CLINICAL STUDY PROTOCOL

Protocol 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 Secondary to Treatment-naïve Diabetic Macular Edema (DME)
Protocol Number:	KS301P104
Version Date:	15 March 2022
Amendment Number:	2.0
Supersedes:	Version 1
Test Product:	KSI-301
Brief Title:	A Study to Evaluate the Efficacy and Safety of KSI-301 Compared to Aflibercept in Participants with Diabetic Macular Edema (DME)
Study Phase:	3
Study Acronym/Name:	GLEAM
Sponsor:	Kodiak Sciences Inc. 2631 Hanover Street Palo Alto, CA 94304 USA
Sponsor Contact & Medical Monitor:	[redacted] Kodiak Sciences Inc.
IND Number:	136167
EudraCT Number:	2020-001062-11

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FOR MEDICAL EMERGENCIES CONTACT:

[redacted]

PROTOCOL APPROVAL – 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 Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME) (GLEAM)

Protocol Number: KS301P104

Version Date: 15 March 2022

Protocol accepted and approved by:

[redacted]

Kodiak Sciences Inc.
2631 Hanover Street
Palo Alto, CA 94304

Signature

Date

PROTOCOL APPROVAL – PRINCIPAL INVESTIGATOR 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 Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME) (GLEAM)

Protocol Number: KS301P104

Version Date: 15 March 2022

I have read the protocol described above. I agree to conduct the study as described in the protocol. I also agree to conduct this study in compliance with Good Clinical Practice (GCP) and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board or Independent Ethics Committee (IRB/IEC) and any other institutional requirements. These are stated in *"Guidance for Good Clinical Practice"* International Council for Harmonisation (ICH) guideline E6(R1) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Declaration of Helsinki, and any other applicable regulatory requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB/IEC.

Principal Investigator:

_____

Print Name of Investigator

_____ _____

Signature Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABC	Antibody biopolymer conjugate
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BP	Blood pressure
BRVO	Branch retinal vein occlusion
BUN	Blood urea nitrogen
CI	Confidence interval
CFP	Color fundus photographs
CFR	Code of federal regulations
CIOMS	Council for international organizations of medical sciences
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
ECG	Electrocardiograph
eCRF	Electronic case report form
EDC	Electronic data capture
EMEA	Europe, Middle East, Africa
ET	Early termination
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FDA	Food and drug administration

FP	Fundus photography
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GLP	Good laboratory practice
hCG	Human chorionic gonadotropin
HIPAA	Health insurance portability and accountability act
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International conference on harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent or institutional ethics committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent to treat
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
ME	Macular edema
MedDRA	Medical dictionary for regulatory activities
NA	North America
NAB	Neutralizing antibody
NI	Non-inferiority
NIMP	Non-investigational medical product
NME	New molecular entity
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
OTC	Over the counter
PDR	Proliferative diabetic retinopathy
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per protocol set
PRP	Pan-retinal photocoagulation

QxW	Once every x weeks; x = 4, 8, 12, 16, 20, or 24
QTL	Quality tolerance limits
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD-OCT	Spectral domain optical coherence tomography
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SmPC	Summary of product characteristics
SoA	Schedule of activities
SUN	Standardization of uveitis nomenclature
SUSAR	Suspected unexpected serious adverse reactions
ULN	Upper limits of normal
USPI	U.S. Prescribing Information
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR1	Vascular endothelial growth factor receptor 1
VEGFR2	Vascular endothelial growth factor receptor 2
wAMD	Wet (neovascular) age-related macular degeneration
WBC	White blood cells
WOCBP	Women of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Protocol Number: KS301P104</td><td>Version: 2.0</td><td rowspan="4">For National Authority Use Only</td></tr>
<tr><td colspan="2">IND Number: 136167</td><td>EudraCT Number: 2020-001062-11</td></tr>
<tr><td colspan="3">Sponsor:
Kodiak Sciences Inc.
2631 Hanover Street
Palo Alto, CA 94304 (USA)</td></tr>
<tr><td colspan="3">Investigational Product:
KSI-301</td></tr>
<tr><td colspan="4">Title of Study:
A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME) (GLEAM)</td></tr>
<tr><td colspan="4">Brief Title:
A Study to Evaluate the Efficacy and Safety of KSI-301 Compared to Aflibercept in Participants with Diabetic Macular Edema (DME)</td></tr>
<tr><td colspan="4">Brief Study Rationale:
KSI-301 is a novel, potent, long-acting biopharmaceutical that inhibits vascular endothelial growth factor (VEGF). Compared to aflibercept, KSI-301 has an extended ocular half-life, which may result in a less frequent treatment regimen. Thus, this study has been designed to evaluate a less frequent treatment regimen of KSI-301 5 mg compared to aflibercept 2 mg in participants with DME.</td></tr>
<tr><td colspan="2">Development Phase: 3</td><td colspan="2">Countries/ Regions: NA (North America), EMEA (Europe, Middle-East, Africa), and APAC (Asia-Pacific)</td></tr>
<tr><td colspan="4">Study Period: Approximately 3 years</td></tr>
</table>

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Objectives and Key Endpoints:

Objectives	Key Endpoints
Primary	
To demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in best corrected visual acuity (BCVA) from Day 1 to Year 1 (average of Weeks 60 and 64).	• Mean change in BCVA from baseline (Day 1) to the average of Weeks 60 and 64 (Year 1) in Early Treatment Diabetic Retinopathy Study (ETDRS) Letters.
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 participants who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time. • Proportion of participants who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time.
To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg over the study duration by assessing anatomical parameters.	• Mean change in optical coherence tomography (OCT) central subfield thickness (CST) and other morphological parameters from baseline to the average of Weeks 60 and 64 (Year 1) and over time. • Proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS DRSS at Week 52.
To evaluate the durability of KSI-301 5 mg compared to aflibercept 2 mg over the study duration.	• Mean number of intravitreal injections over the duration of the study. • Mean number of intravitreal injections from baseline to Week 60 and from Week 64 to 104. • Mean time to first re-treatment after the last monthly dose.
To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg.	• Incidence of ocular and systemic adverse events up to Week 64 and Week 108.
To assess the systemic pharmacokinetics (exposure) and immunogenicity of KSI-301.	• Systemic pharmacokinetic profile over time. • Systemic anti-drug antibody status over time.

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Investigational Product: KSI-301		

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

Design/Methodology/Masking:

This is a prospective, randomized, 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 Year 1 (average of Weeks 60 and 64), in participants with DME that has not been previously treated.

One eye per participant will be enrolled in the study.

Participants will be randomized 1:1 into one of two treatment arms: KSI-301 or aflibercept. Randomization will be stratified by [redacted]. Treatment arm randomization at Day 1 and treatment or sham assignment for the duration of the study will be provided by the interactive response technology (IRT) system.

For masking purposes, sham injections will be administered at each monthly visit if an active treatment is not administered. To preserve masking, two investigators are required for this study. The masked Investigator will be responsible for the examinations and safety assessments, including causality assessments for adverse events. The unmasked Investigator (and unmasked assistants, if any) will perform the intravitreal injections (active treatments and sham) and post-treatment assessments.

This study is divided into a three-week screening period and two efficacy and safety assessment periods, as shown in the schema (Section 1.2):

- Year 1: from Day 1 to Week 64; and
- Year 2: from Week 68 to Week 108.

Number of Participants Planned:	**Gender:**	**Age:**
Approximately 450	Male or female	Adults ≥18 years of age

Diagnosis and Main Criteria for Eligibility:

Eligible participants will have treatment-naïve DME, with vision loss primarily due to DME and center involvement (if present) diagnosed within 9 months of screening; and Type 1 or Type 2 diabetes mellitus with a hemoglobin A1c (HbA1c) ≤12%.

Total Participant Duration:	**Duration of Treatment:**
111 weeks	100 weeks

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Study Intervention (Investigational Medicinal Product), Dose, and Route of Administration:

Treatment Arm A:

- Day 1 to Week 12: KSI-301 5 mg once every 4 weeks for 3 monthly doses via intravitreal injection, followed by a sham injection at Week 12;
- Week 16 to Week 100: KSI-301 5 mg using an individualized dosing regimen via intravitreal injection. The minimum interval between KSI-301 treatments is 8 weeks (± 14 days, considering the respective visit windows) and the maximum interval is 24 weeks (± 14 days, considering the respective visit windows). Sham injections will be administered at each monthly visit if an active treatment is not administered.

Study Intervention (Active Control/ Investigational Medicinal Product), Dose, and Route of Administration:

Treatment Arm B:

- Day 1 to Week 20: Aflibercept 2 mg once every 4 weeks for 5 monthly doses via intravitreal injection, followed by a sham injection at Week 20;
- Week 24 to Week 100: Aflibercept 2 mg once every 8 weeks via intravitreal injection. Sham injections will be administered at each monthly visit if an active treatment is not administered.

Efficacy Evaluation:

Unless stated otherwise, all efficacy analyses will be performed on the intent to treat (ITT) population. The primary endpoint is defined as the mean change in ETDRS BCVA from baseline (Day 1) to Year 1 (average of Weeks 60 and 64). The primary assessment of efficacy will be based on a pairwise comparison in mean change in BCVA between treatment arm A (KSI-301 5 mg) and treatment arm B (aflibercept 2 mg). Other efficacy outcomes will be evaluated using ophthalmic assessments (including tonometry), fundus photography, spectral domain optical coherence tomography (SD-OCT), and fluorescein angiography (FA). Secondary endpoints for efficacy will be assessed at Week 64 and Week 104. Planned time points for all efficacy assessments are provided in the Schedule of Activities (SoA) (Section 1.3).

Safety Evaluation:

After informed consent has been obtained but prior to initiation of study intervention, only serious adverse events (SAEs) caused by a protocol-mandated intervention will be reported. After initiation of study intervention (Day 1), all AE and SAE information will be collected until the final safety follow-up visit at Week 108 or the early termination (ET) visit if applicable, as specified in the SoA (Section 1.3). The safety analysis will use outcomes of all participants who were exposed to study treatment, regardless of adherence to the protocol or treatment outcome. All reported adverse events (ocular and otherwise) in the safety population will be listed by MedDRA term, frequency, severity, association to the study therapy, and treatment group. By-treatment incidence rates will also be calculated for the treatment groups. For certain adverse events, per-injection rates will also be described.

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Pharmacokinetic/Biomarker Evaluation:

Plasma concentrations of study intervention (KSI-301) will be measured, as specified in the SoA (Section 1.3). Blood samples will also be analyzed for anti-drug antibodies (ADAs). For exploratory purposes, [redacted]

Statistical Methods:

The study hypothesis is that treatment with KSI-301 5 mg will provide a non-inferior mean change in BCVA compared to aflibercept 2 mg, while using a less frequent dosing schedule in participants with DME.

Using ETDRS BCVA data collected up to Year 1, the treatment arms will be compared using a non-inferiority analysis, with a margin [redacted] Confidence intervals (CIs) will be 100(1-2α)% or 95% CIs. If the null hypothesis of inferiority is rejected, testing for superiority will be performed.

The sample size of approximately 450 participants (225 per arm) was calculated using the following assumptions:

- 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]
- The maximum, clinically acceptable true difference for KSI-301 to be considered non-inferior, or the "non-inferiority margin" is [redacted]
- The statistical test used to compare the two treatment arms at Year 1 is an independent t-test on the mean change in visual acuity from baseline.
- Lost to follow-up/dropout rate of approximately [redacted]

Analysis of data for the first period of the study will be performed when all participants have either completed the Week 64 visit or have discontinued from the study, all data have been entered into the database, cleaned and verified as appropriate and the database for the primary analysis has been frozen. Likewise, analysis of data for the second period of the study will be performed when all participants have either completed the Week 108 visit or have discontinued from the study, all data have been entered into the database, cleaned and verified as appropriate, and the database has been locked.

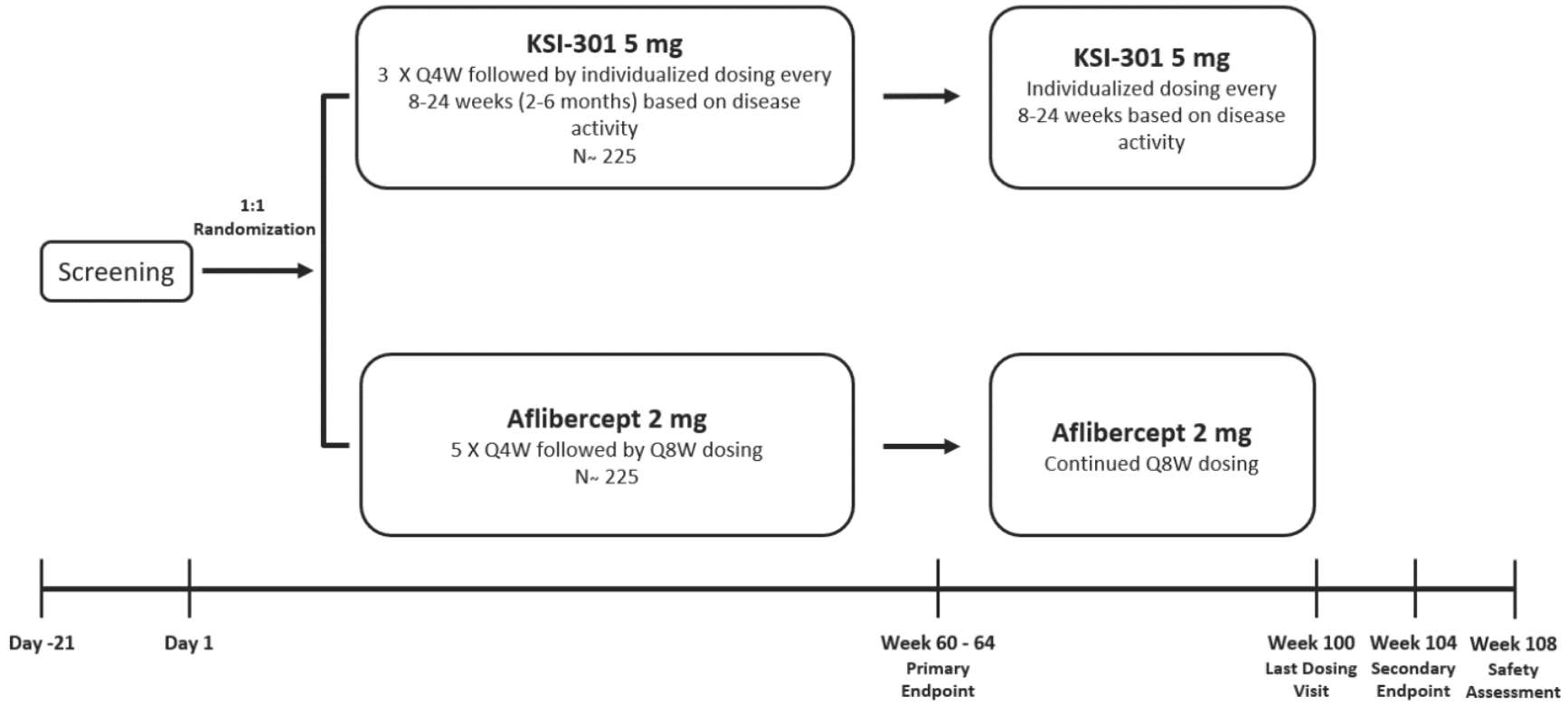
Data Monitoring:

An Independent Data Monitoring Committee (IDMC) will monitor the study conduct and participant safety on an ongoing basis.

Date of Protocol/Amendment:	15 March 2022

1.2 Schema

Figure 1: Protocol KS301P104: Schema



Abbreviations: Q4W = once every four weeks; Q8W = once every 8 weeks.

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

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

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

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

2.0 INTRODUCTION

KSI-301 is a novel, potent, long-acting biopharmaceutical that inhibits vascular endothelial growth factor (VEGF). It is being developed to treat diabetic macular edema (DME), as well as wet age-related macular degeneration (wAMD) and retinal vein occlusion (RVO; branch and central). KSI-301 offers a potential for participants to experience a longer interval between consecutive intravitreal injections compared to existing anti-VEGF therapies. Thus, KSI-301 may have the potential to improve real-world outcomes of anti-VEGF therapy, which are currently limited by both the high treatment burden and insufficient durability of effect in patients with DME.

2.1 Study Rationale

Although substantial visual acuity benefits have been demonstrated with the approved intravitreal VEGF inhibitors (e.g., aflibercept, ranibizumab) in the first-line treatment of DME, the gains require frequent intravitreal injections; this high treatment burden challenges patient compliance (Ciulla 2020). Therefore, there is a substantial medical need for more durable options that reduce treatment burden. Compared to aflibercept, KSI-301 has an extended ocular half-life (Section 2.2.3), which may result in a less frequent treatment regimen. In the ongoing Phase 1b portion of Study KSI-CL-101, the safety and efficacy outcomes of participants with treatment-naïve wAMD, DME/diabetic retinopathy (DR), or RVO (branch (BRVO) and central (CRVO)) treated with KSI-301 5 mg have supported a prolonged treatment interval (2 to ≥6 months in DME/DR and wAMD, and 2 to ≥4 months in RVO). Thus, this study has been designed to evaluate a less frequent treatment regimen of KSI-301 5 mg (individualized dosing in intervals ranging from 2-6 months based on disease activity after only three monthly doses) compared to aflibercept 2 mg (Q8W after five monthly doses) in participants with DME.

2.2 Background

2.2.1 Diabetic Macular Edema

Diabetes mellitus (DM) is a chronic disease that exerts pathologic effects on multiple organ systems, including the retina. Diabetic eye disease is the most common microvascular complication of DM and includes diabetic retinopathy (DR) and diabetic macular edema (DME) (Cheloni 2019). Important features of DR are microaneurysms, vascular leakage, and retinal hemorrhage. Progressive worsening of DR can lead to retinal neovascularization, vitreous hemorrhage, tractional retinal detachment, and severe vision loss due to the development of neovascular (proliferative) disease (Cheung 2008; Yau 2012). Vascular leakage results in collection of fluid, or edema, in the retina. Diabetic macular edema (DME) occurs when there is leakage in the macula, the central region of the retina responsible for fine visual acuity. DME is a leading cause of vision loss in the working age population (Cheloni 2019; Schmidt-Erfurth 2017).

The prevalence of DR and its sight-threatening complications (DME and proliferative diabetic retinopathy (PDR)) are rising worldwide. It has been estimated that nearly one in three people with diabetes have or will develop DR. (Demirel 2016; Duphare 2020)

2.2.2 Vascular Endothelial Growth Factor

VEGF stimulates vascular endothelial cell growth and induces vascular permeability. These biologic activities give it a central role in angiogenesis, both in normal and pathologic conditions. VEGF plays a critical role in the pathophysiology of choroidal and retinal neovascular diseases such as wAMD; diabetic retinopathy (DR), including diabetic macular edema (DME); and ME due to CRVO or BRVO (Rubio 2016). Inhibition of pathologic VEGF activity is both an "anti-angiogenic" and "anti-permeability" approach to treat choroidal and retinal neovascular diseases and has been shown to be effective in preserving and improving visual acuity (Campochiaro 2015; Cheung 2010).

Among the VEGF family members, VEGF-A is the most strongly associated with angiogenesis and vascular leakage (Campochiaro 2015). Intravitreal VEGF-A inhibitors such as aflibercept and ranibizumab have been approved by regulatory authorities worldwide for use in multiple retinal vascular diseases. Both ranibizumab and aflibercept have been evaluated in Phase 3 studies for the management of ME, including DME, where patients treated with monthly ranibizumab or every other month aflibercept (after 5 initial monthly doses) achieved significant functional and anatomic improvements after 12 months of treatment (Demirel 2016; Flaxel 2020; Schmidt-Erfurth 2017).

On account of superior visual acuity and anatomic outcomes, intravitreal VEGF-inhibition therapy has replaced macular laser photocoagulation as the first-line treatment for DME (Flaxel 2020; Schmidt-Erfurth 2017). However, primary concerns with approved anti-VEGF therapies are that the visual acuity gains observed in the early intensive treatment phase require a high treatment burden (monthly or bimonthly injections) and the visual acuity results achieved with frequent therapy are not sustained with less frequent dosing. This is thought to be due to the relatively short intravitreal half-lives of the approved products (in rabbits: ~4 days for aflibercept, ~2.5 days for ranibizumab (Park 2016); in monkeys: ~2.4 days for aflibercept, ~2.7 days for ranibizumab (Christoforidis 2017)). In DME, short ocular half-lives translate to narrow and burdensome retreatment windows, which then result in a high treatment burden that is difficult to successfully maintain (Ciulla 2020).

2.2.3 Description of KSI-301

KSI-301 is an antibody biopolymer conjugate (ABC) developed using the Sponsor's proprietary ABC Platform™ technology. The antibody portion of KSI-301 binds to VEGF-A with high affinity and inhibits the ability of VEGF-A to bind and activate its cognate receptors (VEGFR1 and VEGFR2), thereby acting as an anti-angiogenic and anti-permeability agent. The inert biopolymer portion is an ultra-hydrophilic phosphorylcholine polymer that significantly increases the overall molecular size of KSI-301, which in turn extends its ocular half-life by a

factor of [redacted] and ocular concentrations at three months by a factor of [redacted] compared to aflibercept. Due to the biophysical and biological properties of the ABC Platform on which it is built, KSI-301 is designed to have improved ocular durability, bioavailability, biocompatibility, and stability, and rapid systemic clearance. These properties make KSI-301 an ideal candidate for the management of retinal vascular diseases.

A detailed description of the chemistry, pharmacology, efficacy, and safety of KSI-301 is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of KSI-301 may be found in the IB. A brief overview of known potential benefits and risks is provided in the subsections that follow.

2.3.1 Known Potential Benefits

KSI-301, an intravitreal VEGF inhibitor developed to treat DME, benefits from a well-documented mechanism of action in retinal vascular disease (Homayouni 2009). The efficacy and safety of commercially available intravitreal VEGF inhibitors in DME are also well-documented and established (Demirel 2016; Duphare 2020). Based on its molecular design and structure, *in vitro* and *in vivo* nonclinical testing, and clinical data to date, it is expected that the efficacy and safety of KSI-301 should be at least comparable to standard of care.

Long-term and real-world outcomes of approved anti-VEGF therapies are currently limited by the high treatment burden caused by their insufficient durability. Emerging efficacy data from the ongoing Phase 1b portion of Study KSI-CL-101 support the extended ocular half-life of KSI-301 and a less frequent dose regimen compared to aflibercept. Thus, KSI-301 may provide clinically relevant benefits over existing therapies for patients with DME.

2.3.2 Known Potential Risks

Potential risks of treatment with KSI-301 were identified based on therapeutic protein class effects, VEGF-inhibition class effects, the intravitreal route of administration, nonclinical findings, and Phase 1/1b clinical experience. In consideration of the Coronavirus disease (COVID-19) pandemic caused by the virus SARS-CoV-2 and the impact it may have on clinical trials, COVID-19 related risks to participants are also carefully considered. A summary of known potential risks associated with KSI-301 is provided in Table 1. Risks associated with COVID-19 are discussed below in Section 2.3.2.1.

Table 1: Protocol KS301P104: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Study Intervention [KSI-301]		
Immunogenicity	As with all therapeutic proteins, there is a potential for an immune response in participants treated with KSI-301. Clinical experience with commercially available intravitreal VEGF inhibitors has shown that SAEs related to inflammatory reactions can occur. Additional details are provided in IB Section 5.4.2.1.	Patients will be monitored following the injection and instructed to report any symptoms suggestive of an immune response without delay to facilitate early diagnosis and treatment (Section 8.1.4). Participants with known hypersensitivity to intravitreal agents such as aflibercept or any ingredient of KSI-301 are excluded from this study (Section 5.2.2).
Arterial thromboembolic events (ATEs)	ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). There is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Additional details are provided in IB Section 5.4.2.2.	Participants with recent history (6 months) of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure or any acute coronary event are excluded from this study (Section 5.2.2).
Intraocular inflammation	Intraocular inflammation has been reported following treatment with intravitreal anti-VEGF medicines, including KSI-301. Additional details are provided in IB Section 5.4.2.3.	Patients will be monitored following the injection and instructed to report any symptoms suggestive of intraocular inflammation without delay to facilitate early diagnosis and treatment (Section 8.1.4). Patients with active ocular infection or inflammation in either eye (e.g., blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis) are excluded from this study (Section 5.2.1). Patients with active intraocular inflammation will have study treatment interrupted (Section 7.1.1).
Hypersensitivity	Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/ anaphylactoid reactions, or severe intraocular inflammation. Additional details are provided in IB Section 5.4.2.4.	Participants with known hypersensitivity to intravitreal agents such as aflibercept or any ingredient of KSI-301 are excluded from this study (Section 5.2.2).
Study Procedures		
Risks associated with the method of administration	These risks include endophthalmitis, increases in intraocular pressure, retinal detachment, retinal tear, traumatic cataract, and intraocular hemorrhage. Additional details are provided in IB Section 5.4.2.5.	Proper and aseptic injection technique when administering intravitreal injections will be used (Section 8.1.3). Patients will be monitored following the injection and instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay to facilitate early diagnosis and treatment (Section 8.1.4). Intraocular pressure and the perfusion of the optic nerve head will also be monitored and managed (Section 8.1.4). Patients with active ocular infection or inflammation in either eye (e.g., blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis) are excluded from this study (Section 5.2.1).
Exposure to SARS-CoV-2 virus	Section 2.3.2.1	Section 2.3.2.1

2.3.2.1 Risks Associated with Exposure to the Virus SARS-CoV-2

In consideration of the Coronavirus disease (COVID-19) pandemic caused by the virus SARS-CoV-2 and the impact it may have on clinical trials, COVID-19 related risks to participants are carefully considered and will be documented on an ongoing basis. In DME, early diagnosis and treatment with intravitreal anti-VEGF therapy is associated with better functional outcomes (Brown 2013; Duphare 2020). Moreover, intravitreal anti-VEGF treatment is recognized as an essential healthcare service during the pandemic by ophthalmology physician societies worldwide. This trial affords all participants the opportunity to receive anti-VEGF therapy for their DME. Measures that prioritize trial participant safety and data integrity have been developed in consideration of local guidelines.

In order to minimize any added risk of exposure associated with trial participation beyond that associated with standard of care treatment, the Schedule of Activities (SoA) (Section 1.3) has been optimized to allow for an adequate follow-up and assessment of the safety and efficacy of KSI-301 without unnecessarily increasing participant exposure beyond that which may already exist from their attendance at clinic visits for anti-VEGF treatment of their DME.

As the pandemic situation develops, the Sponsor will reassess risks, which will be documented as part of the Sponsor's trial master file. In the event that escalation of the pandemic during this trial and local circumstances lead to a local change in risk assessment, additional measures may be implemented. In this case, an Investigator-driven risk assessment will be conducted and documented in the Investigator’s site master file and communicated to the Sponsor.

2.3.3 Overall Benefit/Risk Conclusion

The potential benefits of treatment of DME with KSI-301 (longer treatment intervals) have been considered against both the risks associated with KSI-301 treatment and the COVID-19 pandemic. Participants in this study will be carefully monitored with special attention to known and potential risks and managed as appropriate. Exclusion criteria restrict enrollment of participants at higher risk, and routine monitoring and follow-up evaluations will be conducted for early detection of any AEs, as noted in Section 8.3. Reassessment of the risks will continue as the COVID-19 situation develops and any changes to this approach will be documented accordingly.

In DME, early diagnosis and treatment with intravitreal anti-VEGF therapy is associated with better functional outcomes (Duphare 2020). Moreover, intravitreal anti-VEGF treatment is recognized as an essential healthcare service during the pandemic by physician groups worldwide. Therefore, based upon the well-known, clinically demonstrated mechanism of action (Homayouni 2009); favorable nonclinical and Phase 1a/1b safety, tolerability and bioactivity data; and a study design that includes extensive monitoring and COVID-19 risk mitigation, the Sponsor considers that the potential risks of study participation are outweighed by the value of the information to be gained and further study is warranted.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in BCVA from Day 1 to Year 1 (average of Weeks 60 and 64).	• Mean change in BCVA from baseline (Day 1) to the average of Weeks 60 and 64 (Year 1) (ETDRS Letters).
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 participants who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time. • Proportion of participants who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time. • Proportion of participants with BCVA Snellen equivalent of 20/40 or better from baseline over time. • Proportion of participants with BCVA Snellen equivalent of 20/200 or worse from baseline 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 OCT CST and other morphological parameters from baseline to the average of Weeks 60 and 64 (Year 1) and over time. • Proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS DRSS at Week 52.
To evaluate the durability of KSI-301 5 mg compared to aflibercept 2 mg over the study duration.	• Mean number of intravitreal injections over the duration of the study. • Mean number of intravitreal injections from baseline to Week 60 and from Week 64 to 104. • Mean time to first re-treatment after the last monthly dose.
To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg.	• Incidence of ocular and systemic adverse events up to Week 64 and Week 108.
To assess the systemic pharmacokinetics (exposure) and immunogenicity of KSI-301.	• Systemic pharmacokinetic profile over time. • Systemic anti-drug antibody status over time.
Exploratory	
Additional exploratory endpoints will be further described in the Statistical Analysis Plan (SAP).	

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, prospective, randomized, double-masked, two-arm, multi-center study evaluating the efficacy and safety of repeated intravitreal dosing of KSI-301 5 mg in participants with treatment-naïve DME.

The overall duration of the study is approximately 2 years (108 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 108; thus, participant duration is approximately 111 weeks and includes a screening period of up to 21 days (Days -21 to -1), a treatment period of approximately 100 weeks (Day 1 to Week 100), a 4-week follow-up period for safety and efficacy assessments at Week 104, and a final follow-up for safety assessments at Week 108 [redacted] The primary endpoint will be assessed at Week 64 (average of Weeks 60 and 64); additional secondary endpoints for efficacy will be assessed at Weeks 64 and 104.

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 at Screening will be selected as the Study Eye. If both eyes are eligible and have the same BCVA, 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
- Group B: Aflibercept 2 mg

Randomization will be stratified by [redacted]
Additional details of the randomization methods are described in the SAP.

4.1.1 Screening Period

Participants will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the participant's standard care. After providing informed consent, participants will be evaluated for eligibility criteria during the screening period (21 days) before administration of study intervention(s).

Participants who do not meet eligibility criteria within the 21-day screening period will not be eligible for randomization and will be considered as screen-failed. However, a participant may be re-screened up to one additional time at the discretion of the Investigator and in consultation with the Sponsor (Section 5.4).

When re-screening tests and procedures have been completed and results are available indicating that the participant is eligible for study participation, the participant may be enrolled. When re-screening a participant, a new screening/enrollment number will be generated by the IRT system to ensure that there is an audit trail for the screen-failed participant.

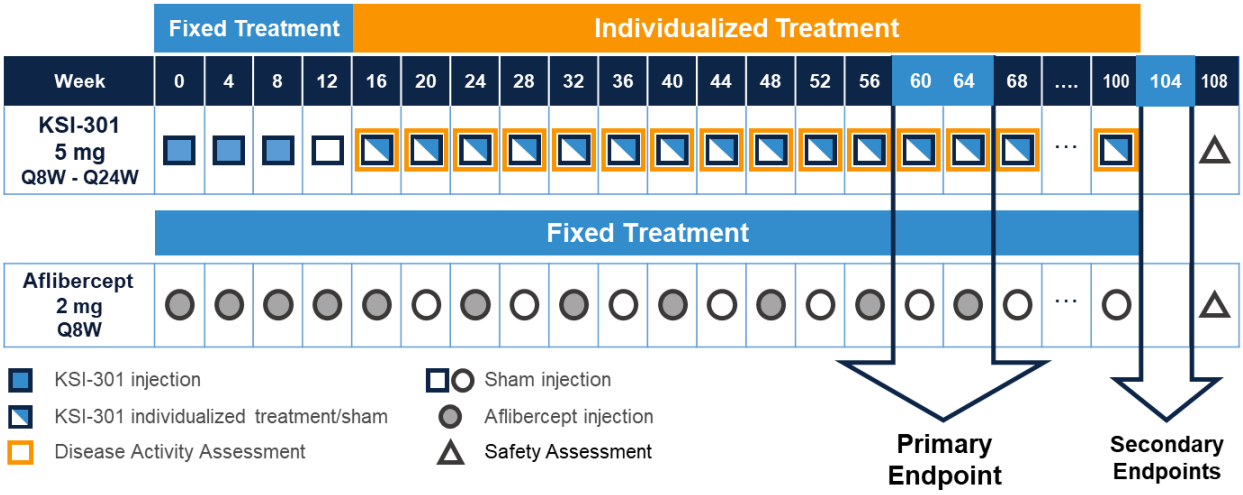
4.1.2 Treatment Period

Participants in this study will be treated until Week 100 and will have an efficacy and safety assessment at Week 104 and a final safety assessment at Week 108, unless the Investigator decides to discontinue treatment, the Sponsor decides to terminate the study, or until any of the reasons for withdrawal/discontinuation provided in Section 7.2 are met.

4.1.3 Administration of Study Intervention

As shown in Section 1.2, all participants will be treated starting on Day 1 through Week 100, according to their respective treatment arm (Figure 2). Administration of KSI-301 5 mg is described in Section 4.1.3.1. Administration of aflibercept 2 mg is described in Section 4.1.3.2.

Figure 2: Protocol KS301P104: Masked Dosing Regimens by Week



Note: For masking purposes, BCVA and OCT CST measurements will be collected and entered in the IRT system every month for all participants in both groups, but no modifications to the treatment schedule will be made by the IRT system for participants in the aflibercept group.

4.1.3.1 Administration of KSI-301 5 mg

As shown in Figure 2 above, KSI-301 will be administered in two separate treatment periods:

- Fixed Interval Treatment Period: Day 1 through Week 12 (as described in Section 4.1.3.1.1 below); and
- Individualized Treatment Period: Week 16 through Week 100 (as described in Section 4.1.3.1.2 below).

4.1.3.1.1 KSI-301 5 mg Fixed Interval Treatment Period (Day 1 Through Week 12)

Starting on Day 1 through Week 12, participants in this group will initially receive 3 monthly (Q4W) doses of KSI-301 5 mg [redacted] (at Day 1, Week 4, and Week 8), followed by a sham injection at Week 12 to preserve masking. The minimum interval between doses is 21 days.

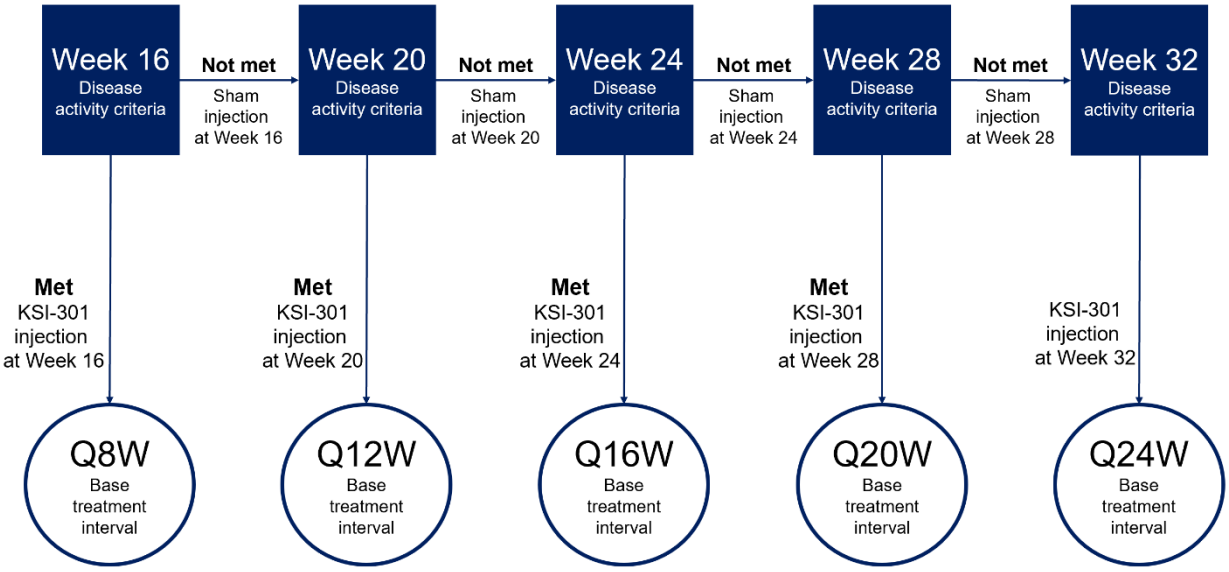
4.1.3.1.2 KSI-301 5 mg Individualized Treatment Period (Week 16 Through Week 100)

Starting at Week 16 until Week 100, participants in this group will be assessed monthly (Q4W) and will receive additional administration of KSI-301 5 mg according to protocol-defined disease activity criteria (defined below). These criteria are based on changes in OCT CST. The minimum interval between active treatments is 8 weeks (± 14 days, considering the respective visit windows) and the maximum interval is 24 weeks (± 14 days, considering the respective visit windows). To preserve masking, sham injections are administered at each visit in which no active treatment with KSI-301 5 mg is indicated.

Base Treatment Interval

At Weeks 16, 20, 24 and 28, participants will be assessed for disease activity criteria to determine their base treatment interval (once every 8, 12, 16, 20, or 24 weeks), as shown in Figure 3. Participants will receive a KSI-301 5 mg dose at the first visit in which any of the disease activity criteria (described in the subsection that follows) are met. If disease activity criteria are not met by Week 32, participants will receive a dose of KSI-301 5 mg at that visit, which corresponds to the maximum 24-week (Q24W) base treatment interval. The base treatment interval is determined by the time between the last loading dose and the first re-treatment.

Figure 3: Protocol KS301P104: Determination of the Base Treatment Interval for Patients Randomized to KSI-301 5 mg



Once established, the base treatment interval determines when participants receive their next KSI-301 5 mg dose. As shown in Figure 3, base treatment intervals are in 4-week increments from a minimum of 8 weeks to a maximum of 24 weeks.

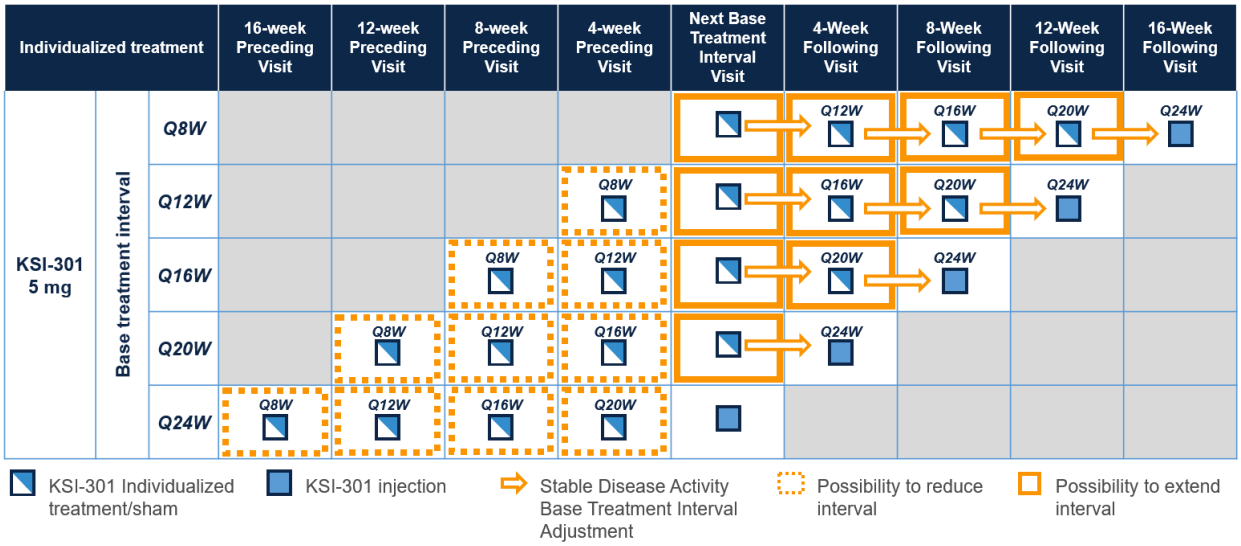
Modification of the Base Treatment Interval

As shown in Figure 4, the base treatment interval can be adjusted as follows:

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

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

Figure 4: Protocol KS301P104: Modification of Base Treatment Interval for Patients Randomized to KSI-301 5 mg



Disease Activity Criteria for KSI-301 5 mg Individualized Treatment Period

Participants will be administered KSI-301 5 mg if any of the following disease activity criteria are met:

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

Disease activity assessments will be conducted by the masked Investigator (Section 6.3.2). The IRT system will make adjustments to the dosing schedule based on disease activity data entered by the study site. The IRT will adjust the dosing schedule in consideration of missed visits, out of window visits, and missing data during a visit.

Disease Stability Criterion for KSI-301 5 mg Individualized Treatment Period

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

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

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

4.1.3.2 Administration of Aflibercept 2 mg

Participants in this group will initially receive 5 monthly doses of aflibercept 2 mg (50 µL) (at Day 1, Week 4, Week 8, Week 12, and Week 16), followed by doses once every 8 weeks (Q8W) until Week 108. Participants will receive a sham injection at each visit that aflibercept is not administered. The minimum interval between doses is 21 days.

4.2 Scientific Rationale for Study Design

This is a randomized, active comparator-controlled, double-masked, multi-center, Phase 3 study to evaluate the efficacy and safety of intravitreal KSI-301 compared with intravitreal aflibercept in treatment-naïve participants with DME. A randomized, double-masked design minimizes bias and is well-established for demonstrating the safety and efficacy of an investigational treatment. The rationales for other key design features are provided below.

4.2.1 Choice of Population

KSI-301 is being evaluated as a first-line anti-VEGF medicinal product to treat DME. Thus, participants must *not* have had prior use of an approved or investigational treatment (e.g., anti-VEGF, intraocular or periocular steroids, macular laser photocoagulation) for DME in the Study Eye. Enrollment of participants who are treatment-naïve for DME also helps minimize biases inherent in the inclusion of participants who have failed prior lines of therapy.

Participants with diabetic macular edema that has been diagnosed within the nine months prior to screening and that has not been previously treated, and with best corrected visual acuity (BCVA) of 78 to 25 letters (~20/25 to 20/320 Snellen equivalent), will be enrolled because they are expected to be broadly representative of the general population of patients treated with first-line anti-VEGF. Additionally, participants with HbA1c ≤12% will be enrolled because it has been demonstrated that the visual and anatomic responses to anti-VEGF therapy are similar irrespective of patients' baseline HbA1c measurements (Singh 2017).

4.2.2 Choice of Active Comparator Control

An active comparator was selected for this trial because an effective treatment currently exists, rendering placebo (sham injection) control unethical.

The European Society of Retina Specialists (EURETINA) and the American Academy of Ophthalmology (AAO) both recommend anti-VEGF agents as the preferred pharmacotherapeutic method of first-line treatment of DME (Flaxel 2020; Schmidt-Erfurth 2017). Intravitreal corticosteroids (triamcinolone and dexamethasone) are considered second-line due to significant ocular side effects, such as secondary glaucoma and cataract formation (Schmidt-Erfurth 2017). Two anti-VEGF agents are currently approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of DME: ranibizumab (Lucentis®) and aflibercept (Eylea®). Aflibercept is chosen as the active comparator for this trial because the majority of patients with DME treated in routine clinical practice with an approved

anti-VEGF receive aflibercept. An additional reason to choose aflibercept as the active comparator for this global study is that a single dose strength of aflibercept (2 mg) is the approved dose for DME worldwide, whereas for Lucentis, different dose strengths are approved for DME in the US versus other regions.

4.2.3 Choice of Primary Endpoint and Analysis

The primary endpoint, mean change in BCVA from baseline to Year 1, was selected based on precedent for Phase 3 studies in DME and health authority feedback.

A non-inferiority (NI) primary analysis was selected because aflibercept results in significant clinical benefit when administered frequently, as in a clinical trial. KSI-301 efficacy outcomes are expected to be comparable (non-inferior) to aflibercept but with a substantially improved (i.e., less frequent) dosing regimen. Consequently, the *a priori* assumption is that it is unlikely that KSI-301 (or any novel anti-VEGF) would demonstrate clinically meaningful superiority in vision outcomes to an approved anti-VEGF agent in a well-conducted, head-to-head trial. As an exploratory analysis, superiority will be tested in a hierarchical manner following the primary test for NI.

A NI margin of [redacted] was selected based on health authority feedback. Five letters represent one line on the ETDRS visual acuity chart and is considered by many physicians to be a clinically meaningful change. Therefore, [redacted] as an upper threshold excludes the potential for clinically meaningful treatment effect differences between KSI-301 and aflibercept.

4.2.4 Choice of Duration of Treatment and Follow-up

The duration of treatment in this study will be the same for both arms (i.e., KSI-301 and aflibercept) and is 100 weeks.

The primary endpoint will be assessed at Year 1. This time point and associated duration of treatment was selected on the basis of precedent for Phase 3 trials in DME and health authority feedback. For example, the Phase 3 studies that established the safety and efficacy of aflibercept in DME used a one-year primary endpoint and two-year supportive secondary endpoints (Korobelnik 2014). Year 1 for this purpose is defined as the average of weeks 60 and 64. This is to allow for subjects randomized to the KSI-301 arm to have two full six-month observation periods in the individualized dosing phase, such that the durability, efficacy and safety of the longer dosing intervals can be evaluated.

The choice of a safety follow-up [redacted]

4.3 Justification for Dose

4.3.1 KSI-301 Dose Rationale

The durability of intravitreal anti-VEGF pharmacological effect is proportional to the dose and the half-life of the drug. A KSI-301 5 mg dose has approximately [redacted] fold the equivalent molar dose of anti-VEGF binding capacity, at the time of injection, relative to 2 mg aflibercept. Preclinical modeling suggests that KSI-301 5 mg results in [redacted] fold the equivalent ocular concentration of aflibercept 2 mg three months after dosing. Both KSI-301 2.5 mg and KSI-301 5 mg dose levels that are being evaluated in the ongoing Phase 1b portion of Study KSI-CL-101 have not resulted in any dose-limiting ocular or systemic toxicities and, as expected, have no clear dose-efficacy response relationship. Because the 5 mg dose of KSI-301 may have incrementally improved durability compared to the 2.5 mg dose, the 5 mg dose has been selected for this study.

The [redacted] injection volume used to deliver a 5 mg dose has been well-tolerated in previous KSI-301 studies (additional information can be found in the IB) as well as in other studies for of [redacted]

The objective of KSI-301 in the treatment of DME is to reduce the number of required intravitreal injections while providing non-inferior efficacy outcomes to aflibercept. The ongoing Phase 1b portion of Study KSI-CL-101 has thus far supported a prolonged dose regimen compared to other anti-VEGF medicinal products approved to treat DME. Therefore, during the fixed treatment period (Day 1 through Week 12), KSI-301 5 mg will be administered three times: at Day 1, Week 4, and Week 8. A sham injection will be administered in Week 12 to participants randomized to treatment with KSI-301 5 mg. During the individualized treatment period (Week 16 to Week 100), the potential for treatment burden reduction will be explored with an individualized dosing approach that is based on disease activity.

4.3.2 Aflibercept Dose Rationale

In both the EU and US, the recommended dose for aflibercept in the treatment of DME is 2 mg (50 µL) administered by intravitreal injection every 4 weeks (± 7 days) (i.e., monthly) for the first 5 injections followed by 2 mg via intravitreal injection once every 8 weeks (2 months). In the EU, but not in the US, the treatment interval after the first 12 months of treatment with aflibercept may be extended, based on visual and/or anatomic outcomes, such as with a treat-and-extend dosing regimen, where the treatment intervals are gradually increased to maintain stable visual and/or anatomic outcomes. Therefore, the Sponsor considers that the following aflibercept posology in this study provides the maximum possible treatment effect and best enables a head-to-head comparison with KSI-301 without undue risk:

- Day 1 to Week 20: participants will receive 5 monthly doses of aflibercept 2 mg at Day 1, Week 4, Week 8, Week 12, and Week 16, followed by a sham injection at Week 20.

- Week 24 to Week 100: participants will receive aflibercept 2 mg once every 8 weeks (Q8W). Sham injections will be administered at each monthly visit when an active treatment is not administered.

4.3.3 Sham Injection Rationale

Sham injections are used to preserve study masking and minimize bias.

Participants in both treatment arms will receive sham injections at each monthly visit when an active treatment is not administered.

4.4 End of Treatment

Participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Every effort should be made to keep participants in the study. The reasons for end-of-treatment/early termination are provided in Section 7.0.

4.5 End of Study Definition

The end of the study is defined as the last follow-up visit of the last participant enrolled (i.e., the last enrolled participant's final visit) or a Sponsor decision to terminate the study, whichever comes first.

A participant is considered to have completed the study if he/she has completed all phases of the study, including the Week 108 safety follow-up assessment.

4.6 Treatment After End of Study

All participants will return to standard of care treatment, at the discretion of their treating physician, after completion of their final follow-up visit or once they discontinue from the study prematurely. The Sponsor will not provide continued access to study treatment following the end of the study or the end of each participant's study treatment period.

5.0 STUDY POPULATION

Participants will be randomized to a specified treatment arm only if they meet all the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the criteria in Sections 5.1.1 and 5.1.2 apply.

5.1.1 Ocular Inclusion Criteria

Where applicable inclusion criteria will be confirmed or assessed by the independent, masked image Reading Center.

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

In cases where both eyes are eligible, the eye with the worse BCVA at the Screening Visit will be selected as the Study Eye. If both eyes are eligible and have the same BCVA, the decision of which eye to select as the Study Eye will be made by the Investigator. Only one eye per participant can be included in the study.

5.1.2 General Inclusion Criteria

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the protocols and restrictions listed in the informed consent form (ICF) and in this protocol.
6. Male or female ≥ 18 years of age with Type 1 or Type 2 diabetes mellitus and a HbA1c of ≤12%.

7. For women of childbearing potential: agreement to remain as abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period [redacted]
   a. A woman is considered of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
   b. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
   c. Contraception methods that do not result in a failure rate of <1% per year such as cap, diaphragm, or sponge with spermicide, or male or female condom with or without spermicide, are not acceptable.
   d. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
8. For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
   a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period [redacted] after the last dose of study intervention. Men must refrain from donating sperm during this same time period.
9. Ability and willingness to undertake all the scheduled visits and assessments.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the criteria in Sections 5.2.1 and 5.2.2 apply.

5.2.1 Ocular Exclusion Criteria

Where applicable, exclusion criteria will be confirmed or assessed by the independent, masked image Reading Center.

1. Macular edema in the Study Eye considered to be secondary to a cause other than DME (e.g., RVO, Irvine-Gass syndrome).
2. Active iris or angle neovascularization or neovascular glaucoma in the Study Eye.
3. High-risk proliferative diabetic retinopathy characteristics in the Study Eye, using any of the following clinical criteria:
   a. Any vitreous or pre-retinal hemorrhage.

b. Neovascularization at optic disc ≥1/3 of the disc area.

c. Neovascularization elsewhere ≥1/2 of the disc area.

4. Structural damage to the center of the macula in the Study Eye that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates in the foveal center.
5. History of cataract surgery and/or minimally invasive glaucoma surgery (MIGS) in the Study Eye within 2 months of screening.
6. History of Yttrium-Aluminum Garnet (YAG) laser capsulotomy in the Study Eye within 2 months of screening.
7. History of Pan-retinal Photocoagulation (PRP) laser in the Study Eye within 3 months of screening.
8. Tractional retinal detachment in the Study Eye.
9. Uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mmHg despite treatment with antiglaucoma medication) in the Study Eye.
10. History of glaucoma-filtering surgery (trabeculectomy or tube shunt) in the Study Eye.
11. History of retinal detachment or treatment or surgery for retinal detachment in the Study Eye.
12. History of uveitis in either eye.
13. Significant media opacities, including cataract, in the Study Eye that might interfere with visual acuity, assessment of safety, OCT or fundus photography.
14. Cataract in the Study Eye that in the judgment of the Investigator is expected to require surgical extraction within 12 months of screening.
15. Aphakia in the Study Eye.
16. Prior vitrectomy in the Study Eye.
17. Active retinal disease other than the condition under investigation in the Study Eye.
18. 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, epiretinal membrane).
19. Active or suspected ocular or periocular infection or inflammation in either eye at Day 1.
20. Any prior use of an approved or investigational treatment for DME in the Study Eye (e.g., anti-VEGF, intraocular or periocular steroids, macular laser photocoagulation).

5.2.2 General Exclusion Criteria

21. Women who are pregnant or lactating or intending to become pregnant during the study.
22. Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to Day 1. If the urine pregnancy test is positive, it must be confirmed with a serum pregnancy test.

23. Uncontrolled blood pressure defined as a systolic value ≥ 180 mmHg or diastolic value ≥100 mmHg while at rest at Screening or on Day 1. If a participant's initial blood pressure measurement exceeds these values, a second reading may be taken later the same day or a different day during the screening period. If the participant's blood pressure is controlled by antihypertensive medications, the participant should be on a stable medication regimen continuously for 30 days prior to Day 1.
24. Recent history (within the 6 months prior to screening) of myocardial infarction, stroke, transient ischemic attack, acute congestive heart failure or any acute coronary event.
25. Kidney failure requiring renal transplant, hemodialysis or peritoneal dialysis or expected to require renal transplant, hemodialysis or peritoneal dialysis during the study.
26. History of a medical condition that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product.
27. History of hypersensitivity to any component of KSI-301, aflibercept, ophthalmic dye (fluorescein), dilating drops, or any of the anesthetic or antimicrobial preparations used during the study, as assessed by the Investigator.
28. Participation in an investigational study within 30 days prior to the screening visit that involved treatment with any drug (excluding vitamins and minerals) or devices.

5.3 Lifestyle Considerations

No specific lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE) caused by a protocol-mandated intervention that occur during the screening period.

Participants who do not meet eligibility criteria within the 21-day screening period will not be eligible for randomization and will be screen-failed. However, a participant may be re-screened up to one additional time at the discretion of the Investigator and in consultation with the Sponsor. When re-screening, the participant must be re-consented if more than 30 days have elapsed since the date of the last informed consent. In the event of re-screening, screening procedures need not be repeated if they fall within the 21-day screening window. If the re-screening occurs outside the 21-day window, all assessments performed at the initial screening visit should be repeated during the re-screening visit except fluorescein angiogram (FA). If the re-screening visit is more than 8 weeks after the original screening visit, the FA should be repeated. For re-screening visits occurring fewer than 8 weeks after the original screening visit, although a new FA will not be required, the previously acquired FA will need to be re-submitted

to the Reading Center labeled with the new participant number, along with the new screening images from the other modalities. This will ensure that all images from the participant are properly labeled, kept within the same directory and that eligible transmission numbers and audit trails are maintained. When re-screening tests and procedures have been completed and results are available indicating the participant is eligible for study participation, the participant may be enrolled.

When re-screening a participant, a new screening/enrollment number will be generated by IRT to ensure there is an audit trail for the screen-failed participant.

5.5 Criteria for Temporarily Delaying Enrollment

There are no specific criteria for temporarily delaying enrollment into the study. Inclusion/Exclusion criteria will be assessed at Screening and on Day 1 to determine a participant's eligibility for the study.

6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Study interventions are summarized in Table 2. For full information regarding the administration of study intervention and the contents of the kit, refer to the Pharmacy Manual. For additional information regarding the administration of aflibercept, refer to the approved prescribing information for aflibercept in your country, such as the Summary of Product Characteristics (SmPC) or U.S. Prescribing Information (USPI). The full instructions for administration of sham are described in the Pharmacy Manual.

Table 2: Protocol KS301P104: Study Interventions

Arm Name	A	B	A or B
Intervention Name	KSI-301 5 mg	Aflibercept 2 mg	Sham
Type	Biological medicinal product	Biological medicinal product	Sham
Dose Formulation	Sterile liquid for intravitreal injection in single-use vials	Sterile liquid for intravitreal injection in single-use vials or prefilled syringes	Empty vial
Unit Dose Strength(s)	[redacted] mg/mL (based on antibody mass)	40 mg/mL	N/A
Dosage Level(s)	5 mg ([redacted]	2 mg (50 µL)	N/A
Route of Administration	Intravitreal injection	Intravitreal injection	Sham injection
Use	Experimental	Active control	Sham (to maintain study masking)
IMP and NIMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Storage	In the original packaging, as provided, until the time of use. Store at 2-8°C before use.	In the original packaging, as provided, until the time of use. Store at 2-8°C before use.	In the original packaging, as provided, until the time of use. Store at 2-8°C before use.
Packaging and Labeling	KSI-301 will be provided in vials that will be labeled as required per country requirement.	Aflibercept will be provided in vials or prefilled syringes that will be labeled as required per country requirement.	Sham will be provided in vials that will be labeled as required per country requirement.
Reconstitution and Handling	KSI-301 is an aqueous solution that is provided in vials and filled into syringes by unmasked site personnel without reconstitution or dilution.	Aflibercept is an aqueous solution that is provided in vials and filled into syringes by unmasked site personnel without reconstitution or dilution or provided in prefilled syringes.	Sham is provided as empty glass vials, which will remain empty throughout the sham treatment procedure. A sham injection mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe, without a needle, against an anesthetized eye.
Current/Former Name(s) or Alias(es)	N/A	Eylea	N/A

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation, Handling, and Storage

Study interventions (KSI-301 and aflibercept) are aqueous solutions provided in vials (or prefilled syringes for aflibercept) and filled into syringes by unmasked site personnel without reconstitution or dilution.

Study drug kits must be stored in a secure refrigerator at a controlled temperature of 2°C to 8°C. All study drug vials or prefilled syringes (for aflibercept) should be stored in the original packaging, as provided, until the time of use.

Please refer to Pharmacy Manual for additional instructions.

6.2.2 Study Intervention Accountability and Reconciliation

Study intervention packaging will be overseen by the Sponsor or its designee and bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling of the study medication will be in accordance with local regulations.

The investigational site will acknowledge receipt of the study intervention, to confirm the shipment condition and content. Any damaged shipments will be replaced. Upon arrival of the study intervention at the site, site personnel will complete the following:

- Check the shipment for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Sponsor or its designee upon discovery. Any study intervention under investigation for integrity or temperature excursion should be quarantined in the IRT and at the site, pending final assessment by the Sponsor or its designee.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The pharmacist responsible for dispensing study treatment, or the designated site personnel, will select the correct study intervention as assigned through the IRT. Instructions for the preparation of KSI-301, aflibercept, or sham for administration, mandatory materials to be used, and pre-treatment and post-treatment procedures are detailed in the Pharmacy Manual.

For more detailed information on the formulation, preparation, and handling of KSI-301, aflibercept, and sham, see the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Masking

6.3.1 Randomization

All participants will be centrally assigned to a randomized study intervention using an IRT system. Before the study is initiated, login information and directions for the IRT will be provided to each site.

Study intervention will be dispensed at the study visits as summarized in the SoA (Section 1.3).

6.3.2 Masking and Unmasking

This is a double-masked study. There must be a minimum of two investigators per site to fulfill the masking requirements of this study, as follows:

- **Masked Evaluating Physician(s)**: At least one Investigator will be designated as the evaluating physician who will be *masked* to participants' treatment assignments and will evaluate all ocular assessments (other than the immediate post-injection assessments done by unmasked personnel, as described below).
- **Unmasked Treating Physician(s)**: At least one other Investigator will be designated as the treating (injecting) physician who will be *unmasked* to participants' treatment assignments and will administer study intervention (KSI-301, aflibercept, or sham). This physician or an unmasked assistant will also conduct the immediate post-injection assessments, including tonometry, in the Study Eye (Section 8.1.4). The unmasked treating physician and unmasked staff must not divulge treatment assignment to anyone.

As shown in Section 6.1, there are three study interventions: (1) KSI-301 (the investigational medicinal product); (2) aflibercept (the active comparator); and (3) sham (for which an injection procedure is simulated but not actually performed). All three study interventions are provided in masked cartons (also referred to as kits).

- **Masked Cartons**: All study interventions are provided in cartons that are identical in appearance and weight, making them indistinguishable from each other.

Each carton is labeled with an identical carton label that includes a unique kit number. The IRT system will direct site personnel which specific carton to pull from inventory and use for a specific participant at a given visit based on the unique kit number printed on the carton label and that subject's treatment at that given visit.

- **Unmasked Vials or Prefilled Syringes within the Masked Cartons**: Owing to differences among vials, syringes, dose-preparation procedures, and treatment procedures that cannot be masked, the treating (injecting) physician is unmasked to study treatment as are any assistants to the treating (injecting) physician. Only unmasked site staff are allowed to open the masked cartons.

Participants, study site personnel (except for the treating physician(s), assistant(s), and pharmacist if any), the designated evaluating physician(s), central Reading Center personnel, and the Sponsor and its agents will be masked to treatment assignment.

The visual acuity (VA) examiner (performing the refraction, BCVA examination) will be masked to the participant's treatment assignment. The BCVA examiner will have no access to the VA scores of a participant's previous visits and may have access only to a participant's refraction data from previous visits.

A participant's treatment assignment will not be unmasked until the end of the study unless medical treatment of the participant depends on knowing the study treatment the participant received. Emergency code break is available to the Investigator online in the IRT. If unmasking is necessary for participant management (for example, in the case of a serious adverse event for which participant management might be affected by knowledge of the treatment assignment), the Investigator will be able to break the treatment code by accessing the IRT system. Treatment codes must not be broken except in emergency situations. If the Investigator wishes to know a participant's treatment assignment for any other, non-emergency reasons, he or she should consult with the Medical Monitor. The Investigator should document and provide an explanation for any non-emergency unmasking (for example, accidental unmasking).

For regulatory reporting purposes and if required by local health authorities, the Sponsor or its agents (e.g., contract research organization (CRO) pharmacovigilance personnel) will break the treatment code for all serious, unexpected suspected adverse reactions (SUSARs) that are considered by the Investigator or Sponsor to be related to study intervention. The participant may continue to receive treatment, and the Investigator, participant, and Sponsor or CRO personnel, except for the pharmacovigilance personnel who must have access to participant treatment assignments to fulfill their roles, will remain masked to treatment assignments.

Additional information regarding masking and unmasking will be outlined in the study Masking Manual.

6.4 Study Intervention Compliance

Only participants enrolled in the study may receive study treatment and only ophthalmologists who have experience administering intravitreal injections may administer study treatment.

The unmasked Investigator is responsible for administering the correct dose of KSI-301 or aflibercept and for the sham administration, according to the study protocol. The date and time of each dose administered in the clinic will be recorded in the source documents and electronic case report form (eCRF). To avoid medication dispensing errors, the study intervention, study participant and Study Eye identification will be confirmed at the time of dosing by a member of the unmasked study site team.

6.5 Dose Modification

Participants can only receive the specified dose for the intervention arm, as follows:

A. KSI-301: 5 mg [redacted]

B. Aflibercept: 2 mg (50 µL).

Alterations of the dosage are not allowed.

6.6 Continued Access to Study Intervention after the End of the Study

After participants complete their final follow-up visit or discontinue from the study prematurely, they will return to standard of care treatment at the discretion of their treating physician. The Sponsor will not provide continued access to study treatment following the end of the study or the end of each participant's study treatment period.

6.7 Treatment of Overdose

For this study, any dose of KSI-301 greater than 5 mg or aflibercept greater than 2 mg at a single study visit will be considered an overdose.

The Sponsor does not recommend any specific treatment for an overdose.

In the event of an accidental overdose, the Investigator/treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether additional steps should be taken.
- Closely monitor the participant for any AE/SAE.
- Document the quantity of the excess dose.

In addition to overdosing, an increased injection volume may cause an increase in intraocular pressure. In case of overdose, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated, including performing pressure lowering procedures (i.e., anterior chamber paracentesis).

6.8 Concomitant Therapy

Use of all concomitant medications will be recorded in the participant's eCRF, except for medications required for carrying out procedures in the SoA (Section 1.3) (e.g., dilating drops, anesthetics, antiseptic, fluorescein, etc.) related with this study. Concomitant medications will include all prescription drugs, herbal products, vitamins, minerals, and over the counter (OTC) medications as used by the participant within 30 days prior to Day 1 through Week 108. Any changes in concomitant medications also will be recorded in the participant's eCRF.

Any concomitant medication deemed necessary for the welfare of the participant during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that all relevant details regarding the medication are recorded in the eCRF. Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

In case the fellow (non-study) eye requires anti-VEGF treatment during the conduct of the study, the participant may be treated at the discretion of the Investigator and according to the standard of care in the respective country. The treatment of the fellow (non-study) eye may be implemented at any time once the Day 1 injection has been administered. Fellow (non-Study Eye) anti-VEGF treatment, including the date of each administration, must be documented as a concomitant medication on the appropriate eCRF. If the non-Study Eye requires treatment at the same visit as the Study Eye, the Study Eye should be treated first, and the non-Study Eye should be treated by the unmasked physician to preserve masking.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 Pan-retinal Photocoagulation (PRP)

Pan-retinal photocoagulation laser is permitted in the Study Eye, if clinically indicated for the treatment of new, active retinal or iris neovascularization due to worsening diabetic retinopathy. PRP will be reported as a concomitant procedure in the appropriate eCRF.

6.8.2 Prohibited Therapy

At the discretion of the Investigator, during the Study participants may start or continue to receive all medications and standard treatments administered for other conditions, **except for the following:**

- Investigational therapies in the non-Study Eye

- Intravitreal anti-VEGF drugs other than study-assigned aflibercept or KSI-301 in the Study Eye
- Systemic anti-VEGF therapy
- Intravitreal or periocular steroids or steroid implants in the Study Eye
- Concurrent use of macular laser photocoagulation in the Study Eye
- Investigational treatment with any drug (other than vitamins and minerals) or device

Participants whose medical care requires use of a prohibited therapy must have study treatment interrupted or be discontinued from the study in order to receive that therapy. After discussion with the Sponsor, subjects whose study treatment has been interrupted but no longer need a prohibited therapy may resume study treatment.

6.8.3 Supportive Care for Adverse Events

Supportive care for the known potential risks associated with anti-VEGF treatment and KSI-301 (summarized in Table 1) should be as per the standard of care in the respective country. No specific prophylactic therapies are recommended.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Every effort should be made to keep participants in the study. If study intervention is discontinued, an end-of-treatment visit should occur 28 +/- 7 days after study treatment is discontinued or before a new treatment regimen begins. The reasons for study discontinuation will be recorded on the appropriate eCRF.

A participant may be withdrawn from the study for any of the following reasons:

1. The participant is noncompliant with the protocol.
2. The participant has a serious or intolerable adverse event(s) (AE(s)) that in the Investigator's opinion requires withdrawal from the study.
3. The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
4. The participant is lost to follow-up.
5. Any medical condition that the Investigator or Sponsor determines may jeopardize the participants' safety if they remain in the study.
6. The participant withdraws consent, or the Investigator or Sponsor decides to discontinue the participant's participation in the study.
7. Pregnancy.

The Investigator will also withdraw a participant if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a participant is discontinued because of an AE, the event will be followed until it is resolved, or no additional improvement is expected by the Investigator (based on a follow-up period of not less than 3 months). Any participant may withdraw his or her consent at any time.

7.1.1 Treatment Interruption and/or Discontinuation due to Adverse Events or Concomitant Procedures

Study treatment interruption and/or participant discontinuation from the study treatment due to certain adverse events or concomitant procedures in the Study Eye will be determined using the criteria provided in Table 3. If any of these are met, treatment will be interrupted (or discontinued if applicable) and notification will be sent to the Medical Monitor. Treatment may be resumed after resolution of the adverse event and upon agreement with both the Investigator and Medical Monitor. The reason for study treatment interruption or discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF.

Table 3: Protocol KS301P104: Treatment Interruption Criteria

Event (MedDRA Preferred Term)	Study Treatment Interruption Criteria
Vision loss	Interrupt study treatment for *treatment-related* decrease of ≥30 letters in BCVA in the Study Eye compared with the most recent prior visit.
Intraocular inflammation	Interrupt study treatment if any active intraocular inflammation is present in the Study Eye.
Intraocular surgery	Interrupt study treatment for intraocular surgery in the Study Eye, for example cataract surgery. Treatment may resume no earlier than 10 days after uncomplicated cataract surgery, provided there is no evidence of post-operative intraocular inflammation. For complicated cataract surgery or following other intraocular surgery, study treatment may be resumed as determined by the Investigator following discussion with the Medical Monitor.
Elevated intraocular pressure	Interrupt study treatment if the pre-injection IOP is >30 mmHg in the Study Eye.
Retinal tear or break	Interrupt study treatment if a retinal tear or break is present in the Study Eye. Treatment may be resumed no earlier than 14 days after successful laser retinopexy, as determined by the Investigator.
Retinal detachment or macular hole	Interrupt study treatment if rhegmatogenous retinal detachment or Stage 3 or Stage 4 macular hole occurs in the Study Eye. Treatment may be resumed no earlier than 14 days after successful treatment, as determined by the Investigator, following discussion with the Medical Monitor.
Active infection	Interrupt study treatment if infectious cellulitis, conjunctivitis, keratitis, scleritis, or endophthalmitis occurs in or around either eye. Infections should be treated as per the local standard of care.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible, with emphasis on the visits at Week 12, 36, 48, 52, 60, 64, 76, 104, and 108 at which key efficacy and safety assessments are performed. However, participants are free to withdraw from the study or study treatment at any time upon request. Participant participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor.

Participants who discontinue study treatment or active participation in the study will no longer receive study intervention. When a participant discontinues from study treatment or active participation in the study, the reason(s) for study treatment discontinuation or withdrawal shall be recorded by the Investigator or designee on the relevant page of the eCRF. Whenever possible, all participants who discontinue study treatment or withdraw from the study

prematurely will undergo an Early Termination visit. Participants who fail to return for final assessments must be contacted by the site by phone and in writing to obtain follow-up.

If a participant exits early from the study between visits, the Investigator or designee must attempt to contact the participant and advise the participant to return for a final visit to complete the exit procedures. If the participant is unable or unwilling to return for the Early Termination visit, the 'date of exit' will be the date that the participant was last seen at the site or contacted by other communication.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

a) The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

b) Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods) and discuss the situation with the Sponsor. These contact attempts should be documented in the participant's medical record.

c) Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Before undertaking any study procedures, all potential participants will sign an ICF. Participants will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the participant. The Investigator or designee will also sign the ICF.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Assessments performed in the event of an unscheduled safety visit (Appendix 5) are at the discretion of the Investigator. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Medical History and Demographic Data

Medical history (general and ophthalmic) includes clinically significant diseases, surgeries and reproductive status. All medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant regularly or within 30 days preceding Day 1 must be recorded. A full ocular history including prior ocular treatments will be noted. Demographic data will include age, sex, and self-reported race and ethnicity.

8.1.2 Ophthalmic Exams

Unless otherwise noted, ophthalmic assessments are captured for the Study Eye only.

Slit-lamp examination, which will include the following:

- Inspection of the eyelids,
- Inspection of the cornea,
- Examination of the anterior chamber,
- Examination of the pupil,
- Examination of the iris,
- Inspection of the lens,
- Inspection of the vitreous body, and

- Inspection of the retina and optic disc.

Dilated indirect ophthalmoscopy will include examination of the peripheral retina.

Tonometry shall be conducted as part of the ophthalmic exam. The method of IOP measurement (such as Goldmann tonometry or Tonopen) must remain the same throughout the study for each participant. Pre-injection tonometry should be performed prior to pupil dilation.

Participants will be instructed to report any signs or symptoms of intraocular inflammation (uveitis) or endophthalmitis such as pain, photophobia, redness, or reduced vision.

8.1.3 Injection Procedure

The unmasked injecting Investigator must be qualified and trained in administering intravitreal injections and follow standard injection procedures in adherence to specific institutional or local policies associated with intravitreal injections. Aseptic technique must be observed by clinic staff involved in the assembly of the injection tray, study intervention preparation, anesthetic preparation, and study treatment administration. To minimize the risk of infection, the periocular skin, eyelid and conjunctiva of the Study Eye must be disinfected, as outlined in the Syringe Preparation and Injection Procedure Guidelines found in the Pharmacy Manual.

The unmasked injecting Investigator will choose one of the acceptable methods of ocular anesthesia on a per participant basis. Subconjunctival anesthesia is recommended (but not required) to maximize participant comfort. In order to maintain masking, the selected method of anesthesia for an individual participant must remain constant for the duration of the trial and at all visits irrespective of the study treatment assigned during the study visit (KSI-301, aflibercept or sham).

Please refer to the Pharmacy Manual for additional instructions on Investigational Medicinal Product (IMP) preparation and administration.

8.1.4 Post Injection Assessments in the Study Eye

Within 5 minutes after the injection, check vision for count fingers or hand motion.

- Tonometry (between 30 and 50 minutes after injection):

  If the IOP is >30 mmHg or has increased by ≥ 10 mmHg from pre-injection, the IOP will be measured again at 60−80 minutes post-injection. If there are no safety concerns, the participant will be permitted to leave the clinic. If the IOP value is of concern to the Investigator, the participant will remain in the clinic and will be managed in accordance with the Investigator's clinical judgment. The latest post-injection IOP measured (prior to any intervention for increased IOP, if applicable) will be recorded on the post-treatment IOP eCRF.

The method of post-injection IOP measurement (such as Goldmann tonometry or Tonopen) must be the same as the pre-injection method and remain the same throughout the study for each participant.

8.1.5 Best Corrected Visual Acuity (BCVA)

BCVA will be measured utilizing the ETDRS method by certified, masked personnel at the study sites. The measurement should be performed following refraction, and prior to any examination requiring contact with the eye and prior to dilating the eyes. A BCVA Testing Procedure Manual and training materials will be provided to all sites by the third-party VA Examiner certification vendor.

8.1.6 Fundus Photography (FP)

Fundus photography will be performed at the study sites by certified, masked personnel. It is mandatory that the same model of device is used for the entire duration of the study.

Additional specifications and instructions regarding acceptable equipment and imaging techniques will be provided by the Reading Center.

8.1.7 Spectral Domain Optical Coherence Tomography (SD-OCT)

SD-OCT will be performed at the study sites by certified, masked personnel on a qualified instrument. It is mandatory that the same model of device is used for the entire duration of the study.

Additional specifications and instructions regarding acceptable equipment and imaging techniques will be provided by the Reading Center.

8.1.8 Optical Coherence Tomography – Angiography (OCT-A)

OCT-A will be performed at select study sites by certified, masked personnel on a qualified instrument. It is mandatory that the same model of device is used for each participant for the entire duration of the study.

Additional specifications and instructions regarding acceptable equipment and imaging techniques will be provided by the Reading Center.

8.1.9 Fluorescein Angiography (FA)

FA will be performed at all the study sites by certified, masked personnel. It is mandatory that the same model of device is used for the entire duration of the study.

Additional specifications and instructions regarding acceptable equipment imaging and imaging techniques will be provided by the Reading Center.

8.1.10 Disease Activity Assessments

The IRT will make the necessary adjustments to the dosing schedule based on disease activity data from the study site. Details of the disease activity assessments are described in Section 4.1.3.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Vital Signs

The following vital signs will be assessed taken with the participant in a seated position after resting for 5 minutes: blood pressure (BP), pulse rate, and body temperature. Height and weight will be recorded at the screening visit only.

8.2.2 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.3 Pregnancy Testing

Participant samples for pregnancy testing will be taken at the Screening and Day 1 visits and then monthly in women of childbearing potential only, as specified in the SoA (Section 1.3). Prior to enrollment in the study, female participants of childbearing potential and male participants must be advised of the importance of avoiding pregnancy or partner pregnancy, respectively, during the trial and the potential risks associated with an unintentional pregnancy. Contraceptive and barrier guidance and collection of pregnancy information is described in Appendix 6.

8.3 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and serious AEs (SAEs) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7.0).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

After informed consent has been obtained but prior to initiation of study intervention, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study intervention (Day 1), all AE and SAE information will be collected until the final safety follow-up visit at Week 108 or the ET visit if applicable.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. At every study visit, open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. The participant will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to participant observations, AEs identified from any study data (e.g., laboratory values, ophthalmic examination findings) or identified from review of other documents that are relevant to participant safety will be documented on the AE page in the eCRF.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

During the study, female and male participants are to be instructed to contact the Investigator immediately if they suspect they might be pregnant or if their partner becomes pregnant,

respectively, and details will be collected. Additional urine or serum pregnancy testing may be performed during the study at the discretion of the Investigator, or in accordance with local requirements or regulations.

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE on a Sponsor prepared form. To ensure participant safety, each pregnancy must be reported to the Sponsor or its designee immediately (within 24 hours) after learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the participant was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the participant has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

Pregnancy is considered a criterion for discontinuation from the study, please refer to Section 7.1 for additional information. Contraceptive and barrier guidance and collection of pregnancy information is described in Appendix 6.

8.3.6 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. These adverse events may be serious or non-serious. Applicable adverse events may require additional investigation in order to characterize and understand, and depending upon the nature of the event, rapid communication by the Sponsor to other parties may also be required.

These AESIs must be reported by the Investigator using the same mechanism (electronic data capture (EDC) or fax) and timeframe (i.e., within 24 hours after learning of the event) as described previously for SAEs. The AESIs include the following:

- AEs resulting from medication error, including overdose, incorrect dose, incorrect drug, incorrect administration, or incorrect kit.
- AEs with sight-threatening potential, meeting one or more of the following criteria:
    - Causes a decrease ≥30 letters in BCVA compared with the last VA assessment;
    - It is associated with severe intraocular inflammation (i.e., endophthalmitis, Grade 4 aqueous flare/aqueous cells, Grade 4 vitreous haze/vitreous cells; see Appendix 4 for grading scales); or

  - Requires surgical intervention to prevent permanent loss of sight.

- Cases of potential liver injury (Appendix 7)

As with all AEs occurring in a study participant, a decision will be made by the Investigator concerning additional exposure to study treatment and further participation in the study.

8.4 Pharmacokinetics

To understand the pharmacokinetic (PK) profile of the study intervention following intravitreal injection (i.e., systemic exposure), the plasma concentration of KSI-301 will be measured. For exploratory purposes, [redacted] Plasma samples of comparator may also be analyzed for systemic PK and systemic biomarkers.

Blood samples of approximately 4 mL will be collected from participants for measurement of plasma concentrations of KSI-301, as specified in the SoA (Section 1.3).

Instructions for the collection and handling of biological samples will be included in the Central Laboratory Manual. The actual date and time when each sample is collected will be recorded.

8.5 Genetics and/or Pharmacogenomics

Genetics and/or pharmacogenomics are not evaluated in this study.

8.6 Biomarkers

Blood samples that were collected from participants for PK analysis (Section 8.4) may also be analyzed for measurement of plasma biomarkers, as specified in the SoA (Section 1.3).

Instructions for the collection and handling of biological samples will be provided by the Central Laboratory Manual. The actual date and time when each sample is collected will be recorded.

8.7 Immunogenicity Assessments

Blood samples of approximately 4 mL will be collected for detection and confirmation of anti-drug antibodies (ADAs), as well as assays to further characterize ADAs as specified in the SoA (Section 1.3). Additionally, plasma samples should also be collected and evaluated at the final visit from participants who discontinued study intervention or were withdrawn from the study as per the SoA.

The detection and characterization of ADAs to KSI-301 will be performed using a validated assay method. Plasma samples will be screened for antibodies binding to KSI-301 and the titer of confirmed positive samples will be reported. Specificity analyses may be performed to further characterize the immunogenicity of KSI-301. Anti-KSI-301 antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study

intervention(s) (neutralizing antibodies (NAB)). All samples collected for detection of antibodies to study intervention will also be evaluated for KSI-301 plasma concentration to enable interpretation of the antibody data.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to KSI-301.

8.8 Health Economics or Medical Resource Utilization and Health Economics

These parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Hypothesis

Treatment with KSI-301 5 mg will provide a non-inferior mean change in BCVA compared to aflibercept 2 mg while using a less frequent dosing schedule in participants with DME.

9.2 Sample Size Determination

The sample size for the comparison of BCVA between treatment arm A (KSI-301 5 mg) and treatment arm B (aflibercept 2 mg) at Year 1 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% confidence intervals (CIs).
- Statistical power of ≥90%.
- Standard deviation of the distribution of change in visual acuity from baseline of [redacted].
- The maximum, clinically acceptable true difference for KSI-301 to be considered non-inferior, or the "non-inferiority margin," is [redacted]
- The statistical test used to compare the two treatment arms at Year 1 is an independent t-test on the mean change in visual acuity from baseline.
- Lost to follow-up/dropout rate of approximately [redacted].

The sample size calculated using the above assumptions is approximately 450 participants (225 per treatment arm). [redacted] Additional details will be provided in the SAP.

Note: "enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening and completing the Day 1 visit. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3 Analysis Sets

For the purpose of analysis, the following analysis sets are defined:

Population	Description
Randomized/ Intent to treat set (ITT)	The ITT will be comprised of all participants who were randomized into one of the study arms. For analyses based on this population, participants will be grouped according to the treatment assigned at randomization.
Evaluable / Per protocol set (PPS)	The PPS will consist of all ITT participants who fulfill all inclusion/exclusion criteria and have no significant protocol deviations that are expected to have a significant impact on the assessment of efficacy, including lack of compliance with study treatment, missing data, and having taken any prohibited medication. All analyses using the PPS will group participants according to the treatment they actually received.
Safety	All participants randomly assigned to study intervention and who receive at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic/ Biomarker/ ADA Evaluable	The PK/biomarker evaluable data set will consist of all participants in the ITT Population with at least one post-Day 1 evaluable sample. The ADA evaluable data set will consist of all participants in the ITT Population with at least one evaluable sample.

9.4 Statistical Analyses

The study SAP will fully specify the statistical methodology and reporting for all aspects of the planned analyses. The SAP will be finalized prior to database lock and executed thereafter, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Additional unplanned analyses may be required after all planned analyses have been completed, and additional analyses of key efficacy metrics may be performed between the primary and final analyses to support marketing applications for various jurisdictions. Any unplanned analyses will be clearly identified in the clinical study report.

Results of the Year-1 analyses may be reported to the public and to health authorities prior to the completion of the Week 108 portion of the study. Participants, masked study site staff, and the Reading Center will remain masked to treatment assignments until the entire study is completed, the database is locked, and the Week 108 analyses are completed.

9.4.1 General Considerations

At baseline (Day 1), participants will be randomized 1:1 into one of two treatment arms:

A. KSI-301 5 mg.

B. Aflibercept 2 mg.

This study is divided into two efficacy and safety assessment periods (Section 1.2), as follows:

- Year 1: from Day 1 to Week 64; and
- Year 2: from Week 68 to Week 108.

Using the average ETDRS BCVA data collected at Weeks 60 and 64, the treatment arms will be compared using a non-inferiority analysis, with a margin of [redacted]. Confidence intervals will be 100(1-2 α)% or 95% CIs. If the null hypothesis of inferiority is rejected, testing for superiority will be performed. That is, if the lower confidence limit for the difference in mean BCVA lies within [redacted], ∞), the null hypothesis of inferiority will be rejected, and non-inferiority will be established. Furthermore, if the lower confidence limit lies within (0, ∞), superiority will be established.

Analysis of data for the first period of the study will be performed when all participants have either completed the Week 64 visit or have discontinued from the study, all data have been entered into the database, cleaned and verified as appropriate, and the database for the primary analysis has been frozen; likewise, analysis of data for the second period of the study will be performed when all participants have either completed the Week 108 visit or have discontinued from the study, all data have been entered into the database, cleaned and verified as appropriate, and the database has been locked.

Details of all preplanned analyses, including imputation approaches for the handling of missing data, subgroup analyses (for example, across key demographic and ocular baseline characteristics), and sensitivity analyses, will be included in the SAP. The results of all analyses detailed in the SAP will appear in the final clinical study report.

9.4.2 Primary Endpoint(s)

The primary endpoint is defined as the mean change in ETDRS BCVA from baseline (Day 1) to Year 1 (average of Weeks 60 and 64). The primary assessment of efficacy will be based on a pairwise comparison in mean change in BCVA between treatment arm A (KSI-301 5 mg) and treatment arm B (aflibercept 2 mg).

Unless stated otherwise, all analyses described will be performed on the ITT population.

Analysis of the primary endpoint data will be performed when the following occur:

- all participants have either completed the Week 64 visit or have discontinued from the study prior to the Week 64 visit, whichever comes later;
- all data up to and including the Week 64 visit have been entered into the database, and have been cleaned, and verified as appropriate; and
- the database for the primary analysis locked.

If there are no imbalances on important prognostic factors at baseline, a simple independent t-test and corresponding CIs will be used for evaluation of treatment differences. If there are imbalances in key prognostic factors at baseline [redacted] generalized linear models or other statistical models (such as mixed effects models) will be used to estimate the difference in mean change in BCVA between treatment arms and CIs derived from the corresponding standard error of the estimate. These models will also include indicator variables for stratification variables. An alpha level of 0.025 will be used for hypothesis testing and CIs will be 100(1-2α)% or 95% CIs. If the null hypothesis of inferiority is rejected, testing for superiority will be performed.

Full details on the statistical testing procedures along with supplementary and sensitivity analyses will be provided in the SAP.

9.4.3 Secondary Endpoint(s)

Key secondary endpoints will be assessed at Week 64 and Week 104:

- Mean change in BCVA (ETDRS Letters) from baseline (Day 1) by visit over time.
- Proportion of participants who gain ≥ 5, ≥10 and ≥15 letters from baseline by visit over time.
- Proportion of participants who lose ≥ 5, ≥10 and ≥15 letters from baseline by visit over time.
- Proportion of participants with BCVA Snellen equivalent of 20/40 or better from baseline over time.
- Proportion of participants with BCVA Snellen equivalent of 20/200 or worse from baseline over time.
- Mean change in OCT central subfield retinal thickness (CST) from baseline to the average of Weeks 60 and 64 and over time.
- Proportion of patients with a ≥ 2-step improvement from baseline on the ETDRS DRSS at Week 52.
- Mean number of intravitreal injections from Day 1 to Week 60, from Week 64 to Week 104, and over the duration of the study.
- Mean time to first re-treatment in the individualized treatment period.
- Distribution of intravitreal injections from Week 16 to Week 104.
- Incidence of ocular and systemic adverse events up to Week 64 and Week 108.
- Systemic anti-drug antibody status over time (in the ADA-evaluable population).

- Systemic pharmacokinetic profile (i.e., systemic exposure) over time (in the PK-evaluable population).

Unless stated otherwise, all analyses described will be performed on the ITT population.

For continuous key secondary efficacy endpoints, the between-group changes from baseline in BCVA at each time point will be computed and compared using t-tests, generalized linear models, mixed effects models, or other approaches as documented in the SAP. In addition, comparisons between groups determined by fixed effects of interest will be performed by analysis of covariance (ANCOVA) in which the dependent variable is the continuous variable of interest at the specified time point, the covariate is the baseline value of the variable of interest. Treatment group as well as stratification variables will be entered as fixed effects. Results of the t-test will be reported as 95% CIs for within group mean change from baseline. Results of ANCOVA will be reported as 95% CI for the difference in adjusted means for the grouping determined by the fixed effects of interest.

For categorical variables, the number and percentage of responders will be presented by treatment group for each time period and will be evaluated among treatment groups using chi-square tests of proportions supplemented with logistic regression models. The distribution of the need for intravitreal injections over the individualized treatment period will be computed and compared using the Kolmogorov-Smirnov test for the equality of distribution functions. The probability of receiving intravitreal injections over time during the individualized treatment period will be compared using a generalized linear model or generalized linear mixed model with appropriate link function (e.g., logit, beta-binomial, etc.).

Additional endpoints and full details on statistical considerations will be provided in the SAP.

9.4.4 Tertiary/Exploratory Endpoint(s)

Exploratory endpoints will be described in the SAP.

9.4.5 Safety Analysis

The safety analysis (using the safety set described in Section 9.3) will use outcomes of all participants who were exposed to study treatment regardless of adherence to the protocol or treatment outcome. Safety analyses will be conducted concurrently with efficacy analyses.

In addition to analyses of ocular safety events, all reported adverse events will be listed by MedDRA term, frequency, severity, association to the study therapy, and treatment group. By-treatment incidence rates will also be calculated for the treatment groups. For certain adverse events, per-injection rates will also be described.

9.4.6 Pharmacokinetic and Biomarker Analysis

PK analyses will be outlined in the PK Analysis Plan; potential exploratory biomarker analyses will be outlined in a biomarker analysis plan.

9.5 Interim Analysis

There is no interim analysis planned for this study.

10.0 APPENDICES WITH SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Appendix 2: Clinical Laboratory Tests

Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Appendix 4: Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreous Cells or Haze

Appendix 5: Unscheduled Safety Assessment Visits

Appendix 6: Contraceptive and Barrier Guidance

Appendix 7: Liver Safety

Appendix 8: Protocol Amendment History

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2 Financial Disclosure and Financial Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements to the appropriate regulatory authorities. In addition, Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor their CRO partner is financially responsible for additional testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor their CRO are financially responsible for further treatment of the participant's disease.

10.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If required by the IRB/EC, participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are re-screened are required to sign a new ICF if it has been more than 30 days from the initial consent date.

The ICF will contain a separate section that addresses the use of remaining samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

Participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant

confidentiality. All records will be kept in a secure storage area with limited access. Upon the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All information provided by the Sponsor, verbally and in writing, is confidential. The Investigator agrees not to disclose any such information without prior written permission of the Sponsor. This document may be disclosed to study personnel under the PI's supervision and to the IRB under the condition that they also agree to maintain its confidentiality. Any supplemental information (e.g., protocol amendment) that may be added to this document is confidential and must also be handled accordingly. The information obtained from the Sponsor may be disclosed to obtain informed consent from participants who wish to participate in the study.

Study documents provided by the Sponsor (protocols, IB, etc.) will be stored appropriately to ensure their confidentiality.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.1.5 Committees Structure

10.1.5.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will monitor the 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. Nominal Type I error penalties for IDMC reviews will be outlined in the SAP.

10.1.6 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 4 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or as required by local regulations.

Investigators must document their review of each laboratory safety report.

Table 4: Protocol KS301P104: Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red blood cell (RBC) Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Hemoglobin A1c
Pregnancy testing	Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[1]			
Other Screening Tests	Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)			

NOTES:

1. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions

10.3.3 The Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator or designee will then record all relevant AE/SAE information.

It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE required form.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The Medical Monitor or other Sponsor representative may contact the PI or investigational site personnel to request additional information regarding the event or to confirm information.

For the purposes of reporting events of infection and inflammation of the eye, the following terms and definitions should be used:

- Iritis: the presence of inflammatory cells in the anterior chamber

- The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for AE reporting purposes.
- Iridocyclitis: the presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: the presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)
- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

Active inflammation in the vitreous should be clinically differentiated from cellular debris from prior episodes of inflammation, hemorrhage, or other causes.

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by dilation and are not red blood cells or white blood cells or the result of any ocular disorder should not be recorded as an AE.

For the purposes of reporting events of elevated intraocular pressure, the following terms and definitions should be used:

- An AE of high IOP after the injection should be recorded as "Increased or Elevated IOP".
- Ocular Hypertension is a syndrome characterized by chronic elevated IOP with no optic nerve damage. Ocular hypertension should not be used to refer to a transient increase in IOP following the injection.
- Glaucoma is a condition with nerve damage, which may or may not have a concomitant high IOP.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The Investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The relationship to the intravitreal injection procedure or to study intervention will be assessed using the following definitions:

- Not Related - There is not a reasonable possibility that the AE is related to the injection procedure or to the study intervention.
- Related - There is a reasonable possibility that the AE is related to the injection procedure or to the study intervention.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology if applicable.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor/medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting are as follows:

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor/Medical Monitor or the SAE coordinator.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting are as follows:

10.4 Appendix 4: Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreous Cells or Haze.

10.4.1 Grading Scales for Anterior Chamber Cells or Flare

The SUN Working Group Grading Scale for Anterior Chamber Cells

Grade	Cells in Field[1]
0	< 1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Abbreviations: SUN = Standardization of uveitis nomenclature.

[1] Field size is a 1 mm by 1 mm slit beam.

Source: (Jabs 2005)

The SUN Working Group Grading Scale for Anterior Chamber Flare

Grade	Cells in Field[1]
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Abbreviations: SUN = Standardization of uveitis nomenclature.

[1] Field size is a 1 mm by 1 mm slit beam.

Source: (Jabs 2005)

10.4.2 Grading Scale for Vitreous Cells

Grade	Description
0	No Cells
½+	1-10
1 +	11-20
2 +	21- 30
3 +	31 - 100
4+	Greater than 100

Source: (Foster 2013)

10.4.3 Grading Scale for Vitreous Haze

Score	Description	Clinical Findings
0	Nil	None
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details slightly hazy
3	Moderate	Posterior pole details very hazy
4	Marked	Posterior pole details barely visible
5	Severe	Fundal details not visible

Source: (Nussenblatt 1985)

10.5 Appendix 5: Unscheduled Safety Assessment Visits

Assessments performed at unscheduled safety visits are at the discretion of the Investigator. The following safety assessments are recommended:

- Vital signs (blood pressure, respiration rate, pulse, temperature);
- Hematology, serum chemistry panel, and coagulation panel;
- Best corrected visual acuity;
- Slit-lamp examination (both eyes);
- Tonometry (both eyes);
- Indirect ophthalmoscopy (both eyes);
- Adverse events;
- Concurrent ocular procedures; and
- Concomitant medications.

The causality of adverse events is to be evaluated by a masked physician.

10.6 Appendix 6: Contraceptive and Barrier Guidance

10.6.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal Female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6.2 Contraception Guidance

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

2) For women of childbearing potential: agreement to remain as abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and [redacted]

    a. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.

    b. Contraception methods that do not result in a failure rate of <1% per year such as cap, diaphragm, or sponge with spermicide, or male or female condom with or without spermicide, are not acceptable.

    c. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

3) For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

    d. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and [redacted] the last dose of study intervention. Men must refrain from donating sperm during this same time period.

10.6.3 Collection of Pregnancy Information

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive any study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.7 Appendix 7: Liver Safety

Investigators must report to the Sponsor immediately (within 24 hours) the following laboratory findings as an AE indicative of severe liver injury (as defined by Hy's Law):

- Treatment-emergent 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)
- Treatment-emergent ALT or AST more than 3 times the ULN in combination with clinical jaundice

The most appropriate diagnosis or (if the diagnosis cannot be established) the abnormal laboratory values should be recorded in the eCRF.

10.8 Appendix 8: Protocol Amendment History

Table 5: Protocol KS301P104: Amendment History

Version	Version Date	Description
2.0	15 March 2022	Changes from Version 1.0 include the following: • [redacted] and • Change in timing of the primary efficacy endpoint assessment.
1	31 July 2020	Original Protocol

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