Official title: A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)
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STATISTICAL ANALYSIS PLAN

A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)

Protocol Number: KSI-CL-102

Sponsor:	Kodiak Sciences Inc. 1200 Page Mill Road Palo Alto, CA 94304 USA
Sponsor Contact & Medical Monitor:	[redacted] Kodiak Sciences Inc.
IND Number:	136167
EUDRACT Number:	2018-003428-35
Test Product:	KSI-301
Statistical Analysis Plan Version:	1
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CONFIDENTIAL

SPONSOR SIGNATORY

Study Title:	A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)
Protocol Code:	KSI-CL-102
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Statistical Analysis Plan Version Date:	February 3, 2022
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ANCOVA	Analysis of Covariance
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AMD	Age-related Macular Degeneration
AST	Aspartate aminotransferase
ATE	Arterial Thromboembolic Events
BCVA	Best-Corrected Visual Acuity
BP	Blood Pressure
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal Neovascularization
CSR	Clinical Study Report
CST	Central Subfield Thickness
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein Angiogram
FASY1	Full-Analysis Set Year 1
FASY2	Full-Analysis Set Year 2
FDA	Food and Drug Administration
FP	Fundus photography
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug (application)
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
LOQ	Level of Quantification
MAR	Missing at Random
MNAR	Missing Not at Random
MedDRA	The Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
OCT	Optical Coherence Tomography
Q8W	Every eight weeks

Q12W	Every twelve weeks
Q16W	Every sixteen weeks
Q20W	Every twenty weeks
RSY1	Randomized Set Year 1
RSY2	Randomized Set Year 2
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSY1	Safety Set Year 1
SSY2	Safety Set Year 2
ULN	Upper Limits of Normal
VEGF	Vascular Endothelial Growth Factor
wAMD	Wet (neovascular) Age-related Macular Degeneration
WHODrug	World Health Organization Drug Dictionary

1.0 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a comprehensive and detailed description of the methods and presentation of data analyses for Study KSI-CL-102 (Protocol Version 3.0, dated 02 June 2021), *A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)*. This study is conducted in accordance with the protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, and any other applicable regulatory requirements.

Descriptions of planned analyses are provided to avoid *post hoc* decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses are consistent with the International Council for Harmonisation (ICH) guidelines *Statistical Principles for Clinical Trials* (E9) (1998) and ICH E9 (R1) *Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials* (2020).

This SAP provides details of the results to be presented in the clinical study report (CSR). Details about the unmasking plan, including the procedures and guidelines that Kodiak, study sites, and vendors will follow to ensure that masking of the study is appropriately maintained in the second year of the study, will be detailed in a separate document. Analyses of pharmacokinetics, biomarkers, and anti-drug antibodies will be addressed in separate analysis plan(s).

Any changes between the statistical methods and study endpoints provided in the clinical study protocol and this SAP will be described and explained herein; any changes or deviations from this SAP relative to the final analyses will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in BCVA from Day 1 to Year 1. Year 1 is defined as the mean of the Week 48 and 52 measurements.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg by assessing visual and anatomical parameters.

- To evaluate the durability of KSI-301 5 mg as measured by the proportion of subjects on Q12W, Q16W or Q20W dosing regimens.
- To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg.
- To assess the systemic pharmacokinetics and immunogenicity of KSI-301.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, randomized, double-masked, active comparator controlled, multi-center Phase 2b/3 study that will evaluate the efficacy and safety of KSI 301 compared with aflibercept in subjects with treatment-naive wAMD.

The schedule of activities is provided in Appendix 1.

The study is divided into a 3-week screening period, a 92-week treatment period, and a final 4-week follow-up period.

First Year (Day 1 through Week 52):

At baseline subjects will be randomized 1:1 into two treatment arms: KSI-301 5 mg and aflibercept 2 mg. All subjects will receive 3 monthly loading doses of their assigned treatment. Thereafter the dosing regimen of subjects in the KSI-301 treatment arm will be Q12W to Q20W based on Year 1 disease activity assessments. The dosing regimen of subjects in the aflibercept treatment arm following the three initial injections will be fixed at Q8W.

Second Year (Week 52 through Week 96):

Beginning at Week 52, the dosing regimen of subjects in the KSI-301 treatment arm will be based on Year 2 Disease Activity Assessments. [redacted]

End of Study Treatment and End of Study Participation

Subjects who discontinue study drug should not be considered withdrawn from the study unless they withdraw consent or there is additional risk to the subject. Subjects who have discontinued study treatment should be encouraged to stay in the study and undergo as many scheduled visits as possible, with emphasis on the Week 48, Week 52 and Week 96 visits.

3.2 Treatments Administered

KSI-301 investigational product will be provided by the Sponsor as a sterile solution for intravitreal injection. KSI-301 Drug Product is an aqueous solution that is provided in single-use vials and filled into syringes by unmasked site personnel without reconstitution or dilution.

The aflibercept active comparator product will be supplied by the Sponsor as a sterile liquid for intravitreal injection. Aflibercept is an aqueous solution that is provided in single-use vials and filled into syringes by unmasked site personnel without reconstitution or dilution.

The sham vial is an empty glass vial which will remain empty throughout the sham treatment procedure. A sham injection is used for masking purposes and mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe, without a needle, against an anesthetized eye. A sham vial is provided to help maintain masking of the study. Sham injections are given at every monthly visit in which an active KSI-301 or aflibercept injection is not administered.

3.3 Method of Assigning Participants to Treatment Groups

Subjects who meet all inclusion criteria and none of the exclusion criteria are randomized using the Interactive Response Technology (IRT) system. Treatment assignments are based on a predetermined randomization schedule developed by The Emmes Company, LLC, Rockville, MD.

Randomization is stratified by baseline [redacted]

3.4 Selection and Timing of Dose for Each Participant

At each visit in which treatment is scheduled to be administered, each participant will receive intravitreal injections of study treatment or a sham injection to maintain masking.

Year 1 (Day 1 through Week 52 [Pre-Treatment]):

KSI-301 Arm:

Following the 3 initial injections, the dosing regimen will be based on disease activity assessments and may vary from Q12W to Q20W.

Aflibercept Arm:

Following the 3 initial monthly injections, subjects randomized to aflibercept will be dosed at a fixed Q8W dosing regimen for the duration of the first year.

Year 2 (Week 52 through Week 96):

KSI-301 Arm:

Beginning at Week 52, dosing regimen adjustments in the KSI-301 group will also be based on disease activity assessments, but the dosing regimens can be adjusted to both reduce or extend the treatment interval in increments of Q4W per dosing cycle, although the adjustment of Q20W to Q12W is also allowed when needed. The minimum dosing interval is Q12W and the maximum dosing interval is Q20W.

[redacted]

[redacted]

[redacted]

4.0 TYPES OF PLANNED ANALYSES

4.1 Data Monitoring Committee Analyses

An Independent Data Monitoring Committee (IDMC) will monitor study conduct and safety on an ongoing basis. Members of the IDMC will be external to the Sponsor and will follow a charter that outlines the IDMC membership and responsibilities, the timing of IDMC meetings, the content of the analysis report for the IDMC meetings, and the communication with the Sponsor. The IDMC can recommend changes to the conduct of the study based on the evaluated data and may recommend stopping the study early for safety reasons only as detailed in the charter.

4.2 Interim Analyses

[redacted] it was not performed.

4.3 Final Analyses

The analysis of the primary (Year 1) data will be performed when all subjects have either completed the Week 52 visit or have discontinued from the study prior to the Week 52 visit, whichever comes later, and the Year 1 data are cleaned and verified as appropriate, frozen, and unmasked. Safeguards will be put in place to ensure that the unmasking does not introduce operational biases in the conduct of the ongoing study. Details of the unmasking plan are described in a separate document.

Analysis of data for Year 2 of the study will be performed when all subjects have either completed the Week 96 visit or have discontinued from the study, and all data have been entered into the database, cleaned and verified as appropriate, and the database locked.

5.0 GENERAL STATISTICAL METHODS

5.1 Statistical Computing Software

SAS Version 9.4 or higher (SAS Institute Inc., Cary NC, USA) will be used for the study analyses described in this SAP.

5.2 Reporting Conventions

Tables and figures will be summarized by treatment group. Tables summarizing demographics and other baseline characteristics will also include a column for all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all randomized subjects. Listings will be ordered by treatment group, subject number, and assessment or event date. The treatment groups will be displayed in the same order as the summary tables. The treatment groups presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. The denominator for percentages for incidence data (such as adverse events) will be based on the number of subjects in the analysis population "at risk." Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Percentages that round down to 0 or up to 100% will be displayed as "<0.1%" and ">99.9%", respectively. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form e.g., on the electronic case report form (eCRF) and are outlined as follows:

- The mean and median will be rounded to an additional decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two additional decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

Unless stated otherwise, statistical significance testing will be two-sided and performed using α=0.05. Confidence intervals (CIs) will be calculated at the 95% level, reflecting a type I error rate of 0.05. P-values will be reported for all statistical tests, rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

5.3 Standard Calculations

Where appropriate, the calculated study day will be presented with the assessment or event date on subject data listings. Study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Start and stop dates will be imputed when partial dates are present as needed, to determine treatment emergent events and concomitant medications/procedures. No imputations will be done for a completely missing start/stop date or for subjects who did not receive study treatment.

Start dates with a missing day but with month and year available will be imputed such that:

- If the provided month and year match the month and year for that subject's first dose date, then the Day 1 date will be used.
- In all other cases the 1st of the month will be used with the provided month and year.

Start dates with a missing day and month but with available year will be imputed such that:

- If the provided year matches the year for that subject's first dose date, then the first dose date will be used.
- In all other cases the 1st of January will be used with the provided year.

Stop dates will be imputed as follows:

- Missing day with a provided year and month will use the last day of the month.
- Missing day and month with provided year will use December 31.

If the imputed stop date is greater than the last study date for the subject, then the imputed date will be replaced with the last available event date for the subject in the study.

Other variables requiring calculations will be derived using the following formulas:

- Days: A duration between two dates expressed in days will be calculated using the following conventions:

- Later date – earlier date + 1.

- Months: A duration expressed in months will be calculated by dividing the duration in days by (365.25 /12).
- Years: A duration expressed in years will be calculated by dividing the duration in days by 365.25.

5.4 Study Definitions and Derived Variables

- Unless otherwise specified, the duration of Study Year 1 is defined as Study Day 1 until Week 52 (pre-treatment), as it is meant to be inclusive both of study treatments leading to the primary efficacy outcome at Year 1 and of safety assessments in that period.
- Similarly, the duration of Study Year 2 is defined as being from Week 52 (post-treatment) onwards until week 96, unless otherwise specified.
- Year 1 baseline values are defined as the most recent values prior to the first dose of study treatment. That is, for values collected at the Day 1 visit pre-treatment, those values will be considered baseline. For data collected only at the screening visit but not at Day 1, the screening visit values will be considered the baseline.
- Baseline for Year 2 for the re-randomized aflibercept group is defined as the last value prior to the re-randomization.

5.5 Analysis Sets

5.5.1 Randomized Set Year 1 (RSY1)

The set will include all randomized subjects in Year 1.

5.5.2 Randomized Set Year 2 (RSY2)

The set will include all subjects who were re-randomized to aflibercept 2 mg or KSI-301 5 mg Q8W. Subjects will be analyzed according to their assigned treatment at re-randomization.

5.5.3 Full Analysis Set Year 1 (FASY1)

The set includes all randomized subjects who received at least one active study treatment (KSI-301 or aflibercept) in Year 1. Subjects will be analyzed according to their randomized treatment.

5.5.4 Full Analysis Set Year 2 (FASY2)

The set includes all randomized subjects who received at least one active study treatment (KSI-301 or aflibercept) in Year 2. Subjects will be analyzed according to their randomized treatment.

5.5.5 Safety Set Year 1 (SSY1)

The set includes all subjects who received any study treatment in Year 1.

5.5.6 Safety Set Year 2 (SSY2)

The set includes all subjects who received any study treatment in Year 2. Subjects will be analyzed according to treatment they actually received.

5.6 Examination of Subgroups

The primary efficacy endpoint will be summarized in the following subgroups of baseline characteristics:

Age	• < 65 years of age • ≥ 65 years of age • < 75 years of age • ≥ 75 years of age
Sex	• Female • Male
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino
BCVA	• BCVA: ≥70 letters • BCVA: 69-50 letters • BCVA: ≤ 49 letters
[redacted]	[redacted]
Geographic location	• North America • Rest of World
Race	• White • Black or African American • Asian • American Indian or Alaska Native • Native Hawaiian or other Pacific Islander • Other
Lens status	• Phakic • Pseudophakic • Aphakic
CNV lesion type	• Classic or Predominantly Classic • Minimally Classic or Occult • Other: RAP or PCV Lesion • Ungradable

Other subgroups analyses may be explored.

5.7 Multiple Comparisons/Multiplicity

A nominal type I error penalty of 0.0001 will be applied for each of the three unmasked safety reviews undertaken by the independent data monitoring committee prior to the primary analysis. Thus, the primary efficacy endpoint will be tested using a two-sided significance level of 0.0497. Multiplicity adjustments are not planned for any other endpoints.

5.8 Multicenter Studies

This is a multicenter, international study. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored, as needed.

5.9 Analysis Visit

For efficacy analyses, unscheduled or early termination visits will be assigned a visit day and then mapped to the appropriate analysis window as detailed in Table 1. In the event where more than one visit falls in the same analysis window, the following rules will be used in sequence to determine the record that will be analyzed:

- If there is a scheduled visit in the analysis window, then the scheduled visit's data will be used.
- If there is no scheduled visit in the analysis visit window, the data closest to the scheduled day/time visit will be used.
- If there is no scheduled visit in the analysis visit window and there is a tie between the visits with regards to the number of days/hours before and after the scheduled day, the later data will be used.

Visit windows will not apply to listings.

Windowing will be applied to the data prior to any missing data imputations or analysis.

Table 1: Windows for Unscheduled Visit

Nominal Visit	Scheduled Study Day	Starting Day for Nominal Visit	Ending Day for Nominal Visit
Day 1	1	1	1

Week 1	7	4	14
Week 4	28	15	42
Week 8 – Week 96	Week*7	(Week*7)-13	(Week*7)+14

5.10 Disposition of Subjects

Subject disposition will be summarized for all subjects by treatment group and for all subjects combined in Year 1. Summaries will include the number of subjects screened and randomized, and number of subjects (%) in the FASY1 and SSY1 populations, completing the treatment in Year 1, and discontinuing Year 1 study treatment early by the reason for discontinuation. Subject disposition will also be summarized separately for each study site.

Summaries for Year 2 will be produced. They will include the number and percentage of subjects [redacted], subjects completing the study, and subjects discontinuing study treatment early by the reason for study discontinuation.

Subject completion status, date of study completion/discontinuation, study day of discontinuation, and reason for discontinuation will be listed.

Inclusion and exclusion eligibility will be listed.

5.11 Baseline Data

5.11.1 Demographics and Other Baseline Characteristics (including Ocular Baseline Characteristics)

Summaries of demographics and baseline characteristics will include

- Sex
- Age continuous
- Age categorical <65, ≥ 65, < 75, ≥75, 65-74, 75-84, >85 years of age
- Ethnicity
- Race
- Geographical region (North America, Rest of World)
- Smoking status
- Systolic and diastolic blood pressure

- Intraocular pressure in the study eye
- Intraocular pressure in the study eye, categorical (≤21, 22-29, >29 mmHg)
- Lens status (phakic, pseudophakic, aphakic)
- BCVA: by stratification categories and continuous
- [redacted]
- LLVA: continuous
- Ocular Imaging:
  - OCT:
    - Central Subfield Thickness (CST; [redacted]
    - Intraretinal fluid: Presence/Absence, presence/absence within the central 1mm
    - Subretinal fluid: Presence/Absence, presence/absence within the central 1mm, height of SRF at center point
    - Subretinal hyperreflective material (SHRM): presence/absence, presence/absence within the central 1mm, height of SHRM at the center point
    - Pigment epithelial detachment (PED): presence/absence, presence/absence in the central 1mm
    - Outer retinal tubulation: presence/absence, presence/absence within the central 1mm
  - FA:
    - Presence/absence of leakage; presence/absence of leakage at the foveal center; area of leakage associated with CNV
    - Total area of CNV
    - Total lesion area
    - Type of lesion (e.g., classic, predominantly classic, minimally classic, occult, RAP lesion, PCV lesion, ungradable)
    - CNV location (e.g., subfoveal, juxtafoveal, extrafoveal)
    - Presence/absence of RPE atrophy
    - Presence/absence of subretinal hemorrhage
    - Presence/absence of fibrosis
  - FP:
    - Hemorrhage: presence/absence, presence/absence inside the central millimeter, involvement of foveal center

- Fibrosis: presence/absence, presence/absence inside the central millimeter, involvement of foveal center
- Drusen: visible/not visible

Results will be presented by treatment group overall and by site for the Year 1 full analysis set population (FASY1), and for Year 2 re-randomized aflibercept subjects (FASY2).

[redacted]

Individual participants' demographics and baseline characteristics used for stratification will be listed.

5.11.2 Ocular and Other Medical History

Medical history including non-ocular events and ocular events for the study and fellow (non-study) eyes will be tabulated by system organ class and preferred term of the MedDRA dictionary. Two listings will be provided: one listing for all non-ocular medical history and an additional one for ocular history by treatment, subject, and study/non-study eye.

5.11.3 Prior Medications

Prior medications (ocular and non-ocular) will be summarized by Anatomical Therapeutic Chemical (ATC4) class and preferred name according to the WHODrug Global medications dictionary. Prior medications are those that have a start date prior to the first study treatment. Ocular medications will be presented separately for the study eye and fellow eye. Prior medications will also be classified as to whether they were still being taken by the patient on Day 1. A listing of all prior medications will be provided.

5.12 Protocol Deviations

All major protocol violations will be determined and categorized prior to Year 1 unmasking and at the end of the study, prior to final database lock and unmasking. The number and percentage of subjects with any major protocol deviation as well as the number and percentage of subjects with deviations within each category of major deviation will be presented.

Major protocol deviations will be summarized by treatment group and all treatment groups combined for the FASY1 and FASY2 populations. The summaries will also be presented by site.

Major protocol deviations will also be listed by subject.

6.0 EFFICACY ANALYSES

6.1 Primary Estimand

6.1.1 Population targeted by the scientific question

The population targeted by the scientific question is patients with active, treatment-naïve choroidal neovascularization (CNV) due to age-related macular degeneration, a condition also called “wet AMD” or “neovascular AMD.”

The most relevant aspects of the study eligibility criteria for defining this population include the following key inclusion and exclusion criteria:

Inclusion criteria

(1) Active, treatment-naïve choroidal neovascularization (CNV) secondary to AMD, including subfoveal, juxtafoveal and extrafoveal lesions or retinal angiomatous proliferations (RAP) lesions with a CNV component that affect the central subfield as evidenced by FA or OCT in the study eye at screening.

(2) A lesion area <30 mm2 (12 disc areas) of any CNV lesion subtype in the study eye.

(3) Intra and/or subretinal fluid and/or SHRM (subretinal hyperreflective material) affecting the central subfield of the study eye on OCT at screening.

(4) BCVA ETDRS score between 80 and 25 letters (20/25 to 20/320 Snellen equivalent), inclusive, in the study eye at screening and reconfirmed at Day 1.

Exclusion criteria

(1) Any approved or investigational treatment for neovascular AMD (other than oral vitamin supplements) in the study eye at any time.

(5) CNV secondary to other causes in the study eye, including pathologic myopia, angioid streaks, prior trauma, ocular histoplasmosis, or other.

(6) Any history of macular pathology unrelated to AMD but affecting vision or contributing to subretinal or intraretinal fluid, such as central serous chorioretinopathy.

6.1.2 Primary Endpoint/Variable of Interest

The variable of interest is visual acuity, a continuous variable measured at each study visit using the ETDRS BCVA approach. The primary efficacy endpoint is the mean change in BCVA from Day 1 to Year 1, with Year 1 is defined as the mean of the Week 48 and 52 measurements.

If the Week 48 or Week 52 assessment is missing, the available value will be used in the analysis.

6.1.3 Hypothesis to be Tested

$\mathbf{H_0}$: $\mu_K - \mu_A \leq$ [redacted] letters vs $\mathbf{H_A}$: $\mu_K - \mu_A >$ [redacted] letters

Where μ_K and μ_A are the mean changes from baseline to the Weeks 48 and 52 average BCVA in the KSI-301 and aflibercept groups respectively.

Non-inferiority will be demonstrated if the lower limit of the two-sided 95.03% confidence interval for the treatment difference (KSI-301 – aflibercept) is greater than the prespecified NI margin [redacted] ETDRS letters. Furthermore, superiority will be established if the lower limit of the two-sided 95.03% confidence interval for the treatment difference (KSI-301 – aflibercept) is greater than zero.

6.1.4 Intercurrent Events (ICE)

The following intercurrent events (ICEs) may impact the assessment of the primary efficacy endpoint:

1. Deviations from key inclusion/exclusion criteria as defined above.
2. Treatment misallocation (including sham or active treatment) of more than 1 study treatment.
3. Use of prohibited wAMD therapies in the study eye.
4. Premature discontinuation from study treatment due to a) study eye adverse events or b) due to lack of efficacy.
5. Premature discontinuation from study treatment due to events unrelated to study treatment such as malignancies, systemic infections, trauma, or other systemic adverse events that are not treatment-related, including discontinuations due to COVID-19.

Intercurrent events will be classified by the Sponsor prior to treatment code unmasking to prevent potential bias.

Intercurrent events will be tabulated by treatment group.

Strategies for addressing the potential impact of these intercurrent events are described below.

6.2 Analysis of the Primary Endpoint

The primary efficacy endpoint will be estimated based on the FASY1, i.e., all randomized subjects who received at least one treatment injection in Year 1 and using all available post-baseline measurements up to Week 52 or until the subject discontinues study treatment. The 'While on-Treatment' policy will be applied for the primary endpoint.

A Mixed Model for Repeated Measurements (MMRM) will be used. MMRM assumes Missing at Random and uses all available data in the prediction model. MMRM balances the benefits of preserving unbiased estimates because of randomization with the desire to obtain estimates for a comparison of true biological treatment effects.

The model will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction and randomization stratification factors as fixed effects. An unstructured subject covariance matrix will be assumed. The change from baseline in BCVA score averaged over Weeks 48 and 52 will be compared between treatment groups. The comparisons will be performed using a contrast over Weeks 48 and 52.

If the model assuming an unstructured covariance matrix does not converge, a heterogenous compound symmetry structure or an AR(1) covariance structure will be fitted.

6.2.1 Sensitivity Analysis – Hypothetical Policy

A sensitivity analysis will be conducted using all subjects who do not have any of the following intercurrent events: deviations from key inclusion/exclusion criteria as defined above, treatment misallocations as defined above, and use of prohibited wAMD therapies in the study eye during the study treatment period.

The sensitivity analysis based on this set is a type of 'Hypothetical Policy' strategy. The same type of MMRM as described for the primary analysis will be used.

6.2.2 Tipping Point Sensitivity Analyses of the Primary Endpoint

Tipping point analyses will be conducted where an offset ('delta based imputation' penalty) is applied to the MAR imputation distribution applying a range of BCVA letters penalties ranging from 0 letter (MAR) [redacted] letters decrease [redacted] the non-inferiority threshold) in 0.5 letter decrements. The delta-based multiple imputations method will pertain to the following 2 groups of subjects:

1. Tipping Point Analysis 1: Subjects randomized to the KSI-301 arm with missing data considered missing not at random (MNAR), i.e. subjects who prematurely discontinue from study treatment due to study eye adverse events or due to lack of efficacy

2. Tipping Point Analysis 2: Subjects randomized to the KSI-301 who discontinue prematurely for any reason

The following steps will be undertaken (see Appendix 4 for SAS syntax):

Step 1a: A fully conditional imputation model (FCS) with predictive mean matching will be applied to all subjects' missing change from baseline BCVA values

Step 1b: A penalty will be applied to the imputed primary efficacy endpoint for the Weeks 48 and 52 in step 1a

Fifteen complete data sets will be generated. The proposed number of imputed datasets will ensure an efficiency of at least 99% assuming a maximum of 12% rate of missing primary efficacy endpoint data using Rubin's approximation (Rubin 1987).

Step 2: a mixed model identical to the one used for the primary analysis will be run for each of the 15 imputed data sets

Step 3: the estimated mean treatment differences from the 15 datasets for all imputations will be combined and Rubin's method will be applied to derive an estimate of the 1-year treatment difference

Steps 1-3 are repeated for each of the two data sets with scenario groups identified above in the KSI-301 treatment arm and for the range of penalties in the BCVA change from baseline. The tipping point in each will be the penalty value that will render the lower bound of the confidence interval for mean treatment differences to be greater than 4 letters decrease. After the tipping point is identified, clinical judgment will determine the plausibility of the assumptions underlying this tipping point.

6.3 Secondary Efficacy Endpoints Year 1

Secondary Efficacy Endpoint	Variable Derivation/Source	Summary Statistics Population	Method of Analysis
Proportion of subjects on the KSI-301 Q12W, Q16W or Q20W dosing regimen at Year 1	For each subject in the KSI-301 arm, the duration (12, 16 or 20 weeks) from the last active treatment prior to Week 48 until the next active treatment at or after Week 48 is identified / IRT	Proportion (%) FASY1	Descriptive
Number of study medication injections received in the KSI-301 and aflibercept groups during the first year of treatment	For each subject the number of active (non-sham) injections received from Day 1 to Week 48 (inclusive) will be summed / IRT	Median, Quartiles, Mean, Distribution FASY1	Descriptive
Mean change from baseline in BCVA over Weeks 36 to 52 and over Weeks 36 to 40	Continuous endpoint. Change from Day 1 to each timepoint. Visual Acuity Score/EDC	Least Squares Mean difference in change from baseline at each time point FASY1	Contrast for average of Weeks 36 to Week 52 and Weeks 36 to 40 using the MMRM model used for deriving the primary endpoint estimate
Proportion of subjects who gain ≥ 5, ≥10 and ≥15 letters from baseline over time in Year 1	Binary endpoints: subject has a BCVA gain ≥ 5 (yes/no); subject has a BCVA gain ≥ 10 (yes/no); subject has a BCVA gain ≥ 15 (yes/no). Visual Acuity Score/EDC	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors
Proportion of subjects who lose ≥ 5, ≥10 and ≥15 letters from baseline over time in Year 1	Binary endpoints: subject has a BCVA loss ≥ 5 (yes/no); subject has a BCVA loss ≥ 10 (yes/no); subject has a BCVA loss ≥ 15 (yes/no). Visual Acuity Score/EDC	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors

Secondary Efficacy Endpoint	Variable Derivation/Source	Summary Statistics Population	Method of Analysis
Mean change from baseline in BCVA over time in Year 1	Continuous endpoint. Change from Day 1 to each timepoint. Visual Acuity Score/EDC	Least Squares Mean difference in change from baseline at each time point FASY1	MMRM model used for deriving the primary endpoint estimate
Proportion of subjects with BCVA Snellen equivalent of 20/40 or better (69 or more ETDRS letters) from baseline over time	Binary endpoint: subject has a BCVA Snellen equivalent of 20/40 or better (yes/no) at the timepoint. Visual Acuity Score/EDC	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors
Proportion of subjects with BCVA Snellen equivalent of 20/200 or worse (38 or fewer ETDRS letters) from baseline over time	Binary endpoint: subject has a BCVA Snellen equivalent of 20/200 or worse (yes/no) at the timepoint. Visual Acuity Score/EDC	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors
Mean change in OCT central subfield retinal thickness (CST) from baseline over time and at Year 1 averaged over Weeks 48 and 52	Continuous Endpoint. Change from Day 1 to each timepoint [redacted]	Least Squares Mean difference in change from baseline to each timepoint FASY1	MMRM adjusting for baseline CST, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix

6.4 Exploratory Efficacy Endpoints Year 1

Analysis of the following exploratory endpoints may be undertaken as deemed appropriate.

Exploratory Endpoint	Variable/Source	Summary Statistics Population	Method of Analysis
Mean change in CNV total lesion area on FA from baseline at Year 1	Continuous endpoint. Change from Day 1 to Year 1 [redacted]	Least Squares Mean difference in change from baseline at Year 1 FASY1	ANCOVA adjusting for baseline total CNV lesion area, with treatment and randomization stratification as factors
Mean change in area of leakage on FA from baseline at Year 1	Continuous endpoint. Change from Day 1 to Year 1 [redacted]	Least Squares Mean difference in change from baseline at Year 1 FASY1	ANCOVA adjusting for baseline total CNV lesion area, with treatment and randomization stratification as factors.
Proportion of subjects without intraretinal fluid on OCT from baseline to Year 1 over time	Binary endpoint. Subject has no intraretinal fluid (yes/no) at the timepoint [redacted]	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors
Proportion of subjects without subretinal fluid on OCT from baseline to Year 1 over time	Binary endpoint. Subject has no subretinal fluid (yes/no) at the timepoint [redacted]	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors
Proportion of subjects without pigment epithelial detachments on OCT from baseline to Year 1 over time	Binary endpoint. Subject has no pigment epithelial detachments (yes/no) at the timepoint [redacted]	Difference in proportions (%) and 95% CI at each time point FASY1	Stratified analysis of the binary endpoint using CMH adjusting for baseline randomization stratification factors

6.5 Year 2 Efficacy Endpoints

The same efficacy endpoints as described above for the Year 1 data set will be subsequently analyzed for the Year 2 data set.

The Year 2 endpoints analyses will use the methodologies as described above for the corresponding Year 1 analyses as appropriate. The analysis population will be the FASY2 set.

[redacted] 2).

6.6 Subgroup Analyses

For the subgroups described in Section 5.5, the change in BCVA from Day 1 to Year 1 (with Year 1 defined as the mean of the Week 48 and 52 measurements) will be analyzed using an MMRM. The model will include the categorical covariates of treatment group, visit, visit-by-treatment group interaction factors as fixed effects and Day 1 as a covariate. An unstructured covariance matrix will be assumed.

7.0 SAFETY EVALUATION

7.1 Exposure to Study Medication

Study eye exposure to study medication will be summarized. Summaries will include:

- Mean (SD) and median number of injections, and number of subjects receiving ≥1 injection, 1, 2, 3, 4, 5, etc. of KSI-301 or aflibercept injections from Day 1 to Week 48 inclusive (SSY1), from Week 52 to Week 96 (SSY2), and from Day 1 to Week 96 (SSY2).
- Duration of study drug exposure (mean [SD] and median, in months) for subjects receiving KSI-301 5 mg or aflibercept 2 mg, for the SSY1 and SSY2 populations.

Listings will include treatment (KSI-301, aflibercept, sham) and date of injection.

A listing of subjects who received study treatment other than the one assigned at randomization will include the randomized treatment, the actual administered treatment, Visit, and study Day.

7.2 Adverse Events

Adverse events will be coded to a Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 23.1 or later. AEs (Adverse Events) and SAEs (Serious Adverse Events) will be summarized and listed by ocular events for the treated eye, ocular events for the non-treated eye, and non-ocular (systemic) events.

Adverse events starting after the first study injection and continuing until 4 weeks (28 days) after the last study injection will be considered treatment emergent AEs (TEAE).

If the severity score of an adverse event is missing, the severity score will be imputed as severe. If the relatedness of an adverse event is missing, the adverse event will be considered related.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization.

Frequency tables including subjects' incidence rates will be provided through Year 1 and separately from Year 1 to Year 2 for the following:

- Ocular TEAEs and treatment-emergent serious AEs [TESAEs] (study eye and fellow eye separately)
- Non-ocular TEAEs and TESAEs
- Ocular TEAEs leading to study treatment discontinuation (study eye and fellow eye separately)
- Per-injection rates of select ocular TESAEs including traumatic cataract, endophthalmitis, intraocular inflammation, and retinal detachment. The rate per injection is calculated as the number of serious events/total number of non-sham study treatment injections.
- Ocular TEAEs by severity (study eye and fellow eye separately)
- Non-ocular TEAEs by severity
- Related ocular TEAEs (study eye and fellow eye separately) by severity
- Related non-ocular TEAEs by severity
- Intraocular Inflammation TEAEs (study and fellow eye separately). See Appendix 3 for preferred terms used to identify events of IOI
- Intraocular Inflammation TESAEs (study and fellow eye separately)
- Intraocular Pressure: mean and mean change from baseline in pre-injection and post-injection IOP, and mean and mean change from pre-injection to post-injection IOP, over time in the study eye. Baseline is defined as the pre-injection value at Day 1.

- Arteriothromboembolic Adverse Events. See Appendix 2 for preferred terms used to identify ATEs.
- Adverse events of special interest [AESI], as defined in the protocol

Adverse event data will be presented in data listings by treatment group, subject, and event date. Serious AEs, AEs leading to discontinuation of the study drug, intraocular inflammation adverse events, and arteriothromboembolic adverse events will be presented in separate data listings.

Adverse events for subjects who remain in the study after study treatment discontinuation will be listed.

7.3 Deaths, Serious Adverse Events, and other Significant Adverse Events

All deaths during the study will be listed by treatment group and subject and will include the primary cause of death. Serious AEs and other significant AEs, including those that led to interruption or withdrawal of the study drug, will be provided in separate subject data listings.

7.4 Pregnancies

Listings of pregnancies, if any, and outcomes will be presented.

7.5 Clinical Laboratory Evaluations

Continuous laboratory parameters will be summarized, using mean, standard deviation, median, and range for each visit assessed. Laboratory parameters as well as change from baseline for each parameter will be presented at Year 1 and at Year 2 in the safety populations.

Subjects with ALT or AST more than 3 times the Upper Limits of Normal (ULN) in combination with an elevated total bilirubin (more than 2 times the ULN); or ALT or AST more than 3 times the ULN in combination with clinical jaundice will be listed.

Other clinical laboratory results through Year 1 and from Year 1 to Year 2 will be listed and values outside the normal ranges will be flagged along with the clinical significance.

For summary of continuous laboratory parameters, values that are lower than the LOQ will be assigned a value that is 1 unit less than the LOQ. Values that are above the LOQ will be assigned a value that is 1 unit higher than the LOQ.

7.6 Vital Signs

Vital signs including pulse, systolic/diastolic blood pressure, body temperature, height, weight, and BMI will be summarized by treatment group. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected. Results will be presented by Year 1 and Year 2 in the safety populations. Vital signs will be listed by treatment group, subject, and visit date.

Vital signs will be summarized by visit and treatment group for the parameters collected. Vital sign parameters will also be listed.

7.7 Concomitant Medications and Procedures

Concomitant medications during study treatment for Year 1 and Year 2 will be summarized.

The number and percentage receiving any medication by ATC drug class (level 4) and generic drug name will be presented. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

The following will be summarized and listed:

- Ocular (study eye and fellow eye separately) and non-ocular concomitant medications that were initiated *before* start of treatment.
- Ocular (study eye and fellow eye separately) and non-ocular concomitant medications that were initiated *after* the start of treatment.
- Medications prescribed after study treatment discontinuation for subjects who remain in the study will be listed separately.
- Concomitant ocular procedures (study eye and fellow eye separately) administered while subjects were on study treatment will be summarized and listed.
- Concomitant study eye procedures administered after study treatment discontinuation for subjects who remain in the study will be listed separately.

8.0 SAMPLE SIZE CONSIDERATIONS

The sample size for this study has been determined based on a two-group evaluation of non-inferiority using a t-distribution (one-sided significance level of 0.025) with a non-inferiority margin [redacted] BCVA letters difference in the change from baseline between treatment groups

A sample size of 550 participants (275 per treatment arm) provides 91% percent power for the evaluation of non-inferiority assuming an expected treatment difference of 0 BCVA letters and a standard deviation of [redacted] letters, and an assumed dropout rate of [redacted] in each treatment arm.

[redacted] No data were unmasked for the determination of the final study sample size.

9.0 SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes in the conduct of the study have occurred relative to the latest version of the protocol at this time.

The study protocol was finalized prior to the FDA's adoption of the ICH E9(R1) guidance on estimands and sensitivity analysis in clinical trials. In this SAP, the Sponsor has defined the primary estimand including the primary efficacy analysis and strategies for addressing intercurrent events, missing data, and a set of sensitivity analyses for the primary efficacy outcome. This overrides the definitions of the study populations and proposed analyses of the primary endpoint in the study protocol which predate the adoption of the ICH E9(R1) guidance.

Other clarifications or changes in planned analyses in this SAP relative to those described in Version 3.0 of the Protocol include the following:

- The definitions of Year 1 and Year 2 as applied to different endpoints were clarified
- The secondary objective for evaluating the durability of KSI-301 was clarified
- The Year 2 efficacy endpoints description was simplified
- Several anatomic OCT endpoints originally described in the protocol as secondary endpoints were reclassified as exploratory endpoints
- The endpoint related to predictability of subjects being maintained over time on a particular dosing regimen was removed because it is not informative given the flexibility of the KSI-301 dosing regimen being evaluated in the study
- Endpoints related to volumetric measurements of fluid parameters on OCT were removed due to data availability

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11.0 APPENDICES

Appendix 1: Schedule of Activities

[redacted]

Appendix 1: Schedule of Activities

Schedule of Activities Year 1

Visit	Screening	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Windows (days)	**D-21 to D-1**		**+/-3**	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed consent	X															
Medical & Ocular History	X															
Inclusion/Exclusion Criteria	X	X														
Randomized study treatment (KSI-301, aflibercept or sham) per IRT designation [1]		X		X	X		X	X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[2]																
BCVA ETDRS (4 meters) [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Low luminance BCVA [4]		X														
Ophthalmic exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-injection assessments [4]		X		X	X		X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photos	X															X
Fluorescein angiogram	X															X
General Assessments																
Vital signs	X	X	X			X										X
Laboratory Assessments	X															X
Plasma ADA samples [5]		X				X						X				X
Plasma PK/biomarker samples [5]		X	X	X		X		X				X				X
Pregnancy test [6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best corrected visual acuity; ET = early termination; ETDRS = early treatment diabetic retinopathy study; IRT = interactive response technology; PK = pharmacokinetics; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; WOCBP = women of childbearing potential.

[1] Participants who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in Section 4.8 of the study protocol.

[2] Ophthalmic assessments will be performed in both eyes at Screening, Week 52 and Week 96, and in the study eye only at all other timepoints.

[3] Perform before any other ophthalmic assessments and prior to dilation.

[4] Post-injection assessments include vision check for counting fingers and tonometry. The post-injection assessments should be performed by unmasked assessors.

[5] Blood draws for ADA, plasma PK, and biomarker samples are to be taken pre-injection.

[6] Urine pregnancy test will be performed locally for women of childbearing potential, prior to fluorescein angiogram and study treatment (if applicable). If urine pregnancy test is positive, it must be confirmed with a serum pregnancy test. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Schedule of Activities Year 2

Visit	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96/ET
Visit Windows (days)	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Randomized study treatment (KSI-301, aflibercept or sham) per IRT designation [1]	X	X	X	X	X	X	X	X	X	X	
Ophthalmic Assessments [2]											
BCVA ETDRS (4 meters) [3]	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic exam	X	X	X	X	X	X	X	X	X	X	X
Post-injection assessments [4]	X	X	X	X	X	X	X	X	X	X	
SD-OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus photos											X
Fluorescein angiogram											X
General Assessments											
Vital signs											X
Laboratory Assessments											X
Plasma ADA samples [5]				X							X
Plasma PK/biomarker samples [5]				X				X			X
Pregnancy test [6]	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best corrected visual acuity; ET = early termination; ETDRS = early treatment diabetic retinopathy study; IRT = interactive response technology; PK = pharmacokinetics; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; WOCBP = women of childbearing potential.

1 Participants who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in Section 4.8 of the study protocol.

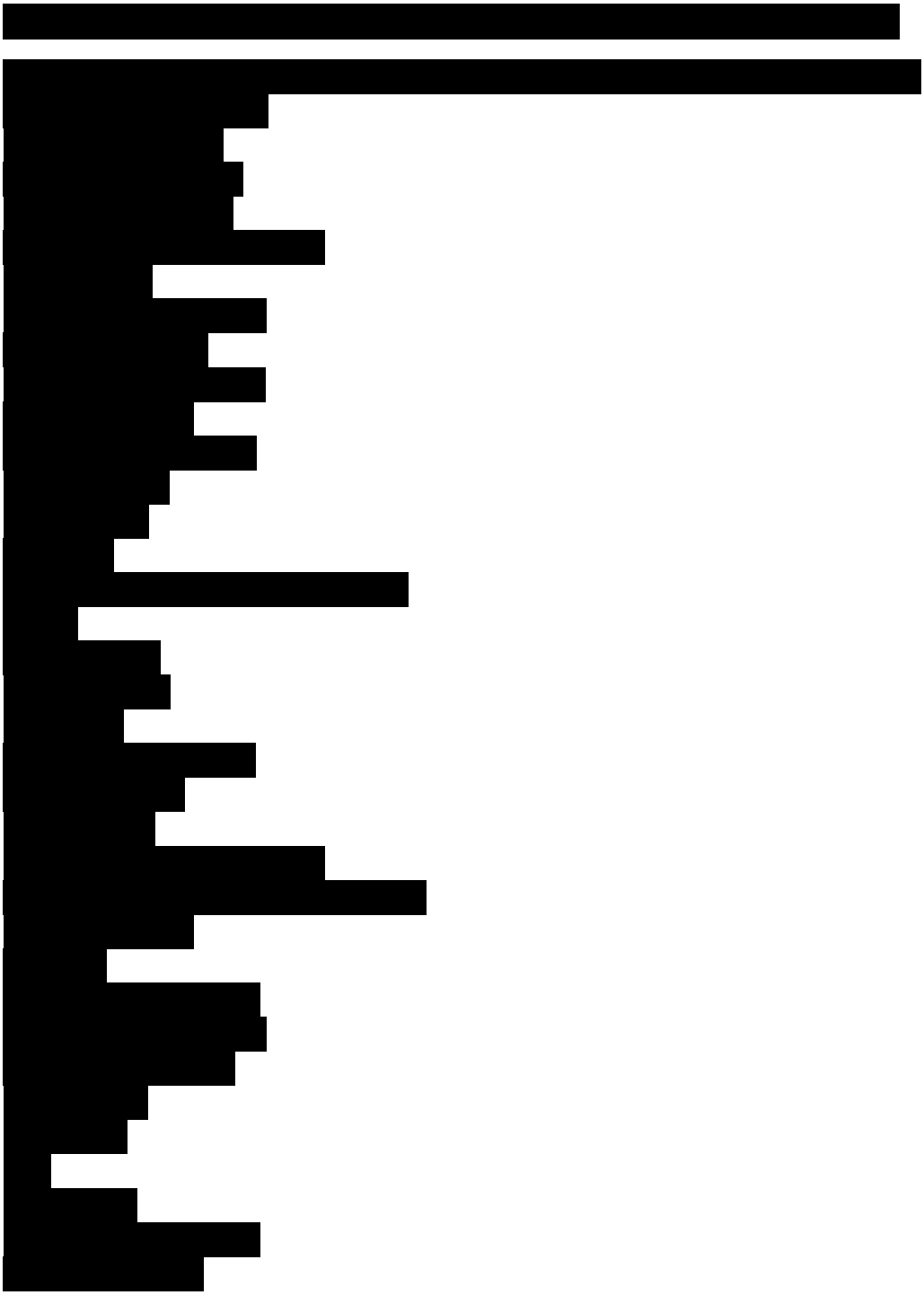
2 Ophthalmic assessments will be performed in both eyes at Screening, Week 52 and Week 96, and in the study eye only at all other timepoints.

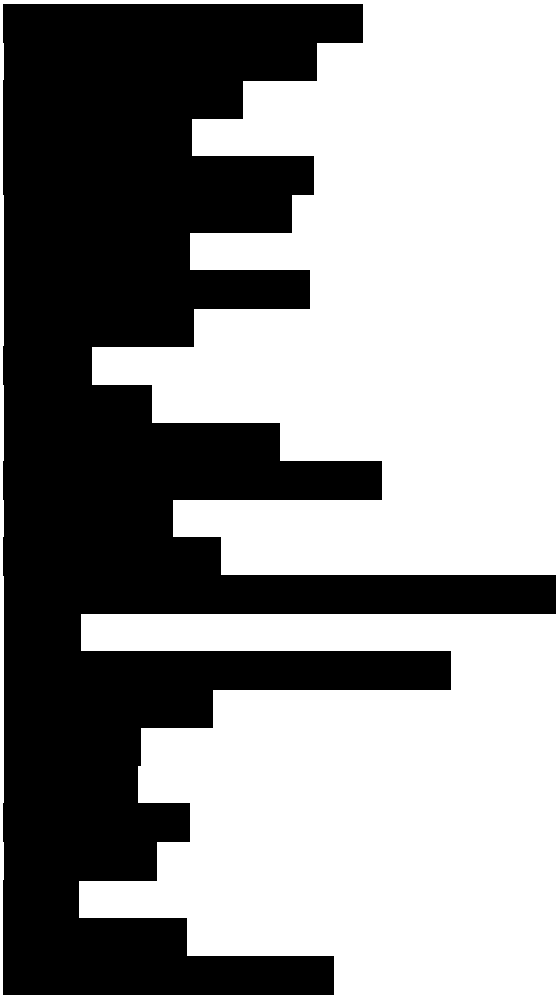
3 Perform before any other ophthalmic assessments and prior to dilation.

4 Post injection assessments include vision check for counting fingers and tonometry. The post-injection assessments should be performed by unmasked assessors.

[5] Blood draws for ADA, plasma PK, and biomarker samples are to be taken pre-injection.

[6] Urine pregnancy test will be performed locally for women of childbearing potential, prior to fluorescein angiogram and study treatment (if applicable). If urine pregnancy test is positive, it must be confirmed with a serum pregnancy test. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.





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