UNITY
BIOTECHNOLOGY

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: UBX1325-03

Extension Phase Analyses (Part B) of A Phase 2, Prospective, Multicenter, Randomized, Double-Masked, Active-Controlled Study to Assess the Safety, Tolerability, and Evidence of Activity of a Repeat Intravitreal Injection of UBX1325 in Patients with Neovascular Age-Related Macular Degeneration

PHASE 2

Version 2.0
Date: September 1, 2023

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Revision History

Version	**Date**	**Summary of Revision**
1.0	10 March 2023	
2.0	01 September 2023	Update Part B analyses to focus on within group comparisons

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List of Abbreviations

Abbreviation	Definition
AAO	American Academy of Ophthalmology
AE	Adverse event
AMD	Age-related Macular Degeneration
AR	Adverse reaction
ATC4	Anatomical Therapeutic Chemical level 4
BCVA	Best corrected visual acuity
BMI	Body mass index
CFBL	Change from baseline
CFP	Color fundus photography
CI	Confidence interval
CNV	Choroidal neovascularization
CST	Central Subfield Thickness
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
Hg	Mercury
IOP	Intraocular pressure
IQR	Interquartile range
IRF	Intraretinal fluid
IVT	Intravitreal
LLVA	Low luminance visual acuity
LO	Last observation
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	Multi-focal electroretinography
MMRM	Mixed model for repeated measures
OCT-A	Optical coherence tomography angiography
POC	Proof of Concept
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	Spectral domain optical coherence tomography
SLE	Split lamp exam
SOC	System organ class
SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
TFL	Tables, figures, and listings
UBX1325	Investigational product
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the final, Week 48 dataset in study UBX1325-03. This SAP is based on the Protocol Version 4.0 Amendment 3 dated 6 February 2023. Specifications for tables, figures, and listings will be provided in a separate document.

Prior analyses (Part A) focused on the Week 24 data that compared UBX1325 vs aflibercept. Part B of the study, the Week 48 analyses, tests different hypotheses given the different dosing during Part B (extension Phase) of the study. The analyses specified in this SAP focus on Part B, post-week 24 through Week 48, with some analyses including data from Week 0 through Week 48. SAP version 1.0 was the basis for analyses of Part A.

This analysis plan was completed after the Week 24 analysis and the interim Week 40 analyses.

1.1. Design overview

This study is a Phase 2, proof-of-concept (POC), multicenter, randomized, double-masked, active-controlled study to assess the safety, tolerability, and evidence of activity of a repeat intravitreal injection (IVT) of UBX1325 in patients with Neovascular Age-Related Macular Degeneration (wet AMD). 50 patients were enrolled 1:1 to the repeat IVT injections of UBX1325 or active-controlled IVT (aflibercept) study arms, to assess the primary, secondary, and exploratory objectives. This is a multi-site clinical trial, with patients enrolled and treated at 14 sites in the US. The study will be active for approximately 31 months, including start-up. All patients will be followed for approximately 48 weeks.

1.2. Study objectives for Part B (extension phase)

1.2.1 Primary objective

- Assess safety, efficacy parameters, and retinal structure of patients from Week 24 through Week 48 in patients:
    1) taking UBX1325 monotherapy after UBX1325 monotherapy through Week 24
    2) taking Coadministration of UBX1325 with aflibercept after aflibercept monotherapy through Week 24.

1.2.2 Exploratory objective

- Explore anatomical and physiological responses within each dosing arm in Part B

1.3 Study endpoints

1.3.1 Primary endpoint

- Ocular and systemic safety and tolerability within each dosing arm in Part B as assessed by treatment emergent adverse events (TEAEs) post-Week 24 through Week 48.

1.3.2 Secondary endpoints

- Within group changes from baseline in BCVA at each Visit from Weeks 0-48 and Weeks 24-48.
- Within group changes from baseline in Low Luminance Visual Acuity (LLVA) at each Visit from Weeks 0-48 and Weeks 24-48.
- Within group changes from baseline in CST at each Visit from Weeks 0-48 and Weeks 24-48, as assessed by SD-OCT and read by a Central Reading Center
- Safety within each dosing arm post-Week 24 through Week 48

1.3.3 Exploratory endpoints

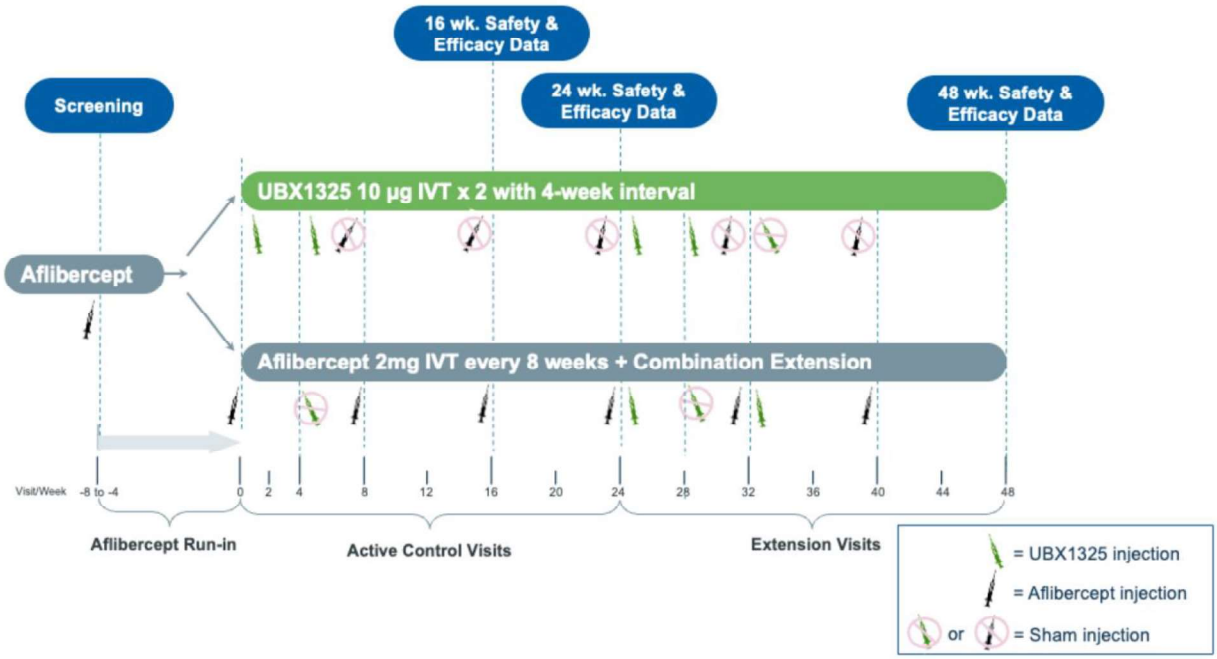
- Proportion of patients within each dosing arm who require anti-VEGF rescue treatments Week 0-48 and post-Week 24-48
- Tabulation of the longest rescue free interval for each patient within each dosing arm, weeks 0-48.
- Visitwise use of rescue medication for each patient.
- Results of multi-focal electroretinography (mfERG).

2. Study Methods

2.1 Trial design

This is a Phase 2, Proof-of-Concept (POC), prospective, randomized, double-masked active-controlled two-arm clinical trial. In Part A, patients meeting inclusion/exclusion criteria received a single run-in injection of aflibercept approximately 8 to 4 weeks prior to Day 1. Patients were randomized in a 1:1 ratio on Day 1 (Visit 1) to receive UBX1325 or aflibercept. Patients randomized to the UBX1325 arm receive a single 50 µL of 0.2 µg/µl solution UBX1325 IVT injection on Day 1 and Weeks 4, 24, and 28, and sham procedure on Weeks 8, 16, 24, 32, and 40. Patients randomized to the aflibercept arm receive aflibercept on Day 1 and Weeks 8, 16, 24, 32, and 40, UBX1325 in combination with aflibercept at weeks 24 and 32, and sham procedure on Weeks 4 and 28. Each patient is followed for up to a total of approximately 56 weeks (8-week screening period + 48-week follow-up period). This is a multicenter trial that enrolled patients at 14 sites in the US. A study schematic is shown below (Figure 1 from the study protocol). Schedule of visits and assessments is presented in Appendix A.

Figure 1 Schematic of Phase 2 Proof-of-Concept Study



2.2 Study population

This study enrolled patients ≥ 50 years of age with wet AMD and best corrected visual acuity (BCVA) between 70 to 20 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to approximately 20/40 to 20/400 on the Snellen chart) at Screening. Patients were required to have at least 2 anti-VEGF treatments in the study eye in the preceding 6 months prior to Screening (Visit 0), with the last injection within 4-8 weeks of Screening.

2.3 Randomization and masking

Randomization personnel of the Sponsor or designee generated the randomization schedule prior to the start of the study. An interactive web response system was used for patient randomization. All randomization information was stored in a secured area, accessible only by authorized personnel.

This study was double-masked, so patients and Investigators were masked to the treatment assigned, while certain designated roles at the site and at the Sponsor were unmasked. Sites had a qualified injector who was unmasked to perform the IVT injection (UBX1325 or aflibercept) or sham procedure, as well as certain post-injection assessments on injection/sham procedure Visits (Visits 1, 3, 4, 6, 8, 9, 10, and 12). Post injection, the unmasked injector did the anterior and posterior segment exams, IOP and AE assessment on the study eye. Other supporting activities such as Study Drug preparation and Study Drug accountability were performed by designated unmasked personnel. The Screening visit could be conducted by

unmasked or masked personnel; however, unmasked personnel should not have been involved in any other study procedures outside of visits when an IVT injection or sham procedure was required. Randomization codes were not revealed to anyone in order to maintain the integrity of the double-masking.

In addition to the patients and Investigators being masked, any Sponsor or designee team members who were actively engaged with sites were masked. There was no planned unmasking during part B. If there was an unplanned or unintentional unmasking, the randomization system was to be used to manage the roles and permissions with respect to the ability to break the masking. The Investigator must contact the Medical Monitor to discuss any need to unmask, unless medical emergency dictated otherwise. The randomization code and records related to the unmasking were to be filed as essential study documents. A patient who had unplanned or unintentional unmasking during the study was to be asked to continue in the study through Week 48 for safety follow-up (AE and concomitant medication reporting, vital signs, physical examinations, and laboratory testing).

2.4 Determination of sample size

Sample size for the study was determined based exclusively on Part A objectives as follows: Approximately 46 subjects were to be randomized 1:1 into the UBX1325 repeat dose or aflibercept arm. With 23 UBX1325 repeat dose subjects, a single group t-test with a 0.10 two-sided significance level was determined to have approximately 80% power to detect a difference between treatments in mean change from baseline to Week 24 of 5-letters, assuming the standard deviation is 9 letters.

3. General Methods

3.1 General considerations

For Part B (extension phase) efficacy analyses, the focus is on within group changes from the respective Part B baselines. However, in some cases results for the 2 treatment arms may be presented side-by-side for economy of presentation. Treatment groups will be labeled in TLGs as “UBX1325 10 µg” and “aflibercept + UBX1325”

All study parameters will be listed, and a selected list of parameters will be summarized descriptively by treatment arm and overall. The descriptive statistics will include number of patients, mean, standard deviation, median, minimum, and maximum for continuous parameters and frequency and percent for categorical parameters.

The following reporting conventions will be implemented:

- All statistical tests will be conducted as 2-sided tests unless otherwise specified.
- Confidence intervals (CIs) will be presented as 2-sided 95%, 90%, and 85% CIs unless otherwise specified.

- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. The percentage will be omitted when the numerator is zero. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0).
- All analysis and summary tables will have the analysis population sample size (*i.e.*, number of participants) wherever applicable.

3.2. Study Day and Baseline

Study Day 1 is defined as the day UBX1325 injection or aflibercept is first administered (Part A). Subsequent days are numbered consecutively (*i.e.,* Day 2, Day 3) and are calculated as: visit date - dosing date + 1. Before Day 1, study days are numbered sequentially with negative values (*i.e.,* Day -1, Day -2) and are calculated as: visit date - dosing date. There is no Day 0.

For Part B (post-week 24 through Week 48) analyses of mean changes from baseline, baseline is defined as the average of Weeks 20 and 24. For analyses based on data from Weeks 0 – 48, baseline is defined as the assessment taken on study day 1.

3.3 Analysis visit window

Analysis visit windowing rules will be applied to ocular parameters (including BCVA and CST), laboratory, and vital sign data to address unscheduled and early termination visits. The assignment of the baseline visit is handled by a separate algorithm for this study, not by the visit windowing rules. Analysis visit windowing rule will be applied to the specified data to choose value at each visit. The rules are described in appendix B.

3.4 Timing of analyses

Analyses to evaluate safety, tolerability, efficacy, and exploratory outcomes will utilize data through Week 48 of follow-up. Separate data locks and analyses were planned for data collected through Week 24 and Week 48. The Week 24 Analyses were documented in a separate SAP. The focus of this SAP is Part B, post-Week 24 through Week 48, although some analyses will include data from Week 0 – 48. This SAP supersedes version 1.0 regarding the plan for analysis of study data from Weeks 24 through 48.

3.5 Early termination

Patients who drop out of the study prematurely will have study data collected at the Early Termination Visit (see Appendix A). The numbers and proportions of participants who terminate study participation prematurely, by arm and overall, will be tabulated (see section 5).

3.6 Interim analysis

The original versions of the protocol specified that no formal interim analyses would be conducted; however, separate data locks and analyses were to be conducted for data collected through Week 24 and Week 48. After the initial read out of the Week 24 data, an interim analysis of the Part B data was planned. Details of those analyses were provided in a separate DMC charter. Results of that interim analysis were documented in DMB minutes, with the determination to continue the study as planned. The purpose of this SAP is to document the planned analyses of Part B data.

3.7 Multiple testing and error control

No formal adjustment for multiple comparisons is planned.

4. Analysis Populations

Full Analysis Set

The Full Analysis Set will include all randomized patients who received study treatment in Part B, have a baseline and at least one post baseline BCVA assessment in Part B. The Full Analysis Set will be the primary population for evaluating all efficacy variables. For analysis, subjects will be grouped by randomized treatment arm.

Safety Analysis Set

The Safety Analysis Set for Part B will include all patients who received study treatment in Part B. The Safety Analysis Set will be the primary population for evaluating all safety variables and patient characteristics. For analysis, subjects will be grouped by actual treatment received.

5. Subject Disposition

The following data will be summarized for each treatment arm, for all subjects, and will be based on data from Week 0 – Week 48:

- Randomized
- Treatment administered
- Completed study
- Did not complete study and reason
- Patients in each analysis population (Full, Safety) randomized

A protocol deviation listing will be provided that includes the start/end date of the deviation and the deviation description. A listing of subject disposition data will also be provided.

6. Demographics and Baseline Characteristics

Demographics and baseline characteristics, including medical history, prior and concomitant medications, will be summarized using the Safety Analysis Set. These data will be listed and summarized for the study overall, as well as for each treatment arm.

6.1 Demographics and baseline characteristics

Demographic and baseline characteristics include age, sex, race, ethnicity, weight, height, and other parameters as appropriate. Body Mass Index (BMI) will be calculated using the following formula: BMI (kg/m^2) = Weight(kg)/(Height(m)]^2.

6.2 Medical history

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) by treatment arm and total. A patient will be counted only once for multiple events within each SOC/PT. Medical History, including a detailed ophthalmic history reported prior to dosing, will be listed by patient.

6.3 Prior and concomitant medications

Prior medication is medication that the patient stopped taking prior to the screening visit. Concomitant medication is medication that the patient continued taking or took from the screening visit through the end of the study. Prior and concomitant medications will be coded using the latest version of World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical level 4 (ATC4) and preferred term (PT) by study arm and total. A patient will be counted only once for multiple events within each ATC4 and PT. Prior and concomitant medications will be summarized in table form. Listings of prior and concomitant medications will also be provided. Concomitant medications will be based on data from Weeks 24 – 48.

7. Safety Analysis

7.1 Adverse events

Ocular and systemic safety and tolerability of a repeat IVT injection of UBX1325 will be evaluated by treatment emergent adverse events (TEAEs). A TEAE is an adverse event that first occurs or worsens after study drug initiation or is a SAE. Summary tables will include only TEAEs, and listings will include all adverse events reported in the clinical database.

The following summaries of TEAE data will be performed by study arm and overall, including in separate analyses of data from Weeks 0-48 and Weeks 24-48:

- Overall summary of TEAEs
- TEAEs by SOC, PT, and severity
- Ocular TEAEs in the study eye by PT
- Treatment-related ocular TEAEs in the study eye by PT, severity
- Treatment-emergent serious adverse events by PT

Overall summary of TEAEs will include the number and percentage of patients experiencing at least one TEAE, related TEAE, grade >=3 TEAE, serious TEAE, and TEAE leading to death.

For summaries by SOC and PT, a patient will only be counted once for each PT and once for the overall count for a SOC. However, patients may be included in more than one PT category within a SOC. For summaries which also include severity, a patient 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 by SOC alphabetically then by descending frequency of PT within SOC based on the overall column.

7.2 Intraocular Pressure

Intraocular Pressure (IOP) will be measured using Goldmann applanation tonometry or equivalent tonometer in both eyes at all scheduled visits. Tonometry should be performed prior to pupillary dilation when possible. IOP will be summarized for each eye by visit and by dose using descriptive statistics. In addition to change from baseline in IOP by visit and treatment group, the number and percentage of patients with the following at any post-baseline visit will also be summarized:

- IOP ≥ 25, ≥30 and ≥35 mmHg
- IOP increase from baseline ≥ 10 mmHg
- IOP increase from baseline ≥ 20 mmHg

Intraocular pressure data will be listed for both eyes at each visit.

7.3 Laboratory data

Laboratory safety parameters are measures of hematology and serum chemistry. These measures were obtained at Screening, Week 24, Week 48, and ET (if applicable). Actual values and CFBL will be summarized within each dosing arm in Part B, and 95% confidence intervals will be calculated for the mean CFBL within each treatment arm. Shift tables of the changes from Week 24 to Week 48/ET will also be presented.

Analysis visit windowing rules will be applied to laboratory data before analysis, according to the rules described in appendix B.

7.4 Electrocardiogram (ECG)

Evaluation will be performed at Screening for baseline reference, Visit 8, Visit 14 and at Unscheduled Visits/ET. ECG results (normal / abnormal) during Part B will be summarized for each treatment arm.

7.5 Vital signs

Vital signs will be taken at all study visits. Actual values and CFBL for each vital sign parameter will be summarized for each treatment arm at each visit, and 95% confidence intervals will be

calculated for the mean CFBL for each treatment arm and visit. Shift tables of the changes from baseline to Week 24/ET and to Week 48/ET will also be presented.

7.6 Physical examinations

Complete physical examinations will be performed at Screening, Visit 8 (Day 169), Visit 14 (Day 337) or Unscheduled Visits/ET. The physical examination data will be listed.

7.7 Multi-focal electroretinography (mfERG)

mfERG data were collected on a subset of subjects and descriptive analyses will be provided.

8. Efficacy Analysis

8.1 Efficacy Analyses

Repeated measures analyses of data from weeks 24-48 will be done as follows:
Longitudinal mean changes from baseline will be analyzed separately for each treatment group using a restricted maximum likelihood based mixed effects model for repeated measures (MMRM). The model will fit change from baseline to each post-baseline visit as the dependent variable and the independent variables are baseline score of the dependent variable (baseline) fit as a continuous covariate and the categorical effect of study Visit, along with the baseline-by-Visit interaction. Within patient errors will be modeled using a heterogeneous compound symmetric (type = CSH) structure. For analyses using data from Weeks 24-48, the baseline value for continuous efficacy endpoints is the average of Weeks 20 and 24. For analyses including data from weeks 0-48, the baseline value for continuous efficacy endpoints is the study day 1 assessment. In addition to displaying visitwise results, a contrast statement will be written that averages the LSMEANS from weeks 40, 44, and 48.

Analyses of change to last observation will be done as follows:
Mean changes from baseline to last observation (LO) (one value per patient) will be analyzed separately for each treatment group using an ANCOVA model in which change from baseline is the dependent variable and the independent variable is the continuous covariate of baseline score.

Results from MMRM analyses will be presented in visitwise tables and in line plots. Results from LO analyses will be presented in tables and histograms.

8.2 Data descriptions

Summary Statistics will be generated for the variables listed below. For continuous variables, summary statistics include mean, standard deviation, median, minimum, maximum, and number of non-missing observations. For categorical variables, summary statistics include the number of observations and percentage.

Demographics and Baseline Characteristics (Age, Sex, Race, Ethnicity, Baseline BCVA, Baseline CST, Baseline LLVA, Duration of Wet AMD, Number of Anti-VEGF Injections in Prior 6 Months, Type of Anti-VEGF Injections Received in Prior 6 Months, BMI, Weight, Height, Systolic Blood Pressure, Diastolic Blood Pressure, Respiratory Rate, Heart Rate, Body Temperature)
BCVA
SD-OCT Findings
FA Findings
OCT-A Findings
CFP Findings
Slit Lamp Exam Findings
Dilated Ophthalmology Exam Findings
IOP
SD-OCT Findings
FA Findings
OCT-A Findings
CFP Findings
Lab results

Individual patient data for BCVA & CST will be displayed in spaghetti plots for data from Week 0-48 and Weeks 24-48. These plots will be done with all patients in a treatment arm in one graph and with one patient per curve. Spaghetti plots will also be produced for each duration of disease subgroup within each treatment arm.

A summary table will be produced showing how many patients received rescue therapy and which of the rescue criteria (BCVA, CST, Both, Neither) triggered the rescue therapy. Additional analyses related to rescue including Patients who did not get rescued though they met criteria along with a table comparing the following illness and demographic characteristics of patient who were rescued vs. those who were not rescued: BCVA, CST, time since diagnosis, number of prior anti-VEGF medications, age, and sex.

8.3 Primary estimands, endpoint and analyses

The primary assessment of efficacy in Part B will be based on the within group mean changes from baseline.

The separate, primary estimands for each dosing arm are:

- The effects of 1) UBX1325 given at Week 24 and Week 28, and 2) aflibercept given at Week 24, Week 32, and Week 40, in combination with UBX-1325 at Week 24 and Week 32.
- The population is patients with neovascular AMD as defined by inclusion/exclusion criteria.

- The primary efficacy endpoint is BCVA.
- The primary summary measure is the within group least square mean changes from baseline to Week 48.
- The intercurrent event of early study discontinuation will be accounted for using a hypothetical strategy to estimate what would have been observed if the patient had not discontinued, and use of rescue medication will be accounted for using a treatment policy strategy in which observations taken after use of rescue medication are included in the analysis.
- The primary analysis will be MMRM as described in Section 8.1, using data from Weeks 24-48. In addition, an MMRM analysis as described in Section 8.1 will be implemented using data from Weeks 0-48.

8.4 Secondary endpoints

The following secondary endpoints will be analyzed with the MMRM model described in section 8.1, using data from Weeks 24-48: CST, LLVA, FA & OCT-A.

The following secondary endpoints will be analyzed with the MMRM model described in section 8.1, using data from Weeks 0-48: CST, LLVA, FA & OCT-A.

The following secondary endpoints will be analyzed with the last observation model described in section 8.1, using data from weeks 24-48: CST, LLVA, FA & OCT-A.

The following secondary endpoints will be analyzed with the last observation model described in section 8.1, using data from weeks 0-48: CST, LLVA, FA & OCT-A.

8.5 Exploratory endpoints

The binary and other exploratory efficacy endpoints and planned visualizations for these endpoints are as follows:

- Proportion of patients within each dosing group who took anti-VEGF rescue treatments post-Week 24 through Week 48 (beyond the assigned aflibercept in the aflibercept arm)
- Proportion of patients within each dosing group who took anti-VEGF rescue treatments for Week 0-48 (beyond the assigned aflibercept in the aflibercept arm)
- A swim lane plot will be used to depict the timing of rescue doses for each patient
- Duration of longest rescue free interval for each patient will be summarized by categories of duration
- Individual patient spaghetti plots of BCVA & CST will be presented for the week 0-48 data and the week 24-48 data
- Bar charts of BCVA change from baseline, and supporting table (0 - 48 & 24 - 48)
- Bar charts and corresponding tables of BCVA changes from baseline will be presented to summarize the proportion of patients in various categories defined by magnitude of

change from baseline (e.g., >=-15, -14 - -10, -9 - -5, -5 -0, 1 – 5, 6 – 10, 11- 15, > 15. The histograms will be produced for data from week 0 – 48 and week 24-48

- Individual patient spaghetti plots of changes from baseline will be generated for BCVA and CST, based on the week 0-48 data and the week 24-48 data.

Criteria for rescue therapy is defined as observing any of the following: new or clinically relevant worsening of IRF/SRF/cysts relative to baseline, new blood or heme present compared to previous visit, decrease in BCVA by ≥ 10 ETDRS letters from peak (best VA) within-study level, or CST increase ≥ 75 µm from trough (lowest). Patients who meet rescue criteria can be rescued with aflibercept. Rescued patients will continue with study visits per protocol.

The time to rescue injection(s) and maximum duration of rescue-free interval endpoints will be assessed by descriptive summary statistics and visualizations.

8.6 Subgroup Analyses

The BCVA and CST will be analyzed separately for each of the following subgroups using the MMRM model described in section 8.1.

- Baseline BCVA (median split for average of Week 20 and 24 BCVA)
- Baseline CST (median split for average of Week 20 and 24 CST)
- Duration of time since diagnosis of neovascular AMD (two cut-offs will be used in separate analyses: 1) ≤2 years or >2 years); and 2) ≤3 years or >3 years)
- Number of prior anti-VEGF treatment in the 6 months prior to enrollment (≥4 injections and ≤3 injections)
- Type of anti-VEGF treatment used in the 6 months prior to enrollment (aflibercept, bevacizumab)

The subgroup categories may be adjusted to balance the number of patients per group if there is insufficient representation within a category. Additional analysis of BCVA and CST with the subgroup as covariate may be performed if clinically significant subgroup difference is observed in the subgroup analysis.

8.7 Responder Analyses

Patients will be categorized as responders (yes/no) based on whether change from the extension phase baseline to Week 48 in BCVA was 3 letters or greater (responder = yes) or less than 3 letters (responder = no). The following baseline demographic and illness characteristics will be compared between the responder categories:

BCVA, CST, time since diagnosis, number of prior anti-VEGF medications, age, sex.

8.8 Sensitivity Analyses

Boxplots will be generated for the Week 0-48 data and the Week 24-48 data to depict the visitwise occurrence of outlier values.

When BCVA outliers occur, a sensitivity analysis will be performed in which patients with outlier values are excluded and the MMRM analysis as described will be applied to the data with outlier patients excluded. If deemed appropriate, other sensitivity analyses may also be considered to assess the impact of outliers.

An outlier is defined using the 3(IQR) Criterion: an observation is classified as an outlier if it is below Q1 – 1.5(IQR) or above Q3 + 1.5(IQR). A far outlier is an observation that is below Q1 – 3(IQR) or above Q3 + 3(IQR).

8.9 Listings

Individual patient listings will be provided for the following items and outcomes:

Disposition
Demographics
Deviations
Medical History
Prior Medications
Concomitant Medications
BCVA
SD-OCT Findings
FA Findings
OCT-A Findings
CFP Findings
Slit Lamp Exam Findings
Dilated Ophthalmology Exam Findings
IOP

9. Quality Assurance

9.1 Software and programming specifications

All statistical programs written to generate TFLs and perform statistical analyses will use either SAS version 9.4 or higher, or R version 4.0 or higher. Every statistical program will be developed and validated for correctness according to a four-stage process. Stage I of the process requires the creation of specification document describing the intent and project guidelines. Stage II comprises program development based on approved specifications and Stage III involves the validation process. Independent replication and peer review procedures are the two types of validation processes. The type of validation procedure will be determined based on category of

program. Stage IV describes generation of validated outputs and documentation of adherence to project requirements.

9.2 File management and data security

Data and program files will be managed according to PharmaLex folder and file structure management. Electronic file security and integrity will be protected by PharmaLex network system and structure.

10. Changes in the Statistical Analysis Plan from the Protocol Analysis Plan

The study protocol noted that details of statistical analyses will be provided in the SAP. The only changes from the protocol to document in the statistical analysis plan are as follows:

- The protocol stated there were no formal confirmatory hypotheses to be tested. The SAP provides details on hypothesis testing.
- Additional endpoints were added, including the following:
    - Change in Low Luminance Visual Acuity (LLVA) from Baseline
    - Maximum duration of rescue-free interval
    - Results of multi-focal electroretinography (mfERG)

The clinical study report will document deviations from and additions to this statistical analysis plan that were applied to the results included in the CSR.

11. Appendices

11.1 Appendix A – Schedule of Events (Protocol Table 1)

Table 1 Schedule of Events

Test/Procedure	Screening Day -56 to Day -28	Visit 1 Week 0 Day 1	Visit 2 Week 2 Day 15 ± 7	Visit 3 Week 4 Day 29 ± 7	Visit 4 Week 8 Day 57 ± 7	Visit 5 Week 12 Day 85 ± 7	Visit 6 Week 16 Day 113 ± 7	Visit 7 Week 20 Day 141 ± 7	Visit 8 Week 24 Day 169 ± 7	Visit 9 Week 28 Day 197 ± 7	Visit 10 Week 32 Day 225 ± 7	Visit 11 Week 36 Day 253 ± 7	Visit 12 Week 40 Day 281 ± 7	Visit 13 Week 44 Day 309 ± 7	Visit 14 Week 48 Day 337 ± 7	Unscheduled Visit/ET[k]
Informed Consent	X															
Demographics	X															
Medical / Ophthalmic History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication History/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[L]	X								X						X	X
Vital Signs and Weight	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Tests: Hematology and Chemistry	X[b]								X						X	X
Pregnancy Test	X (serum)[b]	X (urine)[c]		X (urine)[c]	X (urine)[c]				X (urine)[c]						X (urine)	X (urine)
12-Lead ECG	X[b]								X						X	X
BCVA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anterior Segment Evaluation	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
Posterior Segment Evaluation	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
IOP	X[d]	X[d]	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]	X[d]	X	X[d]	X	X	X
SD-OCT[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[e]	X			X	X		X		X			X			X	X
FA[e]	X			X	X		X		X			X			X	X[f]
CFP[e]	X			X	X		X		X			X			X	X

Test/Procedure	Screening Day -56 to Day -28	Visit 1 Week 0 Day 1	Visit 2 Week 2 Day 15 ± 7	Visit 3 Week 4 Day 29 ± 7	Visit 4 Week 8 Day 57 ± 7	Visit 5 Week 12 Day 85 ± 7	Visit 6 Week 16 Day 113 ± 7	Visit 7 Week 20 Day 141 ± 7	Visit 8 Week 24 Day 169 ± 7	Visit 9 Week 28 Day 197 ± 7	Visit 10 Week 32 Day 225 ± 7	Visit 11 Week 36 Day 253 ± 7	Visit 12 Week 40 Day 281 ± 7	Visit 13 Week 44 Day 309 ± 7	Visit 14 Week 48 Day 337 ± 7	Unscheduled Visit/ET[k]
mfERG[e]		X		X	X				X			X			X	
Low-luminance visual acuity[i]	X			X	X		X		X			X			X	X
Eligibility Criteria	X	X														
Aflibercept Administration	X[g]															
IVT Injection and/or Sham Procedure[h]		X		X	X		X		X[j]	X	X[j]		X			
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; BCVA = best corrected visual acuity; CFP = color fundus photography; ECG = electrocardiogram; ET = early termination; FA = fluorescein angiography; IOP = intraocular pressure; mfERG = multifocal electroretinography; OCT-A = optical coherence tomography angiography; SD-OCT = spectral domain optical coherence tomography

[a] Height should also be measured at Screening

[b] Serum pregnancy test, labs and ECG results are not required prior to aflibercept administration during Screening. The results must be verified prior to Day 1 randomization.

[c] Pre-dose urine dipstick.

[d] Procedure to be performed pre-dose OU and post-dose SE only. On coadministration days, these assessments should be done pre and at each post IVT injection or sham procedure.

[e] CFP, FA, SD-OCT, and OCT-A and mfERG images should be transmitted to the Central Reading Center at each applicable visit. mfERG to be conducted as the first ocular evaluation at sites with the proper equipment available and completed prior to IVT injection

[f] To be completed only if assessment has not been done within the last 30 days.

[g] All patients will receive aflibercept as a run-in injection prior to being randomized on Day 1

[h] IVT injection is either UBX1325 study drug/sham and/or aflibercept/sham, depending on the arm the patient is randomized to. Refer to Study Schematic Figure 1 and Pharmacy Manual. Sham procedure should be administered to maintain the integrity of double-mask. NOTE: After all IVT injections or sham procedures have completed, sites should follow their standard practice with administration of prophylactic antibiotics and document all medication given.

[i] LLVA to be conducted at sites with the proper equipment

[j] Refer to section 7.7, before coadministration, IOP must be ≤ 30 mmHg. Administration of UBX1325 or sham needs to be no less than 15 minutes apart and no longer than 2 hours unless there are safety concerns, in which case the site should contact the unmasked medical monitor.

[k] For Unscheduled Visit, tests/procedures can be performed as PI discretion. For ET all tests/procedures need to be performed.

[l] Complete physical examinations will be performed by a licensed physician (or a physician's assistant or nurse practitioner) at Screening, Visit 8 (Day 169), Visit 14 (Day 337) or ET. Aside from those timepoints, symptom-directed physical examinations are required to be performed as clinically indicated

11.2 Appendix B – Analysis Visit Windowing Rules

Within each window defined below, a single visit will be chosen as the analysis visit (for each eye for ocular parameters and for each subject for other parameters). Note that the assignment of the baseline visit is handled by a separate algorithm for this study, not by the visit windowing rules.

Table B.1: Analysis Windows for ocular and vital sign parameters

Planned Visit Day	Lower Limit	Upper Limit	Visit	Visit Number
	-200	-1	Screening	0
1	1	1	Visit 1 (Baseline)	1
15	2	22	Visit 2	2
29	23	43	Visit 3	3
57	44	70	Visit 4	4
85	71	99	Visit 5	5
113	100	127	Visit 6	6
141	128	155	Visit 7	7
169	156	196	Visit 8	8
197	184	211	Visit 9	9
225	212	239	Visit 10	10
253	240	267	Visit 11	11
281	268	295	Visit 12	12
309	296	323	Visit 13	13
337	324	730	Visit 14	14

Table B.2: Analysis Windows for laboratory parameters (other than urine pregnancy test, which is day 1 only)

Planned Visit Day	Lower Limit	Upper Limit	Visit	Visit Number
	-200	-1	Screening	0
169	1	252	Visit 9	9
253	309	519	Visit 12	12

Rules

1. If there is one visit in a window, assign that visit to be the analysis visit.
2. If there is more than one visit in a window, then calculate the absolute difference (in days) from the planned visit day to each visit.

- If a single visit has the smallest absolute difference, then assign that visit as the analysis visit.
- If multiple visits are tied for the smallest absolute difference, then do the following:

- If there is a single planned visit, set it to be the analysis visit.
- Else if there are multiple planned visits in a tie, take the latest visit as the analysis visit.
  - Exception: take the day 1 pre-dose visit instead of the post-dose visit, if applicable.
- Else if there are no planned visits (*i.e.*, only unscheduled or early termination), then take the latest visit.