KalVista Pharmaceuticals

STATISTICAL ANALYSIS PLAN

A randomized sham-controlled double-masked Phase 2a study of the efficacy, safety and tolerability of the intravitreal plasma kallikrein inhibitor, KVD001, in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (VEGF) treatment

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[redacted]

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Sponsor: KalVista Pharmaceuticals, Ltd.

Protocol Number: KVD001-201

Author: [redacted]

Date: 07NOV2019

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[redacted]

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SAP Version: 2.0

SAP Date: 07NOV2019

Statistical Analysis Plan Approval

Prepared by: [redacted]

Reviewed by: [redacted]

Approved by: [redacted]

[redacted]

Table of Contents

[redacted]

List of Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
anti-VEGF	anti-vascular endothelial growth factor
ATC	anatomical therapeutic chemical
BCVA	best corrected visual acuity
BMI	body mass index
CI	confidence interval
ciDME	center-involving diabetic macular edema
CIRC	central image reading center
CS	clinically significant
CSR	clinical study report
CST	central subfield thickness
DBP	diastolic blood pressure
DME	diabetic macular edema
DRSS	Diabetic Retinopathy Severity Scale
DVM	data validation manual
eCRF	electronic case report form
ED	early discontinuation
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	full analysis set
ICF	informed consent form
ICH	International Conference on Harmonisation
IOP	intraocular pressure
IP	investigational product
IQR	interquartile range
IRT	interactive response technology
ITT	intention-to-treat
IVT	intravitreal
[redacted]	[redacted]
LSMeans	least-squares means
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures

NCS	not clinically significant
OD	right eye
OS	left eye
OU	both eyes
PPS	per protocol set
PR	pulse rate
PT	preferred term
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
[redacted]	[redacted]
SD-OCT	spectral domain optical coherence tomography
SOC	system organ class
SOP	standard operating procedures
SRS	study report specifications
TEAE	treatment-emergent adverse event
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol KVD001-201, dated 09 APR 2018.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, safety and tolerability assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

2. Study Objectives

The primary objective of this study is to evaluate the efficacy of monthly dosing of intravitreal (IVT) injection of KVD001 in subjects with center-involving diabetic macular edema (ciDME) who have had prior anti-vascular endothelial growth factor (anti-VEGF) treatment. The secondary objective is to evaluate the local and systemic safety and tolerability of monthly dosing of KVD001 Injection in subjects with ciDME who have had prior anti-VEGF treatment.

2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in best corrected visual acuity (BCVA) letter count as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) at Week 16.

2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- Change from baseline in central subfield thickness (CST) as measured by Spectral-Domain Optical Coherence Tomography (SD-OCT)
- Proportion of eyes with a ≥2 step improvement from baseline in Diabetic Retinopathy Severity Scale (DRSS) score
- Change from baseline in BCVA letter count as measured by ETDRS at Weeks 4, 8, 12, 20, and 24
- Proportion of study eyes with ≥5, ≥10, and ≥15 BCVA letter change from baseline (gain and loss).

2.3 Safety Endpoints

The safety variables include the following:

- Adverse events (AEs)
- Ophthalmic and physical exam findings
- Laboratory test results (clinical chemistry, hematology, and urinalysis)
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate [PR], temperature, and respiratory rate).

2.4 Statistical Hypotheses

The null hypotheses are that [1] the effect changes from baseline in BCVA letter count at Week 16 for each dose of the KVD001 Injection and the sham procedure on BCVA are identical and [2] the effect changes from baseline in BCVA letter count at Week 16 between the KVD001 Injection doses are identical:

H_0: $\mu_{k3} - \mu_s = \mu_{k6} - \mu_s = \mu_{k6} - \mu_{k3} = 0$,
where μ_{k3} and μ_{k6} are the effect changes from baseline in BCVA letter count at Week 16 for KVD001 3 µg Injection and KVD001 6 µg Injection, respectively, and μ_s is the effect of change from baseline in BCVA letter count at Week 16 for the sham procedure. The alternative hypotheses are that [1] the effect changes from baseline in BCVA letter count at Week 16 for each dose of the KVD001 Injection is larger than the effect of change from baseline in BCVA letter count at Week 16 for the sham procedure and [2] the effect changes from baseline in BCVA letter count at Week 16 for KVD001 6 µg Injection is larger than the effect of change from baseline in BCVA letter count at Week 16 for KVD 3 µg Injection:

H_a: $\mu_{k3} - \mu_s > 0$ or $\mu_{k6} - \mu_s > 0$ or $\mu_{k6} - \mu_{k3} > 0$.

All hypothesis testing will be two-sided with a type I error rate (α) of 0.05. There will be no adjustments for multiple endpoints or multiple treatment comparisons for this early-phase, exploratory study. Specifics of the statistical tests are provided in ***Section 13***.

3. Study Design and Procedures

3.1 General Study Design

This is a phase 2a, randomized, double-masked, sham-controlled, 3-arm study to evaluate the efficacy, safety, and tolerability of KVD001 Injection as monotherapy in adult subjects with ciDME who have had prior anti-VEGF treatment. Approximately 123 eligible subjects will be randomized into the study.

Subjects will undergo screening for fulfilling the inclusion and exclusion criteria in order to be eligible for this study. Eligible subjects will be stratified based on visual acuity and CST, and then randomly

assigned in a 1:1:1 ratio into the 3 groups described below. Stratified randomization will be performed centrally by visual acuity and CST at Day 1.

- KVD001 6 µg by IVT injection;
- KVD001 3 µg by IVT injection;
- Sham procedure.

Rescue intervention (e.g., anti-VEGF, focal/grid macular laser photocoagulation, IVT steroids) may be administered due to worsening DME (i.e., attributable to worsening DME and not another cause) if either of the following occurs and, where possible, after consultation with the Medical Monitor:

- During Treatment Phase
  - BCVA deteriorates 3 lines (15 letters) or more from baseline
  - CST worsening of >100 µm from baseline
- During Follow up Phase (i.e., after week 16)
  - BCVA deteriorates 3 lines (15 letters) or more from highest BCVA during treatment phase or baseline
  - CST worsening of >100 µm from lowest CST during treatment phase or baseline.

Subjects who receive a rescue intervention in the study eye will be discontinued from further study participation. The Week 24/Early Discontinuation (ED) evaluations should be collected prior to study discontinuation and prior to administration of the rescue medication. Details regarding the medications used as rescue treatment must be entered as concomitant medications for the respective study subject.

3.2 Schedule of Visits and Assessments

The schedule of procedures is provided in ***Appendix A***.The screening period will be up to 4 weeks. On the day of first study drug administration (Day 1), eligible subjects will be randomized to a 12-week, double-masked treatment period (a total of 4 doses given at approximately monthly intervals). Subjects will visit the study clinic on Day 1 and Weeks 4, 8, and 12 during the Treatment Phase. The visit window for these visits is -3 days to +7 days. All subjects will visit the clinic at Weeks 16, 20, and 24 after the last study drug administration or sham procedure for safety and ophthalmic assessments. The visit window for Weeks 16, 20, and 24 is ±7 days. For ED visits, the visits will be windowed according to the Protocol windows defined above and in ***Table 1***.

Summaries and analyses utilizing timepoints will be completed using the nominal visit recorded in the electronic case report form (eCRF), except in the case of ED visits where the visit will be windowed to a scheduled visit using ***Table 1***. In the case where a subject has a scheduled visit and a windowed ED

visit mapped to the same visit name, the observation closest to the planned study day will be used for analysis.

Table 1. Study Visit Windows for Early Discontinuation Visits

Scheduled Visit	Planned Study Day	Visit Window
Day 1	1	N/A
Week 4	28	15-42
Week 8	56	43-70
Week 12	84	71-98
Week 16	112	99-126
Week 20	140	127-154
Week 24	168	155-182

4. Study Treatments

Subjects will be randomized by the Interactive Response Technology (IRT) in a 1:1:1 ratio to 1 of the 3 treatment groups: KVD001 Injection (6 µg/eye or 3 µg/eye) or sham. Allocation to the treatments will be stratified by baseline BCVA (≤55 letters vs >55 letters) and CST at Screening (≤450 µm vs >450 µm) as determined by the study center.

1:1:1 randomization:

- KVD001 6 µg by IVT injection;
- KVD001 3 µg by IVT injection;
- Sham procedure.

4.1 Method of Assigning Subjects to Treatment Groups

Screened subjects who sign an informed consent form (ICF) will be assigned a Subject ID number that will be entered on the eCRF. The Subject ID number will consist of 3 digits. Stratified randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced

across treatment groups, to reduce the possible influence of covariates on the drug evaluation, and to enhance the validity of statistical comparisons.

Subjects who satisfy all the entry criteria will be centrally assigned to study medication at the study site on Day 1 after stratification according to visual acuity (Baseline BCVA: ≤55 Letters versus >55 Letters) and CST (screening CST: ≤450 µm versus >450 µm) through the use of the IRT.

4.2 Masking and Unmasking

This is a double-masked study. Subjects, Investigators and site staff, the sponsor [redacted] staff are masked to the treatment group assignments during the randomization process and for the duration of the study.

Under normal circumstances, the mask should not be broken. When medically necessary, an Investigator may need to determine what treatment has been assigned to a subject. The Investigator will contact the Sponsor with the details of the emergency unmasking request. The sponsor will make the final determination if the unmasking request will be granted. If granted, the unmasking information may be accessed through the use of an IRT system or provided by the unmasked designee. The Investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask.

5. Sample Size and Power Considerations

The proposed sample size (41 per treatment group) will provide approximately 80% power to detect a difference in change from baseline of 5 letters between either of the KVD001 treatment groups and sham based on a two-sided, two-sample t-test with significance level 0.05 and assuming a pooled standard deviation (SD) of 7.5 letters.

6. Data Preparation

Data management procedures, including database design, selection of the data dictionary, and coding of all AEs and medications, will be performed [redacted]. All reported study data will be recorded on [redacted] eCRFs supplied [redacted]. Clinical personnel at the study center and [redacted] are responsible for ensuring that the protocol is followed and that the eCRFs are properly completed.

After data are entered into the clinical study database, electronic edit checks will be performed, including checks for missing data, out of range values, discrepancies within and across visits, and cross checks between different data tables. All data validation specifications and procedures are detailed in the Data Validation Manual (DVM), and manual data checks are documented in the Study Report Specifications (SRS). When the database has been declared to be complete and accurate, the database will be locked and treatment codes unmasked. Any changes to the database after that time can only be made with the approval of the Sponsor in consultation with Ora, Inc.[redacted]

All final analyses outlined in this document will be performed after:

- All data management requirements are met according to [redacted] Standard Operating Procedures (SOP), including performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate [redacted] and Ora/Sponsor personnel;
- All protocol deviations have been classified as major or minor and the Per Protocol Set (PPS) has been determined; and
- The treatment codes have been unmasked.

7. Analysis Sets

7.1 Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who received at least one dose of study treatment. Subjects will be included in the analysis according to the treatment to which they were randomized.

7.2 Per Protocol Set

The PPS will include all randomized subjects who:

- Received all four injections of study treatment
- Have a non-missing BCVA ETDRS result at Week 16
- Were not discontinued prior to Week 16 for any reason
- Have not experienced any major protocol deviations that have the potential to impact the efficacy results.

Subjects will be included in the analysis according to the treatment received.

7.3 Safety Set

The Safety Set (SAF) will include all randomized subjects who received at least one dose of study treatment. Subjects will be included in the analysis according to the treatment received.

8. General Statistical Considerations

8.1 Unit of Analysis

Ophthalmic safety endpoints will be analyzed for both eyes. Non-ophthalmic safety endpoints will be analyzed with subject as the unit of analysis. For efficacy endpoints, the unit of analysis will be the study eye.

The study eye will be defined as the eye that meets all of the inclusion and none of the exclusion criteria. If both eyes qualify, the eye with the worse BCVA ETDRS at Day 1 will be used as the study eye. If both

eyes have the same BCVA ETDRS at Day 1, the eye with the highest CST on SD-OCT on Day 1, as assessed by the Investigator, will be used as the study eye. If both eyes qualify and neither is preferred based on the inclusion/exclusion criteria and have the same BCVA ETDRS and CST on Day 1, either eye may be chosen as the study eye. In this instance, the Investigator should select the eye that, in their opinion, is most likely to respond to treatment as the study eye.

8.2 Missing Data Conventions

Partial/missing start and end dates for AEs and concomitant medications will be imputed to create complete dates for the determination of treatment-emergent AEs or medications concomitant with study treatment.

Partial/missing start dates:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc.).

The primary and secondary efficacy data analyses will be performed on the FAS [redacted]. An analysis using observed data only will also be performed in both the FAS and PPS. [redacted] will be used to impute missing data in the FAS for the analysis of the primary and secondary continuous efficacy variables. No exploratory efficacy endpoints or safety endpoints will be imputed.

8.3 Definition of Baseline

The baseline assessment will be the latest, valid pre-dose assessment available. Laboratory data may not be used from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render the values invalid.

8.4 Data Analysis Conventions

All data analysis will be performed [redacted] The final analysis will be performed after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

Quantitative variables will be summarized using descriptive statistics including the number of observations (n), mean, SD, median, interquartile range (IQR), minimum, and maximum values. Means, medians, and confidence intervals (CIs) will be reported based on the level of precision for each variable. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as post-baseline value minus baseline value.

All efficacy analyses will be two-sided at a significance level of 0.05. The CIs for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as “<0.0001”; p-values greater than 0.9999 will be presented as “>0.9999.”

Extra assessments (i.e., unscheduled laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing AEs) will be included in listings, but not summaries. If more than one laboratory value is available for a given visit, the first valid observation will be used in summaries and all observations will be presented in listings. If the relative time is indeterminable, then the average of values at that visit will be used. It is noted that invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid).

8.5 Adjustments for Multiplicity

Adjustments for multiple treatment comparisons, analysis time points, and/or endpoints will not be made for this exploratory study.

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were screened, screen failures, randomized, randomized but not treated, completed the Week 16 visit (without rescue medication/procedure prior to the visit), completed the study, discontinued from the study, and rescued prior to the Week 16 visit. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all enrolled subjects.

The number and percentage of subjects completing the study or who prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation prior to completion include: adverse event, use of rescue medication, subject compliance, withdrawal of consent, lost to follow-up, sponsor termination of study, positive pregnancy test, and other. A subject listing will be provided that includes the date of completion or discontinuation and reason for premature study discontinuation.

The number and percentage of subjects with protocol deviations will be summarized by treatment group for all randomized subjects. A subject listing will be provided that includes the start/end date of the deviation, the deviation description, deviation code, (informed consent, inclusion/exclusion and randomization, test article/study drug administration at site, improper protocol procedures at site, site failure to report serious adverse event (SAE)/AE, visit out of window, subject's use of prohibited concomitant medication, subject's failure to follow instructions, or other reasons) and the classification of whether the deviation was judged to be major or minor.

In addition, listings for all enrolled subjects will be provided that include informed consent date, randomization date/time, randomization number, inclusion and exclusion criteria violations, unmasking information, and exclusions from the FAS and PPS populations.

10. Demographic and Other Baseline Variables

10.1 Demographic Variables

Demographic and baseline characteristics will be summarized by treatment in the FAS and PPS populations.

The demographic variables collected in this study include age, sex, race, ethnicity, iris color, study eye, height, weight, and body mass index (BMI). Subjects who record more than one race will be grouped into a single category denoted as Multiple Race.

Age (years) will be summarized, by treatment, using descriptive statistics for continuous variables. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (Informed Consent Date – Date of Birth) / 365.25, truncated as an integer

The number and percentage of subjects will be presented, by treatment and over all subjects, for age category, sex, race, ethnicity, iris color, and study eye.

A subject listing that includes all demographic variables, including Screening physical examination findings, will be provided.

10.2 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment in the FAS and PPS populations.

Continuous summary statistics (n, mean, SD, median, IQR, minimum, maximum) will be presented for BCVA letter count at baseline, CST at baseline, time since DME diagnosis in the study eye, the estimated or total number of prior anti-VEGF injections administered in the study eye, CST prior to the first anti-VEGF injection, CST prior to each of the last three anti-VEGF injections, the estimated or total number of IVT steroid injections ever administered, and time since last IVT steroid injection.

Categorical summary statistics (counts and percentage) will be presented by treatment and over all subjects for the randomization stratification factors of visual acuity (Baseline BCVA: ≤55 Letters versus >55 Letters), CST (screening CST: ≤450 µm versus >450 µm), duration of DME (<6 months, 6 months-<1 year, 1 year-<2 years, 2 years-<3 years, ≥3 years), time since first anti-VEGF injection (<6 months, 6 months-<1 year, 1 year-<2 years, 2 years-<3 years), and time since last anti-VEGF injection (<6 months, 6 months-<1 year, 1 year-<2 years, 2 years-<3 years). The Snellen visual acuity prior to the first anti-VEGF injection, Snellen visual acuity prior to each of the last three anti-VEGF injections, and investigator assessment of edema and vision in the study eye compared to baseline after at least three anti-VEGF injections will also be summarized.

A listing of baseline disease characteristics will be produced.

11. Medical History and Prior and Concomitant Medications

Ocular and non-ocular medical history and prior and concomitant medications will be summarized separately by treatment in the FAS population.

11.1 Medical History

Medical history will be summarized using discrete summary statistics and presented by treatment group and over all subjects at the subject and event level by system organ class (SOC) and preferred term (PT), separately for ocular and non-ocular SOCs. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, then that SOC will only be reported once. Separate tables will be created for ocular and non-ocular medical history. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 20.1. The summaries will be based on the FAS population.

Listings of medical history will be generated separately for ocular and non-ocular SOCs.

11.2 Prior and Concomitant Medications

Prior medications are defined as medications that were stopped within the 3 months prior to Day 1; concomitant medications are defined as those medications ongoing at or started after Day 1. At the Screening Visit, subjects will be asked what medications they are taking, as well as those the subject may have taken but discontinued within the 3 months prior to Visit 1. At each study visit, subjects will be asked what concomitant medications they are currently taking or if there have been any changes to their medications since their first visit.

All prior and concomitant ocular and non-ocular medications will be listed including preferred name, indication, route of administration, start date, stop date, dosage, and frequency of administration. Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, B3, September 2017 to the appropriate Anatomical Therapeutic Chemical (ATC) classification and WHO generic term.

Counts and percentages of ocular and non-ocular prior and concomitant medications will be summarized separately using ATC classification and preferred name. Summaries will include concomitant ocular medications for each eye (study eye and fellow eye), concomitant non-ocular medications, prior anti-VEGF ocular medications in the study eye, prior non-anti-VEGF ocular medications in the study eye, prior ocular medications in the fellow eye, and prior non-ocular medications. Summaries will be displayed by treatment group and over all subjects. Subjects with multiple medications in the same ATC class or preferred name will be counted only once for that respective ATC class or preferred name.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Subjects who complete the study are scheduled to receive 4 injections [Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12)].

The number of masked injections, either KVD001 injection or a sham procedure, administered and the number of planned injections prior to study discontinuation will be summarized as counts and percentages in the SAF population. The number of planned injections is the number of masked injections that the subject would have taken if all scheduled visits occurred and injections were administered at all scheduled visits prior to discontinuation. If a rescue medication was administered at a visit, then that visit will not contribute to the planned injections.

Compliance will be calculated as

$$\text{Compliance (\%)} = 100 \times \frac{\text{Number of Masked Injections Received}}{\text{Number of Planned Injections}}$$

The number of masked injections administered and the number of planned injections prior to study discontinuation will be summarized as counts and percentages in the SAF Population. Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group, using the SAF population.

Subject listings of study drug assignment, study drug administration, and study treatment compliance will also be produced.

12.2 Treatment Exposure

Treatment exposure will be measured by time-on-study, time from first injection to last injection, and time to last exposure to study treatment for the analysis of on-treatment AEs (time from first injection) plus additional at-risk period following the last injection (the minimum of 28 days and time from last injection to last study visit).

Time on study is defined as

Time on Study (Days) = [Date of Last Visit – Date of Visit 2 (Day 1)] + 1.

Time from first injection to last injection is defined as

Time from First to Last Injection (Days) = (Date of Last Injection – Date of First Injection) + 1.

Time to last exposure to study treatment for the analysis of on-treatment AEs is defined as

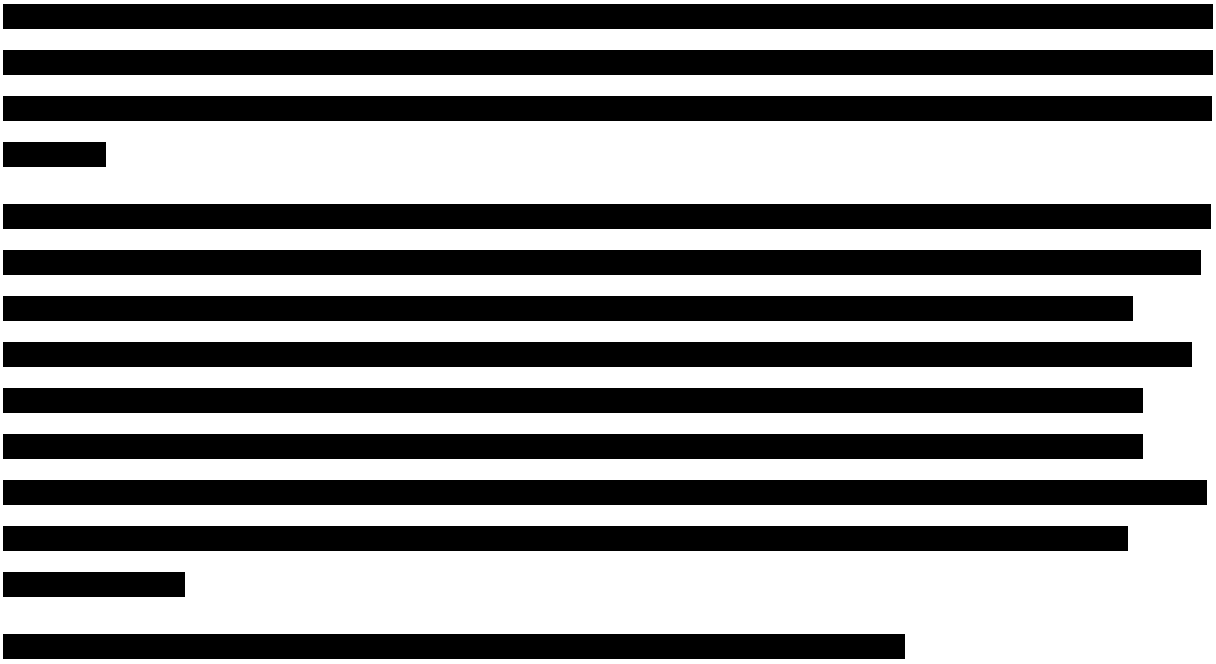
Time Exposed (Days) = (Date of Last Injection – Date of First Injection) + ADT,

where ADT is the additional time exposed after the last injection and is evaluated as

ADT = Minimum (28, Date of Last Visit – Date of Last Injection) +1.

Time on study, time from first injection to last injection, and time exposed for on-treatment adverse event analysis for each subject exposed to study drug will be summarized with continuous descriptive statistics (n, mean, SD, median, IQR, minimum, maximum) for each treatment group, using the SAF population. A subject listing of treatment exposure will also be produced.

13. Efficacy Analyses



13.1 Primary Analysis

The primary efficacy endpoint is change from baseline in BCVA letter count in the study eye at Week 16. Change from baseline in BCVA letter count will be calculated as Week 16 BCVA letter count minus Day 1 BCVA letter count such that a negative difference indicates a worsening in vision. In addition, treatment comparisons between each KVD001 Injection dose and the sham will be calculated as KVD001 Injection minus sham, such that a positive result indicates more letters gained in the KVD001 Injection treatment group. Treatment comparison between the KVD001 Injection doses will be calculated as KVD001 6 µg Injection minus KVD001 3 µg Injection, such that a positive result indicates more letters gained in the KVD001 6 µg Injection treatment group.

The study eye ETDRS letter scores including changes from baseline will be summarized using descriptive statistics for continuous variables. An analysis of covariance (ANCOVA) model will be used

to compare the change from baseline in BCVA letter count at Week 16 between each KVD001 Injection dose and the sham and between the KVD001 Injection doses. [redacted] Least-squares means (LSMeans) for each treatment group and its 95% CI will be presented. The LSMeans difference between each KVD001 Injection dose and the sham and between the KVD001 Injection doses, their corresponding CIs, and the p-values will be presented.

Comparisons will use two-tailed, alpha=0.05 *t*-tests on the LSMeans from the ANCOVA. LSMeans for each treatment, the estimated treatment difference and the 95% CI for the difference will be calculated based on the ANCOVA model. An example of SAS® code implementation for changes from baseline in number of letters read correctly (using BCVA) is as follows:

[redacted]

where

[redacted]

As a safeguard, the normality assumptions of the ANCOVA model used will be checked using a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and the constant variance assumption of the model, respectively) to ensure that the model assumptions are reasonable. If there are any departures from the distributional assumptions, alternative methods of transformations may be explored.

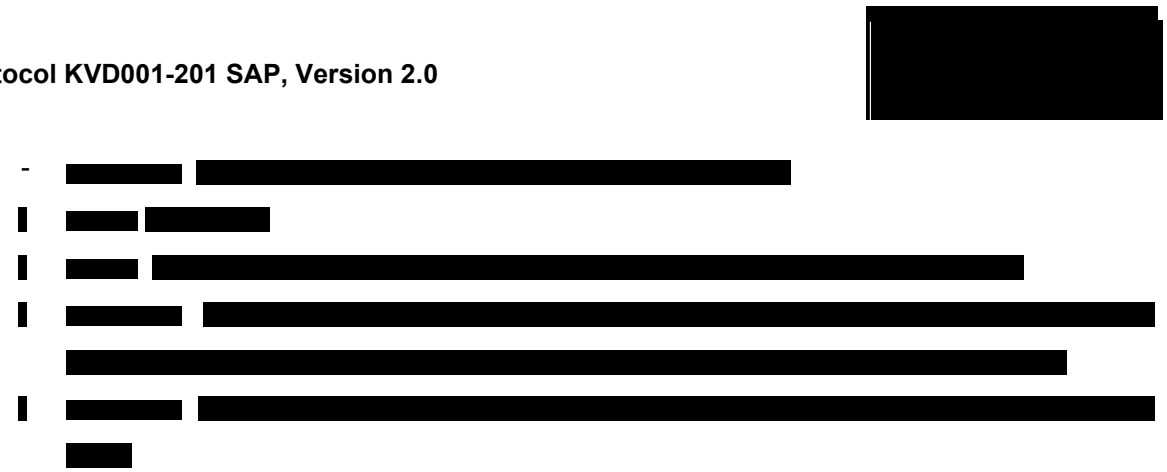
[redacted]

[redacted]

13.2 Additional Analyses of the Primary Endpoint

An analysis using observed data only will also be performed in both the FAS and PPS. Additionally, multiple imputation methodology will be used to impute missing data in the FAS for the analysis of the primary efficacy variables.

[redacted]



As a sensitivity analysis, treatment group differences for changes from baseline in BCVA letter count will be evaluated using a mixed model repeated measures (MMRM) ANCOVA fitted with treatment group, visit and the treatment by visit interaction as categorical variable terms with baseline BCVA letter score and baseline CST as covariates with contrasts included for each visit. LSMeans and 95% CIs for each treatment group, the LSMeans difference between each KVD001 Injection dose and the sham and between the KVD001 Injection doses, the corresponding CIs, and the p-values will be presented for each visit. The covariance matrix will be attempted first with an unstructured covariance matrix, then with autoregressive 1 if the unstructured is not estimable.

Subgroup analyses of the primary endpoint for the study stratification factors will be presented.

13.3 Secondary Analyses

The secondary endpoints are the following:

- Change from baseline in CST as measured by SD-OCT
- Proportion of eyes with a ≥2 step improvement from baseline in DRSS score
- Change from baseline in BCVA letter count as measured by ETDRS
- Proportion of SEs with ≥5, ≥10, and ≥15 BCVA letter gain from baseline and the proportion of SEs with ≥5, ≥10, and ≥15 BCVA letter loss from baseline.

Change from baseline in BCVA letter count as measured by ETDRS in the study eye and change from baseline in CST in the study eye as measured by the central image reading center (CIRC) using SD-OCT will be analyzed using the same method described for the primary efficacy analysis. Note that change from baseline in CST will be in favor of KVD001 if the treatment difference is <0.

The difference in proportion of SEs with improvement of 2 or more steps on the ETDRS DRSS score between each KVD001 injection dose and the sham and between the KVD001 Injection doses will be summarized by visit using discrete summary statistics, including 95% Clopper-Pearson CIs for each treatment group. The difference in proportions between each KVD001 Injection dose and the sham and between the KVD001 Injection doses will be analyzed using a Pearson's chi-squared test. 95% Clopper-

Pearson CIs for the differences in proportions will also be calculated. Fisher's exact tests and exact CIs will be employed in cases of expected counts <5.

The proportion of SEs with ≥5, ≥10 and ≥15 BCVA letter change (gain and loss) between baseline and each post-baseline visit will be analyzed using the same method described for the proportion of SEs with improvement of 2 or more steps on the ETDRS DRSS score. Additionally, as an exploratory endpoint, the proportion of SEs with any BCVA letter loss between baseline and each post-baseline visit will be summarized similarly. Note that the categorizations of ≥5, ≥10 and ≥15 BCVA letter change (gain and loss) or any BCVA letter loss are not mutually exclusive.

14. Safety Analyses

All safety data analyses will be performed on the safety population and displayed in subject data listings and summarized in tables. No statistical inferential testing will be performed for safety variables.

Safety endpoints include AEs, manifest refraction/BCVA, slip lamp biomicroscopy, dilated ophthalmoscopy, intraocular pressure (IOP), SD-OCT, EDTRS DRSS, physical exam findings, laboratory test results, and vital signs.

14.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an investigational product (IP) in humans, whether or not considered IP-related. AEs starting on or after the date of first exposure to study drug and up to 28 days after last injection will be considered treatment-emergent adverse events (TEAEs). AEs with unknown onset dates will be counted as a TEAE. All AEs will be assigned a severity grade of mild, moderate, or severe. Their relationship to study drug will be classified as suspected or not suspected. TEAEs with a missing relationship to study treatment will assume greatest relationship to study treatment (suspected). Only suspected TEAEs are considered as treatment-related. TEAEs with missing severity grades will be categorized as severe for tabulation of TEAEs by severity. The expectedness of an AE will be classified as unexpected, expected or not applicable (not applicable for AEs unrelated to IP). Documentation of AEs will include onset date, location (right eye [OD], left eye [OS], both eyes [OU], not ocular), severity, action(s) taken, relationship to study drug, expectedness, outcome, resolution date, and seriousness. All AEs will be coded using MedDRA classifications with reference to SOCs and PTs (MedDRA version 20.1).

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Medically Significant.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Overall summaries of AEs will be presented showing:

- Number of AEs and number of subjects with any AEs;
- Number of TEAEs and number of subjects with any TEAEs;
- Number of treatment-related TEAEs and number of subjects with any treatment-related TEAEs;
- Number of SAEs and number of subjects with any SAEs;
- Number of treatment-emergent SAEs and number of subjects with any treatment-emergent SAEs;
- Number of subjects with TEAEs leading to premature discontinuation;
- Number of subjects with TEAEs leading to death; and
- Number of subjects with TEAEs by maximum severity.

Overall summaries of AEs will be presented for the following classes of events:

- All AEs (ocular & non-ocular)
- Ocular events for each eye (study eye and fellow eye)
- Non-Ocular events

Frequencies and percentages of subjects with TEAEs, serious TEAEs, TEAEs leading to study drug discontinuation, and treatment-related TEAEs will be provided by treatment group by SOC and PT.

Furthermore, summaries will be given of subjects with TEAEs:

- by SOC, PT, and maximum severity;
- by SOC, PT, and strongest relationship;
- by SOC and PT for SAEs;
- by SOC and PT for TEAEs related to study drug; and
- by SOC, PT, and time of onset (i.e., Day 1 to Week 4 [Days 1-28], > Week 4 to Week 8 [Days 29-56], > Week 8 to Week 12 [Days 57-84], > Week 12 to Week 16 [Days 85-112], > Week 16 [> Day 112]).

Separate analyses will be performed for ocular specific AEs, and all AEs (including systemic).

Summaries of preferred terms (without regard to SOC) will be presented for TEAEs and the most frequent TEAEs (occurring in ≥ 5% of patients treated with KVD001 6 µg or KVD001 3 µg).

Post-treatment AEs, defined as AEs that started or worsened more than 28 days after last injection, will also be summarized.

Subject listings of all AEs including verbatim text will be provided as well as listings of deaths, SAEs, and AEs causing premature discontinuation of study drug.

14.2 BCVA ETDRS

The BCVA of both eyes (study eye and fellow eye) will be assessed using the ETDRS protocol at the beginning of every study visit and will be summarized at each visit using quantitative summary statistics for each eye by treatment group.

BCVA of both eyes will be measured consistent with the standard procedure developed for the ETDRS. The number of letters read correctly will be counted and the total BCVA letter score will be reported. The total BCVA letter score will be summarized for each treatment group and over all subjects using continuous descriptive statistics at each visit for each eye (study eye and fellow eye). Change from baseline will also be summarized by treatment group and visit for [redacted] eye (study eye and fellow eye).

The number of subjects (by eye [study eye and fellow eye]) with a gain or loss in BCVA letter score ≥15, ≥10, and ≥5 or any BCVA letter loss from baseline will be summarized using counts and percentages for each treatment group and over all subjects at each visit.

A subject listing of BCVA and manifest refraction will also be produced.

14.3 SD-OCT

The CIRC SD-OCT parameter values, including changes from baseline will be summarized for each visit (by eye [study eye and fellow eye]) using continuous descriptive statistics. Subject listings of CIRC and Investigator-assessed SD-OCT parameters will also be produced.

14.4 EDTRS DRSS

Color fundus photographs will be taken in both eyes at Screening and in the study eye at subsequent visits to evaluate retinal anatomy and grade DRSS. Photographs will be transferred to the CIRC for independent analysis. The EDTRS DRSS scores for the study eye, including changes from baseline (i.e., ≥2 step improvement, 1 step improvement, no DRSS change, 1 step worsening, ≥2 step worsening), will be summarized for each visit using qualitative summary statistics (frequency counts and percentages). Subject listings of EDTRS DRSS parameters will also be produced.

14.5 Slit-Lamp Biomicroscopy Examination

Slit-lamp biomicroscopy examinations will be conducted on both eyes (study eye and fellow eye) at all scheduled visits. The slit lamp findings will include examinations of the cornea, conjunctiva, anterior chamber, iris/pupil, lens and lid. Each parameter will be graded (normal or abnormal) or marked as not done. Abnormal findings will be further classified as not clinically significant (NCS) or clinically significant (CS).

Slit lamp findings will be summarized by treatment group and visit, for the study eye and fellow eye separately, using qualitative summary statistics (frequency counts and percentages). Percentages will be based on the number of subjects with non-missing responses, including not done, for the treatment group at a given visit for a given parameter.

Shift tables for the slit-lamp biomicroscopy parameters will also be provided comparing each post-baseline visit to baseline. A subject listing of the slit-lamp biomicroscopy examination parameters will also be produced.

14.6 Indirect Dilated Ophthalmoscopy

Indirect dilated ophthalmoscopy examinations will be conducted on both eyes (study eye and fellow eye) at all scheduled visits. Indirect dilated ophthalmoscopy findings will include examinations of the vitreous, macula, optic nerve, retina, and choroid. The findings will be graded as normal or abnormal (NCS or CS). The findings will be summarized using frequency counts and percentages by treatment group at each visit for each eye (study eye and fellow eye). A shift table of changes from baseline will also be presented. Cup-to-disc ratio is also reported for each visit and will be summarized using continuous descriptive statistics. Change from baseline will also be summarized by treatment group for each eye (study eye and fellow eye). A subject listing of the dilated ophthalmoscopy examination parameters will also be produced.

14.7 Intraocular Pressure (IOP)

IOP will be measured in both eyes at all scheduled visits. At visits where the injection is administered [Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12)] IOP will be measured pre-dilation and within 60 minutes after study drug administration. IOP will be summarized using continuous descriptive statistics for each treatment group and over all subjects at each visit, time (pre-dilation, post study drug administration) for each eye (study eye and fellow eye). Change from baseline will also be summarized for each treatment group and over all subjects for each eye (study eye and fellow eye). Categorical summary statistics will also be presented using the following categories: ≤5, 6 to 14, 15 to 21, 22 to 29, and ≥30 mmHg for each visit and using the following categories: ≤-15, -14 to -10, -9 to -5,

-4 to 0, 1 to 4, 5 to 9, 10 to 14, 15 to 19, and ≥20 mmHg for change from baseline to each visit. A subject listing of IOP will also be produced.

14.8 Vital Signs

Vital signs assessments will be conducted at all scheduled visits except Visit 7 (Week 20) and Visit 8 (Week 24). At visits where the injection is administered [Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12)] vital signs will be measured pre-dilation and approximately 30 minutes after study drug administration.

Vital signs assessments, including pulse, respiratory rate, blood pressure (SBP, DBP), and body temperature, and changes from baseline in vital signs assessments will be summarized by visit, time (pre-dilation, post study drug) and treatment group using quantitative summary statistics (n, mean, median, min and max). Change from baseline (Visit 2 [Day 1] pre-dilation to pre-dilation and 30-minutes after administration of study drug at Visit 3 [Week 4], Visit 4 [Week 8], Visit 5 [Week 12] and Visit 6 [Week 16]) will be summarized by treatment group. Systolic and diastolic BP, heart rate, respiration rate, and body temperature will be summarized for the maximum/minimum post-baseline, and the change from baseline values to maximum/minimum post-baseline will also be summarized. A subject listing will also be produced and will include changes from baseline at each visit.

14.9 Urine Pregnancy Test

A listing of urine pregnancy test results at all visits will be presented.

14.10 Laboratory Assessments

Laboratory assay results include hematology, blood chemistry (clinical chemistry, liver enzymes, electrolytes), and urinalysis. Laboratory data will be obtained at all scheduled visits except Visit 7 (Week 20) and Visit 8 (Week 24). Each of the continuous parameters will be summarized using continuous descriptive statistics for each treatment group at each visit. Changes from baseline will also be summarized for each treatment group. Each categorical parameter will be summarized using frequency counts and percentages for each treatment group and for all subjects.

Laboratory data will be classified as high, low or normal. High and low values will be classified as clinically significant or not clinically significant. The high/low criteria will be determined based on the reference ranges provided by the laboratory. A shift table of the changes from baseline to each post-baseline visit will be presented for hematology, blood chemistry (clinical chemistry, liver enzymes, electrolytes), and urinalysis. Shift tables will present a crosstabulation of baseline categories versus post baseline categories for each post-baseline visit as well as shifts from baseline to post-baseline high and post-baseline low.

Listing of blood chemistry (clinical chemistry, liver enzymes, electrolytes), hematology and urinalysis will be presented.

All laboratory values will be presented using SI units.

[redacted].

16. Changes from Protocol-Stated Analyses

The definition of the FAS population has been updated to exclude subjects who did not receive at least 1 dose of study treatment in ***Section 7.1***.

The definition of the PPS population has been updated to exclude subjects who did not receive all four doses of study treatment, have a missing Week 16 BCVA result, or discontinued prior to Week 16 for any reason in ***Section 7.2***.

The definition of prior medications has been extended to include medications prior to Day 1 in ***Section 11.2***.

Between KVD001 Injection dose comparisons were added in ***Section 2.4***, ***Section 13.1***, ***Section 13.2***, and ***Section 13.3***.

Clopper-Pearson CIs instead of asymptotic normal CIs are used for the proportion-based analyses in ***Section 13.3***.

The proportion of SEs with any BCVA letter loss from baseline has been added as an exploratory efficacy endpoint in ***Section 13.3***.

17. References

Graham, J. W. (2007). How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory. *Prevention Science, 8*, 206-213.

18. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

18.1 Revision 01

Summary of Changes

Section #	Description of Change	Rationale
7.1	Update the FAS population definition to further restrict the population to subjects with at	Client request.

Section #	Description of Change	Rationale
	least 1 dose of study treatment.	
7.2	Update the PPS population definition to further restrict the population to subjects who received all 4 injections, have a Week 16 BCVA result, and did not discontinue prior to Week 16 for any reason.	Client request.
11.2	Update the definition of a prior medication.	Client request.
13.2	Increase number of imputations from fifty to 250.	Client request.
13.3	Change the 95% CIs from asymptotic normal CIs to Clopper-Pearson CIs.	Client request.
16	Add the changes from Protocol-stated analysis requested in Sections 7.1, 7.2, 11.2 and 13.3.	Client request.
21	Update the populations of figures to match source tables.	Client request.

19. Tables

Table Number	Title	Population
14.1.1.1	Subject Disposition	All Subjects
14.1.2.1	Demographics and Baseline Characteristics	FAS Population
14.1.2.2	Demographics and Baseline Characteristics	PPS Population
14.1.2.3	Baseline Disease Characteristics	FAS Population
14.1.2.4	Baseline Disease Characteristics	PPS Population
14.1.3.1	Ocular Medical History	FAS Population
14.1.3.2	Non-Ocular Medical History	FAS Population
14.1.4.1	Ocular Concomitant Medications by Eye	FAS Population
14.1.4.2	Non-Ocular Concomitant Medications	FAS Population
14.1.4.4	Prior Anti-VEGF Medications in the Study Eye	FAS Population
14.1.4.5.1	Prior Non-Anti-VEGF Ocular Medications in the Study Eye	FAS Population
14.1.4.5.2	Prior Ocular Medications in the Fellow Eye	FAS Population
14.1.4.6	Prior Non-Ocular Medications	FAS Population
14.1.5.1	Study Treatment Compliance	SAF Population
14.1.7.2	Study Treatment Exposure	SAF Population
14.2.1.1.1	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by Visit	FAS Population [redacted]

14.2.1.1.2	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by BCVA Randomization Stratum and Visit	FAS Population [redacted]
14.2.1.1.3	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by CST Randomization Stratum and Visit	FAS Population [redacted]
14.2.1.2	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by Visit	FAS Population [redacted]
14.2.1.3.1	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by Visit	FAS Population [redacted]
14.2.1.3.2	Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by Visit	PPS Population [redacted]
14.2.1.4	Mixed Model Repeated Measures Analysis of Covariance of Change from Baseline in BCVA Letter Count in the Study Eye by Visit	FAS Population [redacted]
14.2.1.5.1	Proportion of Study Eyes with a ≥ 5, ≥ 10, and ≥ 15 BCVA Change from Baseline (Gain or Loss) by Visit	FAS Population [redacted]
14.2.1.5.2	Proportion of Study Eyes with a ≥ 5, ≥ 10, and ≥ 15 BCVA Change from Baseline (Gain or Loss) by Visit	PPS Population [redacted]
14.2.2.1	Analysis of Covariance of Change from Baseline in Central Subfield Thickness (µm) in the Study Eye by Visit	FAS Population [redacted]
14.2.2.2	Analysis of Covariance of Change from Baseline in Central Subfield Thickness (µm) in the Study Eye by Visit	FAS Population [redacted]
14.2.2.3	Analysis of Covariance of Change from Baseline in Central Subfield Thickness (µm) in the Study Eye by Visit	FAS Population [redacted]
14.2.2.4	Analysis of Covariance of Change from Baseline in Central Subfield Thickness (µm) in the Study Eye by Visit	PPS Population [redacted]
14.2.2.5	Mixed Model Repeated Measures Analysis of Covariance of Change from Baseline in Central Subfield Thickness (µm) in the Study Eye by Visit	FAS Population [redacted]
14.2.3.1	Proportion of Eyes with a ≥2 Step Improvement from Baseline in Diabetic Retinopathy Severity Scale Score by Visit	FAS Population [redacted]
14.2.3.2	Proportion of Eyes with a ≥2 Step Improvement from Baseline in Diabetic Retinopathy Severity Scale Score by Visit	PPS Population [redacted]
14.3.1.1.1	Overall Summary of Adverse Events (Ocular & Non-Ocular) by Treatment Group	SAF Population
14.3.1.1.2	Overall Summary of Adverse Events (Ocular) by Eye and Treatment Group	SAF Population
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF Population
14.3.1.2.2	Ocular Treatment-Emergent Adverse Events by Eye, System Organ Class, and Preferred Term	SAF Population
14.3.1.2.3	Serious Adverse Events by System Organ Class and Preferred Term	SAF Population
14.3.1.2.4	Ocular Serious Adverse Events by Eye, System Organ Class, and Preferred Term	SAF Population

14.3.1.2.5	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term	SAF Population
14.3.1.2.6	Ocular Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by Eye, System Organ Class, and Preferred Term	SAF Population
14.3.1.2.7	Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF Population
14.3.1.2.8	Ocular Treatment-Related Treatment-Emergent Adverse Events by Eye, System Organ Class, and Preferred Term	SAF Population
14.3.1.2.9	Post-Treatment Adverse Events by System Organ Class and Preferred Term	SAF Population
14.3.1.3.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	SAF Population
14.3.1.3.2	Ocular Treatment-Emergent Adverse Events by Eye, System Organ Class, Preferred Term, and Maximum Severity	SAF Population
14.3.1.4.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	SAF Population
14.3.1.4.2	Ocular Treatment-Emergent Adverse Events by Eye, System Organ Class, Preferred Term, and Relationship to Study Drug	SAF Population
14.3.1.5.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Time of Onset	SAF Population
14.3.1.5.2	Ocular Treatment-Emergent Adverse Events by Eye, System Organ Class, Preferred Term, and Time of Onset	SAF Population
14.3.1.6.1	Treatment-Emergent Adverse Events by Preferred Term	SAF Population
14.3.1.6.2	Ocular Treatment-Emergent Adverse Events by Eye and Preferred Term	SAF Population
14.3.1.7.1	Most Frequent (≥ 5% of KVD001-Treated Subjects) Treatment-Emergent Adverse Events by Preferred Term	SAF Population
14.3.1.7.2	Most Frequent (≥ 5% of KVD001-Treated Subjects) Ocular Treatment-Emergent Adverse Events by Eye and Preferred Term	SAF Population
14.3.4.1	Best Corrected Visual Acuity (Letter Count) by Visit and Eye	SAF Population
14.3.4.2	Central Subfield Thickness (µm) by Visit and Eye	SAF Population
14.3.4.3	Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Score in the Study Eye by Visit	SAF Population
14.3.4.4.1	Slit Lamp Biomicroscopy by Visit and Eye	SAF Population
14.3.4.4.2	Shifts from Baseline in Slit Lamp Biomicroscopy by Visit and Eye	SAF Population
14.3.4.5.2	Shifts from Baseline in Indirect Dilated Ophthalmoscopy by Visit and Eye	SAF Population
14.3.4.5.1	Indirect Dilated Ophthalmoscopy	SAF Population

14.3.4.6	Intraocular Pressure (mmHg) by Visit and Eye	SAF Population
14.3.4.7	Vital Signs by Visit	SAF Population
14.3.4.8.1.1	Blood Chemistry by Visit	SAF Population
14.3.4.8.1.2	Shifts from Baseline in Blood Chemistry by Category, Parameter, and Visit	SAF Population
14.3.4.8.2.2	Shifts from Baseline in Hematology by Parameter and Visit	SAF Population
14.3.4.8.2.1	Hematology by Visit	SAF Population
14.3.4.8.3.1	Urinalysis by Visit	SAF Population
14.3.4.8.3.2	Shifts from Baseline in Urinalysis by Parameter and Visit	SAF Population

20. Listings

Listing Number	Title	Population
16.1.7	Randomization Schedule	All Randomized Subjects
16.2.1.1	Subject Disposition	All Randomized Subjects
16.2.1.2	Subject Disposition-Rescue Medication Information	All Randomized Subjects Who Discontinued for Use of Rescue Medication
16.2.1.3	Subject Unmasking	All Randomized Subjects
16.2.2.1	Protocol Deviations	All Randomized Subjects
16.2.2.2	Inclusion/Exclusion Criteria	All Enrolled Subjects
16.2.3.1	Study Population Inclusion	All Randomized Subjects
16.2.3.2	Screen Failures	All Enrolled Subjects Who Were Screen Failures
16.2.4.1.1	Demographics	All Randomized Subjects
16.2.4.1.2	Baseline Disease Characteristics	All Randomized Subjects
16.2.4.1.3	Prior Visual Acuity Measurements in the SE	All Randomized Subjects
16.2.4.1.4	Prior OCT Measurements in the SE	All Randomized Subjects
16.2.4.1.5	Rescue Procedures in the SE	All Randomized Subjects
16.2.4.2.1	Ocular Medical History	All Randomized Subjects
16.2.4.2.2	Non-Ocular Medical History	All Randomized Subjects
16.2.4.3.1	Prior and Concomitant Ocular Medications	All Randomized Subjects
16.2.4.3.2	Prior and Concomitant Non-Ocular Medications	All Randomized Subjects
16.2.4.3.3	Prior Anti-VEGF Medications in the SE	All Randomized Subjects
16.2.4.3.4	Anti-VEGF Medication Log	All Randomized Subjects
16.2.4.3.5	IVT Steroid Use	All Randomized Subjects
16.2.4.3.6	Rescue Therapy Administration in the SE	All Randomized Subjects
16.2.5.1	Study Drug Administration	All Randomized Subjects
16.2.5.2	Exposure and Compliance	All Randomized Subjects
16.2.7.1	All Adverse Events (Ocular and Non-Ocular)	All Randomized Subjects
16.2.7.2	Serious Adverse Events	All Randomized Subjects
16.2.7.3	Adverse Events Causing Premature Discontinuation	All Randomized Subjects
16.2.7.4	Adverse Events Resulting in Death	All Randomized Subjects
16.2.8.1.1	BCVA Observed and Change from Baseline	All Randomized Subjects
16.2.8.1.2	BCVA Manifest Refraction	All Randomized Subjects
16.2.8.1.3	BCVA (EDTRS)	All Randomized Subjects

16.2.8.2	Retinal Central Subfield Thickness (CST) (Using SD-OCT by CIRC and Investigator)	All Randomized Subjects
16.2.8.3	Diabetic Retinopathy Severity Scale (DRSS) Observed and Change from Baseline	All Randomized Subjects
16.2.8.4	Slit Lamp Biomicroscopy	All Randomized Subjects
16.2.8.5	Dilated Indirect Ophthalmoscopy	All Randomized Subjects
16.2.8.6	Intraocular Pressure (IOP)	All Randomized Subjects
16.2.8.7	Fundus Photography	All Randomized Subjects
16.2.9	Vital Signs	All Randomized Subjects
16.2.10.1	Urine Pregnancy Test Results	All Randomized Subjects
16.2.10.2	Blood Chemistry	All Randomized Subjects
16.2.10.3	Hematology	All Randomized Subjects
16.2.10.4	Urinalysis	All Randomized Subjects
16.2.11	Physical Exam	All Randomized Subjects
16.2.12	Biometrics	All Randomized Subjects

21. Figures

Figure Number	Title	Population
14.2.1.1.1	Box Plot of BCVA Letter Count in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.1.1.2	Line Chart of Change from Baseline in BCVA Letter Count in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.1.2.1	Box Plot of BCVA Letter Count in the Study Eye at Scheduled Visits	PPS Population [redacted]
14.2.1.2.2	Line Chart of Change from Baseline in BCVA Letter Count in the Study Eye at Scheduled Visits	PPS Population [redacted]
14.2.2	Line Chart of Change from Baseline in BCVA Letter Count in the Study Eye at Scheduled Visits by Visual Acuity Group	FAS Population [redacted]
14.2.3	Line Chart of Change from Baseline in BCVA Letter Count in the Study Eye at Scheduled Visits by CST Group	FAS Population [redacted]
14.2.4.1.1	Box Plot of Central Subfield Thickness (CST) as Measured by Spectral-Domain OCT (SD-OCT) in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.4.1.2	Line Chart of Change from Baseline in Central Subfield Thickness (CST) as Measured by Spectral-Domain OCT (SD-OCT) in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.5.1	Bar Chart of Proportion of Subjects with BCVA Gain of 15 or More Letters from Baseline in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.5.2	Bar Chart of Proportion of Subjects with BCVA Gain of 10 or More Letters from Baseline in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.5.3	Bar Chart of Proportion of Subjects with BCVA Gain of 5 or More Letters from Baseline in the Study Eye at Scheduled Visits	FAS Population [redacted]

[redacted]

Figure Number	Title	Population
14.2.5.4	Bar Chart of Proportion of Subjects with Any Loss in BCVA Letters from Baseline in the Study Eye at Scheduled Visits	FAS Population [redacted]
14.2.6.1	Bar Chart of Proportion of Eyes with a ≥ 2 Step Improvement from Baseline in DRSS Score	FAS Population [redacted]
14.2.6.2	Bar Chart of Proportion of Eyes with a ≥ 2 Step Improvement from Baseline in DRSS Score	PPS Population [redacted]

Appendix A. Schedule of Procedures

Clinic Visit (V)	Visit 1 Screen	Visit 2	Call	Visit 3	Call	Visit 4	Call	Visit 5	Call	Visit 6	Visit 7	Visit 8/ ED Visit
Day (D)	Week -4 to Day -1	Day 1	Visit 2 +1 day	Week 4 (-3 to +7 days)	Visit 3 +1 day	Week 8 (-3 to +7 days)	Visit 4 +1 day	Week 12 (-3 to +7 days)	Visit 5 +1 Day	Week 16 (±1 Week)	Week 20 (±1 Week)	Week 24 (±1 Week)
Informed Consent	X											
Eligibility Assessment	X	X										
Demographics	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (height, weight, BMI)	X											
Medical/Ocular History	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[a]	X	X		X		X		X		X		
Safety Laboratory[b]	X	X		X		X		X		X		
[redacted]		X										
Study Drug Administration (KVD001 Injection) or Sham Procedure		X		X		X		X				
Urine Pregnancy Test (women)	X	X		X		X		X		X		
Adverse Events[c]	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Clinic Visit (V)	Visit 1 Screen		Visit 2		Call	Visit 3		Call	Visit 4		Call	Visit 5		Call	Visit 6		Visit 7		Visit 8/ ED Visit	
Day (D)	Week -4 to Day -1		Day 1		Visit 2 +1 day	Week 4 (-3 to +7 days)		Visit 3 +1 day	Week 8 (-3 to +7 days)		Visit 4 +1 day	Week 12 (-3 to +7 days)		Visit 5 +1 day	Week 16 (±1 Week)		Week 20 (±1 Week)		Week 24 (±1 Week)	
OCULAR	**SE**	**FE**	**SE**	**FE**		**SE**	**FE**		**SE**	**FE**		**SE**	**FE**		**SE**	**FE**	**SE**	**FE**	**SE**	**FE**
BCVA[d,e]	X	X	X	X		X	X		X	X		X	X		X	X	X	X	X	X
Slit Lamp Biomicroscopy[d]	X	X	X	X		X	X		X	X		X	X		X	X	X	X	X	X
Dilated Indirect Ophthalmoscopy[d]	X	X	X	X		X	X		X	X		X	X		X	X	X	X	X	X
IOP[f]	X	X	X	X		X	X		X	X		X	X		X	X	X	X	X	X
Fundus Photography[d]	X	X	X			X			X			X			X		X		X	
SD-OCT[d]	X	X	X	X		X	X		X	X		X	X		X	X	X	X	X	X

Abbreviations: AEs = Adverse events; BCVA = Best corrected visual acuity; BMI = Body mass index; ED Visit = Early discontinuation visit; FE = Fellow eye; IOP = Intraocular pressure; SD-OCT = Spectral domain optical coherence tomography; SE = Study eye.

[a] Vital signs include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature. Vital signs will be taken prior to and approximately 30 minutes after study drug

[b] Safety labs are detailed in Protocol Section 6.2.2.

[c] AEs to be recorded from time of signing of informed consent form

[d] Procedure will be performed prior to study drug administration or sham procedure on applicable visits.

[e] BCVA will be performed prior to all other ophthalmic procedures.

[f] IOP will be taken prior to and within 60 minutes following study drug administration or sham procedure at applicable visits. Pre-study drug administration IOP must be performed prior to dilation. Post study-drug administration IOP must be performed by unmasked personnel.