REGENERON
Biostatistics and Data Management

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STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:

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

Part A

Compound:	**REGN2222**
Protocol Number:	**R2222-RSV-1332**
Clinical Phase:	**Phase 3**
Sponsor:	**Regeneron Pharmaceuticals, Inc.**
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	**Original Statistical Analysis Plan / Aug 9, 2016**

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

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1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for analyses prior to database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analyses of data for study R2222-RSV-1332 **Part A only**. A separate SAP is prepared for Part B.

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

1.1. Background/Rationale

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

Part A is an open-label PK study of REGN2222 to determine the PK in pre-term infants after a single dose to enable the selection of dosing regimens for Part B. It will also provide initial evaluation of safety and tolerability in infants. A sparse PK sampling scheme is used to reduce the volume of blood collected in infants. Based on observed PK data from R2222-HV-1326, a FIH healthy adult study, a population PK model was developed and scaled to the infant population following age and body weight correction, using the scaling approach adopted by Robbie 2012. A Bayesisan feedback analysis will be used to determine the concordance of observed REGN2222 serum concentration in infants of Part A with model predicted concentrations after administration of a single 30 mg/kg IM dose of REWGN2222. Pre-specified criteria in the protocol will be used to qualify the dosing regimens selected a priori in Part B.

Part B is a randomized, double-blind, placebo-controlled, study designed to evaluate efficacy, safety, monthly concentrations of REGN2222 in serum, and immunogenicity of IM administration of REGN2222 in preterm infants who are not eligible or recommended for, or who do not have access to, palivizumab.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study in Part A is to determine the PK of Intramuscular (IM) administration of REGN2222.

1.2.2. Secondary Objective

The secondary objective of the study in Part A is to evaluate safety, tolerability, and immunogenicity of REGN2222 following IM administration.

1.2.3. Modifications from the Statistical Section in the Final Protocol

Analyses of Preferred Terms (PTs) of interest for hypersensitivity are added to assist safety evaluation.

1.2.4. Modifications from the Approved Statistical Analysis Plan

This is the first version.

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2. INVESTIGATING PLAN

2.1. Study Design and Randomization

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. Subjects will be assigned open-label treatment with a single dose of REGN2222 30 mg/kg during the RSV season.

Part B is a randomized, placebo-controlled, 3-arm, multicenter study. A separate SAP is prepared for Part B.

2.2. Sample Size and Power Considerations

For Part A, the goal of the study is to study infant PK, and therefore no formal sample size calculation was conducted. Twenty-four subjects were planned to be enrolled in Part A.

2.3. Study Plan

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. Subjects will be monitored in the clinic for 3 hours after dosing, followed by a physical examination, and if appropriate, discharge. 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. The study flow diagram for Part A is depicted in Figure 1.

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.

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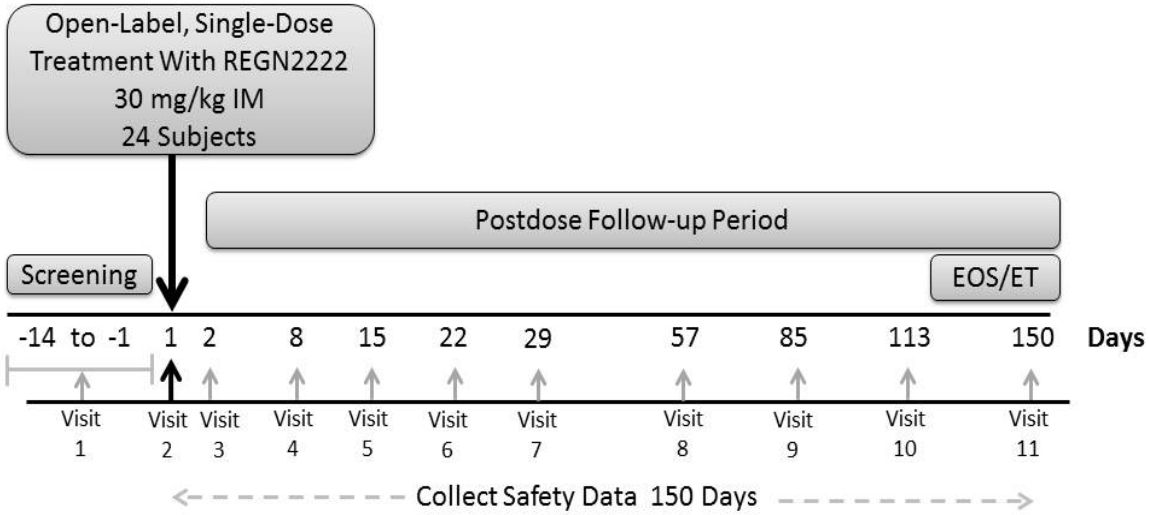
Figure 1: Part A: 30 mg/kg Single Dose



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.

The study schedule of events is presented in Appendix 10.1. As shown in Appendix 10.1, PK samples will be collected at clinical study day 2,8,15,22,29,57,85,113 and 150 (EOS). A sparse sampling strategy is used to reduce the volume of blood collected from infants; there will be 3 PK samples (one provided by each of 3 infants) per each nominal time point, except Day 150, at which all 23 enrolled infants will have a serum sample collected for determination of REGN2222 concentration.

3. ANALYSIS POPULATIONS

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

3.1. The Safety Analysis Set (SAF)

The safety analyses will be based on enrolled subjects who receive any dose of REGN2222.

3.2. The Pharmacokinetic Analysis Set

The PK analysis set will contain subjects who receive a single dose of REGN2222 and have at least 1 measurable concentration of REGN2222 in serum.

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

The ADA analysis set contains subjects who received a single dose of REGN2222 and have at least 1 post-treatment ADA result.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline variables will be summarized:

- Age at screening (weeks)
- Gestational age categories
  - ≤31 weeks 6 days
  - ≥32 weeks 0 days and ≤35 weeks 6 days
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Baseline Weight (kg)
- Country
- Region (North America [United States and Canada], Rest of the world)

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 17.1.

4.3. Prior / Concomitant Medications

Medications/Procedures will be recorded from the day of informed consent until the end of study (EOS) visit or early termination (ET) visit, whichever is applicable. Medications will be coded to the anatomical therapeutic chemical (ATC) classification level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Subjects will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of REGN2222.

Concomitant medications/procedures: medications taken or procedures performed following the dose of REGN2222 through the EOS visit or early termination (ET) visit, whichever is applicable.

4.4. Efficacy Variables

Clinical efficacy variables analyses are not applicable for Part A.

4.5. Safety Variables

Subject safety will be assessed through the collection of adverse events (AEs), laboratory data (hematology, chemistry), vital signs, and physical exam (including weight). For these measures, with the exception of the AEs, the eCRF visit label will be used for temporal summaries. Unless otherwise noted (example: AEs), baseline for these measures is defined as the last chronologically available valid assessment prior to the dose of REGN2222.

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

- The pretreatment period is defined as the time from signing the informed consent form (ICF) to before the first dose of REGN2222.
- The treatment period is defined as the days from the first dose of REGN2222 to the last study visit (ie, Day 150 EOS visit or ET visit, whichever is applicable).

4.5.1. Adverse Events and Serious Adverse Events

The definitions for AEs and serious adverse events (SAEs) are described in Sections 7.1.1 and 7.1.2 of the study protocol, respectively. Additional information on determining whether abnormal laboratory or vital sign results should be considered as AEs is included in Section7.2.6 of the study protocol. AEs and SAEs will be collected from the time of informed consent signature and then at each visit until the end of the study. All AEs are to be coded to a PT and associated primary SOC according to the MedDRA version 17.1.

Treatment-emergent AEs (TEAEs) are defined as AEs that are not present at baseline or represent an exacerbation of a preexisting condition during the treatment period. Therefore, referencing the protocol, TEAEs will be defined programmatically as any AE record with a start date/time on or after the first study treatment administration (greater than or equal to study day 1), inclusive to the end of the study (specifically the EOS visit or ET visit).

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

4.5.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study are hypersensitivity reactions occurring within 48 hours after exposure to the study drug (including but not limited to urticaria, edema, respiratory distress, anaphylaxis, and allergic reactions). Such treatment-emergent AESI are identified by investigator using a tick box on the eCRF AE page.

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

1. Modified narrow Standard MedDRA Query (SMQ [N]) for “hypersensitivity”. The modification is to add PTs: pruritus, pruritus generalised, prurigo, flushing, erythema, generalised erythema, injection site erythema, rash papular, allergic oedema.
2. MedDRA query for all PTs under the high level term (HLT): injection site reaction.

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3. Hypersensitivity PTs of interest per Carbonell-Estrany X 2010 as listed in Appendix 10.2.
4. Hypersensitivity PTs of interest per Feltes TF 2011 as listed in Appendix 10.3 .
5. Acute hypersensitivity reactions **that occur within 48 hours after dosing**, classified in 2 categories, per Shapiro 2010:
    a. Urticarial Reactions which will be identified by search for PTs: urticaria, oedema; low level term (LLT): localized erythema.
    b. Allergic Rash which will be identified by search for PTs: rash, dermatitis allergic, erythema annulare, erythema multiforme, rash maculo-papular. For AEs with the PT of rash, a manual review of their verbatims will be conducted to specifically identify AEs that are acute rash.

4.5.3. Laboratory Safety Variables

Clinical laboratory tests include hematology and blood chemistry. Samples for laboratory testing will be collected at screening, a post-baseline visit according to assigned blood draw schedule (time points specified in the schedule of assessments [Appendix 10.1]), and at EOS or at the time of early termination (ET).

Clinical laboratory values will be in standard international (SI) units, including associated normal ranges provided by the central laboratory, and grouped by function in summary tables. Conventional unit may be provided. Clinical laboratory tests are provided below, sub-grouped by function:

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Blood Chemistry

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

Hematology

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

4.5.4. Vital Signs

The following vital signs parameters will be collected at visit 1, visit 2, visit 3, visit 7, visit 8, visit 9, visit 10, and at EOS or at the time of ET. On the study drug dosing days, vital signs will be assessed prior to collection of blood sample, prior to injection of study drug, and after completion of the injection (Part A at 1, 2, and 3 hours [±10 minutes] after completion of the injection.

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

4.5.5. Physical Examination

Subjects will have a physical examination (including weight) at visit 1, visit 2, visit 3, visit 8, and at EOS or at the time of ET. On study drug-dosing days, physical examinations will be conducted predose and again postdose (excluding weight) prior to discharge. The result for each body system is an outcome of normal or abnormal.

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

Drug concentration in serum at Day 150 will be reported for each infant, however because of the pooled sampling scheme and sparseness of the data, non-compartmental analysis on observed individual concentration-time profiles will not be performed.

Because of the pooled sampling scheme, not all infants will have ADA measurements at the same time.

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

- Total subjects with negative ADA assay response at all times.
- Total subjects with positive ADA assay response at any time.
- Pre-existing immunoreactivity - defined as either a positive ADA assay response at baseline with all post-treatment ADA assay results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 4-fold over baseline titer levels.
- Treatment-emergent - defined as any post-treatment positive ADA assay response when the baseline ADA result is negative or missing.
- Treatment-boosted - defined as any post-treatment positive ADA assay response that is greater than or equal to 4-fold over baseline titer level when baseline is ADA positive in the ADA assay.
- Titer values
- Titer category
  - Low (titer <1000)
  - Moderate (1000 ≤ titer ≤ 10000)
  - High (titer >10000)

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5. STATISTICAL METHODS

Part A is a single cohort PK study, therefore there is no statistical testing and all summaries will be descriptive in nature.

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

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively based on the SAF. Other safety baseline data is presented collectively in the descriptive statistics summary tables containing respective post-baseline data. Listing of demographics and baseline characteristics will be presented.

5.2. Medical History

Medical history will be summarized by primary SOC and PT based on the SAF. Summaries will show subject counts (percentages). The tables will be sorted by SOC in alphabetical order. Within each primary SOC, PTs will be sorted by decreasing frequency of the counts in the study total. A listing for medical history will also be provided.

5.3. Prior / Concomitant Medications

The number and percentage of subjects taking concomitant medication will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4 based on the SAF. The tables will be sorted by alphabetical order of ATC level 2 and ATC level 4 followed by descending order of frequency of preferred name. Number and percentage of subjects taking prior medication will be summarized in a similar fashion to concomitant medication.

Listings of concomitant medications will include generic name and ATC levels 2 and 4, indication, start date, end date, dose, frequency, and route. To separate prior and concomitant medications in the listing, a flag will be added for prior medication. A flag will also be added to the listing to denote a concomitant medication administered to treat an AE.

5.4. Subject Disposition

The following summaries will be provided for subject disposition status. For all categories, percentages will be calculated using the number of enrolled subjects as the denominator except for the screened and screen failure categories, where denominator will be the number of screen subjects.

- Screened subjects (signed the ICF).
- Screen failed subjects and reasons for screen failure.
- Subjects enrolled (received a drug kit assignment in IVRS/IWRS)

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- Subjects treated (SAF population)
- Completed study (from the EOS eCRF)
- Did not complete study (from the EOS eCRF)
- Primary reasons for study discontinuation (from the EOS eCRF)

Study completers are defined as subjects who complete the EOS visit. The following listing will be provided for all enrolled subjects: A listing of subject disposition including dosing date(s), last visit date, completed study or discontinued by reason; a listing of screening failures and reasons.

5.5. Treatment Compliance and Observation Period

As Part A is a single-dose study, treatment compliance is not applicable. The observation period, rather than the treatment exposure, will be presented.

Duration of observation period during the study is calculated as:

(Date of the last study visit – date of the first dose of REGN2222) +1.

The duration of the observation period will be summarized using the number of subjects, mean, median, SD, minimum, Q1, Q3, and maximum.

The number (%) of subjects having observation periods of specific lengths will be summarized according to time period breakdowns as follows: ≥1 to <8 days, ≥ 8 to <15 days, ≥ 15 to <22 days, ≥ 22 to <29 days, ≥ 29 to <57 days, ≥ 57 to <85 days, ≥ 85 to <113 days, ≥ 113 to < 145 days, and ≥ 145 days.

5.6. Analysis of Safety Data

Safety and tolerability will be descriptively summarized, including AEs, clinical laboratory variables, physical exam, and vital signs for the SAF (as defined in Section 3.1).

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

- The baseline value is defined as the last available value obtained up to the date and time of the first dose of REGN2222, except otherwise specified.
- Supplemental assessment is defined in the case of more than 1 assessment collected at a scheduled visit, specifically the later assessment in the visit window will be marked as supplemental assessment. Supplemental measurements will not be included by-visit summaries, therefore the earliest assessment at the visit will be used in summaries and all observations will be presented in listings.
- Assessments repeatedly collected during the study will be defined by the eCRF visit label for temporal summaries and subject listings.
- All data points of safety parameters including central laboratory measurements, vital signs, physical exams, adverse events will be presented by subject in listings.

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- For continuous safety parameters including central laboratory measurements (for selected chemistry parameters) and vital sign scores, descriptive statistics will be used to summarize results and change from baseline values by visit.
- A treatment-emergent Potential Clinically Significant abnormal value (PCSV) is a laboratory value or vital sign that was: normal at baseline but abnormal after treatment with study drug, or: abnormal at baseline and worsened after treatment with study drug. Thresholds for treatment-emergent PCSV in laboratory variables and vital signs are defined in Section 10.4. Treatment-emergent PCSV criteria will determine which subjects had at least 1 treatment-emergent PCSV during the post-baseline observation period, taking into account all assessments including unscheduled or supplemental assessments. Subjects who had post-baseline PCSV but missing baseline value will be regarded as having treatment-emergent PCSV.

5.6.1. Adverse Events

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

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.2.

Summaries of all TEAEs will include:

- Overview of TEAEs, summarizing number and percentage of subjects with any
  - TEAEs.
  - Serious TEAEs.
  - TEAEs leading to death.
  - TEAEs leading to permanent treatment discontinuation.
  - TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal.
  - TEAEs that occurred within 2 days after study drug administration.
- All TEAEs by SOC and PT.
- All TEAEs by SOC, PT, and severity.
- All TEAEs by SOC, PT, and relationship (related, not related) to study drug.
- All TEAEs by SOC, PT, and relationship (related, not related) to injection procedure.
- All TEAEs by PT ordered by decreasing subject frequency.
- Study drug-related TEAEs by SOC and PT.

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- Study drug-related TEAEs by SOC, PT, and severity (this output will not be produced if there is no study drug-related TEAEs).
- Injection procedure-related TEAEs by SOC and PT.
- Injection procedure-related TEAEs by SOC, PT, and severity (this output will not be produced if there is no injection procedure-related TEAEs).
- Summaries of TEAEs of special interest (as defined in Section 4.5.2):
  - TEAEs of special interest (as flagged by the investigator on the eCRF) by SOC and PT.
  - TEAEs that are PTs of interest of hypersensitivity from **modified** SMQ(N) for hypersensitivity by PT.
  - TEAEs that are PTs of interest of hypersensitivity from MedDRA query for all PTs under the HLT of injection site reaction by PT. This analysis will also be performed for subgroups of subjects administered with 1 and 2 injections respectively.
  - TEAEs that are hypersensitivity PTs of interest per Carbonell-Estrany X 2010. by PT.
  - TEAEs that are hypersensitivity PTs of interest per Feltes TF 2011. by PT.
  - TEAEs that are acute hypersensitivity reactions per Shapiro 2010 by PT (or LLT where appropriate).
  - The above TEAEs of special interest may also be presented by PT and severity.
- TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal by SOC, PT, and severity
- Study drug-related TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal by SOC, PT, and severity (this output will not be produced if there is no study drug-related TEAEs).
- Injection procedure-related TEAEs with severity of 3/4/5/Severe/Life-Threatening/Fatal by SOC, PT, and severity (this output will not be produced if there is no injection procedure-related TEAEs).
- Serious TEAEs by SOC and PT.
- Study drug-related serious TEAEs by SOC and PT (this output will not be produced if there is no serious TEAEs).
- Injection procedure-related serious TEAEs by SOC and PT (this output will not be produced if there is no serious TEAEs).
- TEAEs leading to death by SOC and PT.
- Non-serious study drug-related TEAEs by SOC and PT.
- Non-serious injection procedure-related TEAEs by SOC and PT.

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

Primary SOCs will be sorted by alphabetical order. Within each primary SOC, PTs will be sorted by decreasing frequency of the counts for study total.

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

5.6.2. Clinical Laboratory Measurements

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

First summaries will focus on study population changes with the intent of identifying deviations on a large scale across time. This approach for continuous variables summarizes both the actual scores (at both baseline and post-baseline) and the change from baseline scores at each post-baseline scheduled visit. Descriptive statistics include number of subjects, mean, median, standard deviation, minimum, Q1, Q3, and maximum values for each of the 8 blood collection schedule group (Schedule A through H) and for study total (at baseline and EOS visits only). Unscheduled or supplemental measurements will not be included in this summary.

Second, shift tables based on baseline categories of low/normal/high/total will be provided for each post-baseline visit. Numerical shift in lab values (from baseline to post-baseline) will also be visually displayed by graphical plots. Scatter-box plots of lab values over time will be presented with visit plotted on the x-axis and lab values on the y-axis. Unscheduled or supplemental measurements will not be included in these summaries. In addition to the shift analyses, number (and percentage) of subjects with lab values meeting the treatment-emergent PCSV criteria at least once during the post-baseline observation period will be summarized. These laboratory parameters will be presented by the biological functions defined in Section 4.5.3. Subject listings of laboratory measurements with a flag to indicate those meeting the treatment-emergent PCSV criteria will be provided.

Local laboratory measures will only be listed separately.

5.6.3. Vital Signs

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

The obtainment of blood pressure in infants, without cause or suspicion of underlying abnormalities is not routinely done in the outpatient pediatric setting. Specialized equipment, not

routinely present in physician offices, is required. As a result of the issues surrounding the accurate obtainment of blood pressures in the study's infant population, the study protocol was revised to allow investigators to mark that blood pressures are not able to be obtained. In many instances blood pressure results are not available, and in instances where results have been obtained, the accuracy of the recordings can be questioned. As a result, no shift table or treatment-emergent PCSV analyses will be performed on blood pressure measurements.

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

Only the number (and percentage) of subjects with pulse rate and respiratory rate values meeting the treatment-emergent PCSV criteria at least once during the post-baseline observation period will be summarized.

Subject listings of vital sign measurements with a flag to indicate those meeting the treatment-emergent PCSV criteria will be provided.

5.6.4. Physical Examination

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

5.7. Analysis of Pharmacokinetics and Anti-Drug Antibody Data

The analysis in this section will be done by PK/Bioanalytical group and results will be provided in a separate report.

Pooled individual scatter and mean concentration-time plots will be produced and descriptive statistics will be calculated for each time point at day 2, 8, 15, 22, 29, 57, 85, 113 and 150.

Predicted drug concentrations from a previously developed PK model based on REGN2222 adult PK data from the FIH study (REGN-HV-1326) will be compared with observed drug concentration data from Part A using a Bayesian Feedback approach. In this approach, observed REGN2222 drug concentration data is superimposed on the 90% prediction interval generated from the population PK model to confirm a priori PK model estimates and provide a Bayesian estimate of REGN2222 half-life in infants. Given the sparse nature of the drug concentration sampling scheme and the limited number of subjects in part A (N=23), post hoc individual PK estimates will not be determined from part A data. A final population analysis with parameter estimation will be conducted at the end of Part B of the study and will combine both Part A and Part B data. Post hoc PK parameters may be determined from the mean integrated drug concentration time profile using a non-compartmental approach. Given that only a single concentration time profile of the mean data will be available, descriptive satisicis for any PK parameter calculated will not be determined.

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

Possible correlation between changes in PK profile and treatment-emergent positive responses in the ADA assay will be evaluated to identify a potential impact of anti-REGN2222 antibodies on drug exposure. The impact of treatment-emergent ADA assay response may be evaluated separately for subjects with missing baseline ADA results.

6. DATA CONVENTIONS

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

6.1. Definition of Baseline for Safety Variables

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

6.2. Data Handling Convention for Missing Data

Adverse event

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

Missing date

Every effort will be made to collect the start date/time of all AEs and concomitant medications. However, in the case the start date/time of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study drug, except if an incomplete date (eg, month and year) or an indicator variable clearly indicates that the event started prior to treatment. If the partial date indicates the same year (when only year is available) or the same month/year (when both month and year are available) of the first dose of study drug date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed. No imputation is planned for date/time of AE resolution.

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

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

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

Laboratory Safety Variables

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

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6.3. Visit Windows

Assessments repeatedly collected during the study (including those taken outside of protocol allowable windows) will be displayed according to their eCRF visit label for temporal summaries and subject listings. Drug concentration data obtained outside study visit window will be included in the analysis accounting for the actual time elapsed since dosing.

6.4. Unscheduled Assessments

Extra assessments (laboratory data or vital signs associated with unscheduled clinical visits or obtained in the course of investigating or managing AEs) will be included in listings and may also be used to determine treatment-emergent PCSVs., but not in by visit summaries of parameters with descriptive statistics for study population changes. 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.

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7. INTERIM ANALYSIS

An interim population PK analysis using a Bayesian Feedback approach 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. Dose assessment and selection criteria are described in the protocol. The a prior selected dosing regimens in Part B will remain unchanged, if the PK data up to Day 57 (from subjects enrolled in Part A) demonstrates that the individual PK observations are consistent with the model predicted concentrations, following age and body weight corrections.

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8. SOFTWARE

All analyses will be done using SAS Version 9.2 or above.

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9. REFERENCES

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10. APPENDIX

10.1. Schedule of Time and Events

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 Protocol 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 Protocol 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.

10.2. Hypersensitivity PTs of interest per Carbonell-Estrany X 2010.

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

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

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10.3. Hypersensitivity PTs of interest per Feltes TF 2011.

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

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

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

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

Parameter	PCSV	Comments
Potassium, low	< 2.5 mmol/L and baseline ≥ 2.5 mmol/L	
Sodium, high	≥ 154 mmol/L and baseline < 154 mmol/L	
Sodium, low	< 125 mmol/L and baseline ≥ 125 mmol/L	
Uric acid, high	≥ 0.71 mmol/L and baseline < 0.71 mmol/L	
Hematology PCSV based on criteria for infants born at term, considering Grade 3 Severe and above events as per the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0 November 2014).		
WBC, Decreased	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline ≤ 1.499 x 10^9 cells/L for > 7 days of age ≤ 3.999 x 10^9 cells/L for ≤ 7 days of age	
Neutrophils, low	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline < 0.600 x 10^9 cells/L for > 7 days of age < 1.000 x 10^9 cells/L for 2 to 7 days of age < 3.000 x 10^9 cells/L for ≤ 1day of age	
Hemoglobin, low	Meeting the following PCSV criteria for at least one post-baseline measurement and no PCSV at baseline < 6.19 mmol/L for ≤ 7 days of age < 5.57 mmol/L for 8 to ≤ 21 days of age < 4.94 mmol/L for 22 to 35 days of age < 4.32 mmol/L for 36 to 56 days of age < 5.25 mmol/L for ≥ 57 days of age	
Platelets, decreased	< 50.000 x 10^9 cells/L and baseline ≥ 50.000 x 10^9 cells/L	
Vital signs PCSV based on normal ranges in http://health.ny.gov/professionals/ems/pdf/assmttools.pdf		
Respiratory Rate	< 30 breaths per minute and ≥ 30 breaths per minute at baseline > 60 breaths per minute and ≤ 60 breaths per minute at baseline	
Pulse Rate	< 100 beats per minute and ≥ 100 beats per minute at baseline > 160 beats per minute and ≤ 160 beats per minute at baseline	

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