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

Statistical Analysis Plan Date: 22-FEB-2019
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)
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### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic Case Report Form</td>
</tr>
<tr>
<td>IOP</td>
<td>Intraocular Pressure</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>PCS</td>
<td>potentially clinically significant</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SI</td>
<td>Le Système International d’Unités (International System of Units)</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
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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.

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 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:

<table>
<thead>
<tr>
<th>RST-001</th>
<th>LOW Dose</th>
<th>MID Dose</th>
<th>HIGH Dose</th>
</tr>
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</table>

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.
Figure 4–1. Overview of the Treatment Schedule

![Treatment Schedule Diagram]

Table 4–2. Dose Escalation

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group</th>
<th>Number of patients(^a)</th>
<th>Intravitreal Injection</th>
<th>Volume</th>
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<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>3</td>
<td>LOW</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>3</td>
<td>MID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>3</td>
<td>HIGH</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td></td>
<td>6-12(^b)</td>
<td>Choice of dose(^c) from groups A, B, or C</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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
Table 4–4. Study Visit Schedule: Long-term Follow-up Visits
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.

The secondary endpoints include the following efficacy measures of change in visual function:
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
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 other measures. 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.
11.3 SECONDARY OCULAR SAFETY MEASUREMENTS
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:

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.
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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flag</th>
<th>Observed Value</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting systolic blood pressure, mm Hg</td>
<td>High</td>
<td>≥ 180</td>
<td>Increase of ≥ 20</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>≤ 90</td>
<td>Decrease of ≥ 20</td>
</tr>
<tr>
<td>Sitting diastolic blood pressure, mm Hg</td>
<td>High</td>
<td>≥ 105</td>
<td>Increase of ≥ 15</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>≤ 50</td>
<td>Decrease of ≥ 15</td>
</tr>
<tr>
<td>Sitting pulse rate, bpm</td>
<td>High</td>
<td>≥ 120</td>
<td>Increase of ≥ 15</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>≤ 50</td>
<td>Decrease of ≥ 15</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>High</td>
<td>—</td>
<td>Increase of ≥ 7%</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>—</td>
<td>Decrease of ≥ 7%</td>
</tr>
</tbody>
</table>

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.
11.9 OTHER SAFETY PARAMETERS

11.9.1 Physical Examination

The physical examination will be performed at screening visit, Month 6 and Month 12. Physical examination findings from screening visit will be recorded on the Medical and Surgical History eCRF. Physical Examination findings at Month 6 or Month 12 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 approximately 12 patients will be enrolled in Phase 2a for further safety and efficacy evaluation.
14.0 **STATISTICAL SOFTWARE**

Statistical analyses will be performed
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
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 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.
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 described 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 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
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

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