STATISTICAL ANALYSIS PLAN

A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR) (GLOW)

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Study Title:	A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR) (GLOW)
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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
APTC	Antiplatelet Trialists Collaboration 1994
ASNV	Anterior segment neovascularization
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thromboembolic events
BCVA	Best-corrected visual acuity
BMI	Body mass index
BP	Blood pressure
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal Neovascularization
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
ICE	Intercurrent event
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug (application)
IOI	Intraocular inflammation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
LOCF	Last observation carried forward
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
NPDR	Non proliferative diabetic retinopathy

Abbreviation	Definition
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PRP	Panretinal photocoagulation
PT	Preferred term
Q12W	Every twelve weeks
Q24W	Every twenty-four weeks
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SoA-A	Schedule of Activities-A
SoA-B	Schedule of Activities-B
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper Limits of Normal
VA	Visual acuity
VRC	Vienna Reading Center
VEGF	Vascular Endothelial Growth Factor
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 Study KS301P106 (Protocol Amendment 1.1, dated 17 May 2021), entitled *A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR).* 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 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.

2.0 STUDY OBJECTIVES AND ENDPOINTS

Table 1 lists the primary, key secondary and additional 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 superior to sham treatment, with respect to proportion of eyes improving ≥2 steps on Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48.	• The proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48.
Key Secondary	
To demonstrate that KSI-301 5 mg is superior to sham treatment, with respect to proportion of eyes with vision-threatening complications of diabetes, and proportion of eyes improving ≥3 steps on Diabetic Retinopathy Severity Scale (DRSS).	• Proportion of eyes developing any of the following from baseline through Week 48: - PDR or ASNV; - Vitreous hemorrhage or tractional retinal detachment believed to be due to PDR; or - DME. • Proportion of eyes improving ≥3 steps on DRSS from baseline at Week 48. • Proportion of eyes developing PDR through Week 48.
Additional Secondary	
To evaluate the efficacy of KSI-301 5 mg compared to sham treatment.	• Proportion of eyes developing PDR or ASNV from baseline through Week 48. • Proportion of eyes developing vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR, from baseline through Week 48. • Proportion of eyes developing DME from baseline through Week 48. • Proportion of eyes with a ≥2-step worsening from baseline on DRSS from baseline at Week 48. • Proportion of eyes with a ≥3-step worsening from baseline on DRSS from baseline at Week 48. • Time to first development of PDR, ASNV, or DME through Week 48. • Time to first development of PDR or ASNV through Week 48. • Time to first development of vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR through Week 48. • Time to first development of DME through Week 48. • Mean change in SD-OCT central subfield thickness (CST) from baseline by visit over time. • Mean change in BCVA from baseline by visit over time. • Proportion of eyes who lose ≥5, ≥10, or ≥15 letters in BCVA from baseline by visit over time.

Objectives	Corresponding Endpoints
To evaluate the safety and tolerability of KSI-301 5 mg compared to sham treatment.	Incidence of ocular and systemic adverse events up to Week 48.

3.0 INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 3, prospective, randomized, double-masked, two-arm, multi-center study evaluating the efficacy and safety of repeated dosing of KSI-301 5 mg administered by intravitreal injections in participants with treatment-naïve NPDR. A brief description of the study design and study treatment regimen appears below; additional details can be found in the study protocol.

The schedules of activities are provided in Appendix 1 (SoA-A and SoA-B).

The overall duration of the study was intended to be approximately 2 years (100 weeks) after the last participant is randomized to the study. Participant duration is defined as the date a signed written informed consent is provided through the last safety follow-up visit at Week 100; thus, the maximum participant duration is approximately 103 weeks and includes a screening period of up to 21 days (Days -21 to -1), a treatment period of approximately 92 weeks (Day 1 to Week 92), a safety/efficacy assessment at Week 96, and a final follow-up for safety assessments at Week 100 [redacted]. The primary endpoint will be assessed at Week 48; although secondary endpoints for efficacy were intended to be assessed at Weeks 48 and 96, the Sponsor has made a decision as of late July 2023 to discontinue further development of KSI-301, and therefore data collected after Week 48 will be incomplete.

A single eye per participant will be designated as the Study Eye. If both eyes are eligible to become the Study Eye, the eye with worse BCVA and/or worse DR severity at Screening will be selected as the Study Eye. If both eyes are eligible and have the same BCVA and/or DR severity or one eye has worse BCVA and the fellow eye has worse DR, the decision of which eye to select as the Study Eye will be made by the Investigator.

Participants will be randomly assigned (1:1) into one of two treatment arms:

- Group A: KSI-301 5 mg via intravitreal injection at Day 1, Week 8, Week 20, and every 24 weeks thereafter through Week 92.
- Group B: Sham injection at Day 1, Week 8, Week 20, and every 24 weeks thereafter through Week 92.

Participants who develop sight-threatening complications of DR in the Study Eye will be treated with open-label KSI-301 5 mg, irrespective of the treatment group that they were originally randomized into (KSI-301 5 mg or sham). The original treatment group randomization will remain masked throughout the study. Sight-threatening complications of DR in the Study Eye include DME, PDR, and/or ASNV. The diagnosis of DME, PDR, and/or ASNV will be made by the masked Investigator. See protocol Table 3 for definition of each sight-threatening complication.

At the visit that a sight-threatening complication of DR is diagnosed (i.e., the "Dx Visit"), treatment with open-label KSI-301 5 mg will be initiated. Starting at the Dx Visit, participants will no longer follow the study visits and assessments outlined in SoA-A of Appendix 1, nor receive further masked treatments. Instead, they will follow the study visits and assessments outlined in SoA-B of Appendix 1, which is specific to the participants who develop DME, PDR, and/or ASNV.

Treatment of DME, PDR, and/or ASNV will consist of the following:

- Two doses of KSI-301 5 mg, given four weeks apart (+/- 7 days), followed by KSI-301 5 mg once every 12 weeks (Q12W; +/-14 days). Thus, the first dose shall occur during the study visit in which DME, PDR, and/or ASNV was diagnosed, and the second dose shall occur 4 weeks (+/- 7 days) later. Thereafter, subsequent doses shall occur Q12W (+/-14 days).

More frequent visits and more frequent treatments with KSI-301 5 mg and/or pan-retinal photocoagulation (PRP) are at the discretion of the Investigator if the sight-threatening complication(s) are still present. Treatment with KSI-301 5 mg may not be given more often than monthly (28 ± 7 days).

3.2 Study Interventions

Study interventions are summarized in the Protocol Table 4.

3.3 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 48)

4.3.1 Timing of the Primary Analysis

The primary analysis will be performed when all patients have either completed the Week 48 visit or have discontinued from the study prior to the Week 48 visit, whichever comes later, the data up to and including the Week 48 visit have been entered, cleaned and verified as appropriate, and the database for the primary analysis is frozen.

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 48) will be included in the primary analyses:

- Demographics and Baseline Ocular and Non-Ocular Characteristics
- Subject Disposition at Week 48
- Efficacy Analyses
- Sensitivity and Subgroup Analyses for the Primary Efficacy Endpoint
- Secondary Efficacy Analyses up to Week 48
- 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

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 48 analysis is defined as Study Day 1 until Week 48, as it is meant to be inclusive both of study treatments leading to the primary efficacy outcome at Week 48 and of safety assessments in that period.

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

The Full Analysis Set (FAS) includes all patients who received any study treatment (KSI-301 or sham) and have gradable DRSS value at baseline. 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

The Safety Analysis Set includes all patients who received any study treatment (KSI-301 or sham). 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	18-64 years of age 65-74 years of age 75-84 years of age ≥ 85 years of 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
DRSS*	Level ≤47

Characteristics	Subgroup
	Level ≥53
HbA1c level*	≤8.5% >8.5%
Investigational site*	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	Aphakic Pseudophakic Phakic

[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 (including scheduled visits from SoA-B in Appendix 1) 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 (including records from SoA-B in Appendix 1) 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 8	56	2	98
Week 20	140	99	182
Week 32	224	183	266
Week 44	308	267	322
Week 48	336	323	364
Week 56	392	365	434
Week 68	476	435	518
Week 80	560	519	602
Week 92	644	603	658
Week 96	672	659	686

Note: Nominal visits for efficacy assessments are at Day 1, Week 8, every 12 weeks from Week 20 – Week 44, Week 48, every 12 weeks from Week 56 – Week 92, and Week 96.

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 by Week 48 and by end of study
- The number (%) discontinuing the study and the reasons for discontinuation of study by Week 48 and by end 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:

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

Ocular Imaging, OCT:

- Center Subfield Thickness (CST)

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 KSI-301 group. Where groups or terms tie will be sorted by descending order in the sham group, then 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 48 Primary 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 moderately severe or severe NPDR.

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

Inclusion criteria

1. Participants with moderately severe to severe NPDR in the Study Eye (DRSS levels 47 and 53 as determined by the reading center based on color fundus photographs), who have not previously received intravitreal medications for DR or DME, and in whom pan-retinal photocoagulation (PRP) can be safely deferred for at least 6 months per the Investigator.
2. BCVA ETDRS letter score in the Study Eye of ≥69 letters (approximate Snellen equivalent of 20/40 or better) in the Study Eye at Screening and confirmed at Day 1.

Exclusion criteria

1. Presence of center-involved DME in the study eye, defined for this purpose as CST of ≥320 microns on SD-OCT (Heidelberg Spectralis or equivalent value on other OCT instruments).
2. Prior PRP in the Study Eye.
3. Current anterior segment neovascularization (ASNV), vitreous hemorrhage, or tractional retinal detachment in the Study Eye.

7.1.1.2 Primary Efficacy Endpoint/Variable of Interest

The primary efficacy variable of interest is DRSS, a categorical variable measured at each study visit by the reading center based on color fundus photographs. The primary efficacy endpoint is the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48.

7.1.1.3 Hypotheses and Test

The following hypothesis for the primary efficacy variable regarding the proportion of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 48 will be conducted to demonstrate the superiority of the KSI-301 group compared to the sham group.

The hypothesis to be tested is:

H_0: $p_k - p_s = 0$ vs H_1: $p_k - p_s \neq 0$

Where p_k and p_s are the true proportions of patients with a ≥2-step improvement from baseline in DRSS score in the study eye at week 48 in the KSI-301 and sham groups, respectively. The primary efficacy endpoint will be tested at the significance level of $\alpha = 0.0498$.

7.1.1.4 Intercurrent Events

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

1. Treatment misallocation at 1 or more study visits.
2. Use of prohibited medications in the study eye.
3. Development of sight-threatening complication(s) and initiation of open-label KSI-301 5 mg treatment, panretinal photocoagulation, or other treatment for DME, ASNV, and/or PDR.
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 and the time to intercurrent events will be tabulated and listed 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 have gradable DRSS value at baseline.

The statistical analysis will be performed using the Cochran-Mantel-Haenszel (CMH) method, [redacted]

A 'Hypothetical' strategy will be applied for all intercurrent events where measurements after occurrence of intercurrent event will be imputed using the last observation carry forward (LOCF) procedure. For patients who develop sight-threatening complication(s) and have non-gradable value at their first visit where open-label treatment is administered, the non-gradable values will be imputed as no change from baseline. For patients without intercurrent event, missing and non-gradable values at Week 48 will be imputed using LOCF. Baseline will be carried forward if all post-baseline observations are missing or non-gradable. Non-gradable values are observations where DRSS level is 90.

The p-value will be reported for comparison between KSI-301 and sham groups. In addition, the weighted percentages difference between the KSI-301 and sham (i.e., KSI-301 – sham) and 95.02% 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 CMH method as described for the primary efficacy analysis will be used for all sensitivity analyses below.

7.1.3 Sensitivity Analysis 1

In this analysis, a 'Composite' strategy will be applied for all intercurrent events where patients with occurrence of intercurrent event by Week 48 will be considered as non-responders. For patients without intercurrent event, missing and non-gradable values at Week 48 will be imputed using LOCF, and baseline will be carried forward if all post-baseline observations are missing or non-gradable as in the primary analysis.

7.1.4 Sensitivity Analysis 2

This analysis will follow the same 'Hypothetical' strategy for handling of intercurrent events and analysis method as the primary analysis, with the exception that patients with the following significant protocol deviations will be excluded from the analysis: deviation from key inclusion/exclusion criteria as defined in Section 7.1.1.1, treatment misallocation at 1 or more study visits by Week 48, and use of prohibited medications in study eye at any point by Week 48.

7.1.5 Sensitivity Analysis 3

This analysis will follow the same 'Hypothetical' strategy for handling of intercurrent events and analysis method as the primary analysis, with the exception that patients with baseline DRSS level outside of levels 47 and 53 will be excluded from the analysis.

7.2 Key Secondary Efficacy Analyses

The key secondary endpoints will be estimated based on the FAS, defined as in Section 5.4.1.

Together with the primary endpoint and the key secondary endpoints, this family of tests 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.

7.2.1 Proportion of Eyes Developing Any Sight-Threatening Complication

The first key secondary efficacy endpoint of interest is the proportion of eyes developing any of the following from baseline through Week 48:

- PDR or ASNV;
- Vitreous hemorrhage or tractional retinal detachment believed to be due to PDR; or
- DME.

The development of the above sight-threatening complications is tabulated from adverse events, procedures and eCRFs.

The following intercurrent events will be evaluated in this key secondary endpoint:

- Treatment misallocation at 1 or more study visits.
- Use of prohibited medications in the study eye.
- Premature discontinuation from study treatment due to study eye adverse events or due to lack of efficacy.
- 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.

The same analysis method from the primary efficacy endpoint will be used for the first key secondary efficacy endpoint. See Section 7.1.2.

7.2.2 Proportion of Eyes Improving ≥3 Steps on DRSS

The second key secondary efficacy endpoint of interest is proportion of eyes improving ≥3 steps on DRSS from baseline at Week 48. The same intercurrent events and analysis method from the primary efficacy endpoint will be used. See Sections 7.1.1.4 and 7.1.2.

A sensitivity analysis for this key secondary efficacy endpoint will be performed where patients with baseline DRSS level outside of levels 47 and 53 will be excluded from the analysis.

7.2.3 Proportion of Eyes Developing PDR

The third key secondary efficacy endpoint of interest is the proportion of eyes developing PDR from baseline through Week 48. The same intercurrent events and analysis method from the first key secondary efficacy endpoint will be used. See Section 7.2.1.

7.3 Additional Secondary Efficacy Analyses

As specified in Section 4.0, the Primary Analysis will evaluate the efficacy of KSI-301 compared to sham from Day 1 up to Week 48.

Table 4 lists the additional secondary efficacy endpoints, efficacy variable derivations, reporting statistics and analysis methods for the Primary Analysis and until the end of study.

Binary secondary efficacy endpoints will utilize the Cochran-Mantel-Haenszel (CMH) method stratified by the randomization stratification factors (i.e. baseline DRSS level and HbA1c level).

Time to event endpoints will be analyzed using the Kaplan-Meier estimates. The number of observations censored will be provided for each treatment group. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median time to first event in each treatment group. A 2-sided 95% CI will be provided for the estimates. A log-rank test stratified by the randomization stratification factors (i.e. baseline DRSS level and HbA1c level) will be performed to compare the survival distributions between the treatments. The hazard ratio and its 95% CI will be reported from a Cox regression model stratified by the same randomization stratification factors with treatment as the covariate. For patients not known to have had an event at the time of the analysis data cutoff, the time will be censored at the date of the last scheduled study visit at analysis data cutoff.

Continuous endpoints (e.g. mean change from baseline in BCVA) will utilize a Mixed Model for Repeated Measures (MMRM). The model assumes missing at random (MAR). The model will include the change from baseline value as the dependent variable; categorical covariates of treatment group, protocol scheduled visit, treatment × visit interaction, and the randomization stratification factors (i.e. baseline DRSS level and HbA1c level) as well as continuous covariate of baseline BCVA, as fixed effects; and then subject as a random effect. 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.

For all additional secondary efficacy endpoints, data after the occurrence of intercurrent event will be censored, and missing and non-gradable data will not be imputed. Only observed, gradable and non-censored data will be used for analysis.

Table 4: Additional Secondary Efficacy Endpoints and Analysis Methods

Additional Secondary Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Proportion of eyes developing PDR or ASNV from baseline through Week 48	Binary endpoint: patients developed PDR or ASNV (yes/no) [Sight-threatening Complication/EDC]	Difference in proportions (%) and 95% CI at each time point [FAS], up to Week 48	CMH method adjusting for randomization stratification factors (similar to Section 7.1.2)
Proportion of eyes developing vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR, from baseline through Week 48	Binary endpoint: patients developed vitreous hemorrhage or tractional retinal detachment believed to be due to PDR (yes/no) [Sight-threatening Complication/EDC/Review of AEs]		
Proportion of eyes developing DME from baseline through Week 48	Binary endpoint: patients developed DME (yes/no) [Sight-threatening Complication/EDC]		
Proportion of eyes with a ≥2-step or a ≥3-step worsening on DRSS from baseline at Week 48	Binary endpoints: patients with a ≥2-step worsening in DRSS (yes/no); patients with a ≥3-step worsening in DRSS (yes/no); [redacted]		
Proportion of eyes who lose ≥5, ≥10, or ≥15 letters in BCVA from baseline by visit 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]		
Time to first development of PDR, ASNV, or DME through Week 48	Time to event endpoint: Time from first treatment to development of PDR, ASNV, or DME (in months) [Sight-threatening Complication/EDC]		

Additional Secondary Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Time to first development of PDR or ASNV through Week 48	Time to event endpoint: Time from first treatment to development of PDR or ASNV (in months) [Sight-threatening Complication/EDC]	Hazard ratio and 95% CI [FAS], up to Week 48	Kaplan-Meier and Cox regression model stratified by randomization stratification factors (Section 7.3)
Time to first development of vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR through Week 48	Time to event endpoint: Time from first treatment to development of vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR (in months) [Sight-threatening Complication/EDC/Review of AEs]		
Time to first development of DME through Week 48	Time to event endpoint: Time from first treatment to development of DME (in months) [Sight-threatening Complication/EDC]		
Mean change in SD-OCT central subfield thickness (CST) from baseline by visit over time	Continuous Endpoint: Change from baseline to each time point [redacted]	LS Mean difference in change from baseline to each time point and 95% CI [FAS], up to Week 48 [FAS], up to end of study	MMRM (Section 7.3) adjusting for baseline CST, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix
Mean change in BCVA from baseline by visit over time	Continuous Endpoint: Change from baseline to each time point [Visual Acuity Score/EDC]	LS Mean difference in change from baseline to each time point and 95% CI [FAS], up to Week 48 [FAS], up to end of study	MMRM (Section 7.3) adjusting for baseline BCVA, with time, treatment, and time*treatment interaction and randomization stratification as factors Unstructured covariance matrix

7.4 Exploratory Analyses

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

Table 5: Exploratory Efficacy Endpoints and Analysis Methods

Exploratory Efficacy Endpoint	Variable Derivation [Source]	Summary Statistics [Analysis Set]	Method of Analysis
Mean change in SD-OCT central subfield thickness (CST) from baseline until switch to Schedule B by visit over time	Continuous Endpoint: Change from baseline to each time point [redacted]	Mean/Median [Patients who switch to Schedule B], until switch to Schedule B	Descriptive
Mean change in BCVA from baseline until switch to Schedule B by visit over time	Continuous Endpoint: Change from baseline to each time point [Visual Acuity Score/EDC]	Mean/Median [Patients who switch to Schedule B], until switch to Schedule B	Descriptive
Mean change in SD-OCT central subfield thickness (CST) from time moved to Schedule B until end of follow-up by visit over time	Continuous Endpoint: Change from time moved to Schedule B to each time point [EDC]	Mean/Median [Patients who switch to Schedule B], until end of follow-up	Descriptive
Mean change in BCVA from time moved to Schedule B until end of follow-up by visit over time	Continuous Endpoint: Change from time moved to Schedule B to each time point [Visual Acuity Score/EDC]	Mean/Median [Patients who switch to Schedule B], until end of follow-up	Descriptive

7.5 Subgroup Analyses

For each of the subgroups listed in Table 2, the primary efficacy endpoint (i.e., proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48) will be analyzed using the CMH method 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 stratified CMH test.

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

8.0 SAFETY EVALUATION

Safety analyses will be performed for the Safety Analysis Set. In the Primary Analysis, safety data from Day 1 to Week 48 will be summarized by treatment group.

8.1 Exposure to Study Medication

Study eye exposure to study medication will be summarized (open-label KSI-301 5mg treatment will not be included here). 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 sham injections from Day 1 to Week 48 and from Day 1 to the end of study.
- Duration of study drug exposure (mean [SD] and median, in months) for subjects receiving KSI-301 5 mg or sham.
- Listings will include treatment (KSI-301, sham) and date of injection.

For patients who develop sight-threatening complication(s), exposure to open-label KSI-301 5mg treatment will be summarized and listed similarly as above.

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. A separate listing will list patients who receive open-label KSI-301 5mg treatment with the same variables.

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.

Treatment emergent AEs (TEAEs) are events with onset date on or after the initiation of study treatment through the last dose date of study treatment + 28 days, start date of non-study anti-

VEGF in study eye on or after last dose date, or start date of open-label KSI-301 treatment due to development of sight-threatening complication, whichever occurs first.

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 48 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 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 combined), as defined in the protocol Section 8.3.6
- Injection procedure related TEAEs and TESAEs in study eye
- Non-serious TEAEs and TESAEs (study eye, fellow eye and non-ocular combined)

All AEs and serious AEs will be presented separately in data listings by treatment group, subject ID, and event date. Adverse events from patients who remain in the study after study treatment discontinuation will be listed.

For subjects who receive open-label KSI-301 5mg treatment due to development of sight-threatening complications, ocular TEAEs and TESAEs for study eye starting from when subjects switch to open-label KSI-301 treatment will be summarized until the end of study. All AEs (study eye, fellow eye and non-ocular) will be presented in a data listing by subject ID, and event date.

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 48.

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 at Week 48 and Week 96 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

A sample size of approximately 240 participants with a target enrollment of approximately 120 participants in each treatment group (1:1 ratio) was calculated using the following assumptions:

- Anticipated [redacted] of participants with a ≥2-step improvement from baseline in DRSS score in the KSI-301 5 mg Q24W group versus [redacted] in the sham group.
- Statistical power of ≥90%.
- Overall Type I error rate of 0.05.
- The statistical method used to compare the proportion with a ≥2-step improvement from baseline in DRSS score for the KSI-301 treatment group at Week 48 compared with sham will be the Cochran-Manzel Haenszel (CMH) method, [redacted]
- Lost to follow-up/dropout rate of approximately [redacted]

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

The Week 100 analyses will not be performed per protocol, since the study was discontinued early by the Sponsor.

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.

11.0 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.

Littell, Ramon C., George Milliken, Walter W. Stroup, Russell D. Wolfinger, and Oliver Schabenberger (2006) SAS(R) for Mixed Models, 2nd Edition (2006), SAS Institute, Cary NC.

Little, R.J.A. and Rubin, D.B. (2002). Statistical Analysis with Missing Data, 2nd edition, New York: John Wiley.

12.0 APPENDICES

Appendix 1: Schedules of Activities (SoA-A and SoA-B)

Appendix 2: Sample SAS Code

Appendix 1: Schedules of Activities

SoA-A

The following schedule of activities, SoA-A, shall be followed for all visits unless a participant is diagnosed with sight-threatening complication(s) of DR in their Study Eye. Upon diagnosis of sight-threatening complication(s) of DR in their Study Eye, participants shall then follow SoA-B instead of SoA-A.

Visit	Screening	Day 1	Week 8	Week 20	Week 32	Week 44	Week 48	Week 56	Week 68	Week 80	Week 92	Week 96/ET	Week 100[12]
Visit Windows (Days)	**D-21 to D-1**		+/-7	+/-14	+/-14	+/-14	+/-7	+/-14	+/-14	+/-14	+/-14	+/-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
AE/SAE Review[2]		X	X	X	X	X	X	X	X	X	X	X	X
General Assessments													
Vital Signs[3]	X	X		X			X		X			X	
Laboratory[4]	X						X					X	
Plasma ADA/NAB Samples (pre-injection)		X	X		X		X		X			X	
Plasma PK/Biomarker Samples (pre-injection)		X	X		X		X		X			X	
Pregnancy Test[5] (WOCBP only)	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	
Ophthalmic Exam (Slit lamp, IOP[8], dilated indirect ophthalmoscopy)	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	
Fundus Photos[9]	X		X	X	X	X	X	X	X	X	X	X	
Fluorescein Angiogram[9]	X			X			X		X			X	
Randomized study treatment (KSI-301 or sham) per IRT Designation[10]		X	X	X		X			X		X		
Post-injection Assessments (vision check, IOP[8])[11]		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 SAEs caused by a protocol-mandated assessment 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 5.
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 48 and Week 96, 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. Participants 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. Week 100 is a final safety assessment that will be done via telephone call for all participants, except in WOCBP, in which case a site visit is required for the safety assessment that includes a pregnancy test.

SoA-B

The following schedule of activities, SoA-B, shall be followed once a participant is diagnosed with sight-threatening complication(s) of DR in their Study Eye. Upon diagnosis of sight-threatening complication(s) of DR in their Study Eye, participants will be treated with open-label KSI-301 5 mg, regardless of the treatment group that they were originally randomized into, and SoA-B will be followed instead of SoA-A. Additional details are provided in protocol Section 4.1.3.1.

Visit	Dx Visit[1]	Dx Visit + 4 Weeks	Dx Visit + 16 Weeks	Dx Visit + 28 Weeks	Dx Visit + 40 Weeks	Dx Visit + […][12] Weeks	Week 96/ET	Week 100[13]
Visit Windows (Days)		+/-7	+/-14	+/-14	+/-14	+/-14	+/-7	+/-7
Concomitant Medication Review[2]	X	X	X	X	X	X	X	X
AE/SAE Review	X	X	X	X	X	X	X	X
General Assessments								
Vital Signs[3]							X	
Laboratory[4]							X	
Plasma ADA/NAB Samples (pre-injection)	X			X			X	
Plasma PK/Biomarker Samples (pre-injection)	X			X			X	
Pregnancy Test[5] (WOCBP only)	X	X	X	X	X	X	X	X
Ophthalmic Assessments[6]								
BCVA ETDRS (4 meters)[7]	X	X	X	X	X	X	X	
Ophthalmic Exam (Slit lamp, IOP[8], dilated indirect ophthalmoscopy)	X	X	X	X	X	X	X	
SD-OCT[9]	X	X	X	X	X	X	X	
Fundus Photos[9]	X	X	X	X	X	X	X	
Fluorescein Angiogram[9]	X			X			X	
KSI-301 5 mg (Open-label)[10]	X	X	X	X	X	X		
Post-injection Assessments (Vision check, IOP[8])[11]	X	X	X	X	X	X		

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ASNV = anterior segment neovascularization; BCVA = best corrected visual acuity; Dx Visit = the first study visit where a sight-threatening complication of diabetic retinopathy (DME, PDR, and/or ASNV) is diagnosed; DME = diabetic macular edema; ET=Early Termination; ETDRS = early treatment diabetic retinopathy study; IOP = intraocular pressure; NAB = neutralizing antibody; PK = pharmacokinetics; PDR = proliferative diabetic retinopathy; Q12W = once every 12 weeks; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; WOCBP = women of childbearing potential.

1 Dx Visit is the first study visit where a sight-threatening complication of diabetic retinopathy (DME, PDR, and/or ASNV, as defined in protocol Section 4.1.3.1) is diagnosed in the Study Eye; open-label KSI-301 treatment will be initiated at this visit.

2 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.

3 Height and weight will be recorded at the screening visit only.

4 Clinical laboratory tests as described in protocol Appendix 2 and Table 5.

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 Week 96, 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.

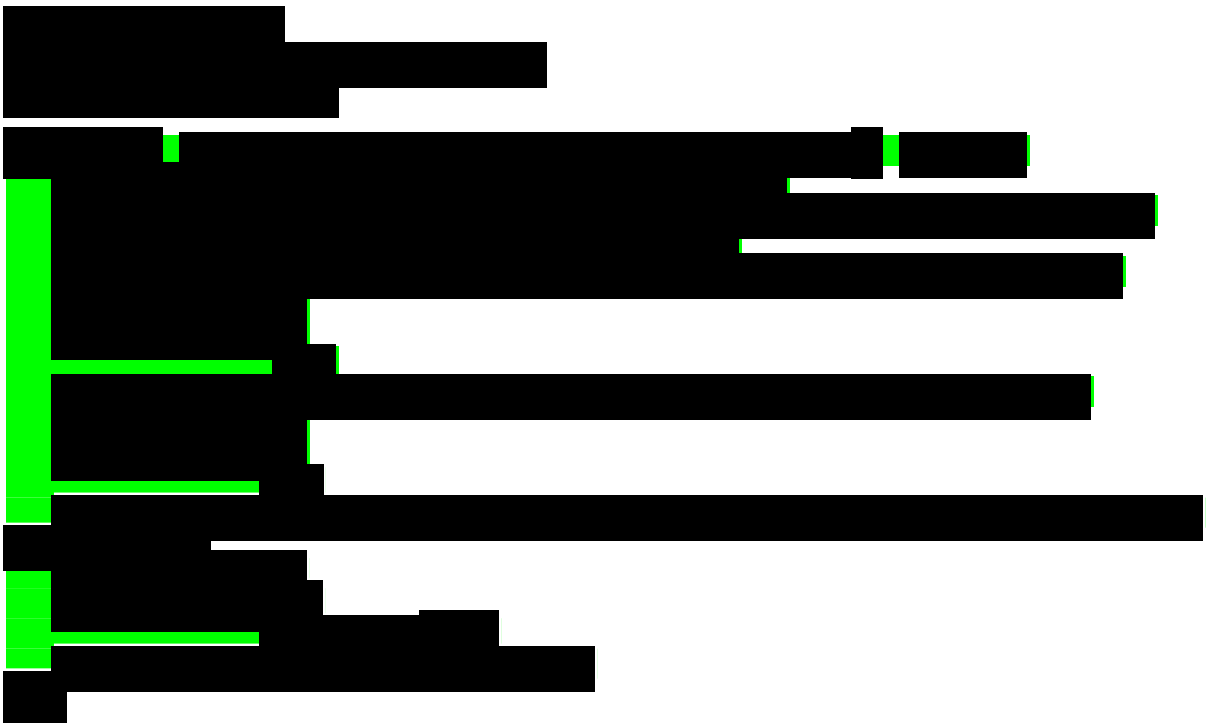
10 Participants who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in protocol Section 7.1.

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

12 Continue visits Q12W until Week 92.

13 Week 100 is a final safety assessment that will be done via telephone call for all participants, except in WOCBP, in which case a site visit is required for the safety assessment that includes a pregnancy test.

Appendix 2: Sample SAS Code



[redacted]

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,

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

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).