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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 4
Phase:	Phase 1/2a
Name of Investigational Product:	RST-001 (AGN-151597)
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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**

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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 3 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] vg/eye • Mid dose = [redacted] vg/eye • High dose = [redacted] vg/eye 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 3 years to monitor the long-term safety of RST-001. This includes a yearly visit for 3 years (Months 36, 48, and 60).

Key Inclusion Criteria	Phase 1 and Phase 2a: 1. Male or female patients, ≥ 18 years of age at time of informed consent 2. Diagnosis of advanced RP defined as: [redacted] Phase 1: 4. Visual acuity (VA) in the study eye of no-better-than hand motion Phase 2a: The DSMC will review the results from Phase 1 to determine if a documented treatment benefit was observed in the patients. If the DSMC identifies a treatment benefit, no changes will be made to the eligibility criteria. If the DSMC does not identify a treatment benefit, VA eligibility criteria will match that of Phase 1 for half of the enrolled patients. VA criteria for the other half of the enrolled patients must range from no-worse-than count fingers to 20/200 vision in the study eye.
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: 1. Pre-existing eye conditions that would preclude the planned treatment (i.e., injection) or interfere with the interpretation of study endpoints or surgical complications (examples include [but not limited to] glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities); 2. Cataract surgery, intraocular and/or peri-ocular injection in the study eye within the prior six months; 3. Prior vitrectomy or aphakia in the study eye; 4. Known sensitivity to any component of the study treatment or medications planned for use in the study; 5. Immunological assays show presence of neutralizing antibodies to AAV2 above 1:1000; 6. Use of anti-platelet and anti-coagulants that may alter clotting within 28 days prior to study treatment administration.
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] vg/eye. In mice, the safe intravitreal doses ranged from [redacted] vg/eye. Additionally, two nonclinical pharmacology studies demonstrated efficacy and safety in mice at a dose range of [redacted] to [redacted] vg/eye 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] vg/eye. 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 100 µL 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 (US) 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 US, 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 macula 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 based on the light-gated ion channel, channelrhodopsin-2 (ChR2). RST-001 comprises a non-replicating recombinant

Adeno-Associated Virus serotype [redacted] containing the [redacted]. RST-001 is manufactured in sterile conditions according to Good Manufacturing Practice (GMP) requirements, which includes screening and elimination of microbes.

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] vg/eye) to the highest dose ([redacted] vg/eye). 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 (vg/mL): [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] vg/eye, [redacted] vg/eye, and [redacted] vg/eye) evaluated as compared with vehicle injected mice, based upon optokinetic responses. The highest dose ([redacted] vg/eye) 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 (hematology, coagulation, clinical chemistry and bone marrow smear evaluation), immunogenicity [redacted], gross necropsy findings, organ weights, and histopathologic examinations, and biodistribution.

3.6.2.1 Dog Study

The dog study was conducted in healthy male and female animals 5-6 months of age. The dog was chosen as the animal model for this study as it is an accepted non-rodent species for preclinical ocular toxicity testing by regulatory agencies. There were 8 dogs 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. Two dogs/sex/time point were administered, in the right eye, a single-[redacted] µL intravitreal injection of vehicle or RST-001. Animals were sacrificed on Day 36 and Day 99.

No noteworthy adverse effects were observed in the body weight, food consumption, clinical pathology or organ weights following administration of RST-001 at any dose level.
RST-001-related findings, consisting of ocular inflammation, were observed beginning at least 5 weeks after administration with an increasing incidence and severity with dose at all dose levels. Ophthalmic findings of anterior uveitis (anterior chamber cells, keratic precipitates and/or cell–like deposits on the corneal endothelium) were observed at Week 5 in 8/8 high dose eyes and 3/8 or 1/8 eyes for the mid and low doses, respectively. During the recovery period, findings generally remained stable or progressed. Findings related to chronic inflammation, including the presence of perivascular retinal opacities in addition to findings in the anterior chamber, were present at all dose levels at the end of the recovery period. In 2/8 high dose animals, the level of inflammation was greater when compared to other animals and was accompanied by anterior chamber flare, fibrin, corneal edema, pupil incomplete dilation, fundus hazy view, corneal vessels and/or lens opacities. These observations correlated with microscopic

findings. At the high dose, these consisted of minimal to marked mixed cell (lymphocytes, macrophages, and rarely, neutrophils) inflammation of the anterior chamber (iridocorneal angle), iris, ciliary body, vitreous body and/or retina. At the mid and low dose, findings were limited to minimal to mild cell inflammation in the ciliary body, vitreous body and/or iris. There were no signs of overt tissue damage due to direct toxicity of the test item and no cellular or humoral immune response to RST-001 was detected at any dose level.

RST-001 DNA was detected predominantly in the spleen, with lower concentrations below the limit of quantitation ([redacted] copies/µg of tissue) also detected within the mandibular lymph node, liver, lacrimal gland, and optic nerve. Preliminary immunohistochemistry evaluation of the dogs' retina suggests ChR2 protein expression persistent throughout the 99 days of follow up.

In conclusion, administration of RST-001 by a single intravitreal injection at a 10-fold difference in nominal doses resulted in dose-related ocular inflammation, with no noteworthy adverse effects observed in the body weight, food consumption, clinical pathology, cellular immune response or organ weight. 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 had minimum biodistribution systemically and was expressed in the retina.

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] copies/µg of tissue)

within the hindbrain and spleen. Dose-dependent minimal to moderate ChR2 immunolabeling occurred in the right treated eye of animals given [redacted] vg/right eye; 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] to [redacted] vg/eye. For the mouse, the safe intravitreal doses ranged from [redacted] to [redacted] vg/eye. Two nonclinical pharmacology studies demonstrated efficacy and safety in the mouse at a dose range of [redacted] to [redacted] vg/eye 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] vg/eye. The dose range in this study ([redacted] to [redacted]1 vg/eye 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 100 µL 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] and [redacted] vg/eye 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 100 µL.

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 ERG contact lens.

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 3 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

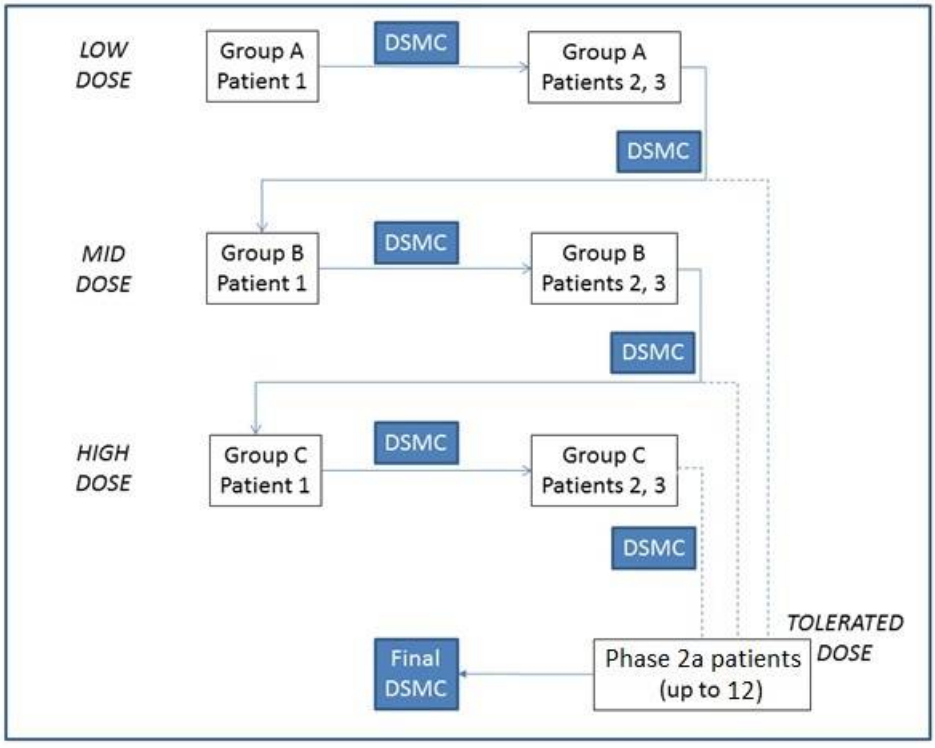

Table 1 Dose Escalation

Phase	Group	Number of patients[a]	Intravitreal Injection	
			Vector concentration	Volume (µL)
1	A	3	LOW	100
	B	3	MID	100
	C	3	HIGH	100
2a		6-12[b]	Choice of dose[c] from groups A, B, or C	100

[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 3 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]

[redacted] This patient group is considered to be a suitable population to assess safety and tolerability in this Phase 1 study. Furthermore, the presence of [redacted] will give a valuable opportunity to evaluate efficacy.

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:

Phase 1

3. VA in the study eye of no-better-than hand motion

Phase 2a

4. If a treatment benefit is identified by the DSMC:
    a. VA eligibility criteria will match that of Phase 1.
5. If a treatment benefit is **not** identified by the DSMC:
    a. VA eligibility criteria will match that of Phase 1 for half of the enrolled patients.
    b. VA criteria for the other half of the enrolled patients must range from no-worse-than count fingers to 20/200 vision in the study eye.

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;
2. Complicating systemic diseases or clinically significant abnormal baseline laboratory values. Complicating systemic diseases include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (i.e., radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). For the procedure on establishing clinically significant abnormal baseline laboratory values, see Section 5.1.2.

3. Immunocompromising diseases, such as hepatitis B, C and HIV, or use of immunosuppressive medications
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
6. Immunogenicity assays show presence of neutralizing antibodies to AAV2 above 1:1000 of dilution
7. Use of anti-platelets and anti-coagulants that may alter clotting within 28 days prior to study treatment administration
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

Ocular Exclusion Criteria:

9. History of prior gene or stem cell therapy (ocular or other)
10. Pre-existing eye conditions that would preclude the planned treatment (i.e., injection) or interfere with the interpretation of study endpoints or surgical complications (examples include (but not limited to) glaucoma, diseases affecting the optic nerve causing significant visual field loss, active uveitis, corneal or lenticular opacities)
11. Cataract surgery, intraocular and/or peri-ocular injection in the study eye within six months prior to Day 0
12. Prior vitrectomy or aphakia in the study eye

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 treatment in this study has been called RST-001. RST-001 constitutes a non-replicating recombinant Adeno-Associated Virus serotype [redacted] vector containing a gene encoding the channelrhodopsin-2 protein (ChR2 ORF) formulated in [redacted]. RST-001 is provided as a sterile frozen liquid.

4.2 Dosage and Administration

The doses of RST-001 evaluated in this study will be:

- LOW dose = [redacted] vg/eye
- MID dose = [redacted] vg/eye
- HIGH dose = [redacted] vg/eye

4.3 Method of Assigning Patients to Dose Groups

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

Escalation is dependent upon the enrollment stopping rules and DSMC recommendation.

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

4.4 Dose Rationale

The highest feasible concentration of RST-001 is constrained by manufacturing capabilities and product stability and has been determined to be approximately [redacted] vg/ml. The highest feasible dose is then limited by the volume that can be delivered to the human vitreous. Based upon estimated vitreous volumes and maximum feasible intravitreal dosing, this maximum

concentration was evaluated as the highest dose in our mouse pharmacology study (dose volume of 1 µl) and mouse (1 µl) and dog (µl) toxicology and biodistribution studies. This dose was demonstrated to be efficacious and no dose-limiting toxicity was observed, respectively. Since the beagle dog vitreous has about half the vitreous volume of the human eye, the HIGH dose for the human study has been determined to be vg/eye given as a single 100 µl 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 of this dose, vg/eye. The MID dose will be of the HIGH dose, vg/eye.

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 as a sterile frozen liquid and must be stored at °C or below. Stability testing indicates RST-001 is stable for at least °C or below. Please refer to the Study Procedures Manual for additional information.

4.8 Study Treatment Preparation and Administration

RST-001 must be prepared under aseptic conditions as described in the Study Procedures Manual. Keep residual study treatment separately from unused study vials.

Immediately prior to study treatment administration, the patient will be placed in the supine position and the patient's eye will be prepared for injection in accordance with the description given in the Study Procedures Manual.

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 3 years. These visits include yearly office visits for 3 years (Months 36, 48, and 60).

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

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as telephone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort is to be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed with agreement from the sponsor:

- If permitted by local regulations, the IRB/IEC, and the subject, postbaseline visits may be conducted virtually.
- Study Visits and/or activities are to be performed as scheduled whenever possible.

Table 2 Study Visit Schedule: Core Study Visits

	Screening[b]	Baseline[b]	Day			Month						
Visit Windows (Days)[a]	-45 to -8	-7 to -1	0	1	7 ± 1	1 ± 7	3 ± 7	6 ± 7	9 ± 7	12 ± 30	18 ± 30	24[c] ± 30
Informed Consent/Authorization	X											
Ophthalmic and Medical History	X	X	X									
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events review	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X											
Pregnancy Test	X	X										
Blood Sample[d]	X	X										
Electrocardiogram (ECG)	X											
Chest X-ray	X											
Visual acuity	X	X										
Full Field Sensitivity Testing (FFST)	X	X										
Object detection and discrimination	X	X										
Pupillometry (at selected sites)		X										
Ambulation		X										
Complete Ophthalmic Examination	X	X										
Intraocular Pressure (IOP)	X	X										
Spectral Domain Optical Coherence Tomography (SD-OCT)	X	X										
Color Fundus Photography and Autofluorescence		X										
Electroretinography (ERG)	X											
Visual Evoked Potentials (VEP)		X										
Quality-of-life questionnaire		X										
Study drug administration[f]												

[redacted]

[a] Assessment administration may extend over more than one day.
[b] If convenient, the Screening and Baseline visits may be combined.
[c] Month 24 or early termination visit.
[d] Blood samples will include hematology, chemistry and RST-001 immunogenicity testing: see Appendix 2 for details.
[e] IOP measurements will be performed pre- and post-injection in the study eye only. After the intravitreal injection, the patient will remain in the supine position and (IOP) intraocular pressure will be monitored for at least 30 min. In the event that the IOP is 30 mmHg or above, this will be managed according to Section 5.3.2.
[f] Topical corticosteroid treatment may be given to the injected eye according to the investigator's standard of care.

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

	Months		
	Clinic Visits		
Visit Windows (Month ± Days)	36 ± 30	48 ± 30	60 ± 30
Concomitant medications and procedures	X	X	X
Adverse Events review	X	X	X
Visual Acuity	X	X	X
Complete Ophthalmic Examination	X	X	X

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 (US 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.

Due to the COVID-19 pandemic, it is possible that protocol modifications may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

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.

- Informed consent and authorization
- Ophthalmic and medical history
- Concomitant medications and procedures
- Physical examination
- Pregnancy test (blood)
- Draw blood sample
- ECG
- Chest X-ray
- Visual acuity
- FFST (full field sensitivity test)
- Object detection and discrimination
- Complete ophthalmic examination
- IOP
- SD-OCT
- ERG
- AE review

5.1.3 Baseline Visit

- Confirm patient still consents
- Ophthalmic and medical history
- Concomitant medications and procedures
- AE review
- Pregnancy test (blood)
- Draw blood sample

- Visual acuity
- FFST
- Object detection and discrimination
- Pupillometry (at selected sites)
- Ambulation
- Complete ophthalmic examination
- IOP
- SD-OCT
- Dilated color fundus photography and autofluorescence
- VEP
- Quality of life questionnaire

5.1.4 Treatment Visit (Day 0)

- Ophthalmic and medical history (pre-injection)
- Concomitant medications and procedures
- AE review
- [redacted]

5.1.5 Post Injection Visit (Day 1)

- Concomitant medications and procedures
- AE review
- [redacted]

[1] IOP measurements will be performed pre- and post-injection in the study eye only. After the intravitreal injection, the patient will remain in the supine position and IOP will be monitored for at least 30 min. In the event that the IOP is 30 mmHg or above, this will be managed according to Section 5.3.2.

5.1.6 Day 7

- Concomitant medications and procedures
- AE review
- [redacted]

5.1.7 Month 1

- Concomitant medications and procedures
- AE review
- [redacted]

5.1.8 Month 3

- Concomitant medications and procedures
- AE review
- [redacted]

- [redacted]

5.1.9 Month 6: Primary Endpoint

- Concomitant medications and procedures
- AE review
- [redacted]

5.1.10 Month 9

- Concomitant medications and procedures
- AE review
- [redacted]

- [redacted]

5.1.11 Month 12

- Concomitant medications and procedures
- AE review
- [redacted]

5.1.12 Month 18

- Concomitant medications and procedures
- AE review
- [redacted]

5.1.13 Month 24 (or Early Termination) Visit

- Concomitant medications and procedures
- AE review
- [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 3-year follow-up period. At Months 36, 48, and 60, patients will undergo the following study assessments conducted at yearly clinic visits:

- Concomitant medications and procedures
- AE review
- Visual acuity
- Complete ophthalmic examination

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

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 electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, the investigator is to contact Allergan. Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit) to prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine is to be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of RST-001 on SARS-CoV-2 vaccination is unknown.

5.2.4 Adverse Event Review

All AEs will be recorded at each study visit. COVID-19 infections should be reported as AEs.

5.2.5 Physical Examination

A complete physical examination will be performed at the Screening visit, 6 months, and at 24 months (or early termination visit), to include vital signs (oral temperature, heart rate, respiratory rate and blood pressure), height, weight and examination of major organ systems (head/eyes/ears/nose/throat, neck, cardiovascular, respiratory, abdomen, musculoskeletal/extremities, skin, lymph nodes and neurological).

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 hematology (hemoglobin, hematocrit, white blood cell count with differential and platelet count), chemistry panel (sodium, potassium, chloride, total protein, albumin, calcium, phosphorous, glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), liver function test panel, and RST-001 immunogenicity testing. Instructions for shipping venous blood for immunological analysis are detailed in the Study Procedures Manual.

5.2.8 ECG (Electrocardiogram)

A standard 12-lead ECG will be performed. An interpretation of the ECG will be performed by a qualified physician, and a signed report will be issued.

5.2.9 Chest X-ray

A standard posterior anterior (PA) chest x-ray will be performed. An interpretation of the x-ray will be performed by a qualified physician, and a signed report will be issued.

5.2.10 Visual Acuity

The visual acuity of each eye will be measured using an electronic visual acuity (EVA) Early Treatment for Diabetic Retinopathy Study (ETDRS) testing protocol, or low vision assessment of hand motion and light perception as described in the Study Procedures Manual.

5.2.11 Full Field Sensitivity Testing (FFST)

Full field sensitivity testing will be performed using the Espion ColorDome™ LED full-field stimulator (Diagnosys LLC, Lowell, MA) (Klein M, Birch DG, 2009) according to the procedures outlined in the Study Procedures Manual.

5.2.12 Object Detection and Discrimination

Patients will perform these two tests concurrently, first identifying if a light displayed on an LED screen can be seen and then if a series of standard images (square, circle, triangle, or star) presented on the screen can be identified. The color of each shape will either be red or blue. For each image tested, the shape, color, and threshold intensity will be recorded.

5.2.13 Pupillometry (at Selected Sites)

The pupil responses of both eyes will be tested using a pupillometry system as described in the Study Procedures Manual.

5.2.14 Ambulation

A patient's ability to navigate within a room will be evaluated according to the procedures outlined in the Study Procedures Manual.

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 a slit lamp biomicroscopic evaluation of the conjunctiva, cornea, anterior chamber, iris, and lens. The posterior segment and fundus will also be evaluated through dilated pupils by indirect ophthalmoscopy. Intraocular pressure will be measured using Goldmann applanation tonometry or a hand held tonometer (using the same instrument for each patient throughout the study, when possible). If Goldmann applanation tonometry is used to measure IOP, then it must be performed after fundus photography and autofluoresence to prevent fluorescein dye from interfering with the images.

5.2.16 Intraocular Pressure (IOP)

IOP measurements will be performed in both eyes at every study visit except on treatment day (Day 0), where there will be a pre- and post-injection IOP measurement in the study eye only. After the intravitreal injection, the patient will remain in the supine position and IOP will be monitored for at least 30 minutes. In the event that the intraocular pressure is 30 mmHg or above, it will be managed according to Section 5.3.2.

5.2.17 Dilated Color Fundus Photography and Autofluorescence

A standardized procedure for the collection of single, non-stereo images of the fundus of both eyes will be obtained. Color and autofluorescence images of the fundus will be maintained at the site until completion of Phase 2a.

5.2.18 Spectral Domain Optical Coherence Tomography (SD-OCT)

Retinal anatomy of both eyes will be evaluated by SD-OCT scans at the [redacted]. Additional SD-OCT scans may be obtained at the discretion of the investigator. Each SD-OCT will be obtained using the site's preferred macular scanning protocol. Use of the same instrument throughout the study for a given patient is recommended.

5.2.19 Electroretinography (ERG)

Electroretinography testing of both eyes will be performed using the full field procedures conducted in accordance with standard protocol provided by the ERG Standardization Committee of the International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Electroretinography will be performed at the [redacted].

5.2.20 Visual Evoked Potentials (VEP)

The pattern of visual evoked potentials will be obtained from each eye using a VEP stimulator according to standard protocols as described in the Study Procedures Manual.

5.2.21 Quality of Life Questionnaire (NEI VFQ-25)

A member of the investigative team will administer the National Eye Institute (NEI) Visual Functioning Questionnaire (VFQ-25).

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

- Visual acuity as measured by low vision assessment of hand motion and light perception
- Evaluation of ocular inflammation. Parameters of anterior segment, vitreous and retinal/choroidal inflammation will be very carefully monitored
- Intraocular pressure measurement (IOP)
- Full dilated slit lamp biomicroscopy
- Color fundus photography and autofluorescence
- Electroretinography (ERG) to ISCEV standards
- Visual evoked potentials
- Full field sensitivity testing
- Spectral domain optical coherence tomography (SD-OCT) of the macula

6.1.1.1 Visual Acuity

- Visual acuity as measured by low vision of assessment of hand motion and light perception.

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, such as OCT and fluorescein angiography, 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).

(a) Anterior chamber cells

Grade	Cells/1mm^2
0+	< 1 cell
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Anterior chamber flare

Grade	Flare
0+	None
1+	Faint
2+	Moderate
3+	Marked
4+	Intense (including fibrin)

Grading of Vitreous haze

Consistent with Nussenblatt RB, Palestine AG, Chan CC et al. Standardisation of vitreal inflammatory activity in intermediate and posterior uveitis (Nussenblatt et al, 1985).

Grade	Vitreous flare	Vitreous Haze	Clinical finding
0	None	No haze	Clear view of optic nerve
1	Minimal	Trace	Slight blurring of optic disc margin
2	Mild	1+	Slightly blurred optic nerve and vessels
3	Moderate	2+	Moderately blurred optic nerve and vessels
4	Marked	3+	Optic nerve head border blurry but visible
5	Severe	4+	Optic nerve head obscured

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
5. ECG and Chest X-ray results
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]

These tests will be performed at several timepoints during the study: [redacted]

There is no diagnostic test available for ocular immunogenicity. Instead, clinical evidence suggestive of immunogenicity will be gathered. Examination findings such as reduced visual acuity in the study eye, intraocular inflammation, uveitis, retinal vasculitis, retinal edema, hemorrhage, exudation and/or detachment will also be gathered. Additional evaluations such as OCT and fluorescein angiography may also aid the clinical identification of an immune response.

Treatment of intraocular inflammation and immunogenicity

In the event that immunogenicity is suspected by the investigator, topical, local, intraocular or systemic corticosteroid, corticosteroid-sparing and immunomodulatory therapy may be initiated, usually in an escalating fashion, in accordance with the investigator's practice, to control the inflammation. The patient will continue in the study and all additional assessments and visits will be documented in the source documents.

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

1. Monitor and review safety and AE data of patients participating in the study.
2. Advise on dose-escalation, Phase 2a sample size/study population, study suspension or termination, as appropriate.
3. Provide review and advice on protocol amendments and changes to the clinical protocol, as appropriate.
4. Provide advice on any other matters as deemed necessary for the safe conduct of the study.
5. Provide assessment as to whether treatment benefits have been observed in Phase 1 of the study.

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:

1. Any Grade 3 or greater AE related to RST-001 (according to Common Terminology Criteria for Adverse Events v4.03)
2. Occurrence of an intraocular infection related to contaminated RST-001 that required treatment would serve as a stopping rule
3. A safety issue has been identified that compromises the benefit or increases the risk balance

Dose-limiting toxicity (DLT) is defined as any adverse event of Grade 3 or higher that is expected to be related to the study treatment.

Dose escalation will stop if a DLT is observed, including:

4. Severe or persistent ocular inflammation
5. Other significant ocular toxicity (e.g., retinal detachment, evidence of direct toxicity)

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.

SARS-CoV-2 infections are to be captured as AEs. If the event meets the criteria for a serious adverse event , then follow the serious adverse event reporting directions.

Reactions known to be associated with the SARS-CoV-2 vaccine are to be reported as AEs. If the event meets the criteria for a serious adverse event, then follow the serious adverse event reporting directions.

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.

Pregnancy

While not an AE, pregnancy in a study participant must be reported to Allergan within 24 hours after the site becomes aware of the pregnancy. If a pregnancy occurs in a study participant or in the partner of a study participant, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to Allergan within 24 hours after the site becomes aware of the event.

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:

- Visual acuity
- Full field sensitivity
- Ambulation
- Object detection and discrimination
- Visual electrophysiological measures (visual evoked potentials)
- Visual function (quality of life as measured by standardized questionnaire)

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. During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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

Visual function measures:

- Change in visual acuity in the study eye
- Change in full field sensitivity in the study eye

- Change in ambulation
- IOP measurements in the study eye
- Changes in anatomical parameters as measured in the study eye by:
    - Fundus photography
    - Spectral domain-OCT (SD-OCT)

11.2 Secondary Endpoints

11.2.1 Measures of Change in Visual function

11.2.1.1 Change in Visual Acuity

Change in visual acuity in the study eye from Baseline (defined as last observed value prior to dosing) to [redacted]

11.2.1.2 Change in Full Field Sensitivity Testing

Change in retinal sensitivity in the study eye from Baseline to [redacted]

11.2.1.3 Change in Ambulation

Change in ambulation scores from Baseline to [redacted]

11.2.1.4 Change in Object Detection and Discrimination

Change in object detection and discrimination scores from Baseline to [redacted]

11.2.1.5 Change in Visual Evoked Potentials and Electroretinography

Change in VEP and ERG scores from Baseline to [redacted]

11.2.1.6 Change in Quality of Life

Change in composite score of NEI VFQ-25 scores from Baseline to [redacted]

11.2.2 Anatomical Endpoints Relating to Retinal Integrity and Survival

11.2.2.1 Fundus Photography

Qualitative assessment of the change in retinal appearance from Baseline to [redacted]

11.2.2.2 Spectral Domain-OCT (SD-OCT)

Qualitative assessment of the change in retinal cross-sectional appearance from Baseline to [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 visual acuity, full field sensitivity, ambulation, quality of life and electrophysiological measures (visual evoked potentials, electroretinography). Visual acuity data will be presented as the number of letters correctly identified at each time point and the calculated logMAR and Snellen equivalent values, or as count fingers, hand motion, and light perception. The Quality-of-life questionnaire will be scored using the NEI VFQ-25 scoring algorithm.

11.3.5 Other Analysis

[redacted]

11.3.6 Interim Analysis

No interim analysis is planned. There will be one database lock for the final analysis. The final analysis will occur when all patients have completed the Month 60 visit or exited early from the study. The details of all analyses will be provided in the analysis plan, which will be finalized before database lock.

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (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 (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source documents) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed informed consent forms (ICFs), pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's and patient's file, as well as the results of diagnostic tests such as x-rays and laboratory tests. The investigator's copy of the CRFs serves as part of the investigator's record of a patient's study-related data.

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)
- US 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 later 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

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20 Appendices

20.1 Appendix 1: Abbreviations

AAV	Adeno-associated Virus
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
BCVA	Best Corrected Visual Acuity
ºC	Degrees Celsius
CFR	Code of Federal Regulations
ChR2	Channelrhodopsin-2
COVID-19	Coronavirus disease - 2019
CRF	Case Report Form
CTC	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERG	Electroretinography
ETDRS	Early Treatment for Diabetic Retinopathy Study
EVA	Electronic Visual Acuity
FDA	Food and Drug Administration, USA
FIH	First-in-Human
FFST	Full Field Sensitivity Testing
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IRAE	Immediately Reportable Adverse Event
IRB	Institutional Review Board
ISCEV	International Society for Clinical Electrophysiology of Vision
mm	Millimeters
NEI	National Eye Institute
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
QoL	Quality of Life
rAAV	Recombinant Adeno-associated Virus
RGC	Retinal Ganglion Cells
RP	Retinitis Pigmentosa
RST-001	RetroSense Therapeutics drug product (AGN-151597)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD-OCT	Spectral Domain - Optical Coherence Tomography
US	United States
VA	Visual Acuity
VEP	Visually Evoked Potential
VFQ	Visual Functioning Questionnaire

20.2 Appendix 2: Clinical Laboratory Tests

Laboratory parameters for blood draws will evaluate the following, at a minimum:

CBC: complete blood count
Hemoglobin
Hematocrit
Red blood cell count
Mean Corpuscular Volume (MCV)
Mean Corpuscular Hemoglobin (MCH)
Mean Corpuscular Hemoglobin Concentration (MCHC)
White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils
Platelet count

Chemistry panel
Sodium
Potassium
Blood Urea Nitrogen (BUN)
Creatinine
Glucose
Chloride

Liver function tests
Albumin
Bilirubin
Total protein
Calcium
Alkaline Phosphatase
AST (SGOT)
ALT (SGPT)
Triglycerides

Serology

Human Immunodeficiency Viral Antibody
Hepatitis B and C Antibody
AAV2 antibody

Pregnancy test

Serology beta-hCG

RST-001 immunogenicity testing

[redacted]

20.3 Protocol Amendment Summary Amendment 1

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

Protocol RST-001-CP-0001 Amendment 1: (March 2017)

Amendment Summary

This summary includes changes made to Protocol RST-001-CP-0001 (approved July 14, 2015). Allergan is taking over the sponsorship of Protocol RST-001-CP-0001. The main reasons for this amendment were to 1) replace Retrosense Therapeutics with Allergan, Inc. and 2) modify and update the protocol to align with Allergan SOPs.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized. Deleted text is indicated by strikethrough and added text is underlined, as appropriate. This summary provides a high-level list of changes to the document.

Section	Revision	Rationale
Title page	Updated the title page information with Allergan personnel	Administrative change
Title page	Added Allergan signatory and the following text in underline: <u>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.</u>	Administrative change
Investigator Signature Page	Removed the investigator name David Birch, Ph.D. Added spaces for additional investigator signatures and date Updated section as per Allergan style.	Administrative change
Title page; Protocol Synopsis; Section 3.6.3; Section 3.15.1; Section 5.4; Section 20.3	Removed the term "uniocular"	Uniocular is not an Allergan term.
Title page; Protocol Synposis and throughout protocol	Added the term "<u>Advanced</u>" before Retinitis Pigmentosa	Added for consistency and clarity with regard to the study.
Protocol Synopsis Objective	To evaluate <u>the</u> safety, tolerability and preliminary efficacy of RST-001 in patients with advanced RP. <u>Preliminary efficacy data will be obtained through ocular evaluations.</u>	Modified to provide clarity

Section	Revision	Rationale
Protocol Synopsis Study Population	~~It expected that up to~~ Fifteen (15) patients ~~with RP~~ will be enrolled into this study. ~~If cohorts need to be expanded this number may increase to 18~~.	Modified to provide better clarity to the sites and investigators.
Protocol Synopsis Study Design	• *Structure:* Open-label, dose-escalation, non-randomized study • *Duration:* 2 years • *Treatment:* Three doses of RST-001 will be evaluated by sequential dose escalation in ~~three~~ the first cohort~~s~~ of three patients (groups A, B, C, each comprising three patients). Patients will receive a single~~, uniocular~~, 100 µL intravitreal injection of RST-001 in the study eye. In Cohort 2, up to six patients may be enrolled and receive RST-001 at the highest tolerated dose or any dose that has been previously evaluated that is both lower and safe. • *Visit Schedule:* Eight visits ~~(including the screening visit)~~ are planned over 6 months including the Screening and Baseline visits, Day 0, Day 1, Day 7, and Months 1, 3, and 6) to reach the primary endpoint. Following the initial 6 months, ~~four more visits are planned up to the end of the two-year observation period~~ patients will be followed for an additional 18 months across four visits (Months 9, 12, 18, and 24).	Modified to provide better clarity to the sites and investigators. Consolidated information from Length of Study and Study Visits and Assessments into Study Design section of Protocol Synopsis
Protocol Synopsis Inclusion and Exclusion Criteria	Modified to include key inclusion and exclusion criteria	Modified as per Allergan style. A full list of inclusion and exclusion criteria is included in the Section 3.15.3.
Protocol Synopsis; Section 6.2.3; Section 6.2.7; Section 6.2.8; Section 6.2.9; Section 6.2.10; Section 6.2.11; Section 6.2.12; Section 6.2.13; Section 6.4.12	Pupillometry (at selected sites)	Modified to provide clarity.
Protocol Synopsis and Section 3.5	RST-001 (AGN-151597)	Added Allergan product code at first use
Protocol Synopsis Monitoring of Safety and Tolerability	Safety monitoring will include a combination of ~~Adverse Event~~ AE reporting, clinical evaluations (~~systemic and~~ ocular and systemic), and laboratory results ~~testing~~. ~~Specific o~~Ocular and systemic safety monitoring will include monitoring for signs of an immune response. ~~Evidence of systemic immune response will also be monitored.~~	Modified to provide clarity.

Section	Revision	Rationale
Protocol Synopsis Clinical Study Progress	~~Participants~~ Patients will be enrolled sequentially. The d~~D~~ecision to dose escalate will be determined with the Data Safety Monitoring Committee (DSMC) upon review of Adverse Event (AE), clinical evaluations (ocular and systemic ~~and ocular~~) and laboratory results ~~testing from enrolled participants~~.	Modified to provide clarity.
Protocol Synopsis Stopping Rules	Enrollment Stopping Rules	Added to provide consistency throughout the document.
	Any Grade 3 (~~National Cancer Institute [NCI] grading system~~ Common Terminology Criteria [CTC] for AEs v4.03) or greater ~~adverse event~~ AE considered related to ~~injection test article~~ the study treatment.	Modified for clarity.
List of Abbreviations	Moved from Section 3 to Section 20.1 (Appendix 1). All subsequent sections of the protocol were renumbered.	Moved for consistency with Allergan protocol template.
Section 3	~~Key Roles~~ Introduction Removed all clinical site and investigator information	No longer applicable to Allergan protocol
Global change	Changed Study Manual of Operations to Study Procedures Manual	Modified to maintain consistency throughout the document.
Section 3.1.5	Removed the sentence: ~~To date, there have been no human studies of optogenetic therapy for vision related disorders. ClinicalTrials.gov currently lists no other human optogenetic clinical trials.~~	Removed due to ongoing current Allergan study
Section 3.7.1	~~Retrosense Therapeutics' preclinical data indicate that no local or systemic immunosuppression will be required~~. Preclinical data indicated that no cellular immune or humoral response to RST-001 was detected at doses up to [redacted] and [redacted] vg/eye in mice and dogs, respectively. ~~Throughout this study,~~ 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.	Modified preclinical text for clarity
Section 3.8	Section renamed: Treatment Administration ~~Surgical Procedure for the Delivery of RST-001~~ RST-001 will be administered ~~delivered~~ by intravitreal injection as specified in the Study Procedures Manual. The injection volume is 100 µL. ~~through the pars plana, in the same fashion as other intravitreal agents in common clinical usage~~. ~~The surgical procedure is detailed in Section 6.5, below.~~ 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.	Added to inform the site that further information can be found in the Study Procedures Manual for this topic.

Section	Revision	Rationale
Section 3.12	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 ~~I~~injection of RST-001 will be performed in the ~~O~~operating ~~R~~room under aseptic conditions by qualified staff in accordance with the Study Procedures Manual ~~surgical team experienced in the performance of the technique~~. After the procedure, ~~E~~each patient will be carefully monitored ~~post operatively~~ for complications. Evidence of an immune response to RST-001 will be monitored (refer to Section 6.2.1). ~~Specific procedures are documented in this protocol in the event of immune reaction or ocular inflammation.~~ The conduct of this study will be overseen by the Data Safety Monitoring Committee (DSMC).	Administrative change
Section 3.13	Any complications arising post injection, ~~as listed above~~ will be managed ~~in compliance with relevant standards of care and~~ in accordance with the investigator's standard of care ~~s' and surgeons normal practices~~. It is not possible for RST-001 to be removed from the eye after injection ~~delivery~~.	Administrative change
Section 3.15.1.1	Enrollment Phase I (Cohort 1) Three groups of patients (A, B, C, each comprising 3 patients) will be enrolled in ~~recruited to~~ this study. ~~with advanced Retinitis Pigmentosa (RP) in accordance with the inclusion and exclusion criteria below.~~ ~~Doses and cohorts are shown in the Table 1. A schematic providing an overview of the treatment schedule is also shown in Figure 1.~~ ~~Three~~ Approximately 3 ~~Group A~~ patients in Group A will receive the lowest dose of RST-001 ~~at the lowest dose level~~ (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. ~~An interval of 1 month (to include visit 6) between dosing the first and subsequent patients will be observed in order to assess the safety and tolerability of RST-001 in these patients~~. If ~~after a minimum interval of 1 month (to include visit 6) from treatment of the final Group A patient,~~ 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 ~~three Group B~~ approximately 3 patients in Group B may ~~also~~ be enrolled and receive a higher dose of RST-001 (MID) following the same guidelines and treatment schedule.	Administrative change

Section	Revision	Rationale
	Similarly, ~~An interval of 1 month (to include visit 6) between dosing the first and subsequent patients will be observed.~~ ~~I~~if ~~after a minimum interval of 1 month (to include visit 6) from treatment of the final Group B patient,~~ 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 ~~three Group C~~ patients in Group C may ~~also~~ be enrolled and receive the ~~a~~ highest~~t~~ dose of RST-001 (HIGH) following the same guidelines and treatment schedule. ~~An interval of 1 month (to include visit 6) between dosing the first and subsequent patients will be observed.~~	
Section 3.15.1.2	~~If after a minimum interval of 1 month (to include visit 6) from treatment of the final patient of any particular group and~~ ~~i~~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 ~~of Cohort 2 either at this highest tolerated dose or any dose that has been previously evaluated that is both lower and safe.~~ In ~~c~~Cohort 2, up to six patients may be enrolled and receive RST-001 at this highest tolerated dose or any dose that has been previously evaluated that is both lower and safe. 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. ~~The primary endpoint of the study is safety at 6 months post RST-001 treatment up to which, participants will attend for 12 scheduled visits. A further 6 visits are planned up to the end of the study at 2 years.~~ ~~At each visit, a battery of visual, ocular and systemic testing will rigorously evaluate the safety of RST-001. Ocular evaluations will also offer the opportunity to obtain potential preliminary efficacy data. Due to the nature of the study and the study drug, only summary statistics will be available and there is no opportunity to evaluate pharmacokinetics.~~ ~~It is anticipated that enrollment will be completed after 18 months.~~	Administrative change
Table 1	Removed the Age column. Added footnotes: (a) Fifteen (15) patients will be enrolled in this study. (b) The highest tolerated dose or any dose that has been previously evaluated in Cohort 1 that is both lower and safe.	Modified to provide clarity.
Section 3.15.1.2 (Figure 1)	Added title: Overview of the Treatment Schedule	Added title to include in table of contents

Section	Revision	Rationale
3.15.2	~~Up to 15 participants~~ ~~A total of~~ Fifteen (15) patients ~~with RP can~~ will be enrolled in~~to~~ this study. ~~though if additional participants are added to groups A-C, then this total may increase to 18.~~	Administrative change
3.15.3.1	Inclusion criteria displayed as general inclusion criteria and ocular inclusion criteria.	Modified for consistency with Allergan protocol template.
3.15.3.2	Exclusion criteria displayed as general exclusion criteria and ocular exclusion criteria.	Modified for consistency with Allergan protocol template.
3.15.4	Early Discontinuation ~~Removal~~ of ~~p~~Patients from the study Patients may voluntarily withdraw from the study at any time or for the following reasons: ~~a) Voluntarily, at any time. Patients that withdraw may be replaced.~~ a) Due to an adverse event (AE) b) ~~At the request of~~ 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 ~~agent~~ may be replaced.	Administrative change
Section 4.8	RST-001 must be prepared under aseptic conditions as described in the Study Procedures Manual. Keep residual study treatment ~~agent~~ separately from unused study vials. [redacted]	Modified to provide better clarity to the sites and investigators.

Section	Revision	Rationale
	[redacted]	
	Immediately prior to study ~~agent~~ treatment administration, the patient will be placed in the supine position and the participant's eye will be prepared for injection in accordance with the description given in the Study Procedures Manual ~~Section 6.5~~	
Section 4.9	The investigator or designated study site personnel is responsible for study ~~agent~~ treatment accountability, reconciliation and record maintenance. Removed sentence: "~~All unused study agent must be returned to Allergan or Allergan designee at the completion of the study.~~"	Modified to provide better clarity to the sites and investigators.
	Added: All study treatment must be returned to Allergan or Allergan designee at the completion of the study.	Language regarding the return of study drug was added to Section 4.9
Section 4.12	During the course of the study, ~~participants~~ patients will be allowed to continue taking ~~all~~ prescribed and ~~non-prescribed~~ over-the-counter medications that are not excluded in the protocol (i.e., anticoagulants and immunosuppressive therapy).	Administrative changes
Section 5	Section 5: Study Assessments and Intravitreal Injection ~~Surgical Procedure~~ ~~Only individuals who have been~~ Patients diagnosed with advanced RP and who are eligible based on inclusion and exclusion criteria will be invited to participate in this clinical study ~~trial~~. After obtaining informed consent and authorization, patients will undergo ~~A~~ complete physical examination and ~~clinical chemistries will be performed at a pre-treatment, screening evaluation~~ laboratory testing ~~to further determine~~ to assess eligibility for the study. ~~Subjects will be considered enrolled when they sign the Informed Consent.~~ 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 (~~d~~Day 0) patients will be assessed on the first post injection day (~~d~~Day 1) and thereafter according to the table below:	Administrative changes
Section 5 (Table 2)	Visit windows for Months 12, 18, and 24 were changed to ± 30 days. The following other changes were made: ~~Review of~~ Ophthalmic and ~~m~~Medical ~~h~~History A row was added for the Concomitant Medications and Procedures to match the same assessment time points for Ophthalmic and Medical History. The row for Fundus autofluorescence was merged and renamed to Color Fundus Photography and Autofluorescence.	Modified to provide better clarity to the sites and investigators and maintain consistency throughout the document.

Section	Revision	Rationale
	~~Eye~~ Complete Ophthalmic Examination The following footnotes were added or edited: (a) If convenient, the Screening and Baseline visits may be combined. (b) Month 24 or early termination visit (c) Any changes in ophthalmic and medical history will be noted post Screening. (d) Blood ~~draw studies~~ samples will include hematology, chemistry and RST-001 immunogenicity testing: see Appendix ~~1~~ 2 details. (e) Topical corticosteroid treatment may be given to the injected eye according to the investigator's standard of care. (f) After the intravitreal injection, the patient will remain in the supine position and (IOP) intraocular pressure will be monitored for at least 30 min. In the event that the IOP is 30 mmHg or above, this will be managed according to Section 5.4.2.	
Section 5 (Table 2)	Added Pregnancy testing at study exit or early termination visit	Added to comply with Allergan standards
Section 5.1 and 5.1.1.	Screening Procedures and Screen Failures removed	Removed to comply with Allergan protocol template.
Section 5.1.1.	Added Section 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.	Administrative change
	Removed section on visit windows	Repetitive information
Sections 5.1.2 to 5.1.13.	The subheadings of each study timepoint were labeled using visit windows instead of visit number. The following assessment titles were modified or added to the bulleted lists for consistency with Table 2 (Study Visit Schedule), where applicable: • Informed consent and authorization • Ophthalmic and ~~M~~medical ~~H~~history~~, concomitant medications~~ • Concomitant medications and procedures • AE review • Physical ~~E~~examination	Administrative change

Section	Revision	Rationale
	• Pregnancy test (blood) • Draw ~~B~~blood sample ~~Draw~~ • Object detection and discrimination • Visual acuity ~~(BCVA, ETDRS)~~ • ~~Visual field testing~~ • ~~Eye exam (full dilated ophthalmic exam)~~ Complete ophthalmic examination • ~~Fundus autofluorescence~~ • Dilated color ~~F~~fundus photography and autofluorescence • ~~Pattern~~ VEP	
Section 5.1.4	Added endnote: After the intravitreal injection, the patient will remain in the supine position and IOP will be monitored for at least 30 min. In the event that the IOP is 30 mmHg or above, this will be managed according to Section 6.5.2	Added to maintain consistency throughout the document.
Section 5.1.13	Added pregnancy test to study exit or early termination visit	Added to maintain consistency throughout the document
Section 5.3.1	For those with low vision, ~~the~~ a verbal consent ~~form~~ will be read out.	Administrative change
Section 5.3.2	Removed bullet: "~~Pertinent family and social history~~"	Modified for better clarity
Section 5.3.4	Symptom-specific examinations may be carried out and recorded during the study as needed ~~necessitated by medically significant events~~.	Modified to provide clarity.
Section 5.3.7	A ~~S~~standard 12-lead ECG will be performed. An interpretation of the ECG will be performed by a qualified physician, ~~cardiologist~~ and a signed report will be issued.	Modified to provide better clarity.
Section 5.3.8	A standard posterior anterior (PA) chest ~~X~~x-ray will be performed. An interpretation of the ~~X~~x-ray will be performed by a qualified physician ~~radiologist,~~ and a signed report will be issued.	Modified for better clarify
Section 5.3.9	The best corrected visual acuity of each eye will be measured ~~performed~~ using ~~the~~ an electronic visual acuity (EVA) ~~ETDRS~~ Early Treatment for Diabetic Retinopathy Study (ETDRS) testing protocol ~~methodology~~, or low vision assessment of hand motion and light perception as described in the Study Procedures Manual.	Modified to provide more details and clarity. Details added to Study Procedures Manual.
Section 5.3.10	Full field sensitivity testing ~~FFST~~ will be performed using the Espion ColorDomeTM LED full-field stimulator (Diagnosys LLC, Lowell, MA) (Klein M, Birch DG, 2009) according to the procedures outlined in the Study Procedures Manual.~~according to standard protocol~~.	Provided more details for clarity.
Section 5.3.11	~~Participants~~ Patients will perform these two tests concurrently, first identifying the location of an LED ~~wall-mounted~~ screen and then identifying a series of standard images (square, circle, triangle, or star) presented on the screen. The color of each shape will either be red or blue. For each image tested, the shape, color, and threshold intensity will be recorded.	Provided more details for clarity.

Section	Revision	Rationale
Section 5.3.12	The pupil responses of both ~~the treated and fellow~~ eyes will be tested using a ~~two semi-automated~~ pupillometry system~~s~~ as described in the Study Procedures Manual.	Modified to provide clarity.
Section 5.3.14	A complete ophthalmic ~~Ophthalmological~~ examination~~s~~ in both eyes will be performed at the Screening and Baseline visits and at each visit after study agent administration. The~~se~~ examination~~s~~ will include a slit lamp biomicroscopic evaluation of the conjunctiva, cornea, anterior chamber, iris, and lens. ~~anterior segment examination, Goldmann tonometry,~~ The ~~dilated~~ posterior segment and fundus will also be evaluated through dilated pupils by indirect ophthalmoscopy. Intraocular pressure will be measured using Goldmann applanation tonometry or a hand held tonometer (using the same instrument for each patient throughout the study, when possible). If Goldmann applanation tonometry is used to measure IOP, then it must be performed after fundus photography and autofluoresence to prevent fluorescein dye from interfering with the images ~~examination~~.	Modified to provide clarity.
Section 5.3.15	Dilated Color Fundus Photography and Autofluorescence A standardized procedure for the collection of ~~S~~single, non-stereo images of the fundus of both eyes will be obtained. Color and autofluorescence images of the fundus will be kept at the site. ~~6.4.16 Fundus Autofluorescence~~ ~~Autofluorescence images of the fundus of both eyes will be obtained.~~	Modified to provide clarity
Section 5.3.16	Added the sentence: Use of the same instrument throughout the study for a given patient is recommended.	Added to provide clear directions to study site.
Section 5.3.17	Electroretinography testing of both eyes will be performed using the ~~F~~full field procedures conducted in accordance with standard protocol provided by the ERG Standardization Committee of the ~~electroretinography (~~to International Society for Clinical Electrophysiology of Vision [(ISCEV)~~]~~ standards~~)~~. Electroretinography will be performed at the Screening visit, 6-months ~~primary end point~~, and ~~conclusion of the study~~ at 24 months (or early termination visit).	Modified to provide clarity.
Section 5.3.19	~~In the event that the patient is unable to complete the questionnaire on their own, the questionnaire will be read to the patient and their answers documented.~~	Removed to provide clarity.
Section 5.4	~~Eligible patients will be treated with a single intravitreal injection of~~ 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. ~~The procedure will be undertaken by the retina-trained faculty physician investigator, except where noted.~~	Details removed and added to Procedure Manual

Section	Revision	Rationale
	[redacted]	
Section 5.4.1	~~Gtts Pred Forte will be given to the injected eye four times daily for two weeks and then twice daily for two weeks.~~ Topical corticosteroid treatment may be given to the injected eye according to the investigator's standard of care.	Modified for better clarity
Section 5.4.2	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 ~~anti-glaucoma~~ medications, oral acetazolamide or anterior chamber paracentesis in order to normalize the intraocular pressure.	Modified to standard Allergan terminology
Section 6.1	Moved all Ocular Safety Measurements prior to Systemic Safety Measurements to correct order of descriptions. The headings are as follows: Section 6.1.1 Ocular Safety Measurements Section 6.1.1.1 Visual Acuity Section 6.1.1.2 Ocular Inflammation Section 6.1.2 Systemic Safety Measurements	Modified for better clarity
Sections 6.1.1 and 6.1.1.1	~~Best corrected~~ visual acuity ~~(BCVA)~~ ~~as measured by EVA modified ETDRS letter score, if possible,~~ as measured ~~or~~ by low vision of assessment of ~~level of~~ hand motion ~~or~~ and light perception.	Modified to provide consistency within the document.
Section 6.2	The following paragraph was modified: 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. ~~All adverse events will be monitored until resolution or stabilization.~~	Added clarity to study sites and following standard Allergan procedures

Section	Revision	Rationale
Section 6.2.1	Removed first sentence: "~~The immunogenicity of the RST-001 product has been evaluated in animal models and it was determined that the doses proposed in this study fall below the Dose Limiting Toxicity.~~"	Modified for clarity. Sentence was not relevant for the section. Immunogenicity in animal models may not necessarily translate to humans.
Section 6.2.4	Modified the following sentence: The Investigator should notify the ~~and~~ sponsor ~~will be informed~~ 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 study exit (Month 24) or early termination visit.	Added to maintain consistency throughout the document
Sections 6.6 to 6.7.2 (original protocol section numbers)	The following sections were removed because these topics are discussed in Section 7.4: Sections 6.6, 6.7, 6.7.1, and 6.7.2.	Redundant Sections were removed to conform to Allergan template
Section 6.8 (original protocol section number)	Removed subheading Long-Term Follow-up Plan	Removed redundant sections within protocol to conform with Allergan template.
Section 7.2.5 (Section number in original protocol)	Removed language regarding patient injury and financial compensation	This will be provided in further detail in the Informed Consent Form
Section 7.4	Modified first paragraph: Enrollment will be suspended pending a complete safety review of all patients including causality to determine the appropriateness of continuing dosing in the occurrence of the following events: ~~immediately suspended in the event that one of the stopping rules below is met:~~	Modified to maintain consistency within the document.
	Removed line item #4: "~~Failure to recruit participants in a practical timescale~~"	Removed to provide clarity
	Added the following: Dose-limiting toxicity (DLT) is defined as any adverse event of Grade 3 or higher that is possibly, probably or definitely related to the study treatment. Dosing will stop if a DLT is observed, including: 4. Severe or persistent ocular inflammation 5. Other significant ocular toxicity (e.g., retinal detachment, evidence of direct toxicity).	Added text for clarity.

Section	Revision	Rationale
Section 8.1	Added the following text: "AEs occurring during the study will be recorded on an AE case report form. If AEs occur, the first concern will be the safety of the study patients. The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study. Phone and fax numbers of relevant Allergan personnel contacts are also on the front page of the protocol."	Modified to align with Allergan standard language.
Section 8.2.3	Added below "or cancers": Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, ~~or~~ the development of drug dependency or drug abuse, or cancers.	Modified to align with Allergan standard language.
Section 8.3.1	Deleted the following sentence: "~~When an AE occurs after written consent has been obtained but prior to the first dose of RST-001, the AE will be considered a non-treatment-emergent AE. An AE that occurs from the time the patient receives his/her first dose of RST-001 until his/her last study visit will be considered a treatment-emergent AE~~."	Sentence deleted to align with Allergan template.
Section 8.3.3	Added bullet point: • Allergan classifies all cancers as SAE's	Added to maintain consistency throughout the document
Section 9	Modified bullet points: • Visual acuity ~~(EVA ETDRS acuity)~~ • Full field ~~Visual field~~ sensitivity ~~(full field sensitivity test)~~ • ~~Navigation and object detection (object detection and discrimination, ambulation)~~ Ambulation • ~~o~~Object detection and ~~(object detection and~~ discrimination~~, ambulation)~~	Modified bullets to provide clarity and keep consistency within protocol.
Section 10.1	Removed all text in Monitoring Section and replaced with Allergan standard language	Modified to align with Allergan standard SOPs
Section 11.1	Added and modified the following: • Change in ~~visual~~ full field sensitivity • Change in ambulation ~~and navigation~~ IOP measurements Changes in ~~A~~anatomical parameters as measured by: • ~~Retinal~~Fundus photography	Modified for clarity. Will be including IOP measurements for safety.
Sections 11.2.1.1 to 11.2.2.2	Removed the 6-month timepoint for the analyses of change in visual acuity, full field sensitivity, ambulation, Fundus photography, and spectral domain-OCT.	6-month time point was added as a secondary endpoint if not captured as a primary endpoint; modified for clarity and consistency.

Section	Revision	Rationale
Section 11.2.1.4	Change in Object Detection and Discrimination Change in object detection and discrimination scores from Baseline to [redacted]. ~~Change in Quality of Life (QOL)~~	Modified to provide clarity.
Section 11.3.2	Listings and descriptive statistics will be provided for baseline characteristics including demographics (race, ethnicity, age, sex,), ~~clinical variables~~ and baseline characteristics (~~temperature, blood pressure, pulse, respiratory rate,~~ height, and body weight)~~, laboratory measurements (hematology, clinical chemistry parameters, and immunogenicity testing), and ocular variables (visual acuity, visual field sensitivity and size, visual function, electrophysiological and anatomical tests).~~	Data provided in other safety listings and not baseline characteristics
Section 11.3.3	~~Safety will be monitored by evaluation of ocular and non-ocular AEs, hematology and clinical chemistry parameters.~~ 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. ~~Adverse events will be coded into MedDRA preferred terms. The number and percentage of participantspatients within each treatment assignment experiencing each specific adverse experience will be tabulated by intensity and by relationship to treatment. For the calculations in these tables, each participant'spatient's adverse experience will be counted once under the maximum intensity or the strongest recorded causal relationship to treatment. A complete listing of serious adverse experiences for each participantpatient will provide details including intensity, relationship to treatment, onset, duration and outcome. Listings and descriptive statistics will be provided for each time point for all laboratory parameters.~~	Modified for consistency throughout the document and to align with the Allergan template.
Section 11.3.6	Enrollment will begin with Group A in Phase 1 and will proceed to subsequent groups after satisfactory review of safety data by a DSMC. After completion of this first phase of the study, ~~participants~~ patients will be treated in Phase IIa ~~part~~ of the study. Before each DSMC review, the investigators and sponsor will prepare a summary of all available data. For DSMC reviews related to enrollment in subsequent groups, this summary will include data ~~at least~~ through a minimum of Month 1 visit ~~6~~ for all available ~~participants~~ patients.	Modified for clarity.
Section 13 and Section 14	Section 13: Data Handling and Record Keeping and Section 14 Data Quality Control and Assurance	Sections were modified to Allergan standard language for clarity.
Section 15	Removed language regarding informed consent and respect for potential and enrolled subjects.	Deleted to align with Allergan template.

Section	Revision	Rationale
Section 16	Removed language regarding protocol deviations.	Deleted to align with Allergan template.
Section 17	Publication Policy section was revised with Allergan standard language	Updated to provide clarity to Investigator and study site
Section 19	Two references were removed: Blacklow et al, 1971 and Maclachlan et al, 2011 Added reference: Klein M, Birch DG	These are not included in the protocol and have been removed from the reference section Klein reference added to verify content.
Section 20	Added Appendix 1: Abbreviations Added Appendix 2: Clinical Laboratory Tests from original protocol. No new information is added. Removed Appendix 2 DSMB Charter, Appendix 3: Investigator Expectations, and Appendix 4: Good Clinical Practice Consolidated Guidance	Added appendix 2 at the end of the protocol as standard Allergan practice. Per Allergan SOPs, these are not necessary to include in the protocol

20.4 Protocol Amendment Summary Amendment 2

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

Protocol RST-001-CP-0001 Amendment 2: (October 2017)

Amendment Summary

This summary includes changes made to Protocol RST-001-CP-0001 Amendment 1 (approved March 06, 2017). The main reasons for this amendment were to 1) incorporate the 13-year long-term follow up period in this protocol, 2) specify that sample size and VA inclusion criteria in Phase 2a are dependent on a DSMC assessment as to whether treatment benefits have been observed in Phase 1, 3) add additional study measures, and 4) add protocol amendment changes made in August 2015 by RetroSense in response to FDA comments after initial protocol review.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized. Deleted text is indicated by strikethrough and added text is underlined, as appropriate. This summary provides a high-level list of changes to the document.

Section	Revision	Rationale
Protocol Synopsis Study Population	Up to approximately 21~~Fifteen (15)~~ patients will be enrolled in this study.	Reflects a potentially larger sample size for Phase 2a
Protocol Synopsis Study Rationale	To provide further guidance toward the design of a pivotal efficacy study, the study also includes the option to expand, by up to ~~6~~approximately 21, the number of patients	Reflects a potentially larger sample size for Phase2
Protocol Synopsis Study Design	• *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 ~~the first cohort of patients (groups A, B, C, each comprising three patients.~~ Phase 1. Patients will receive a single 100 µL intravitreal injection of RST-001 in the study eye. ~~In Cohort 2, up to six~~ In Phase 2a, approximately 6.-12 patients may be enrolled and receive RST-001 at the ~~highest~~ maximum tolerated dose~~ or any dose that has been previously evaluated that is both lower and safe~~. The doses used in the study have been calculated from the pre-clinical animal toxicology studies, as follows: • Low dose = [redacted] vg/eye • Mid dose = [redacted] vg/eye • High dose = [redacted] vg/eye	Changed to reflect incorporation of long-term follow up visits into the existing protocol and to provide further clarity.

Section	Revision	Rationale
	• *Visit Schedule:* • Core Study Visits: Twelve ~~eight~~ visits are planned over 24 ~~6~~ months including the Screening and Baseline visits, Day 0, Day 1, Day 7, and Months 1, 3, ~~and~~ 6, 9, 12, 18, and 24.~~) to reach the primary endpoint.~~ • 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.	
Protocol Synopsis Inclusion Criteria	Phase 1 and Phase 2a: 1. Male or female patients, ≥ 18 years of age at time of informed consent 2. Diagnosis of advanced RP defined as: [redacted] ~~Visual acuity (VA) in the study eye of no better than hand motion~~ ~~VA in the non-study eye of no better than count fingers~~ 3. [redacted] Phase 1: 4. Visual acuity (VA) in the study eye of no-better-than hand motion Phase 2a: 5. The DSMC will review the results from Phase 1 to determine if a documented treatment benefit was observed in the patients. If the DSMC identifies a treatment benefit, no changes will be made to the eligibility criteria. If the DSMC does not identify a treatment benefit, VA eligibility criteria will match that of Phase 1 for half of the enrolled patients. VA criteria for the other half of the enrolled patients must range from no-worse-than count fingers to 20/200 vision in the study eye.	Reflects the potential change in VA criteria for Phase IIa depending on results from Phase I
Protocol Synopsis Exclusion Criteria	6. Use of anti-platelet ~~agents~~and anti-coagulants that may alter ~~coagulation~~clotting within 28 days prior to study treatment administration.	Provides further clarity
Protocol Synopsis Primary endpoints	The primary endpoint is safety at 6 months from ~~Baseline~~ start of study treatment.	Provides further clarity.

Section	Revision	Rationale
Protocol Synopsis Analysis plan	~~No~~The sample size for this study was chosen empirically; no formal sample size computations to meet power requirements were made. ~~The sample size for this study was chosen empirically, as reasonable to answer the primary safety objective.~~ The sample size of approximately 3 patients ~~per single~~for each dose ~~cohort~~group in Phase 1 are typical for ~~Phase I/IIa~~dose escalation studies ~~of this type,~~ , an additional up to approximately 12 patients will be enrolled in Phase 2a for further safety and ~~are expected to provide a sufficient number of observations to meet the objectives of the study~~efficacy evaluation.	Provides further clarity
Section 3.3	Recombinant AAV (rAAV) vectors ~~insert~~are composed of a transgene expression cassette between ~~the~~ inverted terminal ~~repeat~~repeats (ITRs), which guide packaging ~~the~~of vector DNA into AAV capsids.	Provides further clarity
Section 3.4	To date there are no approved products utilizing AAV2 but there are ~~43~~a number of clinical studies that either have been completed or are ongoing worldwide, ~~21 of these are in the United States, 8~~some of which are in the area of ophthalmology, including ~~one in~~indications like neovascular age-related macular degeneration, ~~four in~~ Leber Congenital Amaurosis (LCA), and ~~one in~~ choroideremia.	Removal of outdated information
Section 3.7	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 ~~the second phase. The second phase of the study~~Phase 2a. Phase 2a is aimed at obtaining additional safety data at the ~~highest~~maximum tolerated dose ~~and providing~~. An additional objective of Phase 2a is to provide important additional clinical data to guide the design of future efficacy studies.	Provides further clarity
Section 3.15.1.1	Three groups of patients (A, B, C, each comprising ~~3~~of approximately but no less than three patients) will be enrolled in this study. 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.	Changed to reflect incorporation of long-term follow up visits into the existing protocol.
Section 3.15.1.2	In ~~Cohort 2~~Phase 2a, up to ~~six~~approximately 12 patients may be enrolled and receive RST-001 at ~~this highest~~the maximum tolerated dose. ~~or any dose that has been previously evaluated that is both lower and safe.~~ • 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.	Reflects the potential change in VA criteria for Phase 2a depending on results from Phase 1. Long term follow up is no longer going to be a separate protocol, so that information has been deleted.

Section	Revision	Rationale
	• 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. ~~After completion of the study, each patient will be invited to enroll in a long-term follow-up study, under a separate protocol, for 13 years to monitor the long-term safety of RST 001.~~ 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.	
Figure 1	Phase 2a has been changed to reflect up to 12 patients (original figure had up to 6 patients)	Reflects a potentially larger sample size for Phase 2a
Table 1	Patient size for Phase 2a changed from 6 to 6-12; footnote has been added stating that the number of patient for Phase 2a is dependent upon the DSMC's decision as to whether there's a treatment benefit	Reflects a potentially larger sample size for Phase 2a
Section 3.15.2	The study population consists of patients with advanced RP who have [redacted] This patient group is considered to be a suitable population to assess safety and tolerability in this Phase 1 study. Furthermore, the presence of [redacted] will give a valuable opportunity to evaluate efficacy. ~~Any signal observed will not likely be confused with continued photoreceptor function since these cells will not be present.~~ ~~Fifteen (15)~~Up to approximately 21 patients will be enrolled in this study.	Reflects change in sample size and potential change in enrollment criteria for Phase 2s
Section 3.15.3.1	**Ocular Inclusion Criteria:** ***Phase 1 and Phase 2a*** 1. Diagnosis of advanced RP defined as: [redacted] ***Phase 1*** 3. VA in the study eye of no-better-than hand motion ~~4. VA in the non-study eye of no-better-than count fingers~~	Reflects the potential change in VA criteria for Phase IIa depending on results from Phase I.

Section	Revision	Rationale
	Phase 2a 5. If a treatment benefit is identified by the DSMC: a. VA eligibility criteria will match that of Phase 1. 6. If a treatment benefit is **not** identified by the DSMC: a. VA eligibility criteria will match that of Phase I for half of the enrolled patients. b. VA criteria for the other half of the enrolled patients must range from no-worse-than count fingers to 20/200 vision in the study eye. ~~7. Presence of retinal ganglion cells and/or retinal nerve fiber layer on SD-OCT testing~~	
Section 3.15.3.2	1. Participation in any investigational drug or device study within six months prior to ~~Baseline~~ Day 0; 2. Complicating systemic diseases or clinically significant abnormal baseline laboratory values. Complicating systemic diseases include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (i.e., radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). For the procedure on establishing clinically significant abnormal baseline laboratory values, see Section 5.1.2. 11. Cataract surgery, intraocular and/or peri-ocular injection in the study eye within six months prior to ~~Baseline~~ Day 0	Incorporation of protocol amendments made by RetroSense in response to FDA comments in 2015
Section 4.2	• Low dose = [redacted] vg/eye • Mid dose = [redacted] vg/eye • High dose = [redacted] vg/eye	Provide further clarity
Section 4.3	This is a sequential dose-escalation study. ~~Three~~In Phase 1, three groups, ~~each~~ comprising of approximately but no less than three patients, will be enrolled one after the other, receiving first the low dose, then the mid, and finally the high dose. Escalation is dependent upon the enrollment stopping rules and DSMC recommendation. In Phase 2a, up to ~~an additional six~~approximately 12 patients may then be enrolled in parallel at the maximum tolerated dose.	Reflects change in sample size and provides further clarity.
Section 4.4	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 ~~the first three groups. The fourth dose group~~Phase 1. Phase 2a patients will receive a single intravitreal injection of RST-001 at the ~~highest~~maximum dose tolerated by ~~the prior three groups~~Phase 1 patients.	Provide further clarity.

Section	Revision	Rationale
Section 4.7	The study treatment RST-001 is provided as a sterile frozen liquid and must be stored at [redacted] °C or below. Stability testing indicates RST-001 is stable for at least [redacted] °C or below.	Change requested by CMC
Section 4.9	All study treatment must be returned to Allergan or Allergan designee at the completion of ~~the study~~.patient enrollment.	Changed to reflect the increased duration of the study.
Section 4.12	(i.e., antiplatelets and anticoagulants prior to treatment, and immunosuppressive therapy).	Provide further clarity
Section 5	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). ~~and thereafter according to the table below (Table 2):~~ 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 be invited to participate in a long-term follow-up study for 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.	Changed to reflect incorporation of long-term follow up visits into the existing protocol
Table 2	'Core Study Visits' added to title. Screening date range changed from -90 to -45. Ophthalmic and Medical History performed now at screening, baseline, and day 0. IOP measurement added to table. Footnotes edited.	Minor changes to visit schedule
Table 3	This table was added to show the study visit schedule for long-term follow-up visits.	Changed to reflect incorporation of long-term follow-up visits in to this protocol.
Section 5.1	Please refer to Table 2 and Table 3 for a schematic of the schedule of visits and procedures. IOP has been added to appropriate subheading visits. Ophthalmic and medical history has been removed from visits after Day 0 and replaced with concomitant medications and procedures.	Changed to reflect incorporation of long-term follow-up visits and clarification of study visit procedures.
Section 5.1.2	Prospective patients will be screened for eligibility up to ~~90~~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	Screening period has been shortened; Incorporation of protocol amendments made by RetroSense in response to FDA comments in 2015

Section	Revision	Rationale
	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.	
Section 5.1.13	5.1.13 Month 24 ~~Exit~~ (or Early Termination) Visit	Month 24 is no longer the exit visit
Section 5.1.14	~~5.2~~5.1.14 Long-term Follow Up ~~Protocol~~Visits ~~This study will be conducted under a separate protocol~~. Patients completing the study will participate in a 13-year follow up study. ~~Each~~ Patients completing the Month 24 visit will be asked to report any AEs that occur during this 13-year follow up period. ~~Additionally, from years 1 to 5~~At Months 36, 48, 60, 72, and 84, patients will undergo the following study assessments conducted at ~~a single visit at the end of each year~~yearly clinic visits: • ~~Ophthalmic and medical history~~ • Concomitant medications and procedures • AE review • Visual acuity • Complete ophthalmic examination ~~During years 6-13,~~The procedures for these assessments will be the same as they were for the core study assessments. At Months 96, 108, 120, 132, 144, 156, 168, and 180 patients will not be required to attend for study assessments. Instead, ~~medical history review,~~ concomitant medications and procedures and AE review will be conducted ~~by telephone interview. Patients will continue to be evaluated by their ophthalmological provider and asked to release their medical records for these visits to the investigator at the site where they received the RST-001 study drug~~via annual teleconference interviews.	Changed to reflect incorporation of long-term follow up visits into the existing protocol
Section 5.2.2	Medical History (Review) ~~and Concomitant Medications~~ These will comprise ~~(and be updated throughout the study)~~:	Edited to separate medical history from concomitant medications
Section 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.	Added to separate medical history from concomitant medications
Section 5.2.12	Patients will perform these two tests concurrently, first identifying ~~the location of~~ if a light displayed on an LED screen can be seen and then ~~identifying~~if a series of standard images (square, circle, triangle, or star) presented on the screen can be identified.	Provide further clarity

Section	Revision	Rationale
Section 5.2.16	Intraocular Pressure (IOP) IOP measurements will be performed in both eyes at every study visit except on treatment day (Day 0), where there will be a pre- and post-injection IOP measurement in the study eye only. After the intravitreal injection, the patient will remain in the supine position and IOP will be monitored for at least 30 minutes. In the event that the intraocular pressure is 30 mmHg or above, it will be managed according to Section 5.3.2.	Added for clarity
Section 5.2.17	Color and autofluorescence images of the fundus will be ~~kept~~maintained at the site until completion of Phase 2a.	Provide further clarity
Section 5.2.18	Retinal anatomy of both eyes will be evaluated by SD-OCT scans at the Screening visit, Baseline visit, and each monthly visit after study treatment administration through Month 24.	Added for clarity, given SD-OCT will not be conducted during long-term follow up.
Section 5.3	~~After the intravitreal injection, the patient will remain in the supine position and IOP will be monitored for at least 30 minutes. In the event that the intraocular pressure is 30 mmHg or above, it will be managed according to Section 5.4.2.~~	Moved to Section 5.2.16
Section 6.1.1.2	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.	Incorporation of protocol amendments made by RetroSense in response to FDA comments in 2015
Section 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] These tests will be performed at several timepoints during the study: baseline (pre-dose) [redacted] Treatment of intraocular inflammation and immunogenicity In the event that immunogenicity is suspected by the investigator, topical, local, intraocular or systemic corticosteroid, corticosteroid-sparing and immunomodulatory therapy may be initiated, usually in an escalating fashion, in accordance with the investigator's practice, to control the inflammation. The patient will continue in the study and all additional assessments and visits will be documented in the source documents.	Incorporation of protocol amendments made by RetroSense in response to FDA comments in 2015
Section 6.2.4	Female patients of childbearing potential will require a pregnancy test at ~~study exit~~Month 24 or early termination visit.	Month 24 is no longer study exit

Section	Revision	Rationale
Section 7.3	2. Advise on dose-escalation, Phase 2a sample size/study population, study suspension or termination, as appropriate. 3. Provide review and advice on protocol amendments and changes to the clinical protocol, as appropriate. 4. Provide advice on any other matters as deemed necessary for the safe conduct of the study. 5. Provide assessment as to whether treatment benefits have been observed in Phase 1 of the study.	Reflects the responsibility of establishing the cohort size and eligibility for Phase 2a
Section 7.4	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: 1. Any Grade 3 or greater AE related to RST-001 (according to Common Terminology Criteria for Adverse Events v4.03) 2. Occurrence of an intraocular infection related to contaminated RST-001 that required treatment would serve as a stopping rule. ~~Any evidence that the delivered product carries an infectious agent~~ 3. A safety issue has been identified that compromises the benefit or increases the risk balance Dose-limiting toxicity (DLT) is defined as any adverse event of Grade 3 or higher that is ~~possibly, probably or definitely~~expected ~~to~~ to be related to the study treatment. ~~Dosing~~Dose escalation will stop if a DLT is observed, including:	Incorporation of protocol amendments made by RetroSense in response to FDA comments in 2015
Section 8	The entire Adverse Events section has been removed and replaced with language that aligns with Allergan standards	Change to Allergan standards for consistency in AE reporting
Section 11.2.1.1	Change in visual acuity in the ~~treated~~study eye from Baseline (defined as last observed value prior to dosing) to [redacted].	Edited for clarity.
Section 11.3.1	~~No~~The sample size for this study was chosen empirically; no formal sample size computations to meet power requirements were made. ~~The sample size for this study was chosen empirically, as reasonable to answer the primary safety objective.~~ The sample size of approximately 3 patients ~~per single~~ for each dose ~~cohort and a total of 15 patients~~ group in Phase 1 are typical for ~~Phase I/IIa~~dose escalation studies ~~of this type, and are expected to provide a sufficient number of observations to meet the objectives of the study~~, an additional up to approximately 12 patients will be enrolled in Phase 2a for further safety and efficacy evaluation.	Reflects a potentially larger sample size

Section	Revision	Rationale
Section 11.3.4	Efficacy will be measured by evaluation of visual acuity, full field sensitivity, ambulation, quality of life and electrophysiological measures (visual evoked potentials, electroretinography). Visual acuity data will be presented as the number of letters correctly identified at each time point and the calculated logMAR and Snellen equivalent values., or as count fingers, hand motion, and light perception. The Quality-of-life ~~questionnaires~~questionnaire will be scored using the NEI VFQ-25 scoring algorithm.	Edited for clarity
Section 11.3.5	Immune responses will be measured ~~quantitatively~~ (qualitatively along with [redacted]	Edited for clarity
Section 11.3.6	~~Enrollment will begin with Group A in Phase 1 and will proceed to subsequent groups after satisfactory review of safety data by a DSMC. After completion of this first phase of the study, patients will be treated in Phase IIa of the study.~~ ~~Before each DSMC review, the investigators and sponsor will prepare a summary of all available data. For DSMC reviews related to enrollment in subsequent groups, this summary will include data through a minimum of Month 1Visit for all available patients.~~ 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.	Edited for clarity
Section 17	~~Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements~~	Removed to align with Allergan's publication policy standards.

20.5 Protocol Amendment Summary Amendment 3

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

Protocol RST-001-CP-0001 Amendment 3: (August 2022)

Amendment Summary

This summary includes changes made to Protocol RST-001-CP-0001 Amendment 2 (approved October 19, 2017). The main reason for this amendment was to reduce the long-term follow-up period from 13 years to 3 years in this protocol.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized. Deleted text is indicated by strikethrough and added text is underlined, as appropriate. This summary provides a high-level list of changes to the document.

Section	Revision	Rationale
Title Page	[redacted], MD Tel (office): Tel (mobile) [redacted] Email: [redacted] ~~[redacted], MD~~ ~~Tel (office):~~ ~~Tel (mobile)~~ [redacted] ~~Fax: +1 714 571 2587~~ ~~Email:~~ [redacted]	Change from Medical Safety Physician to Medical Monitor
Title Page	[redacted] ~~, MD~~ [redacted] ~~Allergan – Global Drug Development~~	Remove Allergan signatory to align with current SOPs
Section 2, Protocol Synopsis		Reduce long-term follow-up
Study Design	*Duration:* 2 years (with an additional ~~1~~3 years of long-term follow-up)	
Visit Schedule	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 ~~1~~3 years to monitor the long-term safety of RST-001. This includes a yearly visit for ~~5~~ 3 years (Months 36, 48, and 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.~~	
Section 3.15.1.1, Enrollment Phase 1	After completion of the 2-year core study visits, each patient will be enrolled in a long-term follow-up for an additional ~~1~~3 years to monitor the long-term safety of RST 001.	Reduce long-term follow-up

Section	Revision	Rationale
Section 3.15.1.2, Enrollment Phase 2a	After completion of the 2-year core study visits, each patient will be enrolled in a long-term follow-up for an additional ~~1~~3 years to monitor the long-term safety of RST-001.	Reduce long-term follow-up
Section 5, Study Assessments and Intravitreal Injection	• 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~~ 3 years (Months 36, 48, and 60~~, 72, and 84~~) ~~and yearly teleconference interviews for 8 years (Months 96, 108, 120, 132, 144, 156, 168, and 180)~~. Table 3: Removed columns for Month 72 and 84 visits and all teleconference interviews	Reduce long-term follow-up
Section 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 ~~1~~3-year follow-up period. At Months 36, 48, and 60~~, 72, and 84~~, patients will undergo the following study assessments conducted at yearly clinic visits: • Concomitant medications and procedures • AE review • Visual acuity • Complete ophthalmic examination The procedures for these assessments will be the same as they were for the core study assessments. ~~At Months 96, 108, 120, 132, 144, 156, 168, and 180 patients will not be required to attend for study assessments. Instead, concomitant medications and procedures and AE review will be conducted via annual teleconference interviews.~~	Reduce long-term follow-up
Section 11.3.6, Interim Analysis	No interim analysis is planned. There will be ~~three~~ two database locks. The primary analysis will occur when all patients have completed the Month ~~6~~ 24 visit, or exited ~~earlier~~ early from the study. 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.~~	Reduce the database locks from three to two and revise the timing for the primary analysis

20.6 Protocol Amendment Summary Amendment 4

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 RST-001-CP-0001 Amendment 4: (November 2022)

Amendment Summary

This summary includes changes made to Protocol RST-001-CP-0001 Amendment 4 (approved November 22, 2022). The main reason for this amendment was to include content related to virtual visits in case of COVID-19 and COVID-19 infection reporting, update contact information for AE reporting, and clarify timing for the final analysis.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized. Deleted text is indicated by strikethrough and added text is underlined, as appropriate. This summary provides a high-level list of changes to the document.

Section	Revision	Rationale
Section 5, Study Assessments and Intravitreal Injection	Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as telephone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort is to be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed. During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed with agreement from the sponsor: • If permitted by local regulations, the IRB/IEC, and the subject, postbaseline visits may be conducted virtually. • Study Visits and/or activities are to be performed as scheduled whenever possible.	Provide content related to virtual visits in case of COVID-19
Section 5.1.1, Informed Consent and Patient Privacy	Due to the COVID-19 pandemic, it is possible that protocol modifications may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.	Provide content related to virtual visits in case of COVID-19

Section	Revision	Rationale
Section 5.2.3, Concomitant Medications and Procedures	Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit) to prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated. The decision to receive a locally available vaccine is to be based on local guidance and an individual discussion between the treating physician and the subject. The potential impact of RST-001 on SARS-CoV-2 vaccination is unknown.	Provide content related to the SARS-CoV-2 vaccination
Section 5.2.4, Adverse Event Review	COVID-19 infections should be reported as AEs.	Provide content for reporting COVID-19 infections
Section 8.2, Procedures for Reporting Adverse Events	SARS-CoV-2 infections are to be captured as AEs. If the event meets the criteria for a serious adverse event, then follow the serious adverse event reporting directions. Reactions known to be associated with the SARS-CoV-2 vaccine are to be reported as AEs. If the event meets the criteria for a serious adverse event, then follow the serious adverse event reporting directions.	Provide content for reporting COVID-19 infections
Section 8.3, Procedures for Reporting a Serious Adverse Event	Pregnancy While not an AE, pregnancy in a study participant must be reported to Allergan within 24 hours after the site becomes aware of the pregnancy. If a pregnancy occurs in a study participant or in the partner of a study participant, information regarding the pregnancy and the outcome will be collected. The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to Allergan within 24 hours after the site becomes aware of the event.	Provide content for reporting pregnancies.
Section 10.1, Monitoring	During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.	Provide content for remote data review
Section 11.3.6, Interim Analysis	No interim analysis is planned. There will be ~~two~~one database lock~~s~~ for the final analysis. ~~The primary 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 Month 60 visit or exited early from the study~~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.	Reduce the database lock from two to one and clarify the timing for the primary analysis