STATISTICAL ANALYSIS PLAN COVER PAGE

Official Title of the study / Protocol Title: A Phase I/IIa, Open-label, Multiple-cohort, Dose-escalation Study to Evaluate the Safety and Tolerability of Gene Therapy with RGX-314 in Subjects with Neovascular AMD
(nAMD)

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STATISTICAL ANALYSIS PLAN

A Phase I/IIa, Open-label, Multiple-cohort, Dose-escalation Study to Evaluate the Safety and Tolerability of Gene Therapy with RGX-314 in Subjects with Neovascular AMD (nAMD)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV	Adeno-associated virus
AAV8	Adeno-associated virus serotype 8
AE	Adverse Event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CDPP	Clinical Data Presentation Plan
CI	Confidence Interval(s)
CNV	Choroidal Neovascularization
CSR	Clinical Study Report
CRT	Central Retinal Thickness
eCRF	Electronic Case Report Form
ELISpot	Enzyme-Linked ImmunoSpot
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
Fab	Antibody Fragment
FAF	Fundus Autofluorescence
GC	Genome Copy(ies)
HEK293	Human Embryonic Kidney cells 293
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IOP	Intraocular Pressure
ISC	Internal Safety Committee
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular (wet) Age-Related Macular Degeneration
PI	Primary Investigator
PT	Preferred Term

Abbreviation	Definition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SRT	Safety Review Trigger
TNTC	Too Numerous to Count
ULN	Upper Limit of Normal
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

1. INTRODUCTION

RGX-314 is a recombinant adeno-associated virus (AAV), serotype 8 (AAV8), gene therapy vector carrying a coding sequence for a soluble anti-vascular endothelial growth factor (VEGF) antibody fragment (Fab) protein. The long-term, stable delivery of this therapeutic protein following a one time gene therapy treatment for neovascular age-related macular degeneration (nAMD) could potentially reduce the future treatment burden while maintaining vision with a favorable risk:benefit profile.

This document describes the statistical analysis for protocol RGX-314-001, a Phase I/IIa dose escalation study to evaluate the safety and tolerability of gene therapy with RGX-314 in subjects with nAMD. The Statistical Analysis Plan (SAP) will be used to analyze data after all subjects have completed the primary study period (24 weeks following RGX-314 administration) and the end of the study period (104 weeks of follow-up after treatment with RGX-314). The SAP will be the basis for the final clinical study report (CSR) to provide guidance and a description of statistical methods and procedures used for the final analyses of study data. The final CSR will be completed after all subjects have completed the end of the study period (104 weeks of follow-up after treatment with RGX-314).

An overview of the study is provided in Section 3. Section 4 details the statistical methods relating to each study endpoint and describes general conventions and definitions. A separate document, the Clinical Data Presentation Plan (CDPP), containing tables, listings, figure shells, and programming specifications, has also been created for use in conjunction with this document. The programming specifications portion of the CDPP will be finalized prior to the database lock.

2. STUDY OBJECTIVES

2.1.1 Primary Objective

- To evaluate the safety and tolerability of RGX-314 through Week 26 (24 weeks post a single dose administered by subretinal delivery to subjects with nAMD)

2.1.2 Secondary Objective

- To evaluate the long-term safety and tolerability of RGX-314
- To evaluate the concentration of RGX-314 protein levels in aqueous fluid
- To evaluate the effect of RGX-314 on best corrected visual acuity (BCVA)
- To evaluate the effect of RGX-314 on central retinal thickness (CRT) as measured by Spectral Domain Optical Coherence Tomography (SD-OCT)
- To assess the need for rescue therapy

- To evaluate the effect of RGX-314 on choroidal neovascularization (CNV) lesion growth and leakage as measured by fluorescein angiography (FA)

3. STUDY OVERVIEW

3.1 Study Design

In this Phase I/IIa, first-in-human, open-label, multiple-cohort, dose-escalation study, approximately 42 nAMD subjects will be enrolled into up to 5 dose cohorts of RGX-314. Subjects who meet the inclusion/exclusion criteria will be enrolled and receive a 0.5 mg intravitreal injection of ranibizumab in the study eye (Visit 1). At Visit 2 (7 days after ranibizumab injection), subjects will be evaluated by SD-OCT to confirm anatomic response to the initial anti-VEGF activity associated with the ranibizumab injection compared with their baseline assessment. Subjects who do not have an anatomic response will be withdrawn from the study. For withdrawn subjects, anyone who has an adverse event (AE) associated with the ranibizumab injections on Visit 1 will be followed until the AE resolves (up to 30 days post-injection). At Visit 3 (Week 2), subjects will receive a single dose of RGX-314 administered in an operating room by subretinal delivery.

The term "Early Withdrawal" is used for subjects who dropped out prior to dosing with RGX-314, including those who 1) are considered nonresponsive to initial anti-VEGF response to ranibizumab at Visit 2, which is defined as not meeting the response criteria of reduction in CRT >50 microns or >30% improvement in central fluid by SD-OCT from Visit 1 to Visit 2 as determined by the primary investigator (PI); and/or 2) do not meet central lab results as specified in the study protocol. The term "Early Termination" is used for subjects who exit the study after receiving a dose of RGX-314.

The sentinel subject in each cohort will have vision of ≤20/63 and ≥20/400 (≤63 and ≥19 Early Treatment Diabetic Retinopathy Study [ETDRS] letters). After RGX-314 administration to the sentinel subject, there will be a minimum 4-week observation period for safety. The Internal Safety Committee (ISC) will review the safety data for this subject and if there are no safety concerns, up to 5 (Cohorts 1 to 3) or up to 11 (Cohorts 4 and 5) additional subjects (with expanded vision criteria of ≤20/40 and ≥20/400 [≤73 and ≥19 ETDRS letters]) may be treated with RGX-314, one per day on consecutive calendar days. If no safety review triggers (SRTs) are observed, then 4 weeks after the last subject is dosed (with the exception of Cohort 4 which had an IDMC review 4 weeks after the sixth subject was dosed, prior to cohort expansion to 12 subjects), all available safety data will be evaluated by the Independent Data Monitoring Committee (IDMC). Additionally, if any event meets the criteria of a Stopping Rule, dosing of any new subjects will be suspended until a complete review of all safety data has been performed by REGENXBIO and the IDMC. At any given IDMC meeting, whether called for by an SRT or at the planned IDMC meeting, the IDMC

may recommend to stop the study, proceed to the next dosing cohort, or proceed at a lower dose (up to a half log).

Subjects will have 3 visits within the first 4 weeks after treatment with RGX-314. Starting 4 weeks after RGX-314 administration, subjects may receive intravitreal ranibizumab rescue therapy at the Investigator's discretion if they meet predefined rescue injection criteria. Immunogenicity to the vector and transgene of RGX-314 will be assessed throughout the study.

Safety will be the primary focus for the initial 24 weeks after RGX-314 administration (primary study period). Following completion of the primary study period, subjects will continue to be assessed until 104 weeks following treatment with RGX-314 (Week 106). At the end of the study, subjects will be invited to participate in a long-term follow-up study.

The safety and tolerability of RGX-314 will be assessed in each dosed subject and will be monitored through assessment of ocular and non-ocular AEs and SAEs, chemistry, hematology, coagulation, urinalysis, immunogenicity, ocular examinations and imaging (BCVA, intraocular pressure, slit lamp biomicroscopy, indirect ophthalmoscopy, and SD-OCT), and vital signs.

3.2 Sample Size Determination and Statistical Power

No formal calculation was performed to determine sample size. Approximately 42 previously treated (with an anti-VEGF therapy) nAMD subjects meeting the inclusion/exclusion criteria (Cohorts 1 to 3: 6 subjects per dose cohort; Cohorts 4 and 5: approximately 12 subjects per dose cohort) will be treated with RGX-314. At the discretion of the Sponsor, additional subjects may be enrolled if a subject(s) does not receive a full 250 µL dose in the subretinal space.

3.3 Randomization and Masking

There is no randomization in this Phase I/IIa study and this study is not masked. All eligible subjects who are responsive, which is assessed on Day 8, to ranibizumab received on Day 1 will receive RGX-314 treatment.

3.4 Study Endpoints

3.4.1 Primary Endpoint

- Safety through Week 26 (24 weeks following RGX-314 administration): incidence of ocular and non-ocular adverse events (AEs) and serious AEs (SAEs)

3.4.2 Secondary Endpoints

- Ocular and non-ocular safety over 106 weeks
- Mean change from baseline in aqueous RGX-314 protein over time

- Mean change from baseline in BCVA over time
- Proportion of subjects gaining or losing ≥15 letters compared to baseline as per BCVA at Week 26, Week 54, and Week 106
- Mean change from baseline in CRT as measured by SD-OCT over time
- Mean number of anti-VEGF rescue injections over time
- Time to first anti-VEGF rescue injection
- Mean change from baseline in CNV and lesion size and leakage area based on FA over time
- Immunogenicity measurements (neutralizing antibodies to adeno-associated virus serotype 8 [AAV8], binding antibodies to AAV8, antibodies to RGX-314 protein, and Enzyme-Linked ImmunoSpot [ELISpot])
- Vector shedding analysis in serum and urine

[redacted]

4. STATISTICAL METHODOLOGY

4.1 General Considerations

In general, baseline will be defined as the last non-missing value prior to RGX-314 administration unless stated otherwise (see Sections 4.5.1 and 4.5.2). If a baseline value is missing following the above definition, a baseline value will not be imputed and will be considered missing.

All statistical tests, if applicable, will be two-sided at a significance level of 0.05 unless stated otherwise with corresponding 95% confidence intervals (CI). Nominal p-values will be provided without multiplicity adjustment. Actual p-values will be reported in the outputs.

All safety analyses will be performed on the as-treated population (Section 4.2) unless stated otherwise. All efficacy analyses will be performed on the as-treated population, and the evaluable for efficacy population will be used for sensitivity analyses for selected efficacy endpoints (Section 4.2). All data will be listed in subject-level data listings sorted by dose cohort and subject number. All tabular summaries will be presented by dose cohort, and overall. Categorical data will be summarized by the number and percentage of subjects falling within each category. Continuous variables will be summarized by descriptive statistics, including, number of non-missing observations, mean, standard deviation, median, minimum, and maximum.

All data collected up to the end of study will be included in summaries and analyses based on the visits entered into the clinical database.

Day 1 (visit label) is the day of ranibizumab injection as defined in the protocol. Study Day 1 is defined in the SAP to be the RGX-314 administration date (ie, V3 visit or Week 2 [Day 15] visit). Study Days are calculated as (assessment date – Study Day 1) for prior to RGX-314 administration date and (assessment date – Study Day 1 +1) for post RGX-314 administration date. In this convention, there is no value of Study Day 0.

All tables, figures, and listings will be generated with SAS® (SAS Institute Inc., Cary, North Carolina, USA) Version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to REGENXBIO SAS programming standards and REGENXBIO SAS validation procedures.

4.1.1 Computation Rules for Change from Baseline

Absolute change from baseline at each visit time point is computed as:

([Visit value] – [Baseline value])

Percent change from baseline at each visit time point is computed as:

(([Visit value] – [Baseline value])×100)/[Baseline value]

If either a visit value or the baseline value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing. If a visit value is non-zero, while the baseline value is zero, the absolute change from baseline will be computed but the percent change from baseline will be set to missing along with the number of subjects falling into this category. If a visit value is zero and the baseline value is zero, the percent change from baseline will also be zero.

4.1.2 Method for Imputing Missing or Partial Date

This section applies to imputing missing or partial AE/concomitant medication onset and end dates.

The goal for imputing partially missing data is to select the most conservative date within the possible range specified by the non-missing data. In general this will be the earliest date within the possible range, eg, within the month or year specified. However, the exception to this is when the possible range specified by the non-missing data is inclusive of the treatment start date. In that case the most conservative assumption is to impute the onset date as the treatment start date and the onset time as after the treatment start time. This conservative scheme ensures that an AE or a medication with partial or complete onset date will be treated as an RGX-314-emergent adverse event or a concomitant medication, respectively, as appropriate.

Completely Missing Onset Date:

In the unlikely case that the onset date is completely missing, the onset date will be set to the date of RGX-314 administration.

Partially Missing Onset Date:

In the case that the onset date is missing the day, then the onset date will be imputed as occurring on the 1st day of the given month and year, eg, March 2015 becomes 01 March 2015. In the situation where RGX-314 was administered in the same month and year, the onset date will be imputed as the day of RGX-314 administration (ie, Study Day 1).

In the case that the onset date is missing both the day and the month, then the onset date will be treated as January 1st of the given year, eg, XX-XXX-2015 is imputed as 01 January 2015. In the case that RGX-314 administration occurred in the same year, the onset date will be imputed as the day of RGX-314 administration (ie, Study Day 1).

The following examples assume that RGX-314 administration is on 17 Mar 2015:

Missing/Partial Date Reported	Date Imputed
XX XXX 2014	01 Jan 2014
XX XXX 2015	17 Mar 2015
XX Feb 2014	01 Feb 2014
XX Mar 2015	17 Mar 2015

In the case where the imputed onset date is later than the reported stop date, the imputed date will be set equal to the stop date.

Missing End Date:

Imputation of the end date when day, month, and/or year is missing will be made analogously using the last possible day, month, and/or year that subject was on study.

4.2 Analysis Populations

The analysis populations are defined in the following table:

Table 4-1: Analysis Populations

Population	Description
As-treated population	Subjects who received any dose of RGX-314 will be included in the as-treated population and subjects will be analyzed according to the actual dose level they received.
Evaluable for efficacy population	Subjects with both a baseline and 24 weeks measurements following RGX-314 administration in the study eye for at least one of two efficacy endpoints, BCVA or CRT as measured by SD-OCT. Subjects will be analyzed according to the actual dose level they received.

4.3 Study Subjects

4.3.1 Subject Disposition and Completion Status

Subject disposition information will be summarized for all subjects who signed informed consent form (ICF). The number of subjects who screened, who failed screening, who received ranibizumab during the study run-in, and who did not receive RGX-314 after receiving ranibizumab along with corresponding reasons will be presented. Among subjects who received RGX-314, the number and percentage of subjects who completed the study and who did not complete the study, with the reasons, will be presented by dose cohort and overall. A summary of inclusion/exclusion criteria not met will be provided for 1) screen failed subjects; 2) subjects who received ranibizumab but not RGX-314; and 3) for each dose cohort and overall.

Subject disposition and inclusion/exclusion criteria not met will be listed.

Subject entry information (ie, date first subject received RGX-314 and date last subject evaluated) will be presented for each site and all sites combined by dose cohort and overall.

4.3.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by dose cohort and overall for the as-treated population.

Demographic information includes age at informed consent, gender, race, and ethnicity. A summary of baseline disease characteristics (ocular history) collected on Day 1 includes:

1) Continuous variables to be summarized:

    - Months since the first anti-VEGF injection in the study eye for nAMD
    - Approximate number of anti-VEGF injections the study eye has received since nAMD diagnosis
    - Number of anti-VEGF injections the study/fellow eye has received in the last 12 months
    - Most recent record of central sub-field thickness in OCT assessment for the study eye (prior to signing informed consent)
    - Number of any other retinal therapy the study/fellow eye has received in the last 12 months
    - Day 1 central sub-field thickness in OCT assessment for the study eye
    - Day 1 best corrected visual acuity for the study eye

2) Categorical variables to be summarized:

    - Type of anti-VEGF injection the study/fellow eye has received in the last 12 months (ranibizumab, bevacizumab, and aflibercept)
    - Most recent record of fluid evidence in OCT assessment for the study eye (prior to signing informed consent) (Yes vs No)
    - Most recent record of Snellen fraction in visual acuity (VA) assessment for the study eye (prior to signing informed consent)
    - Most recent record of low vision testing in VA assessment for the study eye (prior to signing informed consent) (count fingers, hand movements, and light projection)

Relevant medical history for the preceding 5 years will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 20.0 (March, 2017) or higher and will be

summarized by dose cohort and overall. The number and percentage of subjects for each system organ class (SOC) will be presented.

4.3.3 RGX-314 Administration

Exposure to RGX-314 administration will be summarized for the as-treated population. The summary of RGX-314 administration will include descriptive statistics for study eye received RGX-314 (right/left eye), duration of procedure (minutes), duration of RGX-314 administration (minutes), number of blebs attempted, number of blebs created, total volume of RGX-314 delivered to the eye across all attempts (mcl), approximate total volume of RGX-314 delivered to subretinal space across all blebs (mcl), and approximate total size of blebs created (disc areas). Location of attempt (multiple categories possible) and complications during the procedure (Yes/No) will be summarized, including number and percentage of subjects in each category.

4.3.4 Anti-VEGF Rescue Injections

Subjects who have received anti-VEGF rescue injections for the study eye will be summarized by dose cohort and overall for the as-treated population. The proportion of subjects having at least one aflibercept rescue injection and/or at least one ranibizumab rescue injection will be summarized. The reason for ranibizumab rescue injections will be summarized per subject (ie, counting each subject only once for each reason) for subjects who received at least one ranibizumab rescue injection. Additionally frequency and percentage of reasons for all ranibizumab rescue injections will be provided by dose cohort and overall.

4.3.5 Prior and Concomitant Medications

All medications administered during the study will be listed and coded using the World Health Organization (WHO) Drug Dictionary (March, 2017 or later). A listing of all prior and concomitant medications including the verbatim term, preferred term (PT), and Anatomical Therapeutic Chemical (ATC) drug clarification, start and stop dates, duration, and other relevant data will be provided. The number and percentage of subjects taking prior and concomitant medications, respectively, will be summarized by PTs by dose cohort and overall for the as-treated population. Concomitant medications include all medications taken at the time of or after providing informed consent, regardless of whether the medication was started before or after informed consent was given. Prior medications include all medications that are taken prior to providing informed consent.

4.4 Safety Analyses

Safety endpoints will be summarized using descriptive statistics, including graphical methods, for continuous variables, and frequency and percentage for categorical variables during the primary

study period (24 weeks following RGX-314 administration). After all subjects have completed the end of the study period (Week 106), analyses will be repeated for all safety endpoints.

4.4.1 Adverse Events and Serious Adverse Events

All AEs, including SAEs, will be collected from the time the subject signs ICF throughout the end of the study (Week 106) on the electronic case report form (eCRF).

An RGX-314-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins or worsens after RGX-314 administration. All RGX-314-emergent AEs, including SAEs, will be listed and coded using the MedDRA Version 20.0 (March, 2017) or higher and the type incidence, severity, and relationship to RGX-314 administration will be summarized by dose cohort and overall. Multiple occurrences of adverse events for a subject will be counted once for each subject at the PT and SOC level for calculating percentages. In addition, a particular subject will be counted once at the highest severity and level of relationship observed. If any associations of interest between adverse events and baseline characteristics are observed, additional stratified results may be presented.

All RGX-314-emergent AEs will be summarized overall, as well as categorized by MedDRA SOC and PT. RGX-314-emergent AEs related to RGX-314 will be categorized by MedDRA SOC and PT. Ocular AEs are defined as AEs that involve the eye(s) as assessed by the investigators. A guide to signs and symptoms of toxicity for eyes is provided in Appendix I. All RGX-314-emergent ocular AEs and SAEs will be summarized overall, as well as categorized by MedDRA SOC and PT. All RGX-314-emergent ocular AEs and SAEs will be summarized by dose cohort and overall for study eye and fellow eye, respectively.

RGX-314-emergent AEs related to ranibizumab will be categorized by MedDRA SOC and PT.

RGX-314-emergent AEs related to study procedures will be summarized for subretinal procedure related AEs and non subretinal procedure related AEs, respectively. Both RGX-314-emergent AEs related to subretinal procedure and RGX-314-emergent AEs related to non subretinal procedure will be categorized by MedDRA SOC and PT.

AEs occurred during study run-in period (ie, occurring prior to administration of RGX-314) will be listed separately.

4.4.2 Deaths due to Adverse Events

Number and percent of subjects with deaths due to RGX-314-emergent AEs will be summarized and separate listings of subjects will be presented.

4.4.3 Clinical Laboratory Tests

4.4.3.1 Safety Laboratory Tests

Laboratory parameters (hematology, chemistry, coagulation, and urinalysis) will be assessed at baseline and throughout the study. Laboratory parameters and change from baseline at each visit time point will be summarized descriptively by dose cohort and overall in conventional and SI units. Clinical laboratory tests for each laboratory parameter are provided in the following table:

Table 4-2: Laboratory Parameters

Laboratory Parameter	Clinical Laboratory Tests
Hematology	Complete blood count with differential and platelet count, including hematocrit, hemoglobin, and red blood cell, white blood cell, platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts as well as mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration
Chemistry	Glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, carbon dioxide, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT, AST, and creatine kinase
Coagulation	PT and partial thromboplastin time
Urinalysis	Dipstick for glucose, ketones, protein, and blood (if warranted, a microscopic evaluation will be completed)

All laboratory parameters will be provided in the listings. Any lab values that are considered of "potential clinical concern" as defined in Appendix II will be listed. Frequency and percentage of subjects having values of "potential clinical concern" will be provided by dose cohort and overall, and the "potential clinical concern" values will be listed in conventional and SI units.

Subjects potentially meeting Hy's Law, ie, alanine transaminase (ALT)/aspartate transaminase (AST) $\geq 3\times$ upper limit of normal (ULN) and total bilirubin $\geq 2\times$ ULN, will be listed.

4.4.3.2 RGX-314 Protein Concentration

RGX-314 protein concentrations (ng/ml) in aqueous fluid and serum and change from Week 6 (Day 42) at each visit time point will be summarized descriptively by dose cohort and overall. The change from Week 6 (Day 42) is to check sustained RGX-314 protein concentration levels. RGX-314 protein concentrations (aqueous and serum) data will be provided in the listings.

4.4.3.3 AAV8 Neutralizing Antibodies

AAV8 neutralizing antibodies titer in HEK293 cells (serum and vitreous) are measured as the reciprocal serum/vitreous dilution at which relative signal was reduced 50% compared to virus control wells with a limit of detection value of 5. A shift table for the serum AAV8 neutralizing antibodies will be presented to compare the baseline titer value to the post-baseline titer value at each visit time point and to the highest titer value assessed during post baseline visits. Frequency and percentage of subjects having vitreous AAV8 neutralizing antibodies at Week 2 will be provided by dose cohort and overall. AAV8 neutralizing antibodies in titer (serum and vitreous) data will be provided in the listings.

4.4.3.4 AAV8 Binding Antibodies

The proportion of subjects having 'Positive' or 'Negative' result for AAV8 binding antibodies (aqueous) will be summarized at each visit time point by dose cohort and overall. The 'Negative' result at each visit time point is defined as having either 'Screen Result' of negative, or 'Screen Result' of positive but 'Confirmed Result' of negative. The 'Positive' result at each visit time point is defined as having both 'Screen Result' of positive and 'Confirmed Result' of positive. A shift table for the aqueous AAV8 binding antibodies will be presented to compare the baseline positive/negative result to the post-baseline positive/negative result at each visit time point. AAV8 binding antibodies (aqueous) data will be provided in the listing.

4.4.3.5 Anti-RGX-314 Protein Antibodies

The proportion of subjects having 'Positive' or 'Negative' result for anti-RGX-314 protein antibodies (aqueous, serum, and vitreous) will be summarized at each visit time point by dose cohort and overall. Negative result at each visit time point is defined as having either 'Screen Result' of negative, or 'Screen Result' of positive but 'Confirmed Result' of negative. Positive result at each visit time point is defined as having both 'Screen Result' of positive and 'Confirmed Result' of positive. A shift table for the aqueous and serum anti-RGX-314 protein antibodies will be presented to compare the baseline positive/negative result to the post-baseline positive/negative result at each visit time point. Anti-RGX-314 protein antibodies (aqueous, serum, and vitreous) data will be provided in the listings.

4.4.3.6 ELISpot

RGX-314 study antigen (AAV8 and anti-VEGF) are valid, as long as:

1. Medium (negative control) is inside of validation range
2. At least 1 of the positive controls (anti-CD3 and PMA+ION) is inside of validation range

Validation range for Medium is ≤ 40 SFU/million PBMCs, for anti-CD3 is ≥27 – too numerous to count (TNTC), and for PMA+ION is ≥40 – TNTC.

RGX-314 study antigens (AAV8 [A, B, and C] and anti-VEGF [A, B, and C]) are considered positive if a sample has a value (1) > 40 SFU/million PBMCs and (2) >= 3 × Medium. For both AAV8 and anti-VEFG, if any of A, B, or C is positive, a sample is considered as positive.

The proportion of subjects having a positive/negative sample for AAV8 and anti-VEFG will be summarized at each visit time point by dose cohort and overall.

ELISpot to AAV8 and RGX-314 anti-VEGF Fab will be listed. The listing includes the following parameters: (1) Medium (negative control) and its range, RGX-314 study antigens (AAV8 [A, B, and C] and anti-VEGF [A, B, and C]) and corresponding response status, CEF, and PHA in SFU/million PBMCs; (2) anti-CD3 (active control) in SFU/2E+4 PBMCs and its range; (3) PMA+ION (active control) in SFU/2E+3 PBMCs and its range.

4.4.3.7 Vector Shedding

The proportion of subjects having 'Positive' (≥ 50 mean copies), '<LLOQ' (0 - < 50 mean copies), or 'Negative' (0 mean copy) for the vector shedding (serum and urine) data will be summarized at each visit time point by dose cohort and overall. Vector shedding (serum and urine) data, including 2 replicates in copies/5µL, mean copies/5µL, coefficient of variation, and test results in mean copies/µg, will be provided in the listings.

4.4.3.8 VEGF

VEGF in aqueous fluid and change from Week 2 (Day 15) at each visit time point will be summarized descriptively by dose cohort and overall. VEGF in aqueous fluid data will be provided in the listing.

4.4.4 Other Safety Evaluations

4.4.4.1 Vital Signs

Vital signs (systolic/diastolic blood pressure and heart rate) will be summarized descriptively at each visit time point by dose cohort and overall. Vital sign change from baseline to post RGX-314 administration at each visit time point will also be summarized by dose cohort and overall. In addition, the proportion of subjects having values of "potential clinical concern" in vital signs as defined in Appendix II will be summarized by dose cohort and overall. The "potential clinical concern" values in vital signs will be provided in the listing.

4.5 Efficacy Analyses

Efficacy data will be collected from two different sources: (1) Clinical Database (Medrio) and (2) Central Reading Center. The clinical database will provide data including BCVA, CRT as measured by SD-OCT, and rescue anti-VEGF injections. The central reading center database will provide data including CRT/volume of fluid as measured by SD-OCT, FA, and FAF.

4.5.1 BCVA

BCVA will be assessed by ETDRS chart at 4 meters. If necessary, the testing may be repeated at 1 meter for lower vision subjects. Bilateral assessments and data are collected in the clinical database.

ETDRS letters and change from baseline at each visit time point will be summarized descriptively by dose cohort and overall for study eye and fellow eye for both as-treated and evaluable for efficacy populations. A sensitivity analysis will be performed for the as-treated population: BCVA data collected after the first anti-VEGF rescue injection will be set to missing and a last observation carried forward method will be applied to impute the BCVA value at the time of first anti-VEGF rescue injection to each subsequent (ie, set to missing) visit time point.

The last non-missing assessment prior to ranibizumab injection on Day 1 will be used as baseline for the primary analysis. As a sensitivity analysis, the last non-missing assessment prior to the RGX-314 administration will be considered as baseline.

ETDRS letters over time as per BCVA will be plotted by subject and dose cohort. ETDRS letters over time for each individual subject will also be plotted and provided in the listing.

The number and percentage of subjects gaining or losing ETDRS letters compared to baseline as per BCVA for the following categories at each visit time point will be summarized by dose cohort and overall for study eye and fellow eye for both as-treated and evaluable for efficacy populations.

- Gaining: ≥15 letters, 10 to <15 letters, 5 to <10 letters
- Gaining or Losing: < 5 letters
- Losing: 5 to <10 letters, 10 to <15 letters, ≥15 letters

4.5.2 CRT by SD-OCT

SD-OCT will be collected using the Heidelberg Spectralis as bilateral assessments. SD-OCT data, as provided by the investigator from the registered values from the SD-OCT machine and entered into the clinical database (primary source) and by a central reading center (secondary source), will be analyzed and reported separately.

The last non-missing assessment prior to ranibizumab injection on Day 1 will be used as baseline for the primary analysis. As a sensitivity analysis, the last non-missing assessment prior to the RGX-314 administration will be considered as baseline.

4.5.2.1 Clinical Database

CRT as measured by SD-OCT and change from baseline at each visit time point will be summarized descriptively by dose cohort and overall for study eye and fellow eye for both as-treated and evaluable for efficacy populations. CRT as measured by SD-OCT over time will be plotted by subject and dose cohort. CRT data over time for each individual subject will also be plotted and provided in the listing.

4.5.2.2 Central Reading Center

The central reading center will provide adjusted CRT and total fluid volume, as well as retinal thickness and fluid volume for each OCT quadrant over time along with characteristics of the study eye for both as-treated and evaluable for efficacy populations.

Following parameters will be listed and summarized based on the data provided by the central reading center:

1) Categorical variables to be summarized:

   - Vitreomacular traction (Yes/No) for both eyes
   - Epiretinal membrane with deformation in the center 1mm (Yes/No) for both eyes
   - Intraretinal fluid cystoid edema (Yes/No) for both eyes
   - Intraretinal fluid in center 1mm (Yes/No) for both eyes
   - Subretinal fluid (Yes/No) for both eyes
   - Subretinal fluid in center 1mm (Yes/No) for both eyes
   - Subretinal fluid at the foveal center (Yes/No) for both eyes
   - Subretinal hyper-reflective material (Yes/No) for both eyes
   - Subretinal hyper-reflective material in center 1mm (Yes/No) for both eyes
   - Subretinal hyper-reflective material at the foveal center (Yes/No) for both eyes
   - Pigment epithelial detachment (Yes/No) for both eyes
   - Pigment epithelial detachment in center 1mm (Yes/No) for both eyes

2) Continuous variables to be summarized:

- Subretinal fluid thickness at the center 1mm for both eyes
- Subretinal hyper-reflective material thickness at the foveal center for both eyes
- Retinal pigment epithelium + pigment epithelial detachment thickness at the foveal center for both eyes
- Neurosensory retinal thickness at the foveal center for both eyes
- Center point thickness for both eyes
- Center subfield thickness for both eyes (corresponding to CRT as measured by SD-OCT in the clinical database)
- Total volume for both eyes
- Volume center 1mm for both eyes
- Volume and thickness for both eyes' quadrants
    - Superior inner/outer retina
    - Inferior inner/outer retina
    - Nasal inner/outer retina
    - Temporal inner/outer retina

4.5.3 Anti-VEGF Rescue Injections

The frequency of anti-VEGF rescue injections will be compared with the historical anti-VEGF injections and analyzed as both (1) the annualized rate of anti-VEGF rescue injections and (2) the mean interval between anti-VEGF rescue injections. Only historical anti-VEGF injections reported within the year prior to the Day 1 ranibizumab injection (Day -365 through Day 1) will be included in the analyses. Additionally, anti-VEGF rescue injections during the study period will be graphically plotted along with the historical anti-VEGF injections collected in the clinical database.

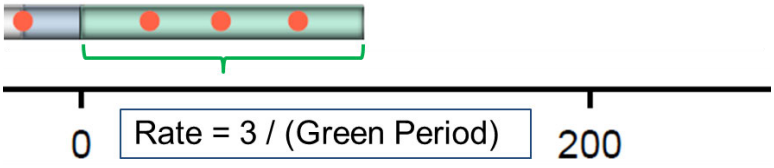
4.5.3.1 Annualized Rate of anti-VEGF Rescue Injections

The baseline anti-VEGF injection annual rate is defined as the number of anti-VEGF injections over a given time period of anti-VEGF up to the Day 1 ranibizumab injection.

A sensitivity analysis will be performed including the time period up until the most recent anti-VEGF prior to the Day 1 ranibizumab injection.

The annual rate of post-baseline rescue medications is calculated using the duration in years between the RGX-314 administration date and the last follow-up visit. No multiple time periods are considered and one rate of rescue medications is provided for each subject. An example is shown in Figure 1.

Figure 1 Rate of Post-Baseline anti-VEGF Rescue Medications

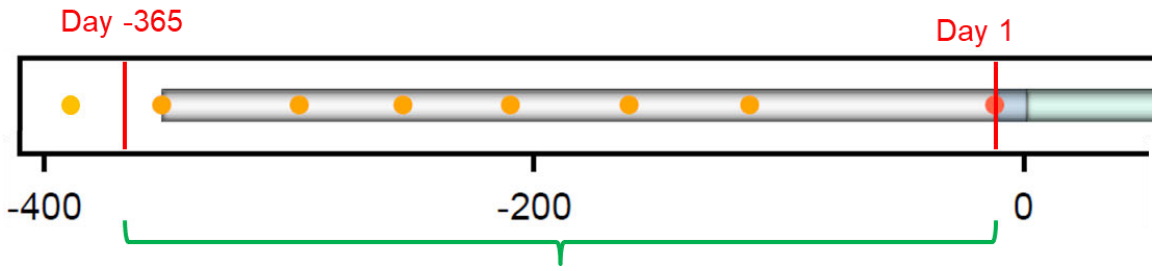


The baseline used for comparison is the period ending on Day 1 ranibizumab injection. A sensitivity analysis will also be conducted utilizing the rate calculated through the most recent anti-VEGF prior to the Day 1 ranibizumab injection.

(1) Primary Baseline for Analysis – Ending at the ranibizumab injection at Day 1

Annual rate of baseline/historical anti-VEGF injections is calculated using the duration in years between Day 1 ranibizumab injection and Day -365 (if the first ever anti-VEGF injection occurred prior to Day -365) or the first anti-VEGF injection reported within past 12 months (if the first ever anti-VEGF injection occurred less than 365 days from the Day 1 ranibizumab injection).

Figure 2 Primary Baseline Calculation for Rate of anti-VEGF Injections



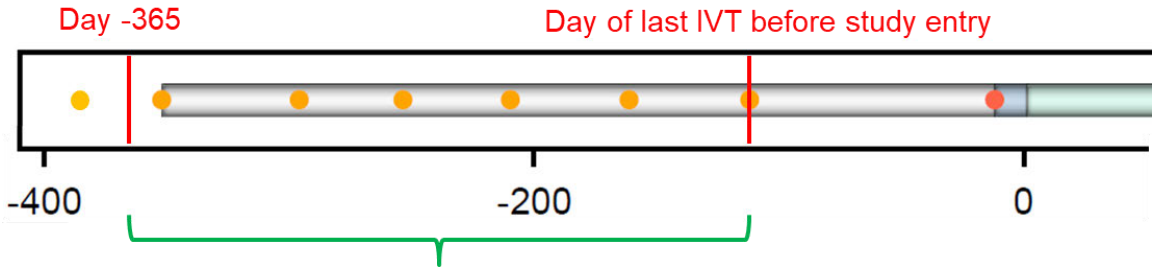
Example: Subject with 7 historical anti-VEGF injections within 12 months including Day 1 ranibizumab injection (the first ever anti-VEGF injection occurred prior to Day -365).

- Annual rate = (7 injections)/(366 days) = 7/(366/365.25) = 7/(1.00 year) = 6.99

(2) Sensitivity Baseline for Analysis – Ending at the most recent anti-VEGF prior to the Day 1 ranibizumab injection

Annual rate of baseline/historical anti-VEGF injections is calculated using the duration in years between the most recent anti-VEGF prior to the Day 1 ranibizumab injection and Day -365 (if the first ever anti-VEGF injection occurred prior to Day -365) or the first anti-VEGF injection reported within past 12 months (if the first ever anti-VEGF injection occurred less than 365 days from the Day 1 ranibizumab injection).

Figure 3 Sensitivity Baseline Calculation for Rate of anti-VEGF Injections



Example: Sujbect with 6 historical anti-VEGF injections between the most recent anti-VEGF prior to the Day 1 ranibizumab injection on Day -109 and Day -365 (the first ever anti-VEGF injection occurred prior to Day -365).

- Annual rate = (6 injections)/(Day -365 – Day -109 + 1) = (6 injections)/(257 days) = 6/(257/365.25) = 6/(0.70 year) = 8.53

4.5.3.2 Anti-VEGF Resuce Injection Rate Reduction

The number and percentage of subjects having rescue injection rate reduction compared with previous year for the following categories will be summarized by dose cohort and overall for the as-treated population for 1) primary baseline for analysis – ending at the ranibizumab injection at Day 1 and 2) sensitivity baseline for analysis – ending at the most recent anti-VEGF prior to the Day 1 ranibizumab injection.

- Rate reduction <0% (equivalent to rate increase)
- Rate reduction 0 to <25%
- Rate reduction 25 to <50%
- Rate reduction 50 to <75%
- Rate reduction 75% to 100%
- Rate reduction 100%

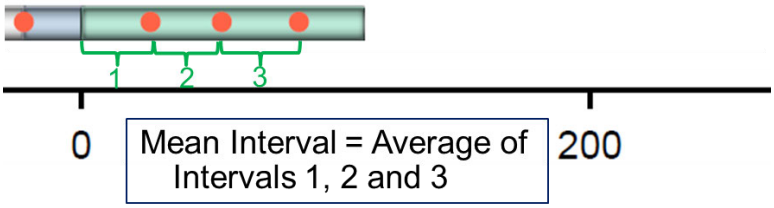
- Rate reduction ≥50%

4.5.3.3 Mean Interval between anti-VEGF Rescue Injections

The mean interval between anti-VEGF rescue injections is calculated as an average of intervals between all available baseline/historical anti-VEGF medications within 365 days from Day 1 (ranibizumab injection). Descriptive statistics, including number of non-missing observations, mean, standard deviation, median, minimum, and maximum, will be provided for each mean interval between baseline/historical anti-VEGF injections.

The mean interval analysis is also performed over anti-VEGF injections on and after the RGX-314 administration date. For analysis purposes, it is assumed that a subject received a rescue medication on the RGX-314 administration date. No multiple time periods are considered but only one mean interval between rescue medications is provided for each subject. If a subject did not receive a rescue medication, this subject will be excluded in the analysis. Figure 4 shows an example of how the post-baseline mean interval is calculated.

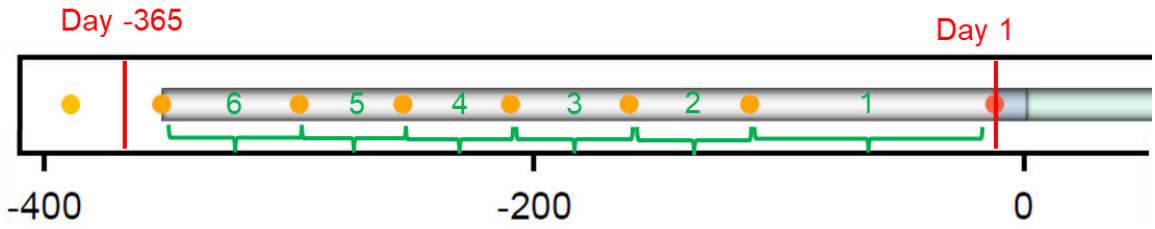
Figure 4 Mean Interval between Post-Baseline anti-VEGF Rescue Medications



(1) Primary Baseline for Analysis – Ending at the ranibizumab injection at Day 1

The mean interval counts anti-VEGF injections using the duration between Day 1 ranibizumab injection and the first anti-VEGF injection reported within past 12 months.

Figure 5 Primary Baseline Calculation for Mean Interval between anti-VEGF Injections

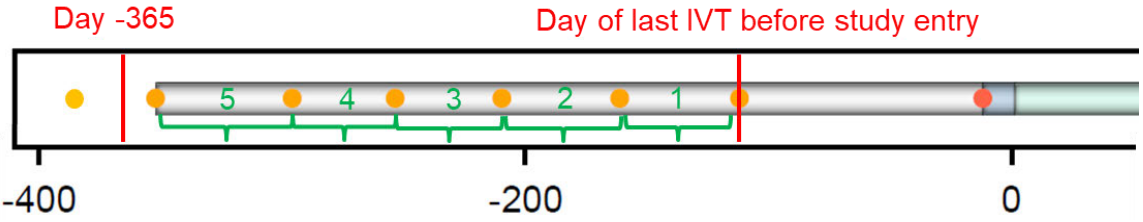


Example: Subject had the first anti-VEGF on Day -360. The mean interval is calculated by averaging intervals 1, 2, 3, 4, 5, and 6.

(2) Sensitivity Baseline for Analysis – Ending at the most recent anti-VEGF prior to the Day 1 ranibizumab injection

The mean interval counts anti-VEGF injections using the duration between the most recent anti-VEGF prior to the Day 1 ranibizumab injection and the first anti-VEGF injection reported within past 12 months.

Figure 6 Sensitivity Baseline Calculation for Mean Interval between anti-VEGF Injections



Example: Subject had the most recent anti-VEGF prior to the Day 1 ranibizumab injection on Day -109. The mean interval is calculated by averaging intervals 1, 2, 3, 4, and 5.

4.5.3.4 Time to First anti-VEGF Rescue Injection

The median time to first anti-VEGF rescue injection (in months) and corresponding 95% CI of the median time will be estimated from the Kaplan-Meier method. For subjects who do not receive any anti-VEGF rescue injection will be censored at the date of the last visit.

Kaplan-Meier curves for time to first anti-VEGF rescue injection will be presented graphically by dose cohort and overall.

4.5.4 Fluorescein Angiography

FA will be done only for the study eye.

4.5.4.1 Clinical Database

The proportion of subjects having presence/absence of leakage on FA will be summarized at each visit time point by dose cohort and overall.

4.5.4.2 Central Reading Center

Change from baseline in CNV lesion size (disc areas or mm^2) at each visit time point will be summarized descriptively by dose cohort and overall.

4.5.5 Fundus Autofluorescence

Exploratory analysis from FAF includes: (1) the proportion of subjects having development of geographic atrophy for subjects without geographic atrophy at baseline and (2) change from

baseline at each visit time point in area of geographic atrophy (disc areas or mm^2) for subjects with geographic atrophy at baseline. FAF will be done only for the study eye.

4.5.6 Handling of Dropouts and Missing Data

No missing data will be imputed for any analyses unless stated otherwise. Analyses will be based on observed data only.

5. APPENDICES

Appendix I GUIDE TO SIGNS AND SYMPTOMS OF TOXICITY

Acute signs and symptoms of toxicity (1-7 days post administration)	Anterior segment: Corneal edema, acute increase of intraocular pressure (IOP) (spike), anterior chamber (AC) inflammatory response (flare and cells), iris neovascularization, episcleritis, scleritis, and eye pain. Posterior segment: acute retinal necrosis, retinal detachment, retinal breaks, intra-retinal and subretinal hemorrhage, retinal vein thrombosis, cotton wool spots, chorioretinitis and inflammation (vitreous cells and haze), retinal edema, retinal vascular permeability changes (leakage and edema), sterile endophthalmitis, infectious endophthalmitis, macular hole, epiretinal membrane, proliferative vitreoretinopathy, retinal arterial occlusion, optic nerve edema, optic nerve infarction, and retinal vasculitis. Functional: acute visual loss, acute visual field loss, and metamorphopsia.
Near-term signs and symptoms of toxicity (2-4 weeks post administration)	Anterior segment: corneal endothelial insufficiency, corneal epithelial changes, increased IOP, and AC inflammatory response (flare and cells). Posterior segment: retinal necrosis, retinal detachment, retinal breaks, intra-retinal and subretinal hemorrhage, retinal vein thrombosis, cotton wool spots, chorioretinitis and inflammation (vitreous cells and haze), retinal vascular permeability changes (leakage and edema), and retinal atrophic changes. Functional: visual acuity decline and visual field defects.
Long-term signs and symptoms of toxicity (months)	Anterior segment: corneal endothelial insufficiency and glaucoma. Posterior segment: retinal atrophic changes, retinal vascular thinning, retinal thinning, loss of retinal layers, low grade inflammation (chorioretinitis, neuroretinitis), atrophic changes in retinal areas, and geographic atrophy. Functional: reduced visual acuity, color vision disturbances, visual field defects (relative and absolute scotomas), and afferent pupillary defect.

Appendix II POTENTIAL CLINICAL CONCERN

Values of "Potential clinical concern" are defined for selected laboratory parameters and vital signs. Data will be summarized by the number and percentage of subjects falling within each category.

Hematology:

Laboratory Test	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Basophils	None	None
Eosinophils	None	None
Hematocrit	>10% decrease	>5% below LLN >4% above ULN
Hemoglobin	>2.5 g/dL decrease	>2.0 g/dL below LLN >1.0 g/dL above ULN
Lymphocytes	None	<0.5 x LLN
Monocytes	None	None
Neutrophils	None	<1 k/µL
Platelets	None	<80 k/µL >500 k/µL
Red Blood Cell Count	None	None
White Blood Cell Count	None	>1 k/µL below LLN >5 k/µL above ULN

Chemistry:

Laboratory Test	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Albumin	None	>0.5 g/dL below LLN >0.5 g/dL above ULN
Bicarbonate (Carbon Dioxide Content)	None	<16 mEq/L >40 mEq/L
BUN	None	>2 x ULN
Calcium	None	<7.2 mg/dL >12 mg/dL
Chloride	None	None
Glucose (fasting)	None	<54.05 mg/dL >396.4 mg/dL
Potassium	None	>0.5 mEq/L below LLN >1.0 mEq/L above ULN
Sodium	None	>5 mEq/L below LLN >5 mEq/L above ULN
Total Protein	None	>1.5 g/dL below LLN >1.5 g/dL above ULN
Alkaline Phosphatase	None	>3 x ULN
ALT	None	>3 x ULN
AST	None	>3 x ULN
Direct Bilirubin	None	>1.35 x ULN
GGT	None	>3 x ULN

Laboratory Test	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Total Bilirubin	None	>1.5 x ULN
Serum Creatinine	None	>2.0 mg/dL

Vital Signs:

Vital sign values or shifts of potential clinical concern:

- Heart rate <50 bpm or >120 bpm
- Heart rate change from baseline >30 bpm increase or decrease
- Systolic blood pressure <95 mmHg or >180 mmHg
- Systolic blood pressure change from baseline >30 mmHg increase or decrease
- Diastolic blood pressure <50 mmHg or >110 mmHg
- Diastolic blood pressure change from baseline >20 mmHg increase or decrease