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Regeneron Pharmaceuticals, Inc.

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Clinical Study Protocol

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

Compound:	REGN2222
Clinical Phase:	3
Protocol Number:	R2222-RSV-1332
Protocol Version:	R2222-RSV-1332.04
Amendment 4 Date of Issue:	See appended electronic signature page
Amendment 3 Date of Issue:	16 MAR 2016
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Scientific/Medical Monitor: [redacted]

Senior Director, Clinical Sciences

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 4

The purpose of this amendment is:

- To revise the approach of handling of missing data in the primary efficacy analysis [redacted]. Specifically, the new statistical approach will directly impute missing data at Day 150 visit. For those subjects who died prior to Day 150 and the deaths are adjudicated to be RSV related, their missing primary endpoint will be imputed as "event occurred". Remaining early termination subjects (including non-RSV deaths) across all treatment groups, will be imputed to the average placebo score (estimated placebo event rate). The approach to estimating the placebo event rate is the Kaplan-Meier estimate at Day 150.

  Rationale: To take into consideration the possibility of a study subject contracting RSV when addressing missing data in the primary efficacy analysis for a study subject that doesn't complete Day 150 follow-up due to early termination.

Enrollment into the study will end with the 2016-2017 RSV season in the Northern Hemisphere due to the Sponsor's administrative decision. The expected enrollment will be approximately 1200 infants resulting in a smaller sample size for analysis. The 2 following changes are a result:

- Added power calculation for anticipated smaller sample size.

  Rationale: To understand the impact of the reduced study enrollment on the primary efficacy analysis.

- Revised statistical approach to controlling the overall type I error for the primary efficacy analysis.

  Rationale: To retain sufficient study power for the primary efficacy endpoint given the reduced sample size.

Other Changes to the Statistical Plan include:

- To remove complete and worst-case sensitivity analyses.

  Rationale: The complete analysis uses only data of a subset of subjects, thus results are not generalizable to the subject population. The worst-case analysis may unrealistically inflate the primary endpoint event rate above the expected small event rate in this subject population.

- To clarify timing of statistical analyses. Specifically, the efficacy analysis will be conducted following completion of the 150-day efficacy assessment period by all subjects. This will represent the final analysis of all efficacy endpoints.

  Rationale: Due to the time sensitivity of future study initiation, this will support timely initiation of such studies and avoid long delays waiting for the start of a RSV season.

Other changes include:

- To add assessment of negative RSV nose swab specimens for other common respiratory pathogens.

  Rationale: [redacted] *to assess common respiratory pathogens, in addition to RSV, in clinical development.*

- To add text to clarify what is meant by "reached primary endpoint" when determining if the second dose of study drug should be administered, ie only those subjects who have had a positive RT-PCR test at the study central laboratory or at a CLIA-certified (or equivalent) laboratory after receipt of Dose #1 of study drug, but prior to receipt of Dose #2 should not receive Dose #2.

  Rationale: To clarify those subjects who should not receive a second dose of study drug at Visit 4, due to reduced potential for benefit.

- To clarify that the symptom of chest wall indrawing used in the definition of the study primary endpoint is to be considered as lower chest wall indrawing.

  Rationale: To align the protocol with the eCRF and our communication with investigators, eg Investigator's Meeting, on this topic. The Sponsor considers that chest wall indrawing and lower chest wall indrawing are implicitly the same; chest wall indrawing is the inward movement of the lower chest wall.

- To clarify wording related to pediatric clinic visits.

  Rationale: To provide more explicit examples of the types of visits to be considered as "outpatient medically attended visits" or "pediatric clinic visits". This information has been collected in the eCRF, but clarifications are made in response to different interpretations noted by investigators as to how they are capturing data within the eCRF.

- To clarify information collected during the Visit 2 (Baseline and First Dosing Visit, Day 1) to assess Risk Factors.

  Rationale: This information has always been collected at Visit 2 [per the EDC], but details are being added to clarify.

- To clarify text related to follow up in the Study Enrollment and Assessment section.

  Rationale: To clarify that the follow up period for the occurrence of medically attended respiratory illnesses will continue only until the end of the 150-day study period.

- To add text related to the Endpoint Adjudication Committee assessment of subject deaths after the first dose of study drug as RSV-related or not.

  Rationale: Text was added that any subject deaths that occur after the administration of the first dose of study drug and prior to Day 150 will be assessed to determine their association with RSV for purposes of determining handling in revised approach to missing data.

- To clarify, in the Temperature/Safety Procedures Section, the specifics related to the restrictions to dosing of febrile subjects and use of antipyretics, including allowance for re-evaluation within 48 hours.

  Rationale: Provide clarity from previous versions of the protocol and to make consistent within all sections of the protocol.

- To clarify, in Table 2, that two vital signs assessments (temperature, blood pressure, pulse, and respiration) will be performed on dosing days, before study drug administration (or blood draw, if applicable) and after.

  Rationale: Provide clarity from previous versions of the protocol.

- To correct the definition of high titer to >10 000 in the Antidrug Antibody Section.

  Rationale: Correction of typographical error from previous versions of the protocol, which had omitted one "0".

- To clarify that safety and tolerability will also be descriptively summarized in the combined REGN2222 treatment arms

  Rationale: Provide clarity from previous versions of the protocol.

- To clarify wording in the Investigator Alert Notification Section that investigators will be notified in a blinded fashion of any SAE that possibly meets the relevant requirements for expedited reporting.

  Rationale: Updated wording to add that the notification will be blinded as per risk management and pharmacovigilance procedures.

- To clarify wording in the Demographic and Baseline characteristics section related to pharmacoeconomics and risk factor assessment.

  Rationale: Provide clarity from previous versions of the protocol.

- To update wording for the safety variables in Part B related to the definitions for the 3 observation periods.

  The PRE-TREATMENT period is defined as the time from signing the ICF to before the first dose of study drug.

  The SAFETY-TREATMENT period is defined as the time from the first dose of study drug up to the day of the last dose of study drug + 180 days.

  The POST-TREATMENT period: defined as starting the day after the end of the TEAE period.

  Rationale: Provide clarity from previous versions of the protocol.

- To clarify that the definition of treatment-emergent AEs in Part B are defined as those that are not present at baseline or represent the exacerbation of a preexisting condition during the SAFETY-TREATMENT period (TEAE period).

  Rationale: Provide clarity and consistency in language from previous versions of the protocol.

- To clarify that the additional evaluation of TEAEs may be conducted for identification of hypersensitivity.

  Rationale: Added for safety evaluation.

- To clarify that an unblinding interim efficacy analysis is not planned.

  Rationale: Provide clarity from the previous version.

- To update the scientific/medical monitor

  Rationale: The name of the Scientific/Medical Monitor was updated due to organizational changes in scope of responsibilities.

- To make minor edits and clarifications and remove redundancy

  Rationale: Editing purposes.

The table that follows outlines both the changes described in the bullet points above and changes/clarifications made throughout the protocol and the affected sections.

Change	**Sections Changed**
Changes in text related to the impact of early termination resulting in reduced sample size. Updated text related to multiplicity considerations.	Section 9.2 Sample Size Section 9.5.2.4 Multiplicity Considerations
Updated text to reflect the handling of missing data for efficacy analyses [redacted] Removed complete and worst-case sensitivity analyses	Clinical Study Protocol Synopsis Section 9.5.2.1 Primary Efficacy Analysis
Clarify timing of statistical analyses and break down of statistical analysis into 2 steps.	Clinical Study Protocol Synopsis Section 5.4.2.1 . Blinding Section 9.5.6 Timing of Statistical Analses Section 9.5.6.1 First Step: Efficacy and Safety Analysis Section 9.5.6.2 Second Step: Final Safety Analysis
To clarify that the symptom chest wall indrawing refers to the lower chest wall that is indrawing.	Clinical Study Protocol Synopsis Section 8.2 Primary Endpoints Section 9.5.2.1 Primary Efficacy Analysis
Clarify that safety and tolerability will also be descriptively summarized in the comnined REGN2222 treatment arms	Section 9.5.3.2 Part B Section 9.5.3.5 Treatment Exposure

Change	Sections Changed
Clarify that the blinded sample size re-estimation was never performed during the study, nor is re-estimation planned during the remainder of the study since enrollment will end with the 2016/2017 RSV season in the Northern Hemisphere due to Sponsor's administrative decision. Clarify that an unblinding interim efficacy analysis is not planned	Clinical Study Protocol Synopsis Section 9.6.2 Part B
Added a bullet : To detect and identify the presence of other common respiratory pathogens from RSV negative nose swab specimens collected from subjects. Added text to note that additional testing for other common respiratory pathogens is only conducted with RSV-negative swabs and will not be used in the primary analyses of the primary and secondary efficacy endpoints. Added an exploratory endpoint: Number and proportion of subjects with other common respiratory pathogens identified by a RT-PCR multiplex respiratory panel which is distinct from the RT-PCR assay being used to test for RSV for the study's efficacy endpoints. The multiplex evaluation will only be conducted on RSV negative swabs collected from subjects and will not be used in the primary analyses of the primary and secondary efficacy endpoints.	Clinical Study Protocol Synopsis Section 2.3 Exploratory Objectives Section 8.4 Exploratory Endpoints Section 6.3.3.3 Virology Testing Section 9.5.2.3 Exploratory Analysis
Clarified wording and added a footnote relating to pediatric clinic visits: "A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit"	Clinical Study Protocol Synopsis Section 2.2 Secondary Objectives Section 6.2.3 Part B: Unscheduled Visit for Potential Respiratory Illness Section 6.5 Pharmacoeconomic Measurement Procedures Section 8.2 Primary Endpoints Section 8.3 Secondary Endpoints Section 8.4 Exploratory Endpoints

Change	Sections Changed
Added a bullet detailing the risk factor information that is collected during Visit 1. Minor edits and added text related to pharmacoeconomics data (risk factors). Details of risk factor information collected at Visit 1 was added to more completely describe current practice.	Table 2 Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M Section 6.2.2.2 Visit 2 (Baseline and First Dosing Visit, Day 1) Section 8.1 Demographic and Baseline Characteristics
Clarified text related to the follow-up period as: The follow-up period for the occurrence of medically attended respiratory illnesses will continue until the end of the 150-day study period.	Section 3.1.2.3 Study Enrollment and Assessments
Added text related to the handling of any subject deaths occurring after the first dose of study drug by the Endpoint Adjudication Committee	Section 3.3.3. Endpoint Adjudication Committee
Temperature: Text was added to clarify that dosing may proceed only if the subject is afebrile without the use of antipyretics and that these subjects would be followed in the study for safety and efficacy if at least one dose of study drug was administered.	Section 6.2.2.2 Visit 2 (Baseline and First Dosing Visit, Day 1) Section 6.2.2.4 Visit 4 (Second Dosing Visit, Day 57±2 Days) Section 6.3.1.1 Temperature Table 2 Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M, footnote #6
Vital signs: The text related to taking vital signs before and after dosing was clarified.	Section 6.2.2.2: Visit 2 (Baseline and First Dosing Visit, Day 1) Table 2 Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M, footnote #6
The definition for High ADA titer was corrected from >1000 to > 10000	Section 8.5 Antidrug Antibody Variables

Change	Sections Changed
Updated to clarify that notification will be blinded as per risk management and pharmacovigilance procedures.	Section 7.5 Investigator Alert Notification
Any subject who has had a positive RT-PCR RSV nasal swab result, either at the study central laboratory or at an outside institution in a CLIA-certified (or equivalent) laboratory, should not receive a second dose of study drug and will be monitored.	Clinical Study Protocol Synopsis Section 3.1.2.3 Study Enrollment and Assessments Table 2 Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M, footnote #5
Updated safety variables from 3 observation periods to 2 observation periods in Part A For safety variables in Part B, added definitions for 3 observation periods and treatment-emergent adverse events. Additional evaluation of TEAEs may be conducted for identification of hypersensitivity Included definition regarding TEAEs in Part B will be defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the safety TEAE period.	Section 9.5.3.3 Adverse Events
Change “Part B” to “Part A” for the cohort that the subjects’ doses will be summarized in	Section 9.5.3.5 Treatment Exposure
Following the completion of Part A, subject data will be locked and reported. This will be done to confirm the dose to move forward with in Part B of the study.	Section 9.6.1 Part A
Added section to provide end of study definition	Section 3.2.1 End of Study Definition
Editorial and Administrative Changes/Updates	Cover Page Section 3.2 Study Stopping Rules Section 4.2 Premature Withdrawal From the Study Table 2 Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M, footnote #7

Amendment 3

[redacted]

- To add 2 secondary endpoints to Part B
  - *Rationale: The addition of secondary endpoints for PK and ADA titers are to align with agreed PIP.*
- To add RSV LRTI Analysis and Alternative LRTI Definition Analysis as sensitivity analyses to the primary endpoint
  - *Rationale: To align with the EU protocol and requested by PDCO, respectively*

[redacted]

- To clarify language in Exclusion Criteria for the Mother
  - *Rationale: To add that infants of mothers who are either 16 years or younger or of an age where they cannot legally provide informed consent in their state/country are excluded.*

The following additional changes were made:

- To update the scientific/medical monitor
- To clarify the window in Part B during which assessment of primary and secondary clinical endpoints will occur
  - *Rationale: Although no change of the actual window in which primary and secondary endpoint acquisition was made, the change was to clarify that the windows end at different times during the study period.*
- To clarify that subjects who complete Day 150 may be eligible to enroll in a subsequent extension study
- To change the screening period in Part B from 14 to 28 days
  - *Rationale: Based on feedback from study PIs that a longer period from screening to enrollment is required if infants are enrolled in the hospital or neonatal intensive care unit but are enrolled in the study clinic.*
- To remove throat swab collection
  - *Rationale: Based on feedback that because of high sensitivity of RT-PCR for diagnosis of RSV, a throat swab in addition to nose swab is not necessary and can be challenging to collect in some preterm infants.*
- To clarify phrasing of the target population definition and Exclusion Criterion #1
  - *Rationale: The original phrase "eligible to receive palivizumab…" was meant to indicate that any infant who is eligible or can access palivizumab as standard of care is excluded from the study. The phrasing was clarified indicate this.*

- To add clarification to 2 exploratory endpoints
  - *Rationale: Clarified that hospitalization is defined as a stay of 24 hours or longer. Added "for RSV-associated illness" to clarify condition for length of stay in hospital.*
- To clarify language and exceptions in Exclusion Criterion #6
  - *Rationale: Certain laboratory abnormalities are expected in preterm infants due to bone growth and physiological or breastfeeding jaundice and is not always considered an underlying medical disorder. Clarification is made to ensure that the upper limit of normal laboratory ranges are appropriate for preterm infants and for neonates, if applicable, as these ranges may be significantly different to full term infants.*
- To add details about sparse blood collection
  - *Rationale: To add an explanation for the blood drawing schedule utilized in this study to minimize the total number of planned blood draws required during the study period*
- To add respiratory syncytial virus (RSV)-positive reverse-transcriptase polymerase chain reaction (RT-PCR) test result after receipt of first dose but prior to second dose as a reason for permanent discontinuation of study drug
  - *Rationale: Although this was already in the protocol in section 3.1.2.3 underlying Study Enrollment and Assessment, it should also be included in the section on Reasons for Study Discontinuation.*
- To add a new section to detail the temperature acquisition method and add a table of conversions for the different modalities of temperature measurement
  - *Rationale: Rectal temperatures are included in the DAIDS severity score table and is considered the most accurate method. However, many sites indicated that rectal temperatures are not routinely measured in preterm infants. A conversion of temperature using different modalities of temperature measurement is included to allow for standardized conversion into an equivalent rectal temperature.*
- To clarify when pharmacoeconomic information will be collected
  - *Rationale: To clarify that pharmacoeconomic information will be collected only in infants who have had a medically attended respiratory visit.*
- To clarify, when a subject has a positive PCR RSV nasal swab result, that the subject should continue in the study and complete all assessments other than receiving the second of study drug and the postdose assessments
  - *Rationale: To clarify what procedures still need to be done in infants who do not receive the second dose of study drug because of having a positive RSV test result*

- To instruct study personnel how to record blood pressure if it is unable to be obtained
  - *Rationale: Blood pressure may be difficult to obtain in some infants because of size and therefore this is to clarify that a systolic blood pressure alone can be recorded or if unable to obtain either systolic or diastolic pressures, "unable to obtain" should be recorded.*
- To add detailed instruction for blood redraw procedures
  - *Rationale: Because of challenges of obtaining adequate blood volumes for screening blood tests, the clarification is to allow for blood redraw as long as the total volume is within the limits outlined by local or national guidelines on blood sampling limits in children.*
- To add detailed instruction for laboratory reference ranges for preterm infants
  - *Rationale: Preterm reference ranges for laboratory tests may be different from full term reference ranges and because there is no standardized universal reference ranges available for preterm infants, the clarification is to provide standard guidance on preterm reference ranges using literature and advice from subject matter experts.*
- To add Version 2.0 of Division of AIDS (DAIDS) (Appendix F), a DAIDS Fever Grading Scale (Appendix G), and to clarify which DAIDS version should be used for evaluation of adverse event (AE) severity
  - *Rationale: The original DAIDS severity scale was version 2004 and was used in the original protocol. An updated scale was published in 2014. Because there are some differences in definition of severity between 2004 and 2014 versions, the original 2004 version is maintained in the amendment with additions from the 2014 version related specifically to preterm infants, such as total bilirubin.*
- To add detailed instructions for how information and test results are collected if an unscheduled visit associated with a medically attended respiratory infection does not occur within 14 days of discharge from a medical facility.
- To update when sample size re-estimation occurs
  - *Rationale: This study will be conducted in multiple hemispheres, therefore the team wanted to be more general about when this analysis will take place*
- To update when an interim analysis occurs
  - *Rationale: This study will be conducted in multiple hemispheres, therefore the team wanted to be more general about when this analysis will take place*

  To make minor clarifications to the text and correct spelling and grammatical errors

Amendment 2

The purposes of this amendment are the following:

- Extend the Part B Post-Dose Follow-up Period from 93 days to 180 days
- Add a section describing the benefit/risk assessment
- Update assessments to be performed at unscheduled visits
- Update the study stopping rules
- Clarify that some standard of care treatments are permitted
- Include axillary temperature equivalents to rectal temperature
- Add a section describing the sponsor's reporting responsibilities
- Add the last 5 pages to the severity grading scale provided in Appendix E
- Make minor clarifications to the text

Amendment 1

The purposes of this amendment were the following:

- To update the status of the FIH study by removing "ongoing"
- To clarify the primary objective for Part B
- To clarify the collection of days on supplemental oxygen
- To clarify, in Part B, that the permitted windows for prophylaxis will be based on geographical area
- To remove references to the study manual
- To clarify, in Part A, the process of dosing for the 24 subjects
- To clarify physical examination assessment time points, including the addition, in Part A and Part B, of a physical examination postdose
- To clarify, in Part A, whether Visit 4 through Visit 6 will be at the clinic (if a blood draw is required) or will be conducted by telephone (if no blood draw is required)
- To clarify IDMC review and recommendation to begin enrollment in Part B
- To clarify Regeneron PK data review to confirm Part B dose and the addition of PK dosing adjustment rules
- To change, in Part B, stratification from country to region
- To clarify the gestational age categories as ≤31 weeks, 6 days GA or from 32 weeks, 0 days to 35 weeks, 6 days GA
- To clarify the Part B treatment arms
- To update, in Part B, monitoring of the subject to 1 hour after dosing
- To clarify, in Part B, the duration of subject participation

- To change the frequency of site contacts to weekly
- To remove heel stick method of blood collection
- To clarify information concerning the Medical Information Packet by changing the name, by updating the contents of the Medical Information Packet (including removal of swab samples), and by defining the time to the associated follow-up visit
- To add the description of the Safety Monitoring Team
- To describe the unscheduled visit for potential respiratory illness, including assessments
- To remove, in Part B, the statement regarding availability of study staff by telephone 7 days a week
- To add study stopping rules
- To clarify the countries and regions where study sites may be located
- To clarify the study population age
- To clarify that the parent(s) or legal guardian(s) must be legally able to provide informed consent
- To update the window for subjects to not receive other vaccinations from within 7 days of dosing to within 2 days of dosing with study drug
- To update the exclusion criteria for laboratory test results from >1.5 to >1.1 times the upper limit of normal
- To clarify the exclusion criteria for excluded concomitant medications or other concurrent treatments
- To update the exclusion criteria of previous reactions to agents or components
- To update the exclusion criteria of the mother to younger than 16 years old
- To clarify the discontinuation rules
- To change the grading system for AEs of special interest
- To clarify, in Part B, procedures relating to the unblinded study staff and their access to unblinded drug kit information
- To clarify permitted medications and procedures
- To clarify participation in optional substudy
- To remove electrocardiogram
- To remove urinalysis testing
- To add unscheduled visit guidance for AEs considered hypersensitivity or anaphylaxis, including complete blood count with differential, liver function test, ADA, and a photo to assess hypersensitivity reactions that result in a rash
- To change body temperature dosing criteria from 100.4°F to 101°F

- To remove from pharmacoeconomic measures the collection of sibling incidence of upper or lower tract respiratory infections
- To remove socioeconomic measures
- To clarify the definition of RSV LRTI
- To remove the primary endpoint of new onset of RSV positive respiratory illness while already in the hospital
- To remove the exploratory endpoint of RSV-associated symptoms
- To clarify the statistical analysis, including updating the primary endpoint analysis
- To clarify the final reporting of the results
- To clarify initiation of Part B and protocol amendments
- To modify the use of the toxicity grading scale
- To clarify that the IVRS/IWRS will assign blood collection schedule

CLINICAL STUDY PROTOCOL SYNOPSIS

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
Site Location	Global
Principal Investigator	
Primary Objectives	**Part A:** • To determine the pharmacokinetics (PK) of intramuscular (IM) administrations of REGN2222 **Part B:** • To demonstrate the efficacy of REGN2222 in preventing medically attended respiratory syncytial virus (RSV) infections (subjects with either RSV-confirmed hospitalizations or outpatient lower respiratory tract infection [LRTI])
Secondary Objectives	**Part A:** • To evaluate safety, tolerability, and immunogenicity of REGN2222 following IM administration **Part B:** • 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 visits[a] • To assess monthly serum levels of different dosing regimens of REGN2222 • To assess the immunogenicity of REGN2222 [a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric office visit, a primary physicianofficevisit,afamilyphysicianvisit,orastudysitevisit.

Exploratory Objectives	• To collect DNA for the prospective study of the association of host biomarkers with RSV infection and severity • To summarize the effect of REGN2222 on RSV-confirmed hospitalization, including the following: – Number of days on RSV mechanical ventilation – Number of days requiring supplemental oxygen • To assess the impact of REGN2222 on pharmacoeconomic outcomes (number of medical visits for RSV infection, total number of medical visits, associated medical interventions or treatments, number of missed days of work by the parent[s] or guardian[s] in association with each medically attended RSV event). • To detect and identify the presence of other common respiratory pathogens from RSV negative nose swab specimens collected from subjects.
Study Design	This is a Phase 3 study that will be conducted in 2 parts. Part A is an open-label, 1-cohort, multicenter PK study. Subjects in Part A may enroll anytime during the RSV season. 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 historic data on the timing and duration of the RSV season. PartA will assess the PK of REGN2222. Subjects will be assigned open-label treatment with a single dose of REGN2222 30 mg/kg during the RSV season. Of the 24 subjects that are planned to be enrolled in Part A, the first 3 subjects will be dosed at least 48 hours apart; safety data through at least Day 3 from the first 3 subjects will be reviewed by the investigators and the sponsor's medical monitor prior to subsequent dosing. The remaining 21 subjects may be dosed with no more than 10 subjects dosed on the same day. After obtaining informed consent from the parent(s) or legal guardian(s), subjects will be assessed for study eligibility at the screening visit. Subjects will undergo screening within 14 days prior to baseline (Day 1). Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 baseline assessments and will receive REGN2222 30 mg/kg (maximum 1 dose). Subjects will be monitored in the clinic for 3 hours after dosing, followed by discharge. An emergency phone number will be provided to parent(s) or guardian(s) who will also be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact the parent(s) or legal guardian(s) at the end of Day 1 to inquire about any change in the subject's status, the subject will return to the study site on Day 2 for Visit 3, and the study staff will contact the parent(s)orlegalguardian(s)onDay3toinquireaboutanychangeinthe

subject's status; this will provide at least daily contact for 48 hours after dosing. Any new signs or symptoms that have developed in the subject since the dose will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff. The end of study will occur 150 days after REGN2222 dose.

DoseSelectionforPartB: Enrollment in Part B will only start following the recommendation to do so by the independent data monitoring committee (IDMC), after the IDMC has reviewed at a minimum the Day 3 safety data of the first 18 subjects who were enrolled in Part A and received a single dose of REGN2222. Regeneron will confirm the dose for Part B. The dose will remain the same as that in part A if the PK data up to Day 57 (from subjects enrolled in Part A) are consistent with the predicted concentrations, after age and body weight corrections.

PartB will assess the efficacy, safety, and immunogenicity of REGN2222.

Subjects (n=1515) will be randomly assigned in a 1:1:1 ratio to 1 of 3 arms (REGN2222 30 mg/kg single dose [maximum 1 dose REGN2222 and 1 dose placebo], REGN2222 30 mg/kg Q8 weeks [maximum 2 doses], or placebo [maximum 2 doses]) and stratified by region (North America or rest of the world) and gestational age (≤31 weeks, 6 days GA or from 32 weeks, 0 days to 35 weeks, 6 days GA) in a multicenter, double-blind study.

Assessment of the primary and secondary clinical endpoints will only occur through Day 150. If a primary endpoint is reached during the study period, ongoing assessments will continue until the end of the study period. Any subject who has had a positive RT PCR RSV nasal swab result, either at the study central laboratory or at an outside institution in a CLIA-certified (or equivalent) laboratory, should not receive a second dose of study drug. The risk of a second RSV infection is reduced substantially (~70%) for 6 months after the first infection and this practice is also consistent with the 2014 American Academy of Pediatrics recommendations for palivizumab (Synagis®) prophylaxis. Subjects who have a RSV infection (positive RT-PCR RSV nasal swab result) will continue to be monitored for additional medically attended acute respiratory infections that may occur during the study period.

After the parent(s) or legal guardian(s) provide informed consent, the subject will be assessed for study eligibility at the screening visit. Subjects will undergo screening within 28 days prior to randomization. Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 baseline assessments and will be randomly assigned to a treatment arm. Subjects will be monitored in the clinic for at least 1 hour after dosing, followed by discharge, when appropriate.

The parent(s) or guardian(s) will be provided with an emergency phone numberandwillbegivenwrittenandverbalinstructionstocallwithany

change in the subject's status. In addition, the study staff will contact parent(s) or legal guardian(s) at the end of the day and daily over 48 hours to inquire about any change in the subject's status. Any new signs or symptoms that have developed in the subject since the last dose will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff. The end of study will occur approximately 180 days after the last dose.

During the study period, data will be collected on subjects with any acute respiratory illness requiring medical attention. After enrollment into the study, subjects taken by their parent(s) or guardian(s) to a healthcare provider (inpatient or outpatient, including emergency room [ER], urgent care [UC], or pediatric clinic visits) for any of the following symptoms will be asked to contact the study staff immediately or soon after seeking medical attention: fever, cough, earache, nasal congestion, rhinorrhea, vomiting after coughing, wheezing, and difficulty breathing (labored, rapid, or shallow). Study site personnel will evaluate the subject during an unscheduled visit within 72 hours or as soon as possible following discharge or the medical visit for respiratory infection. If the unscheduled study visit following a medically attended respiratory infection occurs more than 72 hours but within 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.

Evaluation will include a history of the acute illness. Nose swabs for viral detection will be conducted after the subject presents for medical attention (which may or may not be the study site). All nose swabs will be tested using reverse-transcriptase polymerase chain reaction (RT-PCR) assay for RSV, which will be conducted in a central laboratory. All RSV isolates will be subtyped.

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. For emergency and other visits to a medical facility other than the study site, medical records will be obtained by the investigator to gather information about treatments provided and use of concomitant medications or products.

It is recommended that site personnel contact the parent(s) or legal guardian(s) weekly between routine study visits, to obtain information about medically attended acute respiratory events and to remind the parent(s) or legal guardian(s) about the next scheduled study visit. Parent(s) or guardian(s) will be instructed to contact study personnel to report any abnormalities, including any hospitalizations or doctor visits, during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. The follow-up period for the occurrence of RSV-confirmed medical attention will continue throughDay150.Safety,laboratory,andotherclinicalassessmentswillbe

	performed at specified study visits, until end of study, as noted.
Study Duration	**Part A** This is a single dose study with a treatment and follow-up duration of 150 days from baseline. The total duration of study will be up to 164 days (14-day screening period, single dose, and 150-day follow-up period). **Part B:** This is a repeat dose study with a treatment and follow-up duration of 237 days. The total duration of study will be up to 265 days (28-day screening period, 57-day treatment period, and 180-day follow-up period).
Sample Size:	**Part A**: Approximately 24 infants will be enrolled **Part B:** Approximately 1515 infants will be enrolled
Target Population:	The study population will consist of healthy male and female infants who have a chronological age of ≤6 months at the time of first dose (ie, dosing on or before the subject's 6-month birthday), who have a GA no more than 35 weeks, 6 days, and who are not eligible, recommended for, nor have access to palivizumab by standard practice, local guidelines, or their healthcare provider.
Treatments	
Study Drug Dose/Route/Schedule **Formulation:**	REGN2222 will be supplied as a lyophilized power in a 20 mL glass vial. Each vial contains 265 mg of REGN2222. Upon reconstitution with 1.4 mL of sterile water for IM injection, the composition of the drug product is 150 mg/mL REGN2222.
Placebo	Placebo product will be supplied in vials that match the REGN2222 vial, but without the active protein.
Route:	IM injection
Treatment Dose Schedule:	**Part A:** • Approximately 24 subjects will receive REGN2222 30 mg/kg (maximum 1 dose) **Part B:** • Approximately 505 subjects will receive REGN2222 30 mg/kg on Day 1 (maximum 1 dose) and placebo on Day 57 (maximum 1 dose) • Approximately 505 subjects will receive REGN2222 30 mg/kg (Q8 weeks) on Day 1 and Day 57 (maximum 2 doses) • Approximately 505 subjects will receive placebo on Day 1 and Day 57 (maximum 2 doses)

Endpoints

Primary: The primary endpoints are:

Part A:

- Serum concentration of REGN2222 over time and other PK parameters

Part B:

- Proportion of subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the study period. A medically attended RSV infection 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 (ER, UC, or pediatric clinic visit[a] [for either a sick or well visit]) with RSV LRTI
    - [a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit
- 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

Secondary: The secondary endpoints are:

Part A:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Presence and titer of anti-REGN2222 antibodies

Part B:

- Proportion of subjects who have RSV-confirmed hospitalization, ER, UC, or pediatric clinic visits[a] (for upper or lower tract infections) during the study period.
- PK parameters using sparse sampling
- Presence and titer of anti-REGN2222 antibodies

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric

clinic visit, a primary physician office visit, a family physician visit, or a study site visit

Exploratory:

The exploratory endpoints are:

- Total number of RSV-associated medical visits (hospital, ER, UC, or pediatric visits[a]) for each subject and associated treatments or procedures at these visits
- Total number of medical visits (hospital, ER, UC, or pediatric visits[a]) for each subject and associated treatments or procedures at these visits, during the study period excluding the initial RSV-associated medical visits.

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.

- Number of RSV-confirmed hospitalizations (defined as stay in hospital [or its ER] for 24 hours or longer)
- Number of days with RSV-associated mechanical ventilation
- Number of days with RSV-associated supplemental oxygen
- Length of stay in hospital for RSV-associated illness
- Number of missed days of work for parent(s) or guardian(s) associated with each medically attended RSV event
- Number and proportion of subjects with other common respiratory pathogens identified by a RT-PCR multiplex respiratory panel which is distinct from the RT-PCR assay being used to test for RSV in the primary analyses of the primary and secondary efficacy endpoints.

  Note: Only nose swab specimens determined to be negative for RSV using the RT-PCR assay being utilized for evaluation of the study's efficacy endpoints will be evaluated by the RT-PCR multiplex respiratory panel. RSV positive samples identified by the RT-PCR multiplex respiratory panel will not be taken into account in the primary analyses of the primary and secondary efficacy endpoints.

Procedures and Assessments

Safety Procedures (Part A and Part B)

The safety of REGN2222 will be assessed by evaluating TEAEs, detailed medical history, physical examinations, vital signs, and clinical laboratory testing, as indicated. Concomitant medications and procedures will be collected from time of informed consent to the end of the study. Safety data willbereviewedonanongoingbasisbythesponsor.Anindependentdata

	monitoring committee will be established before study initiation and periodic review and recommendations will be provided to the sponsor regarding safety as specified in the charter. Blood samples will be collected for REGN2222 drug concentrations and antidrug antibody (ADA) levels at predetermined time points. Research samples and samples for exploratory biomarker analyses will also be collected from any remaining PK and ADA samples and will not require a separate blood draw or visit. **Efficacy Procedures (Part B only):** During the study period, efficacy data will be collected by recording all acute respiratory tract infections requiring medical attention that are RSV-confirmed. An RSV LRTI event 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), and/or wheezing or crackles. The RSV LRTI definition is used to assess the occurrence of outpatient or hospitalized visits for RSV that is attributable to RSV LRTIs. Data will be collected on all medical visits for RSV and any associated medications, treatments, or procedures associated with that visit.
Statistical Plan	**Sample Size** **For Part A:** The goal is to confirm infant PK and therefore no formal sample size calculation will be conducted. A total of 24 subjects will receive REGN2222 in Part A as this is considered a sufficient number of subjects to confirm PK parameters. **For Part B:** A total of 1515 subjects are planned to enroll in Part B. Subjects will be randomly assigned 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). There will be at least 90% power to detect the difference between either dose of REGN2222 and placebo using a chi-square test with continuity correction at 2-sided test alpha=0.025 for each comparison between treatment group and placebo assuming the following: a placebo incidence rate of the primary endpoint of 10% and an efficacy of REGN2222 of at least 60% in reducing the rate of the primary endpoint compared with placebo and 5% early dropout rate. Sample size may be re-estimated at the end of each RSV season. If the study is fully enrolled at that time, then the sample size will be re-estimated before database lock. Sample size re-estimation will be based on the blinded and pooled event rate and hypothesized treatment effect. The hypothesized treatment effect for each arm of REGN2222 will be a 60% reduction in event ratescomparedwiththeplaceboarm.Theblindedsamplesizere-estimation

does not affect type I error materially for binomially distributed data. The objective of this sample size re-estimation is to ensure that the study is adequately powered in case of a milder-than-expected RSV season, leading to low medically attended visits for RSV infection.

Statistical Analysis

Primary Efficacy Analyses for Part B: The primary endpoint will be analyzed using Mantel-Haenszel methods to assess the differences in the proportions between each REGN2222 treatment and placebo, stratifying 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).

Safety Analyses: Safety and tolerability will be descriptively summarized by treatment arms, including TEAEs, laboratory variables, vital signs, and physical examination.

For Part B, the analysis will be conducted in 2 steps. The first step analysis will be conducted as soon as the last randomized subject has completed the end of the 150-day efficacy assessment period and all the data have been collected and validated; this will consist of the final analysis of all efficacy endpoints. The safety analyses will be performed on all safety data collected and validated at the time of the first step analysis. The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect. Since all the efficacy measure data collection will have been concluded at the time of this first step analysis, the significance level for the study remains at 2-sided 0.05.

The second step analysis will be performed at the end of the study and will consist of the final analysis of the safety measures.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAP	American Academy of Pediatrics
AE	Adverse event
AESI	Adverse event of special interest
ADA	Antidrug antibody
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CLD	Chronic lung disease
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case report form (electronic)
CTCAE	Common Terminology Criteria for Adverse Events
ED	Effective dose
ER	Emergency room
ERC	Ethics review committee
FIH	First-in-human
GA	Gestational age
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive voice response system

IWRS	Interactive web response system
LRTI	Lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
PCSV	Potential clinical significant value
PK	Pharmacokinetic
PT	Preferred term
Q	every
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RSV	Respiratory syncytial virus
RT-PCR	Reverse-transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SMT	Safety monitoring team
SOC	System organ class
TEAE	Treatment-emergent adverse event
UC	Urgent care
URTI	Upper respiratory tract infection
US	United States
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Globally, respiratory syncytial virus (RSV) is the second leading cause of mortality in infants 1 month to 1 year of age and the most common viral cause of acute lower respiratory tract infection (LRTI) in children under 5 years of age (Lapillonne 2013). Respiratory syncytial virus illness can range from mild upper respiratory tract infection (URTI) to severe LRTI, including bronchiolitis and pneumonia. In the United States (US), compared with influenza, RSV is associated with a 9-fold greater risk for hospitalization (Iwane 2004) and approximately 9-fold higher mortality rate in infants less than 1 year of age (Thompson 2003). Furthermore, RSV disease in early infancy may also predispose children to reactive airway disease in early childhood (American Academy of Pediatrics 2009, Ambrose 2014, Blanken 2013, Yoshihara 2013).

Passive immunoprophylaxis with an RSV neutralizing antibody is a safe and effective approach for reducing RSV-related hospitalizations in infants and has been in use for almost 2 decades. Palivizumab (commercially available as Synagis®), a humanized monoclonal antibody, is the only RSV preventive agent currently available. When given monthly for 5 months during the RSV season, Synagis resulted in a 55% reduction in RSV-related hospitalizations in premature infants with and without chronic lung disease (CLD) compared with placebo (Palivizumab 1998).

Despite the efficacy and excellent safety record of palivizumab, the majority of infants at risk for severe RSV do not receive palivizumab (Hall 2013). While palivizumab is indicated for the broader population of high-risk children for the prevention of serious RSV lower respiratory tract disease, the American Academy of Pediatrics (AAP) and other pediatric society position statements recommends restricting its use to only infants at the highest-risk category due to the high cost of palivizumab (Hall 2013, Robinson 2011). In the US, these highest-risk infants include premature infants who are less than 29 weeks gestational age (GA) and infants with CLD or congenital heart disease during their first year of life (AAPCID 2014). However, infants who are at least 29 weeks GA, including full-term infants, are also at high risk for severe RSV infection (Hall 2013). This burden of RSV infection in all young infants has kept RSV vaccine development a high priority for the past 50 years, although there is still no licensed RSV vaccine available. There remain many challenges in the development of a RSV vaccine for use in infants, including an immature immune system (Anderson 2013, American Academy of Pediatrics 2009).

The purpose of this study is to demonstrate the safety, efficacy, pharmacokinetics (PK), and immunogenicity of REGN2222, a new fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against the RSV fusion glycoprotein in infants born no more than 35 weeks 6 days GA, who are no more than 6 months of age during the RSV season in their respective geographic location. In order to optimize the potential benefit in this vulnerable population, we will conduct this study during the RSV season using dosing regimens that are expected to be effective.

In a first-in-human (FIH) study (R2222-HV-1326) in 132 healthy adults 110 adults were evaluated for safety and tolerability of REGN2222 delivered intravenously and intramuscularly

compared to placebo. The doses studied in the FIH study included a 3 mg/kg intravenous (IV) (maximum 1 dose), 10 mg/kg IV (maximum 1 dose), 30 mg/kg IV Q4 (every 4) weeks (maximum 2 doses), 3 mg/kg intramuscular (IM) Q4 weeks (maximum 2 doses), and 10 mg/kg IM Q4 weeks (maximum 2 doses). REGN2222 was generally well-tolerated at all evaluated doses. There were no serious adverse events (SAEs) or dose-limiting toxicities. The observed treatment-emergent immunogenicity (antidrug antibody [ADA] formation) in 2 subjects was transient and not associated with any adverse events (AEs).

1.2. Rationale

1.2.1. Rationale for Study Design

This is a 2-part study.

Part A is an open-label PK study of REGN2222 to determine the PK in preterm infants after a single dose to enable the selection of dosing regimens for Part B. It will also provide initial evaluation of safety and tolerability in infants. Because the primary goal of Part A is to determine the PK in infants for REGN2222 and not for efficacy, a placebo cohort and blinding of treatment are not required. At a dose of 30 mg/kg of REGN2222, it is expected that protection will be provided to the majority of infants during the RSV season.

Part B is a randomized, double-blind, placebo-controlled, study designed to evaluate efficacy, safety, monthly serum concentration of REGN2222, and immunogenicity of IM administration of REGN2222 in preterm infants who are not eligible, recommended, nor is access to palivizumab available. 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 study design is optimal for evaluating safety, efficacy, PK, and immunogenicity of 2 different dosing regimens of REGN2222 (sample size is further described in Section 9.2). 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.

1.2.2. Rationale for Dose Selection

1.2.2.1. Part A: Pharmacokinetics and Safety of REGN2222

The study drug REGN2222 will be administered as a single dose of 30 mg/kg IM (Figure 1). This dose has been selected based on the safety profile established in nonclinical safety studies and results from the FIH study (R2222-HV-1326) in normal healthy adult subjects.

Nonclinical safety studies in cynomolgus monkeys have shown REGN2222 to be well tolerated at IV, IM, and subcutaneous doses up to 100 mg/kg every week with no observed adverse effect level for 10 weeks. In the FIH study, single and multiple administration of REGN2222 with up to 30 mg/kg for IV doses and 10 mg/kg for IM doses have been well tolerated in a healthy population of adults (132 total; 110 exposed to REGN2222) with no study drug-associated SAEs or drug-limiting toxicities.

For the FIH adult study, PK analyses indicate linear dose proportional kinetics with a relatively long half-life (mean up to 36 days) in healthy adult volunteers. It is expected that dosing regimens of REGN2222 at 30 mg/kg IM dosed Q8 weeks or a 30 mg/kg IM single dose will maintain serum levels similar to the serum levels of REGN2222 in cotton rat experiments that were associated with a 2-log (or 99%) reduction in RSV viral titer in the lung for subtype A (5 µg/mL) and subtype B (27 µg/mL) for most of the RSV season. This serum level is attained at an effective dose (ED) to attain a 99% reduction in lung RSV viral titer, hereafter referred to as ED_{99}. Final dose regimens used in Part B will be informed based on additional safety and PK data from Part A of this study. Alternative dose regimens for Part B may be selected if the PK parameters of REGN2222 observed in infants are significantly different than the one estimated from adult PK data. A dose higher than 30 mg/kg is not included in this study because, as currently formulated, it would require more than 2 simultaneous IM injections in some larger infants.

1.2.2.2. Part B: Safety, Efficacy, and Immunogenicity of 2 Dosing Regimens of REGN2222

Two dosing regimens will be assessed in Part B. The planned regimens are REGN2222 30 mg/kg single dose (maximum 1 dose) and REGN2222 30 mg/kg, Q8 weeks (maximum 2 doses) (Figure 2). However, following evaluation of the PK data from infants studied in Part A, an adjustment to dose level may be implemented (Appendix B).

The currently proposed dose (30 mg/kg) for Part B is proposed based on modeling of available PK data from adults to predict exposure in infants. The prediction will be re-evaluated when complete data are available from the adult study and initial data are available from infants in Part A. If the PK parameters indicate exposure significantly exceeds prediction from the model, a lower dose (eg, 20 mg/kg) will be used in Part B instead of 30 mg/kg.

1.3. Benefit/Risk Assessment

REGN2222, a human IgG1 monoclonal antibody targeting RSV-F, is being developed for use as passive immunization for the prevention of LRTI caused by RSV in infants. REGN2222 may provide a more convenient dosing regimen (less frequent than monthly dosing of palivizumab) to justify use in the larger population of at-risk infants including late preterm and full-term infants, who are not eligible, recommended, nor is access available to prophylaxis according to local standard of care.

There are no identified risks for REGN2222 based on clinical experience to date. [redacted]

The following list of potential risks considered was based on known risks associated with other monoclonal antibodies with a similar mechanism of action, preclinical/toxicology data, as well as risks associated with monoclonal antibody therapies in general, such as changes in salivation, hypersensitivity reactions, and immunogenicity (antidrug antibody formation). The treatment-emergent adverse events (TEAEs) in the FIH adult study described above that were associated with the potential risks of changes in salivation or hypersensitivity reactions were

generally mild and easily manageable. In the IM cohorts, no acute systemic injection reaction TEAEs and no local injection site reaction TEAEs were observed. The observed treatment-emergent immunogenicity (ADA formation) in 2 subjects was transient, and not associated with any AEs. The complete description of previous human experience, potential risks, and monitoring and mitigation strategies for those risks is found in the Investigator's Brochure.

In the current infant study, appropriate exclusion criteria, close monitoring of the subjects, and periodic review of safety data will be performed to minimize and manage the potential risks to the infants. An Independent Data Monitoring Committee (IDMC) is in place to further support the protection of subjects. The safety data available to date and safety precautions that will be taken by the sponsor support the potential benefit of REGN2222 in these infants and continued development of this compound.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Part A:

- To determine the PK of IM administration of REGN2222

Part B:

- To demonstrate the efficacy of REGN2222 in preventing medically attended RSV infections (subjects with either RSV-confirmed hospitalizations or outpatient LRTI)

2.2. Secondary Objectives

Part A:

- To evaluate safety, tolerability, and immunogenicity of REGN2222 following IM administration

Part B:

- 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 visits[a]
- To assess monthly serum levels of different dosing regimens of REGN2222
- To assess immunogenicity of REGN2222

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.

2.3. Exploratory Objectives

The following items were considered exploratory objectives:

- To collect DNA for the prospective study of the association of host biomarkers with RSV infection and severity
- To summarize the effect of REGN2222 on RSV-confirmed hospitalization, including the following:
  - Number of days on RSV mechanical ventilation
  - Number of days requiring supplemental oxygen
- To assess the impact of REGN2222 on pharmacoeconomic outcomes (number of medical visits for RSV infection, total number of medical visits, associated medical interventions or treatments, number of missed days of work by the parent[s] or guardian[s] in association with each medically attended RSV event).
- To detect and identify the presence of other common respiratory pathogens from RSV negative nose swab specimens collected from subjects.

3. STUDY DESIGN

3.1. Study Description and Duration

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

Part A is an open-label, single cohort, multicenter, PK study. Subjects in Part A may enroll any time during the RSV season.

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.

Subjects who complete this study may be eligible to enroll in a subsequent extension study in which they will be monitored for medically attended episodes of wheezing over a 12 month period.

3.1.1. Part A: Pharmacokinetics and Safety of 1 Dose Regimen of REGN2222

Part A will assess the PK as well as initial safety and tolerability of REGN2222 in infants. Blood will be drawn for the purpose of determining the PK or REGN2222.

Subjects will be assigned open-label treatment with a single dose of REGN2222 30 mg/kg during the RSV season. Of the 24 subjects that are planned to be enrolled in Part A, the first 3 subjects will be dosed at least 48 hours apart; safety data through at least Day 3 from the first 3 subjects will be reviewed by the investigators and the sponsor's medical monitor prior to subsequent dosing. After this review, the remaining 21 subjects may be dosed with no more than 10 subjects dosed on the same day. Subjects will have maximum study duration of 150 days from baseline.

After the parent(s) or legal guardian(s) provide informed consent, subjects will be assessed for study eligibility at the screening visit. In Part A, subjects will complete screening within 14 days prior to baseline (Day 1). Subjects who continue to meet eligibility criteria at baseline will undergo Day 1 baseline assessments and will receive a single dose of REGN2222 30 mg/kg IM (maximum 1 dose). Subjects will be monitored in the clinic for 3 hours after dosing, followed by a physical examination, and when appropriate, discharge.

The parent(s) or guardian(s) will be provided with an emergency phone number and will be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact the parent(s) or legal guardian(s) at the end of Day 1 to inquire about any change in the subject's status, the subject will return to the study site on Day 2 for Visit 3, and the study staff will contact the parent(s) or legal guardian(s) on Day 3 to inquire about any change in the subject's status; this will provide at least daily contact for 48 hours after dosing. Any new signs or symptoms that have developed in the subject since being dosed will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff.

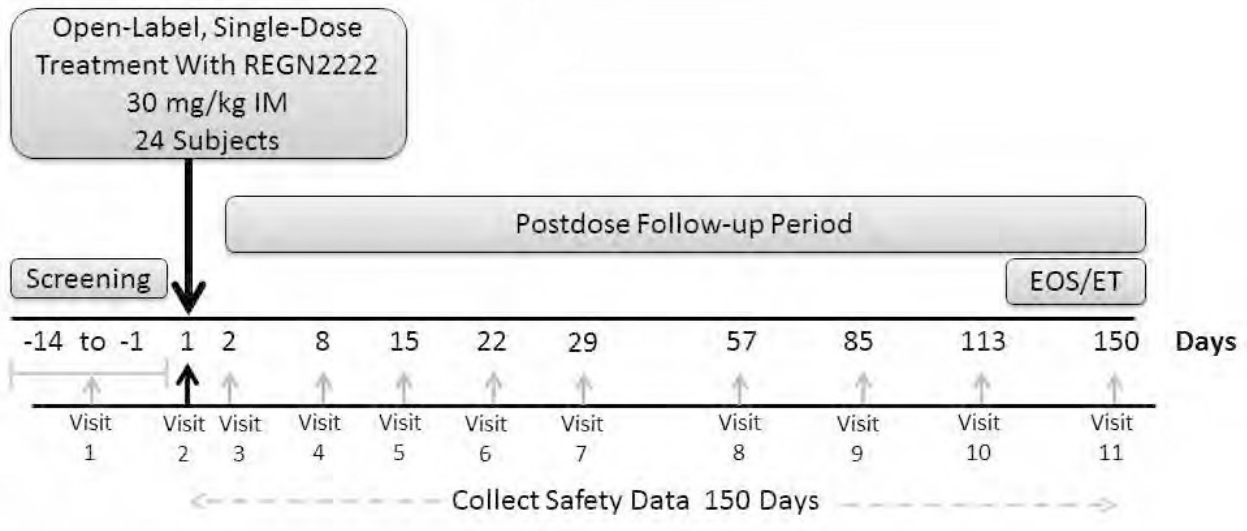
The total duration of the study will be up to 164 days (14-day screening period, a single dose treatment period, and 150-day follow-up period). An interim PK analysis will be conducted on the first 18 infants after at least 1 blood sample is collected for determination of drug concentration following administration of study drug. At study completion, a final PK analysis will be conducted on all infants enrolled in Part A, who have at least 1 blood sample collected. Serious adverse event collection may extend for 30 days past the EOS, as described in Section 7.2.2.

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.

See Section 6.1 for a schedule of study assessments.

The dose cohort for Part A is depicted in Figure 1 for REGN2222 30 mg/kg.

Figure 1: Part A: 30 mg/kg Single Dose (Maximum 1 Dose REGN2222)



EOS=end of study; ET=early termination; IM=intramuscular
Note: The screening visit will occur from Day -14 to Day -1. Black arrow denotes dosing visit. At Visit 2, subjects will be monitored on site for 3 hours after dosing. Grey arrows denote study visits at which dosing does not occur. If a subject does not have a blood draw scheduled at Visit 4, Visit 5, or Visit 6, then the visit will be conducted by telephone. Serious adverse event collection may extend for 30 days past the EOS, as described in Section 7.2.2

3.1.2. Part B: Efficacy, Safety, and Immunogenicity of 2 Dose Regimens of REGN2222

Enrollment of Part B will only start following the recommendation to do so by the IDMC, after the IDMC has reviewed, at a minimum, the Day 3 safety data of the first 18 subjects who were enrolled in Part A and received a single dose of REGN2222.

Regeneron will confirm the dose for Part B. The dose will remain the same as that in part A if the PK data up to Day 57 (from subjects enrolled in Part A) are consistent with the predicted concentrations, after age and body weight corrections, as defined in Appendix B.

The decision to proceed from Part A to Part B, along with the confirmation of the dose regimens to be used in Part B, will be communicated in writing to the investigators, Ethics Committees and the competent authorities (Section 13.4) by the sponsor. Part B will be initiated based on the written communication prior to formally amending the protocol for the purpose of altering the dose, if applicable.

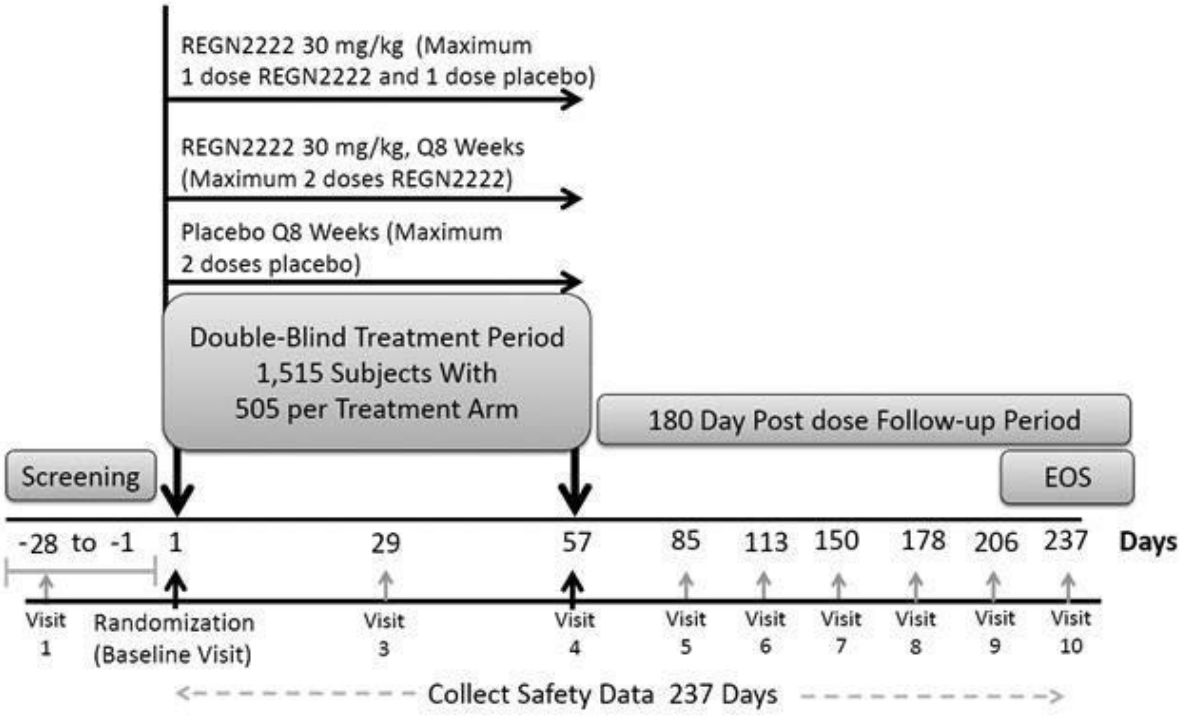
3.1.2.1. Randomization and Stratification for Part B

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 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).

3.1.2.2. Dose Selection for Part B

Two dosing regimens of REGN2222 will be assessed in Part B (Section 1.2.2.2). The treatment arms for Part B are depicted in Figure 2. The placebo arm will include a maximum of 2 doses of placebo.

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



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.

3.1.2.3. Study Enrollment and Assessments

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 at the screening visit. Subjects will undergo screening within 28 days prior to randomization. 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 (maximum 1 dose REGN2222 and 1 dose placebo), REGN2222 30 mg/kg Q8 weeks (maximum 2 doses of REGN2222), or placebo (maximum 2 doses of placebo). Subjects will be monitored in the clinic for at least 1 hour after dosing, followed by discharge, when appropriate.

The parent(s) or guardian(s) will be provided with an emergency phone number and will be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact the parent(s) or legal guardian(s) at the end of the day and daily over

48 hours to inquire about any change in the subject's status. Any new signs or symptoms that have developed in the subject since the last dose will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff.

It is recommended that site personnel contact the parent(s) or legal guardian(s) weekly between routine study visits, to obtain information about medically attended acute respiratory events and to remind the parent(s) or legal guardian(s) about the next scheduled study visit. Parent(s) or guardian(s) will be instructed to contact study personnel to report any abnormalities, including any hospitalizations or doctor visits, during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. The follow-up period for the occurrence of RSV-confirmed medical attention will continue until the end of the 150 day study period.

In Part B, assessment of the primary and secondary clinical endpoints (Section 8.2 and Section 8.3 for endpoints) will only occur during the 150 day study period. Any RSV infection occurring after Day 150 will not be included in the efficacy evaluation. If a primary endpoint is reached during the study period (Section 8.2), ongoing assessments for other endpoints and measurements will continue until the end of the study period. Any subject who has had a positive RT-PCR RSV nasal swab result, either at the study central laboratory or at an outside institution in a Clinical Laboratory Improvement Amendments (CLIA)-certified (or equivalent) laboratory, should not receive a second dose of study drug. The risk of a second RSV infection is substantially (~70%) reduced for 6 months after the first infection and this practice is consistent with recommendations in the 2014 AAP guidelines for palivizumab prophylaxis (Ohuma 2012). 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.

All subjects will be monitored for safety until the end of the study at Day 237. Safety monitoring after Day 150 through Day 237 (end of study) 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. The schedules of events are provided in Section 6.1. Subjects who complete Day 150 may be eligible to enroll in a subsequent extension study in which they will be monitored for medically attended episodes of wheezing over a 12-month period.

The end of study will be approximately 180 days after the last dose or approximately 237 days after the first dose, whichever is longer.

3.1.2.4. Onstudy Potential Respiratory Illness and the Medical Information Packet

During the 150-day efficacy assessment period, data will be collected on subjects with any acute respiratory illness requiring medical attention. After enrollment into the study, subjects taken by their parent(s) or guardian(s) to a healthcare provider (inpatient or outpatient, including hospitalizations, ER, UC, or pediatric clinic) for any of the following symptoms will be asked to contact the study staff immediately or soon after seeking medical attention: fever, cough,

earache, nasal congestion, rhinorrhea, vomiting after coughing, wheezing, and 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. The Medical Information Packet will include important information regarding a potential acute respiratory infection, including information about this clinical trial and a checklist to provide guidance for the healthcare provider in documenting specific signs and symptoms related to the respiratory illness into the medical chart. The Medical Information Packet will be provided to the parents at randomization (Visit 2) (Table 2).

All infants who have a medically attended visit for a respiratory illness will be asked to have an unscheduled study visit (Section 6.2.3) as soon as possible or within 72 hours of discharge from the medical facility. Parents/guardians will be instructed to provide the Medical Informational Packet containing the contact information of the treating healthcare provider to study staff during the unscheduled visit. Medical records will be obtained by the investigator to gather information about LRTI symptoms, as outlined in the checklist; treatments provided; and concomitant medications or products.

Study site personnel will evaluate the subject during an unscheduled visit as soon as possible or within 72 hours after receipt of medical attention. Evaluation will include 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 subtyped. 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. If the child has had an RSV-confirmed medically attended visit, nose swab collection will be required at the unscheduled study visit. 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 Day 151 and Day 237 (end of study) for the purpose of nose swab collection.

A new Medical Information Packet will be provided to the parent(s) or guardian(s) following each potential medically attended respiratory illness visit.

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.

3.1.2.5. Optional Substudy

An optional substudy is to collect a cheek swab from subjects for DNA for future use for the purpose of discovery of predictive biomarkers. See Section 6.1 for a schedule of study assessments.

3.2. Study Stopping Rules

If the following are observed, the study will be temporarily halted (screening, randomization, dosing of study drug) by the sponsor:

- Two similar (by preferred term [PT]) treatment-related Grade 3 SAEs that are not generally reported in the preterm population; or
- One treatment-related Grade 4 SAE that is not generally reported in the preterm population.

In order to assess whether these SAEs are in the treatment arms, only unblinded study members and/or the IDMC will make the assessment for the need to halt the study. The sponsor will follow the relevant regulatory requirements for reporting of SAEs to regulatory authorities and ethics committees and the data will be submitted to the appropriate authorities as required. A full evaluation will be conducted to determine if it is appropriate to continue the study. In the event the study will be restarted, local regulatory procedures will apply.

Generally reported AEs in the preterm population include but are not limited to: hypothermia, hypoglycemia, respiratory distress, apnea (with or without bradycardia), hyperbilirubinemia, feeding difficulties, poor weight gain, dehydration, respiratory disorders (including bronchiolitis), gastrointestinal disorders, and sudden infant death syndrome.

3.2.1. End of Study Definition

The end of study will be approximately 180 days after the last dose or approximately 237 days after the first dose, whichever is longer.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An IDMC, composed of members who are independent from the sponsor and the investigators, will monitor subject safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the subjects enrolled in the study. The IDMC will also recommend any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

3.3.2. Safety Monitoring Team

A cross-functional safety monitoring team (SMT) at Regeneron Pharmaceuticals, Inc. (Regeneron) will meet periodically to review blinded safety data. These data will include, but may not be limited to:

- TEAEs that result in an early study withdrawal

- SAEs
- Selected laboratory test results
- Additional AEs of interest, as determined by the SMT

Any signals identified through this review will be investigated and monitored. The SMT will propose risk management/mitigation activities as needed and will monitor their impact.

3.3.3. Endpoint Adjudication Committee

An adjudication committee will be formed before database lock, to address any categorization of a medically attended respiratory illness event as an endpoint that is unclear. Source documentation will be provided to a blinded adjudication committee for categorization. In addition, any subject deaths occurring after the administration of the first dose of study drug and prior to Day 150 will be assessed to determine their association with RSV.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF SUBJECTS

4.1. Number of Subjects Planned

A total of 1539 subjects are planned to be enrolled, as follows:

- Part A: Single cohort study with approximately 24 subjects planned to receive REGN2222
- Part B: 3-arm study with approximately 505 subjects planned in each of the 3 treatment arms for a total of 1515 subjects (1010 to receive REGN2222 [505 subjects in each of the 2 REGN2222 arms]; 505 to receive placebo)

This study will be conducted at multiple sites in the US, Canada, Australia, and New Zealand, as well as several countries in Europe. Additional countries/regions may be added.

The study population will consist of healthy male and female infants who have a chronological age of ≤6 months at the time of first dose (ie, dosing on or before the subject's 6-month birthday), who have a GA no more than 35 weeks, 6 days, and who are not eligible, recommended, nor have access to receive palivizumab by standard practice, local guidelines, or their healthcare provider.

4.1.1. Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in the study:

1. Preterm, otherwise healthy male or female infant who has a chronological age of ≤6 months of age at the time of the first dose (ie, infant must receive the first dose on or before the subject's 6-month birthday)
2. Gestational age at birth is no more than 35 weeks, 6 days
3. Parent(s) or legal guardian(s) of the infant is able to understand the study requirements, willing to provide informed consent, and legally able to provide informed consent.

4.1.2. Exclusion Criteria

4.1.2.1. Exclusion Criteria for the Infant

An infant who meets any of the following criteria will be excluded from the study:

1. Eligible, recommended, and have access to receive palivizumab per AAP or other local guidelines, standard practice, or by their healthcare provider
2. Diagnosis of CLD defined as requirement of supplemental oxygen for at least 28 days (cumulative) after birth; exceptions are infants who have received supplemental oxygen as standard of care for reasons other than CLD.
3. Known hemodynamically significant congenital heart disease
4. Known immunodeficiency, neuromuscular disease, or congenital abnormalities of the airway
5. Known renal or hepatic dysfunction
6. Serum creatinine, bilirubin, alkaline phosphatase hepatic enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) total that is >1.1 times the upper limit of normal for gestational age and chronological age (Appendix G). Exceptions are if the investigator has evidence that increased alkaline phosphatase corresponds to normal bone growth of preterm infancy, if the investigator has evidence that increased indirect bilirubin corresponds to a Gilbert's-type syndrome, or that it corresponds to an increase in bilirubin due to physiological jaundice, breastfeeding jaundice, or other conditions commonly found in otherwise healthy preterm infants and neonates).
7. Any other laboratory findings showing evidence of organ dysfunction or any clinically significant deviation from the normal range for gestational age and chronological age, as decided by the investigator at the screening visit
8. Use of any concomitant medications within 30 days of the screening visit, including prescription medications (exceptions are those used as standard of care, such as antibiotics, topical analgesic for blood draws [not to be used for IM injections, including vaccines], nutritional supplements, medications for gastroesophageal reflux, topical medications, and eye drops), and over-the-counter medications (except for vitamin supplements, ibuprofen, acetaminophen, or topical creams)
9. Vaccine or other IM drug administration within 2 days before or after dosing of the study drug
10. History of hospitalization prior to screening; exceptions include hospitalization for delivery and the subsequent stay for preterm infants; uncomplicated or elective surgeries (eg, circumcision, repairs of uncomplicated hernia without sequelae).
11. Life expectancy of <6 months
12. Major congenital malformations, including congenital cleft palate, cytogenetic abnormalities, or serious chronic disorders
13. Known or suspected impairment of immunological functions or autoimmune diseases

14. History of anaphylaxis
15. History of a seizure disorder
16. Previously received palivizumab, IV gamma globulin, or any other investigational RSV prophylaxis or vaccine product
17. Previous allergic reaction to IV immunoglobulin, blood products or other foreign proteins, such as vaccines and monoclonal antibodies, or any of the components of the investigational product formulation
18. Participation in any clinical research study evaluating another investigational drug or therapy that is inconsistent with current standard of care within at least 5 half-lives of the investigational drug prior to the screening visit

4.1.2.2. Exclusion Criteria for the Mother

An infant will be excluded from the study if the biological mother meets any of the following criteria:

1. Is younger than 16 years old or is unable to legally provide informed consent at the time of screening of the infant
2. Has self-reported history of illicit drug or alcohol abuse during pregnancy with the infant
3. Has self-reported or confirmed history of human immunodeficiency virus or hepatitis B
4. Has self-reported history of receiving an investigational RSV vaccine

4.2. Premature Withdrawal From the Study

The parent(s) or legal guardian(s) of a subject has the right to withdraw the subject from the study at any time, for any reason, and without repercussions to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The reason for subjects not completing the study will be recorded by the investigator on the relevant page of the case report form (CRF).

The investigator and sponsor have the right to withdraw a subject from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

For subjects who fail to return for assessments, the study site will make every attempt to contact the parent(s) or legal guardian(s) to have them comply with the protocol. A minimum of 3 telephone call attempts should be documented on different days over the course of 14 days following a missed assessment.

A subject who withdraws from the study with an ongoing AE or SAE must be followed until it is resolved or deemed stable. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures. All study assessments are specified in the schedule of study assessments, Section 6.1.

4.3. Replacement of Subjects

Subjects prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

REGN2222 drug product will be supplied as a lyophilized powder in a 20 mL glass vial. Each vial contains 265 mg of REGN2222. Upon reconstitution with 1.4 mL of sterile water for IM injection, the composition of the drug product is 150 mg/mL REGN2222.

Placebo product will be supplied in vials that match the REGN2222 drug product, but will not contain the active protein. Instructions on dosing preparation are provided in the pharmacy manual.

During the screening period, the subject will be evaluated within 2 weeks (from Day -14 to Day -1) in Part A and within 4 weeks (from Day -28 to Day -1) in Part B, prior to receiving any study drug. On Day 1 (baseline), all subjects will be assigned and administered the first dose of study drug.

- In Part A, subjects will be open-label assigned to a single cohort (Section 5.4.1)
- In Part B, subjects will be randomly assigned to 1 of 3 treatment arms (Section 5.4.2)

5.2. Dose Modification and Study Drug Discontinuation Rules

5.2.1. Dose Modification

Dose modification for an individual subject is not allowed in Part A or Part B.

5.2.2. Study Drug Discontinuation

For Part A or Part B, subjects who permanently discontinue from study drug and who do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Subjects who withdraw from the study will be asked to complete study assessments, as specified in Section 6.1.

5.2.2.1. Reasons for Permanent Discontinuation of Study Drug

Part A consists of only 1 dose.

Part B: Study drug dosing in individual subjects will be permanently stopped for any of the following reasons:

- The infant experiences acute systemic injection reactions with AEs including, but not limited to, anaphylaxis, laryngeal/pharyngeal edema, severe bronchospasm, seizure, or severe hypotension
- The infant experiences a Grade 3 or greater drug-related AE

- The infant has an RSV-positive RT-PCR result at the study central laboratory or a CLIA (or equivalent) certified laboratory after receipt of the first dose of study drug, but prior to the second dose of study drug.
- The parent(s) or legal guardian(s) of a subject withdraws consent
- A decision is made by the sponsor to stop treating an individual subject with study drug
- A decision is made by the sponsor to stop the study (Section 3.2)

5.2.2.2. Reasons for Temporary Discontinuation of Study Drug

For Part B only: The investigator may temporarily discontinue study drug dosing at any time, even without consultation with the medical monitor, if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the medical monitor should be contacted as soon as possible in any case of temporary or permanent study drug discontinuation. Resumption of study drug requires consultation and agreement between the investigator and the medical monitor.

5.3. Management of Injection Site Reactions

In both Part A and Part B, injection site reactions will be managed according to the type of reaction.

5.3.1. Acute Systemic Injection Reactions

Acute systemic injection reactions are AEs that occur during the IM injection of study drug or within 2 hours after the injection is completed. Emergency equipment and medication for the treatment of these potential AEs (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Study personnel must be trained to recognize and treat anaphylaxis. If generalized urticaria, wheezing, hypotension, or anaphylaxis occurs, dosing should be discontinued immediately, and treatment will be given for severe symptoms as medically indicated in an appropriate timeframe based on symptom severity.

An acute systemic reaction after injection must be reported as an AE of special interest (AESI) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 criteria for grading allergic reactions and anaphylaxis (Appendix D). Management of acute hypersensitivity reactions is addressed in Section 5.3.3.

5.3.2. Delayed Onset Reactions

A delayed onset reaction (defined as a reaction that occurs from 2 hours to 48 hours after IM injection), which is considered an allergic or hypersensitivity reaction, must be reported as an AESI (Section 7.2.4.2) and graded according to the CTCAE Version 4.0 criteria for grading allergic reactions and anaphylaxis (Appendix D), if the AE is considered to be allergic in nature.

Management of delayed hypersensitivity reactions is addressed in Section 5.3.3.

For delayed injection site reactions that are not considered to be allergic or hypersensitivity reactions, refer to Section 5.3.4.

5.3.3. Hypersensitivity Reactions

Hypersensitivity reactions must be reported as AESIs (Section 7.2.4.2) and graded according to the CTCAE Version 4.0 criteria for grading allergic reactions and anaphylaxis (Appendix D).

Any reaction that is suspected to be a hypersensitivity reaction requires a complete AE work-up and the following additional procedures (Table 4):

- Complete blood count with differential
- Liver function test
- ADA testing
- Photographic documentation of the rash, if present

5.3.4. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to the Modified Toxicity Grading Scale from Division of AIDS for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0, December 2014; Division of AIDS).

5.4. Method of Treatment Assignment

5.4.1. Part A: Open-label Treatment with 30 mg/kg IM (Maximum 1 Dose)

In Part A, subjects will be assigned through the interactive voice response system (IVRS; or interactive web response system [IWRS]) to receive a single dose of open-label REGN2222.

Part A is open-label and there will be no blinding.

5.4.2. Part B: Randomized Treatment with 30 mg/kg (1 Dose REGN2222 and 1 Dose Placebo); or 30 mg/kg IM (2 Doses REGN2222); or Placebo IM (Maximum 2 Doses)

In Part B, a total 1515 subjects will be randomly assigned in a 1:1:1 ratio through the IVRS/IWRS to 2 dosing regimens or placebo (505 subjects in each arm for a total of 1010 subjects assigned to receive REGN2222 [505 subjects in each of the 2 REGN2222 arms] and 505 subjects to receive placebo). Randomization in Part B 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).

An independent randomization team will create the actual randomization schedule and deliver it to the IVRS/IWRS. The randomization schedule is computer-generated using block randomization, 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).

5.4.2.1. Blinding

The parent(s) or guardian(s) of study subjects, the principal investigators, and study site personnel will remain blinded to all subject assignments throughout the study. The sponsor's study director, medical monitor, study monitor, and any other sponsor and contract research

organization personnel who are in regular contact with the study site will remain blinded to all subject assignments.

For Part B, a pharmacist (or other qualified individual) will be unblinded at each site. All unblinded personnel must be appropriately trained to ensure they understand their responsibilities to maintain the blind.

Selected individuals not involved in the conduct of the study may have access to unblinded data as needed for safety review or other data review.

Unblinded (open-label) study drug will be prepared and blinded by the study pharmacist(s)/designee according to the pharmacy manual.

Antidrug antibody results will not be communicated to the sites, and the sponsor's operational team will not have access to results associated with subject identification until after the final database lock.

No study personnel involved in the day-to-day conduct of the study will have access to unblinded data before the database is locked for this study.

While the study is ongoing, it is anticipated that unblinded data, after the first step analysis (Section 9.5.6.1), may be submitted to health authorities. Sponsor representatives who will conduct and review such data analyses for submission to the health authorities will not be part of the study operational team from that point forward, and subject level results will not be provided to the study sites. The analysis process, the measures used to protect the blind and the integrity of the study, and a communication plan and confidentially agreement will be described in a separate document.

5.4.2.2. Emergency Unblinding

Unblinding of treatment assignment for a subject may be necessary due to a medical emergency and other significant medical event or for expedited reporting.

If unblinding is required at the site:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected subject will be unblinded.
- The designated study pharmacist(s) (designee) at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist (or designee) available, the investigator for the site will unblind the subject, using the IVRS/IWRS.
- The investigator will notify the sponsor (designee) before unblinding the subject, whenever possible.

The treatment assignment is not to be provided to site personnel, including the investigator, at any time during the conduct of the study, except in the case of a true emergency.

For individual cases, serious, related (as assessed by investigator and/or company) and unlisted events, pharmacovigilance (designee) will unblind the treatment assignment before reporting to the health authorities. Based on Section 3.3, Section 7.4, and the IDMC charter, the IDMC may also be unblinded as part of the safety review.

5.5. Treatment Logistics and Accountability

5.5.1. Packaging, Labeling, and Storage

A medication numbering system will be used in labeling unblinded investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, these lists will not be accessible to individuals involved in study conduct.

Study drug will be stored at the site [redacted]; storage instructions will be provided in the pharmacy manual.

5.5.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] to the investigator (designee) at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor (designee).

5.5.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, study medication dispensed to each subject, and whether disposed of at the site or returned to the sponsor (designee).

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.5.4. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.6. Concomitant Medications and Procedures

Any treatment administered from the time of the first dose of study drug to the end of study/early termination visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study. Medication considered necessary for the subject's safety and well-being may be given at the discretion of the investigator and recorded. For all concomitant medications, the date, reason given, and dose will be recorded in the CRF.

5.6.1. Prohibited Medications and Procedures

The use of any concomitant medications within 30 days of the screening visit, including prescription medications (except those used as standard of care, such as antibiotics, topical analgesic for blood draws [not to be used for IM injections, including vaccines], nutritional supplements, medications for gastroesophageal reflux, topical medications, and eye drops) and

over-the-counter medications (except for vitamin supplements, ibuprofen, acetaminophen, and topical creams) is prohibited. No vaccinations will be administered within 2 days before or after dosing of the study drug.

5.6.2. Permitted Medications and Procedures

Nutritional supplements (including over-the-counter vitamin supplements), standard of care treatments such as antibiotics, medicines for gastroesophageal reflux, eye drops, ibuprofen, acetaminophen, topical analgesic for blood draws (not to be used for IM injections, including vaccines), topical medications, and topical creams, are permitted.

Routine vaccinations will be allowed. For further information regarding vaccination criteria, see Section 4.1.2.1, exclusion criteria # 9.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

The schedules of events are provided as follows:

- Part A: 30 mg/kg IM single dose (maximum 1 dose REGN2222) in Table 1
- Part B:
  - 30 mg/kg IM single dose (maximum 1 dose of REGN2222 [Day 1] and maximum 1 dose of placebo [Day 57]); or
  - 30 mg/kg IM Q8 weeks (maximum 2 doses of REGN2222); or
  - IM placebo (maximum 2 doses placebo) in Table 2
- Part B: Unscheduled respiratory illness visit for all dosing regimens in Table 3
- Part A and Part B: Unscheduled visits for AEs, including potential hypersensitivity reactions in Table 4

Table 1: Part A: 30 mg/kg IM (Maximum 1 Dose REGN2222); for Subjects with Schedules A through H

Study Periods	**SV[1]**	**BV**	**Postdose Follow-Up**								
Visit	**1**	**2**	**3**	**4[2]**	**5[2]**	**6[2]**	**7**	**8**	**9**	**10**	**11EOS/ET**
Day	**-14 to -1**	**1**	**2**	**8**	**15**	**22**	**29**	**57±5**	**85±5**	**113±5**	**150±5**
Informed Consent	X										
Inclusion/Exclusion	X	X									
Medical History	X										
Demographics	X										
IVRS/IWRS Assigned Blood Collection Schedule[3]		X									
Administer Study Drug		**X**[4]									
Concomitant Medications and Procedures	X	X	X	X[2]	X[2]	X[2]	X	X	X	X	X
Vital Signs[5]	X	X	X				X	X	X	X	X
Physical Examination (including weight)	X	X[6]	X					X			X
Adverse Events[7]	X	X	X	X[2]	X[2]	X[2]	X	X	X	X	X
Hematology	X[8-15]		X[8]	X[9]	X[10]	X[11]	X[12]	X[13]	X[14]	X[15]	X[8-15]
Blood Chemistry	X[8-15]		X[8]	X[9]	X[10]	X[11]	X[12]	X[13]	X[14]	X[15]	X[8-15]
Pharmacokinetics			X[8]	X[9]	X[10]	X[11]	X[12]	X[13]	X[14]	X[15]	X[8-15]
Anti-REGN2222 (ADA)	X[8-15]					X[11]	X[12]	X[13]	X[14]	X[15]	X[8-15]
Optional Sub-study Informed Consent	X										
Optional DNA Sample		X[16]									

ADA=antidrug antibody; BV=baseline visit, EOS/ET=end of study/early termination; IVRS=interactive voice response system; IWRS=interactive web response system; 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. Visit 4, Visit 5, and Visit 6 will be conducted by telephone to collect concomitant medication and adverse event information for all subjects, unless subjects are required by dosing schedule (Schedule C, Schedule D, and Schedule E) to undergo a PK/ADA and hematology/chemistry blood draw. Those subjects assigned to Schedule C (Footnote 11), Schedule D (Footnote 10), and Schedule E (Footnote 9) will have an onsite visit.
3. Subject blood collection schedules are assigned using the IVRS/IWRS.
4. No other vaccinations will be administered within 2 days before or after dosing of the study drug. The study staff will contact the parent(s) or legal guardian(s) at the end of Day 1 and on Day 3 by telephone to inquire about any change in the subject's status.
5. On the study drug dosing day, vital signs (temperature, blood pressure, pulse, and respiration) will be assessed prior to injection of study drug and 1, 2, and 3 hours (±10 minutes) after completion of the injection. If a subject's rectal temperature is 101°F/38.3°C (equivalent to axillary temperature of 100.6°F/38.1°C for infants <4 weeks of age or 99.2°F/ 37.3°C for infants ≥4 weeks of age) or greater on the day of a planned dose administration day, no dosing will occur. 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.
6. Physical examination will be conducted before injection and after injection, prior to discharge from the clinic, at Visit 2.
7. If the adverse event is considered a hypersensitivity or anaphylaxis reaction, then the adverse event will be assessed as outlined in (Table 4). 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 as outlined in (Table 4).
8. The subjects with blood collection Schedule F will have the following collected: hematology/chemistry samples at screening, Day 2, and EOS/ET; PK samples on Day 2 and EOS/ET; and ADA samples at screening and EOS/ET.
9. The subjects with blood collection Schedule E will have the following collected: hematology/chemistry samples at screening, Day 8, and EOS/ET; PK samples on Day 8 and EOS/ET; and ADA samples at screening and EOS/ET.
10. The subjects with blood collection Schedule D will have the following collected: hematology/chemistry samples at screening, Day 15, and EOS/ET; PK samples on Day 15 and EOS/ET; and ADA samples at screening and EOS/ET.
11. The subjects with blood collection Schedule C will have the following collected: hematology/chemistry samples at screening, Day 22, and EOS/ET; PK samples drawn on Day 22 and EOS/ET; and ADA samples drawn at screening, Day 22, and EOS/ET.
12. The subjects with blood collection Schedule B will have the following collected: hematology/chemistry samples at screening, Day 29, and EOS/ET; PK samples on Day 29 and EOS/ET; and ADA samples at screening, Day 29, and EOS/ET.
13. The subjects with blood collection Schedule A will have the following collected: hematology/chemistry samples at screening, Day 57, and EOS/ET; PK samples on Day 57 and EOS/ET; and ADA samples at screening, Day 57, and EOS/ET.
14. The subjects with blood collection Schedule G will have the following collected: hematology/chemistry samples at screening, Day 85, and EOS/ET; PK samples on Day 85 and EOS/ET; and ADA samples at screening, Day 85, and EOS/ET.
15. The subjects with blood collection Schedule H will have the following collected: hematology/chemistry samples at screening, Day 113, and EOS/ET; PK samples on Day 113 and EOS/ET; and ADA samples at screening, Day 113, and EOS/ET.
16. After substudy consent, a cheek swab for DNA in the optional substudy can be obtained at any time during the study period, but preferably at baseline.

Table 2: Part B: 30 mg/kg IM (Maximum 1 Dose REGN2222 and Maximum 1 Dose Placebo); 30 mg/kg IM (Maximum 2 Doses REGN2222); or Placebo IM (Maximum 2 Doses); for Subjects with Schedules I through M

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]			

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**
Optional Substudy Informed Consent	X									
Optional DNA Sample		X[15]								
Pharmacoeconomic Information[16]		X	X	X	X	X	X			
Risk Factors Assessment		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. Any subject who has had a positive RT -PCR RSV nasal swab result, either at the study central laboratory or at an outside institution in a CLIA-certified (or equivalent) laboratory, should not receive a second dose of study drug nor have postdose assessments completed on the day of dosing. The subject should, however, continue in the study and have all other assessments completed during subsequent visits. If the subject has had a positive RSV test using non-PCR assays or any RSV positive test including a RT-PCR test in laboratories that are not CLIA-certified (or equivalent), they should receive the second dose as planned. 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, two vital signs assessments (temperature, blood pressure, pulse, and respiration) will be performed when the child is calm: once prior to blood sample collection (if applicable) and injection of study drug, and again 1 hour (±10 minutes) after completion of the injection. Dosing may only proceed if the subject is afebrile (rectal temperature ≤101°F (38.3°C) without the use of antipyretics in the preceeding 48 hours. If a subject's rectal temperature is ≥101°F (38.3°C) on a dose administration day then no dosing will occur (see Section 6.3.1.1 for temperature conversions). The subject will then be re-evaluated within 48 hours; if the subject's temperature is ≤101°F (38.3°C) without the use of antipyretics during the previous 48 hours then the schedule of assessments may be resumed. Conversely, if the subject's temperature is still ≥101°F (38.3°C) **or** the subject has received antipyretics in the previous 48 hours, then dosing of the subject will be permanently discontinued.
7. Physical examinations will be conducted before injection and after injection, and 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 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 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.

Table 3: Part B: Unscheduled Visit for Potential Respiratory Illness - All Dose Regimens

Visit	Unscheduled Visit
	Within 72 hours of discharge from medical facility where medical attention was provided (including for an acute respiratory illness[1])
Concomitant Medications and Procedures	X
Adverse Events	X
History of Acute Illness (including any treatments or interventions received)	X
LRTI Checklist (included in Medical Information Packet and completed using medical records obtained by site from treating healthcare provider)	X[2]
Nose Swab for RT-PCR if Subject Has Acute Respiratory Tract Symptoms[3]	X
Dispense New Medical Information Packet[4]	X

LRTI=lower respiratory tract infection; RSV=respiratory syncytial virus; RT-PCR=Reverse-transcriptase polymerase chain reaction

Note: Adverse events that require unscheduled visits include medically attended events for potential respiratory illness (Table 3) and for acute injection reactions or suspected hypersensitivity reactions, with or without rash (Table 4)

1. If an unscheduled visit associated with a medically attended respiratory infection occurs >72 hours but within 14 days of discharge from a medical facility, all procedures (as appropriate), including nose swab collection, should occur despite being outside of the 72-hour window.

   If the unscheduled visit associated with a recent medically attended respiratory infection occurs > 14 days of discharge from a medical facility, site must obtain information about any RSV test conducted at that facility. Information will include: Name of assay, type of assay (RT-PCR, antigen test, other), result of assay, date of assay result, and documentation as to whether the laboratory performing the assay is CLIA (clinical laboratory improvement amendments) certified (or equivalent), date of CLIA certification (or equivalent).
2. The LRTI check list is in the Medical Information Packet and should be given by the parent(s) or guardian(s) to study staff with the contact information of the treating healthcare provider. The site will obtain medical records for all inpatient and outpatient respiratory visits from the treating facility.
3. Acute Respiratory Tract Symptoms are described in Section 6.2.3.
4. A Medical Information Packet will be dispensed to all parent(s) or guardian(s) at randomization. When parent(s) or guardian(s) take their child for medical attention outside of the study site catchment areas, they will be instructed to take the Medical Information Packet with them for use by their healthcare provider. A new Medical Information Packet should be dispensed to parent(s) or guardian(s) at every unscheduled visit which is to occur at the clinical site following discharge from a medical facility for an acute respiratory infection.

Table 4: Part A and Part B: Unscheduled Visit Following Any Adverse Events (Including Suspected Hypersensitivities) - All Dose Regimens

Visit	Unscheduled Visit following Adverse Event (including suspected hypersensitivities)
Concomitant Medications and Procedures	X
Vital Signs	X
Physical Examination (including weight)	X
Adverse Events	X
Photograph of Rash (if Present)	X[1]
Complete Blood Count With Differential	X[2]
Liver Function Test	X[2]
Blood Anti-REGN2222 Antibody (ADA)	X[2]
History of Present Illness (including any treatments or interventions received)	X

ADA=antidrug antibody; AE=adverse event
Note: Adverse events that require unscheduled visits include medically attended events for potential respiratory illness (Table 3) and for acute injection reactions or suspected hypersensitivity reactions, with or without rash (Table 4). Other AEs may require unscheduled visits based on the investigator decision and as warranted.

1. If the AE includes a suspected hypersensitivity rash, then a photo will be taken as part of the AE assessment.
2. Only AEs that are suspected to be hypersensitivity reactions require additional tests. Other AEs do not require these procedures.

6.2. Study Procedures

6.2.1. Part A: 30 mg/kg IM (Maximum 1 Dose)

6.2.1.1. Visit 1 (Screening, Day -14 to Day -1)

After the subject's parent(s) or legal guardian(s) have provided informed consent (with or without optional substudy informed consent), the following information will be collected (Table 1):

- Inclusion/exclusion criteria
- Medical history
- Demographics

The following procedures and assessments will be conducted:

- Concomitant medications and procedures
- AEs
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to scheduled collection of blood sample
- Physical examination (including weight)
- Hematology (all subjects [blood collection Schedule A through Schedule H])
- Blood chemistry (all subjects [blood collection Schedule A through Schedule H])
- ADA sampling (all subjects [blood collection Schedule A through Schedule H])

6.2.1.2. Visit 2 (Baseline and Dosing Visit, Day 1)

The following procedures and assessments will be conducted prior to administration of study drug, unless specified otherwise:

- Confirm inclusion/exclusion criteria
- Retrieve IVRS/IWRS-assigned subject blood collection schedule and study drug kit number
- AEs
- Concomitant medications and procedures
- Physical examination (including weight)
- Vital signs (including temperature, blood pressure, pulse and respiration rate)
  - If a subject's rectal temperature is101°F (38.3°C) (equivalent to axillary temperature of 100.6°F [38.1°C] for infants <4 weeks of age or 99.2°F [37.3°C] for infants ≥4 weeks of age) or greater on the day of a planned dose administration day, no dosing will occur. 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.
- If consented, then optional substudy DNA collection (cheek swab to be collected at any time during the study period, but preferably at baseline)

A single dose of REGN2222 30 mg/kg IM will be administered. Subjects will be monitored in the clinic for 3 hours after dosing, followed by discharge, if appropriate. After study drug administration, the following information will be collected, and the following procedures and assessments will be conducted:

- AEs
- Vital signs, including temperature, blood pressure, pulse and respiration rate, assessed at 1, 2, and 3 hours (±10 minutes) after completion of the injection
- Physical examination (including weight) post dose

No vaccinations will be administered within 2 days of dosing of the study drug (Section 4.1.2.1, exclusion criterion #9). An emergency phone number will be provided to parent(s) or guardian(s); they will also be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact parent(s) or legal guardian(s) at the end of Day 1, the subject will return to the study site on Day 2 for Visit 3, and the study staff will contact the parent(s) or legal guardian(s) on Day 3 to inquire about any change in the subject's status; this will provide at least daily contact for 48 hours after dosing. Any new signs or symptoms that have developed in the subject since dosing will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff.

6.2.1.3. Visit 3 (Day 2)

The parent(s) or guardian(s) will bring the subject to the study site on Day 2 for Visit 3 evaluations. The following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- Physical examination (including weight)
- AEs
- Hematology (subjects with blood collection Schedule F only)
- Blood chemistry (subjects with blood collection Schedule F only)
- PK sampling (subjects with blood collection Schedule F only)

The study staff will contact the parent(s) or legal guardian(s) on Day 3 to inquire about any change in the subject's status.

6.2.1.4. Visit 4 (Day 8)

This visit may take place by telephone for all subjects except those with blood collection Schedule E, who will be required to have an onsite visit.

For all subjects (telephone or onsite visit), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Concomitant medications and procedures
- AEs

For subjects that have an onsite visit (subjects with blood collection Schedule E only), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Hematology (subjects with blood collection Schedule E only)
- Blood chemistry (subjects with blood collection Schedule E only)
- PK sampling (subjects with blood collection Schedule E only)

6.2.1.5. Visit 5 (Day 15)

This visit may take place by telephone for all subjects except those with blood collection Schedule D, who will be required to have an onsite visit.

For all subjects (telephone or onsite visit), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Concomitant medications and procedures
- AEs

For subjects that have an onsite visit (subjects with blood collection Schedule D only), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Hematology (subjects with blood collection Schedule D only)
- Blood chemistry (subjects with blood collection Schedule D only)
- PK sampling (subjects with blood collection Schedule D only)

6.2.1.6. Visit 6 (Day 22)

This visit may take place by telephone for all subjects except those with blood collection Schedule C, who will be required to have an onsite visit.

For all subjects (a telephone or onsite visit), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Concomitant medications and procedures
- AEs

For all subjects that have an onsite visit (subjects with blood collection Schedule C only), the following information will be collected, and the following procedures and assessments will be conducted during the visit:

- Hematology (subjects with blood collection Schedule C only)
- Blood chemistry (subjects with blood collection Schedule C only)
- PK sampling (subjects with blood collection Schedule C only)
- ADA sampling (subjects with blood collection Schedule C only)

6.2.1.7. Visit 7 (Day 29)

All subjects will be required to attend an onsite visit.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- AEs
- Hematology (subjects with blood collection Schedule B only)
- Blood chemistry (subjects with blood collection Schedule B only)
- PK sampling (subjects with blood collection Schedule B only)
- ADA sampling (subjects with blood collection Schedule B only)

6.2.1.8. Visit 8 (Day 57±5 Days)

All subjects will have an onsite visit.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- Physical examination (including weight)
- AEs
- Hematology (subjects with blood collection Schedule A only)

- Blood chemistry (subjects with blood collection Schedule A only)
- PK sampling (subjects with blood collection Schedule A only)
- ADA sampling (subjects with blood collection Schedule A only)

6.2.1.9. Visit 9 (Day 85±5 Days)

All subjects will have an onsite visit.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- AEs
- Hematology (subjects with blood collection Schedule G only)
- Blood chemistry (subjects with blood collection Schedule G only)
- PK sampling (subjects with blood collection Schedule G only)
- ADA sampling (subjects with blood collection Schedule G only)

6.2.1.10. Visit 10 (Day 113±5 Days)

All subjects will have an onsite visit.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- AEs
- Hematology (subjects with blood collection Schedule H only)
- Blood chemistry (subjects with blood collection Schedule H only)
- PK sampling (subjects with blood collection Schedule H only)
- ADA sampling (subjects with blood collection Schedule H only)

6.2.1.11. Visit 11 (Day 150±5 Days), End of Study or Early Termination

All subjects will have an onsite visit.

Subjects will return to the clinic for an end of study assessment. Subjects who are withdrawn from the study will be asked to return to the clinic for early termination assessments.

The end of study will occur 150 days after the first dose.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- Physical examination (including weight)
- AEs
- Hematology (all subjects [blood collection Schedule A through Schedule H])
- Blood chemistry (all subjects [blood collection Schedule A through Schedule H])
- PK sampling (all subjects [blood collection Schedule A through Schedule H])
- ADA sampling (all subjects [blood collection Schedule A through Schedule H])

6.2.2. Part B: 30 mg/kg (1 Dose REGN2222 and 1 Dose Placebo); or 30 mg/kg IM (2 Doses REGN2222); or Placebo IM (Maximum 2 Doses)

Informed consent may be obtained from the parent(s) or legal guardian(s) up to 28 days prior to randomization.

6.2.2.1. Visit 1 (Screening, Day -28 to Day -1)

After the subject's parent(s) or legal guardian(s) has provided informed consent (with or without optional substudy informed consent), the following information will be collected:

- Inclusion/exclusion criteria
- Medical history
- Demographics

The following procedures and assessments will be conducted:

- Concomitant medications and procedures
- AEs
- Vital signs taken when the child is calm (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample. Rectal, axillary, temporal, and tympanic temperature acquisitions are permitted.
- Physical examination (including weight)
- Blood sampling
  - Hematology (all subjects [blood collection Schedule I through Schedule M])
  - Blood chemistry (all subjects [blood collection Schedule I through Schedule M])
  - ADA sampling (all subjects [blood collection Schedule I through Schedule M])

- Please see Section 6.3.3 regarding guidance on interpreting abnormal screening laboratory values and redrawing blood samples due to insufficient volumes or hemolyzed samples.

6.2.2.2. Visit 2 (Baseline and First Dosing Visit, Day 1)

The following procedures and assessments will be conducted prior to administration of study drug, unless specified otherwise:

- Confirm inclusion/exclusion criteria
- IVRS/IWRS-assigned subject blood collection schedule
- Randomization to REGN2222 or placebo
- AEs
- Physical examination (including weight)
- Vital signs (including temperature, blood pressure, pulse and respiration rate)
  - On study drug dosing days, vital signs assessments (temperature, blood pressure, pulse, and respiration) will be performed twice when the child is calm: once prior to blood sample collection (if applicable) and injection of study drug, and again 1 hour (±10 minutes) after completion of the injection. Dosing may only proceed if the subject is afebrile (rectal temperature ≤101°F (38.3°C)) without the use of antipyretics in the preceeding 48 hours. If a subject's rectal temperature is ≥101°F (38.3°C) on a dose administration day then no dosing will occur (see Section 6.3.1.1 for temperature conversions). The subject will then be re-evaluated within 48 hours. If the subject's temperature is ≤101°F (38.3°C) without the use of antipyretics during the previous 48 hours, then the schedule of assessments may be resumed. Conversely, if the subject's temperature is still ≥101°F (38.3°C) **or** the subject has received antipyretics in the previous 48 hours then dosing of the subject will be permanently discontinued.
  - Table 5 provides the equivalents for Celsius and Fahrenheit temperatures.
- Risk factor assessment (geographic region, multiple births, small for gestational age, child care status, family history of atopy, asthma, hay fever, or eczema, number of people in the household, including siblings, number of individuals 6 years or younger in the household, parent smoking status and parent work status).
- Dispense Medical Information Packet
- If consented, optional substudy DNA collection (cheek swab to be collected at any time during the study period, but preferably at baseline)
- Concomitant medications and procedures
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit

The first study drug will be administered (REGN2222 or Placebo). Subjects will be monitored in the clinic for at least 1 hour after dosing, followed by discharge, when appropriate.

After randomization and study drug administration, the following information will be collected, and the following procedures and assessments will be conducted:

- AEs
- Vital signs, including temperature, blood pressure, pulse and respiration rate assessed 1 hour (±10 minutes) after completion of the injection
- Physical examination, (excluding weight) post dose

No other vaccinations will be administered within 2 days of dosing of the study drug (Section 4.1.2.1, exclusion criterion #9). An emergency phone number will be provided to parent(s) or guardian(s) and they will also be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact parent(s) or legal guardian(s) at the end of the day and daily over 48 hours to inquire about any change in the subject's status. Any new signs or symptoms that have developed in the subject since the last dose will be assessed by study staff to determine if there is a need for immediate medical attention and if that subject will also need to be seen within 24 hours by the study staff.

6.2.2.3. Visit 3 (Day 29±2 Days)

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs (including temperature, blood pressure, pulse, and respiration rate) prior to any scheduled collection of blood sample
- AEs
- Physical examination (including weight)
- Blood sampling
  - Hematology (subjects with blood collection Schedule M only)
  - Blood chemistry (subjects with blood collection Schedule M only)
  - PK sampling (subjects with blood collection Schedule M only)
  - ADA sampling (subjects with blood collection Schedule M only)
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit

6.2.2.4. Visit 4 (Second Dosing Visit, Day 57±2 Days)

Note: Any subject who has had a positive PCR RSV nasal swab result, either at the study central laboratory or at an outside institution in a CLIA-certified (or equivalent) laboratory, should not receive a second dose of study drug or have postdose assessments completed. The infant should, however, continue in the study and have all other assessments completed during subsequent

visits. If the subject has had a positive RSV test using non-PCR assays or in laboratories that are not CLIA-certified (or equivalent), they should receive the second dose as planned.

The following procedures and assessments will be conducted prior to administration of study drug, unless specified otherwise:

- Physical examination (including weight)
- Vital signs (including temperature, blood pressure, pulse, and respiration rate)

  Dosing may only proceed if the subject is afebrile (rectal temperature <101°F (38.3°C) without the use of antipyretics in the preceeding 48 hours. If a subject's rectal temperature is ≥101°F (38.3°C) on a dose administration day then no dosing will occur (see Section 6.3.1.1 for temperature conversions). The subject will be then be re-evaluated within 48 hours; if the subject's temperature is ≤101°F (38.3°C) without the use of antipyretics during the previous 48 hours, then the schedule of assessments may be resumed. Conversely, if the subject's temperature is still ≥101°F (38.3°C) or the subject has received antipyretics in the previous 48 hours then dosing of the subject will be permanently discontinued.

  – Table 5 provides the equivalents for Celsius and Fahrenheit temperatures.
- Concomitant medications
- AEs
- Blood sampling
  - Hematology (subjects with blood collection Schedule L only)
  - Blood chemistry (subjects with blood collection Schedule L only)
  - PK sampling (subjects with blood collection Schedule L only)
  - ADA sampling (subjects with blood collection Schedule L only)
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit.

The second study drug dose will be administered (REGN2222 or Placebo). Subjects will be monitored in the clinic for at least 1 hour after dosing, followed by discharge, when appropriate.

- Vital signs, including temperature, blood pressure, pulse, and respiration rate assessed 1 hour (±10 minutes) after completion of the injection
- Physical examination (excluding weight) post dose

No other vaccinations will be administered within 2 days of dosing of the study drug (Section 4.1.2.1, exclusion criterion #9). An emergency phone number will be provided to parent(s) or guardian(s) will also be given written and verbal instructions to call with any change in the subject's status. In addition, the study staff will contact parent(s) or legal guardian(s) at the end of the day and daily over 48 hours to inquire about any change in the subject's status. Any new signs or symptoms that have developed in the subject since the last dose will be assessed by

study staff to determine if there is a need for immediate medical attention and that subject will also be seen within 24 hours by the study staff.

6.2.2.5. Visit 5 (Day 85±5 Days)

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs taken when the child is calm (including temperature, blood pressure, pulse, and respiration rate)
- Physical examination (including weight)
- AEs
- Blood sampling
  - Hematology (subjects with blood collection Schedule K only)
  - Blood chemistry (subjects with blood collection Schedule K only)
  - PK sampling (subjects with blood collection Schedule K only)
  - ADA sampling (subjects with blood collection Schedule K only)
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit

6.2.2.6. Visit 6 (Day 113±5 Days)

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs taken when the child is calm (including temperature, blood pressure, pulse, and respiration rate)
- AEs
- Blood sampling
  - Hematology (subjects with blood collection Schedule J only)
  - Blood chemistry (subjects with blood collection Schedule J only)
  - PK sampling (subjects with blood collection Schedule J only)
  - ADA sampling (subjects with blood collection Schedule J only)
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit

6.2.2.7. Visit 7 (Day 150±5 Days), or Early Termination

Subjects will return to the clinic for Visit 7 assessment. Subjects who are withdrawn from the study at any point prior to Visit 7/Day 150 will be asked to return to the clinic for early termination assessments.

The following information will be collected, and the following procedures and assessments will be conducted:

- Concomitant medications and procedures
- Vital signs taken when the child is calm (including temperature, blood pressure, pulse, and respiration rate)
- Physical examination (including weight)
- AEs
- Blood sampling
  - Hematology (all subjects [blood collection Schedule I through Schedule M])
  - Blood chemistry (all subjects [blood collection Schedule I through Schedule M])
  - PK sampling (all subjects [blood collection Schedule I through Schedule M])
  - ADA sampling (all subjects [blood collection Schedule I through Schedule M])
- Pharmacoeconomic information on subjects who have experienced a medically attended respiratory event since last visit

6.2.2.8. Visit 8 (Day 178±10 Days)

The following information will be collected during a telephone visit; subjects will not be required to come to the site unless deemed necessary to follow-up on an AE

- Concomitant medications and procedures
- AEs

6.2.2.9. Visit 9 (Day 206±10 Days)

The following information will be collected during a telephone visit; subjects will not be required to come to the site unless deemed necessary to follow-up on an AE

- Concomitant medications and procedures
- AEs

6.2.2.10. Visit 10 (Day 237±10 Days)/End of Study

The following information will be collected during a telephone visit; subjects will not be required to come to the site unless deemed necessary to follow-up on an AE

- Concomitant medications and procedures
- AEs

6.2.3. Part B: Unscheduled Visit for Potential Respiratory Illness

During the study, data will be collected from subjects with any respiratory illness requiring medical attention (inpatient and outpatient incidences). After enrollment into the study, any subject taken by their parent(s) or guardian(s) to a healthcare provider (inpatient or outpatient, including ER, UC, or pediatric clinic visits[a]) will be asked to contact the study staff immediately after seeking medical attention for any of the following symptoms:

- Fever
- Cough
- Earache
- Nasal congestion
- Rhinorrhea
- Vomiting after coughing
- Wheezing
- Difficulty breathing (labored, rapid, or shallow).

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit

Unscheduled visits are required by the protocol in the event of a potential respiratory illness (Table 3). Other unscheduled visits (Section 6.2.4) may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for acute injection reactions, or for any other reason.

Unscheduled visits for potential respiratory illness should occur within 72 hours of discharge from a medical facility where medical attention was provided (including that for an acute respiratory illness). If an unscheduled visit associated with a medically attended respiratory infection occurs more than 72 hours but within 14 days of discharge from a medical facility, all procedures (as appropriate), including nose swab collection, should occur despite being outside of the 72 hour window.

If an unscheduled visit associated with a medically attended respiratory infection does not occur within 14 days of discharge from the medical facility, a nose swab for RSV RT-PCR testing does not need to be sent to the central laboratory. Instead, site personnel should obtain results of all RSV RT-PCR tests conducted during that illness at outside laboratories, including information on the result of the test, name of the RT-PCR assay used, and whether the laboratory conducting the RT-PCR is a CLIA-certified (or equivalent) laboratory. If an RSV RT-PCR was not conducted but other types of RSV assays were conducted (ie, rapid antigen test), the information outlined above does not need to be collected.

The following information will be collected, and the following procedures and assessments will be conducted for unscheduled visits in the event of a respiratory illness:

- Concomitant medications and procedures
- AEs
- History of acute illness (including any treatments or interventions received)
- LRTI checklist from the Medical Information Packet should be given by the parent(s) or guardian(s) to study staff with the contact information of the treating healthcare provider. The site will obtain medical records for all inpatient and/or outpatient respiratory visits from the treating facility.
- Nose swabs for infants with acute respiratory tract symptoms
  - All nose swabs will be tested using a Food and Drug Administration-cleared and CE (Conformité Européenne)-marked RT-PCR assay for RSV, which will be conducted in a central laboratory. Any subject with an acute respiratory illness who tests positive for RSV by RT-PCR will also have testing of samples to identify the RSV subtype. The RSV subtyping will not require an additional sample or study visit.
- Dispense new Medical Information Packet to the parent(s) or guardian(s) at every unscheduled visit following discharge from a medical facility for an acute respiratory infection

6.2.4. Part A and Part B: Unscheduled Visit Following Any Adverse Event (Including Suspected Hypersensitivities)

Other unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, for acute injection reactions or suspected hypersensitivity reactions (with or without rash), or for any other reason, as warranted (Table 4). Other AEs that require unscheduled visits include medically attended events for potential respiratory illness (Table 3, Section 6.2.3).

The following information will be collected, and the following procedures and assessments will be conducted for unscheduled visits:

- Concomitant medications and procedures
- Vital signs taken when child is calm (including temperature, blood pressure, pulse, and respiration rate)
- Physical examination (including weight)
- AEs
- History of present illness (including any treatments or interventions received)

If the AE is a suspected hypersensitivity reaction, then additional tests are required and include the following (Table 4):

- Complete blood count with differential
- Liver function test
- ADA sampling
- Photograph of suspected hypersensitivity rash, if present

6.3. Safety Procedures

6.3.1. Vital Signs

Vital signs (including temperature, blood pressure, pulse, and respiration rate) will be collected before dosing at time points specified in the schedule of assessments (Section 6.1). On the study drug dosing days, vital signs will be assessed prior to collection of blood sample, prior to injection of study drug, and after completion of the injection (Part A at 1, 2, and 3 hours [±10 minutes] after completion of the injection and Part B at 1 hour [±10 minutes] after completion of the injection).

6.3.1.1. Temperature

Dosing may only proceed if the subject is afebrile (rectal temperature <101°F (38.3°C) without the use of antipyretics in the preceeding 48 hours. If a subject's rectal temperature is ≥101°F (38.3°C) on a dose administration day then no dosing will occur (see Section 6.3.1.1 for temperature conversions). The subject will be then be re-evaluated within 48 hours; if the subject's temperature is ≤101°F (38.3°C) without the use of antipyretics during the previous 48 hours, then the schedule of assessments may be resumed. Conversely, if the subject's temperature is still ≥101°F (38.3°C) or the subject has received antipyretics in the previous 48 hours, dosing of the subject will be permanently discontinued, but the subject will continue to be followed for safety and efficacy, if at least 1 dose of study drug was administered.

Table 5 below provides the equivalents for Celsius and Fahrenheit temperatures.

Temperature acquisition method: It is acknowledged that the method for temperature acquisition is not standard across all sites. Therefore, rectal as well as axillary, temporal, and tympanic measurements will be permitted. There is a recognized difference between temperatures obtained using different modalities and the following conversions (Table 5) must be used when assessing pre-dose temperature to hold dosing.

Table 5: Conversion of Axillary/Temporal Temperatures to Rectal /Tympanic Temperatures in Infants by Age

Infants <4 Weeks Chronological Age				**Infants ≥4 Weeks Chronological Age**			
Axillary/Temporal Temperature		**Rectal/Tympanic (0.2°C+axillary)**		**Axillary/Temporal Temperature**		**Rectal/Tympanic (1.0°C+axillary)**	
°C	**°F**	**°C**	**°F**	**°C**	**°F**	**°C**	**°F**
37.8	100.0	38.0	100.4	37.0	98.6	38.0	100.4
38.1	**100.5**	**38.3**	**100.9**	**37.3**	**99.1**	**38.3**	**100.9**
38.8	101.8	39.0	102.2	38.0	100.4	39.0	102.2
39.8	103.6	40.0	104.0	39.0	102.2	40.0	104.0
40.8	105.4	41.0	105.8	40.0	104.0	41.0	105.8
41.8	107.2	42.0	107.6	41.0	105.8	42.0	107.6

Note: Boldface values in the table indicate a cut-off. At temperatures equal to or greater than those in boldface, no dosing should occur.
Table adapted from Shann F 1996.

6.3.1.2. Blood Pressure

Blood pressure may be difficult to obtain in some infants because of size, therefore a systolic blood pressure alone can be recorded. If site personnel are unable to obtain either systolic or diastolic pressures, "unable to obtain" should be recorded.

6.3.2. Physical Examination

A thorough and complete physical examination, including weighing the subject, will be performed at time points specified in the schedule of assessments (Section 6.1). Care should be taken to examine and assess any abnormalities that may be present, as indicated by the subject's medical history. On study drug-dosing days, physical examinations will be conducted predose and again postdose (excluding weight) prior to discharge.

6.3.3. Laboratory Testing

Hematology and blood chemistry testing samples will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points specified in the schedule of assessments (Section 6.1) and during unscheduled visits (Section 6.2.3).

Blood redraw:

If screening laboratory test results are unavailable due to hemolysis or insufficient specimen volume, redraw of screening blood samples are acceptable if the blood volume withdrawn from the infant does not surpass the ethical and safety recommendations for such procedures according to the informed consent and the site pediatric guidelines (local or national) on total blood volume allowable for blood tests. If specimens are redrawn, it is advised that the redraw occur in a timely manner to allow for rapid enrollment decision and dosing. Visits for blood redraws should be conducted as an unscheduled visit.

Laboratory reference ranges for preterm infants:

Clinical laboratory reference ranges for preterm infants are not standardized therefore the reference ranges currently used in the central laboratory are based on values observed in full-term infants. Because there are no standardized reference ranges for preterm infants the following guidance to Principal Investigators to consider for infants for whom levels creatinine, alkaline phosphatase, AST, or total bilirubin are >1.1 times the central laboratory reported upper limit of normal is provided. The subject may be considered for inclusion into the study if the Principal Investigator concludes the following:

- There is no evidence that the elevated levels are associated with a possible underlying medical condition leading to clinical concern or the need to carry out additional workup or treatment.
- In particular, for renal status, there is no evidence of renal disease which may be manifested by creatinine >1.5 mg/dL (133 µmol/L) along with signs including, but not limited to, a decrease in urine output or abnormal urinalysis.
- For liver status, there is no evidence of liver disease which may be manifested by a total bilirubin level that is >12 mg/dL (205 µmol/L) along with abnormal liver enzymes including but not limited to, ALT >45 U/L, AST >150 U/L (0 to10 days chronological age), AST >80 U/L (10 days to 12 months chronological age), and alkaline phosphatase >700 U/L.

Please refer to Appendix G for laboratory cut-off values to be considered for Exclusion Criterion #6.

6.3.3.1. Blood Chemistry

Tests will include the following:

- Sodium
- Potassium
- Chloride
- Carbon dioxide
- Calcium
- Glucose
- Albumin
- Total protein, serum
- Creatinine
- Blood urea nitrogen
- AST
- ALT
- Alkaline phosphatase
- Lactate dehydrogenase
- Total bilirubin
- Indirect bilirubin
- Uric acid
- Creatine phosphokinase

6.3.3.2. Hematology

Tests will include the following:

- Hemoglobin
- Hematocrit
- Red blood cells (RBCs)
- White blood cells (WBCs)
- Red cell indices
- Platelet count
- Differential:
  - Neutrophils
  - Lymphocytes
  - Monocytes
  - Basophils
  - Eosinophils

6.3.3.3. Virology Testing

Nose swabs collected from respiratory unscheduled visits (Section 6.2.3) will be tested at a central laboratory for RSV by RT-PCR. Positive samples will be sequenced for viral subtyping and resistance monitoring. Further details will be provided in the study manual.

In addition, nose swab specimens negative for RSV using the RT-PCR assay utilized for determination of primary endpoint cases will be evaluated using a second and distinctly different RT-PCR multiplex respiratory panel. The multiplex assay will be performed to determine the presence of other common respiratory pathogens in nose swabs. This multiplex evaluation will only be conducted on RSV negative swabs collected from subjects and will not be used in the primary analyses of the primary and secondary efficacy endpoints.

6.3.3.4. Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 7.2.6.

6.4. Pharmacokinetic and Antibody Procedures

6.4.1. REGN2222-Concentration Measurements and Samples

Serum samples for REGN2222-concentration measurements will be collected at the time points specified in the schedule of assessments (Section 6.1).

6.4.2. Antidrug Antibody Measurements and Samples

Serum samples for ADA assessment will be collected at the time points specified in the schedule of assessments (Section 6.1).

6.4.3. Research Samples

Any remaining serum samples collected for PK and ADA measurements may be banked and used for exploratory research. The samples maybe used to study the effects of the study drug, on prediction of medically attended RSV infection, or severity of RSV infection and resultant long-term sequelae of infection, such as recurrent wheezing or reactive airway disease. The analysis may include, but is not limited to, RSV microneutralization and inflammatory markers.

6.4.4. Substudy - Optional

Parent(s) or legal guardian(s) of subjects who agree to allow their infant to participate in the substudy will be required to sign a separate substudy informed consent form (ICF) before collection of the samples. Subjects are not required to participate in the substudy in order to enroll in the primary study. Cheek swab for DNA extraction may be collected at any time during the study period but preferably at baseline.

DNA samples for the substudy will be double-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Substudy samples may be stored for up to 15 years after the date of the final database lock and may be used for research purposes. [redacted] Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. [redacted]

6.5. Pharmacoeconomic Measurement Procedures

Pharmacoeconomic information will only be collected during Part B. At each scheduled visit (Table 2), the parent(s) or guardian(s) will be asked if the subject had experienced a respiratory infection. Only if the subject had experienced a medically attended respiratory infection, including an RSV infection, would the parent(s) or guardian(s) will be asked to provide additional pharmacoeconomic information.

At each scheduled visit (Table 2), health care resource utilization and respiratory symptoms will be asked of the parent(s) or guardian(s) or the hospital staff (nurse or treating physician) where treatment was received. This will include the number of RSV and non-RSV-associated medical visits (hospital, ER, UC, or pediatric visits[a]); length of stay in hospital, ER, or UC; and treatments or procedures (including number of days) for each visit. In addition, the parent(s) or guardian(s) will be asked to provide information of the number of missed days from work for each medically attended respiratory event. The specific questions will be provided in the study manual.

[a] A pediatric clinic visit represents an outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose and includes the following:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a subject is a passenger).
- Is **life threatening** – in the view of the investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires inpatient **hospitalization** or **prolongation of existing hospitalization**. Inpatient hospitalization is defined as admission to a hospital or an ER for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect
- Is an **important medical event** - important medical events may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an ER or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (designee) will record all AEs that occur from the time the ICF is signed until the end of study. Refer to the study manual for the procedures to be followed.

Information on follow-up for AEs is provided in Section 7.2.7. Laboratory test results or vital signs are to be recorded as AEs as outlined in Section 7.2.6.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug must be reported to the sponsor (designee) within 24 hours. Refer to the study manual for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board/Ethics Review Committee (IRB/ERC) all unanticipated problems involving risks to subjects. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/ERC, regardless of assessed causality.

In the event the investigator is informed of an SAE after the subject completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator will make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

7.2.3. Sponsor's Responsibility

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (Suspected Unexpected Serious Adverse Reaction), to the Health Authorities, ERCs/IRBs as appropriate and to the investigators.

In addition, the sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the study drug to the Health Authorities, according to local regulations.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected.

The sponsor will report all safety observations made during the conduct of the trial in the clinical study report to Health Authorities and ERCs/IRB as appropriate.

7.2.4. Other Events that Require Accelerated Reporting

The events of symptomatic drug overdose and AESI will be reported to the sponsor (designee) within 24 hours of learning of the event. Refer to the study manual for definitions and procedures to be followed.

7.2.4.1. Symptomatic Overdose of Study Drug

Symptomatic overdose is defined in this study as accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window and if associated with an AE.

7.2.4.2. Adverse Events of Special Interest

Adverse events of special interest must be reported to the sponsor (designee) within 24 hours of identification. Adverse events of special interest 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). The severity of AESIs will be graded according to the CTCAE Version 4.0 criteria for grading allergic reactions and anaphylaxis (Appendix D).

7.2.5. Reporting Adverse Events Leading to Withdrawal From the Study

All AEs that lead to a subject withdrawing from the study must be reported to the sponsor's medical monitor within 30 days. Refer to the study manual for the procedures to be followed.

7.2.6. Abnormal Laboratory or Vital Sign Results

The criteria for determining whether an abnormal objective test finding will be reported as an AE include any of the following:

- The test result is associated with accompanying symptoms,
- The test result requires additional diagnostic testing or medical/surgical intervention,
- The test result leads discontinuation from the study treatment, discontinuation from the study, significant additional concomitant drug treatment, or other therapy,
- Grade 3 or higher laboratory test result abnormalities

The investigator will contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions will not constitute an AE. Any abnormal test result that is determined to be an error will not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.7. Adverse Event Follow-up

Adverse event information will be collected until the subject's last study visit.

Serious adverse event information will be collected until the event has resolved or is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of the AE will be graded using 1 of 2 severity scales, and the severity scale used will be determined by the type of AE experienced by the subject.

The severity of AEs related to allergic or anaphylactic reactions (including AESIs) will be graded according to the CTCAE Version 4.0 criteria for grading allergic reactions and anaphylaxis (Appendix D).

The severity of AEs related to other events (excluding allergic or anaphylactic reactions) will be graded according to the Modified Toxicity Grading Scale from Division of AIDS for Grading the Severity of Adult and Pediatric Adverse Events. Two versions are in use for this protocol: Version 1.0, December, 2004; Clarification August 2009 (Appendix E) and Version 2.0, November 2014 (Appendix F, only applicable pages are included).

Notes: Version 2.0 is to be used for grading AEs associated with total bilirubin and hemoglobin. For all other AEs (excluding allergic or anaphylactic reactions) Version 1.0 with the August 2009 clarification should be used.

1. For AEs not identified elsewhere in Appendix E, the AE should be graded using the row describing Estimating Severity Grade.
2. For AEs associated with abnormal glucose and calcium values, a footnote is present in Version 1.0 of the Division of AIDS (DAIDS) scale indicating that the values are associated with full-term infants. This footnote has been removed from Version 2.0 of the DAIDS scale with no resultant changes to the grading cut-off values. Therefore, for the purposes of this protocol, the values present in Version 1.0 of the DAIDS scale are appropriate to use.
3. Any occurrence of fever must be graded according to the scale provided in Version 1.0 of the DAIDS scale. The DAIDS scale specifies a non-axillary temperature range in degrees Celsius. Please refer to Table 6 below for temperature conversion to degrees Fahrenheit and for a breakdown by age of infant.

Table 6: DAIDS Fever Grading Scale

Infants <4 Weeks Chronological Age					**Infants ≥4 Weeks Chronological Age**			
Axillary/Temporal Temperature		**Rectal/Tympanic (0.2°C+axillary)**			**Axillary/Temporal Temperature**		**Rectal/Tympanic (1.0°C+axillary)**	
°C	**°F**	**°C**	**°F**	***Severity***	**°C**	**°F**	**°C**	**°F**
37.5-38.4	99.5-101.2	37.7-38.6	99.8-101.5	*Grade 1*	36.7-37.5	98.1-99.5	37.7-38.6	99.8-101.5
38.5-39.1	101.3-102.4	38.7-39.3	101.6-102.8	*Grade 2*	37.7-38.3	99.8-100.9	38.7-39.3	101.6-102.8
39.2-40.3	102.5-104.5	39.4-40.5	102.9-104.9	*Grade 3*	38.4-39.5	101.2-103.1	39.4-40.5	102.9-104.9
>40.3	>104.5	>40.5	>104.9	*Grade 4*	>39.5	>103.1	>40.5	>104.9

Note: The grading scale and rectal temperatures in this table are from Division of AIDS 2004. The conversions to axillary/temporal temperature were created using information from Shann F 1996.

If a laboratory value is considered an AE, its severity will be based on the degree of physiological impairment the value indicates.

7.3.2. Evaluation of Causality

7.3.2.1. Relationship of AEs to Study Drug

The relationship of AEs to study drug will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by the study drug
- **Related:** There is a reasonable possibility that the event may have been caused by the study drug (ie, a causal relationship cannot reasonably be ruled out)

A list of factors to be considered in assessing the relationship of AEs to study drug are available in Appendix C.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

7.3.2.2. Relationship of AEs to Injection Procedure

The relationship of AEs to injection procedure will be assessed by the investigator, and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the injection procedure?

The possible answers are:

- **Not Related:** There is no reasonable possibility that the event may have been caused by the injection procedure
- **Related:** There is a reasonable possibility that the event may have been caused by the injection procedure

For a list of factors to consider in assessing the relationship of AEs to injection procedure, see Appendix C.

The sponsor will request information to justify the causality assessment of SAEs, as needed.

7.4. Safety Monitoring

The investigator will monitor the safety of study subjects at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management, Biostatistics, and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

An IDMC will monitor subject safety during the course of the study. The composition and activities of the IDMC are described in Section 3.3 and the IDMC charter, composed of members who are independent from the sponsor and the investigators, by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

7.5. Investigator Alert Notification

Sponsor (designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that possibly meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the investigator's brochure, and has a reasonable suspected causal relationship to the study drug) in a blinded fashion.

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Demographics and baseline characteristics will include standard demography (eg, age, race, weight, length), disease characteristics (including medical history and GA at birth, family history, medication history for each subject), pharmacoeconomics (eg, parent employment status [mother and father], full or part-time, unemployed) and risk factor assessment (eg, infant care provided at home or daycare center, number of siblings at home [including age and school status], parent smoking status.)

8.2. Primary Endpoints

The primary endpoints are the following:

Part A:

- Serum concentration of REGN2222 over time and other PK parameters

Part B:

- Proportion of subjects with a medically attended RSV infection (hospitalization or outpatient LRTI) during the study period. A medically attended RSV infection 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 (ER, UC, or pediatric clinic[a] [for either a sick or well visit]) with RSV LRTI.

  [a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.
- 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

An episode of RSV infection will be defined as any medically attended respiratory illness associated with a positive RSV RT-PCR test occurring within a 14-day period. If multiple medical visits (events) are made for the same episode of RSV illness, an RSV positive test by RT-PCR at any medical visit (event) will label that episode as being RSV positive, and it will be counted toward the primary endpoint. If there are multiple events during an episode associated with an RSV positive test, then the most severe event 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 categorization of a medically attended respiratory illness event as an endpoint is unclear, source documentation will be provided to a blinded adjudication committee for categorization.

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 of the event, the missing result will be imputed using results from an RSV RT-PCR assay if it meets the following conditions:

- 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 certified.

Results from non-RT-PCR RSV assays will not be collected. Only medically attended respiratory visits occurring during the first 150-day period will be counted toward the primary endpoint.

8.3. Secondary Endpoints

The secondary endpoints are the following:

Part A:

- Incidence and severity of TEAEs
- Presence and titer of anti-REGN2222 antibodies

Part B:

- Proportion of subjects who have RSV-confirmed hospitalization, ER,UC, or pediatric clinic visits[a] (for upper or lower respiratory infection) during the study period
- PK parameters using sparse sampling
- Presence and titer of anti-REGN2222 antibodies

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.

8.4. Exploratory Endpoints

The exploratory endpoints are the following:Total number of RSV-associated medical visits (hospital, ER, UC, or pediatric visits[a]) for each subject and associated treatments or procedures at these visits

- Total number of medical visits (hospital, ER, UC, or pediatric visits[a]) for each subject and associated treatments or procedures at these visits, during the study period excluding the initial RSV–associated medical visits.
- Number of RSV-confirmed hospitalizations (defined as stay in hospital [or its ER] for 24 hours or longer)
  - Number of days with RSV-associated mechanical ventilation
  - Number of days with RSV-associated supplemental oxygen
- Length of stay in hospital for RSV-associated illness

- Number of missed days of work for parent(s) or guardian(s) associated with each medically attended RSV event
- Number and proportion of subjects with other common respiratory pathogens identified by a RT-PCR multiplex respiratory panel which is distinct from the RT-PCR assay being used to test for RSV for the study's efficacy endpoints.

Note: Only nose swab specimens determined to be negative for RSV using the RT-PCR assay being utilized for evaluation of the study's efficacy endpoints will be evaluated by the RT-PCR multiplex respiratory panel. RSV positive samples identified by the RT-PCR multiplex respiratory panel will not be taken into account for the purpose of the analysis of the study's efficacy endpoints.

[a] A pediatric clinic visit represents any outpatient medically attended visit that could include, but is not limited to, a pediatric clinic visit, a primary physician office visit, a family physician visit, or a study site visit.

8.5. Antidrug Antibody Variables

Antidrug antibody variables include status (positive or negative) and titer as follows:

- Total ADA-positive subjects at any time
- Pre-existing immune reactivity - defined as either an ADA positive response at baseline with all posttreatment ADA results negative, or a positive response at baseline with all posttreatment ADA responses less than 4-fold over baseline titer levels.
- Treatment-emergent - defined as either an ADA positive response after treatment when baseline results are negative, or if any posttreatment ADA-positive response is greater than or equal to 4-fold over baseline titer levels. The treatment-emergent responses will be further characterized into Persistent and Transient.
  - Persistent Response - treatment-emergent ADA positive response with two or more ADA-positive sampling time points during the treatment period (and follow-up phase if any) such that the first and last ADA-positive sample (with no ADA-negative samples in between) is separated by at least a 12-week period or only the last collected sample is ADA-positive.
  - Transient Response - Any treatment-emergent ADA-positive response that is not considered persistent
- Titer values
- Titer category
  - Low (titer <1000)
  - Moderate (1000 ≤ titer ≤ 10 000)
  - High (titer >10 000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

Primary and secondary endpoints are listed in Section 8.2 and Section 8.3, respectively.

Results from Part A and Part B of this study will be analyzed separately.

9.1. Statistical Hypothesis

The null hypothesis of the study is that the proportions of medically attended RSV hospitalization or outpatient LRTI in the placebo group and in the REGN2222 groups are the same (H_0: $p_1 = p_2$). The alternative hypothesis is that the rate for each REGN2222 group is different from the rate for the placebo group (H_1: $p_1 \neq p_2$).

9.2. Sample Size

For Part A, the goal of the study is to study infant PK, and therefore no formal sample size calculation will be conducted.

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. As the event rate may vary over RSV season or geographic region, it is assumed that event rate is 10% for the placebo group, and either dose of RENG2222 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 has 90% power to demonstrate a 60% or greater reduction at 2-sided significance level α=0.025. This sample size also incorporated a 5% early dropout rate. The sample size calculation is based chi-square test with continuity correction and performed using nQuery version 7.0 (Statistical Solutions Ltd, Cork, Ireland).

The significant level of 2-sided 0.025 is set in consideration of multiplicity of 2 comparisons between each of the 2 REGN2222 dose arms with placebo.

With a total of 1515 randomized subjects and 1:1:1 randomization ratio, it is expected 1010 subjects to receive REGN2222 (505 subjects in each of the 2 REGN2222 arms) and 505 subjects to receive placebo and in total, an approximate of 90 primary endpoint events. Also, with 1010 subjects exposed to REGN2222, the regulatory requirement for safety assessment will be met.

Impact of Early Termination on Sample Size and Power

Acknowledging the study enrollment is planned to be terminated with the 2016-2017 RSV season and final enrollment of approximately 1200 subjects, 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. 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

=00.05 for each statistical test) as opposed to the originally planned Bonferroni adjustment (two-sided $\alpha = 0.025$ for each pairwise treatment comparison). (See Section 9.5.2.4).

9.2.1. Blinded Sample Size Re-estimation

Sample size may be re-estimated at the end of each RSV season. If the study is fully enrolled at that time, then the sample size will be re-estimated before database lock. Sample size re-estimation will be based on the blinded and pooled event rate and hypothesized treatment effect. The hypothesized treatment effect for each arm of REGN2222 will be a 60% reduction in event rates compared with the placebo arm. As stated by Gould and Shih (Gould 1998), the blinded sample size re-estimation does not affect type I error materially for binomially distributed data. The objective of this sample size re-estimation is to ensure the study will be adequately powered in case of a milder-than-expected RSV season, leading to low medically attended visits for RSV infection. Sample size re-estimation will be done using the formula from Gould (Gould 1992). If the re-estimated sample size is less than 1665 subjects, or 1.10 times of planned sample size, the study will proceed as is, with no change in planned sample size (the study will have approximately 86% or more power with planed sample size). If the re-estimated sample size is between 1665 and 2200, the study sample size will be increased to the re-estimated sample size. If the re-estimated sample size is greater than 2200 subjects, the sponsor will make an administrative decision to either increase the sample size to 2200 subjects, or keep the planed sample size unchanged.

9.3. Analysis Sets

9.3.1. Part A

The safety analyses will be based on enrolled subjects who receive any study drug. The PK analysis set contains subjects who received a single dose of REGN2222 and have at least 1 measurable serum concentration of REGN2222.

9.3.2. Part B

The efficacy analyses will be based on the full analysis set defined as all randomized subjects who receive any study drug. For all efficacy analyses, subjects will be analyzed as randomized.

The safety analysis set contains all randomized subjects who received at least 1 dose of the study medication. For all safety analyses, subjects will be summarized as treated.

The PK analysis set contains all subjects who received at least 1 dose of REGN2222 and have at least 1 measurable serum concentration of REGN2222.

9.4. Subject Disposition

9.4.1. Part A

The following will be provided:

- The total number of screened subjects: parent(s) or legal guardian(s) who signed the ICF
- The total number of subjects in the safety analysis set and PK analysis set
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects prematurely discontinued from treatment, and the reasons for discontinuation

9.4.2. Part B

The following will be provided:

- The total number of screened subjects: parent(s) or legal guardian(s) who signed the ICF
- The total number of randomized subjects: received a randomization number (subject identification)
- The total number of subjects in the safety analysis set and PK analysis set
- The total number of subjects who discontinued the study, and the reasons for discontinuation
- A listing of subjects prematurely discontinued from treatment, and the reasons for discontinuation

9.5. Statistical Methods

Part A and Part B: For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation, mean, median, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for Part A and by treatment arm for Part B of the study.

9.5.2. Efficacy Analysis

Efficacy analyses apply to Part B and not Part A.

9.5.2.1. Primary Efficacy Analysis

Part B

The primary endpoint will be analyzed using Mantel-Haenszel methods to assess the differences in the proportions between each REGN2222 treatment and placebo, stratifying 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).

The proportion of primary endpoint events for primary analysis will be calculated as number of subjects with a medically attended RSV infection (hospitalization or outpatient RSV LRTI) during the 150-day efficacy assessment period divided by total number of subjects assigned to each treatment group from the full analysis set.

For a subject who discontinued study treatment early (see Section 5.2.2.1), the subject will be followed to Day 150 for assessment of primary endpoint events. The event observed after the early termination of study treatment will be counted as an event and will be included in the primary analysis.

For early termination subjects (ie, those who did not complete Day 150 visit), the 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". [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".
    - Remaining early termination subjects (including non-RSV deaths) across all treatment groups, will be imputed to the average placebo score (estimated placebo event rate). The approach to estimating the placebo event rate is the Kaplan-Meier estimate at Day 150.
- Imputed scores along with observed subject data will be utilized in the Cochran-Mantel-Haenszel analysis. Imputed scores along with observed subject data will be utilized in the Cochran-Mantel-Haenszel (CMH) analysis (with stratum adjusted by Mantel-Haenszel method).

As a sensitivity analysis to the primary endpoint, the following analyses will be performed:

RSV LRTI analysis: For the proportion of subjects with a medically attended RSV infection, only those RSV hospitalizations meeting the protocol-specified definition of LRTI (a subset of all RSV hospitalizations) will be counted towards the hospitalization component; the outpatient component will remain as described for the primary analysis.

Alternative LRTI Definition Analysis: Comparing the proportion of subjects with a medically attended RSV-confirmed infection (hospitalization or outpatient lower respiratory tract infection) during the study period (Day 150) as compared to placebo; using the following definition of LRTI:

- 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

The primary endpoint events of medically attended RSV infection (hospitalization or outpatient LRTI) will also be analyzed by stratified logistic regression and by stratified log-rank test and presented using a Kaplan-Meier curve. For the log-rank test and Kaplan-Meier curve, time to the first primary endpoint event will be analyzed; subjects who do not have a primary endpoint event will be censored at the last time point when the primary endpoint event is assessed.

Additional sensitivity analyses are planned to support the primary analysis, including exact test method (Fisher's), etc. All sensitivity analyses with associated details will be described in the SAP.

9.5.2.2. Secondary Efficacy Analysis

The proportion of subjects who have RSV-confirmed hospitalization, ER, UC, or pediatric visits during the 150-day efficacy assessment period will be analyzed using the same methods described in the analysis of the primary endpoint.

9.5.2.3. Exploratory Analysis

Pharmacoeconomic variables will be summarized descriptively for Part B.

Respiratory syncytial virus 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 2 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.

Pharmacoeconomic variables and proportion of subjects with other common respiratory pathogens identified by a RT-PCR multiplex respiratory panel will be summarized descriptively for Part B. Only nose swab specimens determined to be negative for RSV using the RT-PCR assay being utilized for evaluation of the study's efficacy endpoints will be evaluated by the RT-PCR multiplex respiratory panel.

9.5.2.4. Multiplicity Considerations

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 9.5.6), since the primary and secondary efficacy endpoints will have been concluded at the time of the first step analysis.

9.5.3. Safety Analysis

9.5.3.1. Part A

Safety and tolerability will be descriptively summarized, including TEAEs, laboratory variables, vital signs, and physical examination.

9.5.3.2. Part B

Safety and tolerability will be descriptively summarized by treatment arm and the combined REGN2222 treatment arms, including TEAEs, laboratory variables, vital signs, and physical examination.

Safety evaluations will be performed on the safety analysis set; no formal comparisons and testing against the placebo group or between different treatment arms are planned.

9.5.3.3. Adverse Events

Definitions

For safety variables in Part A, 2 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the days from the first dose of study drug to the Day 150 visit.

Treatment-emergent AEs in Part A are defined as those that are not present at baseline or represent the exacerbation of a preexisting condition during the treatment period.

For safety variables in Part B, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The safety treatment period is defined as the time from the first dose of study drug up to the day of the last dose of study drug + 180 days.
- The post-treatment period: defined as starting the day after the end of the TEAE period.

Treatment-emergent adverse event in Part B are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the safety treatment period (TEAE period).

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the PT, and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group (dose cohort in Part A or treatment arm in Part B) will include:

- The number (n) and percentage (%) of subjects with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), presented by SOC and PT
- TEAEs by relationship to treatment (related, not related), presented by SOC and PT

Deaths, AESIs, and other SAEs will be listed and summarized by dose cohort for Part A and by treatment arm for Part B of the study.

Treatment-emergent AEs leading to permanent treatment discontinuation will be listed and summarized by dose cohort for Part A and by treatment arm for Part B of study.

Additional evaluation of TEAEs may be conducted for identification of hypersensitivity.

9.5.3.4. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of subjects with treatment-emergent potential clinical significant value (PCSV) will be summarized for each vital sign variable. The definition of treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of subject with a treatment-emergent PCSV will be summarized for each clinical laboratory test. The definition of treatment-emergent PCSV will be defined in the SAP.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.5.3.5. Treatment Exposure

Part A:

The observation period (defined as the time between the date of the first study drug administration and the date of the end of study or the last visit), rather than the treatment exposure, will be presented by dose cohort. The number of doses each subject receives will also be summarized by dose cohort for Part A.

Part B:

The number (%) of subjects randomly assigned and exposed to double-blind study drug will be presented by specific time periods for each treatment group and the combined REGN2222 treatment arms. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group and the combined REGN2222 treatment arms using number of subjects, means, standard deviation, minimums, medians, and maximums. A summary of the number of doses by treatment group will also be provided.

9.5.3.6. Treatment Compliance

The compliance with study treatment will be calculated as follows:

$$\text{Treatment Compliance} = \frac{\text{(Number of study drug injections during exposure period)}}{\text{(Number of study drug injections expected during exposure period)}} \times 100\%.$$

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

9.5.4. Pharmacokinetic Analysis

9.5.4.1. Part A

The PK of REGN2222 will be characterized using a population modeling approach. Data from Part A may be combined with data from an additional study in healthy adult volunteers. The details of the population PK analysis will be described in a separate PK analysis plan.

The structural model will contain absorption rate constant, clearance, and volume of distribution as fixed-effect parameters. The intersubject variability of the PK parameter estimates and the random residual error in the data will be estimated with appropriate error models. The best base model will be identified based on standard goodness-of-fit criteria and the covariates that have a significant impact on PK of REGN2222 will be identified, if appropriate. The final population PK model will be evaluated using bootstrapping and visual predictive check.

Individual post hoc PK parameters such as absorption rate constant, clearance, and volume of distribution of REGN2222 will be estimated. Pharmacokinetic simulations will be performed using the final PK model developed in Part A to assist with selection of REGN2222 dosage regimen for Part B.

9.5.4.2. Part B

PK data from Part A will be combined with PK data from Part B and the population PK model developed from Part A data will be refined using the similar approach described in Part A. Data from healthy adult volunteers in the previous study may also be included. Pharmacokinetic simulations using the revised final PK model may be performed to provide insight into any dosage adjustment in infants.

9.5.5. Analysis of Antidrug Antibody Data

9.5.5.1. Part A

Listings of ADA positivity and titers will be presented by subject and time point. Prevalence of ADA will be assessed as absolute occurrence (n) and percent (%) of subjects, grouped by single cohort and ADA-titer level.

9.5.5.2. Part B

Listings of ADA positivity and titers will be presented by subject, time point, and treatment arm. Prevalence of ADA will be assessed as absolute occurrence (n) and percent (%) of subjects, grouped by treatment arms and ADA-titer level.

9.5.5.3. Part A and Part B:

Plots of drug concentrations will be examined, and the influence of ADAs on individual PK profiles will be evaluated. An assessment of impact of ADA on safety may be provided.

9.5.6. Timing of Statistical Analyses

The analysis for Part B will be conducted in 2 steps.

9.5.6.1. First Step: Efficacy and Safety Analysis

The first step analysis will be conducted as soon as the last randomized subject has completed the end of the 150-day efficacy assessment period visit and all the data have been collected and validated; this will consist of the final analysis of all efficacy endpoints. The safety analyses will be performed on all safety data collected through the common cut-off date. For this analysis, the common cut-off date is the date that the last subject completes the day 150 visit (Part B Visit 7; end of 150-day efficacy assessment period).

The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect. Since all the efficacy measure data collection will have been concluded at the time of this first step analysis, the significance level for the study remains at 2-sided 0.05. This first step analysis may be used for submission to health authorities or other interested parties.

Sponsor personnel involved in the first step analysis of the study will not be involved in the conduct of the study afterwards; individual study 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.

9.5.6.2. Second Step: Final Safety Analysis

The second step analysis will be performed at the end of the study and will consist of the final analysis of the safety measures.

9.6. Interim Analysis

9.6.1. Part A

An interim PK analysis will be conducted on the first 18 infants after at least one postdose blood sample is collected for determination of drug concentration following administration of study drug. Following the completion of Part A, subject data will be locked and reported. This will be done to confirm the dose to move forward with in Part B of the study.

9.6.2. Part B

If the sample size of 1515 infants is not achieved via enrollment in the Northern Hemisphere, the study will continue to enroll in subsequent RSV seasons. A study-treatment blinded sample size re-assessment (as detailed in Section 9.2.1) may be proposed at the end of any RSV season. This blinded sample size re-estimation was never performed during the study, nor is re-estimation planned during the remainder of the study since enrollment will end with the 2016/2017 RSV season in the Northern Hemisphere due to Sponsor's administrative decision.

An unblinded interim efficacy analysis is not planned.

9.7. Final Reporting

The results from Part A and Part B of this study will be summarized separately. The results from Part A of the study will be summarized after its completion. The final report will be written after completion of both Part A and Part B of the study.

9.8. Additional Statistical Data Handling Conventions

9.8.1. Definition of Baseline

Unless otherwise specified, the baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of the study drug. For most variables, Day 1 procedures and assessments are considered to be baseline.

9.8.2. General Rules for Handling Missing Data

If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of the study medication date, then the start date by the study medication intake date will be imputed; otherwise, the missing day or month by the first day or the first month will be imputed.

No imputations for missing laboratory data, vital sign data, or physical examination data will be made.

9.8.3. Visit Windows

Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator.

9.8.4. Unscheduled Assessments

Extra assessments (laboratory data or vital signs associated with nonprotocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summarized by study visit. If more than 1 laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

9.9. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. The investigator and Sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at sponsor.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture tool (Medidata rave)

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study include the following:

- IVRS/IWRS system – assignment of subject identification number, blood collection schedule, randomization (Part B only), study drug supply
- Electronic data capture system – data capture
- SAS software – statistical review and analysis

10.2.1. Interactive Voice or Web Response System

An IVRS/IWRS will be used for the assignment of the subject identification number, including order of blood sampling, randomization to a treatment arm (in Part B only), and assignment of study drug kits (Part A: open-label with 1 cohort; Part B: randomized with 3 arms). A subject will be considered to be enrolled in the study upon receipt from the IVRS/IWRS of the subject's blood collection schedule and assignment of study drug kit from the site supply.

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor (designee, eg, contract research organization's monitor) will visit each site prior to enrollment of the first subject, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, subject ICFs, documentation of subject recruitment and follow-up, AEs, SAEs, and concomitant therapy, as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate subject records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every subject enrolled in the study. After review of the clinical data for each subject, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

- Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection.

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/ERC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in the ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/ERC. A copy of the IRB/ERC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator (designee; if acceptable by local regulations) to obtain written informed consent from each subject's parent(s) or legal guardian(s) prior to the subject's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to fullest possible extent in language that the parent(s) or legal guardian(s) can understand. The ICF will be signed and dated by the subject's parent(s) or legal guardian(s) and the same investigator (designee) who explained the ICF.

Local law must be observed in deciding whether the consent of 1 or both parent(s) or legal guardian(s) is required. If only 1 parent or guardian signs the ICF, the investigator must document the reason the other parent or guardian did not sign. The subject's parent(s) or legal guardian(s) may also be required to sign and date the ICF, as determined by the IRB/ERC and in accordance with the local regulations and requirements.

If the subject's parent(s) or legal guardian(s) can write but cannot read, the assent form will be read to them before writing their name on the form. If the subject's parent(s) or legal guardian(s) can understand but can neither write nor read, the ICF will be read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the subject's study record, and a copy of the signed ICF must be given to the subject's parent(s) or legal guardian(s).

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All parent(s) or legal guardian(s) of study subjects must be informed of the new information and provide their written consent if they wish the subject to continue in the study. The original signed revised ICF must be maintained in the subject's study record and a copy must be given to the subject's parent(s) or legal guardian(s).

13.3. Subject Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study subject will be maintained. Subjects will be identified by their initials and a subject identification

number only on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The subject's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor will take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/ERC, as described in the ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the subjects' parent(s) or legal guardian(s) (eg, advertising) before any subject may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the subjects, in which case the IRB/ERC will be informed as soon as possible
- Continuation of study from Part A to Part B with confirmation of the dose regimens to be used in Part B
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk.

In addition, the IRB/ERC will be informed of any event likely to affect the safety of subjects or the continued conduct of the clinical study.

A copy of the IRB/ERC approval letter with a current list of the IRB/ERC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter will include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/ERC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may initiate Part B based on the written communication to investigators, ethics committees and competent authorities prior to formally amending the protocol for the purpose of altering the dose, if applicable. The sponsor may not implement a change in the design of the protocol or ICF without an IRB/ERC-approved amendment. All substantial protocol amendments will be approved by the competent authorities before changes are implemented according to national regulations.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close Out of a Site

The sponsor and the investigator have the right to close out a site prematurely.

15.2.1. Investigator's Decision to Close Out Site

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision will be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

15.2.2. Sponsor's Decision to Close Out Site

The sponsor will notify the investigator(s) of a decision to close out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any subject within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of subjects required for the study is enrolled earlier than expected.

In all cases, the appropriate IRB/ERC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the subjects' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each subject.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

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21. APPENDICES

APPENDIX A. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, 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, Amendment 4, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council on Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/ERC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX B. PART B DOSE SELECTION BASED ON PHARMACOKINETICS PROCESS

The following process will be used to select the dose for Part B.

1. Run individual simulations based on subjects' specific body weights and ages (post-natal age and gestational age), estimate the concentration at each sampling time point (Days 2, 8, 15, 22, 29, and 57)*, and calculate the corresponding 90% prediction interval.
2. Compare the observed with 90% prediction interval:
    - If 16 or more (>88%) of observed values are above the 90% prediction interval; re-estimate the PK model and reduce dose accordingly to achieve target concentration**
    - If 16 or more (>88%) of observed values are below the 90% prediction interval; re-estimate the PK model and evaluate the probability (P) that the target concentration** will be achieved in >40% of subjects; and if (P) <20%, then revise the dose frequency.
    - Otherwise continue the study as planned

*Note: There will be data for 18 patients [1 sample per patient; 3 patients per time point]

**Pharmacokinetic target for subtype A (5 μg/mL) and subtype B (27 μg/mL).

APPENDIX C. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG INJECTION PROCEDURE

Is there a reasonable possibility that the event may have been caused by the study drug injection procedure?

No:

- Due to external causes such as environmental factors or other treatment/s being administered
- Due to the patient's/subject's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug injection procedure
- Does not reappear or worsen when dosing with study drug injection procedure is resumed
- Is not known to be a response to the study drug injection procedure based upon pre-clinical data or prior clinical data

Yes:

- Could not be explained by environmental factors or other treatment/s being administered
- Could not be explained by the patient's/subject's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug injection procedure
- Resolves or improves after discontinuation of study drug injection procedure
- Reappears or worsens when dosing with study drug injection procedure is resumed
- Is known to be a response to the study drug injection procedure based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX D. TOXICITY GRADING SCALE FOR GRADING ALLERGIC REACTIONS AND ANAPHYLAXIS - COMMON TERMINOLOGY CRITERIAL FOR ADVERSE EVENTS (CTCAE; VERSION 4.0, PUBLISHED 28 MAY 2009; V4.03, 14 JUNE 2010)

The CTCAE descriptive terminology will be utilized for reporting AEs of allergic reactions and anaphylaxis. A grading (severity) scale is provided for each AE term.

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen					
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

APPENDIX E. TOXICITY GRADING SCALE - MODIFIED FROM DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009)

The following modification was made: removal of acute systemic allergic reaction. (Division of AIDS 2004)

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C - 38.6°C	38.7°C - 39.3°C	39.4°C - 40.5°C	>40.5°C

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions or hospitalization (other than emergency room visit) indicated
Unintentional weight loss	NA	5% - 9% loss in body weight from baseline	10% - 19% loss in body weight from baseline	≥20% loss in body weight from baseline or aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)
INFECTION				
Infection	Localized, no systemic antimicrobial treatment indicated and symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated or symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated and symptoms causing inability to perform usual social & functional activities or operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb or pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function or hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Pediatric ≤15 years	Erythema or induration or edema present but ≤2.5 cm diameter	Erythema or induration or edema >2.5 cm diameter but <50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema or induration or edema involving ≥50% surface area of the extremity segment (eg, upper arm/thigh) or ulceration or secondary infection or phlebitis or sterile abscess or drainage	Necrosis (involving dermis and deeper tissue)
Pruritus associated with injection See also Skin: Pruritus (itching - no skin lesions)	Itching localized to injection site and relieved spontaneously or with <48 hours treatment	Itching beyond the injection site but not generalized or itching localized to injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SKIN – DERMATOLOGICAL				
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash or target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to 1 site	Extensive or generalized bullous lesions or Stevens-Johnson syndrome or ulceration of mucous membrane involving 2 or more distinct mucosal sites or toxic epidermal necrolysis
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritus (itching – no skin lesions) (See also Injection Site Reactions: Pruritus associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical examination)	Asymptomatic and no intervention indicated	Asymptomatic and nonurgent medical intervention indicated	Symptomatic, nonlife-threatening and non-urgent medical intervention indicated	Life-threatening arrhythmia or urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) or testing consistent with ischemia	Unstable angina or acute myocardial infarction

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (significant acute blood loss)	NA	Symptomatic and no transfusion indicated	Symptomatic and transfusion of ≤2 units packed RBCs (for children ≤10 cc/kg) indicated	Life-threatening hypotension or Transfusion of >2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Pediatric ≤17 years (with repeat testing at same visit)	NA	91st - 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) or hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences or effusion with non-urgent intervention indicated	Life-threatening consequences (eg, tamponade) or urgent intervention indicated
Prolonged PR Interval - Pediatric ≤16 years	first-degree AV block (PR > normal for age and rate)	Type I second-degree AV block	Type II second-degree AV block	Complete AV block

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged QTc - Pediatric ≤16 years	Asymptomatic, QTc interval 0.450 - 0.464 sec	Asymptomatic, QTc interval 0.465 - 0.479 sec	Asymptomatic, QTc interval ≥0.480 sec	Life-threatening consequences, eg, torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/ embolism	NA	Deep vein thrombosis and No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis and Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding and intervention indicated	New onset with symptoms or worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences or aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diarrhea				
Adult and Pediatric ≥1 year	Transient or intermittent episodes of unformed stools or increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools or increase of 4 - 6 stools over baseline per 24-hour period	Bloody diarrhea or increase of ≥7 stools per 24-hour period or IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric <1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools or mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated or hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Nausea	Transient (<24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours or aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock
Pancreatitis	NA	Symptomatic and hospitalization not indicated (other than emergency room visit	Symptomatic and hospitalization indicated (other than emergency room visit)	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension or aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
NEUROLOGIC				
Alteration in personality-behavior or in mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal and homicidal ideation or attempt, acute psychosis) or causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium or obtundation, or Coma
Ataxia	Asymptomatic ataxia detectable on examination or Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cognitive and behavioral/ attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities or specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities or Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities or Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions or Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤16 years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions or hospitalization indicated (other than emergency room visit) or headache with significant impairment of alertness or other neurologic function

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on examination or minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions or respiratory muscle weakness impairing ventilation
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on examination or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure – Pediatric <18 years	Seizure, generalized onset with or without secondary generalization, lasting <5 minutes with <24 hours postictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 to 20 minutes with <24 hours postictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% - 80%	FEV1 or peak flow 50% - 69%	FEV1 or peak flow 25% - 49%	Cyanosis OR FEV1 or peak flow <25% or Intubation
Dyspnea or respiratory distress - Pediatric <14 years	Wheezing or minimal increase in respiratory rate for age	Nasal flaring or Intercostal retractions or Pulse oximetry 90% - 95%	Dyspnea at rest causing inability to perform usual social & functional activities or Pulse oximetry <90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on examination	Symptomatic anterior uveitis or medical intervention indicated	Posterior or pan-uveitis or operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. **Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implement). **Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. **Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks, etc.).				
ENDOCRINE/METABOLIC				

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Abnormal fat accumulation (eg, back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Basic Self-care Functions – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding. **Basic Self-care Functions – Young Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement). **Usual Social & Functional Activities – Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc. **Usual Social & Functional Activities – Young Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).				
HEMATOLOGY Standard International Units are listed in italics				
Absolute CD4+ count – **Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm 3 300 - 400/µL	200 – 299/mm3 200 – 299/µL	100 – 199/mm3 100 – 199/µL	<100/mm3 <100/µL
Absolute lymphocyte count – **Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm3 0.600 x 10^9 – 0.650 x 10^9/L	500 – 599/mm^3 0.500 x 10^9 – 0.599 x 10^9/L	350 – 499/mm^3 0.350 x 10^9 – 0.499 x 10^9/L	<350/mm^3 <0.350 x 10^9/L
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, >7 days	1,000 – 1,300/mm3 1.000 x 10^9 – 1.300 x 10^9/L	750 – 999/mm^3 0.750 x 10^9 – 0.999 x 10^9/L	500 – 749/mm^3 0.500 x 10^9 – 0.749 x 10^9/L	<500/mm^3 <0.500 x 10^9/L
Infant∗† , 2 – ≤ 7 days	1,250 – 1,500/mm^3 1.250 x 10^9 – 1.500 x 10^9/L	1,000 – 1,249/mm^3 1.000 x 10^9 – 1.249 x 10^9/L	750 – 999/mm^3 0.750 x 10^9 – 0.999 x 10^9/L	<750/mm^3 <0.750 x 10^9/L
Infant∗† , ≤1 day	4,000 – 5,000/mm^3 4.000 x 10^9 – 5.000 x 10^9/L	3,000 – 3,999/mm^3 3.000 x 10^9 – 3.999 x10^9/L	1,500 – 2,999/mm^3 1.500 x 10^9 – 2.999 x 10^9/L	<1,500/mm^3 <1.500 x 10^9/L
Comment: Parameter changed from "Infant, < 1 day" to "Infant, ≤1 day"				
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (eg, bilirubin).				

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fibrinogen, decreased	100 – 200 mg/dL 1.00 – 2.00 g/L OR 0.75 – 0.99 x LLN	75 – 99 mg/dL 0.75 – 0.99 g/L OR 0.50 – 0.74 x LLN	50 – 74 mg/dL 0.50 – 0.74 g/L OR 0.25 – 0.49 x LLN	<50 mg/dL <0.50 g/L OR <0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
Comment: The Hgb values in mmol/L have changed because the conversion factor used to convert g/dL to mmol/L has been changed from 0.155 to 0.6206 (the most commonly used conversion factor). For grading Hgb results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for that lab.				
Adult and Pediatric ≥57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL 5.24 – 6.23 mmol/L	7.5 – 8.4 g/dL 4.62–5.23 mmol/L	6.50 – 7.4 g/dL 4.03–4.61 mmol/L	< 6.5 g/dL <4.03 mmol/L
Adult and Pediatric ≥57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL 6.18 – 6.79 mmol/L OR Any decrease 2.5 – 3.4 g/dL 1.58 – 2.13 mmol/L	9.0 – 9.9 g/dL 5.55 - 6.17 mmol/L OR Any decrease 3.5 – 4.4 g/dL 2.14 – 2.78 mmol/L	7.0 – 8.9 g/dL 4.34 - 5.54 mmol/L OR Any decrease ≥4.5 g/dL >2.79 mmol/L	< 7.0 g/dL <4.34 mmol/L
Comment: The decrease is a decrease from baseline				
Infant∗†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL 5.24 – 5.86 mmol/L	7.0 – 8.4 g/dL 4.31 – 5.23 mmol/L	6.0 – 6.9 g/dL 3.72 – 4.30 mmol/L	< 6.00 g/dL <3.72 mmol/L
Infant∗†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL 5.87 - 6.54 mmol/L	8.0 – 9.4 g/dL 4.93 – 5.86 mmol/L	7.0 – 7.9 g/dL 4.34 – 4.92 mmol/L	< 7.00 g/dL <4.34 mmol/L
Infant∗† , ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL 7.42 – 8.09 mmol/L	10.0 – 11.9 g/dL 6.18 – 7.41 mmol/L	9.0 – 9.9 g/dL 5.59- 6.17 mmol/L	< 9.0 g/dL <5.59 mmol/L
Correction: Parameter changed from "Infant < 21 days" to "Infant ≤ 21 days"				
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (eg, bilirubin).				
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm3 100.000 x 10^9 – 124.999 x 10^9/L	50,000 – 99,999/mm^3 50.000 x 10^9 – 99.999 x 10^9/L	25,000 – 49,999/mm^3 25.000 x 10^9 – 49.999 x 10^9/L	< 25,000/mm^3 < 25.000 x 10^9/L
WBC, decreased	2,000 – 2,500/mm^3 2.000 x 10^9 – 2.500 x 10^9/L	1,500 – 1,999/mm^3 1.500 x 10^9 – 1.999 x 10^9/L	1,000 – 1,499/mm^3 1.000 x 10^9 – 1.499 x 109/L	< 1,000/mm^3 <1.000 x 10^9/L
CHEMISTRIES Standard International Units are listed in italics				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN 30 g/L – < LLN	2.0 – 2.9 g/dL 20 - 29 g/L	< 2.0 g/dL < 20 g/L	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low	16.0 mEq/L – < LLN 16.0 mmol/L – < LLN	11.0 – 15.9 mEq/L 11.0 – 15.9 mmol/L	8.0 – 10.9 mEq/L 8.0 – 10.9 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Comment: Some laboratories will report this value as Bicarbonate (HCO_3) and others as Total Carbon Dioxide (CO_2). These are the same tests; values should be graded according to the ranges for Bicarbonate as listed above.				
Bilirubin (Total)				
Adult and Pediatric > 14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant∗† , ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL 342 – 428 µmol/L	25.1 – 30.0 mg/dL 429 – 513 µmol/L	> 30.0 mg/dL >513.0 µmol/L
Infant∗† , ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL 342 – 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Calcium, serum, high				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL 2.65 – 2.88 mmol/L	11.6 – 12.5 mg/dL 2.89 – 3.13 mmol/L	12.6 – 13.5 mg/dL 3.14 – 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (eg, bilirubin).				

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Infant∗†, < 7 days	11.5 – 12.4 mg/dL 2.88 – 3.10 mmol/L	12.5 – 12.9 mg/dL 3.11 – 3.23 mmol/L	13.0 – 13.5 mg/dL 3.245 – 3.38 mmol/L	> 13.5 mg/dL >3.38 mmol/L
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL 1.95 – 2.10 mmol/L	7.0 – 7.7 mg/dL 1.75 – 1.94 mmol/L	6.1 – 6.9 mg/dL 1.53 – 1.74 mmol/L	< 6.1 mg/dL <1.53 mmol/L
Infant∗†, < 7 days	6.5 – 7.5 mg/dL 1.63 – 1.88 mmol/L	6.0 – 6.4 mg/dL 1.50 – 1.62 mmol/L	5.50 – 5.90 mg/dL 1.38 – 1.51 mmol/L	< 5.50 mg/dL <1.38 mmol/L
Comment: Do not adjust Calcium, serum, low or Calcium, serum, high for albumin				
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (e.g., bilirubin).				
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL 5.18 – 6.19 mmol/L	240 – 300 mg/dL 6.20 – 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 years	170 – 199 mg/dL 4.40 – 5.15 mmol/L	200 – 300 mg/dL 5.16 – 7.77 mmol/L	> 300 mg/dL >7.77 mmol/L	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL 6.44 – 8.88 mmol/L	161 – 250 mg/dL 8.89 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL > 27.75 mmol/L
Fasting	110 – 125 mg/dL 6.11 – 6.94 mmol/L	126 – 250 mg/dL 6.95 – 13.88 mmol/L	251 – 500 mg/dL 13.89 – 27.75 mmol/L	> 500 mg/dL >27.75 mmol/L
Glucose, serum, low				

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL 3.05 – 3.55 mmol/L	40 – 54 mg/dL 2.22 – 3.06 mmol/L	30 – 39 mg/dL 1.67 – 2.23 mmol/L	< 30 mg/dL <1.67 mmol/L
Infant∗†, < 1 month	50 – 54 mg/dL 2.78 – 3.00 mmol/L	40 – 49 mg/dL 2.22 – 2.77 mmol/L	30 – 39 mg/dL 1.67 – 2.21 mmol/L	< 30 mg/dL <1.67 mmol/L
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (eg, bilirubin).				
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL 3.37 – 4.12 mmol/L	160 – 190 mg/dL 4.13 – 4.90 mmol/L	≥ 190 mg/dL ≥4.91 mmol/L	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL 2.85 – 3.34 mmol/L	130 – 189 mg/dL 3.35 – 4.90 mmol/L	≥ 190 mg/dL ≥ 4.91 mmol/L	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L 0.60 – 0.70 mmol/L	0.9 – 1.1 mEq/L 0.45 – 0.59 mmol/L	0.6 – 0.8 mEq/L 0.30 – 0.44 mmol/L	< 0.60 mEq/L < 0.30 mmol/L
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low				
Adult and Pediatric > 14 years	2.5 mg/dL – < LLN 0.81 mmol/L – < LLN	2.0 – 2.4 mg/dL 0.65 – 0.80 mmol/L	1.0 – 1.9 mg/dL 0.32 – 0.64 mmol/L	< 1.00 mg/dL < 0.32 mmol/L
Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL 0.97 – 1.13 mmol/L	2.5 – 2.9 mg/dL 0.81 – 0.96 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL <0.48 mmol/L
Pediatric < 1 year	3.5 – 4.5 mg/dL 1.13 – 1.45 mmol/L	2.5 – 3.4 mg/dL 0.81 – 1.12 mmol/L	1.5 – 2.4 mg/dL 0.48 – 0.80 mmol/L	< 1.50 mg/dL < 0.48 mmol/L
Potassium, serum, high	5.6 – 6.0 mEq/L 5.6 – 6.0 mmol/L	6.1 – 6.5 mEq/L 6.1 – 6.5 mmol/L	6.6 – 7.0 mEq/L 6.6 – 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Potassium, serum, low	3.0 – 3.4 mEq/L 3.0 – 3.4 mmol/L	2.5 – 2.9 mEq/L 2.5 – 2.9 mmol/L	2.0 – 2.4 mEq/L 2.0 – 2.4 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Sodium, serum, high	146 – 150 mEq/L 146 – 150 mmol/L	151 – 154 mEq/L 151 – 154 mmol/L	155 – 159 mEq/L 155 – 159 mmol/L	≥ 160 mEq/L ≥ 160 mmol/L
Sodium, serum, low	130 – 135 mEq/L 130 – 135 mmol/L	125 – 129 mEq/L 125 – 129 mmol/L	121 – 124 mEq/L 121 – 124 mmol/L	≤ 120 mEq/L ≤ 120 mmol/L

Parameter	Grade 1 MILD	Grade 2 MODERATE	Grade 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Triglycerides (fasting)	NA	500 – 750 mg/dL 5.65 – 8.48 mmol/L	751 – 1,200 mg/dL 8.49 – 13.56 mmol/L	> 1,200 mg/dL > 13.56 mmol/L
Uric acid	7.5 – 10.0 mg/dL 0.45 – 0.59 mmol/L	10.1 – 12.0 mg/dL 0.60 – 0.71 mmol/L	12.1 – 15.0 mg/dL 0.72 – 0.89 mmol/L	> 15.0 mg/dL > 0.89 mmol/L
URINALYSIS Standard International Units are listed in italics				
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection				
Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h 0.200 – 0.999 g/d	1,000 – 1,999 mg/24 h 1.000 – 1.999 g/d	2,000 – 3,500 mg/24 h 2.000 – 3.500 g/d	> 3,500 mg/24 h > 3.500 g/d
Pediatric > 3 mo - < 10 years	201 – 499 mg/m^2/24 h 0.201 – 0.499 g/d	500 – 799 mg/m^2/24 h 0.500 – 0.799 g/d	800 – 1,000 mg/m2/24 h 0.800 – 1.000 g/d	> 1,000 mg/ m2/24 h > 1.000 g/d
∗ Values are for term infants. Preterm infants should be assessed using local normal ranges. † Use age and sex appropriate values (eg, bilirubin).				
AE=adverse event; AV=atrioventricular; CNS=central nervous system; CVA=cerebral vascular accident; ECG=electrocardiogram; FEV1= forced expiratory volume in the first second; IV=intravenous; NA=not applicable; QTc=corrected QT interval; RBC=red blood cells				

Modified from: 28 Dec-04/Clarification Aug 09 Version 1.0/Clarification 1

APPENDIX F. TOXICITY GRADING SCALE - MODIFIED FROM DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS (VERSION 2.0, NOVEMBER 2014)

The following tables are reproduced from selected pages of Division of AIDS, November 2014.

Hematology[1]				
Parameter	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L)* *>5 years of a*ge *(not HIV infected)*	600 to <650 *0.600 x 10^9 to <0.650 x 10^9*	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.500 x 10^9 to <0.500 x 10^9*	<350 *<0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	<400 *<0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	<750 *<0.750 x 10^9*
≤1 day of age	4,000 to ,5000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	<1,500 *<1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00 x LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75 x LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50 x LLN	<50 *<0.50* OR <0.25 x LLN OR Associated with gross bleeding

Hematology[1]				
Parameter	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin[2], Low (g/dL; *mmol/L*)[3] *≥13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to <10.0 *5.57 to <6.19*	7.0 to <9.0 *4.34 to <5.57*	<7.0 *<4.34*
≥13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *<4.03*
57 days of age to <13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to <9.5 *5.25 to <5.88*	6.5 to <8.5 *4.03 to <5.25*	<6.5 *4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to <8.5 *4.32 to <5.26*	6.0 to <7.0 *3.72 to <4.32*	<6.0 *<3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to <9.5 *4.94 to <5.88*	6.7 to <8.0 *4.15 to <4.94*	<6.7 *<4.15*
8 to ≤21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to <11.0 *5.57 to <6.81*	8.0 to <9.0 *4.96 to <5.57*	<8.0 *<4.96*
≤7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to <13.0 *6.19 to <8.05*	9.0 to <10.0 *5.59 to <6.19*	<9.0 *<5.59*
INR, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 ULN	2.0 to 3.0 x ULN	≥3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%
PTT, High (not on anticoagulation therapy)	1.1 to <1.66 x ULN	1.66 to <2.33 x ULN	2.33 to <3.00 x ULN	≥3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <124,999 *100.000 x 10^9 to <124.999 x 10^9*	50,000 to <100,000 *50.000 x 10^9 to <100,000 x 10^9*	25,000 to <50,000 *25.000 x 10^9 to <50.000 x 10^9*	<25,000 *<25.000 x 10^9*

Hematology[1]				
Parameter	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
PT, High (not on anticoagulation therapy)	1.1 to <1.25 x ULN	1.25 to <1.50 x ULN	1.50 to <3.00 x ULN	≥3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *>7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2,499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	<1,000 *<1.000 x 10^9*
≤7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2,500 x 10^9 to 3.999 x 10^9*	<2,500 *<2.500 x 10^9*

INR=international normalized ratio; LLN=lower limit of normal; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal; WBC=white blood cells

1. DAIDS AE Grading Table Version 2.0, November 2014, pages 27 and 28.
2. Male and female sex are defined as sex at birth.
3. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Total Bilirubin for Term and Preterm Neonates[1]				
Parameter	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Total Bilirubin[2]**, High** (mg/dL; *µmol/L*)[3] ***Term Neonate***[4]				
<24 hours of age	4 to <7 *68.4 to <119.7*	7 to <10 *119.7 to <171*	10 to <17 *171 to <290.7*	≥17 *≥290.7*
24 to <48 hours of age	5 to <8 *85.5 to <136.8*	8 to <12 *136.8 to <205.2*	12 to <19 *205.2 to <324.9*	≥19 *≥324.9*
48 to <72 hours of age	8.5 to <13 *145.35 to <222.3*	13 to <15 *222.3 to <256.5*	15 to <22 *256.5 to <376.2*	≥22 *≥376.2*
72 hours to <7 days of age	11 to <16 *188.1 to <273.6*	16 to <18 *273.6 to <307.8*	18 to <24 *307.8 to <410.4*	≥24 *≥410.4*
7 to 28 days of age (breastfeeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*

Total Bilirubin for Term and Preterm Neonates[1]				
Parameter	**Grade 1 MILD**	**Grade 2 MODERATE**	**Grade 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
7 to 28 days of age (not breast feeding)	1.1 to <1.6 x ULN	1.6 to <2.6 x ULN	2.6 to <5.0 x ULN	≥5.0 x ULN
Preterm Neonate[4] *35 to <37 weeks gestational age*	Same as for *Total Bilirubin, High, Term Neonate* (based on days of age).	Same as for *Total Bilirubin, High, Term Neonate* (based on days of age).	Same as for *Total Bilirubin, High, Term Neonate* (based on days of age).	Same as for *Total Bilirubin, High, Term Neonate* (based on days of age).
32 to <35 weeks gestational age and <7 days of age	NA	NA	10 to <14 *171 to <239.4*	≥14 *≥239.4*
28 to <32 weeks gestational age and <7 days of age	NA	NA	6 to <10 *102.6 to <171*	≥10 *≥171*
<28 weeks gestational age and <7 days of age	NA	NA	5 to <8 *85.5 to <136.8*	≥8 *≥136.8*
7 to 28 days of age (breastfeeding)	5 to <10 *85.5 to <171*	10 to <20 *171 to <342*	20 to <25 *342 to <427.5*	≥25 *≥427.5*
7 to 28 days of age (not breast feeding)	1.1 to 1.6 x ULN	1.6 to <2.6 ULN	2.6 to <5.0 ULN	≥5.0 x ULN

NA=not applicable ULN=upper limit of normal

1. DAIDS AE Grading Table Version 2.0, November 2014, page 30.
2. Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for phototherapy at grade 3 and for exchange transfusion at grade 4.
3. A laboratory value of 1 mg/dL is equivalent to 17.1 μmol/L.
4. Definitions: Term is defined as ≥37 weeks gestational age; near-term, as ≥35 weeks gestational age; preterm, as <35 weeks gestational age; and neonate, as 0 to 28 days of age.

APPENDIX G. PRETERM UPPER LIMIT OF NORMAL (ULN) VALUES SPECIFIED IN EXCLUSION CRITERION 6 AND THE 1.1 TIMES ULN CUT-OFF LIMIT FOR THESE VALUES ABOVE WHICH SUBJECTS WOULD BE EXCLUDED FROM STUDY ENTRY

Parameter		**Conventional Unit**		**SI Unit**	
		ULN	**>1.1 x ULN**	**ULN**	**>1.1 x ULN**
Creatinine		1.5 mg/dL	1.65 mg/dL	133 µmol/L	146.3 µmol/L
Total Bilirubin		12 mg/dL	13.2 mg/dL	205 µmol/L	225.5 µmol/L
ALT		45 U/L	49.5 U/L	45 U/L	49.5 U/L
AST	*0 to10 days of age*	150 U/L	165 U/L	150 U/L	165 U/L
	10 days to < 12 months of age	80 U/L	88 U/L	80 U/L	88 U/L
Alkaline Phosphatase		700 U/L	770 U/L	700 U/L	770 U/L

ALT = alanine aminotransferase, AST = aspartate aminotransferase, SI = International System of Units, ULN = upper limit of normal

Signature of Sponsor's Responsible Officers

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study .

Study 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

Protocol Number: R2222-RSV-1332

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signatu re Page for VV-RIM-00012444 v1.0

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

Signature Page for VV–RIM-00012444 vl.O Approved