NCT Number NCT03362190

Official Study Title: A Phase 2A Open-label Trial to Assess the Safety of ZIMURA™ (Anti-C5) Administered in Combination With LUCENTIS® 0.5 mg in Treatment Naive Subjects With Neovascular Age Related Macular Degeneration

Document: Statistical Analysis Plan

Date of Document: 25-Sep-2018

STATISTICAL ANALYSIS PLAN

SPONSOR:	OPHTHOTECH
PROTOCOL TITLE:	A PHASE 2A OPEN-LABEL TRIAL TO ASSESS THE SAFETY OF ZIMURA™ (ANTI-C5) ADMINISTERED IN COMBINATION WITH LUCENTIS® 0.5 MG IN TREATMENT NAÏVE SUBJECTS WITH NEOVASCULAR AGE RELATED MACULAR DEGENERATION
STUDY CODE:	OPH2007

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

[redacted]

TABLE OF CONTENTS

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
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical Coherence Tomography
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: OPH2007.

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 OBJECTIVE

The objective of this study is to assess the safety of intravitreal Zimura™ administered in combination with Lucentis® 0.5 mg in treatment naïve subjects with neovascular age related macular degeneration (NVAMD)

2.1.1 Safety Endpoints

Safety endpoints include:

- Adverse events (AEs)
- Vital signs (respiration, heart rate, systolic and diastolic blood pressure, etc.)
- ECG recordings
- Ophthalmic variables (visual acuity, IOP, ophthalmologic examination, stereoscopic fundus photography, fluorescein angiography, and spectral domain optical coherence tomography)
- Laboratory variables (blood: hematology, renal function, hepatic function, and electrolytes; urine: urinalysis)

2.2 STUDY DESIGN

OPH2007 is a Phase 2A open-label trial to assess the safety of Zimura™ (ANTI-C5) administered in combination with Lucentis® 0.5mg in treatment naïve subjects with neovascular age related macular degeneration.

There will be 4 dosing cohorts on this trial. Approximately 60 subjects will be enrolled; 10 subjects in cohorts 1 and 2 and 20 subjects in cohorts 3 and 4.

Cohort 1

Administered Day 1 – Month 5, in the following sequence, 2 days apart:

- D0: Lucentis® 0.5 mg/eye
- D2: Zimura™ 4 mg/eye (administered as two injections of Zimura 2 mg/eye)

Cohort 2

Administered Day 1 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 3

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence:

- Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

Cohort 4

Induction Phase: Administered Day 1 – Month 2, in the following sequence, 14 days apart:

- D0: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day
- D14: Zimura™ 2 mg/eye

Maintenance Phase: Administered Month 3 – Month 5, in the following sequence, 2 days apart:

- D0: Zimura™ 2 mg/eye
- D2: Lucentis® 0.5 mg/eye followed by Zimura™ 2 mg/eye on the same day

All subjects will have a final follow-up visit at Month 6.

The first 10 subjects will be enrolled into Cohort 1 according to the procedures noted below.

The first three subjects will be assigned to Cohort 1 (Lucentis® 0.5 mg and Zimura™ 4 mg). Once the 3rd subject completes a safety period of one week after the first dose of Zimura™ 4 mg without the occurrence of a dose limiting toxicity as defined in the Study Protocol, Section 9.2.3 Dose Limiting Toxicity, full enrollment of Cohort 1 may commence.

If a DLT occurs in one or more of the first 3 subjects assigned to Cohort 1, then the Ophthotech medical team will evaluate all available data and either discontinue Cohort 1 or enroll an additional three subjects (for a total of 6 subjects) in Cohort 1. If the three additional subjects are enrolled, and no additional DLT occurs once the second set of 3 subjects in Cohort 1 has reached one week after the first dose of Zimura™ 4 mg/eye, full enrollment of Cohort 1 may commence. If one or more DLTs occur in the second set of 3 subjects, a discussion of safety data will be held among the

Ophthotech medical team to review the observed toxicities and determine whether Cohort 1 may proceed.

Once Cohort 1 has been fully enrolled, or if enrollment has been stopped due to one or more DLTs, then enrollment in the remaining 3 cohorts may commence. Subjects will be randomized in a 1:2:2 ratio to Cohort 2, Cohort 3, or Cohort 4.

2.3 SAMPLE SIZE AND RANDOMIZATION

As this study is not designed to perform formal hypothesis testing, there is no formal sample size calculation. The sample size selected is based on a reasonable number of subjects to understand the safety variables of the proposed regimen and to improve upon the study design prior to performance of controlled trials that may be initiated in the future. Approximately 60 subjects will be enrolled, 10 subjects each in cohorts 1, 2 and 20 subjects each in cohorts 3, 4.

Once all subjects have been enrolled in cohort 1, subjects will be centrally allocated to one of the three remaining treatment cohorts using a randomization list generated by a block randomization.

3 GENERAL ANALYSIS DEFINITIONS

3.1 STUDY PERIOD AND VISIT WINDOW DEFINITIONS

Cohort 1

Assessment	Scr	Day 1[1] (Baseline)		Day 9[7]	Month 1		Month 2		Month 3		Month 4		Month 5		Month 6 /EW
		D0	D2		D0	D2	D0	D2	D0	D2	D0	D2	D0	D2	
Informed consent	X														
Medical & Ophthalmic history	X														
Vital signs/Physical exam[2]	X			X											X
12-Lead ECG	X														X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[8]							X						X
Fluorescein angiography[5]	X	X[8]							X						X
SD-optical coherence tomography (SD-OCT)[5]	X	X[8]		X	X		X		X		X		X		X
Laboratory tests	X			X											X
Serum pregnancy test (if applicable)	X														
Reconfirmation of Eligibility		X													
Zimura™ 4mg/eye: two Zimura™ 2 mg/eye Injections			X			X		X		X		X		X	
Lucentis® 0.5 mg/eye Injection		X			X		X		X		X		X		
3-Day Post-Injection Telephone Safety Check			X			X		X		X		X		X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 Visit 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 at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify any IOP ≥ 30mm Hg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Day 9 will apply to the DLT cohort only. The DLT cohort is defined as the first 3-6 subjects (depending on if DLTs are noted) enrolled in Cohort 1.
[8]Imaging at Day 1 may be repeated if required per section 10.2.1.1 Reconfirmation of Eligibility at Day 1
EW = Early Withdrawal Visit
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.2
D0 = The first day of dosing at each monthly timepoint. D2 = The second day of dosing, 2 days after D0.

Cohort 2

Assessment	Scr	Day1[1] (Baseline)	M1	Month 2	Month 3	Month 4	Month 5	Month 6/ EW
Informed consent	X							
Medical & Ophthalmic history	X							
Vital signs/Physical exam[2]	X							X
12-Lead ECG	X							X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]			X			X
Fluorescein angiography[5]	X	X[7]			X			X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]	X	X	X	X	X	X
Laboratory tests	X							X
Serum pregnancy test (if applicable)	X							
Reconfirmation of Eligibility		X						
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X	X	X	X	X	X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	
Concomitant medication assessment	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X

[1]Day 1 Visit 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 at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify any IOP ≥ 30mm Hg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.3.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.3.

Cohort 3

Assessment	Scr	Induction Phase						Maintenance Phase			Month 6 /EW
		Day 1[1] (Baseline)		Month 1		Month 2		Month 3	Month 4	Month 5	
		D0	D14	D0	D14	D0	D14				
Informed consent	X										
Medical & Ophthalmic history	X										
Vital signs/Physical exam[2]	X										X
12-Lead ECG	X										X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]						X			X
Fluorescein angiography[5]	X	X[7]						X			X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]		X		X		X	X	X	X
Laboratory tests	X										X
Serum pregnancy test (if applicable)	X										
Reconfirmation of Eligibility		X									
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X		X		X		X	X	X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X	X	X	X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X	X	X	X

[1]Day 1 Visit 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 at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify any IOP ≥ 30mm Hg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.4.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.4.
D0 = The first day of dosing at each monthly timepoint. D14 = The second day of dosing, 14 days after D0.

Cohort 4

Assessment	Scr	Induction Phase						Maintenance Phase						Month 6 /EW
		Day 1[1] (Baseline)		Month 1		Month 2		Month 3		Month 4		Month 5		
		D0	D14	D0	D14	D0	D14	D0	D2	D0	D2	D0	D2	
Informed consent	X													
Medical & Ophthalmic history	X													
Vital signs/Physical exam[2]	X													X
12-Lead ECG	X													X
Tonometry[3,4,5]/ Ophthalmologic examination[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protocol refraction and VA using ETDRS chart[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color fundus photography[5]	X	X[7]						X						X
Fluorescein angiography[5]	X	X[7]						X						X
SD-optical coherence tomography (SD-OCT)[5]	X	X[7]		X		X		X		X		X		X
Laboratory tests	X													X
Serum pregnancy test (if applicable)	X													
Reconfirmation of Eligibility		X												
Zimura™ 2 mg/eye Injection		X	X	X	X	X	X	X	X	X	X	X	X	
Lucentis® 0.5 mg/eye Injection		X		X		X			X		X		X	
3-Day Post-Injection Telephone Safety Check		X	X	X	X	X	X		X		X		X	
Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[6]		X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Day 1 Visit 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 at all indicated timepoints.
[3]Goldmann applanation tonometry must be performed at Screening, Day 1, and Month 6/EW. The Tono-Pen may be used at other times; however, Goldmann applanation tonometry must be used to verify any IOP ≥ 30mm Hg occurring more than 30 min post-injection, or any IOP ≥ 30 mmHg at any other time.
[4]Tonometry should be measured prior to the first injection, after the first injection, and after the final injection and at any additional times as specified by the Intravitreal Administration Protocol (see Section 17.4).
[5]Ocular assessments performed at Screening, Month 3, Month 6, and Early Withdrawal should be performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
[6]All adverse events are to be recorded after first injection.
[7]Imaging at Day 1 may be repeated if required per section 10.5.1.1 Reconfirmation of Eligibility at Day 1.
EW = Early Withdrawal Visit.
VISIT WINDOWS: It is essential that subjects adhere to their prescheduled study visits within the specified visit window outlined in section 10.5.
D0 = The first day of dosing at each monthly timepoint. D2 = The second day of dosing, 2 days after D0. D14 = The second day of dosing, 14 days after D0

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 Full Analysis Population

The Full Analysis Population will consist of all subjects enrolled in Cohort 1 or subjects randomized in Cohorts 2, 3, or 4 who did not fail screening.

3.2.2 Safety Population

The Safety population will include all subjects in the Full Analysis Population who received at least one study drug.

3.3 DATA HANDLING CONVENTIONS

3.3.1 General Conventions

Data will be analysed using SAS (Version 9.4 or later) or R. Descriptive analyses will be performed on baseline, safety data. All tables will be created with the 4 dosing cohorts presented in columns, unless otherwise specified.

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.).

3.3.2 Visit Windows

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

Missing scheduled follow-up visits 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**.

3.3.3 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.

3.3.4 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.

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

4 STUDY SUBJECTS

4.1 DISPOSITION OF SUBJECTS

The number of subjects screened, assigned (if Cohort 1)/randomized (if Cohorts 2, 3, or 4), and treated will be presented. The reason for exclusion from one or more analysis sets will be summarized.

Disposition will be summarized for the Safety Population. The frequency and percentage of premature discontinuations from the study prior to Month 6 will be presented by cohort and overall. The primary reason for non-completion of the study will be summarized. The details of the 'Adverse event', 'Protocol violation', '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 cohorts they will be reported for safety analyses:

For example, if subjects were:

- Assigned a cohort (regardless of error) but not treated, then they will be excluded for all safety analyses.
- For Cohorts 2, 3, and 4: Treated but not randomized, then by definition they will be reported under the cohort they actually followed for all safety analyses.

4.3 PROTOCOL VIOLATIONS

All protocol violations will be assessed and identified as "major" or "significant" by the sponsor. The final list of major protocol violations will be provided by the sponsor, and the criteria for significant protocol violation will be determined prior to the database lock. The significant protocol

[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.

violations will be summarized for the Safety population, and the details will be presented in a listing by subject and cohort.

4.4 INCLUSION AND EXCLUSION CRITERIA

A detailed listing of inclusion/exclusion criteria not met will be provided by subject for the Safety Population.

5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided to document baseline demographic information. This information may be used to informally assess similarity of the randomized groups at baseline, although no formal comparison will be conducted.

Descriptive statistics with respect to subject characteristics at baseline will be displayed for the Safety population. 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 pre-injection values.

The variables to be summarized are:

- Gender, Ethnicity, Race, Iris color, Age, Current smoking status, Study Eye, Region
- 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, Respiratory Rate)
- 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
    - Fluorescein Angiography:
        - CNV location (extrafoveal, juxtafoveal, subfoveal)
        - CNV type (predominantly classic, minimally classic, occult)
        - Area of choroidal neovascularization (CNV) (defined as classic CNV + occult CNV + RPE staining in mm^2)
        - Area of total lesion (mm^2)
    - Optical Coherence Tomography (OCT)
        - SHRM within the center 1mm (yes/no)
        - SHRM (µm)
        - RPE elevation
        - Central subfield thickness (µm)

6 PRIOR AND CONCOMITANT MEDICATION

All prior and concomitant medications will be summarized separately by WHO Drug code (Version 3, SEP 2017) on the Safety 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.

7 SAFETY EVALUATION

All safety analyses will be performed on the Safety population. Missing values of safety data will not be imputed and safety summaries will be based on the observed cases.

7.1 EXTENT OF EXPOSURE

Exposure to each study medication will be evaluated for each cohort 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).

7.2 ETDRS VISUAL ACUITY

ETDRS Visual acuity values and changes from baseline will be presented in a summary table by visit and cohort for the Safety Population.

The principal visual acuity outcome measure will be the mean change in visual acuity (MCVA) from Baseline to Month 6. Supportive measures will be the percentage of subjects gaining ≥5,

≥10, ≥15, ≥20 letters, and losing ≥0, ≥10, and ≥15 letters from Baseline to Month 6. Additionally, the number and percentage of subjects meeting each of the following criteria at Month 6 will be summarized: ETDRS Snellen Equivalent of 20/25 or better, ETDRS Snellen Equivalent of 20/40 or better, and ETDRS Snellen Equivalent of 20/125 or worse.

[redacted]

- [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]

[redacted]

7.3 OPTICAL COHERENCE TOMOGRAPHY AND FLUORESCEIN ANGIOGRAPHY

Descriptive analysis will be conducted on the following supportive imaging endpoints:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

[redacted]

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

7.4 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.

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 dose of study drug) and up to and including 30 days after the last dose of study drug.

All AEs will be coded using MedDRA (Version 21.0) 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
- All TEAEs (regardless of the relationship to study drugs) with PT occurring ≥ 5% frequency based on total subjects
- TEAEs related to study drugs
- TEAEs related to injection procedure
- TEAEs by the maximum severity grade
- Systemic TEAEs
- Systemic TEAEs related to study drugs
- Systemic TEAEs related to injection procedure
- 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
- All Ocular TEAEs by fellow eye
- Study drug related Ocular TEAEs by study eye
- Study drug related Ocular TEAEs by fellow eye
- Injection procedure related Ocular TEAEs by study eye
- Injection procedure related Ocular TEAEs by 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
- 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.

7.5 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).

7.6 VITAL SIGNS

Descriptive statistics at each time point up through and including the Month 6 visit will be used to display the changes from Baseline for pulse, respiratory rate, and blood pressure (systolic and diastolic). Mean change of pulse, respiratory rate, and blood pressure (systolic and diastolic) from Baseline to the last measurement will be provided.

7.7 OPHTHALMIC VARIABLES

Ophthalmic Examination. The following ophthalmic examination variables will be analysed by shift table from Baseline to the pre-injection examination on Month 6 and from Baseline to the last visit (pre-injection) available (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 6 and for the last visit available, 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 vitreous haze (0, 1+, 2+, 3+, 4+)
- Examination of 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 (also called Baseline in the protocol) 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 cohort, visit, and injection time (pre-injection, IOP after first injection, IOP after second injection).

"IOP after first/second 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.

7.8 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 6 visit (mean, SD, median, minimum, Q1, Q3, maximum, N)
- Value changes from Baseline to each scheduled visit up through the Month 6 visit (mean, SD, median, minimum, Q1, Q3, maximum, N)

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, Bicarbonate, Calcium, Phosphorus Inorganic, Creatinine, Urea Nitrogen, Total bilirubin, GGT, Alkaline phosphatase, SGOT/AST, SGPT/ALT).

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.

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 6. 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

7.9 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.

8 ANALYSES NOT SPECIFIED IN PROTOCOL

Analysis of ETDRS visual acuity may be conducted on a per-protocol population defined by the subjects who did not have a significant protocol violation (Section 4.3). Any hypothesis testing performed as part of this analysis will be considered exploratory.

APPENDICES

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