STATISTICAL ANALYSIS PLAN

For Studies KS301P104 (GLEAM) and KS301P105 (GLIMMER), each entitled:

A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME)

Sponsor:	Kodiak Sciences Inc. 1200 Page Mill Road Palo Alto, CA 94304 USA
Sponsor Contact & Medical Monitor:	[redacted] Kodiak Sciences Inc.
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Prepared by:	[redacted]

Statistical Analysis Plan Accepted and Approved by:

[redacted] Date

Kodiak Sciences Inc.
1200 Page Mill Rd.
Palo Alto, CA 94304

[redacted] Date

Kodiak Sciences Inc.
1200 Page Mill Rd.
Palo Alto, CA 94304

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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
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	Arteriothromboembolic
BCVA	Best-corrected visual acuity
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CST	Central Subfield Thickness
DME	Diabetic Macular Edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ET	Early Termination
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAS	Full-Analysis Set
FDA	Food and Drug Administration
FP	Fundus photography
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ILM	Inner Limiting Layer
IND	Investigational New Drug (application)
ICE	Intercurrent event
IOI	Intraocular inflammation
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
NI	Non-Inferiority
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical Coherence Tomography

Abbreviation	Definition
PDR	Proliferative diabetic retinopathy
PT	Preferred Term
Q4W	Every four weeks
Q8W	Every eight weeks
Q12W	Every twelve weeks
Q16W	Every sixteen weeks
Q20W	Every twenty weeks
Q24W	Every twenty-four weeks
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent AE
ULN	Upper Limits of Normal
VA	Visual acuity
VEGF	Vascular Endothelial Growth Factor
[redacted]	[redacted]
WHO	World Health Organization

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 Studies KS301P104 and KS301P105 (Protocol Amendment 2.0, dated 15 March 2022), each entitled *A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME).* (Study KS301P104 is also referred to as 'GLEAM' and Study KS301P105 as 'GLIMMER.') These studies are conducted in accordance with the protocols, Good Clinical Practice, the Declaration of Helsinki, and any other applicable regulatory requirements.

Descriptions of planned analyses are provided *a priori* to preserve the validity of the interpretation of the statistical analysis results pertaining to the primary and key secondary efficacy endpoints. 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 statistical analysis results to be presented in the clinical study reports (CSR). Details about the unmasking plan for study treatment assignment, including the procedures and guidelines that Kodiak, study sites, and vendors will follow to ensure that masking of the study is appropriately maintained during the conduct 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 in Section 10.0; any changes or deviations from this SAP relative to the final analyses will be fully documented in the CSRs. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSRs.

Since the studies are identically designed, a single analysis plan has been developed that includes analyses of both individual study outcomes and selected outcomes from pooled data of studies KS301P104 and KS301P105.

2.0 STUDY OBJECTIVES AND ENDPOINTS

Table 1 lists the primary and secondary study objectives, along with their corresponding endpoints.

Table 1: Objectives and Endpoints

Objectives	Corresponding Endpoints
Primary	
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 the average of Weeks 60 and 64	Mean change in BCVA from baseline to the average of Weeks 60 and 64 (using Early Treatment Diabetic Retinopathy Study (ETDRS) Letters)
Key Secondary	
To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg over the study duration by assessing anatomical parameters (focusing on the ETDRS DRSS)	Proportion of subjects with a ≥ 2-step worsening from baseline on the ETDRS DRSS at Week 52 in Studies KS301P104 and KS301P105 combined Proportion of subjects with a ≥ 2-step worsening from baseline on the ETDRS DRSS at Week 52 in individual Study KS301P104/KS301P105
Secondary	
To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg over the study duration by assessing visual parameters	Mean change in BCVA (ETDRS Letters) from baseline over time Proportion of subjects who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time Proportion of subjects who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time Proportion of subjects with BCVA Snellen equivalent of 20/40 (69 or more ETDRS letters) or better over time Proportion of subjects with BCVA Snellen equivalent of 20/200 (38 or less ETDRS letters) or worse over time
To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg over the study duration by assessing anatomical parameters	Mean change in optical coherence tomography (OCT) central subfield thickness (CST) and other morphological parameters from baseline to the average of Weeks 60 and 64 and over time. Proportions of patients with a ≥ 2-step improvement or worsening from baseline on the ETDRS DRSS over time

Objectives	Corresponding Endpoints
To evaluate the durability of KSI-301 5 mg over the study duration	Mean/Median number of intravitreal injections over the duration of the study Mean/Median number of intravitreal injections from baseline through Week 60 and from Week 64 until end of study Mean/Median time to first retreatment after the last monthly dose Proportion of patients in the KSI-301 arm on a Q8W, Q12W, Q16W, Q20W or Q24W treatment interval through the duration of exposure
To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg.	Incidence of ocular and systemic adverse events up to Week 64 and Week 108.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

These are phase 3, prospective, randomized, double-masked, two-arm, multi-center studies evaluating the efficacy and safety of repeated intravitreal dosing of KSI-301 5 mg in patients with treatment naïve DME. A brief description of the study design and study treatment regimen appears below; additional details can be found in the study protocols.

The schedule of activities is provided in Appendix 1.

The studies are divided into a 3-week screening period, a 104-week treatment period, and a final 4-week follow-up period. At baseline, subjects will be randomized 1:1 into two treatment arms: KSI-301 5 mg and aflibercept 2 mg.

KSI-301 5 mg

Patients randomized in KSI-301 5 mg group will initially receive 3 monthly (Q4W) doses of KSI-301 5 mg [redacted] (at Day 1, Week 4, and Week 8), followed by a sham injection at Week 12 to preserve masking. Starting at Week 16 until Week 100, patients in this group will be assessed monthly (Q4W) and will receive additional administration of KSI-301 5 mg according to disease activity criteria defined below. The minimum interval between active treatments is 8 weeks (± 14 days, considering the respective visit windows) and the maximum interval is 24 weeks (± 14 days, considering the respective visit windows). To preserve masking, sham injections are administered at each visit in which no active treatment with KSI-301 5 mg is indicated.

Aflibercept 2 mg

Patients in this group will initially receive 5 monthly doses of aflibercept 2 mg (50 µL) (at Day 1, Week 4, Week 8, Week 12, and Week 16), followed by doses once every 8 weeks (Q8W) until Week 108. Patients will receive a sham injection at each visit that aflibercept is not administered.

3.2 KSI-301 5 mg Individualized Treatment

3.2.1 Base Treatment Interval

At Weeks 16, 20, 24 and 28, patients will be assessed for disease activity criteria to determine their base treatment interval (once every 8, 12, 16, 20, or 24 weeks). Patients will receive a KSI-301 5 mg dose at the first visit in which any of the disease activity criteria are met. If disease activity criteria are not met by Week 32, participants will receive a dose of KSI-301 5 mg at that visit, which corresponds to the maximum 24-week (Q24W) base treatment interval. The base treatment interval is determined by the time between the last loading dose and the first re-treatment. Once established, the base treatment interval determines when participants receive their next KSI-301 5 mg dose.

3.2.2 Modification of the Base Treatment Interval

The base treatment interval can be adjusted as follows:

- ***Shortened*** by 4 weeks or more to a minimum of 8 weeks (when one or more disease activity criteria are met, indicating that the participant requires an injection before their next base treatment interval visit); or
- ***Maintained***, in two scenarios:
  - When one or more disease activity criteria are met at, but not before, their next base treatment interval visit; or
  - When no disease activity criteria are met at their next base treatment interval, but the disease stability criterion is not met; or
- ***Extended*** to a maximum of 24 weeks (when none of the disease activity criteria are met ***and*** the participant's DME is stable according to the disease stability criterion below).

If the base treatment interval is shortened or extended, the new interval will be considered the new base treatment interval for that participant and can be modified throughout the individualized treatment period based on the adjustments described above.

3.2.3 Disease Activity Criteria

Under protocol version 2, patients are administered KSI-301 5 mg if any of the following disease activity criteria are met:

- Increase in OCT CST $\geq$ 40 μm compared to lowest previous measurement, or
- OCT CST $\geq$ 350 μm; or
- New or worsening proliferative DR (PDR): progression from NPDR to PDR, vitreous hemorrhage, iris neovascularization and/or new or worsening retinal neovascularization.

Disease activity assessments will be conducted by the masked Investigator. The IRT system will adjust the dosing schedule based on disease activity data entered by the study site. The IRT will adjust the dosing schedule in consideration of missed visits, out of window visits, and missing data during a visit.

3.2.4 Disease Stability Criteria

Stable disease for the purposes of extending the base treatment interval is determined by the following criterion, which must be met in addition to the *absence* of any of the disease activity criteria:

- No increase in CST of >30 μm compared to the lowest previous measurement.

This criterion must be met at each visit where the base treatment interval is being extended.

3.3 Study Interventions

Study interventions are summarized in the Protocol Table 2.

3.4 Randomization and Stratification

Patients who meet all inclusion criteria and none of the exclusion criteria will be centrally assigned to a randomized study intervention using an Interactive Response Technology (IRT) system. Randomization will be stratified by [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

No interim analyses were planned or performed.

4.3 Primary Analysis (Week 64)

4.3.1 Timing of the Primary Analysis

The primary analysis will be performed when all patients have either completed the Week 64 visit or have discontinued from the study prior to the Week 64 visit, whichever comes later, the data up to and including the Week 64 visit have been entered, cleaned and verified as appropriate, and the database for the primary analysis is frozen.

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.

4.3.2 Data to be Analyzed for the Primary Analysis Period

The following data (up to Week 64) will be included in the primary analyses:

- Demographics and Baseline Ocular and Non-Ocular Characteristics
- Subject Disposition at Week 64
- Primary Efficacy Analyses
  - Sensitivity and Subgroup Analyses for the Primary Efficacy Endpoint
- Selected Secondary Efficacy Analyses
- Interventions
  - Study Treatment and Exposure
- Safety
  - AEs (including SAEs and AESIs), by Event Type (i.e., Study Eye, Fellow-Eye, Non-Ocular)
  - Clinical laboratory
  - Vital signs
  - Concomitant Medications and Procedures

4.4 Final Analysis (Week 108)

4.4.1 Timing of the Final Analysis

The analysis will be performed when all patients have either completed the Study (Week 108 visit) or have discontinued from the study prior to the Week 108 visit, whichever comes later, the data up to and including the Week 108 visit have been entered, cleaned and verified as appropriate, and the database is locked.

4.4.2 Data to be Analyzed for the Final Analysis

The following data (up to Week 108) will be included in the analyses.

- Subject Disposition
- Descriptive Efficacy Analyses
- Interventions
  - Study Treatment and Exposure
- Safety
  - Incidence of ocular and systemic AEs (including SAEs and AESIs) by Event Type (i.e,, Study Eye, Fellow-Eye, Non-Ocular)
  - Clinical laboratory
  - Vital signs
  - Concomitant Medications and Procedures

5.0 GENERAL STATISTICAL METHODS

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

5.1 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 patients combined. In general, all data collected and any derived data will be presented in subject data listings, for all randomized patients. 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 noted 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".

5.2 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.

5.3 Study Definitions and Derived Variables

- Unless otherwise specified, the duration of Week 64 analysis is defined as Study Day 1 until Week 64, as it is meant to be inclusive both of study treatments leading to the primary efficacy outcome at Week 64 and of safety assessments in that period.
- Similarly, the duration of Week 108 analysis is defined as being from Day 1 until week 108, unless otherwise specified.
- Baseline values are defined as the most recent values prior to the first dose of study treatment.

5.4 Analysis Sets

The efficacy and safety analyses that are specified in Sections 7.0 and 8.0 will utilize the analysis sets as specified in this section.

5.4.1 Full Analysis Set (FAS)

The Full Analysis Set includes all patients who received any study treatment (KSI-301 or aflibercept). Patients will be analyzed according to their randomized treatment. The FAS will be used in the primary analyses of efficacy.

5.4.2 Safety Analysis Set (SAF)

The Safety Analysis Set includes all patients who received any study treatment (KSI-301 or aflibercept). Patients will be analyzed according to the study treatment they actually received.

5.5 Examination of Subgroups

The primary efficacy endpoints will be summarized in the following subgroups of baseline characteristics.

Table 2: Subgroups

Characteristics	Subgroup
Age	< 65 years of age ≥ 65 years of age 65-74 years of age 75-84 years of age ≥ 85 years of age < 75 years of age ≥ 75 years of age
Sex	Female Male
Ethnicity	Hispanic or Latino Not Hispanic or Latino
BCVA	BCVA: ≥ 69 letters BCVA: 68-49 letters BCVA: ≤48 letters
OCT CST	≤ 420 microns > 420 microns
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
DRSS	DRSS: less than level 47 DRSS: level 47 or 53 DRSS: greater than level 53

[redacted]

Other subgroup analyses may be explored.

5.6 Multiple Comparisons/Multiplicity

[redacted]

[redacted]

5.7 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.

5.8 Analysis Visit

For efficacy analyses, unscheduled or early termination visits will be assigned a study day and then mapped to the appropriate analysis window as detailed in Table 3. In the event where more than one record falls in the same analysis window, the following rules will be used in sequential order to determine the record that will be used for data analysis:

- 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 record that is the closest to the scheduled study day at a given visit will be used.
- If there is no scheduled visit in the analysis visit window and there is a tie between the two records with regards to the number of days before and after the scheduled study day, the later record will be used.

Analysis visit windows will not apply to subject data listings. Prior to any missing data imputations or analysis, the analysis visit windows will be applied to the data.

Table 3: 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	2	14
Week 4	28	15	42
Week 8 – Week 108	Week×7	(Week×7)-13	(Week×7)+14

Note: Nominal visits are at Day 1, Weeks 1, 4, 8, … every 4 weeks from Week 8 until Week 108.

6.0 BASELINE ANALYSES

6.1 Disposition of Subjects

Subject disposition will be summarized by treatment group and overall. The following will be summarized:

- The number of patients screened

- The number of patients randomized
- The number of patients (%) in the Full Analysis set
- The number (%) in the Safety Analysis set
- The number (%) completing the study treatment
- The number (%) discontinuing the study treatment and the reasons for discontinuation of study treatment
- The number of patients (%) discontinuing study and the reasons for discontinuation of study

Subject disposition will also be summarized separately for each study site. Subject completion status, date of study completion/discontinuation, study day of discontinuation, and reason for discontinuation will be listed.

Patients who did not meet inclusion or exclusion eligibility criteria will be listed.

6.2 Demographic and Other Baseline Characteristics

6.2.1 Demographics and Baseline Characteristics

The following demographics, baseline characteristics, and randomization stratification variables will be summarized by treatment group and overall.

Demographics:

- Sex
- Age continuous and by category (<65, ≥ 65, < 75, ≥75, 65-74, 75-84, >85 years)
- Ethnicity
- Race

Randomization stratification variables:

- [redacted]

Other baseline characteristics:

- Systolic and diastolic blood pressure

Other Baseline Ocular Characteristics:

- Intraocular pressure in the study eye, continuous and by category (≤21, 22-29, >29 mmHg)
- Lens status (phakic, pseudophakic, aphakic)

Ocular Imaging, OCT:

- Center Subfield Thickness (CST)
- Intraretinal fluid
- Subretinal fluid

Ocular Imaging, Fundus fluorescein angiography (FA):

- Foveal Avascular Zone, area in square microns
- Leakage Intensity: in central mm, in inner subfields, in outer subfields

Ocular Imaging, color fundus photography (FP):

- Baseline DRSS score

Individual patients' demographics and baseline characteristics will be listed.

6.2.2 Ocular and Other Medical History

Medical history includes non-ocular events and ocular events for the study and fellow (non-study) eyes. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 23.1] and will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety Analysis Set. Summaries will be presented by treatment group and overall. Two listings will be provided: one listing for all non-ocular medical history and an additional listing for ocular history by treatment, subject, and study/non-study eye.

6.2.3 Prior and Concomitant Medications/Procedures

All medications (ocular and non-ocular) will be coded using the World Health Organization (WHO) Drug Global Dictionary, Format B3 [Version September 2020 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes. Medications will be summarized by treatment group and overall for the Safety Analysis Set. Medication summaries will be presented by Anatomical Therapeutic Chemical (ATC) class level 4 and preferred name. In addition, ocular medications will be presented separately for the study eye and fellow eye.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to the start of the first dose of study treatment
- Concomitant medications are those with
  - a start date on or before the last dose of study treatment *and*
  - a stop date after the first dose of study treatment or are ongoing at the end of the study

See Section 5.2 for imputation of missing or partial dates.

Prior and concomitant medications will be separately summarized by ocular and non-ocular for the Safety Analysis Set as follows:

- The number and percentage of patients with at least one prior / concomitant medication / procedure will be presented.
- The number and percentage of patients with at least one prior / concomitant medication / procedure within each ATC Level 4, and preferred name will be presented.
- Patients reporting use of more than one medication / procedure at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once.
- The summary will be sorted using numerical counts by descending order of Therapeutic Subgroup, then descending order of preferred name in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications (ocular and non-ocular) will be listed separately for the Safety Analysis Set.

The following will be summarized and listed for concomitant medications and procedures:

- 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 patients who remain in the study will be listed separately.
- Concomitant ocular procedures (study eye and fellow eye separately) administered while patients were on study treatment will be summarized and listed.
- Concomitant study eye procedures administered after study treatment discontinuation for patients who remain in the study will be listed separately.

In the listings the relative start and stop day of prior / concomitant medication (ocular and non-ocular) use will be calculated relative to the first dose date of study treatment and will be presented for those patients who received at least one dose of treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.3 Protocol Deviations

All major protocol violations will be determined and categorized by the timing of analyses (see Section 4.0):

- From start of the study to the data freeze for the Week 64 Primary Analysis
- From the start of the study to the data freeze for Week 108 Analysis

Major protocol deviations will be summarized by treatment group and overall for the Full Analysis set. The number and percentage of patients with any major protocol deviation as well as the number and percentage of patients with deviations within each category of major deviation will be presented. The

major protocol deviations will also be summarized by site. Protocol deviations will be listed in a subject data listing.

7.0 EFFICACY ANALYSES

7.1 Primary Efficacy Analysis

7.1.1 Primary Estimand

7.1.1.1 Target Population

The population targeted by the scientific question is treatment-naïve patients with visual impairment from DME.

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

Inclusion criteria

1. Treatment-naïve diabetic macular edema, with vision loss and center involvement (if present) diagnosed within 9 months of screening.
2. BCVA ETDRS letter score ≤78 and ≥ 25 (~20/25 to 20/320 Snellen equivalent) in the Study Eye at Screening and confirmed at Day 1.
3. CST of ≥ 320 microns on SD-OCT (Heidelberg Spectralis or equivalent on other OCT instruments) as determined by the Reading Center at the screening visit.
4. Decrease in vision in the Study Eye determined by the Investigator to be primarily the result of DME.

Exclusion criteria

1. Macular edema in the Study Eye considered to be secondary to a cause other than DME (e.g., RVO, Irvine-Gass syndrome).
2. Active iris or angle neovascularization or neovascular glaucoma in the Study Eye.
3. Structural damage to the center of the macula in the Study Eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates in the foveal center.

7.1.1.2 Primary Efficacy Endpoint/Variable of Interest

The primary efficacy variable of interest is BCVA, 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 the average of Weeks 60 and 64. If the Week 60 or Week 64 assessment is missing, the available value will be used in the analysis.

7.1.1.3 Hypotheses and Test

The maximum clinically acceptable true difference between KSI-301 and aflibercept among DME patients to be considered non-inferior [redacted], i.e. the non-inferiority margin (NI) is [redacted]

The hypothesis to be tested is:

H_0: $\mu_K - \mu_A \leq$ [redacted] vs H_A: $\mu_K - \mu_A >$ [redacted]

Where μ_K and μ_A are the mean changes from baseline to the Weeks 60 and 64 average BCVA in the KSI-301 and aflibercept groups.

If the lower limit of the two-sided 95.04% CI for the difference between the two means is [redacted], NI will be demonstrated. Furthermore, superiority will be established if the lower limit of the two-sided 95.04% confidence interval for the treatment difference (KSI-301 – aflibercept) is greater than zero.

7.1.1.4 Intercurrent Events

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 1 or more study treatments.
3. Use of prohibited medications in the study eye.
4. Premature discontinuation from study treatment due to study eye adverse events or 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 related 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.

7.1.2 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint will be estimated based on the FAS, i.e., all randomized subjects who received at least one treatment injection and using all available post baseline measurements up to Week 64 or until the subject discontinues study treatment. The 'While on-Treatment' policy will be applied for the primary endpoint.

A Mixed Model for Repeated Measures (MMRM) will be used. The model assumes missing at random (MAR) and uses all available data. 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 change from baseline value as the dependent variable; categorical covariates of treatment group, protocol scheduled visit, treatment × visit interaction, [redacted] as well as continuous covariates of baseline BCVA value and baseline OCT CST value, as fixed effects; and then subject as a random effect. Within-subject correlations will be assumed to follow an unstructured covariance matrix. The change from baseline in BCVA score averaged over Weeks 60 and 64 will be compared between treatment groups. The comparisons will be performed using a contrast over Weeks 60 and 64.

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

7.1.3 Sensitivity Analysis 1

A sensitivity analysis, aimed at assessing the robustness of the assumptions used in the statistical model for the main estimator will be conducted to include the FAS patients who did 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 medications 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 MMRM as described for the primary efficacy analyses will be used.

7.1.4 Sensitivity Analysis 2 (Trimmed Mean Analysis)

An additional sensitivity analysis using the trimmed mean approach (Permutt and Li 2017) will be performed.

If any of the following event types denoted by *E* occurred, patients will be considered to have the worst outcomes (defined below) and will be trimmed from the analysis:

- Discontinuation from study treatment due to study eye adverse events or due to lack of efficacy at or prior to Week 64 with no BCVA assessments available at Weeks 60 and 64.
- Administration of prohibited anti-VEGF medication any time during the 64 weeks of treatment.

The equal trimming fraction denoted by *p* will be determined based on a masked assessment of the intercurrent events percentage in the study.

Patients will not be considered "to be trimmed" candidates if they have a Week 60 and/or Week 64 assessments before the occurrence of any event type *E* above.

Patients who have no BCVA assessments available at Weeks 60 and 64 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 related to COVID-19, will be considered missing at random (MAR) and will be removed from the analysis.

A 95.04% confidence interval (CI) for the trimmed mean will be based on the permutation test of 30,000 generated datasets. In each dataset (random sample), the treatment assignments will be randomly

permuted according to the study randomization stratification algorithm (blocked randomization stratified by [redacted]

For each generated random sample:

1. An analysis of covariance (ANCOVA) model with adjustment for treatment, baseline BCVA value (continuous), as well as randomization stratification factors will be derived. The dependent variable in the ANCOVA model will be the average of non-missing values of Weeks 60 and 64 BCVA change from baseline, as for the primary analysis and denoted by Y. If only one assessment is available, then the value will be used.
2. The value Z=Y - β' X will be derived for each patient, where Y is defined above, X is the matrix for the values of the following covariates— baseline BCVA value (continuous), baseline BCVA categorical, baseline OCT CST categorical, and region; β is the ANCOVA estimated coefficient matrix for the covariates.
3. The Z values will be ordered and equal fractions, *p*, from each treatment arm will be trimmed.
4. The patients to be trimmed will always be ranked the lowest regardless of whether their adjusted values are available and trimmed from the analyses. The best (1 - *p*)*100 in each group will be used for the analysis specified in Step 1. If multiple patients have the same model values, they will be ranked randomly relative to each other prior to trimming.
5. The difference between groups in the trimmed means is derived.

Steps 1-5 are repeated 30,000 times.

The empirical permutation distribution of the difference between the trimmed means based on 2.48 and 97.52 percentiles will be derived.

If the proportion of patients “to be trimmed” in either treatment group in the permuted datasets exceeds the planned trimmed fraction *p*, the trimming fraction will be the maximum of the proportions of the "patients to be trimmed" in the two treatment groups.

7.1.5 Sensitivity Analysis 3 (Tipping Point Analysis)

A tipping point analysis will be performed where an offset (Delta based imputation penalty) is applied to the MAR imputation distribution applying a range of BCVA penalties ranging from 0.5 letter to [redacted] decrease [redacted] in 0.5 letter decrements. The Delta-based multiple imputations method will pertain to the following FAS patients:

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. All KSI-301 treated patients with missing Week 60 or 64 assessments.

The following steps will be undertaken (see Appendix 4 for the SAS syntax used and additional details).

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 60 and 64 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 imputed data set.

Step 3: the mixed model mean treatment difference estimates from step 2 for all imputations are combined and Rubin's method is applied to derive an estimate of the treatment difference for the average of Week 60 and Week 64.

Steps 1-3 are repeated for each of the two scenario groups in the KSI-301 treatment arm and for the range of penalties in the BCVA change from baseline. The tipping point will be the penalty value that will render the lower bound of the confidence interval for mean treatment differences to be less than or equal to [redacted]. After the tipping point is identified, clinical judgment will determine the plausibility of the assumptions underlying this tipping point.

7.2 Key Secondary Efficacy Analyses

The first key secondary efficacy analysis of interest is DRSS using Color Fundus Photography defined as the proportion of subjects with a ≥ 2-step worsening from baseline on the ETDRS DRSS at Week 52 in the FAS population for studies KS301P104 and KS301P105 combined.

The maximum clinically acceptable non-inferiority margin between KSI-301 and aflibercept subjects is [redacted] to be considered non- inferior, or the "non-inferiority margin", which translates into the following null/alternative hypothesis.

$\mathbf{H_0}$: $p_K - p_A \geq$ [redacted] Vs $\mathbf{H_A}$: $p_K - p_A <$ [redacted]

Where p_K and p_A are the proportion of subjects with a ≥ 2-step worsening from baseline at Week 52 in the KSI-301 and aflibercept groups respectively.

Non-inferiority will be demonstrated if the upper limit of the two-sided 95.04% confidence interval for the treatment difference (KSI-301 – aflibercept) is less than the prespecified non-inferiority margin of [redacted] Furthermore, superiority will be established if the upper limit of the two-sided 95.04% confidence interval for the treatment difference (KSI-301 – aflibercept) is less than zero.

The key secondary endpoints will be estimated based on the FAS, defined as in Section 5.4.1. The proportions of "responders" for subjects with a ≥ 2-step worsening will be tested between KSI-301 and aflibercept using the Cochran–Mantel–Haenszel (CMH) test by adjusting the baseline randomization stratification factors (Section 3.4) and Study (KS301P104 or KS301P105). If the response rate is low, an unstratified analysis may also be performed. For subjects who missed the assessment or have

ungradable DRSS at Week 52, the last evaluable response prior to week 52 will be used for this analysis. Patients with ungradable or missing baseline DRSS will be excluded from the analysis.

In addition, the weighted percentages difference between the KSI-301 and aflibercept (i.e., KSI-301 – aflibercept) and 95.04% CI of the difference will be presented. Percentages are calculated as 100×number of "responders"/number of patients in FAS. Weighted percentages are based on weighted average of observed estimates across strata using CMH weights. The CI are based on the normal approximation to the binomial proportions.

The second key secondary efficacy analysis of interest is DRSS using Color Fundus Photography defined as the proportion of subjects with a ≥ 2-step worsening from baseline on the ETDRS DRSS at Week 52 in the FAS population for study KS301P104 (or KS301P105) individually. The tested non-inferiority hypothesis and analysis will be the same as described above for the first key secondary endpoint except the study will be excluded from CMH model. If the response rate is low, an unstratified analysis may also be performed.

Together with the primary endpoint point and the key secondary endpoints, this family of tests will be conducted hierarchically to maintain a familywise Type I error rate of 4.96%. Each test within this family will only be conducted at the 4.96% level if the preceding test was significant at the 4.96% level.

7.3 Secondary Efficacy Analyses

As specified in Section 4.0, the Primary Analysis will evaluate the efficacy of KSI-301 compared to aflibercept from Day 1 up to Week 64. The Final Analysis will evaluate the KSI-301 efficacy compared to aflibercept from Day 1 up to Week 104.

Table 4 lists the secondary efficacy endpoints, efficacy variable derivations, reporting statistics and analysis methods for the Primary Analysis and the Final Analysis.

7.3.1 Analysis of Binary Data

The number and percentage of patients who gain or lose ≥ 5, ≥10 and ≥15 letters from baseline over time will be summarized by treatment group and visit, as will the number and percentage of patients with BCVA of 20/40 or better Snellen equivalent, BCVA or 20/200 or worse Snellen equivalent, ≥2-step improvement in DRSS, and OCT CST < 325 microns. The group proportions of "responders" for these categories of binary outcomes will be compared between KSI-301 and aflibercept using the Cochran–Mantel–Haenszel (CMH) test by adjusting the baseline randomization stratification factors (Section 3.4) similar to the analysis for the key secondary endpoints.

The number (%) of patients who fall into these categories from baseline at each post-baseline visit will be presented by treatment group, along with the weighted percentages. In addition, the weighted percentages difference between the KSI-301 and aflibercept (i.e., KSI-301 – aflibercept) and 95% CI of the difference will be presented by protocol specified visit. Percentages are calculated as 100×number of "responders"/number of patients with data at a visit. Weighted percentages are based on weighted

average of observed estimates across strata using CMH weights. The CI are based on the normal approximation to the binomial proportions.

Table 4: Secondary Efficacy Endpoints and Analysis Methods

Secondary Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Mean change from baseline in BCVA (ETDRS Letters) by visit over time	Continuous endpoint: Change from Day 1 to each time point [Visual Acuity Score/EDC]	LS Mean difference in change from baseline at each time point [Primary], up to Wk 64 [Final], up to Wk 104	Using the MMRM model (Section 7.1.2) used for deriving the primary endpoint estimate
Proportion of subjects with a ≥ 2-step improvement from baseline on the ETDRS DRSS over time	Binary Endpoint Patients had a 2-step improvement (yes/no)	Difference in proportions (%) and 95% CI at each scheduled time point [Primary], up to Wk 64 [Final], up to Wk 104	Stratified analysis of the binary endpoint using CMH adjusting for randomization stratification factors (Section 7.3.1)
Proportion of patients who gain ≥ 5, ≥10 and ≥15 letters from baseline over time	Binary endpoints: patients had a BCVA gain ≥ 5 (yes/no); patients had a BCVA gain ≥ 10 (yes/no); patients had a BCVA gain ≥ 15 (yes/no). [Visual Acuity Score/EDC]	Difference in proportions (%) and 95% CI at each time point [Primary], up to Wk 64 [Final], up to Wk 104	Stratified analysis of the binary endpoint using CMH adjusting for randomization stratification factors (Section 7.3.1)
Proportion of patients who lose ≥ 5, ≥10 and ≥15 letters from baseline over time	Binary endpoints: patients had a BCVA loss ≥ 5 (yes/no); patients had a BCVA loss ≥ 10 (yes/no); patients had a BCVA loss ≥ 15 (yes/no). [Visual Acuity Score/EDC]		
Proportion of patients with BCVA Snellen equivalent of 20/40 or better over time (≥69 ETDRS letters)	Binary endpoints: patients had a BCVA Snellen 20/40 or better (yes/no) [Visual Acuity Score/EDC]		
Proportion of patients with BCVA Snellen equivalent of 20/200 or worse (≤ 38 ETDRS letters) over time	Binary endpoints: patients had a BCVA Snellen 20/200 or worse (yes/no) [Visual Acuity Score/EDC]		

Secondary Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Mean change in OCT central subfield retinal thickness (CST) from baseline to the average of Weeks 60 and 64 and over time	Continuous Endpoint: Change from baseline to each time point [redacted]	LS Mean difference in change from baseline to each time point [Primary], up to Wk 64 [Final], up to Wk 104	MMRM (similar to Section 7.1.2) adjusting for baseline CST, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix
Proportion of patients in the KSI-301 arm on a Q8W, Q12W, Q16W, Q20W or Q24W treatment interval through the duration of exposure	Categorical Endpoint: Patient proportion in each category [Exposure/EDC]	Frequency and proportion	Descriptive
Mean/median number of intravitreal injections over the duration of the study Mean/median number of intravitreal injections from baseline through week 60 and from week 64 until the end of study Mean/median time to first retreatment after the last monthly dose	Continuous Endpoints: [Exposure/EDC]	Mean/median	Descriptive

7.4 Exploratory Analyses

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

Table 5: Exploratory Efficacy Endpoints and Analysis Methods

Secondary Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Mean change in area of leakage on FA from baseline over time	Continuous Endpoint: Change from baseline to each time point [redacted]	LS Mean difference in change from baseline to each time point [Primary], up to Wk 64 [Final], up to Wk 104	MMRM (similar to Section 7.1.2) adjusting for baseline area of leakage, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix
Proportion of subjects without intraretinal fluid on OCT over time	Binary endpoint: Subject has no intraretinal fluid (yes/no) [redacted]	Difference in proportions (%) and 95% CI at each time point [Primary], up to Wk 64 [Final], up to Wk 104	Stratified analysis of the binary endpoint using CMH adjusting for randomization stratification factors (Section 7.3.1)
Proportion of subjects without subretinal fluid on OCT over time	Binary endpoint: Subject has no subretinal fluid (yes/no) [redacted]		

7.5 Subgroup Analyses

For each of the subgroups listed in Table 2, the primary efficacy endpoint (i.e., the change in BCVA from Day 1 to the average of Weeks 60 and 64) will be analyzed using an MMRM that is described in Section 7.1.2. When a subgroup is a part of the randomization stratification variable, the corresponding stratification variable will be removed from the MMRM model as a covariate.

A forest plot will be provided to present the treatment effect of these subgroups.

7.6 Additional Pooled Analyses

The efficacy endpoints listed in Table 6 below will be analyzed using data pooled from Studies KS301P104 and KS301P105. The same analysis methods and models used for the individual studies will be applied. An additional fixed effect for Study (KS301P104 or KS301P105) will be added to the models where applicable.

Table 6: Pooled analysis parameters

Parameter	Endpoints
BCVA	Mean change in BCVA (ETDRS Letters) from baseline (Day 1) to the average of Weeks 60 and 64 and over time Proportion of subjects who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time Proportion of subjects who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time Proportion of subjects with BCVA Snellen equivalent of 20/40 (69 or more ETDRS letters) or better over time Proportion of subjects with BCVA Snellen equivalent of 20/200 (38 or less ETDRS letters) or worse over time
OCT CST	Mean change in OCT CST from baseline to the average of Weeks 60 and 64 and over time.
DRSS	Proportion of subjects with a ≥ 2-step worsening from baseline on the ETDRS DRSS over time Proportion of subjects with a ≥ 2-step improvement from baseline on the ETDRS DRSS over time
Durability	Proportion of patients in the KSI-301 arm on a Q8W, Q12W, Q16W, Q20W or Q24W treatment interval through the duration of exposure

8.0 SAFETY EVALUATION

Safety analyses will be performed for the Safety Analysis Set. In the Primary Analysis, the safety data from Day 1 to Week 64 will be summarized by treatment group for the SAF patients. In the Final Analysis, the safety data from Day 1 to Week 108 will be summarized by treatment group for the SAF patients.

8.1 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 patients receiving ≥1 injection, 1, 2, 3, 4, 5, etc. of KSI-301 or aflibercept injections from Day 1 to Week 60, from Week 64 to Week 104 and from Day 1 to Week 104.
- Duration of study drug exposure (mean [SD] and median, in months) for subjects receiving KSI-301 5 mg or aflibercept 2 mg.
- Listings will include treatment (KSI-301, aflibercept, sham) and date of injection.

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

8.2 Adverse Events

Adverse events (AEs) will be coded to a MedDRA version 23.1 or later. AEs and Serious AEs (SAEs) will be summarized and listed by ocular events for the treated eye (or study eye), ocular events for the non-treated eye (or fellow eye), and non-ocular (systemic) events.

Adverse events starting after the first study treatment 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 patients' incidence rates will be provided through Week 64 and through Week 108 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)
- Injection procedure related TEAEs and TESAEs for study eye
- 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 (IOI) TEAEs and TESAEs not associated with infection, autoimmunity, drug toxicity, or traumatic etiologies (study and fellow eye separately).
- IOI TEAEs and TESAEs associated with infection (study and fellow eye separately).
- IOI TEAEs and TESAEs associated with autoimmune, drug toxicity, or trauma (study and fellow eye separately).
- Arteriothromboembolic (ATE) Adverse Events. ATEs will be tabulated as those events meeting the Anti-Platelet Trialists' Collaboration criteria (i.e., nonfatal myocardial infarction, nonfatal stroke, and vascular death, including deaths of unknown cause).
- Adverse events of special interest [AESI] (study eye, fellow eye, and non-ocular separately), as defined in the protocol Section 8.3.6
- Non-serious TEAEs and TESAEs for study eye, fellow eye and non-ocular combined

Exposure adjusted rates may be derived for selected adverse events.

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

Adverse events from patients who remain in the study after study treatment discontinuation will be listed.

8.3 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.

8.4 Pregnancies

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

8.5 Intraocular Pressure

For study eye, pre and post-injection IOP as well as the change from baseline to post baseline values will summarized, using mean, standard deviation, median, and range, by treatment group and protocol specified visit. IOP data will be listed by treatment, subject ID, study eye or non-study eye, and time point.

8.6 Clinical Laboratory Evaluations

Continuous laboratory parameters will be summarized, using mean, standard deviation, median, and range by treatment group and protocol specified visit. Laboratory parameters as well as change from baseline for each parameter will be presented at Week 52 and Week 104.

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 Week 64 and through Week 108 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.

8.7 Vital Signs

Vital signs including pulse, systolic/diastolic blood pressure, body temperature, height, weight, and BMI will be summarized by treatment group and protocol specified visit. Descriptive statistics will be presented for results and change from baseline at each visit. Vital signs will be listed by treatment group, subject, and visit date.

9.0 SAMPLE SIZE CONSIDERATIONS

The sample size for this study is based on a non-inferiority approach. The following assumptions were made in order to calculate the sample size:

- Overall Type I error rate of [redacted]. Testing at the [redacted] level for non-inferiority corresponds to setting 95% CIs.
- Statistical power of ≥90%.
- Standard deviation of the distribution of change in visual acuity from baseline of [redacted] letters.
- Actual expected mean treatment difference between treatments of at most [redacted] letters

- The maximum clinically acceptable true difference for KSI-301 to be considered non- inferior, or the "non-inferiority margin", is [redacted].
- The statistical test used to compare the two treatment arms is an independent t-test on the mean change in visual acuity from baseline.
- Lost to follow-up/dropout rate of approximately [redacted].

The sample size calculated using the above assumptions is approximately 450 patients (225 per treatment arm).

10.0 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.

In this SAP, the Sponsor has defined the primary estimand, analysis populations, and strategies for addressing intercurrent events, missing data, and a set of sensitivity analyses for the primary efficacy outcome. Additional secondary endpoints were pre-specified, including endpoints for the combined KS301P104 and KS301P105 studies. Where relevant, these definitions take precedence over those defined in the study protocol.

11.0 REFERENCES

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12.0 APPENDICES

Appendix 1: Schedule of Activities

Error! Reference source not found.: Sample SAS Code

Appendix 1: Schedule of Activities

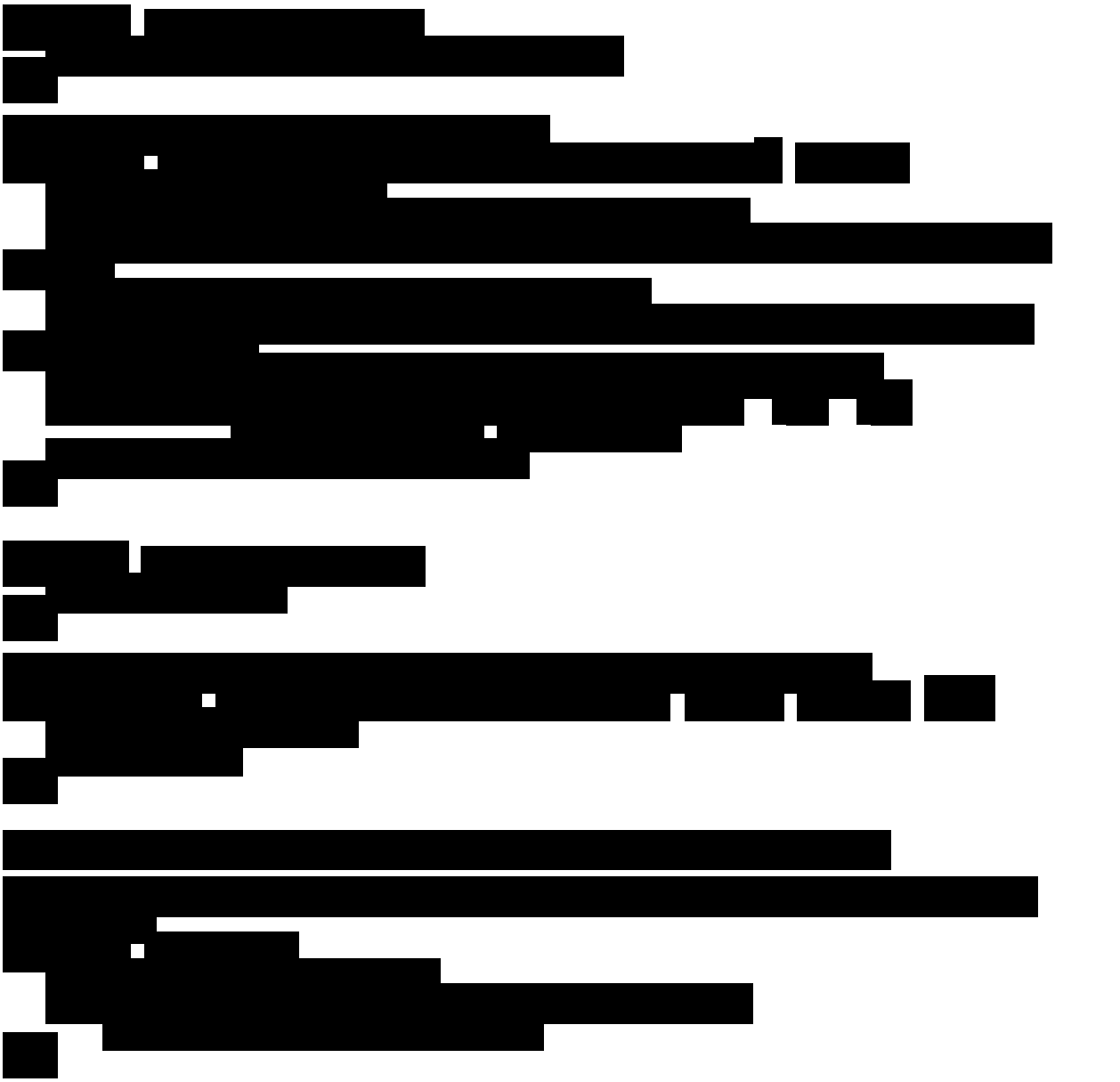
Visit	Screening	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Windows (Days)	**D-21 to D-1**		**+/-3**	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed Consent	X															
Demographics	X															
Medical & Ocular History	X															
Inclusion/Exclusion Criteria Review	X	X														
Concomitant Medication Review[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General Assessments																
Vital Signs[3]	X	X							X							X
Laboratory[4]	X															X
Plasma ADA/NAB Samples (pre-dose)		X						X				X				X
Plasma PK/Biomarker Samples (pre-dose)		X				X	X	X				X				X
Pregnancy Test[5] (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[6]																
BCVA ETDRS (4 meters)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Exam (Slit-lamp, IOP[8], dilated indirect ophthalmoscopy)	X	X	X	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
OCT-Angiography[9-11]		X				X						X				X
Color Fundus Photos[10,11]	X					X						X				X
Fluorescein Angiogram[10]	X															X
Randomized study treatment (KSI-301, aflibercept or sham) per IRT Designation		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Post-injection Assessments (vision check, IOP)		X		X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Week 100	Week 104/ET	Week 108[12]
Visit Windows (Days)	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Concomitant Medication Review[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General Assessments														
Vital Signs [3]						X							X	
Laboratory[4]													X	
Plasma ADA/NAB Samples						X							X	
Plasma PK/Biomarker Samples						X							X	
Pregnancy Test[5] (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[6]														
BCVA ETDRS (4 meters)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmic Exam (Slit-lamp, IOP[8], dilated indirect ophthalmoscopy)	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	
OCT-Angiography [9-11]						X							X	
Color Fundus Photos [10,11]						X							X	
Fluorescein Angiogram[10]													X	
Randomized Study Treatment (KSI-301, aflibercept, or sham) per IRT Designation	X	X	X	X	X	X	X	X	X	X	X	X		
Post-injection Assessments (vision check, IOP)	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; IOP = intraocular pressure; NAB = neutralizing antibody; PK = pharmacokinetics; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; WOCBP = women of childbearing potential.

1. Record any concomitant medication used by the participant within 30 days prior to Day 1. Procedural medications administered (e.g., dilating drops, fluorescein) will not be recorded.
2. After informed consent has been obtained but prior to initiation of study intervention, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study intervention (Day 1), all AEs will be reported until the final study visit or the ET visit if applicable. See protocol section 8.3.1.
3. Height and weight will be recorded at the screening visit only.
4. Clinical laboratory test as described in protocol.
5. 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.
6. Ophthalmic assessments will be performed in both eyes at Screening, Week 52 and Week 104, and in the Study Eye only at all other timepoints.
7. Perform BCVA before any other ophthalmic assessments and prior to dilation.
8. Method used to measure IOP must remain consistent throughout study.
9. OCT-Angiography to be performed at selected sites.
10. It is mandatory that the same model of device is used for the entire duration of the study.
11. For visits that are missed where color fundus photos (CFP) and OCT-Angiography (OCT-A) are scheduled, the CFP and OCT-A should be performed at the next possible visit.
12. [redacted]

Appendix 2: Sample SAS Code



Reference for Weighted Percentages Based on Weighted Average of Observed Estimates Across Strata Using CMH Weights

APPENDIX C
Stratified Estimation of Binomial Proportions in Two Groups

For stratum i ($i = 1, 2, \ldots, K$), let

n_{ij} = number of subjects with treatment j ($j = 0, 1$)

x_{ij} = number of responders with treatment j

$n_i = n_{i0} + n_{i1}$ = total number of subjects

$\hat{p}_{ij} = x_{ij} / n_{ij}$ = observed proportion of responders with treatment j

$\overline{p}_i = \dfrac{n_{i0}\hat{p}_{i0} + n_{i1}\hat{p}_{i1}}{n_{i0} + n_{i1}}$ = pooled observed proportion of responders combining the two treatments

$\hat{\delta}_i = \hat{p}_{i1} - \hat{p}_{i0}$ = observed difference in proportions of responders between the two treatments

$w_i = \dfrac{\dfrac{n_{i0}n_{i1}}{n_{i0} + n_{i1}}}{\displaystyle\sum_{j=1}^{K} \dfrac{n_{j0}n_{j1}}{n_{j0} + n_{j1}}}$ = Cochran–Mantel–Haenszel (CMH) weight

(Cochran 1954; Mantel and Haenszel 1959).

Estimates

The overall proportion of responders with treatment j will be estimated by the weighted average of the observed proportions over the strata for treatment j using the CMH weights,

$$\hat{p}_{wj} = \sum_{i=1}^{K} w_i \hat{p}_{ij} \ ,$$

with estimated variance

$$\hat{V}(\hat{p}_{wj}) = \sum_{i=1}^{K} w_i^2 \frac{\hat{p}_{ij}(1 - \hat{p}_{ij})}{n_{ij}} .$$

The overall difference in proportions of responders between the two treatment groups (treatment 1 vs. treatment 0) will be estimated using the weighted average of the observed differences in proportions between the two treatment groups over the strata using the CMH weights,

$$\hat{\delta}_w = \sum_{i=1}^{K} w_i \left(\hat{p}_{i1} - \hat{p}_{i0} \right),$$

with estimated variance

$$\hat{V}(\hat{\delta}_w) = \sum_{i=1}^{K} w_i^2 \hat{V}(\hat{\delta}_i),$$

where

$$\hat{V}(\hat{\delta}_i) = \frac{\hat{p}_{i0}(1-\hat{p}_{i0})}{n_{i0}} + \frac{\hat{p}_{i1}(1-\hat{p}_{i1})}{n_{i1}}$$

(Cochran 1954; Mehrotra and Railkar 2000).

Two-Sided (1–α) 100% Confidence Interval

The two-sided (1–α) 100% confidence interval for the overall proportion of responders with treatment j will be calculated as

$$\hat{p}_{wj} \pm z_{a/2} \sqrt{\hat{V}(\hat{p}_{wj})}.$$

The two-sided (1–α) 100% confidence interval for the overall difference in proportions of responders between treatment 1 and treatment 0 will be calculated as

$$\hat{\delta}_w \pm z_{a/2} \sqrt{\hat{V}(\hat{\delta}_w)},$$

where $z_{\alpha/2}$ is the upper α/2-th quantile of the standard normal distribution (Mehrotra and Railkar 2000).