1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN - Clinical Study Report

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
Development Phase:	Phase 1/2a
Product Name:	RST-001 (AGN-151597)
Study Statistician:	[redacted] PhD
Sponsor:	Allergan, Inc. 2525 Dupont Drive Irvine, California USA 92612 [redacted]

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
eCRF	electronic Case Report Form
ECG	electrocardiogram, electrocardiographic
ERG	Electroretinography
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
PCS	potentially clinically significant
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SI	*Le Système International d'Unités* (International System of Units)
SOC	System Organ Class
TEAE	treatment-emergent adverse event
VEP	Visual Evoked Potentials

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the safety and efficacy data as specified in the current protocol of Study RST-001-CP-0001 (amendment #2 dated 19 Oct 2017). Specifications of tables, figures, and data listings are contained in a separate document.

Study RST-001-CP-0001 is a Phase 1/2a, open-label, dose-escalation, non-randomized study of safety and tolerability of Intravitreal RST-001 in patients at least 18 years of age who have been diagnosed with advanced RP using criteria including clinical diagnosis, documented retinal electrophysiological evidence of rod-cone photoreceptor degeneration and baseline evidence of <10 microvolts (μV) maximal b-wave electroretinography (ERG) response.

The length of this study participation will be 2 years with an additional 13 years of long-term follow-up.

Patients meeting the inclusion/exclusion criteria will receive a single 100 μL intravitreal injection of RST-001 in the study eye. In Phase 1, three doses of RST-001 (low, mid and high), each group compromising of approximately but no less than three patients) will be evaluated by sequential dose escalation. In Phase 2a, up to 12 patients may be enrolled and receive RST-001 at the maximum tolerated dose. Patients who withdraw from the study prior to receiving the study treatment may be replaced.

The three doses of RST-001 are as follows:

	LOW Dose	***MID Dose***	***HIGH Dose***
RST-001	[redacted] vg/eye	[redacted] vg/eye	[redacted] vg/eye

The study design is shown graphically in Figure 4-1. The dose-escalation cohorts are illustrated in Table 4–1 below. The schedule of evaluations for Study RST-001-CP-0001 is presented in 2 and Table 4-3.

'igure 4–1. Overview of the Treatment Schedule

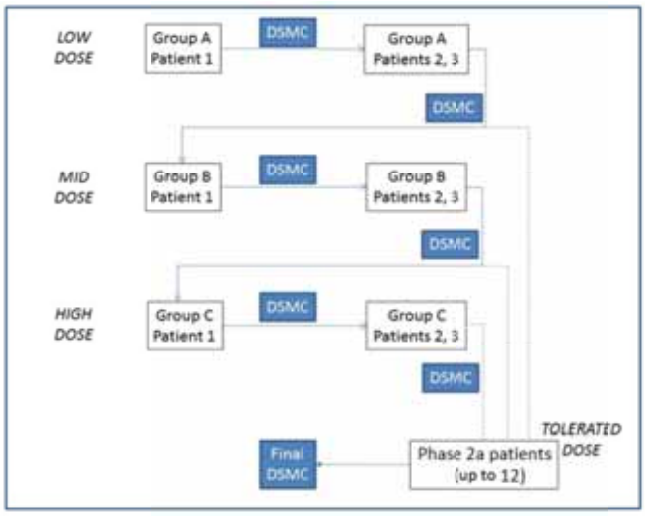

Table 4–2. Dose Escalation

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.

Table 4–3. 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		[redacted]									
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]												

[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 Protocol 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 protocol (Section 5.3.2).

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

Table 4–4. Study Visit Schedule: Long-term Follow-up Visits

	Months												
	Clinic Visits					**Teleconference Interviews**							
Visit Windows (Month ± Days)	36 ± 30	48 ± 30	60 ± 30	72 ± 30	84 ± 30	96 ± 30	108 ± 30	120 ± 30	132 ± 30	144 ± 30	156 ± 30	168 ± 30	180 ± 30
Concomitant medications and procedures	X	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	X
Visual Acuity	X	X	X	X	X								
Complete Ophthalmic Examination	X	X	X	X	X								

5.0 OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the safety of a single intravitreal injection of RST-001.

The secondary objectives of this study are

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

The therapy will be considered safe in the absence of any grade 3 or greater AE considered related to RST-001.

Other safety measurements for the primary objective will be assessed by visual function measures at [redacted] including:

- Change in visual acuity (VA) from baseline (defined as last observed value prior to dosing) in the study eye
- Change in full field sensitivity from baseline in the study eye
- Change in ambulation scores from baseline
- IOP measurements from baseline in the study eye
- Change in anatomical parameters from baseline as measured in the study eye:
    - Fundus photography
    - Spectral domain-OCT (SD-OCT)

The effect of intravitreal injection of RST-001 in improving visual function as measured by a series of psychophysical, electrophysiological and anatomical measures.

The secondary endpoints include the following efficacy measures of change in visual function:

- Change in VA in the study eye from baseline to [redacted]
- Change in full field sensitivity in the study eye from baseline to [redacted]
- Change in ambulation scores from baseline to [redacted]

- Change in object detection and discrimination scores from baseline to [redacted]
- Change in visual evoked potentials (VEP) and electroretinography (ERG) scores from baseline to [redacted]
- Change in composite score of NEI VFQ-25 scores from baseline to [redacted]

The secondary endpoints also include the following measures of anatomical endpoints relating to retinal integrity and survival:

- Qualitative assessment of the change in retinal appearance (fundus photography) from baseline to [redacted]
- Qualitative assessment of the change in retinal cross-sectional appearance (SD-OTC) from baseline to [redacted]

6.0 PATIENT POPULATIONS

6.1 ENROLLED POPULATION

The Enrolled Population will consist of all patients who signed the informed consent and receive a participant ID number.

6.2 SAFETY POPULATION

The Safety Population will consist of all patients in the Enrolled Population who received at least 1 dose of study treatment. The safety analysis will be based on the actual treatment assigned.

This population will be used for all analyses unless otherwise specified.

7.0 PATIENT DISPOSITION

Disposition will be summarized by the number and percentage of patients in each treatment group separately for each phase. The total number of patients screened will be summarized.

Screen-failure patients (i.e., patients screened but not enrolled) and the associated reasons for fail to enroll will be tabulated for the all screened patients. The number and percentage of patients who complete each study phase (Phase 1 or 2a) and patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups separately for each phase. The reasons for premature discontinuation from the corresponding study phases will be summarized (number and percentage) by treatment group separately for each phase. All patients who prematurely discontinue during the corresponding-study phases will be listed by discontinuation reason.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; age group; race; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group separately for each phase.

The number and percentage of patients with medical histories in each system organ class and preferred term will be summarized by treatment group separately for each phase. In addition, ocular medical history will be summarized for the study eye by treatment group separately for each phase.

Concurrent procedure is defined as any procedure performed on or after the date of the first dose of study treatment. The number and percentage of patients with concomitant procedures in each system organ class and preferred term will be summarized by treatment group separately for each phase. In addition, ocular medical history will be summarized for the study eye by treatment group separately for each phase.

Medical histories and concomitant procedures will be coded using the MedDRA, version 21.0 or newer.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. *Concomitant medication* is defined as any medication taken on or after the date of the first dose of study treatment. The World Health Organization (WHO) Drug Dictionary Enhanced will be used to classify prior and concomitant medications by therapeutic class and drug name.

The number and percentage of patients with prior medications will be summarized under each drug class and drug name by treatment group separately for each phase. A separate summary for prior ocular medications used in the study eye under each drug name by treatment group separately for each phase. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc.) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the course of the study and may be pooled under a single coded drug name for analyses.

Similarly, the number and percentage of patients with concomitant medications will be summarized under each drug class and drug name by treatment group separately for each phase separately for Core Study Visits and Long-term Follow-up Visits. A separate summary for concomitant ocular medications used by eye (study eye and fellow eye) under each drug name by treatment group separately for each phase separately for Core Study Visits and Long-term Follow-up Visits.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Number and percent of patients exposed to the study treatment will be summarized by treatment group separately for each phase.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

This is a single dose study and thus treatment compliance is not applicable.

10.0 EFFICACY ANALYSES

All analyses will be based on the observed data. *Baseline* for efficacy is defined as the last non-missing efficacy assessment before the first dose of study treatment. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

The efficacy parameter will be the change from baseline VA, full field sensitivity, ambulation, object detection discrimination, VEP, ERG, QoL (composite score of NEI VFQ-25 scores) for the study eye at the scheduled Post-treatment visits and will be summarized by visit and by treatment group separately for each phase.

The NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one additional general health item. The 11 subscales are general vision (item 2), difficulty with near vision activities (items 5, 6, 7), difficulty with distance vision activities (items 8, 9, 14), limitations in social functioning due to vision (items 11, 13), role limitations due to vision (items 17, 18), dependency on others due to vision (items 20, 23, 24), mental health symptoms due to vision (items 3, 21, 22, 25), driving difficulties (items 15c, 16, 16a), limitations with peripheral vision (item 10), limitation with color vision (item 12), and ocular pain (items 4, 19). The general health item is item 1.

Responses to individual questions are recoded to scores using the following scoring system, with a higher score representing better functionality. For example, for question 1, a score of 100 is applied for a response of "1." The summary score for each subscale is determined by taking the average across multiple items within each corresponding subscale. For subscales calculated based on multiple questions, at least one non-missing response is required (i.e., at least one question is answered). The overall composite score is then calculated by averaging over all 11 vision-targeted subscale scores, excluding the general health score. Items or subscales that are left blank are excluded from the calculation of average scores; e.g., if any of the 11 subscale scores is missing, the overall composite score will be calculated based on the mean of the non-missing subscales.

Table 10–1 VFQ-25 Coded Values for Each Item

Items	Response Level	Coded value
1, 3, 4, 15c[a]	1	100 (best)
	2	75
	3	50
	4	25
	5[b]	0 (worst)
2	1	100 (best)
	2	80
	3	60
	4	40
	5	20
	6	0 (worst)
5-14, 16, 16a	1	100 (best)
	2	75
	3	50
	4	25
	5	0 (worst)
	6	Missing
17-25	1	0 (worst)
	2	25
	3	50
	4	75
	5	100 (best)

a Value assigned to Item 15c also depends on the response to 15b as follows: if 15b = 1 (mainly eyesight), then 15c is set to 5 and recoded to 0; if 15b = 2 (mainly other reasons) or 3 (both eyesight and other reasons), then 15c is set to missing

b Item 15c has 4 response levels and is expanded to 5 levels when 15b = 1

11.0 SAFETY ANALYSES

Safety assessments in this study are divided into measures of ocular safety and measures of systemic safety (Protocol Section 6.1). The safety parameters will include adverse events (AEs), ocular measurements, clinical laboratory tests including immunogenicity tests, vital signs, and ECG parameters. For each safety parameter, the last non-missing assessment before the first dose of study treatment will be used as the baseline for all analyses.

11.1 ADVERSE EVENTS

Adverse events will be coded using *MedDRA,* version 21.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of study treatment or was present before the date of the first dose of study treatment and increased in severity after the first dose of study treatment. If more than 1 AE was reported before the first dose of study treatment and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the reporting periods.

The number and percent of patients reporting TEAEs will be tabulated by treatment group in each phase separately during Core Study Visits and Long-term Follow-up Visits for the following categories:

- All TEAEs
- Treatment related TEAEs
- Ocular TEAEs in the study eye
- Non-ocular TEAEs
- Treatment-related ocular TEAEs
- Serious TEAEs
- Deaths
- AEs leading to study discontinuation

The above categories will also be tabulated by SOC and PT, or by PT only for ocular related categories, with the number and percentage of patients by treatment group in each phase and separately during Core Study Visits and Long-term Follow-up Visits, except for the last 3 categories.

In addition, the number and percent of patients will be tabulated by SOC, PT, and severity, or by PT and severity only for ocular related categories, with the number and percentage of patients by treatment group in each phase and separately during Core Study Visits and Long-term Follow-up Visits for the following categories:

- All TEAEs
- Treatment related TEAEs
- Ocular TEAEs in the study eye
- Non-ocular TEAEs
- Treatment-related ocular TEAEs

If more than 1 AE is coded to the same PT for the same patient, the patient will be counted only once for that PT using the greatest severity and strictest causality for the summarization by severity and causal relationship.

Separate tabular displays will be presented for patients who died, patients with SAEs, and patients with AEs leading to premature discontinuation.

11.2 PRIMARY OCULAR SAFETY MEASUREMENTS

The following visual function measures at 6 months are considered primary safety endpoints. They will be listed and summarized by treatment group separately in each phase.

- Change from baseline in visual acuity in the study eye
- Change from baseline in full field sensitivity in the study
- Change from baseline in ambulation
- IOP measurements in the study eye
- Changes from baseline in anatomical parameters as measured in the study eye by:
    - Fundus photography - Qualitative assessment of the retinal appearance
    - Spectral domain-OCT (SD-OCT) - Qualitative assessment of the retinal cross-sectional appearance

11.3 SECONDARY OCULAR SAFETY MEASUREMENTS

The following ocular safety measures (excluding the primary safety endpoints at 6 months as described in Section 11.2) and their change from baseline values will be listed and summarized by visit and by treatment group separately in each phase. Data collected from the extended follow-up will be included in data listings.

- Change in visual acuity in the study eye from Baseline (defined as last observed value prior to dosing) to [redacted]
- Change in full field sensitivity in the study eye from Baseline to [redacted]
- Change in ambulation scores from Baseline to [redacted]
- Change in object detection and discrimination scores from Baseline to [redacted]
- Change in VEP and ERG scores from Baseline to [redacted]
- Anatomical parameters as measured in the study eye by:
    - Fundus photography - Qualitative assessment of the change in retinal appearance from Baseline to [redacted]
    - Spectral domain-OCT (SD-OCT) - Qualitative assessment of the change in retinal cross-sectional appearance from Baseline to [redacted]

11.4 OTHER OCULAR SAFETY MEASUREMENTS

Other ocular safety measurements include the following assessments during the core study visits and clinic visits of the long-term follow-up visits:

- IOP measurements in the study eye (other assessment at month 6 which is the primary endpoint)
- Findings in the study eye from ocular biomicroscopic examination (Table 11.4–1)
- Findings in the study eye from ophthalmoscopy examination (Table 11.4–2)

Table 11.4–1. Findings and Severity from Ocular Biomicroscopic Examination

Biomicroscopic Eye Area	***Findings***	***Severity[a]***
Eyelids/eyelid margins/lashes	Erythema Edema Crusting Other	+0.5 (Trace) +1 (Mild) +2 (Moderate) +3 (Severe) Not Applicable
Conjunctiva (bulbar or palpebral)	Hyperemia Edema Subconjunctival Hemorrhage Discharge Blanching Follicles Pterygium, encroaching on visual axis Pterygium, not encroaching on visual axis Other	+0.5 (Trace) +1 (Mild) +2 (Moderate) +3 (Severe) Not Applicable
Cornea: • Central Cornea • Peripheral Cornea • Central and Peripheral Cornea	Punctate Epithelial Staining Filaments Infiltrates Edema Corneal Guttata Endothelial Pigment Keratic Precipitates Neovascularization Opacity/Opacities Stromal Haze Other	+0.5 (Trace) +1 (Mild) +2 (Moderate) +3 (Severe) Not Applicable
Anterior chamber	Cells Flare Anterior Synechiae Hypopyon, Details and Levels (mm) Hyphema, Details and Levels (mm) Other	0 (<1 cell, None) +0.5 (1-5) +1 (6-15, Faint) +2 (16-25, Moderate) +3 (26-50, Marked) +4 (>50, Intense (including fibrin)) Not Applicable
Iris/pupil	Rubeosis Iridis, anterior chamber angle involved Rubeosis Iridis, anterior chamber angle not involved Afferent Pupillary Defect (APD) Other	Not Applicable

[a] Severity for Anterior chamber cells and flare are included before or after '/', respectively.

Table 11.4–2. Findings and Severity from Ophthalmoscopy Examination

Ophthalmoscopy Eye Area	***Findings***	***Severity[a]***
Optic Nerve	Cup/Disc Ratio (Value range 0.0 - 1.0)	Not Applicable
Vitreous	Cells Vitreous Haze Vitreous Hemorrhage Posterior Vitreous Detachment Other	+0.5 (None, No Haze) +1 (Minimal, Trace) +2 (Mild, 1+) +3 (Moderate, 2+) +4 (Marked, 3+) +5 (Severe, 4+) Not Evaluable Not Applicable
Optic Nerve	Disc Hemorrhage Other	Not Applicable
Macula	Intraretinal Fluid Subretinal Fluid Intraretinal Hemorrhage Subretinal Hemorrhage Rhegmatogenous Detachment Tractional Detachment Pigment Epithelial Detachment Other	Not Applicable
Fundus	Other	Not Applicable
Retina Periphery	Retinal Hemorrhage Retinal Tear Rhegmatogenous retinal detachment, macula center attached Rhegmatogenous retinal detachment, macula center detached Tractional retinal detachment, macula center attached [Tractional retinal detachment, macula center detached Exudative retinal detachment, macula center attached Exudative retinal detachment, macula center detached Other retinal detachment Round (Atrophic) Retinal Hole Lattice Degeneration Other	Not Applicable

[a] Severity for Vitreous flare and Vitreous Haze are included before or after ‘,’, respectively.

The findings from both ocular biomicroscopic and ophthalmoscopy examinations with prespecified terms will be coded using MedDRA, version 21.0 or newer.

Descriptive statistics for IOP measurements and changes from the baseline values at each visit will be presented by treatment group separately for each phase.

Similarly, descriptive statistics for cup/disc ratio measurements from ophthalmoscopy examination and changes from the baseline values at each visit will be presented by treatment group separately for each phase.

The number and percent of patients with more than one grade increase from baseline for any findings will be summarized by preferred term and by treatment group separately for each phase.

11.5 IMMUNOLOGICAL TESTS

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]

Immune responses will be measured qualitatively along with [redacted] Immunogenicity results will be reported as positive or negative. The number and percent of patients with total negatives including patients with negative neutralizing antibody results as well as with negative binding antibody results will be tabulated at each visit by treatment group separately for each phase. A cumulative analysis that enumerate the number and percent of patients with positive antibody findings at any visit will be performed. Titer data will be summarized by means, standard deviations, minimum, and maximum.

11.6 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each visit will be presented by treatment group separately for each phase for the following laboratory parameters as specified in the protocol amendment 2 (Section 20.2). Only patients with clinical laboratory data at baseline and at least one Post-treatment visit will be included in the summary.

CBC: complete blood count includes 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), and Platelet count.

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

Liver function test include Albumin, Bilirubin, Total protein, Calcium, Alkaline, Phosphatase, AST (SGOT), ALT (SGPT), and Triglycerides.

Pregnancy test results from screening, baseline, and Month 24 will be listed.

Similarly, serology test results from screening visit only will be listed.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in **Error! Reference source not found.**. The number and percentage of patients who have PCS Post-treatment clinical laboratory values will be tabulated by treatment group separately for each phase. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 Post-treatment assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS Post-treatment value. A supportive tabular display of patients with PCS Post-treatment values will be provided, including the participant ID number, baseline and all Post-treatment (including non-PCS) values.

Table 11.6–1. Criteria for Potentially Clinically Significant Laboratory Results

Laboratory Parameter	*SI Unit*	*Conversion Factor*[a]	*Conventional Unit*	*PCS Criterion*[b] *Low Value*	*PCS Criterion*[b] *High Value*
Hematology					
Hemoglobin	g/L	0.1	g/dL	< 0.9 × LLN	—
Hematocrit	Volume fraction	100	%	< 0.9 × LLN	—
Eosinophils	%	1	%	—	> 10
Neutrophils	%	1	%	< 30	> 90
Basophils	%	1	%	—	> 6
Monocytes	%	1	%	—	> 20
Lymphocytes	%	1	%	< 10	> 60
Absolute neutrophil count	$\times 10^9$/L	1	1000/µL	< 1.0	—
Platelet count	$\times 10^9$/L	1	1000/µL	≤ 75	≥ 700
White blood cell count	$\times 10^9$/L	1	1000/µL	≤ 2.5	≥ 15
Chemistry					
Albumin	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN

Table 11.6–1. Criteria for Potentially Clinically Significant Laboratory Results

Laboratory Parameter	***SI Unit***	***Conversion Factor[a]***	***Conventional Unit***	***PCS Criterion[b] Low Value***	***PCS Criterion[b] High Value***
Alkaline phosphatase	U/L	1	U/L	—	≥ 3 × ULN
Alanine aminotransferase (ALT)	U/L	1	U/L	—	≥ 3 × ULN
Aspartate aminotransferase (AST)	U/L	1	U/L	—	≥ 3 × ULN
Gamma-glutamyl transferase (GGT)	U/L	1	U/L	—	≥ 3 × ULN
Lactate dehydrogenase (LDH)	U/L	1	U/L	—	≥ 3 × ULN
Blood urea nitrogen or Urea	mmol/L	2.8011	mg/dL	—	> 1.2 × ULN
Calcium	mmol/L	4.008	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	1	mg/dL	< 0.9 × LLN	> 1.1 × ULN
Total cholesterol	mmol/L	38.6698	mg/dL	—	> 1.3 × ULN
High-density lipoprotein (HDL) cholesterol	mmol/L	39	mg/dL	< 0.8 × LLN	—
Low-density lipoprotein (LDL) cholesterol	mmol/L	39	mg/dL	—	> 1.2 × ULN
Creatine phosphokinase (CPK)	U/L	1	U/L	—	> 1.5 × ULN
Creatinine	µmol/L	0.0113	mg/dL	—	> 1.3 × ULN
Glucose, fasting	mmol/L	18.018	mg/dL	< 0.8 × LLN	> 1.2 × ULN
Magnesium	mmol/L	2	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	1	mEq/L	< 0.9 × LLN	> 1.1 × ULN
Total bilirubin	µmol/L	0.0585	mg/dL	—	> 1.5 × ULN
Total protein	g/L	0.1	g/dL	< 0.9 × LLN	> 1.1 × ULN
Triglycerides, fasting	mmol/L	88.4956	mg/dL	—	> 1.2 × ULN
Uric acid or Urate	µmol/L	0.0168	mg/dL	—	> 1.1 × ULN

a Conversion factor from SI units to conventional (traditional) units.
b Criteria refer to SI units.
Blood urea nitrogen or Urea are the same parameters, and Uric acid or Urate are the same parameters.
LLN = lower limit of normal; PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal laboratory reference range.

11.7 VITAL SIGNS

Descriptive statistics for vital signs (respiratory rate, temperature, systolic and diastolic blood pressures, and pulse rate) and changes from baseline values at each visit will be presented by treatment group separately for each phase.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.7–1. The number and percentage of patients with PCS Post-treatment values will be tabulated by treatment group separately for each phase. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 Post-treatment assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS Post-treatment value. A supportive tabular display of patients with PCS Post-treatment values will be provided, including the participant ID number, baseline and all Post-treatment (including non-PCS) values.

Table 11.7–1. Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***[a]	
		Observed Value	*Change From Baseline*
Sitting systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A Post-treatment value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.

bpm = beats per minute.

11.8 ECG AND X-RAY

ECG and X-ray data will be collected only at screening. An interpretation of the ECG will be listed and summarized by treatment group separately for each phase. An interpretation of the x-ray will be listed.

11.9 OTHER SAFETY PARAMETERS

11.9.1 Physical Examination

The physical examination will be performed at screening visit, [redacted] Physical examination findings from screening visit will be recorded on the Medical and Surgical History eCRF. Physical Examination findings at [redacted] or changes (worsening) since the previous physical examination, will be recorded on the Adverse Events eCRF. Summaries for medical/surgical history and adverse events are described in Sections 8.0 and 11.1, respectively.

12.0 INTERIM ANALYSIS

There will be three database locks. The primary analysis will occur when all patients have completed the Month 6 visit or exited earlier. The second analysis will occur when all patients have completed the Month 24 visit or exited early from the study. The final analysis will occur when all patients have completed the long-term follow-up or have been lost to follow-up.

13.0 DETERMINATION OF SAMPLE SIZE

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.

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

15.0 DATA HANDLING CONVENTIONS

15.1 SUMMARY STATISTICS

The following statistical summaries will be presented for each type of data. Further details are specified in the tables, figures, and listings shells.

- Continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum values).
- Categorical variables will be summarized by frequency distributions (counts and percentages).
- The results for ocular related assessments in the fellow eye will be summarized across the treatment groups, if applicable.

15.2 VISIT TIME WINDOWS

Table 15.2–1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 15.2–1. Visit Time Windows

Derived Visit	***Scheduled Visit (Target Day[a])***	***Window***
Baseline	Day -45 to 0	Days < 0
Day 0	Treatment Visit (Day 0)	Day 0
Day 1	Post Injection Visit (Day 1)	Day 1
Day 7	Day 7 (7)	Days (2, 12)
Month 1	Month 1 (30)	Days (13, 47)
Month 3	Month 3 (91)	Days (48, 135)
Month 6	Month 6 (183)	Days (136, 230)
Month 9	Month 9 (274)	Days (231, 317)
Month 12	Month 12 (365)	Days (318, 412)
Month 18	Month 18 (548)	Days (413, 682)
Month 24	Month 24 (731)	Days (683, 778)
Month 36	Month 36 (1096)	Days (779, 1413)
Month 48	Month 48 (1461)	Days (1414, 1508)
Month 60	Month 60 (1826)	Days (1509, 2144)

Month 72	Month 72 (2192)	Days (2145, 2238)
Month 84	Month 84 (2557)	Days (2239, 2874)
End of study[b]	Final or Termination Visit	

a Relative to the date of the first dose of study treatment. Day 0 = the date of the first dose of study treatment.
b Presented in summary tables for all visit-based parameters.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

If a patient has 2 or more visits within the same window, the last visit with a non-missing value will be used for analysis.

15.3 DERIVED VARIABLES

Analyses visits will be derived per Section 15.2. Observed data will be used for the primary and secondary objectives without derivation.

15.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing Post-treatment assessment will be used as the end-of-study assessment for generating summary statistics. However, all Post-treatment assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

15.5 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

15.6 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.8 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

15.9 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, incomplete (i.e. partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

15.9.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same, but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

15.9.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as descripted in Section 15.4. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

15.10 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Error! Reference source not found. shows examples of how some possible laboratory results should be coded for the analysis.

Table 15.10–1. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test	***Possible Laboratory Results (in SI Units)***	***Coded Value for Analysis***
Chemistry: ALT	< 5	5
Chemistry: AST	< 5	5
Chemistry: bilirubin, total	< 2	2

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

16.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the protocol Amendment 2 (dated 19OCT2017).

17.0 REFERENCES

Not applicable.

DOCUMENT HISTORY PAGE

Effect Date	Revision Number	Primary Author	Description of Change

ALLERGAN

RST-001-CP-0001 Statistical Analysis Plan

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
21-Feb-2019 11:18 GMT-080	[redacted]	Medical Monitor Approval
21-Feb-2019 12:38 GMT-080		Management Approval
22-Feb-2019 08:00 GMT-080		Clinical Development Approval
22-Feb-2019 12:35 GMT-080		Biostatistics Approval
22-Feb-2019 12:54 GMT-080		Biostatistics Approval