CLINICAL STUDY PROTOCOL

Protocol Title:	A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)
Protocol Number:	KS301P106
Version Date:	17 May 2021
Amendment Number:	1.1
Supersedes:	Version 1.0
Test Product:	KSI-301
Brief Title:	A Study to Evaluate the Efficacy and Safety of KSI-301 Compared with Sham Treatment in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)
Study Phase:	3
Study Acronym /Name:	GLOW
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:	2020-001064-29

CONFIDENTIAL

The information in this document is confidential and may not be disclosed to others in whole or in part without express, written authorization from Kodiak Sciences Inc., except to the extent necessary to obtain informed consent from persons receiving the investigational drug or for discussions with local regulatory authorities, institutional review boards (IRB), or persons participating in the conduct of the trial.

FOR MEDICAL EMERGENCIES CONTACT:

[redacted]

PROTOCOL APPROVAL – SPONSOR SIGNATORY

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

Protocol Number: KS301P106

Version Date: 17 May 2021

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

Protocol Number: KS301P106

Version Date: 17 May 2021

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
ANCOVA	Analysis of covariance
APD	Afferent pupillary defect
AST	Aspartate aminotransferase
ASNV	Anterior segment neovascularization
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity as measured on ETDRS chart
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of federal regulations
CMH	Cochran-Manzel Haenszel
CIOMS	Council for international organizations of medical sciences
CONSORT	Consolidated standards of reporting trials
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CST	Central subfield thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity scale
EC	Ethics committee
ECG	Electrocardiograph
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
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
HIPAA	Health insurance portability and accountability act
HRT	Hormonal replacement therapy
IB	Investigator 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
IRMA	Intraretinal microvascular abnormalities
IRT	Interactive response technology
ITT	Intent to treat
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
ME	Macular edema
MedDRA	Medical dictionary for regulatory activities
NAB	Neutralizing antibody
NIMP	Non-investigational medical product
NME	New molecular entity
NOAEL	No observed adverse effect level
NPDR	Non proliferative diabetic retinopathy
NVD	Neovascularization of the disc
NVE	Neovascularization elsewhere
OECD	Organisation for Economic Co-operation and Development
OTC	Over the counter
PDR	Proliferative Diabetic Retinopathy
PI	Principal investigator
PK	Pharmacokinetic
PPS	Per protocol
PRP	Panretinal photocoagulation
Q4W	Once every 4 weeks
Q12W	Once every 12 weeks
Q24W	Once every 24 weeks
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-A	Schedule of Activities-A
SoA-B	Schedule of Activities-B
SPC	Scars of photocoagulation for PDR or severe NPDR
STC	Sight-threatening complications
SUN	Standardization of uveitis nomenclature
SUSAR	Suspected unexpected serious adverse reactions
ULN	Upper limits of normal

VA	Visual acuity
VB	Venous beading
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: KS301P106</td><td>Version: 1.1</td><td rowspan="4">For National Authority Use Only</td></tr>
<tr><td colspan="2">IND Number: 136167</td><td>EudraCT Number: 2020-001064-29</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, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)</td></tr>
<tr><td colspan="4">Brief Title:
A Study to Evaluate the Efficacy and Safety of KSI-301 Compared with Sham Treatment in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)</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). KSI-301 has an extended ocular half-life, which may allow an infrequent treatment frequency suitable for patients with NPDR.</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 3.5 years</td></tr>
</table>

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Title of Study:

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

Objectives and Key Endpoints:

Objectives	Key Endpoints
Primary	
To demonstrate that KSI-301 5 mg is superior to sham treatment, with respect to proportion of eyes improving ≥2 steps on Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48.	• The proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48.
Secondary	
To evaluate the effect of KSI-301 5 mg in decreasing the incidence and delaying the onset of vision-threatening complications of diabetes compared to sham treatment.	• Time to development of and proportion of eyes developing any of the following from baseline over time (individually and as a composite): - Proliferative diabetic retinopathy (PDR) or anterior segment neovascularization (ASNV); - Vitreous hemorrhage or tractional retinal detachment believed to be due to proliferative diabetic retinopathy; or - Diabetic macular edema (DME).
To evaluate the efficacy of KSI-301 5 mg compared to sham treatment.	• Proportion of eyes improving ≥2 or ≥3 steps on DRSS from baseline over time. • Proportion of eyes worsening ≥2 or ≥3 steps on DRSS from baseline over time.
To evaluate the safety and tolerability of KSI-301 5 mg compared to sham treatment.	• Incidence of ocular and systemic adverse events over time.
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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A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)

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 superior to sham treatment, with respect to the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48 in participants with moderately severe to severe NPDR.

One eye per participant will be enrolled in the study.

As shown in Section 1.2.1 (Schema A), participants will be randomized 1:1 into one of two treatment arms: (i) KSI-301 5 mg Q24W or (ii) sham.

Randomization will be stratified by [redacted] Treatment group 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.

Sham injections will be administered for masking purposes. To preserve masking, two Investigators are required for this study. The masked Investigator will be responsible for the ocular 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.

The overall duration of the study is approximately 2 years (100 weeks) after the last participant is randomized to the study. Participant duration is defined as the date a signed written informed consent is provided through the last safety follow-up visit at Week 100; thus, participant duration is approximately 103 weeks and includes a screening period of up to 21 days (Days -21 to -1), a treatment period of approximately 92 weeks (Day 1 to Week 92), a safety/efficacy assessment at Week 96, and a final safety follow-up at Week 100 [redacted] The primary endpoint will be assessed at Week 48; secondary endpoints for efficacy will be assessed at Weeks 48 and 96.

As shown in Section 1.2.2 (Schema B), participants in either treatment group (KSI-301 5 mg or sham) who develop DME, PDR, and/or ASNV in the Study Eye shall be treated with KSI-301 for those complications, according to criteria specified in the protocol. If treatment is administered, DRSS values after the development of the vision-threatening complication will be censored.

Number of Participants Planned:	**Gender:**	**Age:**
Approximately 240	Male or female	Adults ≥18 years of age

Diagnosis and Main Criteria for Eligibility:

- Participants with moderately severe to severe NPDR (ETDRS DRSS levels 47 and 53 on color fundus photographs as evaluated by the reading center) in the Study Eye, who have not previously received intravitreal medications for diabetic retinopathy (DR), and in whom pan-retinal photocoagulation (PRP) can be safely deferred for at least 6 months per the Investigator.
- Participants with Type 1 or Type 2 diabetes mellitus and HbA1c of ≤12%.

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Total Participant Duration:	**Duration of Treatment:**
103 weeks	92 weeks

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

Treatment Group A (Group A)

- KSI-301 5 mg via intravitreal injection on Day 1, Week 8, Week 20 and then once every 24 weeks (Q24W) through Week 92.

Study Intervention (Sham Injection):

Treatment Group B (Group B)

- Sham injection on Day 1, Week 8, Week 20, and then once every 24 weeks (Q24W) through Week 92.

Participants in either treatment arm (KSI-301 5 mg or sham) who develop DME, PDR, or ASNV shall be treated with KSI-301 5 mg once every 4 weeks for two doses and at Q12W intervals thereafter. More frequent treatment with KSI-301 5 mg and/or subsequent PRP are at the discretion of the Investigator.

Efficacy Evaluation:

Unless stated otherwise, all efficacy analyses will be performed on the intent to treat (ITT) population. The primary endpoint is the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48. The primary assessment of efficacy will be based on a pairwise comparison in the proportion of eyes improving ≥2 steps on DRSS between the KSI-301 5 mg treatment group and the sham group. DRSS score is based on fundus photographs graded by the masked independent reading center. Other evaluations include time from baseline to development of and proportion of eyes developing PDR, DME, and/or ASNV; proportion of eyes with ≥2 or ≥3 step improvement or worsening in DRSS; change in BCVA over time; and change in retinal thickness assessed using spectral domain optical coherence tomography (SD-OCT). Secondary endpoints for efficacy will be assessed at Week 48, Week 96, and, if applicable, over time. 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 assessment should be reported. After initiation of study intervention (Day 1), all adverse event (AE) and SAE information will be collected until the final safety follow-up visit at Week 100 or the Early Termination (ET) visit if applicable, as specified in the SoA-A (Section 1.3.1) and the SoA-B (Section 1.3.2). 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 interventions (KSI-301) will be measured, as specified in the SoA-A (Section 1.3.1) and the SoA-B (Section 1.3.2). Blood samples will also be analyzed for anti-drug antibodies. For exploratory purposes, [redacted]

Statistical Methods:

The study hypothesis is that the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48 among participants treated with KSI-301 5 mg will be superior to that in the sham group.

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

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

Analysis of data for the Week 48 primary and secondary endpoints will be performed when all participants have either completed the Week 48 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. Likewise, analysis of data for the Week 96 secondary endpoints and for safety will be performed when all participants have either completed the Week 100 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:

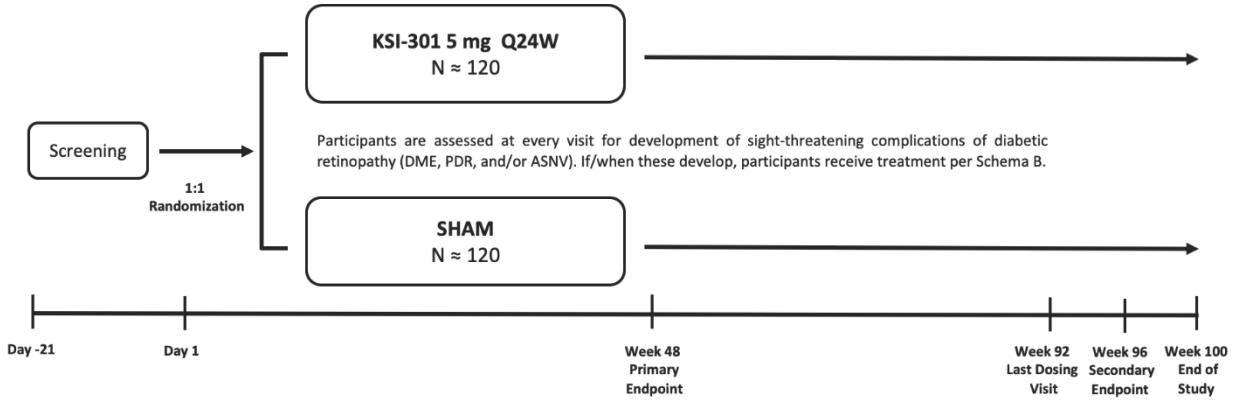
An Independent Data Monitoring Committee (IDMC) will monitor the study conduct and participant safety on an ongoing basis.

Date of Protocol/ Amendment:	17 May 2021

1.2 Schema

1.2.1 Schema A: All Participants

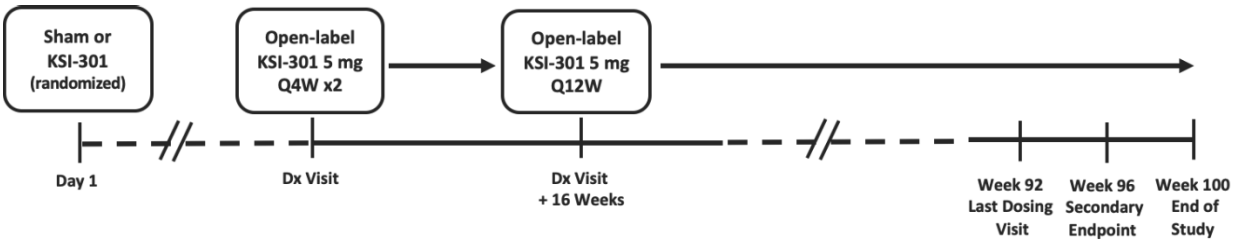
Schema A applies to all participants unless they are diagnosed with DME, PDR, and/or ASNV in their Study Eye during the study. Upon diagnosis of these sight-threatening complication(s) of DR in their Study Eye, Schema B applies.



Abbreviations: ASNV = anterior segment neovascularization; DME = diabetic macular edema; PDR = proliferative diabetic retinopathy; Q24W = once every 24 weeks.

1.2.2 Schema B: Participants Who Develop Sight-threatening Complications of Diabetic Retinopathy

Schema B applies to all participants who are diagnosed with DME, PDR, and/or ASNV in their Study Eye during the study.



Abbreviations: ASNV = anterior segment neovascularization; DME = diabetic macular edema; Dx Visit = the first study visit where a sight-threatening complication of diabetic retinopathy (DME, PDR, and/or ASNV) is diagnosed; PDR = proliferative diabetic retinopathy; Q4W = once every 4 weeks; Q12W = once every 12 weeks.

1.3 Schedule of Activities (SoA)

1.3.1 SoA-A

The following schedule of activities, SoA-A, shall be followed for all visits unless a participant is diagnosed with sight-threatening complication(s) of DR, as defined in Table 3 (Section 4.1.3.1), in their Study Eye. Upon diagnosis of sight-threatening complication(s) of DR in their Study Eye, participants shall then follow SoA-B (Section 1.3.2) instead of SoA-A.

Visit	**Screening**	**Day 1**	**Week 8**	**Week 20**	**Week 32**	**Week 44**	**Week 48**	**Week 56**	**Week 68**	**Week 80**	**Week 92**	**Week 96/ET**	**Week 100[12]**
Visit Windows (Days)	**D-21 to D-1**		**+/-7**	**+/-14**	**+/-14**	**+/-14**	**+/-7**	**+/-14**	**+/-14**	**+/-14**	**+/-14**	**+/-7**	**+/-7**
Informed Consent	X												
Demographics	X												
Medical & Ocular History	X												
Inclusion/Exclusion Criteria Review	X	X											
Concomitant Medication Review[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE Review[2]		X	X	X	X	X	X	X	X	X	X	X	X
General Assessments													
Vital Signs[3]	X	X		X			X		X			X	
Laboratory[4]	X						X					X	
Plasma ADA/NAB Samples (pre-injection)		X	X		X		X		X			X	
Plasma PK/Biomarker Samples (pre-injection)		X	X		X		X		X			X	
Pregnancy Test[5] (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[6]													
BCVA ETDRS (4 meters)[7]	X	X	X	X	X	X	X	X	X	X	X	X	
Ophthalmic Exam (Slit lamp, IOP[8], dilated indirect ophthalmoscopy)	X	X	X	X	X	X	X	X	X	X	X	X	
SD-OCT[9]	X		X	X	X	X	X	X	X	X	X	X	
Fundus Photos[9]	X		X	X	X	X	X	X	X	X	X	X	
Fluorescein Angiogram[9]	X			X			X		X			X	
Randomized study treatment (KSI-301 or sham) per IRT Designation[10]		X	X	X		X			X		X		
Post-injection Assessments (vision check, IOP[8])[11]		X	X	X		X			X		X		

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

[1] Record any concomitant medication used by the participant within 30 days prior to Day 1. Procedural medications administered (e.g., dilating drops, fluorescein) will not be recorded.

[2] After informed consent has been obtained but prior to initiation of study intervention, only SAEs caused by a protocol-mandated assessment should be reported. After initiation of study intervention (Day 1), all AEs will be reported until the final study visit or the ET visit if applicable. See Section 8.3.1.

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

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

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

[6] Ophthalmic assessments will be performed in both eyes at Screening, Week 48 and Week 96, and only in the Study Eye at all other timepoints.

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

[8] Method used to measure IOP must remain consistent throughout study.

[9] It is mandatory that the same model of device is used for the entire duration of the study.

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

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

[12] [redacted]

1.3.2 SoA-B

The following schedule of activities, SoA-B, shall be followed once a participant is diagnosed with sight-threatening complication(s) of DR, as defined in Table 3 (Section 4.1.3.1), in their Study Eye. Upon diagnosis of sight-threatening complication(s) of DR in their Study Eye, participants will be treated with open-label KSI-301 5 mg, regardless of the treatment group that they were originally randomized into, and SoA-B will be followed instead of SoA-A. Additional details are provided in Section 4.1.3.1.

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

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

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

[2] Record any concomitant medication used by the participant within 30 days prior to Day 1. Procedural medications administered (e.g., dilating drops, fluorescein) will not be recorded.

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

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

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

[6] Ophthalmic assessments will be performed in both eyes at Week 96, and only in the Study Eye at all other timepoints.

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

[8] Method used to measure IOP must remain consistent throughout study.

[9] It is mandatory that the same model of device is used for the entire duration of the study.

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

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

[12] Continue visits Q12W until Week 92.

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

2.0 INTRODUCTION

KSI-301 is a novel, potent, long-acting biopharmaceutical that inhibits vascular endothelial growth factor (VEGF) and is being developed to treat non-proliferative diabetic retinopathy (NPDR). KSI-301 has an extended ocular half-life, which may offer the potential for participants to experience a longer interval between consecutive intravitreal injections compared to existing anti-VEGF therapies.

2.1 Study Rationale

Although substantial improvements in diabetic retinopathy (DR) severity have been demonstrated in patients with NPDR following treatment with intravitreal VEGF inhibitors, aflibercept and ranibizumab, the use of intravitreal VEGF inhibitors for the treatment of NPDR is not considered standard of care (Flaxel 2020). NPDR is a slowly progressive asymptomatic condition that affects adults of a working age. Approved intravitreal VEGF inhibitors require a high treatment frequency for improving the severity of NPDR, and the burden of treatment is such that they are not considered standard of care treatment for NPDR in the absence of sight-threatening complications such as diabetic macular edema (DME) or proliferative diabetic retinopathy (PDR) (Flaxel 2020). There is a substantial medical need for a more durable therapeutic option that allows a lower treatment frequency that may be more suitable as a treatment for NPDR. 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-CL101, the safety and efficacy outcomes of participants with diabetic macular edema treated with KSI-301 5 mg have supported a prolonged (2 to 6 months) treatment interval. Study KS301P106 has been designed to evaluate extended treatment intervals of KSI-301 5 mg in participants with NPDR.

2.2 Background

2.2.1 Non-proliferative Diabetic Retinopathy

Diabetes mellitus (diabetes) is a chronic disease that exerts pathologic effects on multiple organ systems, including the microvasculature of the retina. All patients with diabetes are at risk of developing DR, a progressive condition that can result in severe vision loss. DR is a leading cause of vision loss in the working-age population and is classified in routine clinical practice according to the International Clinical Diabetic Retinopathy Disease Severity Scale in order of increasing severity (Flaxel 2020; Wu 2013), as follows:

a) No apparent retinopathy (no diabetic fundus changes);

b) Mild NPDR (few microaneurysms);

c) Moderate NPDR (microaneurysms, intraretinal hemorrhages or venous beading that do not reach the severity of the reference photographs);

d) Severe NPDR (fundus changes consistent with reference photographs); and

e) PDR (neovascularization of the disc, retina, iris, and angle; vitreous hemorrhage; or tractional retinal detachment).

In clinical trials, DR severity is described according to the well-characterized and validated ETDRS Diabetic Retinopathy Severity Scale (DRSS), which divides the above clinical scale into additional, more discrete categories based on standardized grading of retinal color fundus photographs.

Table 1: Abbreviated Summary of ETDRS Diabetic Retinopathy Severity Scale for Individual Eyes

Level	Severity
10	DR absent
20	Micro-aneurisms only
35	Mild NPDR (HE, SE, and/or mild H)
43	Moderate NPDR (mild IRMA or moderate H)
47	Moderately severe NPDR (mild VB, moderate IRMA, or severe H)
53	Severe or very severe NPDR (moderate/severe VB, severe IRMA, and/or very severe H)
60	Scars of photocoagulation for PDR or severe NPDR (SPC)
61	Mild PDR
65	Moderate PDR
71, 75	High risk PDR

Abbreviations: H = Hemorrhage; HE = hard exudates; SE = soft exudates; IRMA = intraretinal microvascular abnormalities; VB = venous beading; DR = diabetic retinopathy; NPDR = non proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

Levels 35-53 require presence of microaneurysms in addition to specified abnormalities. The definition for each level assumes that the definition for any higher level is not met. Severities of abnormalities are defined in References 2 and 6.

Source: Adapted from: Supplementary Appendix from (ACCORD Study Group 2010).

According to the World Health Organization, the global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014. Concomitant with the rising prevalence of diabetes, the prevalence of diabetic retinopathy (DR) in patients with diabetes is also increasing. DR and its clinical sequelae are responsible for vision loss in as many as 2.6-3.7 million patients with diabetes worldwide (Cheloni 2019). The risk of DR increases with diabetes duration. The current global estimate of any DR prevalence among patients with diabetes is approximately 35% (Leasher 2016).

2.2.2 Vascular Endothelial Growth Factor

VEGF stimulates vascular endothelial cell growth and induces vascular permeability. Several mechanisms are involved in the regulation of VEGF gene expression, and hypoxia is a key factor that induces VEGF production. In addition, changes in glucose levels also contribute to VEGF expression and intraocular VEGF levels are elevated in patients with diabetes. In nonclinical

models, over-expression of VEGF leads to retinal pathologic events common in diabetic macular edema and DR. For example, retinal VEGF mRNA and protein levels were increased in rats with background diabetic retinopathy and correlated with the breakdown of the blood-retinal barrier. In addition, experimental injections of VEGF protein into non-human primate eyes recapitulate the DR phenotype including nonperfusion, microaneurysm formation, and preretinal neovascularization. (Aiello 1994; Durham 2011; Lu 1999; Tolentino 2002)

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. Phase 3 studies of intravitreal administration of ranibizumab and aflibercept in patients with DR demonstrated clinically significant improvements in DRSS and lower rates of DRSS worsening relative to sham control. (Bressler 2017; Stewart 2017; Wells 2015; Wells 2016)

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 [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.

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 Investigator's Brochure (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 NPDR, benefits from a well-documented mechanism action in retinal vascular disease (Homayouni 2009). The efficacy and safety of commercially available intravitreal VEGF inhibitors in retinal vascular disease is also well-documented and established. 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 other anti-VEGF biologics such as ranibizumab or aflibercept.

Patients with NPDR are treated for underlying hyperglycemia, hyperlipidemia, and hypertension as clinically indicated. The adoption of approved anti-VEGF therapies for NPDR is constrained 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 KSI-301's extended ocular half-life and less frequent dose regimens. Thus, KSI-301 may provide clinically relevant benefits as an intravitreal therapy for NPDR.

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 2. Risks associated with COVID-19 are discussed below in Section 2.3.2.1.

Table 2: Protocol KS301P106: 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 serious adverse events (SAEs) related to inflammatory reactions can occur. Additional details are provided in IB Section 5.4.2.1.	Participants 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 ranibizumab 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.	Participants 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). Participants 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). Participants 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 ranibizumab or any ingredient of KSI-301 are excluded from this study (Section 5.2.2).

Table 2: Protocol KS301P106: Risk Assessment (Cont'd)

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). Participants 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). Participants 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. Studies suggest that intravitreal anti-VEGF treatment improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME (Lim 2020). This trial affords participants the opportunity to potentially receive anti-VEGF therapy for their NPDR and potential sight-threatening complications of DME, PDR, and/or anterior segment neovascularization (ASNV) that develop during the study period. Measures that prioritize trial participant safety and data integrity have been developed in consideration of local guidelines.

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 of escalation of the pandemic during this trial and local circumstances leading 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 NPDR 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 adverse events (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 eyes with moderately severe to severe NPDR, intravitreal anti-VEGF treatment improved diabetic retinopathy and prevented disease progression (Lim 2020). 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 superior to sham treatment, with respect to proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48.	• The proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48.
Secondary	
To evaluate the effect of KSI-301 5 mg in decreasing the incidence and delaying the onset of vision-threatening complications of diabetes compared to sham treatment.	• Time to development of and proportion of eyes developing any of the following from baseline over time (individually and as a composite): - PDR or ASNV; - Vitreous hemorrhage or tractional retinal detachment believed to be due to proliferative diabetic retinopathy; or - DME.
To evaluate the efficacy of KSI-301 5 mg compared to sham treatment.	• Proportion of eyes improving ≥2 or ≥3 steps on DRSS from baseline over time. • Proportion of eyes worsening ≥2 or ≥3 steps on DRSS from baseline over time.
To evaluate the safety and tolerability of KSI-301 5 mg compared to sham treatment.	• Incidence of ocular and systemic adverse events over time.
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 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 dosing of KSI-301 5 mg administered by intravitreal injections in participants with treatment-naïve NPDR.

The overall duration of the study is approximately 2 years (100 weeks) after the last participant is randomized to the study. Participant duration is defined as the date a signed written informed consent is provided through the last safety follow-up visit at Week 100; thus, participant duration is approximately 103 weeks and includes a screening period of up to 21 days (Days -21 to -1), a treatment period of approximately 92 weeks (Day 1 to Week 92), a safety/efficacy assessment at Week 96, and a final follow-up for safety assessments at Week 100 [redacted]. The primary endpoint will be assessed at Week 48; secondary endpoints for efficacy will be assessed at Weeks 48 and 96.

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

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

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

Randomization will be stratifie [redacted] Additional details of the randomization methods are described in the statistical analysis plan (SAP).

Participants who develop sight-threatening complications of DME, PDR, or ASNV in the study eye will be managed as outlined in Section 4.1.3.1.

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 within 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 rescreened up to one additional time at the discretion of the Investigator and in consultation with the Sponsor (Section 5.4). Instructions for participants who meet all eligibility criteria at the Screening visit but do not meet the BCVA eligibility criteria when they return for the planned Day 1 visit are provided in Section 5.5.

When rescreening tests and procedures have been completed and results are available indicating the participant is eligible for study participation, the participant may be enrolled. When rescreening a participant, a new screening/enrollment number should be selected to ensure there is an audit trail for the screen failed participant.

4.1.2 Treatment Period

Participants in this study will be treated until Week 92 and will have additional efficacy and/or safety follow-up visits at Weeks 96 and 100, 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

All participants will be treated starting on Day 1 through Week 92 according to their respective treatment group. The IRT will determine the dosing schedule and adjust it in consideration of missed visits, out of window visits, and missing data during a visit. If a visit is missed at which study treatment is scheduled to be administered, the missed dose should be made up as close to the originally scheduled visit as possible using an unscheduled visit. Adjustments to study intervention due to development of sight-threatening complications of DR are described in Section 4.1.3.1.

As shown in the dosing regimen schematic provided in Figure 1, participants will be treated according to the group to which they were randomized, as follows:

- Group A - KSI-301 5 mg via Intravitreal Injection:

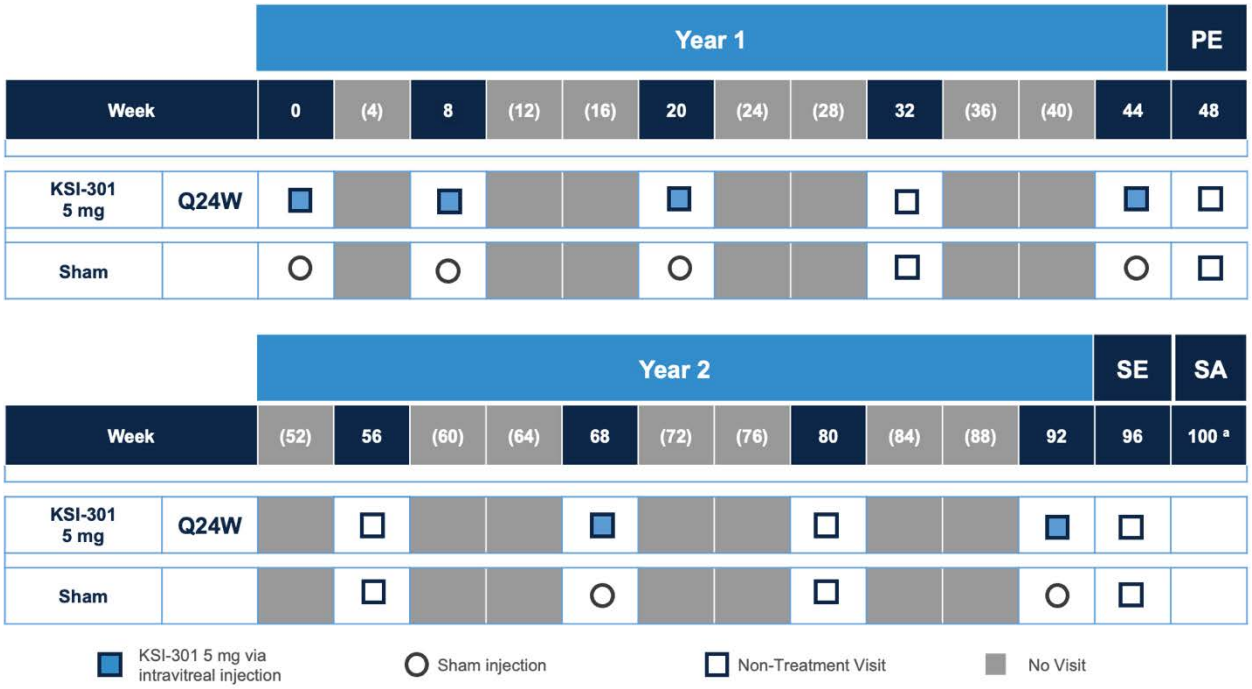
  Intravitreal KSI-301 5 mg injection will be administered on Day 1, Week 8, Week 20, Week 44, Week 68, and Week 92.

- Group B - Sham Injection:

  To preserve study masking, sham injections are administered to Group B participants at visits in which KSI-301 is administered to Group A participants. Thus, sham injections will be administered on Day 1, Week 8, Week 20, Week 44, Week 68, and Week 92.

For all study participants, non-treatment study visits will occur on Week 32, Week 48, Week 56, Week 80, and Week 96. A final safety assessment will occur on Week 100 and will be done via telephone call for all participants, except in WOCBP, in which case a site visit is required to administer a pregnancy test.

Figure 1: Protocol KS301P106: Masked Dosing Regimens by Week



Abbreviations: PE = primary endpoint; Q24W = once every 24 weeks; SA = safety assessment; SE = secondary endpoint.

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

4.1.3.1 Sight-threatening Complications of Diabetic Retinopathy in the Study Eye

Definitions and Documentation of Sight-threatening Complications

In this study, sight-threatening complications of DR in the Study Eye include DME, PDR, and/or ASNV. The protocol definition of each sight-threatening complication in the Study Eye is provided in Table 3. The diagnosis of DME, PDR, and/or ASNV will be made by the masked Investigator.

Because the treatment schedule changes for participants who develop these complications (as described below), it is very important that the imaging and/or clinical documentation described in Table 3 is collected at the time of diagnosis. It is also very important that the color fundus photographs are submitted to the reading center, because the color fundus photographs from this visit will be used for DRSS endpoint assessment.

Table 3: Protocol KS301P106: Sight-threatening Complications of Diabetic Retinopathy: Definitions and Required Documentation for Initial Diagnosis

Sight-threatening Complication	Definition	Required Documentation
Diabetic Macular Edema (DME)	• CST of ≥320 microns on SD-OCT **and** at least 5-letter decrease in best corrected visual acuity from Day 1 due to DME (as assessed by the Investigator); or • CST of ≥350 microns on SD-OCT due to DME (as assessed by the Investigator).	A fundus photograph and OCT (Section 8.1.6) of the Study Eye ***must*** be obtained prior to the first treatment of DME.
Proliferative Diabetic Retinopathy (PDR)	• Neovascularization of the disc (NVD) or neovascularization elsewhere (NVE); • Vitreous hemorrhage; or • Pre-retinal hemorrhage.	PDR ***must*** be documented with fundus photography (Section 8.1.6) [and, optionally, fluorescein angiography (Section 8.1.8)] of the Study Eye prior to initiation of the first treatment of PDR.
Anterior segment neovascularization (ASNV)	• Neovascularization of the iris (at least two cumulative clock hours); • Neovascularization in the iridocorneal angle (as assessed clinically by gonioscopy); or • Neovascular glaucoma.	A fundus photograph of the Study Eye ***must*** be obtained prior to the first treatment of ASNV. ASNV **must** be documented by clinical exam. Anterior segment photographic documentation is preferred if possible, but not required.

Treatment of Sight-threatening Complications of Diabetic Retinopathy

Participants who develop any of the sight-threatening complications of DR in the Study Eye that are described in Table 3 will be treated with open-label KSI-301 5 mg, irrespective of the treatment group that they were originally randomized into (KSI-301 5 mg or sham). The original treatment group randomization will remain masked throughout the study.

At the visit that a sight-threatening complication of DR (DME, PDR and/or ASNV) is diagnosed (i.e., the "Dx Visit"), treatment with open-label KSI-301 5 mg will be initiated. Starting at the Dx Visit, participants will no longer follow the study visits and assessments outlined in Section 1.3.1 (SoA-A), nor receive further masked treatments. Instead, they will follow the study visits and assessments outlined in Section 1.3.2 (SoA-B), which is specific to the participants who develop DME, PDR, and/or ASNV.

As shown in Figure 2, treatment of DME, PDR, and/or ASNV will consist of the following:

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

  More frequent visits and more frequent treatments with KSI-301 5 mg and/or pan-retinal photocoagulation (PRP) are at the discretion of the Investigator if the sight-threatening complication(s) as described in Table 3 are still present. Treatment with KSI-301 5 mg may not be given more often than monthly (28 ± 7 days).

End of Study Considerations

For participants who develop any of the sight-threatening complications described in Table 3, the following shall be considered:

- Participants shall not receive any treatment with KSI-301 5 mg after Week 92 (i.e., 92 weeks after the day of randomization (Day 1)).
- Weeks 96 and 100 (relative to the day of randomization (Day 1)) include final safety assessments that are mandatory and shall also be conducted according to the SoA-B (Section 1.3.2).

Figure 2: Protocol KS301P106: Dosing Regimen by Week for All Participants Who Develop Sight-threatening Complication(s) in the Study Eye

	Q4W (± 7 days)		Q12W (± 14 days)			SE	SA
Week	**Dx Visit**	**Dx Visit + 4 Weeks**	**Dx Visit + 16 Weeks**	**Dx Visit + 28 Weeks**	**…**	**96**	**100 [b]**
KSI-301 5 mg [a]	■	■	■	■	■	□	□

■ KSI-301 5 mg via intravitreal injection □ Non-treatment Visit

Abbreviations: Dx Visit = the first study visit where a sight-threatening complication of diabetic retinopathy (DME, PDR, and/or ASNV) is diagnosed; Q4W = once every 4 weeks; Q12W = once every 12 weeks; SA = safety assessment; SE = secondary endpoint.

[a] *All* participants who develop sight-threatening complication(s) of DME, PDR, and/or ASNV will be treated with open-label KSI-301 5 mg, irrespective of the treatment group that they were originally randomized into. The participant's 'as randomized' treatment group will remain masked. Participants shall not receive any KSI-301 5 mg dose for sight-threatening complications after Week 92.

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

4.1.3.2 Sight-threatening Complications in the Fellow Eye (non-Study Eye)

Treatment of DME, PDR, or ASNV in the fellow eye may be conducted at any time and at the discretion of the Investigator (Section 6.8).

4.2 Scientific Rationale for Study Design

This is a randomized, sham-controlled, double-masked, multi-center, Phase 3 study to evaluate the efficacy and safety of intravitreal KSI-301 in participants with moderately severe to severe treatment-naïve NPDR. A randomized, double-masked design minimizes bias and is well-established for demonstrating the safety and efficacy of an investigational treatment. The rationale for other key design features is provided below.

4.2.1 Choice of Population

This study will enroll participants with moderately severe to severe NPDR (DRSS levels 47 and 53), who have not previously received intravitreal medications for DR in the study eye.

KSI-301 is being evaluated as a first-line anti-VEGF medicinal product to treat NPDR. Thus, participants must *not* have had prior use of an approved or investigational treatment (e.g., anti-VEGF or intraocular steroids) for DR in the Study Eye. Enrollment of participants who have not previously received intravitreal medications for DR in the study eye helps minimize biases inherent in the inclusion of participants who have failed prior lines of therapy.

Moderately severe to severe NPDR (DRSS levels 47 and 53) is a disease level that is most amenable to anti-VEGF therapeutic intervention (Ip 2012), while not meeting the threshold of alternative therapeutic interventions (e.g., panretinal photocoagulation in the case of proliferative DR) (Flaxel 2020). Additionally, and importantly, patients with moderately severe to severe NPDR are at higher risk of sight-threatening DR complications than patients with earlier stages of disease.

4.2.2 Choice of Sham Control

A sham comparator was selected for this trial to demonstrate that treatment with KSI-301 5 mg is superior to standard of care for NPDR, which includes standard-of-care therapeutics for treatment of the patient's underlying hyperglycemia, hyperlipidemia, and hypertension due to diabetes, as clinically indicated. Intravitreal anti-VEGF treatment has improved diabetic retinopathy and prevented disease progression in eyes with moderately severe to severe NPDR in patients without DME (Lim 2020). However, the regulatory status of intravitreal anti-VEGFs as a treatment for NPDR is not globally uniform, and, even more importantly, anti-VEGF has not been established as standard of care therapy for NPDR. For example, ranibizumab and aflibercept are both approved in the US for the treatment of DME and DR (NPDR and DR), however in Europe, only ranibizumab is approved for PDR, and neither is approved in Europe for NPDR. Furthermore, in the US where the intravitreal anti-VEGFs are approved for the treatment of adult patients with DR, they are not standard of care for NPDR (Flaxel 2020).

Hence, the choice of sham comparator does not deprive participants in the control group of access to accepted, standard-of-care therapy. As described in Section 4.1.3.1, all participants with progression of NPDR to the sight-threatening complications of DME, PDR, or ASNV will be identified and treated with KSI-301.

4.2.3 Choice of Primary Endpoint and Analysis

The primary endpoint, the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48, as measured using color fundus photographs graded by an independent, central reading center, was selected based on precedent for Phase 3 studies in NPDR (Lim 2020).

4.2.4 Choice of Duration of Treatment and Follow-up

The duration of treatment in this study will be approximately 92 weeks. The primary endpoint will be assessed at Week 48; secondary endpoints for efficacy will be assessed at Week 48, Week 96, and over time. These endpoints and associated duration of treatment were selected based on precedent for Phase 3 trials in NPDR (Lim 2020).

The choice of a safety follow-up interval of 8 weeks after the last dose is based on the expected duration of effect for KSI-301.

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 aflibercept 2 mg. 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 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. Interim efficacy data from 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. The dosing regimen of KSI-301 5 mg intravitreal injection at Day 1, Week 8, Week 20, and every 24 weeks thereafter through Week 92 was selected in consideration of the increased durability of KSI-301 relative to existing intravitreal anti-VEGF therapies that have been studied in patients with NPDR.

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 studies of [redacted]

4.3.2 Sham Injection Rationale

Sham injections are used as a comparator to KSI-301 and to preserve study masking and minimize bias. Additional details are provided in Section 4.2.2.

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 (ET) 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 100 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 group 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, are not permitted.

Inclusion/exclusion criteria (Sections 5.1 and 5.2) will be assessed at Screening and on Day 1 to determine a participant's eligibility for the study. Instructions for participants who meet all eligibility criteria at the Screening visit but do not meet the BCVA and/or SD-OCT CST eligibility criteria when they return for the planned Day 1 visit are provided in Section 5.5.

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, ocular inclusion criteria will be confirmed or assessed by the independent, masked image reading center.

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

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

5.1.2 General Inclusion Criteria

3. Male or female ≥18 years of age.
4. 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.

5. Type 1 or 2 diabetes mellitus and HbA1c of ≤12%.
6. 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 for at least 90 days after the last dose of study intervention.
    a. A woman is considered of childbearing potential if she is post-menarchal, has not reached a post-menopausal 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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.
7. 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 and for at least [redacted] after the last dose of study intervention. Men must refrain from donating sperm during this same time period.
8. 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 or 5.2.2 apply.

5.2.1 Ocular Exclusion Criteria

Where applicable, ocular exclusion criteria will be determined by an independent, masked image reading center.

1. Presence of center-involved DME in the study eye, defined for this purpose as CST of ≥320 microns on SD-OCT (Heidelberg Spectralis or equivalent value on other OCT instruments).
2. Prior PRP in the Study Eye.

3. Current anterior segment neovascularization (ASNV), vitreous hemorrhage, or tractional retinal detachment in the Study Eye.
4. Prior intravitreal anti-VEGF treatment in the Study Eye for DR or DME.
5. Prior intravitreal or periocular steroid in the Study Eye for DR or DME.
6. Prior use of an investigational intravitreal treatment for DR or DME in the Study Eye.
7. History of vitreoretinal surgery in the Study Eye
8. History of retinal detachment or treatment or surgery for retinal detachment in the Study Eye.
9. History of cataract surgery in the Study Eye within 2 months of screening.
10. History of YAG laser capsulotomy in the Study Eye within 2 months of screening.
11. Uncontrolled glaucoma (defined as intraocular pressure ≥25 mmHg despite treatment with antiglaucoma medication) in the Study Eye.
12. History of glaucoma-filtering surgery (trabeculectomy or tube shunt) in the Study Eye.
13. History of uveitis in either eye.
14. Significant media opacities, including cataract, in the Study Eye that might interfere with visual acuity, assessment of safety, OCT, or FP.
15. Cataract in the Study Eye that in the judgment of the Investigator is expected to require surgical extraction within 12 months of screening.
16. Aphakia 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 in the Study Eye, that in the opinion of the Investigator could require either medical or surgical intervention 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. BCVA of hand motion or worse in the non-Study Eye or non-physical presence of a non-Study Eye (i.e., monocular).

5.2.2 General Exclusion Criteria

21. Women who are pregnant or lactating or intending to become pregnant during the study.
22. Women of child-bearing 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, up to two additional readings may be taken later the same day or on a different day during the screening period. If a participant's blood pressure is controlled by antihypertensive medications, the participant must be on a stable medication regimen continuously for 21 days prior to Day 1.

24. Kidney failure requiring renal transplant, hemodialysis or peritoneal dialysis or expected to require renal transplant, hemodialysis or peritoneal dialysis during the study.
25. 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.
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 intravitreal agents such as aflibercept or ranibizumab or to any component of KSI-301, ophthalmic dye (fluorescein), dilating drops, or any of the anesthetic or antimicrobial preparations used during the study, as assessed by the Investigator.
28. Active cancer within the 12 months prior to Screening except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin cancer, and prostate cancer with a Gleason score of <6 and stable prostate-specific antigen for >12 months.
29. Participation in an investigational study within 30 days prior to the screening visit that involved treatment with any investigational drug (excluding vitamins and minerals) or investigational devices, except for non-therapeutic ophthalmic imaging 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 considered 'screen-failed'. However, a participant may be rescreened up to one additional time at the discretion of the Investigator and in consultation with the Sponsor. When rescreening, 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 rescreening, 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 rescreening visit is more than 8 weeks after the original screening visit, FA should be repeated. For a rescreening visit 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 rescreening tests and procedures have been completed and results are available indicating the participant is eligible for study participation, the participant may be enrolled. When rescreening a participant, a new screening/enrollment number will be generated by IRT system to ensure there is an audit trail for the screen-failed participant.

5.5 Criteria for Temporarily Delaying Enrollment

Inclusion/Exclusion criteria will be assessed at Screening and on Day 1 to determine a participant's eligibility for the study.

If a participant meets all eligibility criteria (Sections 5.1 and 5.2) at the Screening visit but does not meet BCVA eligibility criteria due to expected variability and fluctuation in the BCVA when they return for the planned Day 1 visit, the Sponsor will allow the participant to return one additional time to reassess the BCVA, provided the assessment still occurs within the 21-day screening window. This repeat measurement for Day 1 visit (Repeat Day 1) is not considered a rescreen. Women of childbearing potential who return for a Repeat Day 1 Visit must have a negative pregnancy test during the Repeat Day 1 Visit (i.e., the pregnancy test must be performed and documented as negative on the same day as randomization/first injection). Day 1 and Repeat Day 1 Visit data shall be used/entered in the eCRF and IRT as follows:

- eCRF: In the event that a participant has a Repeat Day 1 Visit, data from assessments conducted at the planned randomization (Day 1) visit shall be clearly documented in the participant's source data. If the participant meets the eligibility criteria at the Repeat Day 1 visit, all data for assessments performed at that visit are entered into the eCRF under Day 1 and the original non-qualifying data will be entered as Unscheduled Visit assessments.
- IRT: In the event that a participant has a Repeat Day 1 Visit and is eligible for this study, the BCVA and SD OCT values from the Repeat Day 1 visit must be used for participant randomization into the IRT system. If the participant *does not* meet eligibility at the Repeat Day 1 visit, the participant must be recorded as a screen failure (Section 5.4) in the IRT system at that time.

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 4. For full information regarding the administration of study intervention and the contents of the kit, refer to the Pharmacy Manual. The full instructions for administration of sham are also described in the Pharmacy Manual.

Table 4: Protocol KS301P106: Study Interventions

Group Name	A	B
Intervention Name	KSI-301 5 mg	Sham
Type	Biological medicinal product	Sham
Dose Formulation	Sterile liquid for intravitreal injection in single-use vials	Empty vial
Unit Dose Strength(s)	[redacted] mg/mL (based on antibody mass)	N/A
Dosage Level(s)	5 mg [redacted]	N/A
Route of Administration	Intravitreal injection	Sham injection
Use	Experimental	Sham (to maintain study masking)
IMP and NIMP	IMP	NIMP
Sourcing	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. Refer to Pharmacy Manual for additional instructions.	In the original packaging, as provided, until the time of use. Store at 2-8°C before use. Refer to Pharmacy Manual for additional instructions.
Packaging and Labeling	KSI-301 will be provided in vials 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 vial and filled into a syringe by unmasked site personnel without reconstitution or dilution.	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	N/A

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation, Handling, and Storage

KSI-301 is an aqueous solution provided in vials 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 should be stored in the original packaging, as provided, until the time of use.

Please refer to the 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 and document receipt in IRT system.
- Report any deviations or product complaints to the Sponsor or its delegate upon discovery. Any study intervention under investigation for integrity or temperature excursion should be quarantined in the IRT, and not used until the 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. Detailed stepwise instructions for the preparation of KSI-301 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 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 assessment 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 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 two study interventions: (1) KSI-301 (the investigational medicinal product); and (2) sham (for which an injection procedure is simulated but not actually performed). The two study interventions are provided are provided in unmasked vials within masked cartons (also referred to as kits), as follows:

- **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 participant's treatment at that given visit.

- **Unmasked Vials 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 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 or 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 an SAE 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 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 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 group, as follows:

A. KSI-301: 5 mg [redacted]

B. Sham injection

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 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 to 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 100. 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 eye (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 eye (non-Study Eye) may be implemented at any time once the Day 1 injection has been administered. Anti-VEGF treatment for the fellow eye, including the date of each administration, must be documented as a concomitant medication on the appropriate eCRF. If the fellow eye requires treatment during the same visit as the Study Eye, the Study Eye should be treated first, and the fellow 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

Pan-retinal photocoagulation (PRP) laser is permitted in the Study Eye if PDR or ASNV develops. 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 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; and
- 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, participants 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 2) 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 treatment is discontinued, an end-of-treatment visit should occur 28 +/- 7 days after study treatment is discontinued or before a new treatment regimen begins. Participants who discontinue study drug should NOT be considered withdrawn from the study. Unless they withdraw consent or there is additional risk to the participant, participants who have discontinued study treatment should be encouraged to stay in the study and undergo as many scheduled visits as possible, with emphasis on the Week 48 (primary endpoint) and Week 96 (secondary endpoint) visits.

The reasons for study treatment discontinuation and/or withdrawal from the study (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 non-compliant 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; or
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 5. 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 5: Protocol KS301P106: 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 10 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 Weeks 48, 96, and 100 safety assessments. 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 ET 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, three 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 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 or designee 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 will be recorded. A full ocular history including prior ocular treatments will be noted. Demographic data will include age, sex, and ethnic origin (also referred to as self-reported race and ethnicity in some regions of the world).

8.1.2 Ophthalmic Exams

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

Slit-lamp examination 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,
- Inspection of the retina, and
- Inspection of the optic disc.

Dilated indirect ophthalmoscopy will include examination of the peripheral retina and vessels.

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 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 or sham) and documented in the site's source documents. Per Section 4.1.3.1, upon initiation of treatment of DME, PDR, and/or ASNV, the method of anesthesia is not required to remain constant.

Please refer to the Pharmacy Manual for 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

Best corrected visual acuity (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

Fundus photography (FP) will be performed at the study sites by certified, masked personnel. Where wide-field devices qualified by the Reading Center are available, wide-field FP should be performed. 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

Spectral domain optical coherence tomography (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 Fluorescein Angiography

Fluorescein angiography (FA) will be performed at all the study sites by certified, masked personnel. Where wide-field devices qualified by the Reading Center are available, wide-field FA should be performed. 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.

8.2 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 with the participant in a seated position after resting for 5 minutes: blood pressure, 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 or designee 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 starting at the Screening visit and then at each visit through the end of the study 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, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided 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 (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 Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study intervention, only SAEs caused by a protocol-mandated assessment should be reported. After initiation of study intervention (Day 1), all AE and SAE information will be collected until the final safety follow-up visit at Week 100 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 AEs or SAEs 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 Adverse Events and Serious Adverse Events

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 Adverse Events and Serious Adverse Events

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 Serious Adverse Events

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 IB 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; 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 in the Study Eye with sight-threatening potential, meeting one or more of the following criteria:
    - Causes a decrease ≥30 letter 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).
    - 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 systemic pharmacokinetic (PK) of the study intervention following intravitreal injection, plasma concentration of KSI-301 will be measured. For exploratory purposes, [redacted]

Blood samples of approximately 4 mL will be collected from participants for measurement of plasma concentrations of KSI-301 or aflibercept, 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 the anti-drug antibodies 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 or 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 Statistical Hypothesis

The study hypothesis is that the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48 among participants treated with KSI-301 5 mg Q24W will be superior to the participants in the sham group.

9.2 Sample Size Determination

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

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

[redacted]

Note: "enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process, 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

Population	Description
Randomized/ Intent to Treat (ITT) Set	The ITT set will consist 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 study intervention assigned at randomization.
Evaluable/Per Protocol (PP) Set	The PP set 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 study intervention they received.
Safety Set	All participants randomly assigned to study intervention and who receive at least one dose of study intervention. Participants will be analyzed according to the intervention they received.
Pharmacokinetic/Biomarker/ADA Evaluable Set	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 Week 48 analyses may be reported to the public and to health authorities before the completion 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 100 analyses are completed.

9.4.1 General Considerations

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

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

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

- Year 1: from baseline to Week 48; and
- Year 2: from Week 52 to Week 100.

At Week 48, the primary endpoint (the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48) will be compared between the KSI-301 5 mg treatment group and sham using the CMH method [redacted] Missing values post-baseline will be imputed using the last observation carried forward (LOCF) procedure. If a participant develops a sight-threatening complication due to DR (DME, PDR, or ASNV), a color fundus photograph for DRSS grading will be obtained and submitted to the reading center at the time of diagnosis, and DRSS scores collected subsequently will be censored. Baseline will be carried forward if all post-baseline observations are missing.

Analysis of data for the first period of the study will be performed when all participants have either completed the Week 48 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.

Likewise, analysis of data for the second period of the study will be performed when all participants have either completed the Week 100 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 alternative 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)

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

The primary endpoint is defined as the proportion of eyes improving ≥2 steps on DRSS from baseline at Week 48. The primary assessment of efficacy will be based on a pairwise comparison of the proportion of eyes improving ≥2 steps on DRSS between the KSI-301 5 mg treatment group compared with the sham group.

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

- all participants have either completed the Week 48 visit or have discontinued from the study prior to the Week 48 visit, whichever comes later; and
- all data up to and including the Week 48 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, the CMH method and corresponding confidence intervals will be used for evaluation of treatment differences. An alpha level of 0.05 will be used for hypothesis testing and confidence intervals will be (1-α) or 95% confidence intervals.

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 48, Week 96 and, if applicable, over time:

- Proportion of eyes developing any of the following from baseline:
  - PDR or ASNV;
  - Vitreous hemorrhage or tractional retinal detachment believe to be due to PDR; or
  - DME.
- Proportion of eyes developing PDR or ASNV from baseline.
- Proportion of eyes developing vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR, from baseline.
- Proportion of eyes developing DME from baseline.
- Proportion of eyes with a ≥2-step improvement from baseline on DRSS from baseline.
- Proportion of eyes with a ≥2-step worsening from baseline on DRSS from baseline.
- Proportion of eyes with a ≥3-step improvement from baseline on DRSS from baseline.
- Proportion of eyes with a ≥3-step worsening from baseline on DRSS from baseline.
- Time to first development of either PDR, ASNV, or DME.
- Time to first development of PDR or ASNV.
- Time to first development of vitreous hemorrhage or tractional retinal detachment, believed to be due to PDR.
- Time to first development of DME.
- Time to first development of a ≥2-step improvement on the DRSS.
- Time to first development of a ≥2-step worsening on the DRSS.
- Time to first development of a ≥3-step improvement on the DRSS.
- Time to first development of a ≥3-step worsening on the DRSS.
- Mean change in SD-OCT central subfield thickness (CST) from baseline.

- Mean change in BCVA from baseline.
- Proportion of eyes who lose ≥5, ≥10, or ≥15 letters in BCVA from baseline.
- Proportion of eyes with a BCVA score of ≥69 letters (20/40 approximate Snellen equivalent).
- Proportion of eyes with prolonged vision loss.
- Incidence of ocular and systemic adverse events up to Week 48 and Week 100.
- 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% confidence intervals for within group mean change from baseline. Results of ANCOVA will be reported as 95% confidence interval for the difference in adjusted means for the grouping determined by the fixed effects of interest.

Time to first development of DME, PDR, and/or ASNV, in combination and individually will be analyzed using Kaplan-Meier estimates. Log-rank tests will be performed, comparing the two treatment groups, as well as 95% confidence intervals for the time to the first 'complication' for the difference of each treatment group. Time to first development of a ≥2-step and ≥3-step worsening on the DRSS will be analyzed similarly.

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.

Similar to the analysis of the primary endpoint, missing efficacy values post-baseline will be imputed using the last observation carried forward (LOCF) procedure. If a participant develops a vision-threatening complication due to DR (DME, PDR, and/or ASNV), DRSS scores collected after the development of the vision-threatening complication will be censored. Baseline will be carried forward if all post-baseline observations are missing.

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 population 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 OECD (Organisation for Economic Co-operation and Development) countries 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 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 and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants 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.

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 Principal Investigator's supervision and to the IRB/IEC 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 electronic CRF 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., Contract Research Organizations).

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 the following:

- 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; and
    - 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 multicenter 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 6 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 6: Protocol KS301P106: Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Red blood cell (RBC) Count			
	Hemoglobin			
	Glycated hemoglobin (HbA1c)			
	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	
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 (to verify non-childbearing potential as required in Section 10.6.1) and estradiol (only if determined to be additionally required by the Investigator to verify non-childbearing potential).			
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/associated procedures) 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 one 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.

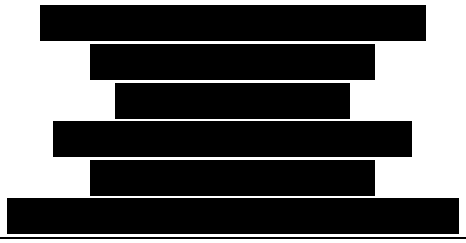
Follow-up of AEs and SAEs

- 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

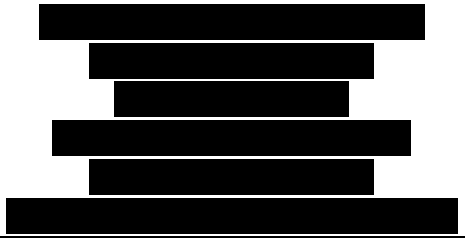
SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- 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.



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.



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.

[14] 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.

[15] 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 and serum chemistry panel;
- Best corrected visual acuity (BCVA);
- 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

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in 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 one 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., Müllerian 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 hormonal replacement therapy (HRT). In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. The Screening Visit FSH will be processed using the chemistry tube and the Day 1 FSH will need to be collected separately and sent to the central lab for analysis. A pregnancy test is required until both FSH measurements have been collected and results have been received that verify the post-menopausal state of the female participant.

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 post-ovulation 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 [redacted] 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

The amendment history for Protocol KS301P106 is provided in Table 7.

Table 7: Protocol KS301P106: Amendment History

Version	Version Date	Description
1.1	17 May 2021	Changes from Version 1.0 include the following: • Minor editorial and administrative revisions.
1.0	20 April 2021	Original protocol; used for pre-submission activities. This version was not submitted to any health authorities or IRBs/ECs, nor was it implemented.

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