Official Title: 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 Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO)
NCT Number: NCT04592419
Document Date: SAP Version 1.0, 22 June 2022

STATISTICAL ANALYSIS PLAN

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 Patients with Visual Impairment Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO) (BEACON)

Sponsor:	Kodiak Sciences Inc. 1200 Page Mill Road Palo Alto, CA 94304 USA
Sponsor Contact & Medical Monitor:	[redacted] Kodiak Sciences Inc.
IND Number:	136167
Protocol Number:	KS301P103
EUDRACT Number:	2020-001061-37
Test Product:	KSI-301
Statistical Analysis Plan Version:	1.0
Statistical Analysis Plan Version Date:	June 22, 2022
Supersedes:	N/A

CONFIDENTIAL

SPONSOR SIGNATORY

Study Title:	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 Patients with Visual Impairment Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO) (BEACON)
Protocol Code:	KS301P103
Statistical Analysis Plan Version:	1.0
Statistical Analysis Plan Version Date:	June 22, 2022
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Statistical Analysis Plan Accepted and Approved by:

June 22, 2022

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Date

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June 22, 2022

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Date

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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
ATE	Arteriothromboembolic
BCVA	Best-corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal Neovascularization
CRVO	Central retinal vein occlusion
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 angiography
FASW24	Full-Analysis Set Week 24
FASW48	Full-Analysis Set Week 48
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
ITP	Individualized Treatment Period
LOQ	Level of Quantification
MAR	Missing at Random
ME	Macular Edema
MNAR	Missing not at Random
MedDRA	The Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
OCT	Optical Coherence Tomography

Abbreviation	Definition
OLEP	Open Label Extension Phase
Q8W	Every eight weeks
RPE	Retinal Pigment Epithelium
RVO	Retinal vein occlusion
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAFOLE	Safety Analysis Set Open-Label Extension
SAP	Statistical Analysis Plan
ULN	Upper Limits of Normal
VA	Visual acuity
VEGF	Vascular Endothelial Growth Factor

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 KS301P103 (Protocol Amendment 2.0, dated 02 June 2021), *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 Patients with Visual Impairment Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO) (BEACON)*. This study is conducted in accordance with the protocol, 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. 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 report (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 9.0; 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 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 administered every 8 weeks after 2 monthly doses is non-inferior to aflibercept 2 mg monthly with respect to mean change in best corrected visual acuity (BCVA) from Day 1 to Week 24	• Mean change in BCVA from baseline (Day 1) to Week 24 (using Early Treatment Diabetic Retinopathy Study (ETDRS) Letters)

Objectives	Corresponding Endpoints
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 (Day 1) by visit over time • Proportion of patients who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time • Proportion of patients who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time • Proportion of patients with BCVA Snellen equivalent of 20/40 (69 or more ETDRS letters) or better over time • Proportion of patients with BCVA Snellen equivalent of 20/200 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) from baseline to Week 24 and over time • Proportion of patients with absence of edema (defined as OCT CST < 325 microns) by visit over time
To evaluate the durability of KSI-301 5 mg compared to aflibercept over the study duration.	• Mean number of intravitreal injections over the duration of the study • Mean number of intravitreal injections from Week 24 to Week 44 and from Week 48 to Week 68 • Mean time to first retreatment in the individualized treatment period (from Week 24 to Week 44) • Distribution of intravitreal injections from Week 24 to Week 44 and from Week 48 to Week 68. • Probability of receiving intravitreal injections over time between Week 24 to Week 48
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 24, Week 52, and Week 76
To assess the systemic pharmacokinetics (exposure) and immunogenicity of KSI-301.	• Systemic pharmacokinetic profile over time • Systemic anti-drug antibody status over time

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, randomized (1:1), double-masked, two-arm, multi-center Phase 3 study 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 Week 24, in patients with visual impairment due to treatment-naïve macular edema (ME) secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). A brief description of the study design and study treatment regimen appears below; additional details can be found in the study protocol.

The schedule of activities is provided in Appendix 1.

The Primary Study is divided into a 21-day screening period (Days -21 to -1) and two efficacy and safety assessment periods, as follows:

- Day 1 to Week 24, which corresponds to the fixed interval treatment period of Day 1 through Week 20 followed by assessment of the primary efficacy and safety endpoints at Week 24;
  - KSI-301 5 mg: Following two initial doses at Day 1 and Week 4, patients will receive one additional dose every 8 weeks (i.e., at Week 12 and Week 20) and will receive sham injections, to preserve study masking, at Week 8 and Week 16
  - Aflibercept 2 mg: Patients will receive treatment every 4 weeks, i.e., at Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20
- Week 24 to Week 52, which corresponds to the individualized treatment period (Week 24 to Week 44) followed by assessment of the secondary efficacy endpoints at Week 48 and the follow-up safety endpoints at Week 52.
  - Starting at Week 24, patients in both treatment arms will be assessed monthly (every 4 weeks) and will receive additional administration of KSI-301 5 mg or aflibercept 2 mg, as per their assigned treatment arm, according to protocol-defined disease activity assessment criteria.
  - These criteria are based on changes in BCVA and/or OCT central subfield thickness (CST). The minimum interval between active treatments is 4 weeks (± 7 days) for all treatment arms. There are no mandatory active injections at any assessment visits and thus, no upper limit to the treatment interval. To preserve study masking, sham injections are administered at visits in which no active treatment is indicated.

Patients who complete the Primary Study are eligible to participate in an optional, open-label, single-arm Extension Phase (Week 48 – Week 72). There is no active comparator in this open-label portion of the study (Week 48 to Week 68). The Extension Phase will evaluate the long-term efficacy and safety of KSI-301 5 mg. Patients who received aflibercept during the first 48-week of the Primary Study will receive KSI-301 5 mg in the Extension Phase to enable collection of information on the effects of KSI-301 5 mg in patients who had previously (i.e. from Day 1 through Week 44) received a defined course of prior anti-VEGF therapy for ME secondary to BRVO/CRVO.

3.2 Disease Activity Assessment Criteria

In the individualized treatment period, protocol-defined disease activity assessments are performed every 4 weeks, starting at Week 24 (See Appendix 1 for details). The disease activity assessment criteria are as follows:

- Increase in OCT CST ≥ 50 µm compared to lowest previous measurement AND a decrease in BCVA of ≥ 5 letters compared to the average of the two best previous BCVA assessments, due to worsening of RVO disease activity, *or*
- Increase in OCT CST ≥ 75 µm compared to lowest previous measurement due to worsening of RVO disease activity.

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] Randomization uses a permuted block design.

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

4.3.1 Timing of the Primary Analysis

The primary analysis will be performed when all patients have either completed the Week 24 visit or have discontinued from the study prior to the Week 24 visit, whichever comes later, the data up to and including the Week 24 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 24) will be included in the primary analyses:

- Demographics and Baseline Ocular and Non-Ocular Characteristics
- Subject Disposition at Week 24
- Primary Efficacy Analyses
  - Sensitivity and Subgroup Analyses for the Primary Efficacy Endpoint
- Selected Secondary Efficacy Analyses up to Week 24
- 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 Individualized Treatment Period (ITP) Analysis

4.4.1 Timing of the ITP Analysis

The analysis will be performed when all patients have either completed the Primary Study (Week 52 visit) or have discontinued from the study prior to the Week 52 visit, whichever comes later, the data up to and including the Week 52 visit have been entered, cleaned and verified as appropriate, and the database for the individualized treatment period (ITP) analysis is frozen.

4.4.2 Data to be Analyzed for the ITP

The following data (up to Week 52) will be included in the analyses.

- Subject Disposition at Week 48
- Descriptive Efficacy Analyses up to Week 48
- Interventions up to Week 48
  - Study Treatment and Exposure
- Safety up to Week 52
  - 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

4.5 Open Label Extension Phase (OLEP) Analysis

The Analysis of the OLEP will be performed when all patients have either completed the Week 76 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. The same relevant endpoints as described in Section 4.4.2 will be subsequently analyzed in the OLEP.

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

5.3.1 Patient Baseline Values

Baseline values are defined as the most recent values prior to the first dose of study treatment.

Baseline (Week 48) for aflibercept patients who opt to continue in the open-label extension phase of the study and receive KSI-301 is defined as the last value prior to the first dose of KSI-301 5 mg.

5.4 Analysis Sets

The efficacy and safety analyses that are specified in Sections 6.0 and 7.0 will utilize the Analysis Sets as specified in this section.

5.4.1 Randomized

The Randomized Analysis Set includes all patients who were randomized into one of the study arms. For analyses based on this population, patients will be analyzed according to the study intervention assigned at randomization.

5.4.2 Safety Analysis Set (SAF)

The Safety Analysis Set includes all patients who received any study treatment. Subjects will be analyzed according to the study treatment they actually received.

5.4.3 Safety Analysis Set (SAFOLE)

The Safety Analysis Set SAFOLE includes all patients who received any study treatment and who have at least one study treatment in the optional Open-Label Extension phase. Subjects will be analyzed according to the study treatment they actually received.

5.4.4 Full Analysis Set Week 24 (FASW24)

The Full Analysis Set Week 24 (FASW24) includes all patients who received any study treatment (KSI-301 or aflibercept) during the fixed interval treatment period. Subjects will be analyzed according to their randomized treatment. The FASW24 will be used in the primary analyses of efficacy.

5.4.5 Full Analysis Set Week 48 (FASW48)

The Full Analysis Set Week 48 (FASW48) includes all patients who did not discontinue study treatment prior to week 24 and have at least one BCVA assessment during the individualized treatment period. Subjects will be analyzed according to the treatment received. The FASW48 will be used for descriptive efficacy analyses of the ITP.

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 • < 75 years of age • ≥ 75 years of age
Sex	• Female • Male
Ethnicity	• Hispanic or Latino • Not Hispanic or Latino
RVO subtype*	• CRVO • BRVO
BCVA*	• BCVA: ≥ 70 letters • BCVA: 69-50 letters • BCVA: < 50 letters
Disease duration*	• < 3 months • ≥ 3 months
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
[redacted]	

Other subgroup analyses may be explored.

5.6 Multiple Comparisons/Multiplicity

[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	4	14
Week 4	28	15	42
Week 8 – Week 76	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 76.

5.9 Disposition of Subjects

Subject disposition will be summarized by treatment group, RVO type (BRVO, [redacted]) and overall. The following will be summarized:

- First 24 Weeks
  - The number of patients screened
  - The number of patients randomized
  - The number of subjects (%) in the Full Analysis set (FAS24)
  - The number (%) in the Safety set (SAF)
  - The number (%) completing the study treatment
  - The number (%) discontinuing the study treatment and the reasons for discontinuation of study treatment

- First 48 Weeks
  - The number (%) in the FASW48
  - The number (%) completing the study treatment
  - The number (%) discontinuing study treatment early and the reasons for discontinuation of study treatment
  - The number (%) discontinuing from the study prior to week 48 and the reasons for discontinuation

- Optional Open-Label Extension
  - The number (%) treated in the extension study
  - The number (%) completing the study treatment
  - The number (%) discontinuing study treatment early and the reasons for discontinuation
  - The number (%) discontinuing from the study early and the reasons for discontinuation

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.

5.10 Demographic and Other Baseline Characteristics

5.10.1 Demographics and Baseline Characteristics

The following demographics, baseline characteristics, and randomization stratification variables will be summarized by treatment group by treatment group, RVO type (BRVO, [redacted]) and overall for the randomized patients.

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)
- Center Point Thickness (CPT)
- Intraretinal fluid/cystoid spaces: Presence/Absence, localization
- Subretinal fluid: Presence/Absence, localization

Ocular Imaging, Fundus fluorescein angiography (FA):

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

Individual patients' demographics and baseline characteristics will be listed.

5.10.2 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 RVO type (BRVO[redacted]) 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.

5.10.3 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 SAF 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 SAF 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 SAF 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 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.

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.

5.11 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 24 Primary Analysis
- From the start of the study to the data freeze for the individualized treatment period (ITP) Analysis
- From the ITP Analysis to the final database lock (OLEP)

Major protocol deviations will be summarized by timeframe (see above), treatment group, RVO type (BRVO[redacted]) and overall, for analysis sets of FASW24, FASW48, and SAFOLE, as appropriate. 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.

6.0 EFFICACY ANALYSES

6.1 Primary Efficacy Analysis

6.1.1 Primary Estimand

6.1.1.1 Target Population

The population targeted by the scientific question is patients with visual impairment from macular edema due to RVO.

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 macular edema and visual impairment of ≤ 6 months secondary to CRVO or BRVO. Patients with HRVO will also be considered eligible for this study and will be included as CRVO. Eyes classified as having CRVO or HRVO will comprise at least 20% and not more than 35% of the total planned sample size.

2. BCVA ETDRS letter score ≤ 80 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 and confirmed by the Investigator at Day 1.
4. Decrease in vision in the Study Eye determined by the Investigator to be primarily the result of macular edema secondary to RVO.

Exclusion criteria

1. Macular edema in the Study Eye considered to be secondary to a cause other than RVO (e.g. diabetic macular edema, Irvine-Gass syndrome).
2. Active iris or angle neovascularization, neovascular glaucoma, neovascularization of the optic disc, retinal neovascularization or vitreous hemorrhage in the Study Eye.
3. Significant media opacities, including cataract, in the Study Eye that might interfere with visual acuity, assessment of safety, optical coherence tomography or fundus photography.
4. Prior vitrectomy in the Study Eye.
5. Active retinal disease other than the condition under investigation in the Study Eye.
6. Any history or evidence of a concurrent ocular condition present that in the opinion of the Investigator could require either medical or surgical intervention or affect macular edema or alter visual acuity during the study (e.g. vitreomacular traction).

6.1.1.2 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 Week 24.

6.1.1.3 Hypotheses and Test

The maximum clinically acceptable true difference between KSI-301 and aflibercept among RVO patients to be considered non-inferior is 4.5 ETDRS letters, i.e. the non-inferiority margin (NI) is 4.5 letters.

Two analyses will be conducted:

1. First, non-inferiority will be assessed in BRVO patients. Hypothesis 1:
   H0: $\mu_K - \mu_A \leq -4.5$ letters Vs HA: $\mu_K - \mu_A > -4.5$ letters

   Where μ_K and μ_A are the mean changes from baseline to the Week 24 BCVA in the KSI-301 and aflibercept groups of in BRVO patients, respectively.

   If the lower limit of the two-sided 95.02% CI for the difference between the two means is >-4.5 letters, NI will be demonstrated.

2. If NI is demonstrated in BRVO patients, a second analysis will assess NI in BRVO+CRVO patients. Hypothesis 2:

H0: $\mu_K - \mu_A \leq -4.5$ letters Vs HA: $\mu_K - \mu_A > -4.5$ letters

Where μ_K and μ_A are the mean changes from baseline to the Week 24 BCVA in the KSI-301 and aflibercept groups of in BRVO+CRVO patients, respectively.

If the lower limit of the two-sided 95.02% CI for the difference between the two means is >-4.5 letters, NI will be demonstrated.

The analyses will be conducted hierarchically to maintain a familywise Type I error rate of 4.98%. Each test within this family will be conducted at the 4.98% level if the preceding test was significant at the 4.98% level.

Furthermore, superiority will be established if the lower limit of the two-sided 95.02% confidence interval for the treatment difference (KSI-301 – aflibercept) is greater than zero.

6.1.1.4 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 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.

6.1.2 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint will be estimated based on the FASW24, i.e., all randomized subjects who received at least one treatment injection in the first 24 weeks and using all available post baseline measurements up to Week 24 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; treatment group, protocol scheduled visit, treatment × visit interaction as fixed effects; subject as a random

effect; and the randomization stratification factors (i.e., RVO subtype as assessed by the investigator [for Hypothesis 2 only], baseline BCVA, disease duration, and geographical location) as covariates. Within-subject correlations will be assumed to follow an unstructured covariance matrix. 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.

6.1.3 Sensitivity Analysis 1

A sensitivity analysis will be conducted to include the FASW24 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.

6.1.4 Tipping Point Sensitivity Analysis of the Primary Endpoint

A tipping point analysis 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 4.5 letters decrease (-4.5 is the non-inferiority threshold) in 0.5 letter decrements. The Delta-based multiple imputations method will pertain to the following FASW24 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 24 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 delta-adjusted imputation will be applied to missing values in step 1a for missing subjects' change from baseline BCVA values post study treatment discontinuation.

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 Week 24 treatment difference.

Steps 1-3 are repeated for each of the two potential MNAR 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 greater than -4.5 letters.

6.2 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 24. The ITP Analysis will evaluate the KSI-301 efficacy comparing to aflibercept using the secondary endpoint data from Day 1 up to Week 48. The OLEP Analysis will evaluate the KSI-301 efficacy using the secondary endpoint data from Week 48 up to Week 68.

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

In the OLEP, because aflibercept treated patients will be treated with KSI-301 from Week 48 to week 68, the baseline for these patients will be recalculated for the purpose of data analysis in the extension phase. In the OLEP Analysis, the treatment group will be dropped from statistical models, as appropriate.

6.2.1 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, 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).

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 [FASW24], up to Wk 24 [FASW48], up to Wk 48 [SAFOLE], Wk 48 to Wk 68	Using the MMRM model (Section 6.1.2) used for deriving the primary endpoint estimate
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 [FASW24], up to Wk 24 [FASW48], up to Wk 48 [SAFOLE], Wk 48 to Wk 68	Stratified analysis of the binary endpoint using CMH adjusting for randomization stratification factors (Section 6.2.1)
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]		
Proportion of patients with absence of macular edema (defined as OCT CST < 325 microns) over time	Binary endpoints: Patient had a OCT CST < 325 microns (yes/no) [redacted]		

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 Week 24 and over time	Continuous Endpoint: Change from baseline to each time point [redacted]	LS Mean difference in change from baseline to each time point [FASW24], up to Wk 24 [FASW48], up to Wk 48 [SAFOLE], Wk 48 to Wk 68	MMRM (similar to Section 6.1.2) adjusting for baseline CST, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix
Mean change in OCT center point retinal thickness (CPT) from baseline to Week 24 and over time	Continuous Endpoint: Change from baseline to each time point [redacted]	LS Mean difference in change from baseline to each time point [FASW24], up to Wk 24 [FASW48], up to Wk 48 [SAFOLE], Wk 48 to Wk 68	MMRM (similar to Section 6.1.2) adjusting for baseline CPT, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix

6.3 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 Week 24) will be analyzed using an MMRM that is described in Section 6.1.2. 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.

6.4 Exploratory Analyses

Exploratory analysis may be conducted to include the FASW24 patients who received 4 or more does of active study treatment (KSI-301 or aflibercept). Additionally, an exploratory analysis may be conducted to include the FASW24 patients who 1) received 4 or more does of active study treatment (KSI-301 or aflibercept), 2) did not have any of the intercurrent events as defined for Sensitivity Analysis 1, and 3) did not discontinue assigned study treatment prematurely except for reasons related to study eye adverse events or lack of efficacy.

The same MMRM as described for the primary efficacy analyses will be used.

Additional exploratory analyses may be conducted.

7.0 SAFETY EVALUATION

Safety analyses will be performed for the SAF patients and SAFOLE patients, as appropriate. In the Primary Analysis, the safety data from Day 1 to Week 24 will be summarized by treatment group for the SAF patients. In the ITP Analysis, the safety data from Day 1 to Week 48/52 will be summarized by treatment group for the SAF patients. In the OLEP Analysis, the safety data from Week 48 to Week 68/72 will be summarized for the SAFOLE patients. The safety summaries will be presented by RVO type (BRVO, [redacted]) and overall.

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 patients receiving ≥1 injection, 1, 2, 3, 4, 5, etc. of KSI-301 or aflibercept injections from Day 1 to Week 20, from Week 24 to Week 44, and from Week 48 to Week 68.
- 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.

7.2 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 24, from Week 28 to Week 52 and through Week 52, separately; and from Week 52 to Week 76 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)
- 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 intraocular inflammation (IOI)
- Intraocular Inflammation TESAEs (study and fellow eye separately)
- Arteriothromboembolic (ATE) Adverse Events. See Appendix 2 for preferred terms used to identify ATEs.
- Adverse events of special interest [AESI], as defined in the protocol Section 8.3.6

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.

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 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.

7.6 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 24, Week 48, and Week 72.

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 24, from Week 24 to Week 48, and from Week 48 to Week 72 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.

7.7 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.

8.0 SAMPLE SIZE CONSIDERATIONS

The sample size for the comparison of BCVA between treatment KSI-301 5 mg q8w after 2 monthly doses and aflibercept 2 mg q4w at Week 24 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 0.025. Testing at the 0.025 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 -0.6 letters
- The maximum clinically acceptable true difference for KSI-301 to be considered non- inferior, or the "non-inferiority margin", is 4.5 letters.
- The statistical test used to compare the two treatment arms at Week 24 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 550 patients (275 per treatment arm).

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.

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. Where relevant, these definitions take precedence over those defined in the study protocol.

10.0 REFERENCES

US Food and Drug Administration Guidance Document - E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (May 2021). Available at https://www.fda.gov/media/148473/download.

US Food and Drug Administration Guidance Document – Non-Inferiority Clinical Trials to Establish Effectiveness (November 2016). Available at https://www.fda.gov/media/78504/download. Accessed November 13, 2021.

11.0 APPENDICES

Appendix 1: Schedule of Activities

[redacted]

Appendix 1: Schedule of Activities

Primary Study SoA

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/ET [12]	Week 52 [12, 13]
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	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						X	
Plasma ADA/NAB Samples (pre-dose)		X			X				X						X	
Plasma PK/Biomarker Samples (pre-dose)		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																
BCVA ETDRS (4 meters) [6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmic Exam [6] (Slit-lamp, IOP [8], dilated indirect ophthalmoscopy)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SD-OCT [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Color Fundus Photos [9]	X								X						X	
Fluorescein Angiogram [9]	X								X						X	
Randomized Study Treatment (KSI-301, aflibercept, or sham) per IRT Designation [10]		X		X,	X	X	X	X	X	X	X	X	X	X		
Post-injection Assessments (vision check, IOP) [11]		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; ETDRS = early treatment diabetic retinopathy study; ET = early termination; 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 patient 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 Appendix 2 and Table 4.
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. BCVA and Ophthalmic Exam will be performed in both eyes at Screening, Week 24 and Week 48, and only in the Study Eye 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. It is mandatory that the same model of device is used for the entire duration of the study.
10. Patients who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in Protocol Section 7.1.
11. Post-injection assessments include vision check for counting fingers and tonometry. The post-injection assessments should be performed by unmasked assessors.
12. For patients continuing in the Extension Phase, the Week 48 and Week 52 procedures listed in Protocol Section 1.3.2 should be performed instead of those listed here.
13. For patients not continuing into the Extension Phase, Week 52 is a final safety assessment that will be done via telephone call for all patients, except in WOCBP, in which case a site visit is required for the safety assessment that includes a pregnancy test.

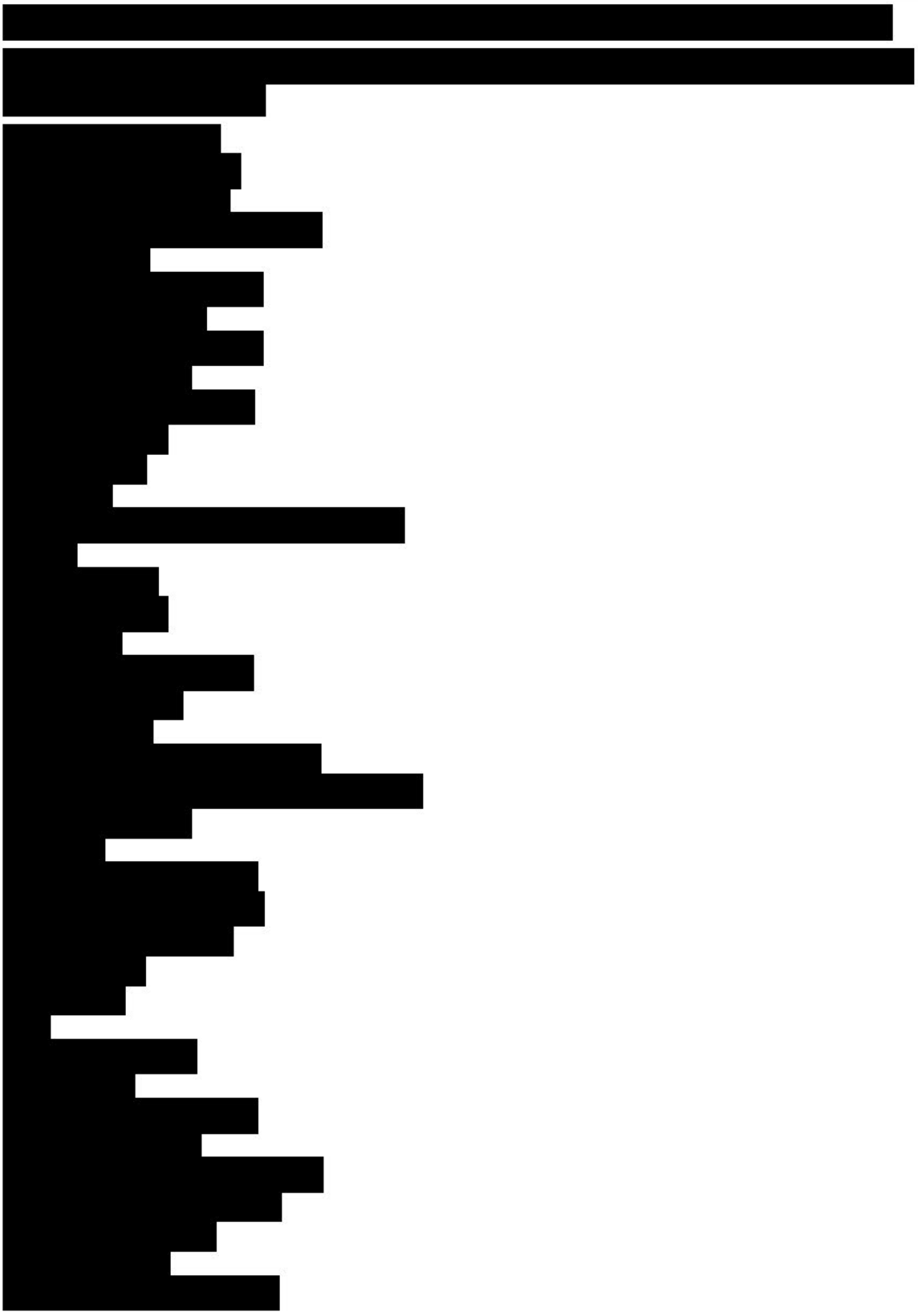
Optional Open-Label Extension Phase SoA

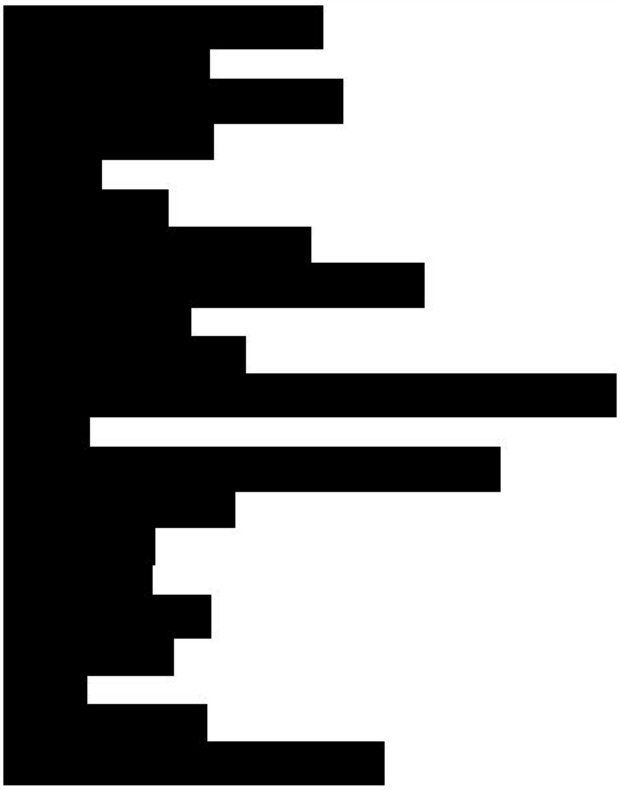
Visit	Week 48 [11]	Week 52 [11]	Week 56	Week 60	Week 64	Week 68	Week 72/ET	Week 76 [12]
Visit Windows (Days)	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed Consent	X							
Concomitant Medication Review [1]	X	X	X	X	X	X	X	X
AE/SAE Review [2]	X	X	X	X	X	X	X	X
General Assessments								
Vital Signs	X						X	
Laboratory [3]	X						X	
Plasma ADA/NAB Samples (pre-dose)	X						X	
Plasma PK/Biomarker Samples (pre-dose)	X						X	
Pregnancy Test [4] (WOCBP only)	X	X	X	X	X	X	X	X
Ophthalmic Assessments								
BCVA ETDRS (4 meters) [5,6]	X	X	X	X	X	X	X	
Ophthalmic Exam [5] (Slit-lamp, IOP [7], dilated indirect ophthalmoscopy)	X	X	X	X	X	X	X	
SD-OCT [8]	X	X	X	X	X	X	X	
Color Fundus Photos [8]	X						X	
Fluorescein Angiogram [8]	X						X	
Study Treatment (KSI-301) [9]	X	X	X	X	X	X		
Post-injection Assessments (vision check, IOP) [10]	X	X	X	X	X	X		

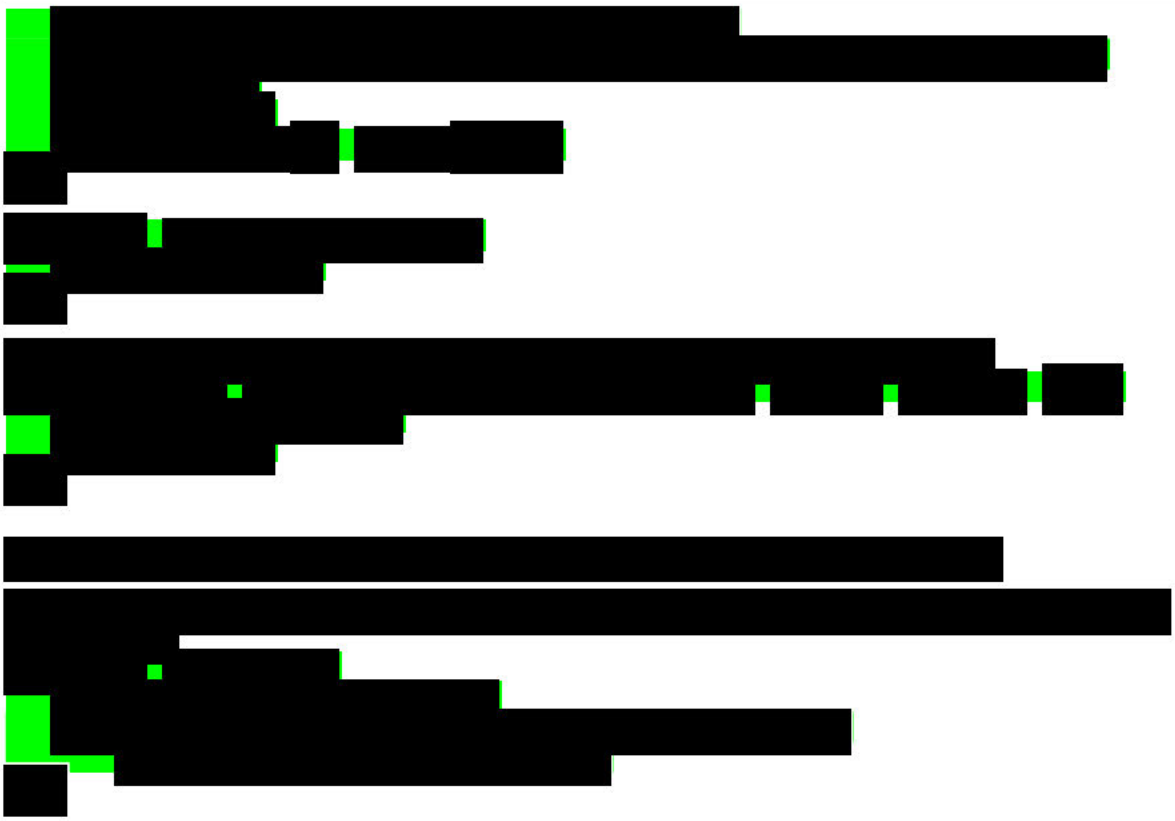
Abbreviations: ADA = anti-drug antibody; AE = adverse event; BCVA = best corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; ET = early termination; IOP = intraocular pressure; NAB = neutralizing antibody; PK = pharmacokinetics; SAE = serious adverse event; SD-OCT = spectral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

1. Record any concomitant medication used by the patient 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 Section 8.3.1.
3. Clinical laboratory test, as described in Appendix 2 and Table 4.
4. 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.
5. BCVA and Ophthalmic Exam will be performed in both eyes at Week 72 and only in the Study Eye at all different timepoints.
6. Perform BCVA before any other ophthalmic assessments and prior to dilation.
7. Method used to measure IOP must remain consistent throughout study.

8. It is mandatory that the same model of device is used for the entire duration of the study.
9. Patients who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in Section 7.1.
10. Post injection assessments include vision check for counting fingers and tonometry. The post-injection assessments should be performed by unmasked assessors.
11. For patients in the Extension Phase, the Week 48 and Week 52 procedures listed here should be performed instead of those listed in Section 1.3.1.
12. For patients in the Extension Phase, Week 76 is a final safety assessment that will be done via telephone call for all patients, except in WOCBP, in which case a site visit is required for the safety assessment that includes a pregnancy test.







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