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STATISTICAL ANALYSIS PLAN

SPONSOR:	OPHTHOTECH
PROTOCOL TITLE:	A PHASE 3 RANDOMIZED, DOUBLE-MASKED, CONTROLLED TRIAL TO ESTABLISH THE SAFETY AND EFFICACY OF INTRAVITREOUS ADMINISTRATION OF FOVISTA® (ANTI PDGF-B PEGYLATED APTAMER) ADMINISTERED IN COMBINATION WITH EITHER AVASTIN® OR EYLEA® COMPARED TO AVASTIN® OR EYLEA® MONOTHERAPY IN SUBJECTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION
STUDY CODE:	OPH1004

The undersigned certify that they have read, reviewed and approved this document.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
AMD	Age-Related Macular Degeneration
ATC	Anatomic Therapeutic Classification
BUN	Blood Urea Nitrogen
CNV	Choroidal Neovascularization
CRF	Case Report Form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ETDRS	Early Treatment Diabetic Retinopathy Trial
FA	Fluorescein Angiography
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NEI-VFQ	National Eye Institute - Visual Function Questionnaire
OCT	Optical Coherence Tomography
PP	Per-Protocol
PDGF	Platelet Derived Growth Factor
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Study Eye
SHRM	Subretinal Hyper-Reflective Material
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan describes the statistical methodology and data handling for the clinical trial with Protocol Number: OPH1004.

The trial consists of 2 years treatment periods. This SAP covers only the analysis of the Year-1 data. Any efficacy claims and conclusions will be based on this analysis. A separate Statistical Analysis Plan will be written when the Year-2 data are available.

The ICH guideline E3 "Structure and Content of Clinical Study Reports" is used as a guide to the writing of the plan.

2 STUDY DESIGN AND OBJECTIVES

2.1 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy of Fovista® intravitreous administration when administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).

2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline to Month 12.

2.1.2 Secondary Efficacy Endpoints

Three secondary efficacy endpoints are pre-specified:

1. The proportion of subjects gaining ≥ 20 ETDRS letters from baseline to Month 12.
2. The proportion of subjects losing ≥ 5 ETDRS letters from baseline to Month 12.
3. The proportion of subjects achieving visual acuity of 20/25 or better at Month 12.

2.1.3 Supportive Efficacy Endpoints

The following supportive endpoints will be evaluated:

[redacted]

[redacted]

2.1.4 Quality of Life (QoL)

Visual function (National Eye Institute Visual Function Questionnaire, NEI-VFQ 25) will be assessed by

- The mean change in score from baseline at the Month 12 visit for each NEI-VFQ 25 subscale and the composite score
- The proportion of subjects gaining ≥ 10 points in score from baseline at the Month 12 visit for the 4 pre-specified NEI-VFQ 25 subscales
- The proportion of subjects losing ≥ 10 points in score from baseline at the Month 12 visit for the 4 pre-specified NEI-VFQ 25 subscales

2.1.5 Safety and Tolerability Endpoints

Safety and tolerability endpoints are:

- All adverse events reported, whether or not deemed related to the injection procedure or study drugs
- All serious adverse events (SAE), whether or not deemed related to the injection procedure or study drugs
- Laboratory data (blood: hematology, renal function, hepatic function, and electrolytes; urinalysis)
- Ophthalmic variables (IOP, ophthalmic examination, fluorescein angiography and OCT)
- Vital sign measurements
- ECG

2.2 STUDY DESIGN

OPH1004 is a phase 3 randomized, double-masked, controlled trial to establish the safety and efficacy of intravitreous administration of Fovista® administered in combination with either Avastin® or Eylea® compared to Avastin® or Eylea® monotherapy in subjects with subfoveal neovascular age related macular degeneration.

Subjects will be randomized in a 1:1:1:1 ratio to the following dose groups:

Fovista® 1.5 mg/eye + Avastin® 1.25 mg/eye
Fovista® 1.5 mg/eye + Eylea® 2 mg/eye
Sham + Avastin® 1.25 mg/eye
Sham + Eylea® 2 mg/eye

Subjects randomized to receive Avastin® will be treated with Fovista® or sham in combination with Avastin® monthly for 24 months.

Subjects randomized to receive Eylea® will be treated with Fovista® or sham in combination with Eylea® every month for the first 3 doses (Day 1, Month 1, and Month 2) and every other month thereafter (i.e. Months 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22).

Therefore, subjects randomized to receive Avastin® will be treated with Fovista® or sham in combination with Avastin® for a total of 24 administrations. Subjects randomized to receive

Eylea® will be treated with Fovista® or sham in combination with Eylea® for a total of 13 administrations.

All subjects will have a final follow-up visit at Month 24.

2.3 SAMPLE SIZE AND RANDOMIZATION

For the primary endpoint (the mean change in visual acuity from baseline at Month 12 visit), the Fovista®/(Avastin® or Eylea®) treatment arm will be compared to the Sham/(Avastin® or Eylea®) treatment arm.

[redacted]

for dropouts, approximately 311 subjects will be recruited in each group, for a total of approximately 622 subjects enrolled.

[redacted]

3 GENERAL ANALYSIS DEFINITIONS

3.1 STUDY PERIOD AND VISIT WINDOW DEFINITIONS

Year 1

Assessment	SCR	Day 1[1]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Informed Consent	X													
Medical & Ophthalmic History, Performance status	X													
Vital Signs/ Physical Exam[2]	X	X						X						X
12-Lead ECG	X													X
Protocol refraction and visual acuity using ETDRS chart[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[2,6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photographs[3]	X	*						X						X
Fluorescein Angiogram[3]	X	*						X						X
Optical Coherence Tomography (OCT)[3]	X	*			X			X			X			X
Laboratory Tests (hematology, chemistry, urinalysis)	X							X						X
Serum pregnancy test (if applicable)	X													
Visual Function Questionnaire (VFQ-25)		X			X			X			X			X
Randomization		X*												
Subjects Randomized to Fovista™/Sham + Avastin®		X	X	X	X	X	X	X	X	X	X	X	X	X
Subjects Randomized to Fovista™/Sham + Eylea®		X	X	X		X		X		X		X		X
3-Day Post-Injection Telephone Safety Check		A/E	A/E	A/E	A	A/E	A	A/E	A	A/E	A	A/E	A	A/E
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]		X	X	X	X	X	X	X	X	X	X	X	X	X

Year 2

Assessment	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24	Early Withdrawal
Informed Consent													
Medical & Ophthalmic History, Performance status													
Vital Signs/ Physical Exam[2]						X						X	X
12-Lead ECG												X	X
Protocol refraction and visual acuity using ETDRS chart[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry[3,4,5]/Ophthalmologic Examination[2,6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photographs[3]						X						X	X
Fluorescein Angiogram[3]						X						X	X
Optical Coherence Tomography (OCT)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests (hematology, chemistry, urinalysis)						X						X	X
Serum pregnancy test (if applicable)													
Visual Function Questionnaire (VFQ-25)						X						X	X
Randomization													
Subjects Randomized to Fovista™/Sham + Avastin®	X	X	X	X	X	X	X	X	X	X	X		
Subjects Randomized to Fovista™/Sham + Eylea®		X		X		X		X		X			
3-Day Post-Injection Telephone Safety Check	A	A/E	A	A/E	A	A/E	A	A/E	A	A/E	A		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[7]	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Day 1 assessments should be performed within 14 days of Screening.
2 Physical examination is performed at Screening and at the investigator's discretion thereafter. Vital Signs are performed at all indicated timepoints.
3 Ocular assessments are performed at Screening, Months 6, 12, 18 and Month 24/Early Withdrawal on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
4 Goldmann applanation tonometry must be performed at Screening. The tonopen may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30 mmHg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
5 Tonometry should be measured prior to the first injection, at least 30 minutes after the Fovista®/Sham injection, and at any additional times as specified by the Intravitreous Administration Protocol (see Section 17.5)
6 Ophthalmic exam should be performed twice at the injection visits; once prior to the first injection, and again after the second injection.
7 Adverse events are to be recorded after the first dose of study drug.
* Under certain conditions (i.e. significant anatomic change or significant change in VA since screening as defined in Section 10.2.2.1), ocular imaging must be repeated before randomization can be considered. See Section 10.2.2.1, Reconfirmation of Eligibility at Day 1, for details.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the following visit windows: Months 1 to 24: ± 7 days.

3.2 DEFINITION OF POPULATIONS

The analysis and reporting of the data from this study will be performed using the following analysis populations:

3.2.1 Intention-To-Treat (ITT) Population

The Intention-To-Treat population (ITT) will consist of all randomized subjects who received at least one dose of study drug, irrespective of the dose actually received. Subjects will be analyzed in the treatment group assigned at randomization. Subjects will be included in a particular analysis, for a particular population, if relevant data is available for analysis (e.g., the primary analysis will require both baseline and at least one post-baseline VA measurement, to calculate a change score).

3.2.2 Per-protocol (PP) Population

The per-protocol population (PP) will consist of all ITT subjects without any significant violation of the protocol. The significant and major protocol violations will be defined prior to database lock in a masked fashion.

3.2.3 Safety Population

The Safety population will include all subjects who received at least one study drug. In the event that subjects receive a dose that differs from the one assigned according to the randomization schedule, safety analyses will be conducted according to the dose actually received rather than according to the dose assigned by randomization. However, subjects who have ever received an injection of Fovista® will be analyzed in the Fovista® group.

[redacted]

3.4 DATA HANDLING CONVENTIONS

3.4.1 General Conventions

Data will be analysed using SAS (Version 9.3 or later) or R. Descriptive analyses will be performed on baseline, safety and efficacy data. All tables will be created by the following treatment arms:

- Fovista® 1.5 mg + Avastin® 1.25 mg
- Fovista® 1.5 mg + Eylea® 2 mg
- Fovista® 1.5 mg + (Avastin® 1.25 mg or Eylea® 2mg)
- Sham + Avastin® 1.25 mg
- Sham + Eylea® 2 mg
- Sham + (Avastin® 1.25 mg or Eylea® 2mg)

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.

- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, 1st quartile (Q1), 3rd quartile (Q3), and maximum values.

Listings with individual Subjects' data will be provided for all CRF (including derived data) and central laboratory data or other external data. Data collected on the CRF that are *not* present in a table will also be listed (e.g. time and method of tonometry, comments fields, data on Fatal Outcomes page, Unscheduled Visit pages, etc.).

Inferential analyses on the primary efficacy endpoint will compare the following two treatment groups only:

- Fovista® 1.5 mg + (Avastin® 1.25 mg or Eylea® 2mg)
- Sham + (Avastin® 1.25 mg or Eylea® 2mg)

3.4.2 Visit Windows

The scheduled visits will be used in the analyses over time.

Missing scheduled follow-up visit will be substituted by an unscheduled or early withdrawal visit occurring within each follow-up visit window, if there is only one unscheduled or early withdrawal visit occurring within the window. If there are multiple unscheduled or early withdrawal visits occurring within the window, the closest one within the visit window will be used. If no unscheduled or early withdrawal visit occurred within the window, the visit will be considered as missing. The details are tabulated in **Appendix 1**.

[redacted]

3.4.4 Handling Missing Data in Descriptive Analyses

When summarizing categorical variables, subjects with missing data are generally not included in calculations of percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of subjects with missing data is presented.

When summarizing continuous variables, subjects with missing data are not included in calculations. No imputations are made.

3.4.5 Handling Missing or Partially Missing Dates

Missing or partially missing dates will not be imputed at data level. However, assumptions for missing or partially missing dates for important variables will be made to allow inclusion of appropriate data records in the analyses. In general, the assumptions about the missing or partially missing dates, when needed, are made conservative to avoid overestimation of treatment effect and underestimation of adverse effects.

If a medication date or time is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered both as a prior and a concomitant medication.

If the partial AE onset date information does not indicate whether the AE started prior to treatment or after treatment, the AE will be classified as after treatment.

3.4.6 Visual Acuity Conventions

The following conventions will be used to calculate the ETDRS Visual Acuity Score, its baseline value and the change relative to baseline, as well as the Snellen Visual Acuity Equivalent:

[redacted]

[redacted]

4 STUDY SUBJECTS

4.1 DISPOSITION OF SUBJECTS

The number of subjects screened, randomized, and treated will be presented. The reason for exclusion from one or more analysis sets will be summarized.

The frequency of premature discontinuations from the study prior to Month 12 will be given for the ITT and PP populations by treatment arm and overall. The primary reason for non-completion of the study will be summarized. The details of the 'Adverse event', 'Protocol violation',

[1] The ETDRS lines in order, from largest to smallest, are 20/800, 20/640, 20/500, 20/400, 20/320, 20/250, 20/200, 20/160, 20/125, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, 20/20, 20/16, 20/13, 20/10.

'Investigator decision', 'Sponsor decision', 'Subject request', 'Lost to follow-up', 'Subject non-compliance' or 'Other' will be included in a listing.

4.2 TREATMENT MISALLOCATIONS

For subjects with errors in treatment allocation, the following is described under which treatment groups they will be reported for efficacy and safety analyses:

For example, if subjects were:

- Randomized (regardless of error) but not treated, then they will be excluded for all efficacy and safety analyses. These subjects will be included in the summary of subject dispositions.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomization is missing, but will be reported under the treatment they actually received for all safety analyses.
- Randomized but were administered the incorrect treatment at any time during the study, then they will be reported under their randomized treatment group for efficacy analyses on ITT population, but will be reported under the treatment they actually received for all safety analyses on the safetypopulation (see Section 3.2.3); specifically, this implies that for safety analyses, a patient who ever received Fovista® will be included in the Fovista® group.

4.3 PROTOCOL VIOLATIONS

All protocol violations will be assessed and identified prior to database lock in a masked fashion to determine whether they are major by the sponsor. The final list of major protocol violations will be provided prior to the database lock.

[redacted]

The major protocol violations and significant protocol violations will be summarized for the ITT population. The details will be listed by subject and by treatment arm.

4.4 INCLUSION AND EXCLUSION CRITERIA

A frequency table of all inclusion and exclusion criteria not met will be provided for the ITT population by treatment arm and overall. A detailed listing will be provided by subject.

5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided to document baseline and on-trial comparability, including demographic information and treatment administration.

Descriptive statistics with respect to Subject characteristics at baseline will be displayed for the ITT population; if the PP and safety populations are different than the ITT population, demographic data will also be provided for these populations. When several measurements are available before the first administration of study drug, the baseline value is the last available value prior to first dose, except for the baseline visual acuity score and baseline intraocular pressure which are the mean of the screening and Day 1 values.

The variables to be summarized are:

- Gender, Ethnicity, Race, Iris color, Age, Current smoking status.
- Prior ocular history, both eyes (by MedDRA preferred term, including number and percentage of all Subjects with at least one prior ocular history)
- Medical history (excluding ocular history) (by body system and preferred term, with number and percentage for both; including number and percentage of all subjects with at least one prior medical history)
- Prior surgeries/procedures (by body system and preferred term, with number and percentage for both; including number and percentage of all Subjects with at least one prior surgery/procedure)
- Vital signs (Height, Weight, Pulse, Blood pressure)
- ECOG performance status
- Visual acuity, both eyes
- Tonometry, both eyes
- ECG
- Ophthalmic exam, both eyes (Motility, Lids/Lacrimal/Lashes, Conjunctiva/Sclera, Cornea, Anterior chamber activity: cells, Iris, Pupils, Lens Status, Vitreous haze, Vitreous hemorrhage, Posterior vitreous detachment, Optic nerve, Macula, Retinal vessels, Peripheral retina)
- Imaging Assessments, study eye

[redacted]

[redacted]

6 PRIOR AND CONCOMITANT MEDICATION

All prior and concomitant medications will be summarized separately by WHO Drug code (Version 3, 2016) on the ITT population. Medication usage will be summarized according to the 2nd level (main therapeutic level) and the 4th level (preferred term level) Anatomic Therapeutic Chemical (ATC) classification. Subjects will only be included once in the summaries within each ATC 2nd level or ATC 4th level category. The summaries will include the number and percentage of all subjects with at least one concomitant medication, respectively.

[redacted]

[redacted]

7.3 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

Three secondary efficacy endpoints are pre-specified:

1. The proportion of subjects gaining $\geq$ 20 ETDRS letters from baseline to Month 12.
2. The proportion of subjects losing $\geq$ 5 ETDRS letters from baseline to Month 12.
3. The proportion of subjects achieving visual acuity of 20/25 or better at Month 12.

Secondary efficacy analysis will be conducted for ITT and PP populations for these pre-specified secondary endpoints with descriptive intent only.

Descriptive tables will be provided for secondary endpoints based on the observed data, but due caution will be exercised in interpreting descriptive tables because of the potential impact of missing data. Sensitivity analyses of the secondary endpoints will also be performed (see Section 7.6).

7.4 ANALYSIS OF SUPPORTIVE EFFICACY ENDPOINTS

Descriptive analysis will be conducted on the following supportive endpoints:

[redacted]

[redacted]

Descriptive tables will be used for the supportive endpoints based on observed data (i.e. missing data will not be imputed for the supportive endpoints).

7.5 QUALITY OF LIFE ANALYSES

The VFQ-25 will be administered at Baseline (Day 1), Month 3, 6, 9, 12, 18, and 24. Based on the VFQ-25 and the scoring rules, the 12 VFQ-25 sub-scales and the composite score will be generated, computed and used in the QOL analyses (See Appendix 2).

Of the 12 VFQ-25 sub-scales, 4 are considered of interest in this trial:

- Near vision activities
- Distance vision activities
- Dependency
- Role difficulties

The composite score will be used as an overall measure of vision-targeted health related quality of life.

7.5.1 Descriptive Summaries by Visit

The change in score from baseline will be analyzed as continuous variables. The composite score and the scores of each sub-scale at Baseline and the changes from Baseline will be summarized descriptively by visit and by treatment group using the observed cases (missing values will not be imputed).

The proportions (%) of subjects gaining/losing ≥ 10 points in score for the 4 pre-specified sub-scales, as well as the Composite score, will be tabulated by visit and by treatment group using the observed cases (missing values will not be imputed).

Change in mean score from Baseline over time will be plotted by visit and by treatment group.

No inferential treatment comparisons will be performed for QOL data.

7.6 [redacted]

[redacted]

[redacted]

[redacted]

7.7 SUBSET ANALYSES

The trial is not sized to test for the presence of treatment by subset interactions. Thus true treatment by subset interactions will likely be missed, unless they are quite substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this will not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone.

With these caveats in mind, exploratory subset analyses on the primary efficacy endpoint will be performed to identify any major effect that might be worth testing in future trials. The subgroups have been defined in Section 3.4.

These analyses will be considered as supportive efficacy analyses and conducted without any alpha-level adjustment.

8 SAFETY EVALUATION

All safety analyses will be performed on the Safety population. The analyses will be conducted according to the treatment that they actually received. However, subjects who have ever received an injection of Fovista® will be analyzed in the Fovista® group. Missing values of safety data will not be imputed and safety summaries will be based on the observed cases.

8.1 EXTENT OF EXPOSURE

Exposure to study medication will be evaluated for each treatment group and overall with respect to treatment duration (= Last injection date – First injection date + 31, in days), number of subjects treated at each planned visit, total injections received, using descriptive statistics (N, mean, standard deviation, median, minimum, Q1, Q3, maximum).

8.2 ADVERSE EVENTS

Adverse events (AEs) will be recorded starting after the first dose of study drug and continuing until 30 days after the last dose or until the last follow-up visit required by the protocol, whichever comes later.

Only first year AE data will be included in the following analyses. First year will be defined as starting after the first dose of study drug until prior to the first injection at Month 12. If a Month 12 injection does not exist, the end of first year is defined as the Month 12 visit (or target of 365.25 days after the date of first dose if no Month 12 visit) or 30 days after the last injection, whichever is later. AEs from the first year will be defined as AEs from the start of the first dose until prior to the first injection at Month 12 or 30 days after the last dose, within the first year as defined above.

The safety analyses on AEs will be primarily based on the Treatment-Emergent Adverse Events (TEAEs), which is defined as an AE occurring after the first injection on Day 1 (day of the first planned dose of study drug) or up to and including 30 days after the last dose of study drug, within the first year as defined above.

All AEs will be coded using MedDRA (the most recent Version 18.1) terms.

An overview of TEAEs will be provided. A second overview of TEAEs will be provided which displays the overall summary of TEAEs by the categories 'Study Eye', 'Non-Study Eye', and 'Non-Ocular'. In addition, the number and percentage of patients with TEAEs will be tabulated for each treatment group and in total by system organ class (SOC) and preferred term (PT). The number and percentage of the subjects who experienced at least one TEAE will be included. Subjects will only be counted once for each preferred term. In case that a subject experienced the same event more than once, the worst severity will be presented.

Tabular summaries of the following AEs will be provided by SOC and PT:

- All TEAEs regardless of the relationship to study drugs
- TEAEs related to study drugs
- TEAEs related to injection procedure
- TEAEs by the maximum severity grade
- TEAEs related to study drugs by the maximum severity grade
- TEAEs related to injection procedure by the maximum severity grade
- All Ocular TEAEs by study eye and fellow eye
- Study drug related Ocular TEAEs by study eye and fellow eye
- Injection procedure related Ocular TEAEs by study eye and fellow eye
- Ocular TEAEs (study eye) by the maximum severity grade
- Study drug related Ocular TEAEs (study eye) by the maximum severity grade
- Injection procedure related Ocular TEAEs (study eye) by the maximum severity grade
- Severe TEAEs

- Severe TEAEs related to study drugs
- Severe TEAEs related to injection procedure
- Ocular Severe TEAEs (study eye)
- Ocular Severe TEAEs (study eye) related to study drugs
- Ocular Severe TEAEs (study eye) related to injection procedure
- TEAEs leading to discontinuation of study drug
- Study drug related TEAEs leading to discontinuation of study drug
- Injection procedure related TEAEs leading to discontinuation of study drug
- Ocular TEAEs (study eye) leading to discontinuation of study drug
- TEAEs leading to death
- Study drug related TEAEs leading to death
- Injection procedure related TEAEs leading to death

Ocular TEAEs has been defined as TEAEs linked to the "Eye Disorders" system organ class and the 'Intraocular pressure increased' preferred term.

All AEs, including non-TEAEs, will be included in individual subject listings.

The listings will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study drug/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved /unresolved / fatal).

The same listings will be provided separately for severe AEs, AEs leading to permanent discontinuation of the study drug, and for AEs leading to death.

8.3 SERIOUS ADVERSE EVENTS AND DEATHS

Treatment-Emergent Serious adverse events (SAEs) will be summarized by system organ class and preferred term. The number and percentage of the subjects who experienced at least one SAE will be included.

Tabular summaries of the following SAEs will be provided:

- All SAEs regardless of the relationship to study drug
- SAEs related to study drug
- SAEs related to injection procedure
- Ocular SAEs (study eye) regardless of the relationship to study drug

- Ocular SAEs (study eye) related to study drug
- Ocular SAEs (study eye) related to injection procedure

In addition, separate listings will be created for deaths and all SAEs. List for SAEs will include the subject identifier, age, sex, verbatim term, preferred term, eye (N/A/OD/OS/OU), serious (yes/no), date of onset, relative study day of onset, duration of the event (or continuing), severity (mild/moderate/severe), causality (relationship to study drug/injection procedure), action taken (study drug permanently discontinued: yes/no), treatment (yes/no), and outcome (resolved/unresolved/fatal).

8.4 VITAL SIGNS

Descriptive statistics at each time point up through and including the Month 12 visit will be used to display the changes from Baseline for pulse and blood pressure (systolic and diastolic). Mean change of pulse and blood pressure (systolic and diastolic) from Baseline to the last measurement will be provided.

8.5 OPHTHALMIC VARIABLES

Ophthalmic Examination. The following ophthalmic examination variables will be analysed by shift table from baseline to the pre-injection examination on Month 12 or last visit available whichever comes later (normal/abnormal, unless otherwise specified below).:

- Examination of the motility
- Inspection of the lids/lacrimal/lashes
- Examination of the conjunctiva/sclera
- Inspection of the cornea
- Examination of the iris
- Examination of the pupils
- Inspection of the lens status (aphakic, pseudo-phakic, phakic; if phakic, nuclear/PSC/cortical 0, 1, 2, 3, 4), including a listing of subjects with a change in lens status for study eye and (separately) for fellow eye
- Examination of the posterior vitreous detachment
- Inspection of the optic nerve
- Inspection of the macula
- Examination of the retinal vessels

The following ophthalmic examination variables will be analysed by shift table from Baseline through Month 12 or last visit available whichever comes later, on a monthly basis

(normal/abnormal, unless otherwise specified below), and from pre-injection to post-injection at each monthly injection

- Examination of the anterior chamber activity: Cells (0, trace, 1+, 2+, 3+, 4+)
- Inspection of the vitreous haze (0, 1+, 2+, 3+, 4+)
- Examination of the vitreous haemorrhage
- Examination of peripheral retina

Intraocular Pressure.

The Baseline intraocular pressure within an eye will be determined as the average of the Screening and Day 1 (pre-injection) measurements. Non-integer values for the average will be rounded up prior to subsequent calculations of change from baseline.

IOP will be summarized by visit, including all pre-injection, "IOP after first injection" and "IOP after second injection" measurements. An additional tabular summary of the percentage of subjects in categories of IOP will be presented by treatment group, visit, and injection time (pre-injection, IOP after first injection, IOP after second injection).

"IOP after injection" is defined as the IOP measurement that is closest in time to the protocol-specified post-injection timepoint (but at least 25 minutes post-injection). If there are two closest measurements equidistant to this timepoint, then the measurement after the protocol-specified timepoint will be used.

Mean IOP over time of all scheduled measurements (pre-injection, IOP after first injection, and IOP after second injection) will be plotted.

8.6 CLINICAL LABORATORY DETERMINATION

All laboratory data will be listed and values falling outside normal ranges will be identified, whether they will be deemed clinically relevant or not.

- Laboratory data will also be summarized in tables presenting values at each scheduled visit up through the Month 12 visit (mean, SD, median, minimum, Q1, Q3, maximum, N)
- Value changes from Baseline to each scheduled visit up through the Month 12 visit (mean, SD, median, minimum, Q1, Q3, maximum, N)
- A summary table of all analytes with the Baseline mean and the mean change from baseline to the last value observed
- A summary table of all analytes with the Baseline median and the median change from Baseline to the last value observed

for the following parameters: Hematological parameters (Hemoglobin, White blood cells, Platelets, Neutrophils (absolute numbers), Lymphocytes (absolute numbers), Monocytes (absolute

numbers), Eosinophils (absolute numbers), Basophils (absolute numbers), Biochemical parameters (Sodium, Potassium, Chloride, Calcium, Phosphorus Inorganic, Creatinine, Urea Nitrogen, Total bilirubin, GGT, Alkaline phosphatase, ASAT, ALAT).

The incidence of subjects with "Notable Laboratory Values" after the first dose of study drug will be evaluated using the criteria for Notable Laboratory Values given below. Only data collected in the first year after the first dose of study drug, up to the laboratory data taken at the Month 12 visit (before Month 12 treatment is administered) will be included; if there is no Month 12 visit, data will be included up to a target of 365.25 days after date of first dose, or 30 days after the last dose of study drug, whichever is later.

By-subject listings of all notable laboratory values will also be provided; for each subject who has an analyte with a notable value, all values of that particular analyte taken during the study will be presented in the listing, and the notable value, and any values outside of normal limits, will be identified.

For this "Notable Laboratory Values" analysis, *all* laboratory values after randomization will be taken in account, i.e., any values obtained after Day 1, at unscheduled visits, as well as values from the regularly scheduled laboratory visit at Month 12. Three Notable Laboratory Values tables and accompanying by-subject listings will be presented: (1) notable abnormalities for subjects with normal Baseline results, (2) notable abnormalities for subjects with abnormal Baseline results and (3) notable abnormalities without regard to Baseline abnormalities (i.e., normal or abnormal Baseline results). The table without regard to Baseline abnormalities will be a composite of the previous two tables (normal Baseline, abnormal Baseline).

Lab analytes and primary criteria used for Notable Laboratory Values:

a. HEMATOLOGY
    i. Hemoglobin < 0.75x baseline
    ii. Platelets < 75 or > 750 (10^9/L)
    iii. WBC count < 2.5 or > 17.5 (10^9/L)
    iv. Neutrophils (absolute) < 0.5x LLN or > 1.5xULN
    v. Eosinophils (absolute) > 1.5xULN
    vi. Lymphocytes (absolute) < 0.5x LLN or > 1.5xULN
b. LIVER FUNCTION
    i. Total bilirubin > 1.5xULN
    ii. Alkaline phosphatase > 1.5xULN
    iii. ASAT (SGOT) > 3xULN
    iv. ALAT (SGPT) > 3xULN

v. GGT > 3xULN

c. RENAL FUNCTION

i. BUN > 1.3XULN

ii. Creatinine > 1.3xULN

d. ELECTROLYTES

i. Potassium < 0.9xLLN or > 1.1xULN

ii. Sodium < 0.9xLLN or > 1.1xULN

iii. Calcium < 0.9xLLN or > 1.1xULN

Notable abnormalities for subjects with abnormal Baseline results are subject to the primary criteria above and the following secondary criteria:

a. HEMATOLOGY

i. Hemoglobin < 0.75x baseline (same as primary criterion)

ii. Platelets < 0.75x baseline or > 1.25x baseline

iii. WBC count < 0.75 baseline or > 1.25x baseline

iv. Neutrophils (absolute) < 0.5x baseline or > 1.5x baseline

v. Eosinophils (absolute) > 1.5x baseline

vi. Lymphocytes (absolute) < 0.5x baseline or > 1.5x baseline

b. LIVER FUNCTION

i. Total bilirubin > 1.5x baseline

ii. Alkaline phosphatase > 1.5x baseline

iii. ASAT (SGOT) > 1.5x baseline

iv. ALAT (SGPT) > 1.5x baseline

v. GGT > 1.5x baseline

c. RENAL FUNCTION

i. BUN > 1.3x baseline

ii. Creatinine > 1.3x baseline

d. ELECTROLYTES

i. Potassium < 0.9x baseline or > 1.1x baseline

ii. Sodium < 0.9x baseline or > 1.1x baseline

iii. Calcium < 0.9x baseline or > 1.1x baseline

8.7 ECG

ECG results will be tabulated at Baseline as “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”. At follow-up visits, ECG results will be tabulated as “no change from Baseline”, “NOT clinically significant change from Baseline” or “clinically significant change from Baseline”. A by-patient listing will be provided for ECGs which are deemed clinically significant.

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APPENDICES

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APPENDIX 2 VFQ-25 SCORE CALCULATION

The scoring of VFQ-25[2, 3] with or without optional items will be based on the following two-step process:

Step 1. VFQ-25 Scoring rules

Original numeric values from the survey are re-coded following the scoring rules outlined in Table 1. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

Table 1. Scoring Key: Recording of Items

Item (Question) Numbers	Change original response category[(a)]	To recoded value of:
1,3,4,15c[(b)]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25,	1	0
	2	25
	3	50
	4	75
	5	100

(a). Precoded response choices as printed in the questionnaire.
(b). Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.
* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Step 2. Sub-scale Scoring

Items within each sub-scale were averaged together to create the 12 sub-scale scores. Items that were left blank (missing data) were not taken into account when calculating the scale scores. Sub-scales with at least one item answered could be used to generate a sub-scale score. Hence, scores represented the average for all items in the sub-scale that the respondent answered.

Table 2 shows 12 vision-targeted subscales that were generated by averaging the items contributing to each specific sub-scale.

Table 2. Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of Items	Items to be Averaged
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Vision Activities	3	5, 6, 7
Distance Vision Activities	3	8, 9, 14
Vision Specific		
• Social Functioning	2	11, 13
• Mental Health	4	3, 21, 22, 25
• Role Difficulties	2	17, 18
• Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Composite Score Calculation:

To calculate an overall composite score for the VFQ-25, the vision-targeted sub-scale scores are simply averaged, excluding the general health-rating question. By averaging the sub-scale scores rather than the individual items, equal weight is given to each sub-scale.