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Study X82-OPH-201 v4.0

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Statistical Analysis Plan

Sponsor:	TYROGENEX
Protocol Title:	A RANDOMIZED, DOUBLE-MASKED, PLACEBO-CONTROLLED, DOSE-FINDING, NON-INFERIORITY STUDY OF X-82 PLUS *PRN* ivt anti-VEGF COMPARED TO *PRN* ivt anti-VEGF MONOTHERAPY IN NEOVASCULAR AMD
Study Code:	X82-OPH-201

For IDDI:

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For Sponsor:

Reviewer: Jen Cerami, Clinical Research Manager

Approver: Daniel E. Salazar, Ph.D., Senior Vice President, Development

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Revision History

Version	Summary of Revisions
1.0	N/A
2.0	Updated footer with correct date (from 28 November 2016 to 13 January 2017) and changed Version: 'DRAFT' to 'FINAL'.
3.0	Changed main analysis set from PP to ITT. Added an additional other efficacy outcome: Proportion of patients maintaining vision at week 52 (losing <15 letters on ETDRS chart). Changed Daniel E. Salazar from reviewer to approver.
4.0	Added a second interim analysis. Added other efficacy outcomes for subjects enrolled with unilateral disease: Conversion of fellow eye by 52 Weeks, change in visual acuity, and number of injections per year at 52 weeks in fellow eye. Defined major deviation criteria for exclusion from Per Protocol Population. Specified other OCT variables. Added safety outcome: Cardiovascular adverse events of interest.

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1. List of Abbreviations and Definition of Terms

Abbreviation	Term	
AE	Adverse Event	
AMD	Age-related Macular Degeneration	
ATC	Anatomic Therapeutic Chemical Classification	
BCVA	Best Corrected Visual Acuity	
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration	
CNV	Choroidal Neovascularization	
DSMB	Data and Safety Monitoring Board	
ETDRS	Early Treatment Diabetic Retinopathy Study	
FA	Fluorescein Angiography	
ICH	International Conference on Harmonization	
IOP	Intraocular Pressure	
IRC	Independent Reading Center	
IVT	Intravitreous	
MAR	Missing at Random	
MedDRA	Medical Dictionary for Regulatory Activities	
MNAR	Missing Not at Random	
MRM	Model for Repeated Measures	
NCI-CTC	National Cancer Institute – Common Terminology Criteria	
NCMV	Neighboring-Case Missing Value	
OS	Oculus Sinister	
OD	Oculus Dexter	
OU	Oculi Uterque	
PT	Preferred Term	
REML	Restricted Maximum Likelihood	
SAE	Serious Adverse Event	
SAP	Statistical Analysis Plan	
SD	Standard Deviation	
SD-OCT	Spectral Domain Optical Coherence Tomography	
SOC	System Organ Class	
TEAE	Treatment-Emergent Adverse Event	
VEGF	Vascular Endothelial Growth Factor	

2. Introduction

This statistical analysis plan (SAP) was written to detail the planned statistical analyses of efficacy and safety data for the primary analysis of clinical trial X82-OPH-201 conducted in the United States. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of the plan.

This statistical analysis plan does not describe the analyses of safety which will be conducted for Data and Safety Monitoring Board (DSMB) review. Please refer to the DSMB charter for more information on these analyses.

This statistical analysis plan is based on the Study Protocol Version 10.

3. Study Design and Objectives

3.1 Study Objective

The objective of this study is to evaluate the efficacy and safety of X-82 at three doses, in subjects with wet AMD as determined by comparison of the mean ETDRS visual acuity scores at Week 52.

3.1.1 Primary Efficacy Outcome

The primary outcome is the change in visual acuity score from Day -1 to 52 Weeks after randomization in study eye.

3.1.2 Secondary Efficacy Outcome

The secondary outcome is the number of ivt anti-VEGF injections during the first 52 Weeks after randomization in study eye.

3.1.3 Other Efficacy Outcomes

- Proportion of subjects maintaining vision at 52 Weeks (losing <15 letters from Day -1 on ETDRS chart) in study eye and fellow eye.
- Mean changes in CNV, total and active lesion sizes on FA from Day -1 at 52 Weeks in study eye and fellow eye
- Mean changes in retinal thickness on SD-OCT from Day -1 at 52 Weeks in study eye and fellow eye
- Other variables derived from the SD-OCT measurements in study eye and fellow eye
- Time from Day 1 to first anti-VEGF injection in study eye
- Conversion of fellow eye by 52 Weeks in subjects enrolled with unilateral disease
- Mean change in visual acuity score from Day -1 to 52 Weeks after randomization in fellow eye
- Mean change in visual acuity score from Day -1 to 52 Weeks after randomization in fellow eye of subjects enrolled with unilateral disease
- Number of ivt anti-VEGF injections during the first 52 Weeks after randomization in fellow eye
- Number of ivt anti-VEGF injections during the first 52 Weeks after randomization in fellow eye of subjects enrolled with unilateral disease

3.1.4 Safety Outcomes

- Incidence of serious adverse events (SAEs) and adverse events (AEs)
- Ophthalmic variables (including IOP)
- Laboratory Assessments
- Vital Signs
- ECG
- Cardiovascular adverse events of interest

3.2 Study Design

This is a randomized, double-masked, placebo-controlled study in which at least 132 subjects will be randomized to receive 50 mg, 100 mg, 200 mg of X-82, or matching placebo tablets daily for 52 weeks. Subjects requiring frequent injections of ivt anti-VEGF (an interval no greater than 8 weeks) and with the presence of any macular fluid and macular thickness on SD-OCT will receive an injection of anti-VEGF during Screening Visit 1 and return for Screening Visit 2 to document a reduction in macular fluid or macular thickness, which will be confirmed by the Independent Reading Center (IRC). If a subject does not demonstrate any reduction of macular fluid or macular thickness at Screening Visit 2 and the investigator believes the subject may not have had enough time to achieve such a reduction, subjects may be re-screened for Screening Visit 2 as long as the visit occurs within the protocol specified window [Day -14 (+/- 7 days)]. Subjects with a reduction in macular fluid or macular thickness will undergo additional screening assessments and be enrolled into the study. Subjects will receive a further injection of anti-VEGF at Day -1 and start study treatment the following day. All subjects will remain on study treatment for 52 weeks and be assessed for the need for further injections of anti-VEGF every 4 weeks for that period.

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Schedule of Assessments

Assessment	Screening Visit 1	Screening Visit 2	Day -1	Weeks 4 to 48	Week 52	1 Month Post-Treatment Follow-up	Early Termination
Visit Window	Day -29	Day -14 (-7/+7)	Day -1 (+3)	±7 days	±7 days	±7 days	
Informed Consent	X[3]						
Randomization			X				
Demographics	X						
Med History/Con Meds	X						
Ophthalmic History	X						
Vital Signs		X		X	X	X	X
Height and Weight		X			X*		X*
Labs and Urinalysis		X		X	X	X	X
Pharmacokinetic Sampling				X[1]			
Pharmacogenetic Sampling					X		X
ECG		X		X[2]	X		X
Urine Pregnancy Test		X					
Ophthalmic Exam		X	X	X	X	X	X
IOP		X	X	X	X	X	X
ETDRS Visual Acuity		X	X	X	X	X	X
Study Medication Dispensed & Review of Dispensing Log			X	X			
FA & Photos (sent to IRC)		X			X		X
SD-OCT (sent to IRC)	X	X	X	X	X	X	X
Mandatory anti-VEGF Injection	X		X				
anti-VEGF injection if required (*prn*)				X	X	X**	X
AEs/ConMed Changes	X	X	X	X	X	X	X

** Anti-VEGF therapy after week 52 will be standard of care for each ophthalmology practice

* weight only

[1] Week 4, Week 16 ***or*** Week 20, ***and*** Week 40, 44 ***or*** Week 48 only

[2] Week 4 only

[3] Consent obtained from patients prior to any pre-screening which results in the change of the patients' standard of care or management

3.3 Sample Size Justification

At least one hundred and thirty two (132) subjects will be randomized to 50, 100, 200 mg X-82 or placebo qd in a 1:1:1:1 ratio (33:33:33:33 subjects) at 35 to 45 sites in the US.

Based on similarly designed trials with this outcome in this population of previously treated AMD subjects, the SD of the change in visual acuity was assumed equal to 15. However, upon recalculation of the sample size, the correct SD to reproduce the required sample size is 14.3. With a sample size of 132 subjects, the trial will have at least 80% power to conclude the non-inferiority of X-82 plus ivt anti-VEGF *prn* as compared to ivt anti-VEGF *prn* plus placebo in terms of visual acuity, using a non-inferiority margin equal to 9 ETDRS letters and a one-sided significance level of 0.05. This sample size was calculated assuming all doses are equally as efficacious, testing a difference in means for all 3 doses against placebo (i.e. using a randomization ratio of 3:1). Of note, this sample size calculation makes the conservative assumption that the dropout rate is as high as 20%, and that there is no treatment effect among dropouts; the required sample size is obtained by multiplying the randomized sample size by (1-dropout rate)^2. If assuming an allocation ratio of 1:1 to better examine the power of a pairwise comparison, there is 80% power accounting for a dropout rate up to 20% if the true SD is 11. Based on previous studies, a SD of less than 14 is reasonable [Busbee,2013].

3.4 Interim Analyses

3.4.1 Interim Analysis 1

An interim analysis is deemed necessary to enable the DSMB of the trial to perform a benefit/risk assessment including all efficacy and safety outcomes. This analysis will be conducted after 60 patients have reached their week 24 visit. The primary efficacy outcome of non-inferiority in change from randomization in VAS will be tested using an O'Brien-Fleming type Lan-DeMets alpha spending function, where the information fraction will be the percentage of patients that have completed their 52 week visit, though all available data will be used in the repeated measures model [DeMets, 1994]. There is no intention to stop early for efficacy, and the interim analysis will not be adequately powered to enable the DSMB to make such a recommendation. The spending function will however be used to adjust the significance level of the final analysis, given that the interim analysis is performed, should the trial continue unchanged. The adjustment has very little impact on the power of the trial, should the trial continue unchanged. If one or more of the doses of X82 is stopped for any reason, the final analysis will make allowance for this adaptive design change by considering that the doses dropped would have failed to reach significance in the Hochberg procedure described in Section 8.2.4. This approach protects the significance level for each of the doses tested in the final analysis.

An O'Brien-Fleming type Lan-DeMets beta spending function (using beta of 20%) will be used to assess futility at the time of the interim analysis. The futility boundary will be non-binding and used for information only.

3.4.2 Interim Analysis 2

After the first interim analysis was conducted, it was determined an additional interim analysis will be necessary to enable the Sponsor to plan future trials of X82 in wet AMD or other indications and to determine if 1,2, or all doses should be

discontinued. The second interim analysis will be reviewed by the DSMB and by a small group of individuals designated by the Sponsor.

The second interim analysis is planned to be performed once approximately 90% of all subjects have reached their week 36 visit. The primary efficacy outcome will be tested using the O-Brien-Fleming type Lan-Demets alpha spending function using the same approach as described in section 3.4.1. The calculation will take into consideration the first interim analysis, i.e. the first information fraction will be used in the calculation, along with the second information fraction. This accounts for the alpha that was spent at the first interim analysis, thus preserving the overall type I error of the entire trial. Since the purpose of this interim analysis is to fully explore the data to inform the design of a phase III trial, all endpoints, except the fluorescein angiogram endpoints, will be analyzed and a complete set of tables and figures will be produced for the interim as well as for the final analysis. If one or more of the doses of X82 is stopped for any reason, any hypothesis test result from the final analysis regarding those dropped doses will be considered exploratory. The Hochberg procedure described in Section 8.2.4 will be applied to all 3 doses to preserve the significance level at final analysis for testing of the doses not dropped.

4. General Analysis Definitions

Data will be analyzed using SAS (Version 9.3 or higher) or R version (3.0 or higher). Descriptive analyses will be performed on baseline, safety, and efficacy data. All tables will be created by treatment arm (X-82 50 mg, X-82 100 mg, X-82 200 mg, Placebo) and Overall, unless otherwise specified.

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them must be attributed to chance.

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 and maximum values.

Listings with individual values will be provided for all data presented in the tables.

4.1 Definition of Populations

4.1.1 Intention-To-Treat (ITT) Population

The Intention-To-Treat population (ITT) will consist of all randomized subjects, whether or not they receive one dose of study drug. Subjects who receive the wrong study medication will be analyzed in the arm to which they were randomized.

The primary, secondary, and other efficacy outcome analyses will be performed on the ITT population. This will be considered the main analysis set.

4.1.2 Per Protocol (PP) Population

The Per Protocol Population will consist of all ITT subjects without any major deviation of the protocol. Major deviations are deviations that will likely have a

significant impact on the primary analysis of visual acuity. These are considered major deviations:

1. Inclusion/exclusion criteria not met
2. Receiving an incorrect treatment kit (regardless of the treatment contained in the kit)
3. Missing >=15% of planned X-82 doses for the entire study

Subjects to be excluded from the Per Protocol Population based on the criteria above will be finalized at a pre-analysis meeting before database lock. This process is described in a separate document entitled 'Per Protocol Population Adjudication Process'.

The analyses of primary and secondary efficacy outcomes will be performed on the Per Protocol Population as a sensitivity analysis. Demographic information will also be provided on the Per Protocol Population.

4.1.3 Safety (SAF) Population

The Safety population will include all subjects who received at least one dose of study medication. Subjects will be analyzed according to the treatment arm corresponding to the majority of doses they actually received. For example, a subject randomized to the 50 mg arm where the majority of doses actually taken were 100 mg doses, the subject would be included in the 100 mg arm for safety analyses.

4.2 Definition of Baseline

A baseline measurement is defined as the last non-missing measurement taken on or before Day -1.

4.3 Study Completion

For the purposes of analysis, a subject will be considered a study completer if the subject has completed the Week 52 visit and has not answered "yes" to the question, "did the subject prematurely discontinue".

4.4 Calculated Variables

4.4.1 Study Day

The day of the first day of X-82 treatment is considered Study Day 1. The day before the first day of X-82 treatment is considered Day -1 (there is no Day 0). Calculation of Study Day is as follows:

- If the event date is ≥ date of first day of X-82 treatment, then Study Day = (event date – first day of X-82 treatment + 1)
- If the event date is < date of first day of X-82 treatment, then Study Day = (event date – first day of X-82 treatment)

4.4.2 Duration

The duration (days) between a start and stop date is calculated as (stop date – start date + 1).

4.5 Handling of Unscheduled and Early Withdrawal Visits

4.5.1 Visual Acuity Outcome

For by-visit summary tables of the visual acuity outcome, data from unscheduled visits will not be included, and early withdrawal will be considered a separate visit. Unscheduled visits will be included in the listing.

For the efficacy analyses of visual acuity using the model for repeated measures and proportion of subjects maintaining vision at week 52 (see Section 8 of this SAP), visit windowing will be used to assign unscheduled or early withdrawal visits in place of scheduled visits with missing visual acuity. The below table defines the windows (low, high) where an unscheduled or early withdrawal visit would be mapped to a visit. The process is as follows:

Consider all visits (scheduled, unscheduled, or early withdrawal) occurring in the visit windows defined below.

- If a scheduled visit exists with non-missing visual acuity, the data from this visit will be used in the analysis.
- If visual acuity is missing at a scheduled visit but unscheduled or early withdrawal visits occur in the visit window, the data from the visit closest to the Study Day Target (including before/after) will be used in the analysis. If there are two or more unscheduled or early withdrawal visits both closest and equidistant from the Study Day Target, the average of the visual acuity values from these visits will be used.

Study Day Target	Low	High	Assigned Visit
Day 29	1	43	Week 4
Day 57	44	71	Week 8
Day 85	72	99	Week 12
Day 113	100	127	Week 16
Day 141	128	155	Week 20
Day 169	156	183	Week 24
Day 197	184	211	Week 28
Day 225	212	239	Week 32
Day 253	240	267	Week 36
Day 281	268	295	Week 40
Day 309	296	323	Week 44
Day 337	324	351	Week 48
Day 365	352	379	Week 52

4.5.2 Safety Outcomes

For by-visit summary tables, data from unscheduled visits will not be included, and early withdrawal will be considered a separate visit. There will be no visit windowing for unscheduled visits.

Data from both unscheduled and early withdrawal visits will be considered for summaries of the worst post-baseline value.

4.6 Partial Dates

Missing or partially missing dates will not be imputed at the 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 effects 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 started after treatment.

4.7 Methods To Be Used For Handling Missing Data

4.7.1 Descriptive Analyses

When summarizing categorical variables, subjects with missing data are generally not included in the 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.

4.7.2 Inferential Analyses

Methods that take into account the presence of missing data and that yield valid estimates under the assumption of data missing at random (MAR) will be used for the primary efficacy analysis. In particular, a Model for Repeated Measures fitted by Restricted Maximum Likelihood (REML) will be used. Multiple imputation will be used in sensitivity analyses of the primary efficacy outcome to impute the missing VA data. No imputations will be made for analyses of secondary or other efficacy outcomes.

4.8 Additional Analyses not Listed in the Protocol

There may be additional exploratory analyses performed on the FA or OCT data as described in section 8.4.3 which are not listed in the protocol.

5. Study Subjects

5.1 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 number of subjects in each of the following randomization strata will also be presented:

1. Previous Treatment Schedule: every 6 weeks or less versus every 8 weeks (includes anything more than 6 weeks)
2. Anti-VEGF received: Eylea, Avastin, Lucentis

The frequency of premature discontinuations from the study will be given for the ITT population by treatment arm and overall. The primary reason for non-completion of the study will be summarized.

The details of the reason for the premature discontinuation ('Serious Adverse Event', 'Protocol Deviation', 'Adverse Event', 'Pregnancy', 'Withdrawal of Consent', 'Death', 'Investigator's Decision', 'Subject Never Took Study Treatment', 'Other') will be included in a listing.

5.2 Protocol Deviations

All protocol deviations will be assessed and identified prior to database lock to determine whether they are major. Subjects with major protocol deviations will be excluded from the Per-Protocol Population, as described in section 4.1.2.

The major protocol deviations will be summarized for the ITT Population. The details will be listed by subject and by treatment arm.

5.3 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.

5.4 Out of Window Visits

Visits that occur out of window according to the schedule of visits in protocol Section 9 and appendix 1 will be summarized by visit by dose, overall, and by subject.

5.5 Re-treatment Criteria Adherence

A cross tabulation of subjects who received re-treatment with anti-VEGF and who met re-treatment criteria in section 6.3 of protocol version 7 will be summarized. A listing of discrepancies will be provided by subject. The listing will include treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, anti-VEGF injection received at visit (Yes/No), re-treatment criteria met (Yes/No), and which re-treatment criteria was met (if applicable). This listing will be sorted by treatment arm, subject ID, and date of visit.

5.6 Food and Alcohol Intake

The percentages of subjects who report taking study drug with food and without alcohol as specified in the protocol section 6.2 will be summarized by visit overall and by dose. A listing of alcohol intake will be provided by subject. The listing will include treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, and alcohol taken with study drug (Yes/No/Do not recall). This listing will be sorted by treatment arm, subject ID, and date of visit.

6. 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. Demographic data will also be provided for the PP population.

The variables to be summarized are:

- Sex, Age, Race, Ethnicity
- Prior Ocular History (other than AMD) – Study Eye
- Medical History (other than Ocular History)
- Wet AMD History – Study Eye
- Vital Signs (Height, Weight, Pulse, Blood Pressure)
- Pregnancy Test (if done)
- Visual Acuity, both eyes
- Tonometry, both eyes
- ECG
- Ophthalmic exam, both eyes
- Imaging assessments, study eye

Prior ocular history (other than AMD) and medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. Subjects will only appear in the table once per System Organ Class (SOC) or Preferred Term (PT), although they may have experienced multiple events. Summary tables will be sorted alphabetically by SOC then by PT within SOC based on descending frequency in the Overall column.

A summary table will be created for Wet AMD History in the study eye and will contain the following information:

- Eye affected by Wet AMD (OS/OD)
- Time since diagnosis of Wet AMD (months), defined as (Date of Randomization – Date of diagnosis)/30.4375
- Prior Treatment for Wet AMD (Yes/No). If yes, number and percentage of subjects receiving Lucentis/ Avastin/ Macugen/ Eylea/ Other

The following listings will be created for demographics and other baseline characteristics:

- Demographics: treatment arm, subject ID, age, sex, race, and ethnicity. This listing will be sorted by treatment arm and subject ID.
- Prior Ocular History (other than AMD) – Both Eyes: treatment arm, subject ID, age sex, race, eye (OS, OD, OU), SOC, PT, reported term, start date, stop date, and concomitant treatment (Yes/No). This listing will be sorted by treatment arm, subject ID, start date, and reported term.
- Medical History (other than Ocular History): treatment arm, subject ID, age, sex, race, SOC, PT, reported term, start date, and stop date. This listing will be sorted by treatment arm, subject ID, start date, and reported term.
- Wet AMD History: treatment arm, subject ID, age, sex, race, eye (OS, OD, OU), affected by Wet AMD (Yes/No), date of diagnosis, prior treatment for AMD (Lucentis/ Avastin/ Macugen/ Eylea/ Other, specify), and number of injections. This listing will be sorted by treatment arm, subject ID, eye, prior treatment for AMD.

Baseline information for other safety and efficacy parameters are presented in listings as described in later sections of this SAP.

7. Prior and Concomitant Treatment

Prior treatments are defined as treatments which start or stop prior to the first dose of study drug. Concomitant treatments are defined as treatments which start or stop after the first dose of study drug. Treatments can be both prior and concomitant. If a strict determination can not be made due to missing date or month, the treatment may be considered both prior and concomitant.

7.1 Prior and Concomitant Medications

All prior and concomitant medications will be summarized separately by WHO Drug Code (Version 3 2014) on the ITT Population. Medication usage will be summarized according to the 1st level and the 4th level Anatomic Therapeutic Chemical (ATC) classification.

Subjects will only be included once in the respective summaries for any ATC level 1 (ATC1) or any ATC level 4 (ATC4) classification. The summary tables will be sorted alphabetically by ATC1 then by ATC4 within ATC1 based on descending frequency within the Overall column.

Prior and concomitant medications will be presented in a listing. This listing will display treatment arm, subject ID, age, sex, race, ATC1, ATC4, medication name, start date (Study Day of Start), stop date (Study Day of Stop), prior/concomitant (P/C), associated eye (OD, OS, OU), indication, and given to treat AE (Yes/No). This listing will be sorted by treatment arm, subject ID, start date, and reported term.

7.2 Prior and Concomitant Surgeries/Procedures

Prior and Concomitant surgeries/procedures will be coded using the same version of MedDRA as for Medical History. Summary tables will present prior and concomitant surgeries/procedures by SOC and PT for the ITT Population. Subjects will only be included in each summary once per SOC or PT. Each summary will be sorted alphabetically by SOC then by PT within SOC based on descending frequency within the Overall column.

A listing of all surgeries/procedures will be created. This listing will display treatment arm, subject ID, age, sex, race, SOC, PT, reported term, surgery/procedure date (Study Day), prior/concomitant (P/C), indication, and given to treat AE (Yes/No). The listing will be sorted by treatment arm, subject ID, surgery/procedure date, and reported term.

8. Efficacy Evaluation

Efficacy analyses will be conducted for the ITT Population and the primary and secondary efficacy outcome analyses will be repeated using the PP Population. The primary analysis will be based on a Model for Repeated Measures (MRM). This analysis provides valid estimates as long as the missing data mechanism fulfills the Missing at Random (MAR) assumption. No imputation will be done for the primary analysis.

Sensitivity analyses may be performed to assess the potential magnitude and direction of the impact of missing data.

Unless otherwise stated, summary tables will have columns for each treatment arm and an Overall column.

8.1 Control of Type I Error

The overall level of significance for the primary efficacy analysis is set at 5% (one-sided).

For the primary efficacy evaluation, a Hochberg adjustment will be used for the pairwise comparisons of each X-82 treatment arm with placebo at the 2 interim and final analyses, tested at an α determined by the O'Brien-Fleming type Lan-DeMets alpha spending function, where the information fractions will be the percentage of patients that have completed their 52 week visit. If one or more of the doses of X82 is stopped for any reason after the second interim analysis, any hypothesis test result from the final analysis regarding those dropped doses will be considered exploratory. The Hochberg procedure described in Section 8.2.4 will be applied to all 3 doses to preserve the significance level at final analysis for testing of the doses not dropped.

8.2 Analysis of Primary Efficacy Outcome

8.2.1 Best Corrected Visual Acuity (BCVA)

The Best Corrected Visual Acuity (BCVA) will be determined for each subject in each eye at each visit. The BCVA in the study eye will be used for the analyses. Details of the procedure are in Appendix 7 of the Study Protocol. The BCVA is calculated as follows:

- If 20 or more ETDRS letters are read correctly at 4 meters, the BCVA is calculated as that number of letters plus 30.
- If fewer than 20 ETDRS letters are read correctly at 4 meters, the BCVA is calculated as the number of letters read correctly at 1 meter plus the number, if any, read at 4 meters.
- If no letters are read correctly at either 4 meters or 1 meter, the BCVA score is recorded as 0.

8.2.2 MRM Model

The mean change in visual acuity (ETDRS BCVA) in each of the X-82 arms will be compared to the mean change in VA in the placebo arm from Day -1 up to and including the Week 52 visit for the study eye. A restricted maximum likelihood (REML)-based repeated measures approach will be used [Mallinckrodt,2008].

Data from all scheduled post-baseline visits up to and including the outcome visit (52 weeks) will be used in the analysis. The repeated measures model will include the fixed, categorical effects of treatment and visit and the treatment-by-visit interaction; the continuous, fixed covariate of baseline visual acuity score; the fixed, categorical effect of type of anti-VEGF received (Eylea, Avastin, Lucentis); and the baseline score-by-visit interaction.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The 3 pair-wise comparisons will be the tests for the treatment effect at the endpoint visit (52 weeks) obtained by using an appropriate contrast of the treatment-related model parameters. See Section 8.2.3 for testing details.

Pseudo code:

```
proc mixed data=VAdata method=reml;
 class usubjid trtn injtype visit;
 model vas_dif= visit trtn baseva injtype trtn*visit baseva*visit /
       ddfm=kenwardroger solution;
 repeated visit / type= UN subject=usubjid;
lsestimate trtn*visit "Placebo - Dose 1 at Week 52" [1,1 13] [-1,2 13]
       /lower testvalue=9 alpha=0.05 CL;
lsestimate trtn*visit "Placebo - Dose 2 at Week 52" [1,1 13] [-1,3 13]
       /lower testvalue=9 alpha=0.05 CL;
lsestimate trtn*visit "Placebo - Dose 3 at Week 52" [1,1 13] [-1,4 13]
       /lower testvalue=9 alpha=0.05 CL;
run;
```

Where

trtn= treatment assignment

Baseva= baseline VAS (continuous)

Injtype= injection type

8.2.3 Variance-Covariance Structure

An unstructured covariance matrix will first be used to model the within-subject errors, allowing flexibility in the variance and correlation estimates. If there are convergence problems in fitting the model, a heterogeneous Toeplitz covariance matrix will be used. This structure allows the correlation between observations to vary depending on the position of the observation in the longitudinal sequence. For example, the correlations between adjacent observations are assumed to be identical but are allowed to differ from the correlation between observations that are two positions apart in the sequence.

If there are still convergence problems, a first-order heterogeneous autoregressive structure will be considered in order to simplify the variance-covariance structure. This structure does allow the correlation between observations to depend on the position of the observations in the longitudinal sequence. However, it is less flexible than the heterogeneous Toeplitz structure because it assumes that the correlation is a function of the distance between observations, with observations measured further apart being less correlated.

If convergence problems remain, an autoregressive structure of order 1 will be considered as the final candidate. This structure allows the correlation between observations to depend on the position of those observations in the longitudinal sequence. However, it assumes that the correlation is a function of a single parameter.

8.2.4 Testing Procedure

The Hochberg procedure will be followed for testing the non-inferiority of the three doses versus placebo for both the interim and final analyses. The individual null hypotheses are that the doses are inferior to placebo by at least 9 letters. The overall alpha level for the testing procedure will be calculated at the 2 interim and final analyses using an alpha spending function to control for the type I error of 0.05.

Let θ_1, θ_2, and θ_3 represent the pairwise differences of each dose of X-82 with placebo in mean changes from baseline in VA at 52 weeks (placebo-treatment). Assume, without loss of generality, p_1, p_2, and p_3 are the unadjusted p-values from individual tests of H_{0i}: $\theta_i >= 9$, i=1,2,3 and assume $p_1 \geq p_2 \geq p_3$. Let α be the significance level appropriate for the analysis (interim or final), provided by the O'Brien-Fleming type Lan-DeMets alpha spending function, given the information fraction at the time of the analysis.

If $p_1 < \alpha$, then the conclusion is that all three doses are non-inferior to placebo and the choice of dose must be based on other considerations.

Otherwise, testing will proceed as follows: If $p_1 \geq \alpha$ and $p_2 < \alpha/2$, the doses corresponding to p_2 and p_3 are non-inferior to placebo. If $p_1 \geq \alpha$ and $p_2 \geq \alpha/2$ and $p_3 < \alpha/3$, the dose corresponding to p_3 is non-inferior to placebo. If $p_1 \geq \alpha$ and $p_2 \geq \alpha/2$ and $p_3 \geq \alpha/3$, no dose can be declared non-inferior to placebo.

8.2.5 Data Displays

A summary table will present summary statistics for VA at baseline and 52 weeks as well as the change from baseline at 52 weeks. Inferential statistics from the MRM model (difference in least squares means, standard error, Wald test statistic, p-value, and 95% asymptotic confidence interval) will be presented for the pairwise comparisons of each dose of X-82 with placebo. These will be obtained via appropriate contrasts in the MRM model.

A separate summary table will present summary statistics by treatment arm and by visit for VA and the change from baseline.

Plots of the mean VA over time will be created with overlay by treatment arm.

A listing will display the VA for each subject at each time point. This listing will include treatment arm, subject ID, age, sex, race, date of assessment, visit, and VA result. This listing will be sorted by treatment arm, subject ID, and date of assessment.

8.3 Analysis of Secondary Efficacy Outcome

A summary table will be created which will display summary statistics in each treatment arm for the number of anti-VEGF injections received (normalized for the number of months on study) during the first 52 weeks after randomization. The normalization will be calculated as

(number of anti-VEGF injections received)*12/(time on study in months)

Where the time on study (months) = (date of study completion/early discontinuation – date of randomization + 1)/30.4375.

A separate summary table will be created which will display the summary statistics in each treatment arm for the number of anti-VEGF injections received during the

first 52 weeks after randomization, in the subset of subjects who completed the study (see Section 4.3).

In addition, the secondary efficacy outcome (number of injections per year) will be tested for any dose reaching significance for the primary outcome (visual acuity) at the time of final analysis. A two-way analysis of variance will be performed with treatment arm and type of anti-VEGF (Eylea, Avastin, Lucentis) as categorical grouping variables and will be adjusted for previous treatment schedule as entered into the IWRS at the time of randomization (every 6 weeks or less versus every 8 weeks). Pairwise comparisons of X-82 dose groups with placebo will be conducted. The tests will use the same significance level for the secondary efficacy outcome as for the primary outcome (e.g. if α=0.04 at the final analysis for the primary efficacy outcome, the secondary efficacy outcome will be tested at α=0.04) and will use the Hochberg procedure. The normal distribution assumption will be checked by visual inspection of histograms of the distribution of the number of anti-VEGF injections within each treatment arm.

8.4 Analysis of Other Efficacy Outcomes

8.4.1 Analysis of Maintaining Vision at Week 52

Proportion of subjects maintaining vision at week 52 (loss of less than 15 letters from Day -1) will be summarized descriptively and any inferential analyses will be considered exploratory.

8.4.2 Imaging-Based Outcomes

Summary statistics for the following fluorescein angiogram endpoints in the study eye and fellow eye (of all subjects and of subjects with unilateral disease) will be presented by treatment arm and overall. The values at screening visit 2 and 52 weeks, as well as the change from screening visit 2 at 52 weeks will be presented for:

- Observed Classic, Occult, and Total CNV area (mm^2)
- Observed total lesion size (mm^2)
- Observed area of fibrosis (mm^2)
- Observed area of hemorrhage (mm^2)

Summary statistics for the following SD-OCT endpoints in the study eye and fellow eye (of all subjects and of subjects with unilateral disease) will be presented by treatment arm and overall. The values at screening visit 2 and 52 weeks as well as the change from screening visit 2 at 52 weeks will be presented for:

Main outcomes

- Observed central retinal lesion thickness (µm)
- Observed central subfield thickness (µm)
- Observed macular volume (mm^3)

Additional outcomes

- Observed greatest subretinal fluid height (µm)
- Presence of subretinal fluid(yes or no)
- Observed height of the RPE elevation (PED) (µm)
- Presence of inter-retinal cysts(yes or no)

Continuous imaging-based measurements by multiple readers will be averaged.

Separate listings will be produced for the FA and SD-OCT parameters. The listings will include treatment group, subject identifier, visit date (Study Day), visit, parameter, units, and result. The listings will be sorted by treatment group, subject identifier, and visit date.

8.4.3 Supportive Analysis of Time to First anti-VEGF Injection

The time from Day 1 to first anti-VEGF injection will be analyzed as a time-to-event variable using Kaplan-Meier methods. For subjects who receive an anti-VEGF injection after Day 1, the time to first injection (in Weeks) will be calculated as (Date of first anti-VEGF injection after Day 1 - Date of Day 1 + 1)/7. Otherwise, subjects who do not have an anti-VEGF injection after Day 1 will be censored at the date of their last visit. The Kaplan-Meier curves will be plotted for each treatment arm. Additionally, the median time to first anti-VEGF injection will be calculated for each treatment arm and displayed on the plot.

8.4.4 Analyses in Fellow Eye

It is of interest to examine how study drug affects the non-affected fellow eye. Analysis of the endpoints listed below will be conducted in the fellow eye. Endpoints will be summarized descriptively, and any inferential analyses will be considered exploratory:

The following analysis will be done only in subjects with unilateral disease. Subjects with unilateral disease are those with Wet AMD diagnosed only in the study eye at baseline:

- Conversion of Fellow Eye

Proportion of subjects developing bilateral AMD by 52 Weeks will be summarized descriptively. The development of Wet AMD in the fellow eye will be captured as an adverse event with MedDRA preferred term(AEDECOD) of 'Neovascular age-related macular degeneration'.

The following analyses will be done in all subjects as well as subjects with unilateral disease:

- Mean change in Visual Acuity

Mean change in visual acuity from Day -1 to Week 52 will be analyzed using the repeated measures model described in section 8.2.2.

- Number of Injections per Year

Mean number of injections per year will be analyzed using the approach described in 8.3.

8.5 Sensitivity Analyses

The primary and secondary efficacy analyses will be repeated on the PP Population.

For the primary efficacy analysis, multiple imputation may be applied to assess the impact of missing data. A model compatible with the following Missing Not At Random (MNAR) missingness mechanism 'pattern-mixture-model imputation' will be implemented (using SAS PROC MI). The missing values at a particular visit will

be imputed by using the pattern-mixture-model restrictions. In particular, Neighboring-Case Missing Value (NCMV) restrictions will be applied.

This approach can be applied to data with monotone missing data patterns. Hence, if necessary to apply the approach, the data will be transformed into the monotone patterns by considering the longest uninterrupted sequences of the measurements for the subjects and/or excluding a few measurement visits from modelling, to increase the number of monotone patterns in the data. In case data are re-shaped, the primary analysis MRM model will be applied to the re-shaped data as well.

No data imputations will be performed on the secondary efficacy analyses or other efficacy analyses.

9. Safety Evaluation

All safety analyses will be performed on the Safety Population. The analyses will be conducted according to the treatment that subjects actually received. Missing values of safety data will not be imputed, and safety summaries will be based on the observed cases. All safety summaries will be descriptive; there will be no inferential statistics produced for any safety endpoints.

All Safety summary tables will be presented by treatment arm and overall, unless otherwise specified.

9.1 Extent of Exposure

9.1.1 Exposure to X-82

A summary table of exposure to study drug will be created and will contain the following information:

- Frequency and percentage of subjects receiving all study drug
  1. If No, summary statistics of total number of days dose of study drug interrupted
  2. If No, frequency and percentage of subjects with reason for interruption of study drug ('Took only one of the two pills', 'Forgot to take the two pills', 'SAE/AE', 'Took four pills'). *Note: A subject may have more than one reason for dose interruption of study drug*

A dose interruption is defined by at least one or more days where a subject deviated from the planned dose.

A listing of exposure to study treatment will be created. The listing will include treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, anti-VEGF injection received at visit (Yes/No), did subject take all X-82 since last visit (Yes/No), number of days X-82 dose interrupted, and reason for X-82 dose interruption. This listing will be sorted by treatment arm, subject ID, and date of visit.

For all treatment arms, including placebo, a summary table of number of missed doses by subject by visit and for the entire 52-week period will be created. In addition, number of missed doses by visit and for the entire 52-week period per treatment group will be presented in a summary table for the ITT population. For subjects that terminate early, any doses after early termination will not be counted as missed.

9.1.2 Exposure to anti-VEGF Treatment

A summary table of exposure to anti-VEGF treatments will be created and will contain the following information:

- Frequency and percentage of subjects receiving anti-VEGF injection at Screening Visit 1 by type (Eylea, Avastin, Lucentis)
- Frequency and percentage of subjects receiving anti-VEGF injection on Day -1 by type (Eylea, Avastin, Lucentis)
- Summary statistics of number of Eylea injections received
- Summary statistics of number of Avastin injections received
- Summary statistics of number of Lucentis injections received

A listing of anti-VEGF exposure will be created. The listing will include treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, and anti-VEGF injection received (Eylea, Avastin, Lucentis). This listing will be sorted by treatment arm, subject ID, and date of visit.

9.2 Adverse Events

Adverse events which begin on or after 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 will be considered treatment-emergent adverse events (TEAEs). All adverse events will be coded using MedDRA version 17.1.

For TEAEs related to X-82, the possible option as entered in the eCRF is 'Related'. Refer to the Clinical Trial Protocol for specific definitions. Adverse events where the relationship to study drug is unknown will be classified as 'Related'. Related adverse events will further be classified by the Sponsor as 'Expected' or 'Unexpected' based on the definitions in the Study Protocol.

Ophthalmic TEAEs are those TEAEs which have a SOC of 'Eye Disorders', or SOC of 'Investigations' with PT 'Intraocular pressure increased'.

Cardiovascular events of interest(EOI) are those considered as acquired, non-traumatic heart or blood vessel diagnoses. Cardiovascular EOI are TEAEs which satisfy one of the following conditions:

1. SOC "Cardiac disorders", without high level group term (HLGT) "Congenital cardiac disorders"
2. SOC "Vascular disorders", without HLGT "Lymphatic vessel disorders", without HLGT "Vascular injuries"
3. SOC "Eye disorders", with only HLGT "Ocular haemorrhages and vascular disorders NEC"
4. SOC "Nervous system disorders", with only HLGT "Central nervous system vascular disorders", without high level term (HLT) "Traumatic central nervous system haemorrhages"

Summary tables will include only TEAEs, and listings will include all adverse events reported in the clinical database.

The following summaries of TEAEs will be provided:

- Overall summary of TEAEs (including number of subjects with at least one TEAE, number of subjects with at least one related TEAE, number of

subjects with at least one serious TEAE, number of subjects with at least one related serious TEAE, number of subjects with at least one severe TEAE, number of subjects with a TEAE leading to discontinuation, and number of subjects with a TEAE leading to death)

- TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Expected TEAEs by SOC and PT
- TEAEs by SOC, PT, and Severity
- Related TEAEs by SOC, PT, and Severity
- Ophthalmic TEAEs in Study Eye by PT
- Related Ophthalmic TEAEs in Study Eye by PT
- Ophthalmic TEAEs in Fellow Eye by PT
- Related Ophthalmic TEAEs in Fellow Eye by PT
- Cardiovascular Events of Interest by PT and Severity
- TEAEs leading to permanent discontinuation of study drug
- Related TEAEs leading to permanent discontinuation of study drug
- TEAEs leading to death
- Related TEAEs leading to death

For summaries by SOC and PT, a subject will only be counted once for each PT and once for the overall count for a SOC. However, subjects may be included in more than one PT category within a SOC. For summaries which also include severity, a subject who experiences the same event more than once will have the event with the worst severity counted in the summary. Summaries by SOC and PT will be presented alphabetically within SOC then by descending frequency of PT within SOC based on the overall column.

In addition to tabular summaries, listings will be created as follows:

- Overall listing of AEs containing treatment arm, subject ID, age, sex, race, SOC, PT, reported term, start date (Study Day of Start), stop date (Study Day of Stop), duration, TEAE (Y/N), serious (Y/N), associated eye (OD/OS/OU), severity (Mild/Moderate/Severe), relationship (Related/Not Related), outcome, action taken.
- Listing of Cardiovasular AEs will contain the same information as the Overall AE listing (the listing will only include AEs identified as Cardiovascular AEs)
- Listing of AEs leading to permanent discontinuation will contain the same information as the overall listing of AEs except for action taken (the listing will only include AEs with action = drug withdrawn).
- Listing of AEs leading to death will contain the same information as the overall listing of AEs except for outcome (the listing will only include AEs with outcome = fatal).

The adverse event listings will be sorted by treatment arm, subject ID, start date, and reported term.

9.3 Deaths and Serious Adverse Events

Serious adverse events (SAEs) will be summarized grouped by SOC and PT. Deaths will be summarized in a separate table which will include tabulations of the number of subjects who died as well as the reason for death.

In addition to tabular summaries, the following listings will be created:

- Listing of serious adverse events will be created by treatment arm including the treatment arm, subject ID, age, sex, race, SOC, PT, reported term, start date (Study Day of Start), stop date (Study Day of Stop), duration, TEAE (Y/N), associated eye (OD/OS/OU), severity (Mild/Moderate/Severe), relationship (Related/Not Related), outcome, action taken.
- Listing of deaths will be created which will include treatment arm, subject ID, age, sex, race, death date, reason for death, details (as provided in eCRF).

The SAE listing will be sorted by treatment arm, subject ID, start date, and reported term. The death listing will be sorted by treatment arm and subject ID.

9.4 Clinical Laboratory Determination

Clinical laboratory parameters will be graded (as applicable) using the National Cancer Institute's Common Terminology Criteria (NCI-CTC) version 4.03. Laboratory parameters which cannot be graded will be given the designation of 'Normal' or 'Abnormal', where 'Abnormal' is defined as outside of the range of [LLN, ULN].

Parameters to be summarized are as follows:

- **Hematology**: White Blood Cells, Absolute Neutrophil Count, Absolute Basophil Count, Absolute Eosinophil Count, Absolute Lymphocyte Count, Hematocrit, Hemoglobin, Platelets, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC)
- **Biochemistry**: Blood Glucose, Blood Urea Nitrogen, Creatinine, Sodium, Potassium, Magnesium, Chloride, Calcium, Phosphate, Carbon Dioxide, Alkaline Phosphatase, AST (SGOT), ALT (SGPT), Total Bilirubin, Total Protein, Albumin, Estimated Glomerular Filtration Rate (using the CKD-EPI equation)
- **Coagulation**: PT, PTT, INR
- **Thyroid Function**: Serum TSH, total T3, free T4
- **Additional Serum**: Lipase, Amylase, Creatinine Kinase
- **Urinalysis**: pH, Specific Gravity, Microscopic Examination

For continuous laboratory parameters, summaries of the values and changes from baseline will be presented for each visit by parameter. Plots of mean changes in laboratory values over time will be presented by dose group separately for the following parameters: ALT, AST, WBC, Absolute Neutrophil Count, Absolute Lymphocyte Count, Platelets, TSH, Free T4, Total T3.

For categorical laboratory parameters, the frequencies and percentages of subjects in each category at each visit will be presented by parameter.

Where applicable, the shift from baseline NCI-CTC grade to worst post-baseline NCI-CTC grade will be presented for each parameter. This summary will include all scheduled and unscheduled post-baseline visits in the derivation of worst post-baseline grade.

For parameters without NCI-CTC grading, the shift from baseline abnormality categorization ('Normal','Abnormal') to worst post-baseline abnormality categorization ('Normal','Abnormal') will be presented for each parameter. This

summary will include all scheduled and unscheduled post-baseline visits in the derivation of the worst post-baseline abnormality categorization.

A listing of clinical laboratory values will be created. This listing will include treatment arm, subject ID, age, sex, race, laboratory category, laboratory parameter, date of collection (Study Day), visit, result, units, LLN, ULN, NCI-CTC Grade (if applicable). Values to be considered abnormal (<LLN or >ULN) will be flagged in the listing. This listing will be sorted by treatment arm, subject ID, laboratory category, laboratory parameter, and date of collection.

9.5 Vital Signs, Physical Findings and Other Observations Related to Safety

9.5.1 Vital Signs

A summary table will be created to display the values and changes from baseline for vital sign parameters by visit. The vital sign parameters to be summarized are Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Pulse Rate (beats/min), Weight (kg), and Height (cm). Height will only be summarized at baseline.

A listing of vital signs will also be presented. This listing will display treatment arm, subject ID, age, sex, race, vital sign parameter (units), date of visit (Study Day), visit, results. This listing will be sorted by treatment arm, subject ID, vital sign parameter, and date of visit. Vitals signs which are outside of the following reference ranges will be flagged on the individual subject data listings: systolic blood pressure (100-150 mmHg), diastolic blood pressure (45-90 mmHg), heart rate (50-100 beats per minute [bpm]), body temperature (35.0°C-37.5°C), and respiratory rate (8-20 breaths/min).

9.5.2 Ophthalmic Examination

A by-visit summary table will be created to display the frequencies and percentages of subjects who have a lens status of 'Aphakic', 'Pseudo-phakic', or 'Phakic' for the study eye. For those subjects with lens status of 'Phakic' at a visit, the frequency and percentage of subjects with <1, 1.0, 1.5, 2.0, 2.5, 3.0, and >3 will be summarized separately for Nuclear, PSC, and Cortical categories.

A listing will be created to display the results of the ophthalmic examinations at all visits. This listing will display treatment arm, subject ID, age, sex, race, date of examination (Study Day), visit, OS Lens status (Nuclear, PSC, and Cortical, if phakic), and OD Lens status (Nuclear, PSC, and Cortical, if phakic). This listing will be sorted by treatment arm, subject ID, and date of examination.

9.5.3 Tonometry

A summary table will be created to display the values and changes from baseline for intraocular pressure (IOP) in the study eye by visit.

A listing will be created to display the IOP values at each visit. This listing will display treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, IOP value (OS), IOP value (OD), and IOP method. This listing will be sorted by treatment arm, subject ID, and date of visit.

9.5.4 ECG

A summary table will be created to display ECG results at baseline and at post-baseline visits. The frequencies and percentages of subjects in the 'Normal', 'Abnormal, Not Clinically Significant', 'Abnormal, Clinically Significant', 'Not Done' categories will be displayed.

A separate table will summarize values and changes from baseline in the ECG parameters at each visit. The parameters included will be Ventricular Heart Rate (beats/min), PR Interval (msec), RR Interval (msec), QRS Interval (msec), QT Interval (msec), and QTcF Interval (msec). QTcF (Fridericia's correction) is calculated as $QT/\sqrt[3]{RR}$, where QT is the QT interval measured in milliseconds, and RR is the RR interval measured in seconds.

A by-visit summary table will also be created to display the number and percentage of subjects who meet the following criteria:

- Increase in QTcF > 30 msec from baseline
- Increase in QTcF > 60 msec from baseline

Subjects who meet the criteria of Increase in > 60 msec will also be included in the count of subjects who meet the criteria of Increase in > 30 msec.

A listing will be created to display the parameter values and results from ECGs taken at all visits. The listing will display treatment arm, subject ID, age, sex, race, date of visit (Study Day), visit, time, Ventricular Heart Rate (beats/min), PR Interval (msec), RR Interval (msec), QRS Interval (msec), QT Interval (msec), and QTcF Interval (msec). This listing will be sorted by treatment arm, subject ID, ECG parameter, and date of visit. Values outside the following reference ranges will be flagged as low (L) or high (H) in the listing: Ventricular Heart Rate (45-90 beats/min); PR interval (111-209 msec), RR interval (667-1330 msec), QRS interval (<121 msec), QT interval (<481 msec), QTcF interval (<431 msec).

10. References

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11. List of Tables/Graphs/Listings

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14.2.14.3	Values and Mean Change from Screening Visit 2 in Height of the RPE elevation(PED) (µm) at 52 weeks in Subjects with Unilateral Disease – Fellow Eye - ITT Population
14.2.15.1	Presence of Inter-Retinal Cysts at Screening Visit 2 and 52 weeks – Study Eye - ITT Population
14.2.14.2	Presence of Inter-Retinal Cysts at Screening Visit 2 and 52 weeks in Subjects with Unilateral Disease– Fellow Eye - ITT Population
14.2.14.3	Presence of Inter-Retinal Cysts at Screening Visit 2 and 52 weeks in Subjects with Unilateral Disease – Fellow Eye - ITT Population
14.2.15.1	Conversion of Fellow Eye in Unilateral Subjects by 52 weeks – ITT Population
14.2.16.1	Mean Change from Baseline in VA at 52 weeks in Fellow Eye – ITT Population
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14.2.17.1	Anti-VEGF Injections received through 52 weeks after randomization in Fellow Eye – ITT Population
14.2.17.2	Anti-VEGF Injections received through 52 weeks after randomization in Fellow Eye in Subjects with Unilateral Disease– ITT Population

14.3.1.1	Extent of Exposure – X-82 – SAF Population
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14.3.1.3	Number of Missed Doses by Treatment and Overall by Visit and Overall- ITT Population
14.3.1.4	Number of Missed Doses by Subject by Visit and Overall
14.3.1.5	Summary of Food and Alcohol Intake - SAF Population
14.3.2.1	Summary of Treatment-Emergent Adverse Events – SAF Population
14.3.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – SAF Population
14.3.2.3	Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – SAF Population
14.3.2.4	Expected Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – SAF Population
14.3.3.1	Treatment-Emergent Adverse Events by Severity, by System Organ Class and Preferred Term – SAF Population
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14.3.4.1	Ophthalmic TEAEs by Preferred Term – Study Eye - SAF Population
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14.3.4.3	Ophthalmic TEAEs by Preferred Term – Fellow Eye - SAF Population
14.3.4.4	Related Ophthalmic TEAEs by Preferred Term – Fellow Eye - SAF Population
14.3.4.5	Cardiovascular Adverse Events of Interest by Preferred Term- SAF Population
14.3.5.1	Treatment-Emergent Adverse Events leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term – SAF Population
14.3.5.2	Related Treatment-Emergent Adverse Events leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term – SAF Population
14.3.6.1	Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term – SAF Population
14.3.6.2	Related Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term – SAF Population
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14.3.8	Deaths – SAF Population
14.3.9.1	Laboratory Data: Descriptive Statistics (Values and Changes from Baseline) by Visit – SAF Population
14.3.9.2	Laboratory Data: Descriptive Statistics (Frequencies per visit) – SAF Population
14.3.9.3	Laboratory Data: Baseline vs Worst Treatment-Emergent NCI-CTC Grade – SAF Population
14.3.9.4	Laboratory Data: Baseline vs Worst Treatment-Emergent Abnormality Grade – SAF Population
14.3.10	Summary of Vital Signs by Visit – SAF Population
14.3.11	Summary of Ophthalmic Examination Results by Visit – Study Eye – SAF Population

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14.3.12	Tonometry Intraocular Pressure (IOP) Values and Changes from Baseline by visit – Study Eye - Safety Population
14.3.13.1	Shifts in 12-Lead ECG Status by Visit – SAF Population
14.3.13.2	Summary of 12-Lead ECG Parameters by Visit – SAF Population
14.3.13.3	Abnormal Values of 12-Lead ECG Parameters – SAF Population

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11.2 List of Graphs

Graph Number	Title
14.2.1.1	Mean change in VA over time in Study Eye – ITT Population
14.2.1.2	Mean change in VA over time in Study Eye – PP Population
14.2.1.3	Mean change in VA over time in Fellow Eye– ITT Population
14.2.1.4	Mean change in VA over time in Fellow Eye in Subjects with Unilateral Disease – ITT Population
14.2.2.1	Mean VA over time in Study Eye – ITT Population
14.2.2.2	Mean VA over time in Study Eye – PP Population
14.2.2.3	Mean VA over time in Fellow Eye – ITT Population
14.2.2.4	Mean VA over time in Fellow Eye in Subjects with Unilateral Disease – ITT Population
14.2.3.1	Number of Anti-VEGF Injections per Year in Study Eye – ITT population
14.2.3.2	Number of Anti-VEGF Injections per Year in Fellow Eye in Subjects with Unilateral Disease-ITT population
14.2.3.3	Number of Anti-VEGF Injections per Year in Fellow Eye - ITT population
14.2.4.1	Kaplan-Meier Plot of Time from Day 1 to First Anti-VEGF Injection – ITT Population
14.3.1.1	Mean Change in ALT (U/L) over time – SAF Population
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14.3.1.3	Mean Change in WBC (THOU/MCL) over time – SAF Population
14.3.1.4	Mean Change in Absolute Neutrophil Count (THOU/MCL) over time – SAF Population
14.3.1.5	Mean Change in Absolute Lymphocyte Count (THOU/MCL) over time – SAF Population
14.3.1.6	Mean Change in Platelets (PER CUMM) over time – SAF Population
14.3.1.7	Mean Change in TSH (MCIU/ML) over time – SAF Population
14.3.1.8	Mean Change in Free T4 (NG/DL) over time – SAF Population
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11.3 List of Derived Data Listings

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16.1.2.2	Listing of Inclusion and Exclusion Criteria Not Met – ITT Population
16.1.2.3	Listing of Discrepancies between Stratification Factors in ID-net and MARVIN
16.1.2.4	Listing of Discrepancies between Retreatment Criteria and Retreatment by Applicable Protocol Amendment
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16.1.5.1	Listing of Prior and Concomitant Surgeries/Procedures – ITT Population
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16.3.2.2	Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug – SAF Population
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16.3.2.5	Listing of Cardiovascular Adverse Events of Interest- SAF Population
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16.3.4	Listing of Laboratory Data –SAF Population
16.3.5	Listing of Vital Signs – SAF Population
16.3.6	Listing of Ophthalmic Examination Results – SAF Population
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