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Study ID: RST-001-CP-0001

Title: Phase I/IIa, Open-Label, Dose-Escalation Study of Safety and Tolerability of Intravitreal RST-001 in Patients with Advanced Retinitis Pigmentosa (RP)

Protocol Date: 19-Oct-2017

ALLERGAN [redacted]

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Phase I/IIa, Open-Label, Dose-Escalation Study of Safety and Tolerability of Intravitreal RST-001 in Patients with Advanced Retinitis Pigmentosa (RP)

Protocol Number:	RST-001-CP-0001, Amendment 2
Phase:	Phase 1/2a
Name of Investigational Product:	RST-001 (AGN-151597)
Sponsor:	Allergan, Inc. 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500
Emergency Telephone Number(s):	North America: [redacted]
Serious Adverse Event Reporting Fax Number(s):	[redacted]
Allergan Medical Safety Physician Contact Information:	[redacted]

Approval Date: 19-Oct-2017

Allergan Signatory: [redacted]

Therapeutic Area Head
Glaucoma and Retina
Allergan – Global Drug Development

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on United States FDA Form 1572 and/or study contacts page and/or the Trial Master File: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of each reviewing Institutional Review Board (IRB); US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

Investigator:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	**Signature**	**Date**

1 Table of Contents

List of Tables

List of Figures

2 Protocol Synopsis

Sponsor	Allergan, Inc.
Study Compound	RST-001 (AGN-151597)
Protocol Number	RST-001-CP-0001
Title	Phase I/IIa, Open-Label, Dose-Escalation Study of Safety and Tolerability of Intravitreal RST-001 in Patients with Advanced Retinitis Pigmentosa (RP)
Phase	1/2a
Indication	Advanced RP
Objective	To evaluate the safety, tolerability and preliminary efficacy of RST-001 in patients with advanced RP. Preliminary efficacy data will be obtained through ocular evaluations.
Study Population	Up to approximately 21 patients will be enrolled in this study.
Study Rationale	• First-in-human (FIH) study, designed to evaluate whether RST-001 is safe and well tolerated in patients with advanced RP. • This is an open label dose-escalation study of three doses of RST-001 • To provide further guidance toward the design of a pivotal efficacy study, the study also includes the option to expand, by up to approximately 21, the number of patients
Study Design	• *Structure:* Open-label, dose-escalation, non-randomized study • *Duration:* 2 years (with an additional 13 years of long-term follow-up) • *Treatment:* Three doses of RST-001 (low, mid, and high, each group comprising of approximately but no less than three patients) will be evaluated by sequential dose escalation in Phase 1 Patients will receive a single 100 µL intravitreal injection of RST-001 in the study eye. In Phase 2a, approximately 6-12 patients may be enrolled and receive RST-001 at the maximum tolerated dose. The doses used in the study have been calculated from the pre-clinical animal toxicology studies, as follows: • Low dose = [redacted] • Mid dose = [redacted] • High dose = [redacted] An independent Data Safety and Monitoring Committee (DSMC) will advise on dose-escalation and cohort expansion • *Visit Schedule:* • Core study visits: Twelve visits are planned over 24 months including the Screening and Baseline visits, Day 0, Day 1, Day 7, and Months 1, 3, 6, 9, 12, 18, and 24. • Long-term follow-up: After completion of the Month 24 visit, each patient will participate in a long-term follow-up study for an additional 13 years to monitor the long-term safety of RST 001. This includes a yearly visit for 5 years (Months 36, 48, 60, 72, and 84). After 5 years, telephone interviews will be conducted over an 8-year period (Months 96, 108, 120, 132, 144, 156, 168, and 180) for a total 13 years of long-term follow-up.

Key Inclusion Criteria	Phase 1 and Phase 2a: 1. Male or female patients, ≥ 18 years of age at time of informed consent [redacted]
Key Exclusion Criteria	Patients will ***not*** be excluded if the molecular diagnosis underlying their advanced RP is not known or if there is presence of macular edema due to advanced RP. However, any one of the following will exclude patients from being enrolled in the study: [redacted] 4. Known sensitivity to any component of the study treatment or medications planned for use in the study; [redacted]
Justification for dose	The doses and injection volume of RST-001 have been calculated by allometric scaling from pre-clinical animal studies. Vitreous humor volume was the scaling factor across species. Therefore, the scaling factor of the vitreous volume from mice and dogs to humans is 1:100 and 1:2, respectively. Two nonclinical toxicology studies were conducted in dogs and mice. The safe intravitreal doses in the dog ranged from [redacted]. In mice, the safe intravitreal doses ranged from [redacted]. Additionally, two nonclinical pharmacology studies demonstrated efficacy and safety in mice at a dose range of [redacted] to [redacted] in a dose range comparable to the toxicology study. Based on these studies, the expected safe dose range of RST-001 in humans is between [redacted] and [redacted] In summary, the dose range in this FIH study ([redacted]) is based on the more conservative exposure in the dog, inclusion of potentially efficacious doses, the ability of the manufacturer to concentrate investigational product, and a safe injection volume of [redacted] per eye in humans.
Surgical procedure	A single intravitreal injection of RST-001 in the study eye of patients with advanced RP.

Clinical Study progress	Patients will be enrolled sequentially. The decision to dose escalate will be determined with the DSMC upon review of adverse events (AE), clinical evaluations (ocular and systemic) and laboratory results.
Monitoring of safety and tolerability	Safety monitoring will include a combination of AE reporting, clinical evaluations (ocular and systemic), and laboratory results. Ocular and systemic safety monitoring will include monitoring for signs of an immune response.
Enrollment Stopping rules	Any Grade 3 (Common Terminology Criteria [CTC] for AEs v4.03) or greater AE considered related to the study treatment.
Primary endpoints: Assessment of safety	The primary endpoint is safety at 6 months from start of study treatment. The therapy will be considered safe in the absence of any grade 3 or greater AE considered related to RST-001.
Secondary endpoints	The effect of intravitreal injection of RST-001 in improving visual function as measured by a series of psychophysical, electrophysiological and anatomical measures.
Analysis plan	The sample size for this study was chosen empirically; no formal sample size computations to meet power requirements were made. The sample size of approximately 3 patients for each dose group in Phase 1 are typical for dose escalation studies, an additional up to approximately 12 patients will be enrolled in Phase 2a for further safety and efficacy evaluation. Summary tables and listings of data will be provided per Statistical Analysis Plan. All summaries of categorical data will present frequencies and percentages. All summaries of continuous data will present the number of non-missing values, mean, standard deviation, minimum, median and maximum.

3 Introduction

3.1 Background and Rationale

3.1.1 Retinitis pigmentosa (RP)

Retinitis pigmentosa (RP) is a hereditary, slowly-progressive, neurodegenerative disease of the retina. It is estimated that the prevalence of RP in the United States (U.S.) is approximately 100,000 individuals (Sohocki et al., 2001) with 10-20% suffering severe vision loss from this condition. A similar prevalence rate is thought to occur worldwide. RP is most frequently inherited as an isolated ocular disease though it is a manifestation of many syndromes.

RP is genetically heterogeneous with more than forty causative genes and perhaps only 50% of genes have been identified. In the U.S., RP is most commonly inherited as an autosomal dominant trait.

3.1.2 Clinical features

Early disease manifests as night-blindness and peripheral visual field defects. As the disease progresses, the visual field constricts relatively symmetrically. Unless complicated by cystoid macular edema, visual acuity (VA) is preserved until advanced disease. A patient with advanced disease will have poor VA and minimal preserved visual field. In some instances, all vision is lost.

Examination findings include abnormal pigmentary changes in the retina, classically appearing as discrete bone-spicules, outer retinal atrophy, optic nerve pallor and retinal vascular attenuation.

3.1.3 Cellular pathology

RP is primarily a disease of the rod photoreceptors which are gradually lost as the disease progresses (Daiger et al., 2007). Cone photoreceptors subsequently degenerate, together with the retinal pigment epithelium. Loss of the photoreceptors results in changes in the inner retina, which include cell reorganization, disorganization and cell loss. Even in the advanced stages, retinal ganglion cells, which comprise the innermost layer of the retina, persist and maintain their connections with the brain.

3.1.4 Pathogenesis

Given the large number of causative genes and the diverse properties of the proteins they encode, the precise molecular pathology of RP remains elusive. It is likely that the molecular pathology stresses the photoreceptor cells eventually resulting in the activation of cell death pathways.

Photoreceptors and other neuronal cells of the retina have little or no replicative function and cell loss results therefore in progressive deficit.

3.1.5 Treatment

Currently, there is no approved drug treatment for RP. Supplemental doses of Vitamin A may reduce the rate of degeneration in certain individuals but the effects are insubstantial (Rayapudi et al., 2013). The Argus II retinal prosthesis (an opto-electronic implant developed by Second Sight Medical Products Inc., Sylmar, CA) has been approved by the FDA, on a humanitarian basis, for those most severely affected by RP (Dorn et al., 2013).

3.2 Adeno-Associated Virus

Adeno-associated virus (AAV) is a parvovirus with a single-stranded DNA genome (Muzyczka N, Berns KI, 2001). It requires a helper virus to complete its replication cycle in culture and in humans (Blacklow NR, Hoggan MD, 1967). AAV does not appear to integrate in humans (Schnepp BC, et al 2005) and has not been associated with human disease (Flotte TR, Carter BJ, 1995).

3.3 Recombinant AAV Vectors

Recombinant AAV (rAAV) vectors are composed of a transgene expression cassette between inverted terminal repeats (ITRs), which guide packaging of vector DNA into AAV capsids. rAAV vectors are non-toxic, highly efficient at transducing a wide variety of non-dividing cell types, and persist for long periods potentially leading to long-term expression of the transgene (Carter PJ, Samulski RJ 2000).

3.4 Human Clinical Experience with AAV2 Vectors

AAV2 is currently being used as the vector of choice in multiple clinical studies around the world setting a precedent as a safe delivery system for gene therapy. Specifically, AAV2 has been used as a vector in clinical studies within the United States since 2004. To date there are no approved products utilizing AAV2 but there are a number of clinical studies that either have been completed or are ongoing worldwide, some of which are in the area of ophthalmology, including indications like neovascular age-related macular degeneration, Leber Congenital Amaurosis (LCA), and choroideremia.

3.5 RST-001

RST-001 (AGN-151597) is a gene therapy product [redacted]

[redacted]

3.6 Nonclinical Studies with RST-001

3.6.1 Pharmacology Studies

Two studies were conducted in mice, collectively covering a 10-fold range of dose exposure from the lowest ([redacted]) to the highest dose ([redacted]). The objective of these studies was to test the behavioral efficacy of a single-1 µL intravitreal injection in both eyes of RST-001 (dosing solutions [redacted]): [redacted] (Low); [redacted] (Mid); [redacted] (High)) on visual function in C3H/HeJ-Pde6b^{rd1} mice ([redacted]; hereafter "C3H"). These mice are homozygous for the retinal degeneration 1 mutation (*Pde6b*^{rd1}), which causes blindness by weaning age. The sighted control mice were C3Sn.BLiA-Pde6b+/DnJ ([redacted]; hereafter "C3Sn"). Behavioral assessments were done prior to AAV2-ChR2 (RST-001) (when mice are ~ 8 weeks old; hereafter "Baseline"), again starting at P120 (hereafter "Test 1"), and finally at 6 months post injection (hereafter "Test 2"). Viral injections were done around 9 weeks old.

There were no injection-related complications and no animals died during the perioperative time period. At the two-month time point, there was evidence of improved visual function in rd1 mice treated with RST-001 at all doses ([redacted]) evaluated as compared with vehicle injected mice, based upon optokinetic responses. The highest dose ([redacted]) also showed efficacy for visual placement responses. These effects were investigated in the high dose at 6 months post injection, but were not reproduced. However, electrophysiological measures appear to have verified ChR2-driven light responses at the ganglion cell layer 10 months post injection.

Non-GLP safety observations were also conducted in conjunction with this pharmacology study. RST-001 produced no signs of test article related effects on body weights, food consumption, clinical observations or during ophthalmic examinations. There were no gross lesions at terminal necropsy related to the test article treatment. Histological evaluations were conducted for animals in the control and highest dose group. No test item-related microscopic findings were

noted in the tissues examined (brain, epididymis, eye, heart, kidney, liver, lung, mandibular and mesenteric lymph nodes, optic nerve, parotid salivary gland, spleen and testis).

3.6.2 Toxicology and Biodistribution Studies

Two nonclinical GLP toxicology and biodistribution studies have been completed in two species, beagle dogs and mice. The objectives of both studies were to determine the potential ocular toxicity of RST-001 when given by a single intravitreal injection and to evaluate the potential reversibility of any findings within 99 days of treatment.

The following parameters and end points were evaluated: clinical signs, body weights, food consumption, ophthalmology, clinical pathology parameters [redacted], gross necropsy findings, organ weights, and histopathologic examinations, and biodistribution.

[redacted]

[redacted]

3.6.2.2 Mice Study

The purpose of this study was to evaluate the toxicity of the test article, RST-001, when given as a single 1 µL intravitreal injection in the right eye to C3H/HeJ-Pde6b^{rd1} mice.

Mice historically have been used in safety evaluation studies and this particular strain is a disease model for advanced RP, the indication of RST-001.

There were 64 mice per dose group and 4 dose groups. Actual doses verified were: vehicle (control); [redacted] (Low), [redacted] (Mid), and [redacted] (High) vg/eye of RST-001. After dosing, animals were observed post dose for at least 29 (interim sacrifice) or 89 days (terminal sacrifice). There were 16 animals/sex/group at each terminal sacrifice.

There are no signs of test article related effects on body weights, food consumption, and clinical observations or during ophthalmic examinations through Week 4 of the dosing phase. There were no gross lesions at any of the terminal necropsy intervals that appear to be related to the test article treatment. There were no signs of overt tissue damage due to direct toxicity of the test item and no cellular immune or humoral response to RST-001 was detected at any dose level.

RST-001 was present at the highest level in the right eye and optic nerve of all animals tested. RST-001 was also detected just above the minimum level of detection [redacted]

within the hindbrain and spleen. Dose-dependent minimal to moderate ChR2 immunolabeling occurred in the right treated eye of animals given [redacted]; minimal ChR2 immunolabeling was also present in the right optic nerve of some animals with ChR2 immunolabeling in the right eye.

In conclusion, administration of RST-001 by a single intravitreal injection at a 10-fold difference in nominal doses resulted in no dose-related effects. RST-001 had minimum biodistribution systemically and was expressed in the retina.

3.6.3 Justification for Human Dose

The doses and injection volume have been calculated by allometric scaling from pre-clinical animal studies. Vitreous humor volume was the scaling factor across species. In general, scaling of the vitreous volume from mice and dogs to humans is 1:100 and 1:2, respectively. Two nonclinical toxicology studies were conducted in the dog and mouse. The safe intravitreal doses in the dog ranged from [redacted]. For the mouse, the safe intravitreal doses ranged from [redacted]. Two nonclinical pharmacology studies demonstrated efficacy and safety in the mouse at a dose range of [redacted] in a dose range comparable to the toxicology study. Based on these studies, the expected safe dose range in humans is between [redacted] and [redacted]. The dose range in this study ([redacted] to [redacted] of RST-001) is based on the more conservative exposure in the dog, inclusion of potentially efficacious doses, the ability of the manufacturer to concentrate investigational product, and a safe injection volume of [redacted] per eye in humans.

3.7 RST-001 Study Rationale: Optogenetic Therapy for Advanced Retinitis Pigmentosa

RST-001 is a gene therapeutic treatment that renders cells in the retina sensitive to light. This light sensitivity is conveyed to the brain and is a photoreceptor substitute in conditions such as advanced RP where the normal light sensitive cells are lost.

The disease of advanced RP results in the irreversible loss of photoreceptors, which are the only cells in the retina that are able to convert the light entering the eye into an electrical signal that can be relayed to the brain and interpreted as vision. Although these cells degenerate, many of the other neuronal cell types that receive input from the photoreceptors persist. In particular, the innermost retinal cells, the retinal ganglion cells (RGCs) survive in significant numbers late into the disease and axons from these cells remain connected directly to the brain.

Direct electrical stimulation of the RGCs using surgically-implanted electronic devices have provided a proof of concept that vision can be mediated through these cells.

RST-001 delivers a gene encoding a photo switch, channelrhodopsin-2, to the RGCs. When expressed, the channelrhodopsin-2 protein can depolarize in response to light thus generating a signal that is transmitted to the brain. The components of RST-001 are shown in detail above.

The study is composed of two phases. An initial dose-escalation study (Phase 1) is proposed whereby three dose levels of RST-001 will be studied in three separate groups of adult patients with advanced disease. Phase 1 is aimed at determining a single dose of the experimental treatment which is safe and well tolerated, to further evaluate in a fourth group of patients. If the Data Safety Monitoring Committee (DSMC) considers the safety and tolerability of RST-001 satisfactory in the first phase, then the study may proceed to Phase 2a. Phase 2a is aimed at obtaining additional safety data at the maximum tolerated dose. An additional objective of Phase 2a is to provide important additional clinical data to guide the design of future efficacy studies.

3.7.1 Immunogenicity of RST-001

Preclinical data indicated that no cellular or humoral immune response to RST-001 was detected at doses up to [redacted] in mice and dogs, respectively. In this study, evidence of an immune response to the product will be carefully assessed by monitoring for systemic measurement of humoral and cellular immunity. Local or systemic immune suppression may be initiated if clinically indicated.

3.8 Treatment Administration

RST-001 will be administered by intravitreal injection as specified in the Study Procedures Manual. The injection volume is [redacted].

Prior to study treatment administration, the study eye of each patient will be prepared using a standard protocol as described in the Study Procedures Manual.

3.9 Objectives of the Study

3.9.1 Primary Objective:

To evaluate the safety of a single intravitreal injection of RST-001.

3.9.2 Secondary Objectives:

1. To establish the maximum tolerated dose of RST-001.
2. To evaluate the preliminary efficacy of RST-001 in patients with advanced RP.

3.10 Study conduct and GCP Compliance Statement

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB), and according to Good Clinical Practice (GCP) standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research patient. In such case, the deviation will be reported to the IRB as soon as possible.

3.11 Risks and Benefits

3.11.1 Potential Risks

The risks associated with this study can be divided into those related to the intravitreal injection of RST-001, the RST-001 treatment and study procedures.

3.11.1.1 Intravitreal Injection

These risks are well recognized and include transient conjunctival hyperemia and hemorrhage at the injection site. Serious complications such as retinal tears/holes, retinal detachment, vitreous hemorrhage and endophthalmitis are uncommon or rare but may result in reduced vision and may require surgical intervention.

3.11.1.2 RST-001 Treatment

The risks of intravitreally-administered RST-001 are not known. Potential risks include an immune response, which may result in ocular inflammation and the associated consequences.

3.11.1.3 Study Procedures

The risk from the tests performed in this study carry minimal risks and mostly relate to the need for pupillary dilation, which typically results in temporary blurred vision and increased light sensitivity. On occasion, a corneal abrasion can result from the use of the [redacted]

3.12 Protection from Risks

The RST-001 drug product has been manufactured in compliance with current Good Manufacturing Practice (cGMP). Extensive testing has been performed to ensure infective agents and pathogens are not present.

Intravitreal injection of RST-001 will be performed in the operating room under aseptic conditions by qualified staff in accordance with the Study Procedures Manual.

After the procedure, each patient will be carefully monitored for complications. Evidence of an immune response to RST-001 will be monitored (refer to Section 6.2.1).

The conduct of this study will be overseen by the DSMC.

3.13 Provisions for Injury

Any complications arising post injection will be managed in accordance with the investigator's standard of care.

It is not possible for RST-001 to be removed from the eye after injection.

3.14 Potential Benefits

Patients may not benefit directly from the study. It is theoretical at this time as to whether any visual benefit will be afforded by RST-001. The primary objective of this particular study is to establish safety of RST-001.

3.14.1 Risk Benefit Analysis

Since RST-001 has not yet been shown, in humans, to be efficacious, investigators and patients will need to weigh carefully the risks shown above with the theoretical possibility of improved or preserved visual function.

3.15 Study Overview

3.15.1 Study Design

This is an open-label, dose-escalation study to evaluate the safety and tolerability of RST-001 administered as a single intravitreal injection in patients with advanced RP.

3.15.1.1 Enrollment Phase 1

Three groups of patients (A, B, C, each comprising of approximately but no less than three patients) will be enrolled in this study.

Approximately 3 patients in Group A will receive the lowest dose of RST-001 (LOW). The safety and tolerability of RST-001 will be assessed in the first patient for a minimum of one month (to include Month 1 Visit). If the DSMC considers the safety and tolerability of the first patient satisfactory and the enrollment stopping rules have not been met, then the remaining patients in Group A can be enrolled and receive treatment.

If the DSMC considers the safety and tolerability of Group A satisfactory and the enrollment stopping rules have not been met after a minimum assessment of one month (to include Month 1 Visit) from the last treatment group, then approximately 3 patients in Group B may be enrolled and receive a higher dose of RST-001 (MID) following the same guidelines and treatment schedule.

Similarly, if the DSMC considers the safety and tolerability of Group B satisfactory and the enrollment stopping rules have not been met after a minimum assessment of one month (to include Month 1 Visit) from the last treatment group, then approximately 3 patients in Group C may be enrolled and receive the highest dose of RST-001 (HIGH) following the same guidelines and treatment schedule.

After completion of the 2-year core study visits, each patient will be enrolled in a long-term follow-up for an additional 13 years to monitor the long-term safety of RST-001.

3.15.1.2 Enrollment Phase 2a

If the DSMC considers the safety and tolerability satisfactory and the enrollment stopping rules have not been met after a minimum assessment of one month (to include Month 1 Visit) from treatment of the final patient in Groups A, B, or C, then the sponsor may elect to start enrollment in the second cohort of patients. In Phase 2a, up to approximately 12 patients may be enrolled and receive RST-001 at the maximum tolerated dose.

- If the DSMC considers the data from Phase 1, in their opinion, to be indicative of a treatment benefit for visual acuity/function, then approximately 6 patients will be enrolled in Phase 2a and follow the same eligibility criteria as Phase 1.
- If the DSMC considers the data from Phase 1, in their opinion, to **not** be indicative of a treatment benefit, then approximately 12 patients will be enrolled in Phase 2a.
    - 6 patients must have VA of no-better-than hand motion in the study eye.
    - 6 patients must have VA in the study eye to range from no-worse-than count fingers to 20/200 vision.

A schematic providing an overview of the treatment schedule is illustrated in Figure 1, and the dose-escalation cohorts are illustrated in Table 1 below.

Figure 1 Overview of the Treatment Schedule

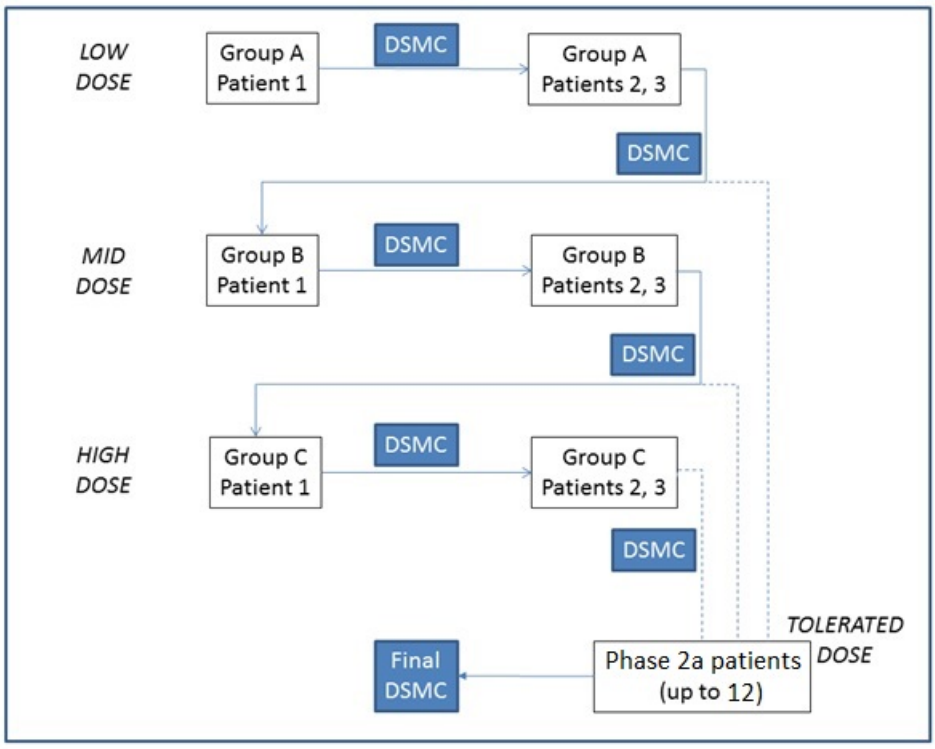

Table 1 Dose Escalation

Phase	Group	Number of patients[a]	Intravitreal Injection	
			Vector concentration	Volume [redacted]
1	A	3	LOW	[redacted]
	B	3	MID	[redacted]
	C	3	HIGH	[redacted]
2a		6-12[b]	Choice of dose[c] from groups A, B, or C	[redacted]

[a] Up to approximately 21 patients will be enrolled in this study.
[b] Number of patients is dependent upon whether or not the DSMC determines that, in their opinion, a treatment benefit for visual acuity/function has been observed in Phase 1.
[c] The maximum tolerated dose.

After completion of the 2-year core study visits, each patient will be enrolled in a long-term follow-up for an additional 13 years to monitor the long-term safety of RST-001.

3.15.2 Study Population

The study population consists of patients with advanced RP [redacted] This patient group is considered to be a suitable population to assess safety and tolerability in this Phase 1 study. [redacted]

Up to approximately 21 patients will be enrolled in this study.

3.15.3 Eligibility Criteria

3.15.3.1 Inclusion Criteria

The following are requirements for entry in the study:

General Inclusion Criteria:

1. Male or female patients, ≥ 18 years of age at time of informed consent
2. Patient has provided written informed consent and written Authorization for Use and Release of Health and Research Study Information have been obtained prior to any study related procedures
3. Patient has the ability to understand and willingness to follow study instructions and is likely to complete all required visits and procedures
4. Women of childbearing potential must have a negative pregnancy test at Screening and at Baseline, and agree to use an effective form of contraception, or be surgically sterile or post menopausal (defined as last menstrual period greater than two years prior to Baseline). Acceptable methods of contraception include hormonal contraception (i.e., birth control pills, injected hormones, dermal patch or vaginal ring), intrauterine device, barrier methods (diaphragm, condom) with spermicide, or surgical sterilization (tubal ligation)
5. Males must use two forms of contraception (including one barrier method for three months following study treatment administration if their partner is of child-bearing potential), or must be surgically sterile

Ocular Inclusion Criteria:

Phase 1 and Phase 2a

1. Diagnosis of advanced RP defined as:

[redacted]

3.15.3.2 Exclusion Criteria

Patients will ***not*** be excluded if the molecular diagnosis underlying their RP is not known or if there is presence of macular edema due to advanced RP.

However, any one of the following will exclude patients from being enrolled into the study:

General Exclusion Criteria:

1. Participation in any investigational drug or device study within six months prior to Day 0;

[redacted]

4. Females who are pregnant, nursing, planning a pregnancy during the study or who are of childbearing potential not using a reliable method of contraception during their participation in the study
5. History or current evidence of hypersensitivity to any component of the study treatment, medications, or diagnostic agents used in the study

[redacted]

8. Any other condition that would not allow the potential patient to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the prospective patient unsuitable for the study

[redacted]

3.15.4 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time or for the following reasons:

a) Due to an adverse event (AE)
b) If deemed necessary by the investigator or the sponsor that it is unsafe for the patient to continue in the study

When possible, the decision to withdraw a patient from study treatment or the study should be discussed with the sponsor. Notification of early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate Case Report Form (CRF).

In the case of a withdrawing patient, every reasonable attempt will be made to complete a final early termination visit (as shown in the study visit table). Patients who withdraw from the study prior to receiving the study treatment may be replaced.

4 Treatments

4.1 Identity of Investigational Product

The trea ment in this study has been called RST-001. [redacted]

4.2 Dosage and Administration

The dos s of RST-0 01 evaluated in this study will be:

- OW dose = [redacted]
- IID dose = [redacted]
- IIGH dose = [redacted]

4.3 Met od of Assigning Patients to ose Gro ps

This is a sequential lose-escalation study. In Phase 1, th ee groups comprising of approximately but no less than thre patients, will be enrolled one after the other, r ceiving first the low dose, then the mid, and finally the high dose.

Escalati n is dependent upon the enrollment stopping rules and DSMC recommendation.

In Phase 2a, up to approximately 12 patients may then be enrolled i parallel at the maximum tolerated dose.

4.4 Dose Rationale

The hig est feasible concentration of RST-001 is constr ined by ma ufacturing capabilities and product stability and has been determined to be approximately [redacted] The highest feasible dose is then limited by the volume that can be delivered to the human vitreous. Based upon estimated vitre ous volumes and maximum feasible intravitreal dosing, this maximum concentration was e aluated as the highest dose in our mouse pharmacology study (dose volume of [redacted]) nd mouse [redacted] and dog ([redacted]) toxicology and biodistrib tion studies. This dose was demonstrated to be efficacious and no dose-limiting toxicity was ob served, respectively. Since the beagle dog vitre us has about half the vitreous volume of the hu man eye, the HIGH dose for the hum n study has been determined to be [redacted] given as a single [redacted] intravitreal

injection. In order to be safe and conservative but also balanced with the potential for delivering an active dose, Allergan proposes that the LOW initial starting dose for the first-in-human study be [redacted] of this dose, [redacted]. The MID dose will be [redacted] of the HIGH dose, [redacted]

Dose escalation will proceed according to Table 1, only after review by the DSMC (see Figure 1, above). Three doses have been chosen with the safety as the priority but will provide a good opportunity to observe biological effect.

The rationale for the dosing schedule is once again based primarily on patient safety. Thus, at each dose a single patient will receive treatment followed by an intensive period of observation for any evidence of AEs prior to dosing the remaining two patients in the group. The safety and tolerability and optimal single dose of RST-001 will therefore be established in Phase 1. Phase 2a patients will receive a single intravitreal injection of RST-001 at the maximum dose tolerated by Phase 1 patients.

4.5 Patient and Investigator Masking

This is an open-label study so that patients and investigators will know which eye is treated and what dose of RST-001 was given.

4.6 Packaging and Labeling

Correct product identity, labeling and patient specificity will be assured by the use of standard operating procedures in accordance with FDA regulations. These operating procedures will include identifiers to ensure correct labeling to identity study treatment throughout manufacture, handling and administration.

4.7 Handling and Storage

The study treatment RST-001 is provided [redacted] Please refer to the Study Procedures Manual for additional information.

4.8 Study Treatment Preparation and Administration

[redacted]

[redacted]

4.9 Product Accountability

Study treatment will be shipped to the site after receipt of required documents in accordance with applicable regulatory requirements. RST-001 study treatment will be handled in accordance with regulatory and institutional requirements. RST-001 will only be administered to patients enrolled in the study who meet the eligibility criteria and who have signed the informed consent form. RST-001 will only be administered in accordance with the surgical procedure described in this document. Study treatment must be stored in a secure temperature-controlled area with access limited to the investigator and authorized study site personnel. The investigator or designated study site personnel is responsible for study treatment accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study site personnel must maintain study treatment accountability records throughout the course of the study. All study treatment must be returned to Allergan or Allergan designee at the completion of patient enrollment.

4.10 Assessment of Compliance

Deviations with respect to dosage and administration will be documented by the investigator. Such deviations will be immediately reported to Allergan, the medical monitor, the institutional review board and the FDA, as appropriate.

4.11 Treatment of RST-001 Overdose

There is no known treatment in the event of an overdose of RST-001.

4.12 Prior and Concomitant Therapy

During the course of the study, patients will be allowed to continue taking prescribed and over-the-counter medications that are not excluded in the protocol (i.e., antiplatelets and anticoagulants prior to treatment, and immunosuppressive therapy).

5 Study Assessments and Intravitreal Injection

Patients diagnosed with advanced RP and who are eligible based on inclusion and exclusion criteria will be invited to participate in this study. After obtaining informed consent and authorization, patients will undergo a complete physical examination and laboratory testing to assess eligibility for the study.

Patients who meet inclusion criteria will be considered eligible for study entry and will receive a single intravitreal injection of RST-001. Following RST-001 administration (Day 0) patients will be assessed on the first post injection day (Day 1).

The visit schedule includes:

- Core study visits: Twelve visits are planned over 24 months, including Screening and Baseline visits, Day 0, Day 1, Day 7, and Months 1, 3, 6, 9, 12, 18, and 24.
- Long-term follow-up: After completion of the Month 24 visit, each patient will participate in a long-term follow-up study for a total of an additional 13 years. These visits include yearly office visits for 5 years (Months 36, 48, 60, 72, and 84) and yearly teleconference interviews for 8 years (Months 96, 108, 120, 132, 144, 156, 168, and 180).

Core study visits are described in Table 2 and long-term follow-up visits are described in Table 3.

Table 2 Study Visit Schedule: Core Study Visits

[redacted]

Table 3 Study Visit Schedule: Long-term Follow-up Visits

[redacted]

5.1 Schedule of Procedures by Visit

Please refer to Table 2 and Table 3 for a schematic of the schedule of visits and procedures.

5.1.1 Informed Consent and Patient Privacy

The study will be discussed with the patient and patient's impartial witness or legally acceptable representative. A patient wishing to participate must give informed consent and authorization prior to any study-related procedures. The patient must also give authorization (U.S. only) and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment. Each patient that provides informed consent and assent will be assigned a patient number that will be used on patient documentation throughout the study.

5.1.2 Screening Visit

Prospective patients will be screened for eligibility up to 45 days prior to enrollment and the procedures will be performed as specified below. If convenient, the Screening and Baseline visits may be combined.

It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result in which the value of the test lies outside the normal range (see Appendix 2 for reference values), the investigator needs to ascertain if this is an abnormal (ie, clinically significant) result for the individual subject. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If the laboratory value is determined by the investigator to be clinically significantly abnormal for that subject, the subject will be excluded from the study.

Records will be maintained of those individuals who are screened but do not meet the eligibility criteria for participation in the study.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.14 Long-term Follow-up Visits

Patients completing the Month 24 visit will participate in long-term follow-up visits. Patients will be asked to report any AEs that occur during this 13-year follow-up period. At Months 36, 48, 60, 72, and 84, patients will undergo the following study assessments conducted at yearly clinic visits:

[redacted]

The procedures for these assessments will be the same as they were for the core study assessments.

[redacted]

5.2 Description of Study Procedures

5.2.1 Informed Consent

During the Screening visit, prospective patients will be invited to provide written informed consent prior to any screening evaluations. An investigator or study coordinator will provide a full explanation of the study, including potential risks of participation and that they may withdraw from the study at any time and for any reason without jeopardizing their future treatment, and an investigator will provide answers to all questions raised by the prospective patient. For those with low vision, a verbal consent will be read out. After ensuring that all questions have been answered, written documentation of the informed consent decision will be obtained and the consent form will be countersigned by a witness to indicate informed consent was obtained.

No study-related procedures will be performed until after informed consent/assent is obtained.

5.2.2 Medical History (Review)

These will comprise:

- Documentation of presenting complaints, and history thereof
- Ocular medical and surgical history
- General medical and surgical history
- Current medication use (ocular and other)

5.2.3 Concomitant Medications and Procedures

All medications and procedures will be recorded on the eCRF. If the permissibility of a specific medication/treatment is in question, the investigator is to contact Allergan.

5.2.4 Adverse Event Review

All AEs will be recorded at each study visit.

5.2.5 Physical Examination

A complete physical examination will be performed [redacted]

Symptom-specific examinations may be carried out and recorded during the study as needed.

5.2.6 Pregnancy Test

Women of childbearing potential will undergo blood serum beta-hCG testing, to be analyzed at the site's preferred certified laboratory.

5.2.7 Blood Sample

A venous sample will be collected from a peripheral vein and laboratory tests will be conducted at the preferred certified laboratory.

Blood sample testing will include [redacted]

Instructions for shipping venous blood for immunological analysis are detailed in the Study Procedures Manual.

[redacted]

[redacted]

5.2.15 Complete Ophthalmic Examination

A complete ophthalmic examination will be performed in both eyes at the Screening and Baseline visits and at each visit after study treatment administration. The examination will include [redacted]

[redacted]

5.3 Treatment Administration

RST-001 will be administered by intravitreal injection as specified in the Study Procedures Manual.

Prior to study treatment administration, the study eye of each patient will be prepared using the standard protocol as described in the Study Procedures Manual.

5.3.1 Post Injection Medications

Topical corticosteroid treatment may be given to the injected eye according to the investigator's standard of care.

5.3.2 Management of Post Injection Intraocular Pressure

The investigator shall have the ability to determine the optimum management of a raised intraocular pressure and may use any combination of topical IOP-lowering medications, oral acetazolamide or anterior chamber paracentesis in order to normalize the intraocular pressure.

6 Safety Assessments

6.1 Overview of Safety Assessments

Safety assessments in this study can be divided into measures of ocular safety and measures of systemic safety.

6.1.1 Ocular Safety Measurements

[redacted]

[redacted]

6.1.1.2 Ocular Inflammation

Owing to the potential for intraocular inflammation (as noted in the preclinical dog study) or immunogenicity, signs of ocular inflammation will be carefully monitored throughout the study and reported to the DSMC. Active inflammation of the anterior chamber, vitreous and retina/choroid will be documented in the case report forms according to recognized international criteria shown in Table 4, below. Additional investigations, [redacted] may be performed at the discretion of the investigator according to clinical findings and accepted standards of care.

Table 4 Biomicroscopic Grading of Anterior Chamber Cells and Flare

This is compliant with the standardization of uveitis nomenclature [SUN] working group (Jabs et al., 2005).

[redacted]

[redacted]

6.1.2 Systemic Safety Measurements

1. Patient-reported and investigator-reported adverse events (AEs)
2. Physical examination findings including vital signs
3. Findings of blood and serum laboratory testing
4. Findings of immunological testing

[redacted]

6. Other clinical and laboratory testing performed by the investigator(s) based upon clinical observation, such as:

   - Vital signs
   - Clinical safety laboratory parameters
   - Immune response to RST-001 administration as measured by the testing detailed in Section 6.2.1 below.

6.2 Clinical Management of Safety Parameters

The need for additional clinical evaluations, assessments and visits shall be determined by the investigator(s) in accordance with accepted clinical practice and standards of care, where applicable. All activity will be recorded in the patient's source documentation.

Adverse events definitions and reporting requirements can be found in the Section 8.1 below.

6.2.1 Intraocular Inflammation and Immunogenicity Related to RST-001

During the study, evidence of immune response to RST-001 will be monitored by systemic measurement of humoral and cellular immunity as follows:

[redacted]

6.2.2 Complications of the Intravitreal Injection

The complications of intravitreal injection commonly include mild conjunctival hyperemia and subconjunctival hemorrhage. Other uncommon complications include endophthalmitis, retinal tears/breaks/detachment, choroidal, vitreous and retinal hemorrhage.

In all instances, management of these complications will be determined by the investigator in accordance with his/her practice and standard-of-care, where applicable.

6.2.3 Occupational Safety

The consequences of exposure of clinical personnel to the RST-001 drug are unknown. Precautions will be taken to avoid any exposure to the RST-001 product. No antidote is available for the RST-001 drug product.

6.2.4 Pregnancy and Exposure to RST-001 *In Utero*

Females who are pregnant at the Screening and/or Baseline visit will be excluded from the study. Females of child-bearing potential are required to maintain contraception during their participation in the study. In the event that a female becomes pregnant during the course of the study, the patient will continue to be followed in the study. The investigator should notify the sponsor within 24 hours of becoming aware that a female patient or female partner becomes pregnant during the course of the study. Female patients of childbearing potential will require a pregnancy test at Month 24 or early termination visit.

The potential effects of *in utero* exposure to RST-001 are not known.

7 Data Safety Monitoring Committee (DSMC)

7.1 Composition

An independent Data Safety Monitoring Committee (DSMC) will be formed to monitor the data from the study. The members of the DSMC will comprise ophthalmologists, physicians and statistician(s) with experience in this field of research.

7.2 Role

The primary role of the DSMC is to ensure the protection and safety of patients participating in the study. The DSMC will review the general progress and conduct of the study and assist in resolving any issues that may arise. The composition and responsibilities, together with the agreed schedule for reviewing data will be detailed in the DSMC Charter.

7.3 Responsibilities

[redacted]

7.4 Enrollment Stopping Rules

Enrollment will be suspended pending a complete safety review by the sponsor of all patients including causality to determine the appropriateness of continuing dosing in the occurrence of the following events:

[redacted]

8 Adverse Events

Adverse events occurring during the study will be recorded on an adverse event CRF. If adverse events occur, the first concern will be the safety of the study participants.

8.1 Definitions

8.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event 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. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study treatment.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the CRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate CRF.

8.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, congenital anomaly or birth defect, significant disability, hospitalization, or life threatening. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

8.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.

8.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

A study procedure occurring during the screening/baseline period can include a study required diagnostic procedure.

For treatment-related adverse events, the investigator will note on the CRF whether the event is related to the study drug, and/or the injection procedure.

8.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate CRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing IRB as required by the IRB, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the exit visit must be followed-up as appropriate.

8.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 28 days after study exit must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan) as listed on the Allergan Study Contacts Sheet and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the

outcomes reported. The investigator must supply Allergan and the IRB with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB of the serious adverse event as required by the IRB, local regulations, and the governing health authorities.

9 Efficacy Assessments

A variety of parameters that encompass visual function will be evaluated in the study eye in order to identify a signal of efficacy, as follows:

[redacted]

10 Clinical Monitoring Structure

10.1 Monitoring

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study. Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.2 Study and Site Closure

The study can be terminated at any time. The study will be considered complete after the final patient has completed study visits and assessments.

11 Data Analysis and Statistical Considerations

11.1 Primary (Safety) Endpoint

The primary endpoint is safety at 6 months, as assessed by

[redacted]

11.2 Secondary Endpoints

11.2.1 Measures of Change in Visual function

[redacted]

[redacted]

11.3 Statistical Analysis Plans

Summary tables and listings of data will be provided per Statistical Analysis Plan. All summaries of categorical data will present frequencies and percentages. All summaries of continuous data will present the number of non-missing values, mean, standard deviation, minimum, median and maximum.

11.3.1 Power and Sample Size Considerations

The sample size for this study was chosen empirically; no formal sample size computations to meet power requirements were made. The sample size of approximately 3 patients for each dose group in Phase 1 are typical for dose escalation studies, an additional up to approximately12 patients will be enrolled in Phase 2a for further safety and efficacy evaluation.

11.3.2 Baseline Characteristics

Listings and descriptive statistics will be provided for baseline characteristics including demographics (race, ethnicity, age, sex) and baseline characteristics (height and body weight).

11.3.3 Safety Analysis

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code AEs. Adverse events will be coded from the verbatim text into preferred term and system organ class (SOC). The number and percent of patients reporting treatment emergent AEs will be tabulated based on the primary SOC and preferred terms. Summary tables will be generated for all AEs regardless of causality as well as treatment-related AEs. Further details regarding the safety analyses will be presented in the Statistical Analysis Plan.

11.3.4 Efficacy Analysis

Efficacy will be measured by evaluation of [redacted]

[redacted]

11.3.6 Interim Analysis

There will be three database locks. The primary analysis will occur when all patients have completed the Month 6 visit, or exited earlier. The second analysis will occur when all patients have completed the Month 24 visit or exited early from the study. The final analysis will occur when all patients have completed the long-term follow-up or have been lost to follow-up. The details of all analyses will be provided in the analysis plan which will be finalized before database lock for the primary analysis at Month 6.

12 Investigator Responsibilities

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible for:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of patients under the investigator's care
- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

13 Data Handling and Record Keeping

Data must be collected in an accurate, consistent, complete and reliable manner in accordance with ICH GCP guidelines.

13.1 Data Management Responsibilities

All clinical information including the results of genetic testing, if performed, will be stored in de-identified form on a database maintained by Allergan or Allergan designees.

13.1.1 Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically [redacted]

[redacted]

13.1.2 Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

[redacted]

14 Study Termination

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study treatment development

15 Regulatory and Ethical Considerations

15.1 Ethical Conduct of the Study

This section has been extracted from the NIH guidance on Ethics in Clinical Research (http://clinicalcenter.nih.gov/recruit/ethics.html):

The goal of clinical research is to develop generalizable knowledge that improves human health or increases understanding of human biology. People who participate in clinical research make it possible to secure that knowledge. The path to finding out if a new drug or treatment is safe or effective, for example, is to test it on patient volunteers. But by placing some people at risk of harm for the good of others, clinical research has the potential to exploit patient volunteers. The purpose of ethical guidelines is both to protect patient volunteers and to preserve the integrity of the science.

The ethical guidelines in place today were primarily a response to past abuses, the most notorious of which in America was an experiment in Tuskegee, Alabama, in which treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. Various ethical guidelines were developed in the 20th century in response to such studies.

Some of the influential codes of ethics and regulations that guide ethical clinical research include:

- Nuremberg Code (1947)
- Declaration of Helsinki (2000)
- Belmont Report (1979)
- CIOMS (2002)
- U.S. Common Rule (1991)

Using these sources of guidance and others, seven main principles have been described as guiding the conduct of ethical research:

- Social and clinical value
- Scientific validity
- Fair patient selection
- Favorable risk-benefit ratio

- Independent review
- Informed consent
- Respect for potential and enrolled patients

Social and clinical value

Every research study is designed to answer a specific question. Answering certain questions will have significant value for society or for present or future patients with a particular illness. An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others. In other words, answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease. Only if society will gain useful knowledge — which requires sharing results, both negative and positive — can exposing human patients to the risk and burden of research be justified.

Scientific validity

A study should be designed in a way that will get an understandable answer to the valuable research question. This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices. It is also important that statistical plans be of sufficient power to definitively test the objective, for example, and for data analysis. Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose.

Fair patient selection

Who does the study need to include, to answer the question it is asking? The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study — not vulnerability, privilege, or other factors unrelated to the purposes of the study. Consistent with the scientific purpose, people should be chosen in a way that minimizes risks and enhances benefits to individuals and society. Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens. Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk.

Favorable risk-benefit ratio

Uncertainty about the degree of risks and benefits associated with a drug, device, or procedure being tested is inherent in clinical research — otherwise there would be little point to doing the research. And by definition, there is more uncertainty about risks and benefits in early-phase

research than in late research. Depending on the particulars of a study, research risks might be trivial or serious, might cause transient discomfort or long-term changes. Risks can be physical (death, disability, infection), psychological (depression, anxiety), economic (job loss), or social (for example, discrimination or stigma from participating in a certain study). Prior to initiating this study, reasonable efforts have been taken to minimize the risks and inconvenience to research patients, to maximize the potential benefits, and to determine that the potential benefits to individuals and society are proportionate to, or outweigh, the risks.

Independent review

To minimize potential conflicts of interest and make sure a study is ethically acceptable before it even starts, an independent review panel with no vested interest in the particular study should review the proposal and ask important questions, including: Are those conducting the study sufficiently free of bias? Is the study doing all it can to protect research volunteers? Has the study been ethically designed and is the risk–benefit ratio favorable? In the United States, independent evaluation of research projects is done through granting agencies, local institutional review boards (IRBs), and Data Safety Monitoring Committees. These groups also monitor a study while it is ongoing.

16 Management of Protocol Amendments and Deviations

16.1 Protocol Amendments

The investigator will conduct the study in accordance with this Clinical Study Protocol. Implementation of changes to the protocol will only be made following review and approval of Protocol Amendment(s) by the sponsor, investigator, Institutional Review Board and the FDA, as required.

17 Publication Policy

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

18 Sponsor's Final Report

A final report will be prepared by the sponsor.

19 References

Blacklow NR, Hoggan MD and Rowe WP. Isolation of adeno virus-associated viruses from man. Proc Natl Acad Sci USA. 1967;58:1410-1415.

Carter PJ, Samulski RJ. Adeno-associated viral vectors as gene delivery vehicles. Int J Mol Med. 2000;6:17-27.

Daiger SP, Bowne SJ, and Sullivan LS. Perspective on genes and mutations causing retinitis pigmentosa. Arch Ophthalmol. 2007;125:151-158.

Dorn JD, Ahuja AK, Caspi A, da Cruz L, Dagnelie G, Sahel JA, gus, I.I.S.G. The detection of motion by blind subjects with the epiretinal 60-electrode (argus II) retinal prosthesis. JAMA Ophthalmol. 2013;131:183-189.

Flotte TR, Carter BJ. Adeno-associated virus vectors for gene therapy. Gene Ther. 1995;2:357-362.

Jabs DA, Nussenblatt RB, Rosenbaum JT, and Standardization of Uveitis Nomenclature Working, G. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.

Klein M, Birch DG. Psychophysical assessment of low vision function in patients with retinal degenerative diseases (RDDs) with the Diagnosys full-field stimulus threshold (D-FST). Doc Ophthalmol. 2009;119:217–224.

Muzyczka N, Berns KI. Parvoviridae: the viruses and their replication. In: Knipe DM, Howley PM, eds. Fields Virology. Philadelphia: Lippincott Williams & Wilkins, 2001:2327-2359.

Nussenblatt RB, Palestine AG, Chan C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92:467–471.

Rayapudi S, Schwartz SG, Wang X, and Chavis P. Vitamin A and fish oils for retinitis pigmentosa. 2013. Cochrane Database Syst Rev 12, CD008428.

Schnepp BC, Jensen RL, Chen CL, Johnson PR and Clark KR. Characterization of adeno associated virus genomes isolated from human tissues. J Virol. 2005;79:14793-14803.

Sohocki MM, Daiger SP, Bowne SJ, Rodriquez JA, Northrup H, Heckenlively JR, Sullivan LS. Prevalence of mutations causing retinitis pigmentosa and other inherited retinopathies. Hum Mutat. 2001;17:42-51.

20 Appendices

20.1 Appendix 1: Abbreviations

AE	Adverse Event
AST	Aspartate aminotransferase
BCVA	Best Corrected Visual Acuity
°C	Degrees Celsius
CFR	Code of Federal Regulations
CRF	Case Report Form
CTC	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSMC	Data Safety Monitoring Committee
[redacted]	
ETDRS	Early Treatment for Diabetic Retinopathy Study
[redacted]	
FDA	Food and Drug Administration, USA
FIH	First-in-Human
[redacted]	
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IND	Investigational New Drug
IOP	Intraocular Pressure
IRAE	Immediately Reportable Adverse Event
ISCEV	International Society for Clinical Electrophysiology of Vision
mm	Millimeters
NEI	National Eye Institute
NIH	National Institutes of Health
QoL	Quality of Life
RGC	Retinal Ganglion Cells
RP	Retinitis Pigmentosa
RST-001	RetroSense Therapeutics drug product (AGN-151597)
[redacted]	
USA	United States of America
[redacted]	
VFQ	Visual Functioning Questionnaire