STUDY PROTOCOL 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)

Protocol Number: RGX-314-001

NCT Number: NCT03066258

Document Date: 10 February 2020; Version 10

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)

Protocol Number:	RGX-314-001
Original Protocol:	02 August 2016
Current Protocol:	10 February 2020; Version 10
Indication:	Neovascular age-related macular degeneration (nAMD)
IND Number:	17280
EudraCT Number:	N/A
Sponsor:	REGENXBIO Inc. 9600 Blackwell Road, Suite 210 Rockville, MD, USA 20850
Sponsor's Responsible Medical Director:	[redacted]

This study is to be performed in compliance with the protocol, International Council on Harmonisation E6: Good Clinical Practice: Consolidated Guideline (ICH E6), and applicable regulatory requirements.

1 SYNOPSIS

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)

PROTOCOL NUMBER:

RGX-314-001

RATIONALE:

Excessive vascular endothelial growth factor (VEGF) plays a key part in promoting neovascularization and edema in neovascular (wet) age-related macular degeneration (nAMD). Counteracting the effects of VEGF provides significant therapeutic benefit to subjects suffering from this disorder (AAO PPP, 2015). VEGF inhibitors (anti-VEGF), including ranibizumab (LUCENTIS®, Genentech) and aflibercept (EYLEA®, Regeneron), have been shown to be safe and effective for treating nAMD and have demonstrated improvement in vision. However, anti-VEGF therapy is administered frequently via intravitreal injection and can be a significant burden to the patients. The heavy treatment burden can lead to noncompliance, which can result in vision decline over time (Cohen et al, 2013; Holekamp et al, 2014). When given as needed according to a flexible dosing regimen, patients on average receive around 7 injections of ranibizumab in the 1st year of disease and 4 to 5 injections in the 2nd year (CATT Research Group, 2012; Ho et al, 2014). Frequent intravitreal injections are associated with increased cumulative risk of vision-threatening adverse events (AEs) (Day et al, 2011).

RGX-314 is a recombinant adeno-associated virus (AAV) gene therapy vector carrying a coding sequence for a soluble anti-VEGF protein. The long-term, stable delivery of this therapeutic protein following a 1-time gene therapy treatment for nAMD could potentially reduce the treatment burden of currently available therapies while maintaining vision with a favorable benefit:risk profile.

PHASE OF DEVELOPMENT:

Phase I/IIa

INVESTIGATIONAL PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

RGX-314: AAV8.CB7.CI.amd42.RBG

Up to 5 dose levels: 3×10^9 genome copies (GC)/eye (1.2×10^{10} GC/mL), 1×10^{10} GC/eye (4×10^{10} GC/mL), 6×10^{10} GC/eye (2.4×10^{11} GC/mL), 1.6×10^{11} GC/eye (6.2×10^{11} GC/mL), and 2.5×10^{11} GC/eye (1×10^{12} GC/mL).

Single-dose subretinal delivery after pars plana vitrectomy under local anesthesia.

REFERENCE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Ranibizumab (LUCENTIS, Genentech) 0.5 mg will be administered by intravitreal injection on Visit 1, 14 days prior to RGX-314 subretinal delivery.

RESCUE THERAPY, DOSE, AND MODE OF ADMINISTRATION:

Starting at 4 weeks post-RGX-314 administration, the subject may receive intravitreal ranibizumab rescue therapy at the Investigator's discretion in the study eye for disease activity if 1 or more of the following rescue criteria apply:

- Vision loss of ≥5 letters (per Best Corrected Visual Acuity [BCVA]) associated with accumulation of retinal fluid on Spectral Domain Optical Coherence Tomography (SD-OCT)

- Choroidal neovascularization (CNV)-related increased, new, or persistent subretinal or intraretinal fluid on SD-OCT
- New ocular hemorrhage

Further rescue injections may be deferred per the Investigator's discretion if one of the following sets of findings occur:

- Visual acuity is 20/20 or better and central retinal thickness (CRT) is "normal" as assessed by SD-OCT
- Visual acuity and SD-OCT are stable after 2 consecutive injections.

If injections are deferred, they will be resumed if visual acuity or SD-OCT get worse per the criteria above.

OBJECTIVES:

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)

Secondary Objectives:

- To evaluate the long-term safety and tolerability of RGX-314
- To evaluate the concentration of RGX-314 protein levels in aqueous humor
- To evaluate the effect of RGX-314 on BCVA
- To evaluate the effect of RGX-314 on CRT as measured by SD-OCT
- To assess the need for rescue therapy
- To evaluate the effect of RGX-314 on CNV lesion growth and leakage as measured by fluorescein angiography (FA)

ENDPOINTS:

Primary Endpoint:

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

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 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)
- Vector shedding analysis in serum and urine

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INVESTIGATIONAL SITES:

Approximately 8 sites in North America will participate in this study.

NUMBER OF SUBJECTS PLANNED:

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.

DIAGNOSIS AND CRITERIA FOR INCLUSION AND EXCLUSION:

Subjects must have a diagnosis of nAMD that is recurrent and persistent, responsive to anti-VEGF therapy, and requires frequent injections and meet the following criteria in order to be eligible for this study:

Inclusion Criteria:

1. Males or females aged ≥ 50 years and ≤ 89 years.
2. Sentinel (1st) subject for each dose cohort must have a BCVA ≤20/63 and ≥20/400 (≤63 and ≥19 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in the study eye. Following the sentinel subject evaluation, the rest of the subjects in the dose cohort must have a BCVA between ≤20/40 and ≥20/400 (≤73 and ≥19 ETDRS letters)
3. In the case both eyes are eligible, study eye must be the subject's worse-seeing eye, as determined by the Investigator.
4. Must have a documented diagnosis of subfoveal CNV secondary to AMD in the study eye.
    a. CNV lesion characteristics: lesion size needs to be less than 10 disc areas (typical disc area is 2.54 mm^2), blood <50% of the lesion size.
5. Must have received at least 4 intravitreal injections of an anti-VEGF agent for treatment of nAMD in the study eye in approximately 8 months (or less) prior to Visit 1, with anatomical response documented on SD-OCT.
6. Must have subretinal or intraretinal fluid in the center subfield present at Visit 1 in the study eye, evidenced on SD-OCT unless the subject is a re-screen.
    a. Subjects who have previously met all inclusion criteria including the Visit 2 responsiveness criterion on OCT, but did not receive RGX-314 within the window, may be re-screened and do not need to have fluid on entry or meet the Visit 2 responsiveness criterion again subject to discussion with and approval by Sponsor's Medical Director.
7. Must be pseudophakic (status post cataract surgery) in the study eye.
8. Must be willing and able to comply with all study procedures and be available for the duration of the study.

9. Females of childbearing potential must have a negative urine pregnancy test at the screening visit, have negative serum results by Day 8, and be willing to have additional pregnancy tests during the study.
10. Sexually active subjects (both female and male) must be willing to use a medically accepted method of barrier contraception (eg, condom, diaphragm, or abstinence) from screening visit until 24 weeks after vector administration. Cessation of birth control after this point should be discussed with a responsible physician.
11. Must be willing and able to provide written, signed informed consent.

Exclusion Criteria:

1. CNV or macular edema in the study eye secondary to any causes other than AMD.
2. Blood occupying ≥50% of the AMD lesion or blood >1.0 mm^2 underlying the fovea of the study eye.
3. Any condition preventing visual acuity improvement in the study eye, eg, fibrosis, atrophy, or retinal epithelial tear in the center of the fovea.
4. Active or history of retinal detachment in the study eye.
5. Advanced glaucoma in the study eye.
6. Any condition in the study eye that, in the opinion of the Investigator, may increase the risk to the subject, require either medical or surgical intervention during the course of the study to prevent or treat vision loss, or interfere with study procedures or assessments.
7. History of intraocular surgery in the study eye within 12 weeks prior to the screening visit. Yttrium aluminum garnet capsulotomy is permitted if performed >10 weeks prior to the screening visit.
8. History of intravitreal therapy in the study eye, such as intravitreal steroid injection or investigational product, other than anti-VEGF therapy, in the 6 months prior to screening.
9. Presence of an implant in the study eye at screening (excluding intraocular lens).
10. History of malignancy requiring chemotherapy and/or radiation in the 5 years prior to screening. Localized basal cell carcinoma will be permitted.
11. Receipt of any investigational product within the 30 days of enrollment or 5 half-lives of the investigational product, whichever is longer.
12. Participation in any other gene therapy study.
13. History of therapy known to have caused retinal toxicity, or concomitant therapy with any drug that may affect visual acuity or with known retinal toxicity, eg, chloroquine or hydroxychloroquine.
14. Ocular or periocular infection in the study eye that may interfere with the surgical procedure.
15. Myocardial infarction, cerebrovascular accident, or transient ischemic attacks within the past 6 months.
16. Uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg, diastolic BP >100 mmHg) despite maximal medical treatment.
17. Any concomitant treatment that, in the opinion of the Investigator, may interfere with ocular surgical procedure or healing process.
18. Known hypersensitivity to ranibizumab or any of its components or past hypersensitivity (in the Investigator's opinion) to agents like RGX-314.
19. Has a serious, chronic, or unstable medical or psychological condition that, in the opinion of the Investigator, may compromise the subject's safety or ability to complete all assessments and follow-up in the study.

Criteria for continuing study after receiving ranibizumab:

At Visit 2, subjects (with the exception of re-screens who have met this criterion in the past) will be assessed for initial anti-VEGF response to ranibizumab. Subjects will undergo both SD-OCT and BCVA, which will be compared by the Investigator with the Visit 1 values:

1. Responsive (subjects will continue in the study): response is defined as reduction in CRT >50 µm or >30% improvement in central fluid by SD-OCT.
2. Non-responsive (subjects will exit the study as early withdrawals): non-response is defined as not meeting the criteria above. Additional subjects will continue to be enrolled until up to 6 subjects (Cohorts 1 to 3) or up to 12 subjects (Cohorts 4 and 5) in each cohort receive a single dose of RGX-314.

At this visit central lab results will be reviewed. Any subjects with the following values will be withdrawn:

3. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN)
4. Total bilirubin >1.5 × ULN unless the subject has a previously known history of Gilbert's syndrome and a fractionated bilirubin that shows conjugated bilirubin <35% of total bilirubin
5. Prothrombin time (PT) >1.5 × ULN
6. Hemoglobin <10 g/dL for male subjects and <9 g/dL for female subjects
7. Platelets <100 × 10^3/µL
8. Estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2

STUDY DESIGN AND METHODOLOGY:

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 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 sentinel subject in each cohort will have vision of ≤20/63 and ≥20/400 (≤63 and ≥19 ETDRS letters). After RGX-314 administration to the sentinel subject, there will be a minimum of 4-week observation period for safety. The Internal Safety Committee 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 Independent Data Monitoring Committee (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 IDMC. Given that gene therapy studies in nAMD to date (Campochiaro et al, 2016; Constable et al, 2016; Rakoczy et al, 2015) have had events either related to the procedure or occasional inflammation that is mild and transient (resolving in a few weeks), 4 weeks will be adequate to assess these acute events in the sentinel subject. 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 (1 day post-procedure and 1 week and 4 weeks post-procedure). 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 product 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, SD-OCT, fluorescein angiography [FA], fundus autofluorescence [FAF], and color fundus photography [CFP]), and vital signs. Because of pigmentary changes observed in some subjects, starting with Protocol Version 10, additional ophthalmic assessments will include Optos Ultra-widefield FAF (in addition to Heidelberg Spectralis FAF), electroretinography if available, visual field test (Humphrey Full Field 120 or microperimetry), and, if applicable, additional SD-OCT in the area of pigmentary change.

All Investigators will be preselected based on their previous experience with subretinal delivery in clinical practice and will be further trained on the procedure as part of the proposed clinical study. A detailed description of the procedures can be found in the Administration Manual.

STATISTICAL METHODS:

All data will be presented in subject data listings. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum, and maximum). Graphical displays will be presented as appropriate.

Safety and efficacy will be reported by dose cohort and may also be reported for all the dose cohorts combined.

Sample Size and Power Calculation:

No formal calculation was performed to determine sample size.

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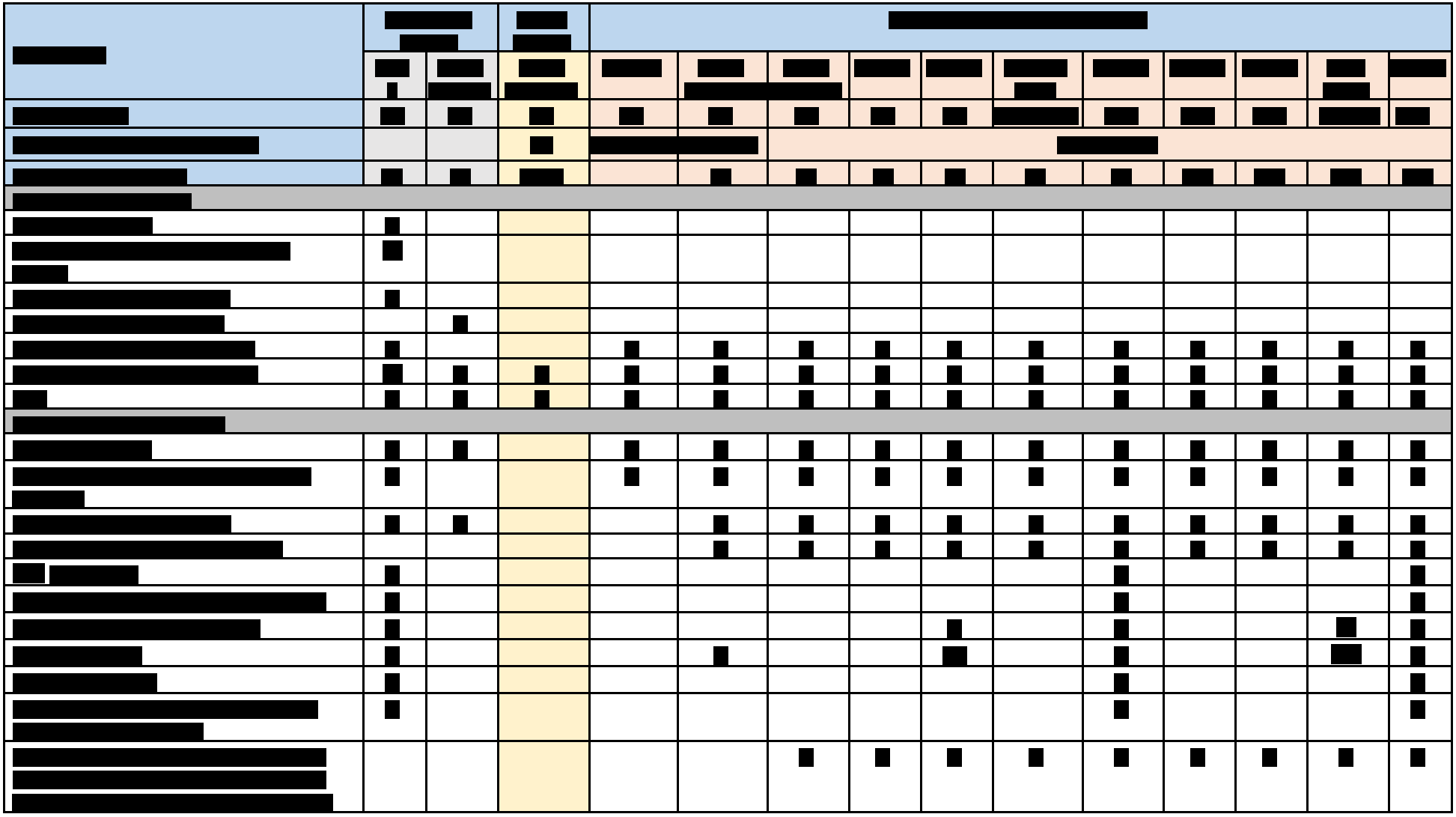

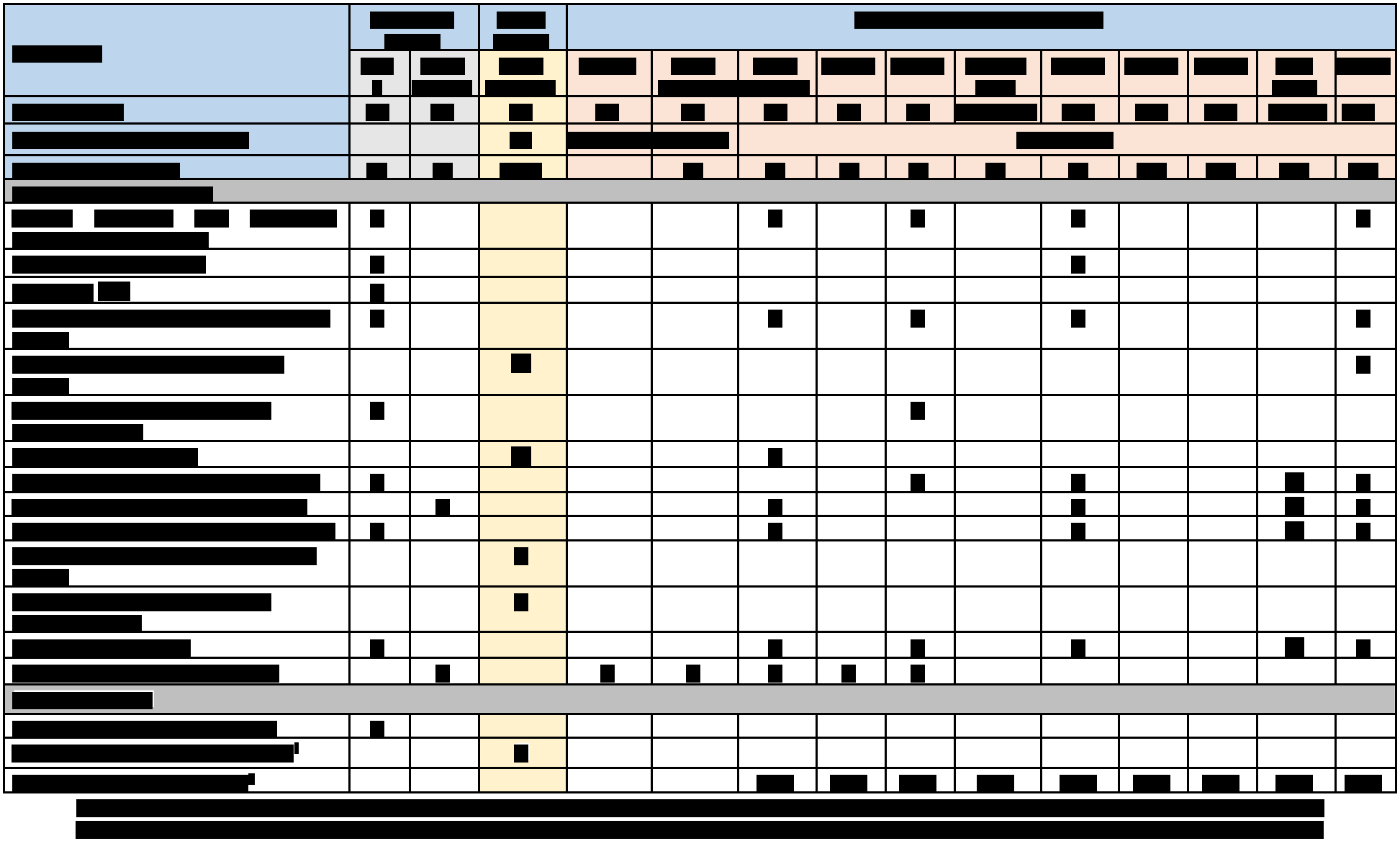

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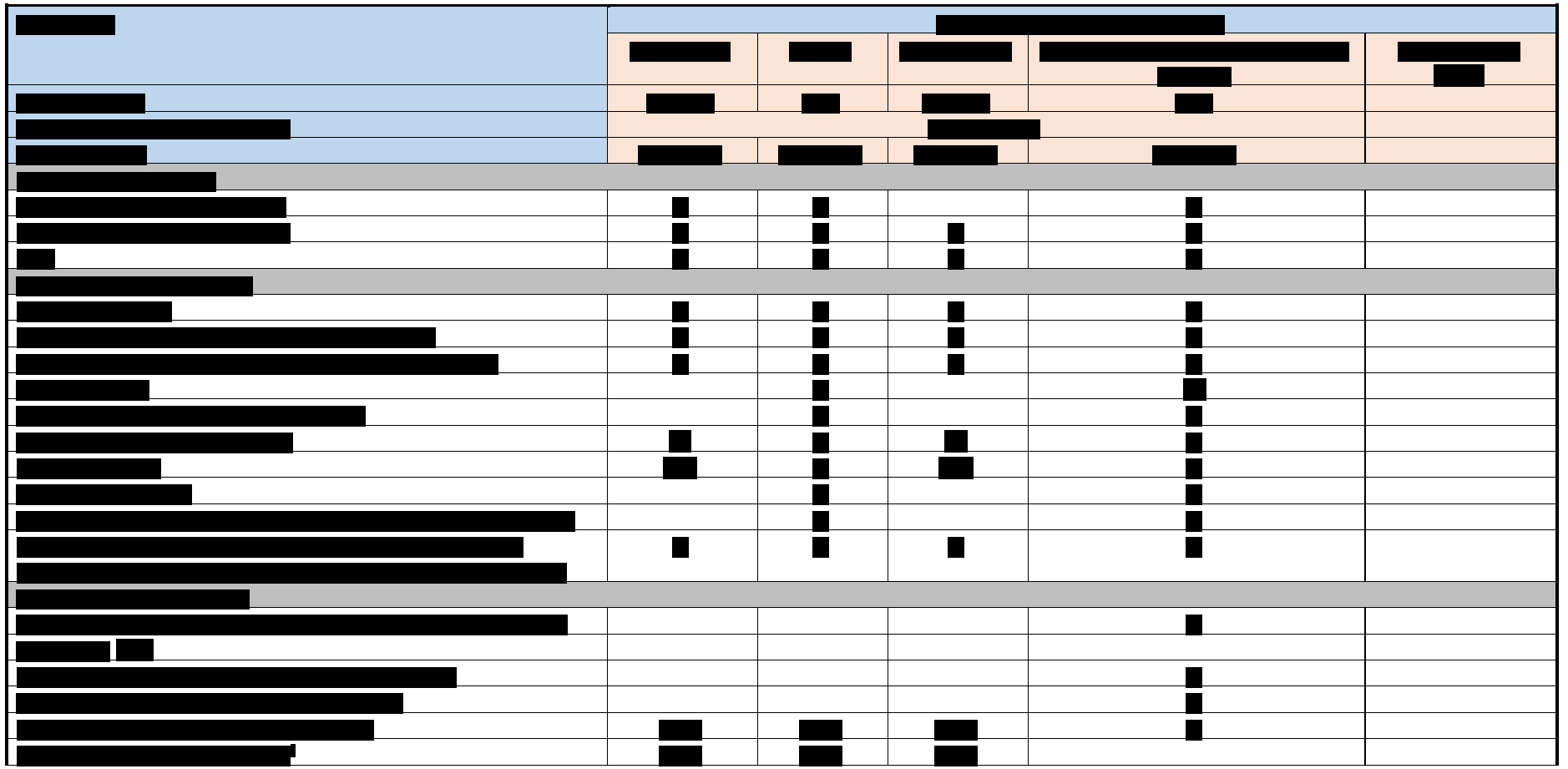

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3 ABBREVIATIONS

Abbreviation	Term
AAV	Adeno-associated virus
AAV2	Adeno-associated virus serotype 2
AAV8	Adeno-associated virus serotype 8
AC	Anterior chamber
ACF	Anterior chamber fluid
AE	Adverse event
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
AST	Aspartate aminotransferase
ATPA	Anti-transgene product antibody
BCVA	Best Corrected Visual Acuity
BP	Blood pressure
C	Celsius
CB7	Hybrid of cytomegalovirus immediate-early enhancer and the chicken β-actin promoter
CFP	Color fundus photography
CFR	Code of Federal Regulations
CNV	Choroidal neovascularization
CMV	Cytomegalovirus
CRF	Case report form
CRT	Central retinal thickness
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-Linked ImmunoSpot
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
Fab	Antigen-binding fragment
FAF	Fundus autofluorescence
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GC	Genome copies
GLP	Good Laboratory Practice

HIPAA	Health Insurance Portability and Accounting Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL2	Interleukin 2
IOP	Intraocular pressure
IRB	Institutional Review Board
IRES	Internal ribosome entry site
mAb	Monoclonal antibody
MED	Minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NAb	Neutralizing antibodies
nAMD	Neovascular (wet) age-related macular degeneration
NCI	National Cancer Institute
NIR-FAF	Near infrared reflectance fundus autofluorescence
NHP	Nonhuman primate
NOAEL	No observed adverse effect level
OCT	Optical Coherence Tomography
OD	Right eye
ONL	Outer nuclear layer
OS	Left eye
PBS	Phosphate buffered saline
PK	Pharmacokinetic
PT	Preferred term/Prothrombin time
RGX-314	AAV8.CB7.CI.amd42.RBG; also referred to as AAV8.CB7.CI.amd42.rBG
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD-OCT	Spectral Domain Optical Coherence Tomography
SDV	Source document verification
SOC	System Organ Class
SRT	Safety review trigger
TPA	Tissue plasminogen activator
UbC	Ubiquitin C gene promoter
µL	Microliter
ULN	Upper limit of normal
US	United States
USM	Urgent Safety Measure
UWF	Ultra-widefield
VA	Visual acuity
VEGF	Vascular endothelial growth factor

4 INTRODUCTION

4.1 DISEASE BACKGROUND AND CURRENT THERAPEUTIC OPTIONS

Age-related macular degeneration (AMD) is a progressive degenerative macular disease attacking the region of highest visual acuity (VA), the macula. The neovascular or "wet" (nAMD) form of the disease is characterized by choroidal neovascularization (CNV), which is marked by proliferation of blood vessels and cells including those of the retinal pigment epithelium (RPE) (Carmeliet, 2005). Ultimately, photoreceptor death and scar formation result in a severe loss of central vision and the inability to read, write, recognize faces, or drive. Many patients can no longer maintain gainful employment or carry out daily activities and consequently report a diminished quality of life (Mitchell and Bradley, 2006). Preventive therapies have demonstrated little effect, and therapeutic strategies have focused primarily on treating the neovascular lesion.

Excessive vascular endothelial growth factor (VEGF) plays a key part in promoting neovascularization and edema in nAMD. Counteracting the effects of VEGF provides significant therapeutic benefit to subjects suffering from this disorder (AAO PPP, 2015). Currently available anti-VEGF agents approved for nAMD treatment, such as ranibizumab (LUCENTIS®, Genentech) or aflibercept (EYLEA®, Regeneron), have been shown to increase Best Corrected Visual Acuity (BCVA) over time (Schmidt-Erfurth et al, 2014a), but their effects may be limited in duration of effectiveness (CATT Research Group, 2016; Rofagha et al, 2013).

While long-term anti-VEGF therapies may improve vision or slow the progression of vision loss, none of these treatments prevent neovascularization from recurring (Brown et al, 2006; Rofagha et al, 2013). Therapy typically must be re-administered to prevent the disease from worsening. The need for repeat treatments can incur additional risks (ie, endophthalmitis) and is inconvenient for patients (LUCENTIS USPI). Patients treated with ranibizumab as needed were given an average of 13.3 injections over 2 years (5.6 injections in year 2). In the Phase III VIEW studies for aflibercept, in the second year of the studies (Weeks 52 to 96), patients treated with aflibercept 2.0 mg as needed received 4.1 injections on average and patients treated with ranibizumab 0.5 mg as needed received 4.7 injections on average (Schmidt-Erfurth et al, 2014b). In real-life conditions, outside clinical studies, patients seem to be generally undertreated because of challenges with compliance (CATT Research Group, 2012; CATT Research Group, 2016; Cohen et al, 2013; Holekamp et al, 2014). Thus, there is significant need for a long-acting therapeutic. An effective gene therapy product with a long duration of action may have a significant benefit for patients by substantially reducing the number of injections required to maintain a positive treatment effect, providing the potential for a profound impact on the treatment of this disease.

Ranibizumab is a recombinant, humanized immunoglobulin G1 kappa isotype monoclonal antigen-binding fragment (Fab) that binds and inhibits the biological activity of human VEGF-A (LUCENTIS USPI). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors VEGFR-1 and VEGFR-2 on the surface of endothelial cells. This binding inhibits endothelial cell proliferation and neovascularization, as well as vascular leakage, all of which are thought to contribute to

the progression of the nAMD. Ranibizumab has been approved by the United States (US) Food and Drug Administration (FDA) for intravitreal injection treatment in patients with nAMD (initially approved in 2006). From the studies supporting the ranibizumab approval, as well as studies and clinical experience since the approval, the activity (efficacy) and safety of this anti-VEGF therapy in treating nAMD have been established.

4.2 BRIEF OVERVIEW OF THE DEVELOPMENT OF THE INVESTIGATIONAL PRODUCT

Gene therapy is considered an approach that, with a single intervention, could potentially lead to long-term anti-VEGF activity. Adeno-associated viruses (AAVs) are considered promising candidates for ocular gene therapy due to their lack of human pathogenicity, low toxicity, and (in particular) their long-term expression while remaining episomal. Adeno-associated virus serotype 2 (AAV2)- and adeno-associated virus serotype 8 (AAV8)-based gene therapy vectors are currently being evaluated in many ocular gene therapy studies (www.clinicaltrials.gov), including: choroideremia (NCT02341807), achromatopsia (NCT02599922, NCT02610582), Leber's congenital amaurosis (NCT00821340, NCT00481546, NCT00999609, NCT00643747), retinitis pigmentosa (NCT01482195, NCT01505062), Stargardt's disease (NCT01367444), X-linked retinoschisis (NCT02416622, NCT02122952, NCT02317887), and nAMD (NCT01024998, NCT01301443, NCT01494805). In recent studies, AAV was used to deliver a therapeutic gene to nAMD patients, including GeMCRIS Protocol #1501-1380, in which a subretinal injection of AAV2 was used to deliver sFlt-1, a naturally occurring anti-VEGF Fab protein; in GeMCRIS Protocol #0810-948, an intravitreal injection of AAV2 was used to deliver sFLT-01, an engineered sFlt protein fused to an immunoglobulin constant region and the GEM study in which a subretinal injection of equine infectious anemia virus was used to deliver endostatin and angiostatin (Campochiaro et al, 2016).

RGX-314 gene therapy is a recombinant AAV8 viral vector containing a transgene that leads to the production of a soluble anti-VEGF Fab protein. RGX-314 is administered via a subretinal delivery and could potentially provide long-term treatment with a single intervention. The AAV8 vector was selected because studies have shown that it is more efficient than the AAV2 vector in transducing the RPE cells following subretinal injections (Vandenberghe et al, 2011). [redacted]. To maximize expression of the protein from the retina pigment epithelium, subretinal delivery of RGX-314 directly into the subretinal space will be employed in clinical studies, as subretinal delivery has been shown to produce optimal expression in animal models (Lebherz et al, 2008) and in nonhuman primates (NHP) (Bennett et al, 1999; Schmidt-Erfurth et al, 2014b; Stieger et al, 2009).

4.2.1 Nonclinical Data

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4.2.1.1 Primary Pharmacology

AAV8 was selected for initial studies based on its efficiency in transducing retinal cells. [redacted]. The genes of the heavy and light chains were separated by an encoded furin cleavage site-F/F2A linker to assure equal molar expression of both chains. Initial studies to optimize other vector characteristics were performed. [redacted]

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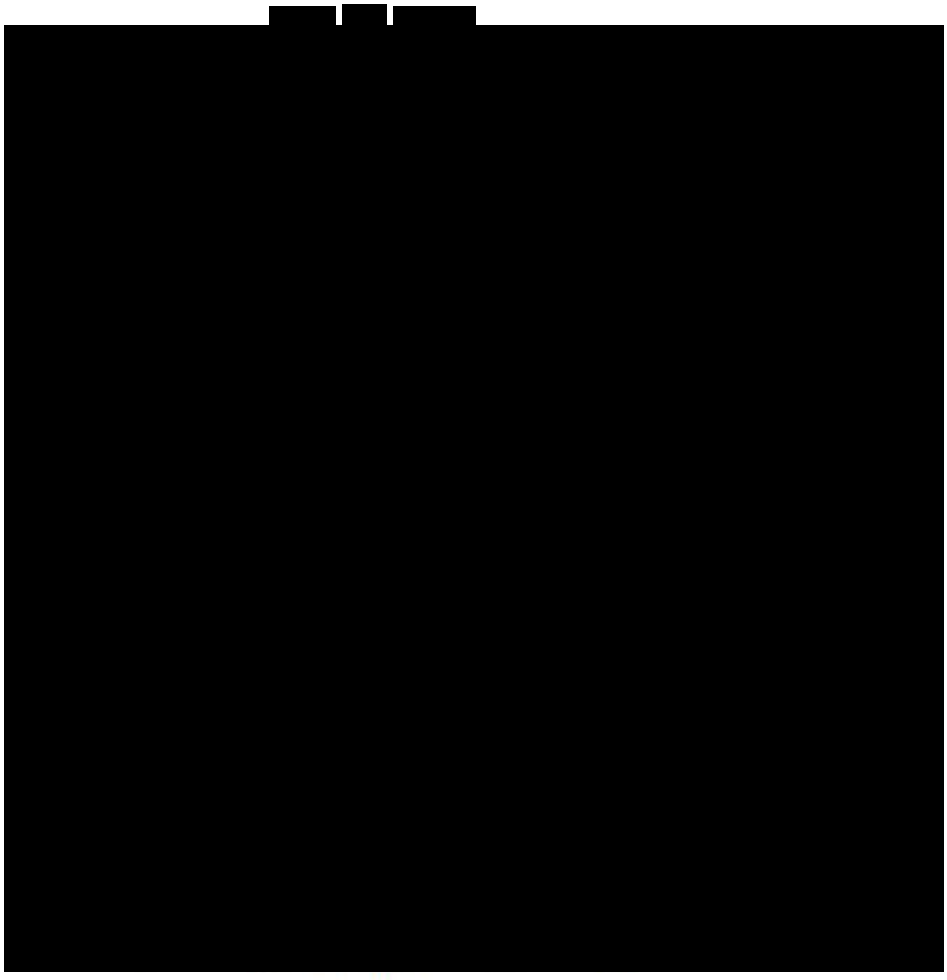

Study day

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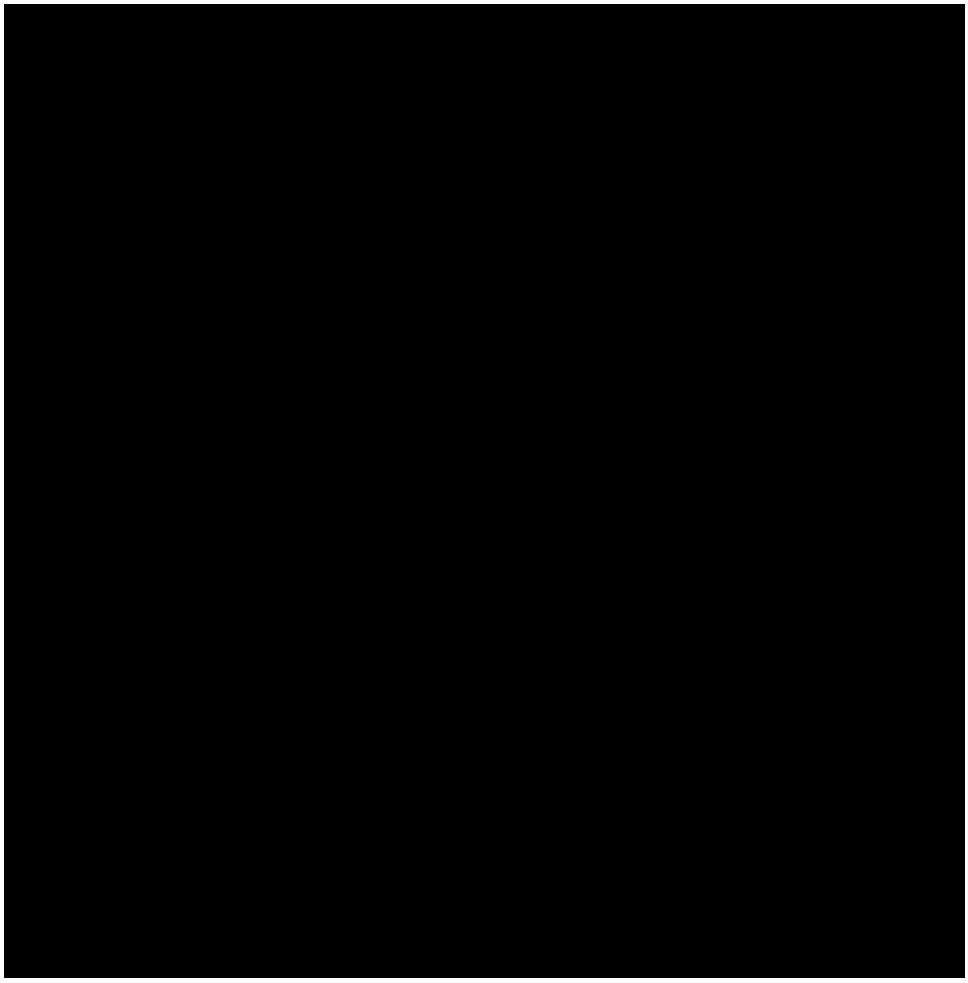

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4.2.2 Clinical Data

This is the first-in-human study of RGX-314. Preliminary safety data from this study that support the safety of continued subject dosing may be found in the IB.

4.3 SUMMARY OF POTENTIAL RISKS AND BENEFITS

4.3.1 Observed and Potential Risks

AAV serotypes (2, 8, and 9) have been studied in several clinical studies such as hemophilia B (Nathwani et al, 2011b; Nathwani et al, 2014), Leber's congenital amaurosis (Maguire et al, 2008), and spinal muscular atrophy (NCT02122952), and appear to be safe.

However, direct clinical data addressing long-term benefits and risks of AAV-mediated gene transfer are limited, and the long-term risks remain unknown.

No studies have been conducted to evaluate the genotoxicity or carcinogenicity of RGX-314. The persistence of RGX-314 vector DNA was observed in the eye and was not seen in any non-ocular tissue in the NHP studies conducted. The genome of recombinant AAVs does not undergo site-specific integration in the host DNA, but remains episomal in the nucleus of transduced cells and the risk of insertional mutagenesis in cells of the retina is considered low. From a TP perspective, genotoxicity or carcinogenicity studies are not considered relevant, as with other anti-VEGF Fabs or monoclonal antibodies (mAbs).

RGX-314 gene therapy is a recombinant AAV8 viral vector containing a transgene that leads to the production of an anti-VEGF Fab protein. [redacted]). [redacted] With gene therapy, there is a possibility that the eye may overexpress anti-VEGF Fab, resulting in levels higher than that currently given in intravitreal therapy. Patients receiving RGX-314 should be monitored for any ocular AEs that could be considered indicative of toxicity (and not expected as a result of the surgical procedure). Potential signs and symptoms of ocular toxicity are listed in Appendix, Section 14.1.

As with all therapeutic proteins, there is a potential for an immune response. The subretinal space within the eye is considered immune privileged (ie, it is able to tolerate the introduction of antigens without eliciting an inflammatory immune response), and AAV NAbs have not had effects on subretinally delivered gene therapies (Bennett et al, 2012; Constable et al, 2016; Kotterman et al, 2015). For the proposed clinical study, samples to be assayed for AAV8 NAbs will be collected from within the eye prior to RGX-314 administration to assess for any correlation with outcomes, but subjects will not be excluded based on the presence of AAV8 NAbs at baseline, as these are not expected to have a clinically relevant effect. If a subject were to experience an immune response, inflammation may occur. The symptoms of inflammation will be monitored closely in the proposed clinical study and treated if necessary (Appendix, Section 14.1).

[redacted]

[redacted]

For this study, an injection site away from the macula was selected for gene therapy delivery and retinal anatomy including the site of injection/bleb area is monitored regularly with SD-OCT. [redacted]

Since bleb area SD-OCT scans were performed monthly since treatment, these SD-OCTs were reviewed by the reading center consultant. [redacted]

For subjects with inferior retina findings, crosshair (radial) SD-OCT scans are being collected to review over time. Similar findings to those described for SD-OCTs in the bleb

area were observed.

[redacted]

Additional functional assessments, including Humphrey visual field test or microperimetry and electroretinography (ERG), have been obtained in some of these subjects. To date no clear visual function deficit has been observed on any of these assessments, though these subjects will be assessed to confirm no significant change over time. Regarding underlying nAMD status and central vision, the majority of these subjects have improved BCVA compared to baseline with greatly decreased anti-VEGF intravitreal injection frequency compared to treatment burden prior to RGX-314 administration, and no subjects have had significant BCVA decrease. The lone subject with pigmentary changes in the perimacular area (Cohort 5) as of the Month 6 visit has gained +6 letters compared with baseline without need for anti-VEGF injections.

Following subretinal delivery of AAV gene therapy, pigmentary changes in the area of the bleb have been noted previously (Dimopoulos et al, 2018; Xue et al, 2018; Weleber et al, 2016). This appears as hyperpigmentation of the RPE cells and has been noted to have hyper and hypo fluorescence on FA. Additionally, hyperpigmentation inferior to the bleb has been described following subretinal delivery of tissue plasminogen activator (TPA) (Hesse et al, 1999). No clinical consequence has been reported in the literature as a result of these findings. Background pigmentary changes in the periphery on UWF imaging has recently been reported to be highly prevalent in the nAMD population, and the potential significance of such peripheral imaging findings is unknown (Forshaw et al, 2019).

All subjects administred in RGX-314 in clinical trials will have retinal imaging performed at baseline and periodically thereafter including UWF CFP, SD-OCT, FAF, and FA. Post-treatment SD-OCTs of the bleb area(s) and any area developing pigmentary changes will also be performed. To assess visual function, BCVA, visual field test (Humphrey Full Field 120 or microperimetry) and (if available) ERG will be performed.

The potential for the vector transgene to spread to unintended recipients from shedding (release of vectors that did not infect the target cells and were cleared from the body via feces or bodily fluids), mobilization (transgene replication and transfer out of the target cell), or germ line transmission (genetic transmission to offspring through semen) is considered to be low. Refer to the protocol-specified precautionary measures for use of appropriate birth control in sexually active female and male subjects from screening through 24 weeks after vector administration and for precluding any use in pregnant females or in females planning to become pregnant within 24 weeks after administration.

The vector can be handled under BSL-1 conditions (or RG1).

RGX-314 will be administered subretinally by a trained retinal surgeon with the subject under local anesthesia. The procedure will involve standard 3-port pars plana vitrectomy with a core vitrectomy followed by subretinal delivery. Pars plana vitrectomy is considered to be part of usual retina care and is not part of an experimental protocol. It is a routine retinal surgery that can usually be performed safely as an outpatient procedure.

Vitrectomy-related complications include inflammation or redness, swelling, pain, increased or reduced IOP, bleeding, cataract (not applicable to pseudophakic subjects), retinal tears, retinal detachments, retinal and vitreous incarceration, vitreous hemorrhage, and endophthalmitis. The procedure is also associated with risks for the long-term development of open-angle glaucoma due to increased oxygen tension in the eye and potential oxidative damage to the trabecular meshwork. Very rarely, vitrectomy also increases the risks of developing a visual field defect, visual loss due to macular toxicity of light or dye (if used) or manipulation, and optic neuropathy (AAO, 2015-2016). The vitrectomy performed in this study will not include the use of dyes and will be performed in pseudophakic eyes.

Subretinal delivery is a less common technique performed by vitreoretinal surgeons. Most retinal surgeons have experience with the technique for the delivery of TPA for the treatment of submacular hemorrhage. More recently, the technique is being used in several other gene therapy studies for inherited retinal diseases (Bainbridge et al, 2008; Gil-Farina et al, 2016; Hauswirth et al, 2008; MacLaren et al, 2014; Maguire et al, 2008; and ongoing studies noted in Section 4.2) and results previously reported from 2 nAMD programs (Campochiaro et al, 2016; Constable et al, 2016; Rakoczy et al, 2015). No serious adverse events (SAEs) related to investigational product were observed in these studies; mild adverse events (AEs) consistent with vitrectomy were noted, and 1 patient developed a macular hole of which the patient was unaware (Maguire et al, 2008). The serious risks associated with subretinal delivery include retinal and vitreous hemorrhage, inflammation, increases in IOP, retinal tear, macular hole, retinal detachment, or severe endophthalmitis. As described above, subretinal delivery of gene therapy and TPA has been associated with pigmentary changes in the area of the bleb and/or inferior retina. All Investigators will be preselected based on their previous retinal surgery experience in complex retinal procedures (such as subretinal delivery) and experience with surgical clinical studies. Surgeons will receive further training on the study procedure as part of the proposed clinical study. A detailed description of the procedure can be found in the Administration Manual.

A theoretical administration risk to subjects stems from transfer of silicone from the inner coating of the syringe into the subject's eye during the administration procedure (Melo et al, 2019). While this risk is considered to be low because of the air-fluid exchange at the end of the vitrectomy, low flow rate of injection of RGX-314, and single RGX-314 administration, investigators should monitor subjects for signs of inflammation or floaters and record any change from the subjects' baseline condition as an AE.

Detailed discussion of the risks of RGX-314 and its administration can be found in the IB.

4.3.2 Potential Benefits

RGX-314 delivers a transgene that leads to the production of an anti-VEGF Fab protein. Anti-VEGFs are currently approved for the treatment of nAMD. Ranibizumab, aflibercept, and more recently brolucizumab (Brolucizumab Prescribing Information) have provided evidence for the ability of anti-VEGFs in improving vision and macular edema in patients with nAMD. However, these therapies require frequent injections for extended periods, often for years.

The proposed treatment with RGX-314 is a single administration expected to provide continuous levels of anti-VEGF activity in the range where established efficacy has been seen in ranibizumab models. A long-term duration of efficacy following a single intervention will be a significant benefit to patients who currently must undergo monthly or otherwise frequent injections. RGX-314 may offer patients an alternative treatment to approved anti-VEGF therapies and may provide a similar benefit but with less need for repeated intravitreal injections.

4.4 STUDY RATIONALES

4.4.1 Rationale for Proposed Doses

RGX-314 will be administered as a single subretinal delivery to the subretinal space. This replicates the route of administration used in the nonclinical studies. Dose scaling from animals to humans took into consideration approximate differences in retinal surface area and injection volume.

When selecting a starting human dose, one key consideration was that the ability to readminister the vector may not be possible due to potential immune responses. Given that subsequent administration of a higher dose in an individual subject may not be feasible due to anatomic and manufacturing constraints, it is necessary to select a starting clinical dose that is both safe and carries a reasonable expectation of benefit in this patient population. The proposed starting dose in the present study is based on the MED and MTD as determined in mouse models of disease and in NHPs, respectively.

[redacted]

[redacted]

[redacted]

In order to reduce the risk of toxicity, doses at or below the MTD will be used; additional risk will be mitigated by the location of administration. Subretinal delivery in this study will be targeted to the area superior to the fovea within the vascular arcades, which will avoid the macula with all blebs to remain outside the fovea by at least 2 disc diameters to mitigate any potential risk. As an additional clinical safety assessment, the protocol includes SD-OCT imaging of the bleb area to evaluate retinal thickness over time.

The proposed doses represent an acceptable benefit:risk profile, where the dose is expected to be in the therapeutic range (and, therefore, may offer clinical benefit) and potential risks are managed through targeted administration and regular SD-OCT monitoring.

4.4.2 Rationale for use of a Sentinel Subject

For each dose cohort, a sentinel subject with BCVA of ≤20/63 and ≥20/400 (≤63 and ≥19 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) will be assessed out to 4 weeks post-RGX-314 administration prior to dosing anyone further in the dose cohort. The doses chosen in this study are considered safe based on the nonclinical animal data. Because this is a first-in-human study to explore safety, a subject with worse vision will be treated initially and assessed for safety at that dose before expanding the vision criteria for the remainder of the subjects in a given cohort. Given that gene therapy studies in nAMD to date (Campochiaro et al, 2016; Constable et al, 2016; Rakoczy et al, 2015) have had events either related to the procedure or occasional inflammation that were mild and transient (resolving in a few weeks), 4 weeks will be adequate to assess these acute events in the sentinel subject. Following the sentinel subject evaluation, the remaining subjects in the dose cohort must have BCVA ≤20/40 and ≥20/400 (≤73 and ≥19 ETDRS letters).

5 STUDY OBJECTIVES

5.1 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)

5.2 SECONDARY OBJECTIVES

- To evaluate the long-term safety and tolerability of RGX-314
- To evaluate the concentration of RGX-314 protein levels in aqueous humor
- To evaluate the effect of RGX-314 on BCVA
- To evaluate the effect of RGX-314 on central retinal thickness (CRT) as measured by SD-OCT
- To assess the need for rescue therapy
- To evaluate the effect of RGX-314 on CNV lesion growth and leakage as measured by fluorescein angiography (FA)

6 INVESTIGATIONAL PLAN

6.1 ENDPOINTS

6.1.1 Primary Endpoints

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

6.1.2 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 1st anti-VEGF rescue injection
- Mean change from baseline in CNV lesion size and leakage area based on FA over time
- Immunogenicity measurements (NAb to AAV8, binding antibodies to AAV8, antibodies to RGX-314 protein, and Enzyme-Linked ImmunoSpot [ELISpot])
- Vector shedding analysis in serum and urine

[redacted]

6.2 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 (response defined in Section 7.1.3). For withdrawn subjects, anyone who has an 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 1st subject in each cohort (sentinel subject) will have vision of ≤20/63 and ≥20/400 (≤63 and ≥19 ETDRS letters). After RGX-314 administration to the 1st subject, there will be a minimum of 4-week observation period for safety. The Internal Safety Committee 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, 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 Independent Data Monitoring Committee [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 IDMC. Given that gene therapy studies in nAMD to date (Campochiaro et al, 2016; Constable et al, 2016; Rakoczy et al, 2015) have had events either related to the procedure or occasional inflammation that were mild and transient (resolving in a few weeks), 4 weeks will be adequate to assess these acute events in the sentinel subject. 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 (1 day post-procedure and 1 week and 4 weeks post-procedure). 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 (Section 8.1.2). Immunogenicity to the vector and transgene product 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 as shown in Section 8.4. The safety and tolerability of RGX-314 will be monitored through assessment of ocular and non-ocular AEs and SAEs, chemistry, hematology, coagulation, urinalysis, immunogenicity, ocular examinations and imaging (BCVA, IOP, slit lamp biomicroscopy, indirect ophthalmoscopy, SD-OCT, FA, Heidelberg Spectralis FAF, and CFP), and vital signs. Because of pigmentary changes observed in some subjects, starting with Protocol Version 10, additional ophthalmic assessments will include Optos UWF FAF (in addition to Heidelberg Spectralis FAF), ERG if available, visual field test (Humphrey Full Field 120 or microperimetry), and, if applicable, additional SD-OCT in the area of pigmentary change.

All Investigators will be preselected based on their previous experience with subretinal delivery in clinical practice and will be further trained on the procedure as part of the proposed clinical study. A detailed description of the procedures can be found in the Administration Manual.

7 SUBJECT POPULATION AND SELECTION

7.1 SELECTION OF STUDY POPULATION

Subjects must have a diagnosis of nAMD that is recurrent and persistent, responsive to anti-VEGF therapy, and requires frequent injections and meet the criteria below in order to be potentially eligible for this study.

7.1.1 Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Males or females aged ≥ 50 years and ≤ 89 years.
2. Sentinel subject for each dose cohort must have a BCVA ≤20/63 and ≥20/400 (≤63 and ≥19 ETDRS letters) in the study eye. Following the sentinel subject evaluation, the rest of the subjects in the dose cohort must have a BCVA between ≤20/40 and ≥20/400 (≤73 and ≥19 ETDRS letters).
3. In the case both eyes are eligible, study eye must be the subject's worse-seeing eye, as determined by the Investigator.
4. Must have a documented diagnosis of subfoveal CNV secondary to AMD in the study eye.
    a. CNV lesion characteristics: lesion size needs to be less than 10 disc areas (typical disc area is 2.54 mm^2), blood <50% of the lesion size.
5. Must have received at least 4 intravitreal injections of an anti-VEGF agent for treatment of nAMD in the study eye in approximately 8 months (or less) prior to Visit 1, with anatomical response documented on SD-OCT.
6. Must have subretinal or intraretinal fluid in the center subfield present at Visit 1 in the study eye, evidenced on SD-OCT unless the subject is a re-screen.
    a. Subjects who have previously met all inclusion criteria including the Visit 2 responsiveness criterion on OCT, but did not receive RGX-314 within the window, may be re-screened and do not need to have fluid on entry or meet the Visit 2 responsiveness criterion again subject to discussion with and approval by Sponsor's Medical Director.
7. Must be pseudophakic (status post cataract surgery) in the study eye.
8. Must be willing and able to comply with all study procedures and be available for the duration of the study.
9. Females of childbearing potential (defined in Section 9.5.2) must have a negative urine pregnancy test at the screening visit, have negative serum results by Day 8, and be willing to have additional pregnancy tests during the study.

10. Sexually active subjects (both female and male) must be willing to use a medically accepted method of barrier contraception (eg, condom, diaphragm, or abstinence) from screening visit until 24 weeks after vector administration. Cessation of birth control after this point should be discussed with a responsible physician.
11. Must be willing and able to provide written, signed informed consent.

7.1.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. CNV or macular edema in the study eye secondary to any causes other than AMD.
2. Blood occupying ≥50% of the AMD lesion or blood >1.0 mm^2 underlying the fovea in the study eye.
3. Any condition preventing VA improvement in the study eye, eg, fibrosis, atrophy, or retinal epithelial tear in the center of the fovea.
4. Active or history of retinal detachment in the study eye.
5. Advanced glaucoma in the study eye.
6. Any condition in the study eye that, in the opinion of the Investigator, may increase the risk to the subject, require either medical or surgical intervention during the course of the study to prevent or treat vision loss, or interfere with study procedures or assessments.
7. History of intraocular surgery in the study eye within 12 weeks prior to the screening visit. Yttrium aluminum garnet capsulotomy is permitted if performed >10 weeks prior to the screening visit.
8. History of intravitreal therapy in the study eye, such as intravitreal steroid injection or investigational product, other than anti-VEGF therapy, in the 6 months prior to screening.
9. Presence of an implant in the study eye at screening (excluding intraocular lens).
10. History of malignancy requiring chemotherapy and/or radiation in the 5 years prior to screening. Localized basal cell carcinoma will be permitted.
11. Receipt of any investigational product within the 30 days of enrollment or 5 half-lives of the investigational product, whichever is longer.
12. Participation in any other gene therapy study.
13. History of therapy known to have caused retinal toxicity, or concomitant therapy with any drug that may affect visual acuity or with known retinal toxicity, eg, chloroquine or hydroxychloroquine.
14. Ocular or periocular infection in the study eye that may interfere with the surgical procedure.
15. Myocardial infarction, cerebrovascular accident, or transient ischemic attacks within the past 6 months.

16. Uncontrolled hypertension (systolic blood pressure [BP] >180 mmHg, diastolic BP >100 mmHg) despite maximal medical treatment.
17. Any concomitant treatment that, in the opinion of the Investigator, may interfere with ocular surgical procedure or healing process.
18. Known hypersensitivity to ranibizumab or any of its components or past hypersensitivity (in the Investigator's opinion) to agents like RGX-314.
19. Any serious, chronic, or unstable medical or psychological condition that, in the opinion of the Investigator, may compromise the subject's safety or ability to complete all assessments and follow-up in the study.

7.1.3 Criteria for Continuing Study After Receiving Ranibizumab

At Visit 2, subjects (with the exception of re-screens who have met this criterion in the past) will be assessed for initial anti-VEGF response to ranibizumab. Subjects will undergo both SD-OCT and BCVA, which will be compared by the Investigator with the Visit 1 values:

1. Responsive (subjects will continue in the study): Response is defined as reduction in CRT >50 µm or >30% improvement in central fluid by SD-OCT.
2. Non-responsive (subjects will exit the study as early withdrawals): Non-response is defined as not meeting the criteria above. Additional subjects will continue to be enrolled until up to 6 subjects (Cohorts 1 to 3) or up to 12 subjects (Cohorts 4 and 5) in each cohort receive a single dose of RGX-314.

At this visit central lab results will be reviewed. Any subjects with the following values will be withdrawn:

3. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN)
4. Total bilirubin >1.5 × ULN unless the subject has a previously known history of Gilbert's syndrome and a fractionated bilirubin that shows conjugated bilirubin <35% of total bilirubin
5. Prothrombin time (PT) >1.5 × ULN
6. Hemoglobin <10 g/dL for male subjects and <9 g/dL for female subjects
7. Platelets $<100 \times 10^3/\mu L$
8. Estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2

7.2 SUBJECT RECRUITMENT AND SCREENING

Subjects will be recruited from the population of patients with nAMD by participating clinical sites.

Subjects meeting eligibility that do not make RGX-314 administration (Visit 3) due to unforeseen circumstances may be considered for re-screen at a later time by the Sponsor's Medical Director. Refer to the Study Reference Manual for additional information.

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.

7.3 WITHDRAWAL OF SUBJECTS

Every effort should be made to keep subjects in the study. However, subjects are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment.

A subject may be withdrawn from the study for the following reasons:

- Considered non-responsive to ranibizumab (per Section 7.1.3)
- Lost to follow-up
- Termination of study by REGENXBIO
- Protocol deviation
- Noncompliance with study visits
- Subject or Investigator decides to discontinue the subject's participation in the study

The term "Early Withdrawal" is used for subjects who dropped out prior to dosing with RGX-314, including those who are considered nonresponsive (per Section 7.1.3). An Early Termination Visit is not required for these subjects. The term "Early Termination" is used for subjects who exit the study after receiving a dose of RGX-314. These subjects should complete all tests of the Early Termination Visit. (See Table 2: Schedule of Events After End of Year 1 Through Year 2.)

At the end of the subject's participation, the Investigator will complete the discontinuation page of the case report form (CRF) and document the reason(s) for study discontinuation.

8 TREATMENTS ADMINISTERED

8.1 RANIBIZUMAB

8.1.1 Initial Treatment in the Study Eye

All subjects will receive a single intravitreal injection of ranibizumab 0.5 mg on Visit 1 (14 days prior to RGX-314 delivery).

8.1.2 Rescue Therapy

Starting at 4 weeks post-RGX-314 administration, the subject may receive intravitreal ranibizumab rescue therapy in the study eye at the Investigator's discretion for disease activity if 1 or more of the following rescue criteria apply:

- Vision loss of ≥5 letters (per BCVA) associated with accumulation of retinal fluid on SD-OCT
- CNV-related increased, new, or persistent subretinal or intraretinal fluid on SD-OCT
- New ocular hemorrhage

Injection may be deferred at the Investigator's discretion if 1 of the following sets of findings occur:

- VA is 20/20 or better and CRT is "normal" as assessed by SD-OCT
- VA and SD-OCT are stable after 2 consecutive injections.

If injections are deferred, they will be resumed if VA or SD-OCT get worse per the criteria above.

With approval from the Sponsor's Medical Director, the Investigator may recommend changing the study eye rescue therapy from ranibizumab to aflibercept. Only ranibizumab will be provided as part of the study.

8.2 INVESTIGATIONAL PRODUCT

RGX-314 [redacted] is a non-replicating recombinant AAV8 viral vector containing a transgene that leads to the production of an anti-VEGF Fab protein [redacted]

[redacted]

[redacted]

Final investigational product is supplied as a frozen solution of the AAV vector active ingredient [redacted] in a formulation buffer [redacted]

The investigational product (RGX-314) will be given as a single dose via subretinal delivery in the subject's worse-seeing eye (ie, designated "study eye") as decided by the

Investigator. [redacted]

RGX-314 is given by a single subretinal delivery by a retinal surgeon with the subject under local anesthesia. The procedure will involve a standard 3-port pars plana vitrectomy with a core vitrectomy followed by subretinal delivery of RGX-314 into the subretinal space by a subretinal cannula (38 gauge). [redacted]

8.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT

This is an open-label study. Refer to Section 6.2 for a description of a plan to sequentially dose subjects, including review of safety data after the 1st subject in each cohort and after at least 6 subjects in each cohort have been dosed at any dose level prior to dose escalation. The rationale for the proposed dose levels is provided in Section 4.4.1.

8.4 STOPPING RULES

The safety and tolerability of RGX-314 will be assessed in each dosed subject as shown in Table 6.

Table 6: Safety Review Trigger Events and Actions

Safety Review Trigger (SRT) Event	Safety Review Action
A Stopping Rule is met	An external IDMC will review all available safety data and provide a recommendation on whether to enroll additional subjects.
Any Grade 4 or 5 AE regardless of relationship to treatment	The chairs of the Internal Safety Committee and the external IDMC will review and decide whether to allow enrollment to continue or convene a full IDMC review of all available safety data which will then provide a recommendation on whether to enroll additional subjects.
Any Grade 3 AE considered treatment-related (by the Investigator)	
Any Grade 3 AE considered unrelated to treatment (by the Investigator)	An Internal Safety Committee will review all available safety data. If safety concerns arise while a cohort is being enrolled, the committee may ask the IDMC to review and make a recommendation on whether to keep enrolling subjects in that cohort.
Any report by the Investigator of technical issues with the surgical procedure that may warrant modifications to the procedure	

AE = adverse event; IDMC = Independent Data Monitoring Committee.

If any of the following events occur, a Stopping Rule will be considered to have been met and dosing of any new subjects will be suspended until a complete review of all safety data has been performed by REGENXBIO and the IDMC:

- The subject dies, and the Investigator considers the death to be related to the investigational product or procedure.

- Any occurrence of a treatment-emergent AE of arterial thromboembolism.
- An ocular AE listed in the Appendix, Section 14.1 reported as a Grade 4 or 5 AE regardless of relationship to treatment or reported as a Grade 3 AE that is considered treatment-related (by the Investigator).
- An acute or near-term severe vision loss defined as a 15 letter loss in vision within 4-weeks after RGX-314 administration that the PI considers related to gene therapy.

Stopping Rules and SRTs must follow the reporting requirements for SAEs as defined in Section 10.4.

8.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

While at the clinical site, investigational product must be stored in a secure limited access location at a controlled temperature as described in the IB, Pharmacy Manual, and according to product packaging. The storage facility must be available for inspection by the Study Monitor at any time during the study.

An investigational product accountability log must be maintained for all investigational product received, dispensed, returned, destroyed, and/or lost during the study, as applicable. The record must be kept current and made available to the Study Monitor for inspection. Following the closeout of the study, all unused investigational product must be returned to REGENXBIO and/or its designee unless other instructions have been provided for final disposition of the investigational product.

8.6 PRIOR AND CONCOMITANT ANTI-VEGF MEDICATIONS AND THERAPEUTIC PROCEDURES

Prior anti-VEGF therapy and ocular history for the subject from 12 months prior to providing informed consent will be recorded into the CRF after retrospective chart review.

Prior medications will be defined as medications that are taken prior to providing informed consent.

Concomitant medications will be defined as medications that are taken at the time of or after providing informed consent and will be recorded in the CRF. All medications, other than RGX-314, received as part of any study procedures will also be recorded on the CRF. The initial ranibizumab injection and any injections as rescue medication will be recorded on the CRF also.

Anti-VEGF treatment of nAMD in the fellow eye will be at the discretion of the Investigator but restricted to ranibizumab or aflibercept. Ranibizumab will be provided for the fellow eye as part of the study.

8.6.1 Prohibited Medications and Procedures

Subjects may not:

- Receive rescue treatment of the study eye or treatment of the fellow eye with bevacizumab (Avastin®, Genentech).
- Receive any experimental medication or therapy within 4 weeks of screening or within 5 half-lives of the investigational product, or at any time during the study.
- Receive any concomitant treatment that, in the opinion of the Investigator, may interfere with ocular surgical procedure or healing process

8.6.2 Permitted Medications and Procedures

Treatment of the fellow eye will be at the discretion of the Investigator but restricted to ranibizumab or aflibercept. Ranibizumab will be provided for the fellow eye as part of the study.

8.7 PRECAUTIONS

The replication defective recombinant AAV8 vector to be used in this program is a non-infectious and non-pathogenic material as defined by the NIH (NIH, 2016) and the vector can be handled under biosafety level-1 conditions (or Risk Group 1). Risk Group 1 agents are not associated with disease in healthy adult humans. Staff who may come into contact with any bodily fluids of subjects treated with RGX-314 should use appropriate precautions (eg, gloves, masks, lab coats) to prevent direct contact. Labs handling these bodily fluids should use their normal standard operating procedures, and personnel should wash their hands with soap and clean running water.

9 VISION AND SAFETY ASSESSMENTS

9.1 SCHEDULE OF EVENTS

The parameters to be assessed for this study, along with the timing of assessments, are provided in the Schedule of Events (Table 1 [Year 1] and Table 2 [Year 2]). Refer to the Study Reference Manual for additional information. Additional assessments not specified in the Schedule of Events needed for pre-operative evaluations may be performed per institutional standards.

9.2 DEMOGRAPHICS

Demographic data such as age, sex, and race will be collected in the CRF.

9.3 MEDICAL AND MEDICATION HISTORY

The Investigator or designee will collect a relevant medical and surgical history. Medical history will include information on the subject's concurrent medical conditions. Medical history will include a complete ocular history. Prior anti-VEGF therapy and ocular history from the previous 12 months will be recorded on the medical history CRF.

Medication history will include information on the subject's current medications. Medication history will include previous treatments for nAMD including other anti-VEGF therapy. All findings will be recorded on the prior medication CRF.

9.4 OPHTHALMIC ASSESSMENTS

At study visits specified in the Schedule of Events (Table 1 [Year 1] and Table 2 [Year 2]), the following ocular assessments may be performed. When applicable, assessments should be performed in the order listed. Images will be stored in a central imaging repository; refer to the Study Reference Manual for additional information:

- Full ophthalmic exam – slit lamp biomicroscopy, IOP, and dilated ophthalmoscopy
- BCVA using ETDRS at 4 meters, repeated at 1 meter, if necessary (bilateral)
- SD-OCT using the Heidelberg Spectralis (bilateral macula and study eye bleb area(s))
- Starting with Protocol Version 10: additional SD-OCT (radial scan if possible) in the area of study eye pigmentary change – subjects with pigmentary changes only
- FAF (study eye) using the Heidelberg Spectralis and, starting with Protocol Version 10, also Optos UWF
- Color fundus photography (study eye)
- FA (study eye)
- Starting with Protocol Version 10: visual field test consisting of the Humphrey Full Field 120 or microperimetry; once a test is selected, the same test must be performed at subsequent time points of assessment
- Starting with Protocol Version 10: ERG if available

9.5 SAFETY ASSESSMENTS

9.5.1 Adverse Events

All AEs will be recorded from the time the subject signs the informed consent form (ICF). The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 10. At each study visit, subjects will be asked about any new or ongoing AEs since the previous visit. AEs for ocular inflammation will be graded based on the scales shown in Appendix, Section 14.2. Assessments of AEs will occur at the time points shown in the Schedule of Events (Table 1 [Year 1] and Table 2 [Year 2]).

9.5.2 Pregnancy Testing

Female subjects of childbearing potential with a positive urine or serum pregnancy test prior to RGX-314 administration (Visit 3) do not meet eligibility criteria for enrollment and will not be enrolled in the study. Females considered not of childbearing potential include those who have had total hysterectomy, have been in menopause for at least 2 years, or have had tubal ligation at least 1 year prior to Screening.

Additional urine pregnancy tests will be performed at any visit in which pregnancy status is in question. A serum pregnancy test will be performed in the event of a positive or equivocal urine pregnancy test result. Refer to the Study Reference Manual for additional information. In the case of a confirmed pregnancy, refer to Section 10.5.

9.5.3 Clinical Laboratory Tests

The following clinical laboratory and antibody tests will be assessed as specified in the Schedule of Events (Table 1 [Year 1] and Table 2 [Year 2]):

- 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.
- 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
- Coagulation: PT and partial thromboplastin time
- Urinalysis: Dipstick for glucose, ketones, protein, and blood (if warranted, a microscopic evaluation will be completed)
- RGX-314 protein concentration in serum and aqueous humor
- Immunogenicity measurements:
  - NAb to AAV8 (serum and vitreous humor)
  - AAV8 binding antibodies (aqueous humor)
  - Antibodies to RGX-314 protein (aqueous humor, vitreous humor, and serum)

- ELISpot (whole blood)
- Vector shedding analysis in serum and urine
- VEGF in aqueous humor

Laboratory reports from the central laboratory will be made available to the Investigator in a timely manner to ensure appropriate clinical review. The Investigator is responsible for reviewing and signing all laboratory reports. Any abnormal findings that meet the definition of an AE per Section 10.1 will be recorded on the AE CRF.

Procedures for the collection, handling and shipment of all laboratory samples to be sent to the central laboratory will be included in a separate manual.

9.5.4 Vital Signs

Assessment of vital signs (BP and heart rate) will be obtained/performed at visits specified in the Schedule of Events (Table 1 [Year 1] and Table 2 [Year 2]).

9.6 APPROPRIATENESS OF MEASURES

The assessments of safety and efficacy are standard assessments for studies in subjects with nAMD treated with anti-VEGF therapy.

10 ADVERSE EVENT HANDLING AND SAFETY REPORTING

10.1 DEFINITIONS

10.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)
- Abnormal laboratory findings, as defined in Section 10.2.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

10.1.2 Definition of a Serious Adverse Event

An AE is considered to be an SAE if, in the view of the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE

  NOTE: Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization

  NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Persistent or significant incapacity/disability

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- A congenital anomaly/birth defect
- All events of possible drug-induced liver injury with hyperbilirubinemia having the following 3 components termed "Hy's Law" events.

  1. ALT ≥3× ULN or AST ≥3× ULN
  2. Total bilirubin ≥2× ULN
  3. No other reason can be found to explain the changes observed in #1 and #2 above.

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such events are ocular inflammation resulting in severe vision loss (>6 lines on ETDRS chart).

10.2 LABORATORY AND OTHER SAFETY ASSESSMENT ABNORMALITIES REPORTED AS AES AND SAES

Any abnormal laboratory test results (hematology, chemistry, coagulation, or urinalysis) or other safety assessments (eg, vital sign measurements), including those that worsen from baseline and are thought to be clinically significant in the medical and scientific judgement of the Investigator, are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

10.3 EVALUATION OF ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

10.3.1 Relationship to Study Treatment and/or Study Procedures

The Investigator will assess the potential relationship of the AEs to study treatment or procedures using the following definitions:

- **Not Related:** This category applies to an AE that is clearly not related to the investigational product/procedure, beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the exposure to investigational product and/or causal relationship is considered biologically implausible.
- **Possibly Related:** This category applies to an AE that follows a reasonable temporal sequence from administration of the investigational product and that follows a known or expected response pattern to the suspected investigational product, but that could readily have been produced by a number of other factors.
- **Probably Related:** This category applies to an AE that follows a reasonable temporal sequence from administration of the investigational product and that follows a known or expected response pattern to the suspected investigational product and that could not be reasonably explained by the subject's concurrent disease or other drugs or chemicals.

10.3.2 Severity or Intensity Grading of Adverse Event Scoring

Wherever possible, the severity of all AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 4.03). The majority of AEs can be graded using the CTCAE criteria; however, if an AE cannot be graded using the CTCAE criteria, it should be graded according to the following definitions:

- **Mild (Grade 1):** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- **Moderate (Grade 2):** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe (Grade 3):** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.
- **Life-threatening (Grade 4):** Events that place the subject at immediate risk of death or are disabling requiring urgent intervention.
- **Death (Grade 5):** Events that result in death.

The concept of "SAEs" and "Severe Adverse Events" is often confused. Severity is not synonymous with seriousness. The term "severe" is often used to describe the intensity (severity) of a specific event (eg, mild, moderate, or severe); however, the event itself may be of relatively minor medical significance. For example, a headache is severe, if it causes intense pain. On the other hand, a headache is not usually serious (but may be in case of subarachnoid hemorrhage, subdural bleed, even a migraine may temporally fit "serious" criteria), unless it also satisfies the criteria for seriousness as defined in Section 10.1.2. Similarly, a severe rash is not likely to be an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.

An SAE is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. In other words, an SAE requires an additional reporting process (reported to corporate global drug safety group or pharmacovigilance group, regulatory authorities, Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]).

All events of ocular inflammation must additionally be graded according to the Ocular Inflammation Grading Scales (Appendix, Section 14.2).

10.4 SERIOUS ADVERSE EVENTS, SERIOUS ADVERSE DRUG REACTIONS, AND REQUIREMENTS FOR IMMEDIATE REPORTING

Any SAE that occurs at any time during the study, including a clinically significant abnormal laboratory test result that is considered serious, must be reported within 24 hours of knowledge of the event to REGENXBIO or its designee. These requirements apply equally to all subjects, regardless of the study phase or the subject's treatment assignment or dose. The reporting requirement for SAEs is from the time of signing the ICF through 30 days following the last study visit.

A death occurring during the study and within 30 days after the last study visit must be reported to REGENXBIO or its designee within 24 hours of knowledge of the death whether or not it is considered treatment-related.

Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. In addition, the Investigator

must notify the IRB/IEC of the SAE occurrence in accordance with the IRB/IEC reporting requirements. A copy of this notification must be provided to REGENXBIO or its designee.

REGENXBIO has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. REGENXBIO will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to Investigators as necessary.

10.5 PREGNANCY REPORTING

Any pregnancy that occurs during study participation either to a study subject or to the female partner of a male subject must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to REGENXBIO within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the investigational product, must be reported to REGENXBIO within 24 hours of knowledge of the event.

10.6 URGENT SAFETY MEASURES

The regulations governing clinical studies state that REGENXBIO and the Investigator are required to take appropriate Urgent Safety Measures (USMs) to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations.

USMs are procedures that are not defined by the protocol, which can be put in place with immediate effect without needing to gain prior authorization by the IRB (and regulatory authorities, where applicable), in order to protect subjects from any immediate hazard to their health and safety.

The reporting period for USMs is from signing the ICF through completion of the last study visit. It is the Investigator's responsibility to notify REGENXBIO or its designee of any USMs within 24 hours of occurrence.

11 STATISTICAL METHODS AND PLANNED ANALYSES

REGENXBIO or its designee will perform the statistical analysis of the data from this study. All analyses will be fully described in a statistical analysis plan (SAP), which will be finalized before any analyses are conducted.

All data will be presented in subject data listings. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum, and maximum). Graphical displays will be presented as appropriate.

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

11.1 DETERMINATION OF SAMPLE SIZE

No formal calculation was performed to determine sample size.

11.2 ANALYSIS POPULATIONS

- As-treated Population: Includes all subjects who received any dose of RGX-314.
- Evaluable for Efficacy Population: Includes all subjects with both a baseline and 24 weeks following RGX-314 administration measurement for the efficacy endpoints.

11.3 DISPOSITION

The number of subjects enrolled, the number of subjects who complete the study, and the number of subjects who withdraw from the study, along with the reasons for their withdrawal, will be summarized by dose cohort and by the study overall. In addition, the total number of subjects screened and the number of screen failures, along with the reason for screen failure, will be summarized.

11.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized descriptively by dose cohort, as well as for the study overall.

11.5 SAFETY ANALYSES

11.5.1 Adverse Events

AEs occurring prior to administration of RGX-314 or in the fellow eye will be listed and presented separately from those that occur during or after investigational product administration. The incidence of TEAEs, treatment-related TEAEs, and TEAEs by severity (intensity) will be summarized. All AEs will be coded using the most recent version of the

Medical Dictionary for Regulatory Activities (MedDRA), and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

11.5.2 Clinical Laboratory Tests

Observed values and changes from baseline (as applicable) through 104 weeks following RGX-314 administration will be summarized descriptively by dose cohort and by the study overall for each hematology, chemistry, coagulation, and urinalysis parameter. In addition, the incidence of subjects who meet predefined criteria for a clinically significant abnormal values (or abnormal change) may also be summarized by dose cohort and by the study overall.

11.5.3 Vital Signs

Observed values and changes from baseline (as applicable) through 104 weeks following RGX-314 administration will be summarized descriptively by dose cohort and by the study overall. In addition, the incidence of subjects who meet predefined criteria for clinically significant abnormal values (or abnormal change) may also be summarized by dose cohort and by the study overall.

11.6 EFFICACY ANALYSES

Observed values and changes from baseline over time (as applicable) will be summarized descriptively and a 95% confidence interval will be provided by dose cohort and by the study overall for the efficacy endpoints (defined in the SAP).

11.7 OTHER STATISTICAL ISSUES

11.7.1 Significance Levels

Significance level will be 5% and no multiple comparison adjustment will be performed, as all analyses are descriptive.

11.7.2 Missing or Invalid Data

Due to the small number of subjects, missing or invalid data will be excluded from analyses. Analyses will be based on observed data only.

11.8 INTERIM ANALYSIS

No interim analysis is planned.

12 SPECIAL REQUIREMENTS AND PROCEDURES

12.1 ETHICAL CONDUCT OF THE STUDY

The Investigator will ensure that this study is conducted in full conformity with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) including any subsequent amendments and clarifications to these principles, current US FDA regulations, International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and local ethical and regulatory requirements. Should a conflict arise, the Investigator should follow whichever regulation or guideline affords the greater protection to the individual subject.

12.1.1 Institutional Review Board

The IRB must be a properly constituted board or committee operating in accordance with 21 Code of Federal Regulations (CFR) Part 56: Institutional Review Boards and ICH E6: Guideline for GCP. This protocol, any protocol amendments, and ICFs must be submitted to the IRB for review and must be approved before screening of any subject into the study. Investigational product will not be shipped to the Investigator until REGENXBIO or its designee has received a copy of the IRB approval letter or certificate of approval from the IRB for the protocol, any amendments, and ICFs. Site-specific ICFs must be approved by REGENXBIO prior to IRB submission.

In addition, all subject recruitment and/or advertising materials and subject instructions, if applicable, must be submitted to the IRB for review and approval prior to implementation. Approval by REGENXBIO is required prior to IRB submission of any subject recruitment and/or advertising materials and subject instructions, if applicable.

IRB approval of any protocol amendment must be received before any of the changes defined in the protocol amendment are implemented, except when the protocol amendment has been enacted to protect study subjects. In these circumstances, the chair of the IRB should be notified immediately and the amendment forwarded to the IRB for review and approval.

12.1.2 Subject Information and Informed Consent

Informed consent is the process that is initiated prior to the potential subject's agreement to participate in the study and continues throughout the subject's study participation. It is the Investigator's responsibility to obtain signed written informed consent from each potential study subject prior to the performance of any study-related procedure. Written informed consent will be obtained only after the nature of the study including potential risks have been fully explained to each potential subject. The subject and/or subject's legal guardian(s) will be given the opportunity to ask any questions during informed consent as well as throughout the study, and all of the subject's questions must be answered to the subject's satisfaction. The Investigator must explain to each subject that participation in the study is completely voluntary and that the subject can decline participation or withdraw from participation at any time. If the subject is unable to provide informed consent, then informed assent will be obtained and informed consent must be provided by the subject's legal guardian(s).

The process of obtaining and documenting informed consent will comply with 21 CFR Part 50: Protection of Human Subjects, ICH GCP guidelines, the Health Insurance Portability and Accounting Act (HIPAA), and all other applicable regulatory requirements. Subjects will be given a copy of the signed ICF and will be provided any new information during their participation in the study that may affect their continued willingness to participate in the study. If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised IRB/IEC-approved ICF.

Informed consent will be documented in the subject's study file and in the CRF. The signed ICF will remain in each subject's study file and must be made available to the Study Monitor(s) at all times.

12.2 DATA HANDLING AND RECORD KEEPING

12.2.1 Monitoring and Access to Study Records

A representative of REGENXBIO and/or its designee will perform routine monitoring and auditing of the study to ensure compliance with FDA and ICH GCP guidelines. REGENXBIO's designated representative (the Monitor) will visit the Investigator to verify the Investigator's qualifications, to inspect the clinical site facilities, and to inspect study records, including adherence to regulatory requirements (ie, IRB/IEC review and approval documents). In addition, the Monitor will be responsible for confirming that the study is being conducted in adherence to the study protocol, performing Source Document Verification (SDV), and ensuring the integrity of the data.

The Monitor will maintain frequent contact with the study site throughout the course of the study. The Investigator and all other site personnel agree to cooperate fully with the Monitor and will work collaboratively with the Monitor to resolve all questions and issues identified by the Monitor. It is the responsibility of the Investigator to be present or available for consultation during these routine monitoring visits.

The Investigator understands and agrees that regulatory authorities, the IRB, and/or REGENXBIO or its designee have the right to access all study-related documents (eg, CRFs, source documents, etc) during on-site inspections and routine monitoring visits and will retain this right from the beginning of the study until at least 2 years after the last approval of a marketing application or for at least 2 years after the discontinuation of the clinical development of the investigational product under study. It is the responsibility of the Investigator to guarantee access to these documents and to cooperate with and support such inspections and routine monitoring visits.

12.2.2 Source Documents and Case Report Forms

It is the Investigator's responsibility to prepare and maintain adequate and accurate case histories that record all observations and other data related to the study for each subject. Case histories include the CRFs and supporting data (ie, source documents) such as signed and dated ICFs, medical records, laboratory reports, etc. Case histories for each subject will document that informed consent was obtained prior to participation in the study.

A validated Electronic Data Capture (EDC) system will be used for entry of the data into electronic CRFs designed and approved by REGENXBIO. All data entered into the CRF must be verifiable; therefore, CRFs will be routinely monitored for accuracy, completeness, and clarity and will be cross-checked for consistency with source documents.

12.2.3 Data Quality Assurance

During routine monitoring visits, the Monitor will perform SDV against CRFs to ensure data accuracy, completeness, and clarity, including laboratory reports and other subject records with the stipulation that subject confidentiality will be strictly maintained in accordance with local and federal regulations, including HIPAA requirements. Instances of missing or uninterruptable data will be resolved in coordination with the Investigator.

In addition to routine monitoring of the data by the Monitor, the EDC system will include internal quality controls by employing Skip Logics and Edit Checks. Skip Logics are programs in the database that restrict entry to particular data fields based on previous entered data, thus restricting the entry of irrelevant data. Edit Checks are a set of programmed instructions in the database to identify and flag discrepancies in the entered data.

12.2.4 Record Retention

All study-related documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with REGENXBIO. All study-related documents must be stored in a secure limited access facility.

12.3 INDEPENDENT DATA MONITORING COMMITTEE

This study will be conducted under the auspices of an IDMC. The membership and activities are outlined in the IDMC Charter.

12.4 INTERNAL SAFETY COMMITTEE

The Internal Safety Committee will be comprised of REGENXBIO employees and designees and be charged with Sponsor oversight for the safe conduct of the study.

12.5 FINANCING AND INSURANCE

Financing and insurance for this study will be addressed in the Clinical Trial Agreement with the study site(s).

12.6 PROVISION OF STUDY RESULTS AND INFORMATION TO INVESTIGATORS AND PUBLICATION

Study information from this protocol will be posted on www.clinicaltrials.gov within 21 days of enrollment of the 1st participant.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a REGENXBIO site or other mutually agreeable location.

REGENXBIO will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate. The results summary will be posted to clinicaltrials.gov no later than 12 months after the last subject's last visit or sooner if required by legal agreement, local law, or regulation. A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge and will be submitted to a peer-reviewed journal for publication within 18 months of the last subject's last visit.

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14 APPENDICES

14.1 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: VA 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 VA, color vision disturbances, visual field defects (relative and absolute scotomas), and afferent pupillary defect.

AC = anterior chamber; IOP = intraocular pressure; VA = visual acuity.

14.2 Ocular Inflammation Grading Scales

Ocular inflammation will be assessed during slit-lamp biomicroscopy and independent ophthalmoscopy and graded using the following scales. The standard practice for slit-lamp biomicroscopy and indirect ophthalmoscopy assessment should be used.

Table 7: Grading Scale for Ocular Inflammation: Anterior Chamber Cells and Anterior Chamber Flare

Anterior Chamber Cells	
Grade	**Cells in Field (1 mm × 1 mm slit beam)**
0	None
+0.5	1–5
+1	6–15
+2	16–25
+3	26–50
+4	>50
Anterior Chamber Flare	
Grade	**Description**
0	None
+1	Trace
+2	Moderate (iris and lens detail clear)
+3	Marked (iris and lens detail hazy)
+4	Intense (fibrin or plastic aqueous)

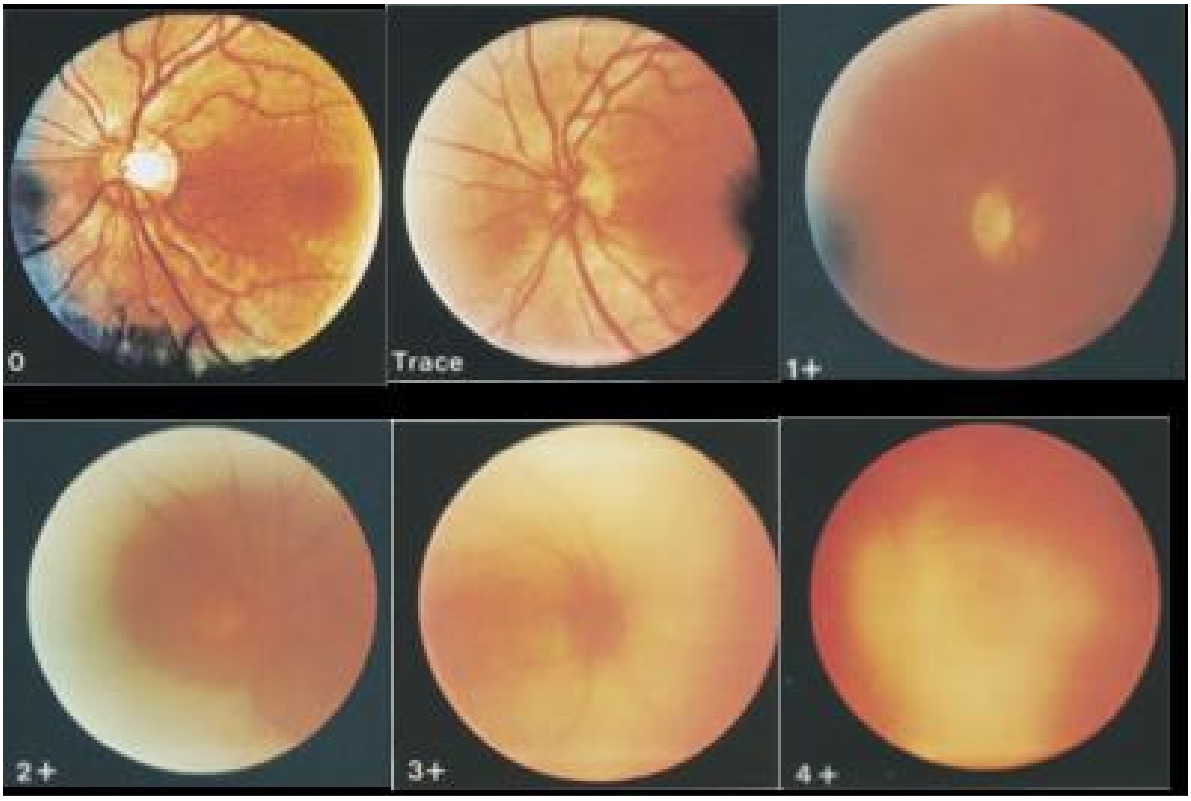
Source: This article was published in Am J Ophthalmol, Vol 140(3). Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Pages 509-16. Copyright Elsevier 2005. Jabs, 2005

Table 8: Grading Scale for Vitreous Haze

Grade	Amount of Vitreal Haze
0	None
+0.5	Trace
+1	Clear optic disc and vessels; hazy nerve fiber layer
+2	Hazy optic disc and vessels
+3	Optic disk visible
+4	Optic disc not visible

Source: This article was published in Am J Ophthalmol, Vol 40(3). Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Pages 509-16. Copyright Elsevier 2005. Nussenblatt, 1985. Refer also to Figure 10.

Figure 10: Gradations of Vitreous Haze



Source: Nussenblatt, 1985

15 SIGNATURE PAGE

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)

Protocol Number: RGX-314-001

Investigator Signature:

I have read Protocol RGX-314-001. I agree to conduct the study as detailed in this protocol and in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

_____ _____

Investigator Signature Date

Printed Name: _____

Sponsor Signature:

As the Sponsor representative, I confirm that REGENXBIO will comply with all Sponsor obligations as detailed in applicable guidelines and regulations. I will ensure that the Investigator is informed of all relevant information in a timely manner that becomes available during the conduct of this study.

[redacted]

_____ _____

[redacted]

[redacted].

Signature Page for RGX-RIM-003896 v3.0