Statistical analysis plan:

Title: A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of RBM-007 monotherapy and RBM-007 in Combination with Eylea® Compared to Eylea® Monotherapy in Subjects with Wet Age-related Macular Degeneration – TOFU Study

NCT04200248

Date: 14 December 2021

Statistical Analysis Plan

RBM-007-002

A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of RBM-007 monotherapy and RBM-007 in Combination with Eylea® Compared to Eylea® Monotherapy in Subjects with Wet Age-related Macular Degeneration – TOFU Study

Author: [redacted]

Version Number and Date of Protocol: Amendment 1, 15 Nov 2019

Statistical Analysis Plan Signature Page

Statistical Analysis Plan for Protocol RBM-007-002.

	Name	Signature	Date
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Position:	Biostatistician		
Company:	Tech Observer		

Upon review of this document, the undersigned approve this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Modification History

Version Number	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	13 Dec 2021	[redacted]	Not Applicable – First Version

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMD	Age-related Macular Degeneration
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BDRM	Blinded Data Review Meeting
BP	Blood Pressure
BMI	Body Mass Index
CSR	Clinical Study Report
CST	Central Subfield Thickness
ENR	Enrolled
EOT	End of Treatment
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
ICF	Informed Consent Form
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IVT	Intravitreal
LOCF	Last Observation Carried Forward
LSMEANS	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviation
PT	Preferred Term
PP	Per-Protocol
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SOC	System Organ Class
SRT	Safety Review Team
SHRM	Subretinal Hyper Reflective Material
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHODrug Global	World Health Organization Drug Dictionary

2. INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from the RBM-007-002 study. This document is based on the protocol version Amendment 1, dated 15 November 2019. This Statistical Analysis Plan (SAP) has been developed prior to database lock for interim or final analysis for the TOFU study. Any changes from the planned analysis as described in the protocol for RBM-007-002 and its amendments (as applicable) are detailed here, and any differences described here supersede the analysis presented in the protocol. Any additional analyses are conducted to supplement the planned analyses and any deviations from the planned analyses described in this SAP will be documented in the Clinical Study Report (CSR).

2.1. RESPONSIBILITIES

Tech Observer will perform the statistical analyses and will be responsible for the production and quality control of all tables, figures and listings. This SAP describes the efficacy and safety analyses.

2.2. TIMING OF ANALYSES

The primary analysis of efficacy and safety is planned after all subjects complete the study visit for Week 16 or withdraw early from the study. The final analysis is planned after all subjects complete the final study visit (Week 20) or withdraw early from the study. No interim analysis is planned for this study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this study is to assess the safety and efficacy of repeated intravitreal injections of RBM-007 (2.0 mg/eye) given as monotherapy and RBM-007 (2.0 mg/eye) in combination with Eylea® in subjects with wet age-related macular degeneration (AMD) compared with Eylea® alone.

3.2. SECONDARY OBJECTIVES

The secondary objective of this study is to evaluate durability of effect for RBM-007 in subjects with exudative age-related macular degeneration.

4. STUDY DESIGN

This is a multicenter, active-controlled, double masked study assessing the safety, efficacy and durability of four monthly intravitreal (IVT) injections of RBM-007 monotherapy, and four monthly RBM-007 injections in combination with Eylea® dosed at every other month, compared to Eylea® monotherapy dosed at every other month in approximately eighty-one subjects with exudative age-related macular degeneration (AMD).

Subjects aged 55 years or older diagnosed with active exudative AMD in the study eye, for which previous standard treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have demonstrated incomplete resolution of exudation assessed by spectral domain optical coherence tomography (SD-OCT) will be enrolled. Other inclusion criteria are: Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of 78 to 24 letters (≤20/32 to ≥20/320 Snellen vision equivalent); presence of macular edema or subretinal fluid on SD-OCT; absence of central atrophy or retinal epithelial tear in the fovea or any condition preventing VA improvement in the study eye.

At the Screening Visit, best corrected visual acuity (BCVA), spectral-domain optical coherence tomography (SD-OCT) imaging, fluorescein angiography (FA) and color fundus photography will be performed and reviewed by a trained technician for the determination of subject eligibility based upon the lesion attributes specified in the inclusion criteria. Randomization occurs after the Screening Visit when the subject has been determined to be eligible and the study site completes the randomization request.

The study eye must meet all inclusion and exclusion criteria. If both eyes are eligible based on inclusion and exclusion criteria, the study eye of an eligible subject is defined as the eye with the worst vision. If both eyes have the same vision, the right eye (OD) will be determined as the study eye.

Subjects who meet all inclusion and none of the exclusion criteria will return to the clinic for the Baseline Visit 1 (Day 1). Approximately 81 eligible subjects with exudative age-related macular degeneration (AMD) will be randomized in a 1:1:1 ratio to receive one of the following treatment arms for up to three months in the study eye:

- Arm 1: Sham + RBM-007 Injectable Solution (2.0 mg/eye)
- Arm 2: RBM-007 Injectable Solution (2.0 mg/eye) + Eylea®
- Arm 3: Sham + Eylea®.

Subjects are eligible to receive rescue therapy with Eylea® or other treatment anytime during the study except for those visits with Eylea® injection as per protocol, if a BCVA decrease of >10 letters and a central subfield thickness (CST) increase of >50μm from the last (previous) per-protocol scheduled assessment visit or at the discretion of the investigator.

Total duration of the study will be approximately 24 months. The total study period for each subject will include a screening period of up to 28-days and a treatment period and a follow up period that totals 20 weeks. Study assessment visits include a screening visit (Visit 0), Baseline/Day 1 (Visit 1), post treatment visits at Week 1 (Visit 2), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5), Week 16 (Visit 6) and Week 20 (Visit 7). The schematic for injections is shown below and the schedule of assessments is presented in Appendix 1 (Time and Events Schedule).

								Primary Endpoint	Last Visit
		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
		SCN	D1	W1	W4	W8	W12	W16	W20
Arm 1 (N=27)	Sham injection + RBM-007 2.0mg		⇧		↑	⇧	↑		
Arm 2 (N=27)	RBM-007 2.0mg + Eylea®		⇧		↑	⇧	↑		
Arm 3 (N=27)	Sham injection +Eylea®		⇧		⇧	⇧	⇧		

↑ RBM-007 2.0mg ⇧ Eylea® ⇧ Sham injection

*Follow-up period: Two-month period between Visit 5 (Week 12) and Visit 7 (Week 20)

5. TREATMENT ASSIGNMENT AND MASKING

Subjects who satisfy all of the inclusion and none of the exclusion criteria will be randomized in a 1:1:1 ratio to receive one of the following three treatment arms in the study eye for up to 3 months according to a study randomization scheme:

- Arm 1: Sham + RBM-007 Injectable Solution (2.0 mg/eye)
- Arm 2: RBM-007 Injectable Solution (2.0 mg/eye) + Eylea®
- Arm 3: Sham + Eylea®.

This is a double-masked study. The subjects, efficacy assessors (including photographer(s) and BCVA technician(s)), Investigators, Sponsor, and any monitors involved in reporting, obtaining and/or reviewing the clinical evaluations will be masked to the specific treatment being administered. In addition, Biostatistics staff who are directly involved in the analysis of the study results will remain masked to the treatment assignment. However, the designated injection physician (not the investigator) will not be masked to the treatment regimen. To keep masking of the clinical trial, the investigator and authorized study staffs must follow the following procedures:

- The designated injecting physician and the designated injection staff must ensure any information regarding clinical study drug injections during the study is inaccessible to other study staff.
- The designated injecting physician and the designated injection staff cannot perform any assessments, examinations, or procedures for the study other than clinical study drug injection procedures and examinations post drug injections.
- Study staff not designated to do study drug injections, including investigators, examiner, and other clinical site staff, cannot participate in any procedures for clinical study drug injections and examinations post drug injections.

The designated Safety Review Team (SRT) will review the masked safety data periodically to determine if the safety and tolerability of the doses are acceptable. In case of a medical emergency, the Principal Investigator or site staff may reveal the treatment information by unmasking to know which treatment the subject has received. The Principal Investigator should contact RIBOMIC, or

RIBOMIC's designee, before taking this measure, if there is sufficient time. RIBOMIC, or RIBOMIC's designee, must be informed of all instances where the code is broken and of the reasons for such instances.

6. ANALYSIS POPULATIONS

6.1. ALL ENROLLED POPULATION

The All Enrolled (ENR) population will contain all subjects who signed an informed consent for this study. This analysis population will be used to summarize subject disposition and pre-treatment adverse events.

6.2. SAFETY POPULATION

The safety population will include all randomized subjects who received at least one injection of study medication. Subjects in the safety population will be analyzed according to the treatment received. The safety population will be used for all safety analyses.

6.3. INTENT-TO-TREAT (ITT) POPULATION

The ITT population will include all subjects who are randomized to a treatment assignment. Subjects in the ITT population will be analyzed according to the treatment group to which they are assigned at randomization. This analysis population will be used to summarize subject's demographic and baseline characteristics.

6.4. FULL ANALYSIS SET

The Full Analysis Set (FAS) will include all randomized subjects who received at least one injection and provided at least one scheduled post-baseline BCVA measurement. Subjects in the FAS will be analyzed according to the treatment group they are assigned at randomization. The FAS will censor data after receiving rescue therapy (i.e., all visits/assessments after rescue therapy will be excluded while data collected on the date of rescue therapy are considered prior to rescue therapy) and use last-observation carried forward (LOCF). The FAS population will be the primary analysis population for all efficacy analyses.

6.5. PER-PROTOCOL (PP) POPULATION

The PP population is a subset of FAS. It includes all FAS subjects without any major protocol violations that could affect the assessment of primary efficacy endpoint at Week 16. Classification of protocol violations as major or minor will be assessed at a Blinded Data Review Meeting (BDRM) prior to database lock. The PP population will be the supportive analysis population for all efficacy analysis. All assessments after rescue treatment will be excluded from the analysis.

6.6. PROTOCOL DEVIATIONS

Protocol deviations (PDs) will be documented separately in a stand-alone document before database lock which include deviation category (e.g., violation of inclusion and exclusion criteria at screening, use of excluded concomitant medications, received the wrong treatment or incorrect dose), deviation description, severity (minor/major), visit/time point for each PD. Major PDs are defined as those deviations from the protocol that threaten the integrity of the data, adversely affect subjects and/or could influence/affect the outcome of the study endpoints(or part of it).

Protocol deviations pertaining to the effects of the COVID-19 pandemic and related measures may be seen on this trial, and there may be an increase in the number of PDs seen due to the pandemic. All discussions pertaining to the COVID-19 pandemic and related PDs affecting inclusion/exclusion of Analysis Populations, and any adjustments to data handling and/or analysis of data will be documented in the BDRM Report. Both the BDRM Report and this document (SAP) will be finalized before database lock. A by-subject listing of major and minor PDs will be provided for the safety population.

7. GENERAL CONSIDERATIONS

Continuous data will be summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max).

The number of observations (n) will be presented with no decimal place, mean and median will be presented up to one decimal place from the original value, standard deviation up to two decimal places from the original value, and min and max as an original value.

Categorical variables will be summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies will be presented up to 0 decimal places and percentage up to 1 decimal place, unless specified otherwise. For all percentage calculations, the denominator will be the number of subjects in the analysis population for the treatment group, unless otherwise stated.

All data will be summarized by treatment group unless otherwise specified. Only data from protocol scheduled visits will be included in the summary tables. All data entered into the database will be included in the subject data listings.

Unless otherwise specified, all discussion of efficacy endpoints and analyses are specific to outcomes in the study eye.

7.1. Reference Start Date and Study Day

The study day will be calculated from the reference start date, defined as the day of the first injection, and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference date, then: Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then: Study Day = (date of event – reference date).

If the event date is partial or missing, study day, and any corresponding durations will appear partial or missing in the listings.

7.2. Baseline

Baseline is defined as the last non-missing measurement taken prior to the first injection of the study drug (including unscheduled assessments). If the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline. It will be assumed that all assessments on Day 1 (Baseline) occur prior to the injection of the study drug, except those assignments that are designated as post-injection.

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled measurements and retests will not be included in by-visit summaries but will contribute to incidence of significant abnormality tables.

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries. Early discontinuation data will be mapped to the End of Treatment (EoT) visit for by-visit summaries. Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4. TREATMENT PERIOD

The treatment period includes the duration that a subject is under treatment in the study between the date of first injection received and the date of last injection received.

7.5. COMMON CALCULATIONS

For quantitative measurements, change from baseline values will be calculated as test value at post-treatment visit X – Baseline value.

Percent change from baseline values will be calculated as (test value at post-treatment visit X – Baseline value)*100/Baseline value.

7.6. CODING DICTIONARY

Where applicable, safety data will be coded using the following coding dictionaries:

Dictionary	Version
Medical Dictionary for Regulatory Activities (MedDRA)	23.0
World Health Organization Drug Dictionary (WHODrug Global)	March 2020

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. SAMPLE SIZE AND POWER CALCULATIONS

Due to the exploratory nature of this study, the sample size was not based on a statistical power. Approximately 81 subjects (Arm 1: 27 subjects, Arm 2: 27 subjects, and Arm 3: 27 subjects) with wet AMD will be enrolled at 8 sites.

9. INTERIM ANALYSIS

No interim analysis is planned for this study.

10. SUBJECT CHARACTERISITCS AND STUDY CONDUCT SUMMARIES

10.1. SUBJECT DISPOSITION

Subject disposition table will be summarized based on all enrolled subjects who are consented to participate in the study. The following summaries will be included in the disposition table: total number of subjects screened in the study, number of subjects who failed screening, number of subjects who were randomized, number of subjects received treatment, number of subjects who completed the study, and number and percentage of subjects who discontinued from the study with reason for discontinuation. Percentages will be based on the number of subjects who are randomized. This tabulation will be done overall as well as by treatment assignment. In addition, the number of subjects included in each of the analysis population (ITT, FAS, PP and Safety) will be presented. A by-subject listing of disposition will be provided for the ENR population.

10.2. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subjects' demographics and baseline characteristics will be summarized overall and by treatment group for the Safety, ITT, FAS and PP populations.

Continuous variables (e.g., age and weight) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Qualitative variables (e.g., sex, race, and ethnicity) will be summarized with counts and percentages.

The demographic parameters will include age category (55 to 64, 65 to 74, 75 to 84 and ≥85 years), gender, race, and ethnicity. Age will also be summarized as a continuous variable. The baseline parameters include, time since diagnosis for the study eye, BCVA (both as a continuous variable

and using categories (<55 and ≥55 letters), central subfield thickness (CST) (both as a continuous variable and using categories (<400, ≥400 µm) and total macular volume.

By-subject listings of demographic and other baseline characteristics will be provided for the safety populations.

10.3. MEDICAL AND SURGICAL HISTORY

Medical and surgical (ocular and non-ocular) history will be coded using a central coding dictionary, the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Medical and surgical history will be defined as any significant past medical conditions that ended before screening or current medical conditions that were ongoing at Screening. Medical and surgical histories (ocular and non-ocular) will be summarized by system organ class (SOC) and preferred term (PT) overall and for each treatment group for the Safety population. Ocular histories will be presented by study and non-study eye. Summaries will be sorted alphabetically by SOC, and by descending order of frequency for PTs according to the total column. Subjects with more than one of the same PTs within an SOC will be counted only once. A by-subject listing will be provided for the safety population.

10.4. MEDICATIONS

Prior medications are medications which started and stopped before the first IVT injection. Any changes to prior medications (dose, regimen, etc.) during the study will be considered a new concomitant medication. Prior and concomitant medications will be coded using the Anatomical Therapeutic Chemical (ATC) classification text from the World Health Organization Drug Dictionary and summarized separately. The counts and percentage of subjects taking a medication will be displayed by therapeutic class (ATC Level 3) and preferred name. If a therapeutic subgroup or preferred term is unavailable, ‘Not coded’ will be used. Summaries will be sorted alphabetically by ATC-Level 3, and by descending order of frequency for preferred name according to the total column. Subjects with more than one of the same preferred name within an ATC-Level 3 will be counted only once. Ocular medications will be presented separately for the study eye and non-study eye.

A by-subject listing of prior and concomitant medications will be provided for the safety population.

11. EFFICACY ANALYSIS STRATEGY

11.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the mean change in BCVA from Baseline at Week 16.

11.1.1. Hypothesis

This is an exploratory study. No formal testing of hypothesis is planned.

11.1.2. Statistical Methods

The analysis for the primary efficacy end point, BCVA change from baseline at Week 16 will be performed using analysis of covariance model, including visit and treatment as factors and baseline value as a covariate. A separate analysis will be conducted between Arm 1 (Sham + RBM-007) versus Arm 3 (Sham + Eylea®) and Arm 2 (RBM-007 + Eylea®) versus Arm 3 (Sham + Eylea®). The estimate of LS Means for the treatment differences (Arm 1 and Arm 2 versus Arm 3) and two-sided 95% confidence interval of the LSMEANS difference will be presented. Observed and change from baseline values in BCVA will be summarized descriptively at each visit by treatment group. The following figures will be provided for BCVA:

- Line plot for actual BCVA by visit and treatment (Mean ± SE)
- Line plot for change from baseline in BCVA by visit and treatment (Mean ± SE)

11.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are:

- Proportion of subjects with BCVA gain of ≥5, ≥10 and ≥15 ETDRS letters and BCVA loss of ≥15 ETDRS letters relative to baseline at Week 16.
- Change from Baseline in CST at Week 16 by SD-OCT
- Change from Baseline in macular volume at Week 16 by SD-OCT
- Change from Baseline in characteristics of SHRM
- Change from Baseline in characteristics of fibrosis

- Proportion of subjects that do not require anti-VEGF treatment during follow-up period
- Mean numbers of rescue injections in the monotherapy arm (Arm 1)
- Proportion of subjects requiring rescue therapy

11.2.1. Statistical Methods

Counts and percentage of subjects with the categorical improvement of BCVA relative to baseline (≥1 letter gain, ≥5 letters gain, ≥10 letters gain and ≥15 letters gain) and categorical worsening of BCVA (≥5 letters loss, ≥10 letters loss and ≥15 letters loss) will be presented by visit and treatment group.

Analysis of change from baseline in CST and Macular Volume at Week 16 will be performed similar to the primary efficacy endpoint analysis. Observed and change from baseline values in CST and Macular Volume will be summarized descriptively at each visit by treatment group. Characteristics of SHRM/fibrosis will be evaluated in post-hoc analyses. Counts and percentage of subjects that do not require anti-VEGF treatment and counts and percentage of subjects who received rescue injections in the RBM-007 monotherapy arm (Arm 1) during the study period will be presented. In addition, the number of subjects that received rescue injections will be summarized descriptively. The following figures will be provided for the secondary efficacy endpoints.

- Bar-diagram for categorical changes in BCVA by visit and treatment
- Line plot of actual CST by visit and treatment (Mean ± SE)
- Line plot of change from baseline in CST by visit and treatment (Mean ± SE)
- Line plot of Macular Volume by visit and treatment (Mean ± SE)
- Line plot of change from baseline in Macular volume by visit and treatment (Mean ± SE)

11.3. SUBGROUP ANALYSIS

The following sub populations will be investigated for BCVA and CST parameters to assess the impact of these sub populations on overall study results, and to assess the efficacy in each sub population. These analyses will be performed for the FAS population with LOCF.

- Age category (<75 years and ≥75 years)
- Gender (Male and Female).
- Baseline BCVA categories (<55 and ≥55 letters)

- Baseline CST categories (<400, ≥400 μm).

Descriptive summaries will be presented for change from baseline in BCVA and CST by visit and treatment. In addition, forest plots for treatment differences in change from BCVA and CST at Week 16 will be presented.

11.4. MULTIPILICTY

Not applicable. This study is descriptive in nature. No formal testing of hypothesis will be conducted.

11.5. IMPUTATION OF MISSING DATA

Every effort will be made to prevent subjects early terminating the study. Where missing data exist for primary and secondary efficacy endpoints, imputation will occur where specified.

For the primary analysis based on the FAS, a last observation carried forward (LOCF) approach will be used to handle missing or in-valid data. No baseline observation will be carried forward for the missing data.

11.6. SENSITIVITY ANALYSIS

A sensitivity analysis to explore the robustness of the efficacy results with respect to the protocol deviations will be performed using the per-protocol population. In addition, the results from the primary efficacy analysis using the FAS population will be compared to the results using all observed data irrespective of rescue treatment and observed data excluding data collected after rescue treatment without imputation.

The three analyses (all data censoring post rescue measurements and using LOCF, all observed data irrespective of rescue treatment, and observed data excluding measurements collected after rescue treatment without imputation) will be repeated using the PP population.

12 SAFETY ANALYSIS STRATEGY

All analyses described in this section will be performed on the Safety Population and will be presented by treatment group. The results will be descriptive in nature. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section. All data will be summarized and listed.

Safety will be assessed based on the following assessments:

- Extent of Exposure
- Adverse Events
- Slit-lamp Biomicroscopy
- Indirect Ophthalmoscopy
- Intraocular Pressure
- External Ocular Exam (Lid and Lashes)
- Loss in BCVA
- Physical Examination Findings at Screening Visit
- Vital Signs at Screening Visit

12.1 EXTENT OF EXPOSURE

Extent of exposure to study drug is calculated as the number of injections received during the study period. Counts and percentages will be provided for the number of injections received by treatment group.

12.2 ADVERSE EVENTS

The applicable definition of an Adverse Event (AE) is in the study protocol Section 12.1. All AEs occurring from when a subject signed informed consent to when a subject exits the study will be accounted for in the reporting.

A pre-treatment AE is defined as any AE with an onset date before the date of first injection of the study drug. A treatment-emergent AE is an event not present prior to exposure to the study drug or any pre-existing event that worsens following exposure to study drug. The period for treatment-

emergent AE analysis starts from the first injection of the study drug until the subject exits the study.

All AEs will be coded using the MedDRA coding dictionary (version 23.0). See Appendix 2 for imputation of partial dates for AEs. Imputed dates will be used to determine treatment emergent status. For the treatment-emergent AE analyses, analyses will be performed for study eye and non-study eye separately.

Summaries of number and percentage of subjects within each of the categories described in the sub-sections below, will be provided by treatment group for the safety population. A by-subject listing will include TEAEs and pre-treatment AEs for the safety population.

Overall summary of TEAEs:

- Subjects with at least one TEAE
- Subjects with at least one ocular AE
- Subjects with at least one non-ocular AE
- Subjects with at least one TEAE related to study drug
- Subjects with at least one TEAE related to injection procedure
- Subjects with at least one Serious TEAE
- Subjects with at least one serious TEAE related to study drug
- Subjects with at least one serious TEAE related to injection procedure
- Subjects with at least one TEAE leading to premature discontinuation
- Subjects with at least one TEAE leading to death

12.2.1. All Treatment-emergent Adverse Events

The incidence of TEAEs will be presented by system organ class (SOC) and preferred term (PT), and also be broken down further by maximum severity and relationship to study drug. A separate summary of TEAEs in descending order of preferred terms will be provided.

12.2.2. Severity

A summary of ocular and non-ocular TEAEs by SOC/PT and highest severity will be provided. If a subject reports a TEAE more than once within that SOC/PT, the AE with the worst-case severity will

be used in the corresponding severity summaries. An adverse event with an unknown severity will be considered as missing.

12.2.3. Relationship to Study Drug

Relationship, as indicated by the Investigator, is classified as not related, possibly related, related and related to the injection procedure. A 'related' TEAE is defined as a TEAE with a relationship of 'possibly related' or 'related' to study drug. A summary of TEAEs by SOC/PT and highest relationship to study drug will be provided. If a subject reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study drug will be used in the corresponding relationship summaries. An adverse event with an unknown relationship to study drug will be considered as missing.

12.2.4. TEAEs Leading to Discontinuation of Study Drug

The incidence of TEAEs leading to discontinuation of study drug will be presented by SOC and PT.

12.2.5. Serious Adverse Events

The incidence of treatment-emergent SAEs will be presented by SOC and PT. Serious AEs are those events recorded as 'Serious' on the AEs page of the eCRF.

12.2.6. Adverse Events Leading to Death

The incidence of AEs leading to death will be presented by SOC and PT. The TEAEs leading to death are those events which are recorded as 'Fatal' as the outcome variable on the AE page of the eCRF.

12.3 INTRAOCULAR PRESSURE

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest integer in mmHg. IOP measurements will be conducted at Screening, Baseline (Day 1), Week 1, Week 4, Week 8, Week 12, Week 16 and Week 20. Post-injection IOP assessments will be conducted on the injection days.

Descriptive summaries of observed values and change from baseline values will be presented at each study visit by treatment. Line plots of the mean observed values and change in IOP values with error bars representing +/- 1 standard error by visit and treatment will be presented using the study eye.

A summary table with counts and percentages of subjects in each category of IOP change from baseline to last on-treatment IOP assessment, maximum IOP increase from baseline to any post-baseline assessment visit and maximum IOP decrease from baseline to any post-baseline assessment visit for the study eye will be presented according to the following categories: >30 mmHg increase, 21 to 30 mmHg increase, 11 to 20 mmHg increase, 6 to 10 mmHg increase, 5 mmHg increase to 5 mmHg decrease, 6 to 10 mmHg decrease, 11 to 20 mmHg decrease, 21 to 30 mmHg decrease, and > 30 mmHg decrease. For the presentation of maximum increase, subjects who did not have an increase in IOP will be summarized under the category “≤ 5 mmHg increase”. For the presentation of maximum decrease, subjects who did not have a decrease in IOP will be summarized under the category “≤ 5 mmHg decrease”.

A subject listing of all IOP measurements will be presented by visit. In addition, a listing of all subjects with an increase or decrease in IOP of more than 10 mmHg at any visit compared to the same eye at Baseline will be presented.

Measurements taken at the post-injection assessments (40, 60 and 90 minutes after injection) will not be included in the summary tables, but will be included in the subject listings.

12.4 Slit Lamp Examination

A slit-lamp examination will be performed at Screening, Baseline (Day 1), Week 1, Week 4, Week 8, Week 12, Week 16 and Week 20 to evaluate the anterior segment of the eye, including, conjunctiva, sclera, cornea, lens and iris. Findings on conjunctiva, cornea, and iris that are deemed clinically significant by the investigator will be reported as adverse events.

For each slit-lamp parameter, counts and percentages of subjects in each grading category will be presented by visit. A shift table showing fundus grade at baseline relative to last post-baseline will be presented

A listing will be provided for all slit-lamp parameters. An additional listing will be provided which presents all subjects with a worsening of any slit-lamp parameter status at any visit in the study eye compared to the status of the same eye at Baseline.

12.5 INDIRECT OPHTHALMOSCOPY

The indirect ophthalmoscopy will be performed to evaluate the health of the retina, macula, optic nerve, and vitreous. Findings on retina, macula, vitreous or optic nerve deemed to be clinically significant by the investigator will be reported as adverse events. Fundus examination will be conducted at Screening, Baseline (Day 1), Week 1, Week 4, Week 8, Week 12, Week 16, and Week 20.

For each fundus parameter, counts and percentages of subjects in each grading category will be presented by visit. A shift table showing fundus grade at baseline relative to last post-baseline will be presented.

A listing will be provided for all indirect ophthalmoscopy parameters. An additional listing will be provided which presents all subjects with an increase in any fundus parameter at any visit compared to the grade for the same eye at Baseline.

12.6 EXTERNAL OCULAR EXAMINATION

An external ocular exam will be performed at Screening, Baseline (Day 1), Week 1, Week 4, Week 8, Week 12, Week 16, and Week 20 to evaluate the anterior segment of the eye, including lids, lashes and pupils. Findings on lids, lashes and pupils that are deemed clinically significant by the investigator will be reported as adverse events.

For each external ocular examination parameter, counts and percentages of subjects in each grading category will be presented by visit. A shift table showing fundus grade at baseline relative to last post-baseline will be presented

A listing will be provided for all external ocular examination parameters. An additional listing will be provided which presents all subjects with a worsening of any external ocular examination parameter status at any visit in the study eye compared to the status of the same eye at Baseline.

12.7 LOSS IN BCVA

Counts and percentages of subjects who experience a pre-specified category of change from Baseline to last on-treatment assessment and maximum loss from Baseline to any post-baseline assessment visit will be presented according to the following mutually categories: <5 letter loss, ≥5 letter loss, ≥10 letter loss and ≥15 letter loss.

A listing of all BCVA values by visit will be presented. In addition, a listing of all subjects with a ≥15 letter loss in BCVA from baseline to any post-baseline visit will be presented. For subjects who had ≥15 letters loss at any visit, BCVA values at all visits will be presented.

12.8 VITAL SIGNS

The following vital signs measurements will be assessed at the screening visit:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (Beats per min)
- Respiratory Rate (Breaths per min)
- Temperature (°F)

A by-subject listing for all the above parameters will be provided for the safety population. No summaries will be provided for the vital sign parameters.

12.9 PHYSICAL EXAMINATION

The physical examination assessment will be conducted at the screening visit. A by-subject listing of physical examination results will be provided including specification of any abnormalities observed for the safety population. No summaries will be provided for the physical examination results.

12.10 OTHER ASSESSMENTS

A listing of urine pregnancy test data will be provided for the safety population.

APPENDIX 1. SCHEDULE OF EVENTS

Visit Number	Visit 0 (SCRN)	Visit 1 (Injection)		Visit 2	Visit 3 (Injection)		Visit 4 (Injection)		Visit 5 (Injection)		Visit 6	Visit 7 (Exit)
Visit Schedule (Time window; days)	D-28 to -1	D1		W1 D8 (±1)	W4 D29 (±4)		W8 D57 (±4)		W12 D85 (±4)		W16 D113 (±7)	W20 D141 (±7)
		Pre	Post		Pre	Post	Pre	Post	Pre	Post		
Informed consent [a]	X											
Demographics/Eligibility	X											
Medical/surgical history, Concomitant medication	X	X		X	X		X		X		X	X
Physical examination	X											
Vital signs	X											
BCVA (ETDRS)	X	X		X	X		X		X		X	X
External ocular exam	X	X		X	X		X		X		X	X
Intraocular pressure (IOP) [b,c]	X	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy [d]	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy [d]	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X		X	X		X		X		X	X
OCT angiography [e]		X									X	
Fundus photography	X	X			X		X		X		X	X
Fluorescein angiography		X									X	
Urine pregnancy test [f]	X	X										X
IVT injection [g]		X			X		X		X			
Adverse event		X		X	X		X		X		X	X

SCRN= Screening; D=Day; W=Week;

[a] Informed Consent - obtain prior to conducting any study-related activities.

[b] On Day 1 and Week 8, IOP will be performed before the first injection and 40 (±10) minutes after the first injection. If IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, perform IOP again at 60 (±10) minutes after the first injection. If IOP is still > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, perform IOP again at 90 (±10) minutes after the first injection. If the IOP is ≤ 21 mmHg and no concern regarding retinal artery perfusion, the second injection can be administered. After the second injection, the same IOP monitoring procedure will be followed.

[c] On Week 4 and Week 12, IOP will be performed before the IVT injection and 40 (±10) minutes after the IVT injection. If IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, perform IOP again at 60 (±10) minutes after the injection. If IOP is still > 21 mmHg after eye massage and/or aqueous tap performed per PI discretion, perform IOP again at 90 (±10) minutes after the injection. This will be also applied for the post IVT injection of Rescue treatment.

[d] On days when any IVT injections are administered, slit lamp biomicroscopy and indirect ophthalmoscopy will be performed prior to the (first) injection and within 30 minutes after the (second) injection. This will be also applied for the post IVT injection of Rescue treatment.

[e] Selected sites will conduct OCT angiography in subjects showing subretinal hyper reflective material (SHRM) in the screening SD-OCT.

APPENDIX 2. MISSING DATE PROCEDURE

Prior/Concomitant Medications

For the purpose of assessing whether a medication is prior or concomitant, if a medication has a completely missing start date it will be considered a prior medication, and if a medication has a completely missing stop date it will be considered a concomitant medication. If a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01" • Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	Impute day with last day of the month
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with "01JAN" • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with "31DEC"
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with "JAN" • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with "DEC"
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of medication. • No stop date will be imputed if the treatment is ongoing.	

Adverse Events

For the purpose of assessing whether an AE is treatment emergent, if an AE has a completely missing start and stop date, it will be considered treatment emergent; if the stop date is not missing, but the start date is completely missing, it will be considered treatment emergent unless the stop date occurs prior to the first dose of study drug.

For assessing treatment emergence or for calculation of duration of AE, if a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01".	Impute day with last day of the month

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
	• Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with “01JAN”. • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with “31DEC”
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with “JAN”. • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with “DEC”
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of AE.	

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