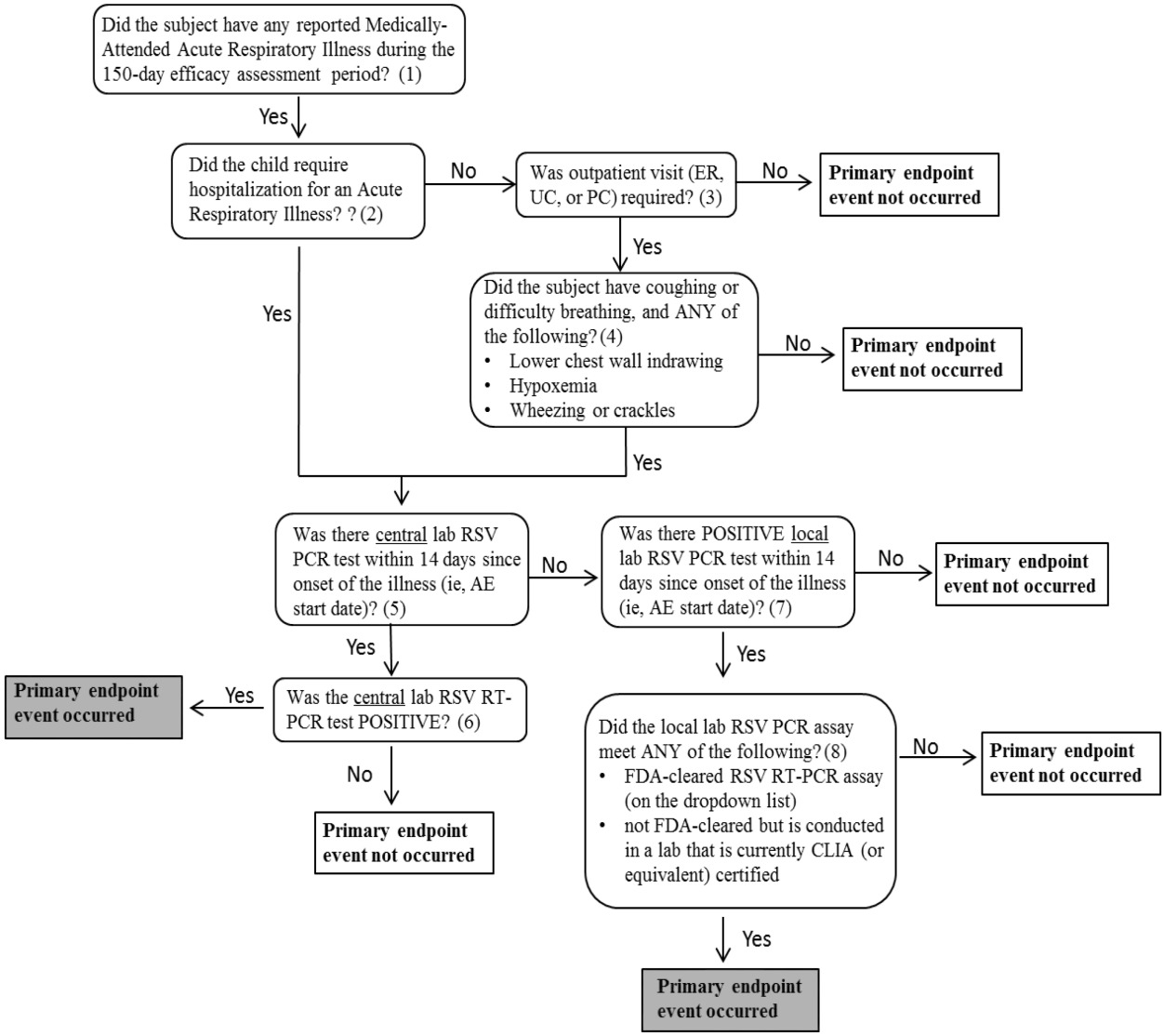
Only medically attended respiratory illness occurring during the 150-day efficacy assessment period will be considered for the primary endpoint. If categorization of a MARI event as an endpoint is unclear, source documentation will be provided to a blinded adjudication committee for categorization prior to database lock.

If an infant has a medically attended respiratory event but did not have an RT-PCR test conducted in the central laboratory within 14 days after onset of the episode of RSV illness, results from a RSV RT-PCR assay conducted in the local lab will be used to determine RSV infection if the RSV RT-PCR assay is reviewed by jurisdictional health authority and released for commercial distribution, or conducted in a laboratory that is currently certified for human diagnostic testing. To that end, protocol has specified the following conditions for acceptable local lab RSV RT-PCR assays:

- Assay is a FDA-cleared RSV RT-PCR assay or
- Assay is an RSV RT-PCR assay that is not FDA-cleared but is conducted in a laboratory that is currently CLIA (or equivalent) certified.

The algorithm to programmatically derive an observed primary endpoint event is depicted in Figure 2.

Figure 2 Flow diagram to depict the programmatic derivation of an observed primary endpoint event



Answers to questions (1) through (7) in the flow diagram are collected from the following electronic case report form (eCRF) pages and other source data:

- Questions (1) and (3): eCRF page of "History of Medically-Attended Acute Respiratory Illness (MARI) Questionnaire".
- Question (2): eCRF page of "Hospitalization for Respiratory Illness Questionnaire".
- Question (4): eCRF page of "Lower Respiratory Infection (LRI) Questionnaire".
- Questions (5): eCRF page of "Central Laboratory" for nose swab collection and eCRF page of "History of Medically-Attended Acute Respiratory Illness (MARI) Questionnaire" for AE start date.
- Question (6): Central lab RSV RT-PCR test results from Viracor.
- Questions (7) and (8): eCRF page of "Unscheduled RSV RT-PCR (Local Lab)"

On the eCRFs, the MARI questionnaire, the LRI questionnaire, and the central (or local) lab RSV PCR test(s) are designated by the investigator to a corresponding medically-attended acute respiratory adverse event (AE). Therefore, the corresponding AE serves as the key variable to programmatically merge information from the MARI and LRI pages with RSV PCR test(s) for each episode of illness.

Missing Data Handling for the Primary Efficacy Endpoint

For early termination (ET) subjects those who did not complete the 150-day efficacy assessment period, their primary endpoint will be handled according to the following rules in the primary analysis:

- Early termination subjects who had a primary endpoint event during the 150-day efficacy assessment period (regardless of treatment status, ie, whether the subject received all study drug doses or discontinued dosing) will be used in the primary analysis and included as "event occurred". [Observed, thus no imputation]
- Direct imputation of missing primary endpoint at Day 150 visit:
  - Subject deaths prior to Day 150 that are adjudicated to be RSV related will be included as "event occurred" at the onset date of the adverse event that led to death.
  - Remaining early termination subjects (including non-RSV deaths) across all treatment groups, will be imputed to the average placebo score (estimated placebo event rate).
    - Approach to estimating the placebo event rate is the Kaplan-Meier (KM) estimate at Day 150 based on all randomized subjects in the placebo group. Early termination subjects in the placebo group who had no primary endpoint event will be censored in the KM procedure at the last time point when their primary endpoint event is assessed (ie, at the last visit completed by the subject, scheduled or unscheduled, prior to Day 150 visit). Placebo subjects who completed Day 150 visit with no primary endpoint event will be censored at the date of their Day 150 visit. The derivation of study day is detailed in Appendix 11.3.
- Imputed scores along with observed subject data will be utilized in the Cochran-Mantel-Haenszel (CMH) analysis.

4.6.2. Secondary Efficacy Variable

The secondary efficacy variable is the proportion of FAS subjects who have RSV-confirmed hospitalization, ER, UC, or pediatric clinic visits (for upper or lower respiratory infection) during the 150-day efficacy assessment period. This secondary endpoint will be derived in the same way as the primary endpoint (including imputation for missing endpoint event) except that the RSV-confirmed outpatient visit (ER, UC, or pediatric clinic visits) can be for either upper or lower respiratory infection (ie, Question 4 in Figure 2 can have the answer of either YES or NO). For ET subjects who did not complete Day 150 visit, their secondary endpoint will be handled according to the same rule as specified for the primary endpoint, with secondary endpoint event in place of primary endpoint event in the rule.

4.6.3. Exploratory Efficacy Variable(s)

Other secondary efficacy variables will be studied as exploratory endpoints and include the following measures during the 150-day efficacy assessment period:

1) Number of days from first dose of study drug to first **primary** efficacy endpoint event. Subject deaths prior to Day 150 that are adjudicated to be RSV related will be included as event at the onset date of the adverse event that led to death. For subjects who didn't have a primary efficacy endpoint event, this endpoint will be defined as the number of days from the first dose of study drug to the last time point when their primary endpoint is assessed, ie, Day 150 visit or last visit completed for ET subjects.
2) Number of days from first dose of study drug to first **secondary** efficacy endpoint event. Subject deaths prior to Day 150 that are adjudicated to be RSV related will be included as event at the onset date of the event that led to death. For subjects who didn't have a secondary efficacy endpoint event, this endpoint will be defined as the number of days from the first dose of study drug to the last time point when their secondary endpoint is assessed, ie, Day 150 visit or last visit completed for ET subjects.
3) Proportion of FAS subjects with RSV-confirmed hospitalization.
4) Total number of RSV-associated hospital visits (for upper or lower respiratory infection).
5) Total number of RSV-associated ER visits (for upper or lower respiratory infection).
6) Total number of RSV-associated UC visits (for upper or lower respiratory infection).
7) Total number of RSV-associated pediatric clinic visits (for upper or lower respiratory infection) visits.
8) Concomitant medications or procedures associated with RSV infection.
9) Total number of all-cause respiratory illness-associated hospital visits (for upper or lower respiratory infection).
10) Total number of all-cause respiratory illness-associated ER visits (for upper or lower respiratory infection).
11) Total number of all-cause respiratory illness-associated UC visits (for upper or lower respiratory infection).
12) Total number of all-cause respiratory illness-associated pediatric clinic visits (for upper or lower respiratory infection).
13) Concomitant medications or procedures for all-cause respiratory illness.
14) Repeat items 9) through 13) above with the single exception to count the number of all-cause respiratory illness-associated visits **after** the initial episode of RSV illness.
15) Total number of days with RSV-associated mechanical ventilation for subjects with RSV-confirmed hospitalizations.
16) Total number of days with RSV-associated supplemental oxygen for subjects with RSV-confirmed hospitalizations.

17) Total length of stay in hospital for subjects with RSV-confirmed hospitalizations.

18) Total number of missed days of work for parent(s) or guardian(s) associated with each medically attended RSV event.

19) Number and prevalence rate of other common respiratory pathogens identified by a RT-PCR multiplex respiratory panel for nose swab specimens determined to be negative for RSV (using the protocol specified Lyra RT-PCR assay [Quidel Molecular RSV/hMPV assay]).

20) Proportion of FAS subjects with the primary endpoint event, with the single exception of using an alternative definition for LRTI.

    Instead of the LRTI definition in Section 4.6.1, the following definition of LRTI will be used for medically attended RSV infection (hospitalization or outpatient LRTI) as agreed in the Pediatric Investigational Plan (PIP) :

    Infant with RSV-proven infection who presents with cough or difficulty breathing **and 2** of the following criteria:

    - Lower chest wall indrawing
    - Hypoxemia (peripheral capillary oxygen saturation <95% breathing room air)
    - Wheezing or crackles
    - Ventilatory failure (needing ventilator support in any form)
    - New onset apnea
    - Increased respiratory rate using WHO criteria for fast breathing for age (Wingerter 2012) as below:

Age	Increased Respiratory Rate (breaths/min)
< 60 days	≥ 60
60 - 364 days	≥ 50
365 days - 5 years	≥ 40

Age in days = Onset date of the episode of RSV illness – birth date +1.

21) Proportion of FAS subjects with the primary endpoint event, with the single exception of the removal of RSV hospitalization non-LRTI.

22) Proportion of FAS subjects with the primary endpoint, with the single exception of accepting positive RSV detection results from the multiplex RT-PCR respiratory panel in deriving the primary endpoint event.

23) Proportion of FAS subjects with the secondary efficacy endpoint, with the single exception of accepting positive RSV detection results from the multiplex RT-PCR respiratory panel in deriving the secondary efficacy endpoint event.

Note 1: For a RSV RT-PCR test to be considered positive for the analysis, the specimen collection has to occur within a 14 day period since the onset of the episode of RSV illness.

Note 2: All-cause respiratory illness is defined as without consideration of RSV positivity or negativity.

4.7. Safety Variables

Subject safety will be assessed through the collection of AEs, laboratory data (hematology, chemistry), vital signs, and physical exam (including weight). For these measures, with the exception of the AEs, all measurements will be assigned to analysis windows for temporal summaries. Unless otherwise noted (eg, AEs), baseline for these measures is defined as the last chronologically available valid assessment prior to the first dose of study drug.

The period of safety observation starts from the time when the informed consent is given and continues into the following periods:

- The PRE-TREATMENT period: defined as the day from the signed informed consent form (ICF) to before the first study drug injection.
- The SAFETY TREATMENT period: defined as the day from the first study drug injection up to the day of the last study drug injection plus 180 days.
- The POST-TREATMENT period: defined as starting the day after the end of the SAFETY TREATMENT period.

4.7.1. Adverse Events and Serious Adverse Events

The definitions for AEs and serious adverse events (SAEs) are described in Sections 7.1.1 and 7.1.2 of the study protocol, respectively. Additional information on determining whether abnormal laboratory or vital sign results should be considered as AEs is included in Section 7.2.6 of the study protocol. AEs and SAEs will be collected from the time of informed consent signature and then at each visit until the end of the study.

The severity of AEs is graded using 1 of 2 severity scales. The severity scale used is determined by the type of AE experienced by the subject; more detail is provided in Section 7.3.1 of the protocol.

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent AEs (TEAEs) are defined as AEs that are not present at baseline or represent the exacerbation of a preexisting condition during the SAFETY TREATMENT period (TEAE period). Therefore, referencing the protocol, TEAEs will be defined programmatically as any AE record with a start date/time on or after the first study drug administration (greater than or equal to study day 1), inclusive to the end of the TEAE period.
- Post-treatment AEs are AEs that developed or worsened or became serious during the POST-TREATMENT period.

4.7.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol Section 7.2.4.2. AESIs for this study are hypersensitivity reactions occurring within 48 hours after exposure to the study drug (including but not limited to urticaria, edema, respiratory distress, anaphylaxis, and allergic reactions). Such treatment-emergent AESI are identified by investigator using a tick box on the eCRF AE page.

Preferred Terms of Interest for Identification of Hypersensitivity

As part of the safety assessment, in addition to evaluation of treatment-emergent AEs that are considered to be AESI by the investigator, the following sets of pre-defined PTs of interest for identification of treatment-emergent hypersensitivity AEs will also be monitored and summarized:

1. Modified narrow Standard MedDRA Query (SMQ [N]) for "hypersensitivity". The modification is to add PTs: pruritus, pruritus generalised, prurigo, flushing, erythema, generalised erythema, injection site erythema, rash papular, allergic oedema.
2. MedDRA query for all PTs under the high level term (HLT): injection site reactions.
3. Hypersensitivity PTs of interest per Carbonell-Estrany X. 2010 as listed in Appendix 11.5.
4. Hypersensitivity PTs of interest per Feltes TF 2011 as listed in Appendix 11.6.
5. Acute hypersensitivity reactions **that occur within 2 days after dosing**, classified in 2 categories, per Shapiro 2010:
    a. Urticarial Reactions which will be identified by search for PTs: urticaria, oedema; low level term (LLT): localized erythema.
    b. Allergic Rash which will be identified by search for PTs: rash, dermatitis allergic, erythema annulare, erythema multiforme, rash maculo-papular. For AEs coded to the PT of rash, a manual review of their verbatims will be conducted to identify AEs that are acute rash.

4.7.3. Laboratory Safety Variables

Clinical laboratory tests include hematology and blood chemistry. Samples for laboratory testing will be collected at screening, a post-baseline visit according to assigned blood draw schedule (time points specified in the schedule of assessments [Appendix 11.2]), and at Visit 7 or at the time of ET if the subject discontinued prior to Visit 7.

Clinical laboratory values will be in standard international (SI) units, including associated normal ranges provided by the central laboratory, and grouped by function in summary tables. Conventional unit may be provided. There are no universally accepted normal ranges for preterm infants. Therefore, the ranges provided by the central laboratory are associated with full-term infants and consequently, the ranges are to be used with caution in interpretation of results.

Clinical laboratory tests are provided below, sub-grouped by function. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in central lab result summaries. Potentially clinically significant values (PCSV) ranges will be applied to central lab test values as applicable (see Appendix 11.4 for PCSV definitions).

Blood Chemistry

Electrolytes	Liver function	Metabolism	Renal function
Sodium	AST	Total protein, serum	Blood Urea Nitrogen
Potassium	ALT	Glucose	Creatinine
Chloride	Alkaline phosphatase	Albumin	Uric acid
Carbon dioxide	Total bilirubin	Creatine phosphokinase	
Calcium	Indirect bilirubin		
	Lactate dehydrogenase		

Hematology

Red blood cells and platelets	White blood cells
Hemoglobin	White blood cells (WBCs)
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
Red cell indices	Monocytes
Platelet count	Basophils
	Eosinophils

4.7.4. Vital Signs

The following vital signs parameters will be collected at Visit 1 (screening visit), Visit 2 (baseline visit), Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 or at the time of ET. On the study drug dosing days, vital signs will be assessed prior to collection of blood sample, prior to injection of study drug, and at 1 hour [±10 minutes] after completion of the injection.

- Respiration rate (breaths/min)
- Pulse rate (beat/min)
- Systolic and diastolic blood pressures (mmHg). Blood pressure may be difficult to obtain in some infants because of size, therefore a systolic blood pressure alone can be recorded.
- Temperature (°C / °F)

Both actual values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in vital sign result summaries. Potentially clinically significant values (PCSV) ranges will be applied to vital sign values as applicable (see Appendix 11.4 for PCSV definitions).

4.7.5. Physical Examination Variables

Subjects will have a physical examination (including weight) at Visit 1 (screening visit), Visit 2 (baseline visit), Visit 3, Visit 4, Visit 5, and Visit 7 or at the time of ET. On study drug-dosing days, physical examinations will be conducted predose and again postdose (excluding weight) prior to discharge. The result for each body system is an outcome of normal or abnormal.

4.8. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

4.8.1. Pharmacokinetic Variables

Drug concentration in serum through Day 150 visit will be reported.

4.8.2. Anti-Drug Antibody Variables

Antidrug antibody variables include status and titer as follows. If ADA collected at screening is missing, it will be considered as negative at baseline.

- Total subjects with negative ADA assay response at all time points analyzed.
- Pre-existing immunoreactivity - defined as either a baseline positive ADA assay response (assessed with the sample collected at screen visit) with all post-baseline ADA assay results negative, or a baseline positive assay response with all post-baseline ADA assay responses less than 4-fold over baseline titer levels.
- Treatment-emergent - defined as any post-baseline positive ADA assay response after the initiation of study drug when the baseline ADA result is negative or missing.
  - Treatment-emergent will be further characterized:
    - persistent - defined as consecutive positive responses over at least a 12-week period
    - indeterminate - defined as positive only at the last sample analyzed
    - transient - defined as not persistent or indeterminate
- Treatment-boosted - defined as any post-baseline positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline response is ADA positive in the ADA assay.
- Titer values
- Titer category
  - Low (titer <1000)
  - Moderate ($1000 \leq$ titer ≤ 10000)
  - High (titer >10000)

4.9. Pharmacodynamic/Genomics Variables

An optional substudy, which requires separate informed consent, is being conducted to collect DNA from cheek swab samples for future use for the purpose of discovery of predictive biomarkers related to RSV infection and severity.

4.10. RSV Subtyping

RSV subtype analysis will be conducted by RSV-G gene sequencing of RNA derived from the nose swab samples in subjects who tested positive on the RSV Lyra RT-PCR assay. Classification to subtype A and subtype B categories will be performed based on the determined sequence.

4.11. RSV RT-PCR

Study site personnel should evaluate the subject during an unscheduled visit as soon as possible or within 72 hours after receipt of medical attention, including nose swab collections for viral detection. All nose swabs will be tested using the RSV Lyra RT-PCR assay, which will be conducted in a central laboratory.

The central laboratory reports a qualitative result of RSV positive or negative and a quantitative result of cycle threshold (Ct) levels. Ct levels are inversely related to the amount of RSV RNA in the sample.

For infants who do not have an RSV RT-PCR assay for RSV infection done by the central laboratory, study site personnel will obtain and record information about any RSV RT-PCR assays done in a medical facility, including result(s), name of the assay(s) and whether the laboratory(ies) conducting the RT-PCR is a CLIA (Clinical Laboratory Improvement Amendments) certified (or equivalent) laboratory. Type of specimen obtained (nasopharyngeal Swab, nasopharyngeal aspirate, or nasal swab) is collected for local laboratory RSV testing.

4.12. Respiratory Pathogen Panel RT-PCR

An RT-PCR multiplex respiratory panel that includes RSV detection along with detection and identification of other respiratory pathogens will be used as part of the assessment of nasal swab samples. Only RSV negative samples on the RSV Lyra RT-PCR assay will be tested on the multiplex RT-PCR respiratory panel.

The introduction of the use of a multiplex RT-PCR respiratory panel is to explore the alternative etiologies of RSV-negative respiratory tract infections per a comment received from the US FDA while the study was ongoing. RSV test results from the multiplex RT-PCR respiratory panel will **not** be used to derive primary or secondary efficacy endpoints. All efficacy endpoints and RSV detection will be based on RSV Lyra RT-PCR assay as described in the protocol unless otherwise specified in this analysis plan.

5. STATISTICAL METHODS

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics (including risk factors as listed in Section 4.1) will be summarized descriptively for all FAS subjects by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo), and for the study total. Similar summaries will be made for subjects within each of the 2 stratification factors (ie, gestational age [GA] category and region) as recorded in IVRS/IWRS.

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation (SD), minimum, the first and third quartiles (Q1 and Q3), and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Other safety baseline data such as vital signs and clinical laboratory measures will be presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

5.2. Medical History

Medical history will be summarized descriptively based on the SAF population by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo), and for the study total. Summaries will show subject counts (percentages) by primary SOC and PT. The tables will be sorted by decreasing frequency of SOC in the combined REGN2222 group. Within each primary SOC, PTs will be sorted by decreasing frequency in the combined REGN2222 group.

5.3. Prior/concomitant Illnesses and Medications

Number and percentage of subjects taking concomitant medication will be summarized based on the SAF population by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo), and for the study total. The tables will be sorted by decreasing frequency of ATC Level 2,ATC Level 4, and preferred term in the combined REGN2222 group. Number and percentage of subjects taking prior medication will be summarized in a similar fashion to concomitant medication.

5.4. Prohibited Medications

Number and percentage of subjects taking prohibited medication will be summarized by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo) and for the study total, for the SAF population. The tables will be sorted by decreasing frequency of ATC level 2, ATC level 4, and preferred term in the combined REGN2222 group.

5.5. Subject Disposition

Subject disposition includes the description of subject status at major milestone decisions in the study.

Subject study status will be summarized by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo) and for the study total unless otherwise specified.

Summaries will provide the frequency (and percentage as applicable) of subjects that met the criteria for the following variables:

- Screened subjects (signed the ICF).
- Screen failed subjects.
- Subjects randomized.
- Subjects randomized but not treated.
- Subjects randomized and treated (SAF population).
- Completed study (ie, Day 237 Visit) as collected on the End of Study eCRF page.
- Completed efficacy assessment period (ie, Day 150 Visit) as collected on the End of Study eCRF page.
- Did not complete study (ie, Day 237 Visit).
  - Did not complete efficacy evaluation period (ie, Day 150 Visit) on the End of Study eCRF page.
- Subjects ongoing in the study (only applicable at the time of the first step analysis [see Section 8 for the definition of first step analysis]).
- Primary reasons for discontinuation from study (ie, Day 237 Visit).
- Primary reasons for discontinuation from study for subjects who did not complete efficacy evaluation period (ie, Day 150 visit).

In addition, summary of the number (and percentage) of subjects in each analysis population (as defined in Section 3) will be presented by treatment group, and for the study total. Percentages will be calculated using the number of randomized subjects as the denominator.

The following listing will be provided: A listing of subject disposition including randomization date, dosing date(s), last visit date, completed efficacy evaluation period (ie, Day 150 Visit) or not with reason, completed study (ie, Day 237 Visit) or discontinued by reason; a listing of screening failures and reasons for all screen failed subjects.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. Exposure to Investigational product

Exposure to investigational product will be examined based on the SAF population. Descriptive statistics including the number of subjects reflected in the calculation (n), mean, median, SD, minimum, Q1 and Q3, and maximum will be used to summarize the following variables:

- The calculated actual dose (in the unit of mg/kg) of each study treatment.
- Length of observation period.

A tabulation of the number (and percentage) of subjects will be used to summarize the following variables:

- The total number of study doses administered.

- Number of injections received for each dose.
- The number (and percentage) of subjects having observation periods of specific lengths will be summarized according to time period breakdowns as follows: ≥1 to <27 days, ≥ 27 to <55 days, ≥ 55 to <80 days, ≥ 80 to <108 days, ≥ 108 to < 145 days, ≥ 145 to <168 days, ≥ 168 to <196 days, ≥ 196 to <227 days, and ≥ 227 days. These categories are determined by the minimum number of days allowed by the protocol specified windows for scheduled visits.
- The number (and percentage) of subjects having observation periods of at least 27, 55, 80, 108, 145, 168, 196, and 227 days will be presented.

5.6.2. Measurement of Compliance

Study treatment compliance parameters will be examined based on the SAF population. For the compliance ratio (categorical), the frequency (percentage) of subjects will be provided for each category. Descriptive statistics including the number of subjects reflected in the calculation (n), mean, median, SD, minimum, Q1 and Q3, and maximum will be used to summarize the compliance ratio (continuous).

All major and minor protocol deviations potentially impacting efficacy analyses, randomization and drug-dispensing irregularities, as well as other deviations, have been collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Definitions Document (PDDD). Both monitored and CRF derived protocol deviations will be summarized for subjects incurring any major deviation by count and percentage, and subjects incurring each type of major deviation by count and percentage. A subject listing of all major and minor protocol deviations will be provided.

5.7. Analyses of Efficacy Variables

The null hypothesis of the primary efficacy variable is that the proportions of FAS subjects with medically attended RSV hospitalization or outpatient LRTI in the placebo group and in the REGN2222 group are the same (H_0: p1 = p2). The alternative hypothesis is that the rate for each REGN2222 group is different from the rate for the placebo group (H_1: p1 ≠ p2).

5.7.1. Analysis of Primary Efficacy Variable

The primary efficacy variable is the proportion of subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the 150-day efficacy assessment period. Details regarding the derivation of observed primary endpoint event and imputation of missing primary endpoint at Day 150 visit are described in Section 4.6.1.

The primary efficacy variable will be analyzed by CMH statistics with randomization stratum adjusted by the Mantel-Haenzel (MH) method to assess the pairwise comparisons of each REGN2222 treatment arm to placebo. The stratification factors used in the CMH analysis are region and GA per IVRS/IWRS, which will give rise to the following 4 strata:

- North America and ≤ 31 weeks 6 days GA.
- North America and ≥ 32 weeks 0 days and < 35 weeks 6 days GA.
- Rest of the world and ≤ 31 weeks 6 days GA.

- Rest of the world and ≥ 32 weeks, 0 days and < 35 weeks 6 days GA.

This stratum-adjusted difference (ie, absolute risk reduction) based on the MH method is weighted by the harmonic mean of sample size per treatment group for each stratum. Point estimate, 95% confidence interval (CI), and p-value of the proportion difference between 2 treatment groups will be calculated as follows:

If $\hat{n}_{1h}$ and $\hat{n}_{2h}$ are the FAS sample sizes of the two treatment groups 1 and 2 in stratum h, then the weight

$$w_h = \frac{\hat{n}_{1h}\hat{n}_{2h}}{\hat{n}_{1h} + \hat{n}_{2h}}$$

is used for stratum h in calculating the overall difference.

Let $\hat{d}_h = \hat{p}_{1h} - \hat{p}_{2h}$ be the treatment difference in the proportion of subjects with primary endpoint events in stratum h, where $\hat{p}_{1h}$ and $\hat{p}_{2h}$ are calculated as:

$$\hat{p}_{1h} = \frac{\hat{x}_{1h} + \hat{m} \times \hat{y}_{1h}}{\hat{n}_{1h}}, \qquad \hat{p}_{2h} = \frac{\hat{x}_{2h} + \hat{m} \times \hat{y}_{2h}}{\hat{n}_{2h}}$$

with $\hat{x}_{1h}$ and $\hat{x}_{2h}$ being the number of subjects with **observed** primary endpoint event(s) in treatment groups 1 and 2, respectively (including ET subjects who had their primary endpoint missing but died prior to Day 150 due to causes adjudicated to be RSV related), $\hat{y}_{1h}$ and $\hat{y}_{2h}$ being the number of early termination subjects **missing** the primary endpoint in treatment groups 1 and 2, respectively, and $\hat{m}$ being the KM estimate of the primary endpoint event rate in all subjects randomized to the placebo group (see Section 4.6.1). Then the point estimate of stratum-adjusted proportion difference is

$$\hat{d} = \frac{\sum \hat{w}_h \hat{d}_h}{\sum \hat{w}_h}$$

The continuity-corrected variance of $\hat{d}$ is

$$\hat{v}_d = \frac{\sum \hat{w}_h^2 \left(\frac{\hat{p}^*_{1h}(1-\hat{p}^*_{1h})}{\hat{n}_{1h}+1} + \frac{\hat{p}^*_{2h}(1-\hat{p}^*_{2h})}{\hat{n}_{2h}+1} \right)}{\left(\sum \hat{w}_h\right)^2}$$

where

$$\hat{p}^*_{1h} = \frac{\hat{x}_{1h} + \hat{m} \times \hat{y}_{1h} + 0.5}{\hat{n}_{1h} + 1}, \qquad \hat{p}^*_{2h} = \frac{\hat{x}_{2h} + \hat{m} \times \hat{y}_{2h} + 0.5}{\hat{n}_{2h} + 1}$$

The 95% asymptotic CI of $\hat{d}$ is $[\hat{d} - \hat{v}_{0.975} * \hat{v}_d, \hat{d} + \hat{v}_{0.975} * \hat{v}_d]$ where $\hat{v}_{0.9875}$ is the 98.75th percentile of the standard normal distribution. The p-value will be computed from the z-score = $\hat{d}/\hat{v}_d$. A SAS macro will be used to calculate all the above statistics.

In addition to the absolute risk difference, the stratum-adjusted relative risk of the primary efficacy variable will be provided for the pairwise comparisons of each REGN2222 treatment arm to placebo for descriptive purpose. The number of subjects with primary endpoint event(s)

in each stratum will be rounded to its nearest integer for the calculation of relative risk. The

stratum-specific relative risks will be combined based on the MH method to compute the point estimate and asymptotic 95% CI of stratum-adjusted relative risk using the SAS FREQ procedure. In the event that there are zero table cells in any strata, the exact CI for the relative risk may be computed in lieu of the asymptotic CI by specifying the RELRISK option in the EXACT statement of the SAS FREQ procedure.

The statistical testing of the 2 pairwise comparisons of each REGN2222 treatment arm to placebo for the primary measure will be evaluated at a 2-sided significance level of 0.05 per pairwise comparison, adjusting for multiplicity through a hierarchical inferential approach. In the hierarchy testing sequence, the comparison of REGN2222 2 doses arm to placebo is the first pairwise treatment comparison, and the comparison of REGN2222 1 dose arm to placebo is the second pairwise treatment comparison.

5.7.1.1. Model Assumption Checks

In order to check the homogeneity of treatment effect across strata, the treatment differences and corresponding 95% CI will be calculated and graphically presented for each stratum h, following the same continuity correction method for variance as in the primary approach.

5.7.1.2. Supportive Analyses for the Primary Efficacy Endpoint

The following statistical analyses will be used to further assess the primary efficacy endpoint. As appropriate, p values will be provided for descriptive purpose only.

Sensitivity to small event rate

The adequacy of the CMH statistics may be of concern in the case of an unexpectedly very small event rate. The Fisher's exact test is valid regardless of the cell sizes and therefore will be employed as a supportive statistical approach to confirm the results from the primary approach.

The Fisher's exact test will be applied to the whole FAS for comparisons of each REGN2222 arm to placebo. The number of subjects with primary endpoint event(s) will be $(\hat{n}_i + \hat{p} \times \hat{m}_i)$ rounded to its nearest integer, where $\hat{n}_i$ is the number of subjects with **observed** primary endpoint event(s) in treatment group i (including ET subjects who had their primary endpoint missing but died prior to Day 150 due to causes adjudicated to be RSV related), $\hat{m}_i$ is the number of early termination subjects **missing** the primary endpoint in treatment group i, and $\hat{p}$ is the KM
estimate of the primary endpoint event rate in all subjects randomized to the placebo group.

The Fisher's exact test will also be applied to subgroups defined by stratification variables (ie, test in the subgroups of North America, rest of the world, ≤ 31 weeks 6 days GA, and GA ≥ 32 weeks 0 days and < 35 weeks 6 days, respectively). The number of subjects with primary endpoint event(s) in each of the subgroups will be calculated in the same fashion as for the whole FAS except that $\hat{n}_i$ and $\hat{m}_i$ will be stratified group specific. This analysis will only be performed if there are enough subjects in each stratification level.

The SAS FREQ procedure with the option FISHER in the TABLE statement will be used to compute the 2-sided p-value of the Fisher's exact test.

In order to check the homogeneity of treatment effect across strata, the Fisher's exact test will also be run for each stratum h.

Regression method adjusting for covariates

The primary approach based on the CMH statistics tests for absolute difference in proportions between treatment groups. As a supportive approach, the logistic regression will use odds ratio to test for relative treatment effect of each REGN2222 arm over placebo on the primary efficacy variable. The number of subjects with primary endpoint event(s) will be $(\hat{p}_{ih} + \hat{\delta} \times \hat{p}_{ih})$ rounded to its nearest integer for treatment group i within each stratum h (a total of 4 strata as defined in the primary approach). The model for the logistic regression will include treatment group, region and gestational age category as factors. The maximum likelihood (ML) estimates of the odds ratio, and asymptotic normality based 95% CIs and p-values will be computed using the SAS LOGISTIC procedure. In the event that quasi-complete separation of data points occurs (ie, the outcome variable separates a predictor variable or a combination of predictor variable to an almost full degree), Firth's penalized likelihood approach may be employed to reduce bias in logistic regression. This approached will use the SAS LOGISTIC procedure with option=Firth.

In order to check the homogeneity of treatment effect across strata, the terms of interaction between treatment and strata (ie, region and gestational age group) will be added to the logistic regression model to obtain p values for the interaction terms for descriptive purpose. Stratum specific odds ratios and 95% CIs will also be reported.

5.7.1.3. Sensitivity to the Handling of Missing Data

The following analyses will be conducted to assess the results from the primary analysis with regards to the handling of missing data. As appropriate, p values will be provided for descriptive purpose only.

Observed-Case Analysis

In the observed-case analysis, for each treatment group, the proportion of subjects considered to have primary endpoint event occurrence will be calculated with the numerator being the number of subjects with observed primary endpoint event(s) (including ET subjects who had their primary endpoint missing but died prior to Day 150 due to causes adjudicated to be RSV related), and the denominator being the number of subjects in the FAS. The observed-case based proportion difference will be calculated for each stratum h and then combinded across strata to generate the CMH statistics following the same method as in the primary approach.

Tipping Point Analysis

A tipping point analysis will be employed to explore the degree of shift from the placebo event rate used in the imputation of missing data in REGN2222 arms. The tipping point analysis will include the following steps to impute missing primary endpoint at Day 150 visit:

1. Subject deaths prior to Day 150 that are adjudicated to be RSV related will be included as "event occurred".
2. Remaining early termination subjects (including non-RSV deaths) in the **placebo** group will be imputed to the average placebo score (ie, the KM estimate of the primary endpoint event rate in all subjects randomized to the placebo group).
3. Remaining early termination subjects (including non-RSV deaths) in the **REGN2222** arm will be imputed to $\delta \times \hat{p}_{h}$ [illegible], where $\delta = 2$. (Note: $\delta = 1$ is equivalent to the primary analysis)

4. Repeat the step 3 with $\delta = 3, 4, 5$, etc. until reaching the point that the treatment effect of REGN2222 will be lost (ie, the difference [REGN2222 – placebo] in the proportion of subjects with primary endpoint event[s] is ≥ 0).

The tipping point analysis will be conducted for the pairwise comparisons of each REGN2222 arm to placebo separately, using the same CMH statistics as in the primary approach.

5.7.1.4. Individual Endpoints

The primary efficacy variable can be considered as a composite endpoint comprising the 2 individual endpoints:

- Subjects hospitalized for RSV infection during the 150-day efficacy assessment period.
- Subjects who had outpatient visit (ie, ER, UC, or PC visit) with RSV LRTI during the 150-day efficacy assessment period.

In order to examine which whether an individual endpoint will be driving the treatment difference observed for the primary efficacy variable, each of the 2 individual endpoints will be analyzed using the primary approach for the primary efficacy variable, including handling of missing data (Section 4.6.1) and the CMH statistics (Section 5.7.1). In addition, Fisher's exact test described in Section 5.7.1.2 will be performed for these 2 individual endpoints to confirm the results.

5.7.1.5. Sensitivity to GCP Non-compliance Site

To assess the impact of study data collected from an investigational study site that was not compliant with GCP standards, the primary efficacy analysis will be repeated excluding subject data from the non-compliant site.

5.7.1.6. Sensitivity to Stratification at Randomization

In order to assess the robustness of the primary analysis to stratification mistakes made at the time of randomization (ie, the stratum recorded in IVRS/IWRS differs from the actual stratum recorded in the eCRF), the primary efficacy analysis will be repeated replacing the IVRS/IWRS strata with the eCRF actual strata.

5.7.1.7. Subgroup Analysis

To assess the homogeneity of treatment effect across various subgroups, the primary efficacy variable will be analyzed using the same CMH method as in the primary approach for each subgroup of subjects defined by the following baseline characteristics, risk factors, geographic areas, or enrolment season:

- Race (White, other)
- Chronological age (≤ 3 months, > 3 months)
- Sex (Female , Male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Region (NA, rest of the world)

- Gestational age (≤31 weeks 6 days GA, ≥ 32 weeks 0 days and < 35 weeks 6 days GA)
- Hemisphere (Northern, Southern)
- Enrollment season (2015-2016 Northern Hemisphere, 2016 Southern Hemisphere, 2016-2017 Northern Hemisphere)
- Study subjects in child care (Yes, No)
- Children, 6 years or younger, live in study subject's household (Yes, No)

For ET subjects those who did not complete Day 150 visit, their primary endpoint will be handled according to the rules used in the primary analysis (Section 4.6.1) before conducting the CMH analysis for each subgroup.

Point estimates and 95% CIs of the treatment effect will be calculated for each subgroup if that subgroup is of reasonable size to perform the evaluation. Since the study sample size is not powered for subgroups, CIs are provided for descriptive purpose. Results for treatment difference in the subgroups of subjects will be graphically displayed in the form of forest plots.

In addition to the CMH statistics, logistic regression will be run with treatment, region, gestational age category, subgroup variable (eg, race), treatment-by-subgroup variable interaction term in the model. The p value of the treatment-by-subgroup variable interaction term will be reported for descriptive purpose to assist the evaluation of treatment effect differentiation across the levels of a subgroup variable.

As small cell size is more likely to occur in subgroup analyses, the Fisher's exact test will be applied to the whole FAS within each subgroup in a similar fashion to the method described in Section 5.7.1.2 with the only difference being that $\hat{p}_i$ and $\hat{p}_i$ will be subgroup specific.

5.7.2. Analysis of Secondary Efficacy Variable

The secondary efficacy variable is the proportion of subjects who have RSV-confirmed hospitalization, ER, UC, or pediatric clinic visits (for upper or lower respiratory infection) during the 150-day efficacy assessment period. This secondary endpoint is different from the primary endpoint in the way that the RSV-confirmed outpatient visit (ER, UC, or pediatric clinic visits) for either upper or lower respiratory infection is included as the secondary endpoint event while only the RSV-confirmed outpatient visit for lower respiratory infection is included in the primary endpoint event. The secondary endpoint will be analyzed by the same set of analyses as for the primary efficacy variable including the primary statistical approach, model assumption checks, supportive statistical approaches, individual endpoints, sensitivity analyses, and subgroup analyses.

To understand if REGN2222 can provide any benefit in preventing upper respiratory RSV infection, the proportion of subjects who had observed secondary endpoint event(s) but no observed primary endpoint event(s) will be descriptively summarized for each treatment group.

5.7.3. Adjustment for Multiple Comparison

To control the 5% overall Type I error for the 2 pairwise comparisons in the primary analysis, the overall study α level will be controlled by the use of a hierarchical inferential approach.

Statistical significance of the first pairwise treatment comparison (REGN2222 2 doses arm to placebo) is required before drawing inferential conclusions about the second pairwise treatment comparison (REGN2222 1 dose arm to placebo) at the 0.05 alpha level. This fixed hierarchical approach will ensure a strong control of the overall Type I error rate at the 0.05 level for each REGN2222 dose regimen comparison.

Further, in the case that the primary efficacy endpoint is statistically significant at 0.05 (2-sided) alpha level for both pairwise treatment group comparisons specified in the above paragraph, the secondary efficacy endpoint will be tested using the same hierarchical inferential approach as used for the primary efficacy endpoint.

This multiple testing procedure ensures a strong control of the overall Type I error rate at the 0.05 level. No further adjustments will be made for other analyses for which p-values will be provided for descriptive purpose only.

No adjustment will be made for the first step and second step statistical analyses (Section 8), since the primary and secondary efficacy endpoints will have been concluded at the time of the first step analysis.

5.7.4. Analysis of Exploratory Efficacy Variables

Time to event endpoints

Number of days to the first efficacy endpoint event will be analyzed with stratified log-rank test. Different from the primary analysis, this time to event analysis will treat missing primary endpoint at Day 150 visit through a censoring method as described in Section 4.6.3.

The SAS LIFETEST procedure will be used to run the stratified log-rank test by specifying region and gestational age category in the STRATA statement as 2 stratifying variables, and specifying treatment group in the GROUP= option. In addition, for each treatment group, Kaplan-Meier curve will be used to graphically depict the proportion of subject who remained event free across time during the 150-day efficacy assessment period. Cox regression will be used to obtain hazard ratios and their confidence intervals. The Cox regression model will include the fixed categorical effects of treatment group, region, and gestational age category.

Continuous efficacy endpoints

Descriptive statistics including the number of subjects reflected in the calculation (n), sum, mean, median, SD, minimum, Q1 and Q3, and maximum will be used to summarize the continuous exploratory endpoints (eg, total number of medical visit, length of stay in hospital, etc., as defined in Section 4.6.3) for each treatment group and their treatment difference between each REGN2222 arm and placebo. For each exploratory endpoint, this descriptive summary will include only those subjects who had at least 1 endpoint specific event.

To account for subjects who had no endpoint specific event, a separate analysis will be performed for each exploratory endpoint to include these subjects by treating their endpoint value as zero. In this analysis, the event rate adjusted by subject-year of follow-up will be provided for each treatment group. For each subject, the duration calculated as (end of efficacy evaluation - first dose date +1)/365.25 will be counted toward the subject-year of follow-up, except that for the endpoint of total number of respiratory illness-associated hospital, ER, UC, or PC visits **after** the initial episode of RSV illness, the duration will be (end of efficacy

evaluation - the day after the stop date of the initial episode of RSV illness + 1)/365.25. The end of efficacy evaluation is the last visit completed by a subject, scheduled or unscheduled, up to Visit 7. Negative binomial regression will be used to estimate the relative risk reduction associated with each REGN2222 arm as compared to placebo.

Categorical efficacy endpoints

RSV confirmed hospitalization, a component of the primary composite endpoint, will be explored using the same statistical methodology as the primary efficacy analysis. For this exploratory analysis, the two REGN2222 treatment groups will be combined for comparison to the placebo group, with the intent to evaluate the REGN2222 effect on subjects with RSV confirmed hospitalization.

Number and percentage of subjects taking medications associated with RSV or respiratory illness will be summarized by treatment group. The denominator used to calculate percentage will be the number of subject in the FAS assigned to each treatment group. The tables will be sorted by alphabetical order of ATC level 2 followed by ATC level 4.

The procedures associated with RSV or respiratory illness will only be listed for subjects in each treatment group.

The same CMH statistics as used in the primary approach for the primary efficacy variable will used to analyze the following exploratory endpoints. Missing data will be addressed using the same same rules as used in the primary analysis for the primary efficacy variable (Section 4.6.1).

- Proportion of FAS subjects with the primary endpoint event, with the single exception of using an alternative definition for LRTI.
- Proportion of subjects with the primary endpoint event, with the single exception of the removal of RSV hospitalization non-LRTI

5.7.5. Other Exploratory Analyses

5.7.5.1. Potentially Pre-incubated RSV infection Prior to Study Treatment

Subjects who had their primary endpoint event occurrence by study day 7 (study day 1 being the day when the first dose of study drug was administered) could have potentially already contracted the RSV infection before receiving study drug. To assess the sensitivity of efficacy results to those potentially pre-incubated RSV infections, such subjects will be considered as having no primary endpoint unless the subject had another primary endpoint event with onset more than 7 days after the first dose during the study (ie, on or after study day 8). In this sensitivity analysis, for ET subjects who did not complete Day 150 visit, their missing endpoint will be handled according to the same rules as used in the primary analysis for the primary efficacy variable (Section 4.6.1), however, all primary endpoint event occurrences by study day 7 will neither be included as events in the construction of KM estimate nor be considered as events in the analysis of treatment effect using the CMH statistics.

5.7.5.2. RSV Subtype Analysis

The primary endpoint and its component endpoints (as described in Section 5.7.1.4) will be summarized for each RSV subtype (ie, subtype A and subtype B, respectively) by treatment

group. Only **observed** primary endpoint events with **available** RSV subtype information will be included as events in this analysis. Treatment effect of each REGN2222 arm (over placebo) in prophylaxis against each RSV subtype will be assessed using CMH statistics with randomization stratum adjusted by the MH method previously described in 5.7.1. Confidence intervals will be provided only for exploratory purpose.

5.7.5.3. Non-RSV Medically Attended Respiratory Illness

To evaluate the effect of REGN2222 on the non-RSV MARI, the proportion of subjects who had medically attended respiratory illness (hospitalization or outpatient LRTI) not confirmed to be related to RSV (either all negative RSV or missing RSV testing results within 14 days since AE onset) will be summarized for each treatment group. If a subject had both non-RSV MARI and RSV MARI (ie, the primary endpoint event), they will not be included in the numerator when calculating the proportion. For this particular analysis, only observed events will be included as events. Treatment difference in this proportion will be summarized using descriptive statistics.

5.8. Analysis of Safety Data

Safety and tolerability will be descriptively summarized, including AEs, clinical laboratory variables, physical exam, and vital signs for the SAF. The summary of safety results will be presented for the treatment groups of combined REGN2222 dose arms with the intent to maximize efforts to detect potential safety signals. The individual REGN22222 dose arms will also be presented with the intent to support the combined regimens. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available value obtained up to the date and time of the first dose of study drug, unless otherwise specified.
- For clinical laboratory, physical exam, and vital signs variables, all measurements, scheduled or unscheduled, will be assigned to analysis windows defined in Appendix 11.3 in order to provide an assessment for Visit 3 to Visit 7 time points.
- For continuous safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize results and change from baseline values by visit.
- A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value or vital sign that was: normal at baseline but abnormal after treatment with study drug during the TEAE period, or: abnormal at baseline and worsened after treatment with study drug during the TEAE period. Thresholds for treatment-emergent PCSV in laboratory variables and vital signs are defined in Appendix 11.4. Treatment-emergent PCSV criteria will determine which subjects had at least 1 treatment-emergent PCSV, taking into account all assessments including unscheduled assessments. Subjects who had post-baseline PCSV during the TEAE period but missing baseline value will be regarded as having treatment-emergent PCSV. There are no universally accepted normal ranges for preterm infants. The ranges used to determine PCSV criteria are associated with full-term infants (except

for bilirubin) and consequently, the TEPCSV results are to be interpreted with caution.

The summary of safety results will be presented by treatment group (REGN2222 1 dose, REGN2222 2 doses, REGN2222 combined, and placebo).

5.8.1. Adverse Events

The verbatim text, the PT, and the primary SOC will be listed in subject listings. Summaries that include frequencies and proportions of subjects reporting AEs will include the PTs and the SOCs as appropriate.

The focus of adverse event reporting in the clinical study report will be on TEAEs. Pre-treatment and post-treatment AEs will be provided separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment status. For details on handling missing data and partial dates, see Section 6.3.

Summaries of all TEAEs in each treatment group will include:

- Overview of TEAEs, summarizing number and percentage of subjects with any
  - TEAEs.
  - Serious TEAEs.
  - TEAEs leading to death.
  - TEAEs leading to permanent treatment discontinuation.
  - TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal (if multiple occurrences of an event for a subject, then worst severity is counted).
  - TEAEs that occurred within 2 days after either the first dose or the second dose (ie, post dose TEAE start date - dosing date ≤ 2).
- All TEAEs by SOC and PT.
- All TEAEs by SOC, PT, and severity.
- All TEAEs by SOC, PT, and relationship (related, not related) to study drug.
- All TEAEs by SOC, PT, and relationship (related, not related) to injection procedure.
- TEAEs reported by $\geq 5\%$ of subjects in any treatment group by PT ordered by decreasing subject frequency in the combined REGN2222 group.
- TEAEs reported by $\geq 1\%$ of subjects in any treatment group by PT ordered by decreasing subject frequency in the combined REGN2222 group.
- Study drug-related TEAEs by SOC and PT.
- Study drug-related TEAEs by SOC, PT, and severity.
- Injection procedure-related TEAEs by SOC and PT.
- Injection procedure-related TEAEs by SOC, PT, and severity.

- Serious adverse events: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
- Death: All, study drug-related, and injection procedure-related TEAEs by SOC and PT. TEAEs leading to death are TEAEs that led to death regardless of timing of death in relation to study drug injection (ie, death occurring in the TEAE period or during the post-treatment period)
- Discontinuation of study drug: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
- TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
- Non-serious study drug-related or injection procedure-related TEAEs by SOC and PT.
- TEAEs according to time of occurrence in relation to dosing:
  - TEAEs that occurred after the first dose and before the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT. For subjects who did not receive the second dose, only TEAEs that occurred up to Day 57 (Day 1 being the day when the first dose was administered) will be included.
  - TEAEs that occurred after the second dose in subjects who received the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - Serious TEAEs that occurred after the first dose and before the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT. For subjects who did not receive the second dose, only serious TEAEs that occurred up to Day 57 (Day 1 being the day when the first dose was administered) will be included.
  - Serious TEAEs that occurred after the second dose in subjects who received the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal that occurred after the first dose and before the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT. For subjects who did not receive the second dose, only relevant TEAEs that occurred up to Day 57 (Day 1 being the day when the first dose was administered) will be included.
  - TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal that occurred after the second dose in subjects who received the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs that occurred within 2 days after either the first dose or the second dose (ie, post dose TEAE start date - dosing date ≤ 2): All, study drug-related, and injection procedure-related TEAEs by SOC and PT.

  - TEAEs that occurred within 2 days after the first dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs that occurred within 2 days after the second dose in subjects who received the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs that occurred within 7 days after either the first dose or the second dose (ie, post dose TEAE start date - dosing date ≤ 7): All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs that occurred within 7 days after the first dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
  - TEAEs that occurred within 7 days after the second dose in subjects who received the second dose: All, study drug-related, and injection procedure-related TEAEs by SOC and PT.
- Two event rate estimations adjusted by subject year of follow-up will be provided for all TEAEs by SOC and PT:
  - Total number of events divided by the total length of the TEAE period over all subjects in the SAF of each treatment group.
  - Total number of subjects with an event in question divided by the total length of the TEAE period. For a subject with event, the time from first dose to the first event will be counted towards the denominator. For a subject without event, the time from first dose to the end of the TEAE period will be counted towards the denominator.

The above TEAE summaries will present the number (n) and percentage (%) of subjects experiencing an TEAE by SOC and PT. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. Relatedness to study drug or injection procedure is according to investigator's opinion.

Primary SOCs will be sorted by decreasing frequency in the combined REGN2222 group. Within each primary SOC, PTs will be sorted by decreasing frequency in the combined REGN2222 group.

The description of TEAEs reported by ≥ 5% of subjects in any treatment group will also be performed for demographic and baseline factors including: sex, chronological age (≤ 3 months, > 3 months), gestational age (≤ 31 weeks 6 days, ≥ 32 weeks 0 days and ≤ 35 weeks 6 days), and region.

Subject listings for deaths, all serious TEAEs, TEAEs leading to permanent treatment discontinuation, TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal, and treatment-emergent AESIs will be provided.

5.8.2. Analysis of Adverse Events of Special Interest and Preferred Terms of Interest for Identification of Hypersensitivity

Treatment emergent AESIs and PTs of interest for identification of hypersensitivity (as defined in Section 4.7.2) will be presented by SOC and PT, or by PT alone. The summaries will be sorted by decreasing incidence of PT within each SOC in the combined REGN2222 group if presented by SOC and PT. In addition, the following analyses will be performed to further characterize the safety profile in each treatment group:

- TEAEs that are PTs under the HLT of injection site reaction will be summarized by:
  - Number (and percentage) of subjects who experienced 1 vs. >1 events of injection site reaction.
  - Number (and percentage) of subjects who experienced at least one event of injection site reaction by highest severity.
  - Descriptive statistics including number of subjects, mean, median, standard deviation, minimum, Q1, Q3, and maximum will be provided for the following measures:
    - Number of events divided by the number of study drug injections each subject received. Note each dose of study drug can be administered via more than 1 injections according to the total volume of study drug determined by the subject's body weight.
    - Mean duration of events. The duration of an event is defined as (AE stop date - AE start date +1). If an AE is ongoing at the end of the study, the last visit date will be used in lieu of AE stop date. Mean duration is calculated as the duration averaged over all events experienced by a subject.
    - Number of days following the most recent study drug injection to the first event of injection site reaction.
  - Number of events and number (and percentage) of subjects with events that occurred within 2 days after dosing by PT. For subjects who did not receive the second dose, only those events that occurred up to Day 57 (Day 1 being the day when the first dose was administered) will be included.
  - Number of events and number (and percentage) of subjects with events that occurred beyond 2 days after dosing by PT. Only subjects who received the second dose will be included in this analysis.

5.8.3. Clinical Laboratory Measurements

Central laboratory measures for chemistry and hematology parameters will be explored through two methods:

First, summaries will focus on study population changes with the intent of identifying deviations on a large scale across time. This approach for continuous variables summarizes both the actual results (at both baseline and post-baseline) and the change from baseline results at each post-baseline scheduled visit. Descriptive statistics include number of subjects, mean, median,

standard deviation, minimum, Q1, Q3, and maximum values for each of the 5 blood collection schedule group (Schedule I through M) by treatment group.

Second, shift tables based on baseline categories of low/normal/high/total will be provided for each post-baseline visit by treatment group. In addition, line plots of change from baseline in lab values over time will be presented with visit plotted on the x-axis and lab values on the y-axis, with treatment group side by side at each time point. In addition to the shift analyses, number (and percentage) of subjects with lab values meeting the treatment-emergent PCSV criteria at least once during the TEAE period will be summarized. These laboratory parameters will be presented by the biological functions defined in Section 4.7.3. Subject listings of laboratory measurements that meet treatment-emergent PCSV criteria will be provided.

5.8.4. Analysis of Vital Signs

All collected vital sign measures (pulse rate, respiratory rate, sitting blood pressures, and temperature) will be will be explored through summaries of both the actual measurements (at both baseline and post-baseline) and the change from baseline measurements at each post-baseline scheduled visit. Descriptive statistics include number of subjects, mean, median, standard deviation, minimum, Q1, Q3, and maximum values for each treatment group. In addition, body weight will be summarized in the same fashion.

The obtainment of blood pressure in infants, without cause or suspicion of underlying abnormalities is not routinely done in the outpatient pediatric setting. Specialized equipment, not routinely present in pediatric physician offices, is required. As a result of the issues surrounding the accurate obtainment of blood pressures in the study's infant population, the study protocol was revised to allow investigators to record that blood pressures are not able to be obtained. In many instances blood pressure results are not available, and in instances where results have been obtained, the accuracy of the recordings can be questioned. As a result, no shift table or treatment-emergent PCSV analyses will be performed on blood pressure measurements.

The protocol allows for the measurement of subject temperature using different modalities, eg, temporal, axillary, rectal and tympanic. Temperatures measured using different modalities are not equivalent and conversions are necessary to allow comparison. Furthermore, as the child ages throughout their time participating in the study, elevations in temperature that would be of concern change. Therefore due to the complexities to standardize reporting of temperatures and to accommodate changes reflecting the age of the child over time, no shift table or treatment-emergent PCSV analyses will be performed on temperature measurements.

Only the number (and percentage) of subjects with pulse rate and respiratory rate values meeting the treatment-emergent PCSV criteria at least once during the TEAE period will be summarized. Subject listings of vital sign measurements that meet treatment-emergent PCSV criteria will be provided.

5.8.5. Physical Exams

The number (n) and percentage (%) of subjects with abnormal physical examination at baseline and each scheduled post-baseline assessment will be summarized for each treatment group.

5.9. Analysis of Pharmacokinetic and Antibody Data

The analyses in this section will be performed by the Bioanalytical or Pharmacometrics groups.

5.9.1. Analysis of Pharmacokinetic Data

Concentration data will be summarized by descriptive statistics at each nominal time point. Pooled individual data and mean REGN2222 concentration-time plots will be produced.

These data may be utilized in a population PK analysis. If conducted, results be reported separately.

5.9.2. Analysis of Anti-drug Antibody Variables

Listings of ADA positivity and titers will be presented by subject and time point. Prevalence of ADA including treatment-emergent and treatment-boosted ADA will be assessed as absolute occurrence (n) and percent (%) of subjects.

ADA titer levels and persistent ADA will also be evaluated.

Possible correlation between changes in drug concentration and ADA assay response will be evaluated. Additionally, possible correlation between ADA assay response and safety or efficacy will also be assessed.

5.10. Analysis of Pharmacodynamic/Genomics Variables

Pharmacogenomic analysis of subject genetic variants associated with adverse events or efficacy may also be performed. Statistical plan for subject genetic analysis will be described in a separate document.

5.11. Analysis of RSV RT-PCR Data

The number (and percentage) of subjects with at least one nose swab collected and of subjects with at least one RSV positive nose swab will be summarized respectively for the FAS by treatment group.

A listing of local laboratory RSV RT-PCR assay results that were used to incur a primary endpoint event will be provided.

5.12. Analysis of Multiplex Respiratory Pathogen RT-PCR Data

Nose swab specimens tested negative on the RSV Lyra RT-PCR assay will be tested on the multiplex RT-PCR respiratory panel for alternative etiologies of RSV-negative respiratory tract infections.

The number and percentage of **subjects** with non-RSV medically attended respiratory illness (as defined in Section 5.7.5.3) who tested positive for any and each type of non-RSV pathogen on the RT-PCR multiplex respiratory panel will be summarized by treatment group. The denominator used to calculate percentage will be the number of FAS subjects in each treatment group.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline assessment for all measurements will be the last chronologically available valid measurement taken prior to the administration of the first dose of study drug. For most variables, Day 1 procedures and assessments are considered to be baseline. For variables such as ADA, samples collected at the screening visit will be considered to be baseline.

6.2. Data Handling Convention for Efficacy Variables

Rules for handling missing data for primary and secondary efficacy variables are described in Section 4.6.1 and Section 4.6.2.

For other secondary variables, missing data will not be imputed, that is, only observed data will be included in the descriptive summaries.

6.3. Data Handling Convention for Missing Data

Adverse event

If the severity/toxicity grade of a TEAE is missing, it will be classified as "severe" in the frequency tables by severity of TEAEs. If the assessment of relationship of a TEAE to the study drug or injection procedure is missing, it will be classified as related to the study drug or injection procedure.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset, worsening, seriousness

Missing or partial AE dates and times will be imputed so that if the partial AE date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Baseline definition if "time" of the administration of study drug or time of assessment at Day1 visit is missing

If time of the administration of study drug or time of assessment at Day 1 visit is missing, then the baseline value is defined as the last available value obtained before or on the day of the study drug administration.

Laboratory Safety Variables

For central laboratory data below the lower limit of quantification (LLOQ), half of the lower limit value (ie, LLOQ/2) will be used for quantitative analyses. For central laboratory data above the upper limit of quantification (ULOQ), the upper limit value (ie, ULOQ) will be used for quantitative analyses.

6.4. Visit Windows

Visit windows will be programmatically imposed on those safety measures repeatedly collected over the course of the study. These visit windows are derived from the number of days in study, specifically assigning day ranges to mimic the study assessment schedule provided in the protocol. Data analyzed by time point (including laboratory safety data, vital signs, physical exam) will be summarized using the analysis windows given in Appendix 11.3. These analysis windows will be applicable for the aforementioned safety analyses, and they are defined to provide more homogeneous data for time point-specific analyses. If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within the same day, then the first value of the day will be selected when time is available, or the scheduled visit will be selected.

6.5. Unscheduled Assessments

For safety laboratory data, vital signs, and physical exams, unscheduled visit measurements may be used to provide a measurement for a time point, a baseline, a last, or a worst value, if appropriate according to their definitions. The measurements may also be used to determine abnormal values and treatment-emergent PCSVs.

6.6. Pooling of Centers for Statistical Analyses

The randomization scheme was not stratified by center because the RSV infection component of the primary efficacy variable is centrally assessed and expected not to be influenced by the center when other factors such as gestational age are already controlled. Therefore, the center will not be added as a factor in the primary analysis model.

6.7. Statistical Technical Issues

Not applicable.

7. INTERIM ANALYSIS

Sample size re-estimation based on the blinded and pooled event rate and hypothesized treatment effect was designed for the originally planned sample size and was allowed to be proposed at the end of each RSV season according to the study protocol Section 9.2.1. This blinded sample size re-estimation has not been performed for this study.

A study treatment unblinding interim efficacy analysis is not planned.

8. TIMING OF STATISTICAL ANALYSIS

Efficacy and safety analyses for this study will be performed in two steps, specifically for subject data collected up to the time the last subject completes efficacy assessments at Day 150 visit (step 1) and at the end of the study Day 237 visit (step 2). No formal interim analysis for efficacy is planned since analyses of primary and secondary efficacy endpoints will be final at the time of first step analysis. Therefore, no multiplicity adjustment for multiple analyses is needed (see Section 5.7.3). The timing for subject data to be reported is defined below for each step:

- First step: efficacy analyses through Day 150 visit and interim safety analysis
  - This analysis will be conducted on all randomized subjects when all subjects will have all their efficacy data up to Day 150 visit collected and validated.
  - The efficacy analyses will be performed up to Day 150 visit. Analyses of endpoints up to Day 150 visit will correspond to the final analyses for these endpoints.
  - The safety analyses will be performed on all safety data collected up to the common cut-off date. For this analysis, the common cut-off date is defined as date of the last Day 150 visit.
- Second step: final safety analysis
  - This analysis will be conducted at the end of the study and will consist of the final safety analysis.

Individuals involved in the first step analysis of the study will not be involved in the conduct of the study afterwards; individual subject identification will not be released to anyone who is directly involved in the conduct of the study. The first step analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document. The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. The first analysis will be used for planning the design of a separate efficacy study and communication with health authorities.

Analysis methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply to analyses performed at first step analysis:

- Any efficacy assessments up to Day 150 visit will be taken into account.
- Subjects with EOS visit (ie, Day 237 visit) yet to be performed at the time of the cut-off date will be considered as ongoing and followed up to the cut-off date for the purpose of safety analyses. Therefore:
  - Subjects who did not complete Day 237/EOS (or early termination) visit at cut-off date will be analyzed as "ongoing" in the disposition summary.
  - Their TEAE period and on-study observation period will end at the cut-off date.
  - Their on-study observation period duration will be derived by considering date of cut-off as last study visit date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications and deaths occurring after the cut-off date will not be included in the analyses.

9. SOFTWARE

All clinical data analyses will be done using SAS Version 9.2 and above.

10. REFERENCES

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11. APPENDIX

11.1. Summary of Statistical Analyses

Primary and Secondary Efficacy Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
Proportion of subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the 150-day efficacy assessment period.	FAS	Proportion difference	CMH statistics with randomization stratum adjusted by the Mantel-Haenzel (MH) method	Yes Fisher's exact test; Logistic regression; Time to first event; Missing data handling	Yes	Stratification; RSV LRTI; Alternative LRTI Definition
Secondary Endpoint						
Proportion of subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the 150-day efficacy assessment period.	FAS	Proportion difference	CMH statistics with randomization stratum adjusted by the Mantel-Haenzel (MH) method	Yes Fisher's exact test; Logistic regression; Time to first event; Missing data handling	Yes	Stratification

11.2. Schedule of Time and Events

Study Periods	**SV[1]**	**BV**	**Treatment Period**		**Postdose Follow-Up**					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7/ET**	**8[17]**	**9[17]**	**10/EOS[17]**
Day	**-28 to -1**	**1**	**29±2**	**57±2**	**85±5**	**113±5**	**150±5**	**178±10**	**206±10**	**237±10**
Informed Consent[18]	X									
Inclusion/Exclusion	X	X								
Medical History	X									
Demographics	X									
Randomization[2]		X								
Dispense Medical Information Packet[3]		X								
Administer Study Drug[4]		**X[5]**		**X[5]**						
Concomitant Medications and Procedures	X	X	X	X	X	X	X	X	X	X
Vital Signs[6]	X	X	X	X	X	X	X			
Physical Examination (including weight)	X	X[7]	X	X[7]	X		X			
Adverse Events[8]	X	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9, 17]	X[9, 17]	X[9, 17]
Blood Sampling										
Hematology	X[10-14]		X[10]	X[11]	X[12]	X[13]	X[10-14]			
Blood Chemistry	X[10-14]		X[10]	X[11]	X[12]	X[13]	X[10-14]			
Pharmacokinetics			X[10]	X[11]	X[12]	X[13]	X[10-14]			
Anti-REGN2222 (ADA)	X[10-14]		X[10]	X[11]	X\[12]	X[13]	X[10-14]			
Optional Substudy Informed Consent	X									
Optional DNA Sample		X[15]								
Pharmacoeconomic Information[16]		X	X	X	X	X	X			

ADA=antidrug antibody; BV=baseline visit, EOS/ET=end of study/early termination; IM=intramuscular; SV=screening visit; X=all subjects unless otherwise specified

1. All safety assessments performed at screening must be normal and checked against the inclusion/exclusion criteria before REGN2222 administration on Day 1(baseline)
2. Subject randomization and blood collection schedules are assigned using the interactive voice response system (or interactive web response system) at Visit 2. Depending on the availability of the study pharmacist or designee, subjects may be randomly assigned on Day -1 or Day 1.

3. When parent(s) or guardian(s) take their child for medical attention outside of the study site, the parents/guardians are instructed to take the Medical Information Packet with them for use by their healthcare provider. Data on medically attended RSV infections will be collected for all subjects until Day 150.
4. Subjects randomly assigned to the 30 mg/kg Q8w arm will receive REGN2222 on Day 1 and Day 57. Subjects randomly assigned to the single 30 mg/kg arm will receive REGN2222 on Day 1 and placebo on Day 57. Subjects randomly assigned to the placebo arm will receive placebo on Day 1 and Day 57.
5. No other vaccinations will be administered within 2 days before or after dosing of the study drug. Subjects who have reached the primary endpoint should not receive additional doses of study drug. The study staff will contact the parent(s) or legal guardian(s) by telephone at the end of each dosing day and daily over 48 hours following a dose to inquire about any change in the subject's status.
6. On study drug dosing days, vital signs when the child is calm (temperature, blood pressure, pulse, and respiration) will be assessed prior to blood sample collection, prior to injection of study drug, and 1 hour (±10 minutes) after completion of the injection. If a subject's rectal temperature is 101°F (38.3°C) or greater on the day of a planned dose administration day, no dosing will occur (see Section 6.3.1.1 of protocol for temperature conversions). The subject will be re-evaluated within 48 hours and if the subject's temperature is below 101°F (38.3°C) without the use of antipyretics during the previous 48 hours, the schedule of assessments may be resumed. If the subject's temperature is 101°F (38.3°C) or greater or the subject has received antipyretics in the previous 48 hours, dosing of the subject will be permanently discontinued.
7. Physical examinations will be conducted before injection and after injection, prior to discharge, from the clinic at Visit 2 and Visit 4. Weight collection is not required post-injection.
8. If the adverse event is considered a hypersensitivity or anaphylaxis reaction, then the adverse event will be assessed at as outlined in Protocol Table 4.
9. If the adverse event is a hypersensitivity reaction that results in a rash, then a photo will be taken as part of the adverse event assessment (also see Protocol Table 4).
10. The subjects with Schedule M will have the following collected: hematology/chemistry samples at screening, Day 29, and Day 150/ET; PK samples at Day 29 and Day 150/ET; and ADA samples at screening, Day 29, and Day 150/ET.
11. The subjects with blood collection Schedule L will have the following collected: hematology/chemistry samples at screening, Day 57 (predose), and Day 150/ET; PK samples at Day 57 (predose) and Day 150/ET; and ADA samples at screening, Day 57 (predose), and Day 150/ET.
12. The subjects with blood collection Schedule K will have the following collected: hematology/chemistry samples at screening, Day 85, and Day 150/ET; PK samples at Day 85 and Day 150/ET; and ADA samples at screening, Day 85, and Day 150/ET.
13. The subjects with blood collection Schedule J will have the following collected: hematology/chemistry samples at screening, Day 113, and Day 150/ET; PK samples at Day 113 and Day 150/ET; and ADA samples at screening, Day 113, and Day 150/ET.
14. The subjects with blood collection Schedule I will have the following collected: hematology/chemistry samples at screening and Day 150/ET; PK samples at Day 150/ET; and ADA samples at screening and Day 150/ET.
15. After substudy consent, the cheek swab for DNA in the optional substudy can be obtained at any time during the study period, but preferably at baseline.
16. If the subject experiences a medically attended respiratory infection since the previous scheduled visit, then the parent(s) or guardian(s) will be asked to provide additional pharmacoeconomic information on the event.
17. Visits 8, 9, and 10 will be done by telephone contact. In the event an AE is reported during a phone call visit, an unscheduled onsite visit may be required to follow-up, per investigator.
18. Informed consent may be obtained from the parent(s) or legal guardian(s) up to 28 days prior to randomization. Consent can occur outside the screening visit or on the same day as the screening visit, but must occur prior to the screening visit.

11.3. Windows for Analysis Time Points

Below are the definitions for the visit windows programmatically imposed on measures repeatedly collected over the course of the study. These visit windows reflect the study schedule of assessments as described in the protocol. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the date of the first study drug administration, and is labeled as baseline for most variables. Since the protocol specifies that measurements be collected before study drug is administered on a given day, it is appropriate that baseline include Day 1. For randomized but not treated subjects, Day 1 is the day of randomization.

Time point	Target Week	Target study day	Analysis window in study days
Visit 3 (Day 29)	Week 4	29	15 to 42
Visit 4 (Day 57)	Week 8	57	43 to 71
Visit 5 (Day 85)	Week 12	85	72 to 99
Visit 6 (Day 113)	Week 16	113	100 to 132
Visit 7 (Day 150)	Week 21	150	133 to 164

11.4. Criteria for Treatment-Emergent Potentially Clinically Significant Values (PCSV)

Parameter	PCSV	Comments
Clinical chemistry PCSV based on criteria for infants born at term, except for total bilirubin where specific criteria are available for pre-term infants, considering Grade 3 Severe and above events as per the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0 November 2014).		
ALT, high	≥ 5 ULN and baseline < 5 ULN	
Albumin, low	< 20 g/L and baseline ≥ 20 g/L	
AST, high	≥ 5 ULN and baseline < 5 ULN	
Alkaline Phosphatase, high	≥ 5 ULN and baseline < 5 ULN	
Calcium, high	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline ≥ 3.13 mmol/L for ≥ 7 days of age ≥ 3.23 mmol/L for < 7 days of age	
Calcium, low	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline <1.75 mmol/L for ≥ 7 days of age <1.50 mmol/L for < 7 days of age	
Carbon Dioxide, low	<11.0 mmol/L and baseline ≥ 11.0 mmol/L	
Creatinine, high	> 1.8 ULN and baseline ≤ 1.8 ULN, or Increase of 1.5 x above baseline	
Total Bilirubin, high	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline ≥ 307.8 µmol/L for ≥35 weeks gestational age and < 7 days of age ≥ 171 µmol/L for 32 to < 35 weeks gestational age and < 7 days of age* ≥ 102.6 µmol/L for 28 to < 32 weeks gestational age and < 7 days of age* ≥ 85.5 µmol/L for < 28 weeks gestational age and < 7 days of age* ≥ 342 µmol/L for 7 to 28 days of age ≥ 2.6 x ULN for > 28 days of age	*Criteria are specific for preterm infants
Glucose, high	≥ 13.89 mmol/L and baseline < 13.89 mmol/L	
Glucose, low	< 2.22 mmol/L and baseline ≥ 2.22 mmol/L	
Potassium, high	≥ 6.5 mmol/L and baseline < 6.5 mmol/L	
Potassium, low	< 2.5 mmol/L and baseline ≥ 2.5 mmol/L	

Parameter	PCSV	Comments
Sodium, high	≥ 154 mmol/L and baseline < 154 mmol/L	
Sodium, low	< 125 mmol/L and baseline ≥ 125 mmol/L	
Uric acid, high	≥ 0.71 mmol/L and baseline < 0.71 mmol/L	
Hematology PCSV based on criteria for infants born at term, considering Grade 3 Severe and above events as per the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0 November 2014).		
WBC, Decreased	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline ≤ 1.499 x 10^9 cells/L for > 7 days of age ≤ 3.999 x 10^9 cells/L for ≤ 7 days of age	
Neutrophils, low	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline < 0.600 x 10^9 cells/L for > 7 days of age < 1.000 x 10^9 cells/L for 2 to 7 days of age < 3.000 x 10^9 cells/L for ≤ 1day of age	
Hemoglobin, low	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline < 6.19 mmol/L (100 g/L) for ≤ 7 days of age < 5.57 mmol/L (90 g/L) for 8 to ≤ 21 days of age < 4.94 mmol/L (80 g/L) for 22 to 35 days of age < 4.32 mmol/L (70 g/L) for 36 to 56 days of age < 5.25 mmol/L (85 g/L) for ≥ 57 days of age	
Platelets, decreased	< 50.000 x 10^9 cells/L and baseline ≥ 50.000 x 10^9 cells/L	
Vital signs PCSV based on normal ranges in http://health.ny.gov/professionals/ems/pdf/assmttools.pdf		
Respiratory Rate	< 30 breaths per minute and ≥ 30 breaths per minute at baseline > 60 breaths per minute and ≤ 60 breaths per minute at baseline	
Pulse Rate	< 100 beats per minute and ≥ 100 beats per minute at baseline > 160 beats per minute and ≤ 160 beats per minute at baseline	

11.5. Hypersensitivity PTs of interest per Carbonell-Estrany X et al.

Non-Specific PTs	Specific PTs
Erythema	Anaphylactoid reaction
Flushing	Angioedema
Pruritus	Dermatitis allergic
Rash	Drug eruption
Rash erythematous	Drug hypersensitivity
Rash macular	Oedema
Rash maculo-papular	Erythema annulare
Rash pruritic	Erythema marginatum
	Erythema multiforme
	Eye swelling
	Eyelid oedema Face
	oedema
	Hypersensitivity
	Injection site erythema
	Laryngeal oedema
	Lip swelling
	Periorbital oedema
	Rash generalised
	Swelling
	Swelling face
	Tracheal oedema
	Urticaria
	Urticariapapular

Note: The following terms listed in Carbonell-Estrany's manuscript are LLTs that code into PTs as follows:
LLT: Angioneurotic oedema codes to PT: Angioedema
LLT: Exanthema codes to PT: Rash
LLT: Urticaria generalised codes to PT: Urticaria.

11.6. Hypersensitivity PTs of interest per Feltes TF et al.

Non-Specific PTs	Specific PTs
Erythema	Allergic oedema
Fixed Drug Eruption	Anaphylactoid reaction
Generalised oedema	Angioedema
Pruritus	Bronchial oedema
Pruritus generalised	Circumoral oedema
Rash	Dermatitis allergic
Rash erythematous	Drug eruption
Rash macular	Drug hypersensitivity
Rash maculo-papular	Erythema annulare
Rash papular	Erythema marginatum
Rash pruritic	Erythema multiforme
	Eye oedema
	Eye swelling
	Eyelid oedema
	Face oedema
	Flushing
	Generalised Erythema
	Hypersensitivity
	Laryngeal oedema
	Laryngotracheal oedema
	Lip oedema
	Lip swelling
	Oedema
	Oedema mouth
	Oropharyngeal swelling
	Periorbital oedema
	Pharyngeal oedema
	Pharyngeal ulceration
	Pruritus allergic
	Rash generalised
	Skin swelling
	Swelling
	Swelling face
	Swollen tongue
	Tongue oedema
	Tracheal oedema
	Urticaria

Note: The following terms listed in Feltes TF's manuscript are LLTs that code into PTs as follows:
LLT: Angioneurotic oedema codes to PT: Angioedema
LLT: Fixed Eruption codes to PT: Fixed Drug Eruption
LLT: Urticaria generalised codes to PT: Urticaria

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