Official title: A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)

NCT Number: NCT04049266

Document Date: Protocol Version 3.0, 02 June 2021

CLINICAL STUDY PROTOCOL

A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)

Protocol Number: KSI-CL-102

Sponsor:	Kodiak Sciences Inc. 2631 Hanover Street Palo Alto, CA 94304 USA
Sponsor Contact & Medical Monitor:	[redacted]
IND Number:	136167
EUDRACT Number:	2018-003428-35
Test Product:	KSI-301
Version Date:	02 June 2021
Protocol Version Number:	3.0
Supersedes:	Protocol Version 2.0 dated 03 August 2020

CONFIDENTIAL

FOR MEDICAL EMERGENCIES CONTACT:

[redacted]

Protocol Approval – Sponsor Signatory

Study Title: A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)

Protocol Number: KSI-CL-102 Version 3.0

Protocol Date: 02 June 2021

Protocol accepted and approved by:

[redacted]

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

Signature

Date

Principal Investigator Signature

Study Title: A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)

Protocol Number: KSI-CL-102 Version 3.0

Protocol Date: 02 June 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
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AR	Adverse reaction
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic events
AUC	Area under the curve (total exposure)
BCVA	Best corrected visual acuity
BP	Blood pressure
BUN	Blood urea nitrogen
CFR	Code of federal regulations
Cmax	Maximum concentration observed
CNV	Choroidal neovascularization
COVID-19	Coronavirus-19
CRO	Contract research organization
CSR	Clinical study report
CST	Central subfield thickness
DME	Diabetic macular edema
DR	Diabetic retinopathy
DVD	Digital Video Disc
EC	Ethics committee
ECG	Electrocardiograph
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
ETDRS	Early treatment diabetic retinopathy study
EU	European Union
FA	Fundus fluorescein angiography
FAS	Full-analysis set
FDA	Food and Drug Administration
FP	Fundus photography
GCP	Good clinical practice

Abbreviation	Definition
GGT	Gamma-glutamyl-transferase
GLP	Good laboratory practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International conference on harmonization
ICMJE	International committee of medical journal editors
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
IEC	Independent or institutional ethics committee
IRC	Intraretinal cysts
IRF	Intraretinal fluid
ITT	Intent to treat
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVT	Intravitreal
LLBCVA	Low luminance best corrected visual acuity
LPLO	Last subject last observation
ME	Macular edema
MedDRA	The medical dictionary for regulatory activities
NAB	Neutralizing antibody
NOAEL	No observed adverse effect level
OCT	Optical coherence tomography
OU	Both eyes
PI	Principal Investigator
PK	Pharmacokinetic
Q8W	Every eight weeks
Q12W	Every twelve weeks
Q16W	Every sixteen weeks
Q20W	Every twenty weeks
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
SAE	Serious adverse event

Abbreviation	Definition
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SAR-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD-OCT	Spectral domain optical coherence tomography
SDV	Source data verification
SE	Study Eye
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of activities
SRF	Subretinal fluid
SUN	Standardization of uveitis nomenclature
SUSAR	Suspected unexpected serious adverse reactions
TEAEs	Treatment emergent adverse events
ULN	Upper limits of normal
VA	Visual acuity
VEGF	Vascular endothelial growth factor
wAMD	Wet (neovascular) age-related macular degeneration
WBC	White blood cell
WHODrug	World health organization drug dictionary
WMA	World medical association
WOCBP	Women of childbearing potential

PROTOCOL SYNOPSIS

Protocol Number:	KSI-CL-102
Version:	3.0
IND Number:	136167
Eudra CT Number:	2018-003428-35
Title:	A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects with Neovascular (Wet) Age-related Macular Degeneration (DAZZLE)
Sponsor:	Kodiak Sciences Inc 2631 Hanover Street Palo Alto, CA 94304 USA
Phase of Development:	2b/3
Study Rationale:	KSI-301 is an antibody biopolymer conjugate that inhibits vascular endothelial growth factor (VEGF). It is designed to provide similar (non-inferior) improvements in visual acuity with an extended intraocular half-life and longer treatment intervals compared to aflibercept.
Number of Sites/Facilities Enrolling Subjects:	Approximately 110-125 sites in 10-15 countries globally.
Test Product (Dosage and Route of Administration):	KSI-301 5 mg [redacted] administered via intravitreal injection
Comparator Product (Dosage and Route of Administration):	Aflibercept 2 mg (50 µL) administered via intravitreal injection
Non-Investigational Medicinal Products:	Sham intravitreal injection procedure, to preserve masking.
Study Objectives:	**Primary:** To demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in best corrected visual acuity (BCVA) from Day 1 to Year 1. Year 1 is defined as the mean of the Week 48 and 52 measurements. **Secondary:** • To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg from Day 1 to Week 96 by assessing visual and anatomical parameters. • To evaluate the proportion of subjects maintained on a Q12W, Q16W, or Q20W dosing regimen of KSI-301 over the duration of the first 52 weeks. • To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg. • To assess the systemic pharmacokinetics and immunogenicity of KSI-301.

Study Population:	Male and female subjects ≥ 50 years with treatment-naïve wet (neovascular) age-related macular degeneration (wAMD).
Number of Subjects (Planned):	Approximately 550 subjects (275 per arm).
Study Design:	This is a prospective, randomized, double-masked, active comparator controlled, multi-center Phase 2b/3 study that will evaluate the efficacy and safety of KSI-301 compared with aflibercept in subjects with wAMD. • This study is divided into a 3-week screening period, a 92-week treatment period, and a final 4-week follow-up period (Figure 1, Study Schematic). **First Year (Day 1 Visit through Week 52 Visit):** At baseline subjects will be randomized 1:1 into two treatment arms: KSI-301 5 mg and aflibercept 2 mg. All subjects will receive 3 monthly loading doses of their assigned treatment. Thereafter the dosing regimen of subjects in the KSI-301 treatment arm will be based on Year 1 Disease Activity Assessments. The dosing regimen of subjects in the aflibercept treatment arm following the three initial injections will be fixed at Q8W. **Second Year (Week 52 Visit through Week 96 Visit):** The dosing regimen of subjects in the KSI-301 treatment arm will be based on Year 2 Disease Activity Assessments. [redacted] Treatment assignment and dose frequency adjustments will be provided by the interactive response technology (IRT) system.
Study Duration:	Approximately 3 years
Treatment Duration:	92 weeks
Participant Duration:	Up to approximately 99 weeks.
Efficacy Assessments:	• Changes in BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing; • Optical coherence tomography (OCT); and • Fluorescein angiography (FA) Efficacy evaluations will be conducted according to the Schedule of Activities (SoA) provided in Table 1 (Year 1) and Table 2 (Year 2).
Systemic Pharmacokinetic or Biomarker Assessments:	• Pharmacokinetic (PK): plasma concentration of study drug; • Biomarker: systemic biomarker levels may be evaluated for exploratory purposes; • Immunogenicity: detection of anti-drug antibodies (ADA) in subject plasma samples. Additional immunogenicity testing of samples may be performed to further characterize the ADA response for specificity and/or neutralizing antibodies (NAB);

Safety Assessments:	• Incidence of adverse events (AEs), including serious AEs (SAEs) and AEs of special interest (AESIs); • Ophthalmic examination with slit-lamp biomicroscopy and indirect ophthalmoscopy; • Intraocular pressure measurement (IOP); and • BCVA by the ETDRS acuity test. Assessments performed in the event of an unscheduled safety visit are at the discretion of the Investigator.
Key Ocular Eligibility Criteria:	**Key Ocular Inclusion Criteria:** 1. Active, treatment-naïve choroidal neovascularization (CNV) secondary to AMD, including subfoveal, juxtafoveal and extrafoveal lesions or retinal angiomatous proliferation (RAP) lesions with a CNV component that affect the central subfield as evidenced by FA or OCT in the Study Eye at Screening. 2. The CNV area in the Study Eye must be at least 50% of total lesion size at Screening. 3. A lesion area <30 mm^2 (12 disc areas) of any CNV lesion subtype in the Study Eye. 4. Intra and/or subretinal fluid and/or SHRM (subretinal hyperreflective material) affecting the central subfield of the Study Eye on OCT at Screening. 5. BCVA ETDRS score between 80 and 25 letters (20/25 to 20/320 Snellen equivalent), inclusive, in the Study Eye at Screening and reconfirmed at Day 1. 6. Decrease in vision in the Study Eye determined by the Investigator to be primarily the result of wAMD. Only one eye per subject is eligible to participate in the study. **Key Ocular Exclusion Criteria:** 1. BCVA of hand motion or worse in the non-Study Eye or non-physical presence of a non-Study Eye (i.e., monocular). 2. Active or suspected ocular or periocular infection or inflammation in either eye at Day 1. 3. CNV secondary to other causes in the Study Eye, including pathologic myopia, angioid streaks, prior trauma, ocular histoplasmosis, or others. 4. Any history of macular pathology unrelated to AMD but affecting vision or contributing to subretinal or intraretinal fluid, such as central serous chorioretinopathy. 5. Fibrosis or atrophy of >50% of the lesion size and/or involving the foveal center of the Study Eye at Screening. 6. Subretinal blood affecting the foveal center of the Study Eye and/or more than 50% of the lesion size at Screening. 7. Any approved or investigational treatment for neovascular AMD (other than oral vitamin supplements) in the Study Eye at any time.

	8. Prior macular laser (e.g., thermal laser or photodynamic therapy laser) in the Study Eye.
Statistical Methods:	**General Considerations:** In general, continuous data will be summarized by descriptive statistics, including number of subjects (N), mean, standard deviation or standard error of the mean, median, maximum, and minimum. Categorical data will be summarized by frequency and percentage of subjects. The following assumptions were made to calculate the sample size of 550 subjects (275 per treatment group): • Overall Type I error rate of 0.025. Testing at the 0.025 level corresponds to setting 95% confidence intervals. • Statistical power of ≥90%. • Standard deviation of the distribution of change in visual acuity from baseline [redacted] (averaged over Weeks 48 and 52). • The maximum clinically acceptable true difference for KSI-301 to be considered non-inferior, or the "non-inferiority margin," [redacted]. • The anticipated true difference in mean change from baseline in BCVA between treatment groups is 0. That is, both treatment arms are expected to have the same efficacy. • The statistical test used to compare the two treatment groups at Week 52 is an independent t-test on the mean change in visual acuity from baseline. • Lost to follow-up rate [redacted] **Efficacy:** Unless stated otherwise, all analyses described will be performed on the ITT population. The primary endpoint is defined as the mean change in ETDRS BCVA from Day 1 to Year 1. The primary assessment of efficacy will be based on a non-inferiority comparison in mean change in BCVA between the two treatment groups. Confidence intervals will be 100(1-2 α) or 95% confidence intervals. If the null hypothesis of inferiority is rejected, testing for superiority will be performed. **Safety**: All safety data will be summarized for the Safety Population using descriptive statistics by treatment arm. **Interim Analyses**: [redacted].
Independent Data Monitoring Committee (IDMC):	An IDMC will monitor the study conduct and subject safety on an ongoing basis.
Date of Protocol/ Amendment	02 June 2021/Amendment 3.0

Figure 1. Protocol KSI-CL-102: Study Schematic

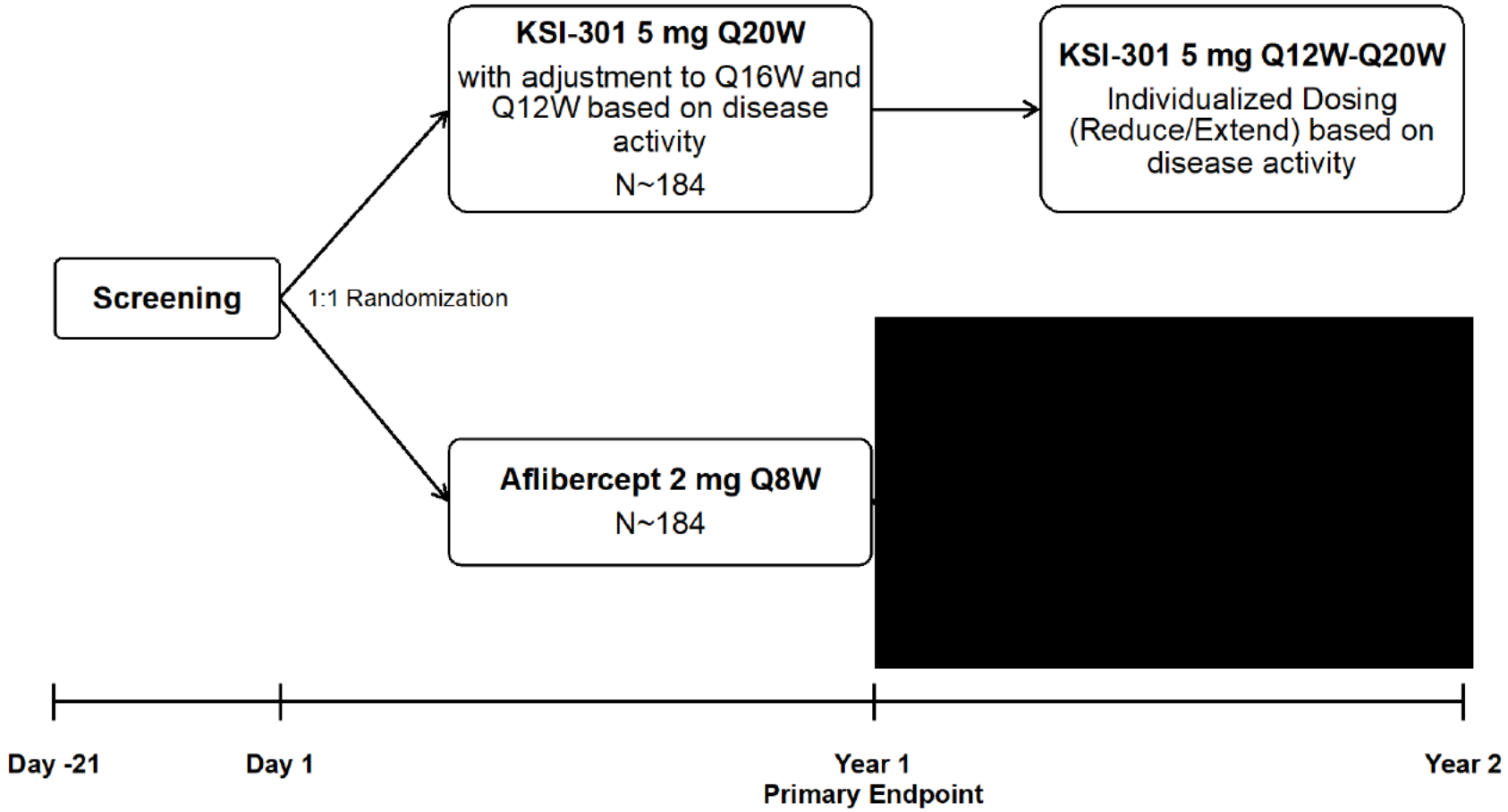

Table 1. Protocol KSI-CL-102: Schedule of Activities (SoA) – First Year

Visit	Screening	Day 1	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Windows (days)	**D-21 to D-1**		+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed consent	X															
Medical & Ocular History	X															
Inclusion/Exclusion Criteria	X	X														
Randomized study treatment (KSI-301, aflibercept or sham) per IRT designation [1]		X		X	X		X	X	X	X	X	X	X	X	X	X
Ophthalmic Assessments[2]																
BCVA ETDRS (4 meters) [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Low luminance BCVA [4]		X														
Ophthalmic exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-injection assessments [4]		X		X	X		X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fundus photos	X															X
Fluorescein angiogram	X															X
General Assessments																
Vital signs	X	X	X			X										X
Laboratory Assessments	X															X
Plasma ADA samples [5]		X				X						X				X
Plasma PK/biomarker samples [5]		X	X	X		X		X				X				X
Pregnancy test [6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

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

[1] Participants who discontinue study treatment should NOT be considered withdrawn from the study. Additional details are provided in Section 4.8.

[2] Ophthalmic assessments will be performed in both eyes at Screening, Week 52 and Week 96, and in the Study Eye only at all other timepoints.

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

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

[5] Blood draws for ADA, plasma PK, and biomarker samples are to be taken pre-injection.

[6] 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.

Table 2. Protocol KSI-CL-102: Schedule of Activities (SoA) – Second Year

Visit	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96/ET
Visit Windows (days)	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Randomized study treatment (KSI-301, aflibercept or sham) per IRT designation [1]	X	X	X	X	X	X	X	X	X	X	
Ophthalmic Assessments [2]											
BCVA ETDRS (4 meters) [3]	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic exam	X	X	X	X	X	X	X	X	X	X	X
Post-injection assessments [4]	X	X	X	X	X	X	X	X	X	X	
SD-OCT	X	X	X	X	X	X	X	X	X	X	X
Fundus photos											X
Fluorescein angiogram											X
General Assessments											
Vital signs											X
Laboratory Assessments											X
Plasma ADA samples [5]				X							X
Plasma PK/biomarker samples [5]				X				X			X
Pregnancy test [6]	X	X	X	X	X	X	X	X	X	X	X

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

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1.0 INTRODUCTION

1.1 Study Rationale

KSI-301 is an anti-VEGF biopharmaceutical with an extended ocular half-life. KSI-301 offers a potential for subjects to experience a longer interval between consecutive intravitreal injections. Furthermore, KSI-301 may improve real-world outcomes of anti-VEGF therapy which are currently restricted by both the high treatment burden and insufficient durability of existing anti-VEGF agents. KSI-301 may offer a particularly important and clinically relevant benefit over existing therapies for patients with wAMD.

1.1.1 Research Hypothesis

Treatment with KSI-301 will provide non-inferior mean change in BCVA with a less frequent dosing schedule than aflibercept in subjects with previously untreated wAMD.

1.2 Background

1.2.1 Wet Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a common eye condition affecting people 50 years of age and older throughout the world. Population-based studies have shown that AMD accounts for 8.7% of all blindness worldwide and it is the most common cause of blindness in developed countries. As the world's population continues to both grow and age, more individuals will be afflicted with AMD, and it is estimated that 196 million people will have AMD in the year 2020 (Wong 2014). AMD is a progressive disease affecting the central portion of the retina, known as the macula, which is the region of the eye responsible for sharp, central vision and color perception. The likelihood of AMD progression and associated vision loss increases with age.

Wet AMD (wAMD, also known as neovascular AMD) is an advanced form of AMD characterized by choroidal neovascularization and fluid leakage within and under the retina. Wet AMD is the leading cause of severe vision loss in people over the age of 50 in the United States and the European Union (EU), with a reported prevalence of approximately 1.25 million and an annual incidence of approximately 148,000 new cases each year in the United States (Wong 2014). The likelihood of disease progression increases with age, and both the prevalence and incidence of wAMD are projected to accelerate worldwide. It has additionally been observed that approximately 50% of patients presenting with wAMD in one eye will develop wAMD in the other eye within five years, leading to a substantial number of subjects requiring treatment in both eyes (Chew 2014). In many eyes with wAMD, the disease can progress quickly with rapid loss of central vision needed for activities such as reading and driving. Untreated or undertreated wAMD can result in subretinal scarring with irreversible photoreceptor damage and loss and can lead to permanent vision impairment or even blindness.

1.2.2 Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) stimulates vascular endothelial cell growth and induces vascular permeability. These biologic activities give it a central role in angiogenesis, both in normal and pathologic conditions. VEGF plays a critical role in the pathophysiology of choroidal and retinal neovascular diseases such as wAMD, diabetic retinopathy (DR), including diabetic macular edema (DME), and macular edema due to retinal vein occlusion (RVO) (Rubio 2016). Inhibition of inappropriate VEGF activity is both an "anti-angiogenic" and "anti-permeability" approach to treatment of these diseases and has been an effective method of preserving and even improving visual acuity in subjects with these retinal vascular diseases (Campochiaro 2015; Cheung 2010).

Among the VEGF isoforms, VEGF-A is known to be most strongly linked to 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 these retinal vascular diseases. Phase 3 clinical trials of ranibizumab demonstrated that monthly injections of ranibizumab for DME and wAMD resulted in substantial visual acuity gains on average. (Brown 2006, Rosenfeld 2006, Nguyen 2012). Similarly, the Phase 3 clinical trials of aflibercept in patients with wAMD demonstrated that every 8-week (Q8W) dosing of aflibercept (after 3 once-monthly loading doses) was non-inferior to monthly ranibizumab (Heier 2012).

A primary concern with current therapies used to treat neovascular diseases of the retina is that the visual acuity gains observed in the early intensive treatment phase are not sustained in real-world practice. This is thought to be due to their relatively short ocular tissue half-lives (Eylea [aflibercept] $t_{1/2}$ = 4-5 days; Lucentis [ranibizumab] $t_{1/2}$ = 3-4 days, in nonclinical models such as rabbits). This results in narrow re-treatment windows and repeated undertreatment, burdensome treatment regimens, and diminishing patient compliance (Chong 2016; Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group, 2014). There is a substantial medical need to find better therapeutic options that could address the high treatment burden. Specifically, new agents that can inhibit VEGF while also having a longer duration of action, thus requiring fewer office visits and fewer injections while still maintaining adequate disease control, would be desirable to patients and their caregivers, physicians and their teams, as well as healthcare payors and healthcare systems.

1.2.3 Description of KSI-301

KSI-301 is a new molecular entity (NME) that is an antibody biopolymer conjugate. The antibody portion of KSI-301 binds to huVEGF-A with high affinity and inhibits the ability of huVEGF-A to bind and activate its cognate receptors (VEGFR1 and VEGFR2). The inert phosphorylcholine biopolymer moiety of KSI-301 significantly increases the overall molecular size of KSI-301, which in turn extends its ocular half-life compared to other anti-VEGF biologics [redacted]. 4-5 days for aflibercept in nonclinical models).

Thus, similar to other anti-VEGF biologics such as aflibercept and ranibizumab, intravitreal KSI-301 is expected to act as an anti-angiogenic and anti-permeability agent with clinical benefit in VEGF-A mediated disorders such as wAMD, but with improved ocular durability.

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

1.2.4 Dose Rationale

1.2.4.1 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 dose of 5 mg is approximately [redacted] fold the equivalent molar dose of anti-VEGF binding capacity, at the time of injection, relative to 2 mg aflibercept (the marketed aflibercept dose for the treatment of wAMD). Given this and the improved ocular pharmacokinetics of KSI-301 relative to unconjugated antibodies or biologics, preclinical modeling suggests that the 5 mg dose of KSI-301 results in [redacted]-fold the equivalent ocular concentration of aflibercept at 3 months after dosing. Because both the 2.5 mg ([redacted] µL) and 5 mg ([redacted] µL) doses under study in the ongoing Phase 1b study have been well-tolerated, the higher 5 mg dose of KSI-301 is a desirable target dose for the treatment of wAMD subjects because it is expected to further extend the durability of the pharmacological anti-VEGF effect compared to aflibercept.

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

As shown in the IB, there were no KSI-301 dose limiting toxicities up through the maximum feasible dose of [redacted] bilaterally dosed monthly for seven doses up to 40 weeks of observations and histopathological analysis for the recovery group. Thus, dosing at longer intervals (i.e., Q8W and Q12W) are supported with a greater safety margin. Based on the volume of the vitreous, the nonclinical NOAEL [redacted] safety margin for the starting to highest dose, respectively, for the Phase 1 study.

This current Phase 2b/3 study is designed to test whether KSI-301 5 mg dosed Q12W to Q20 is non-inferior to aflibercept dosed Q8W. [redacted]

1.2.4.2 Aflibercept Dose Rationale

A variety of dosing regimens are approved for aflibercept. In this global study, aflibercept 2 mg (0.05 mL) is administered via intravitreal injection every 4 weeks (approximately every 28 days) for the first 3 doses, followed by an injection once every 8 weeks. This regimen is approved and well-accepted globally and is considered a standard of care regimen for which an appropriate non-inferiority margin for the present study can be derived.

1.3 Benefit/Risk Assessment

1.3.1 Known Potential Benefits

KSI-301, an intravitreal VEGF inhibitor developed to treat wAMD, 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 standard of care.

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

1.3.2 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 subjects are also carefully considered. A summary of known potential risks associated with KSI-301 is provided in Table 3. Risks associated with exposure to the virus SARS-CoV-2 are discussed below in Section 1.3.2.1.

Table 3. Protocol KSI-CL-102: 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 subjects treated with KSI-301. Clinical experience with commercially available intravitreal VEGF inhibitors has shown that SAEs related to inflammatory reactions can occur. Additional details are provided in IB Section 5.4.2.1.	Subjects 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 6.1.11.2). Subjects with known hypersensitivity to intravitreal agents such as aflibercept or any ingredient of KSI-301 are excluded from this study (Section 3.1.2.2).
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.	Subjects with recent history (6 months) of myocardial infarction or stroke are excluded from this study (Section 3.1.2.2).
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.	Subjects 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 6.1.11.9). Subjects with active or suspected ocular infection or inflammation in either eye (e.g., blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis) are excluded from this study (Section 3.1.2.1). During the study, subjects with active intraocular inflammation will have study treatment interrupted (Section 4.8.2)

Table 3. Protocol KSI-CL-102: Risk Assessment (Cont'd)

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.	Subjects with known hypersensitivity to intravitreal agents such as aflibercept or any ingredient of KSI-301 are excluded from this study (Section 3.1.2.2).
Study Procedures		
Risks associated with the method of administration	These risks include endophthalmitis, increases in intraocular pressure, retinal detachment, retinal tear, traumatic cataract, and intraocular hemorrhage. Additional details are provided in IB Section 5.4.2.5.	Proper and aseptic injection technique when administering intravitreal injections will be used (Section 6.1.3). Subjects will be monitored following the injection and instructed to report any symptoms suggestive of severe intraocular inflammation without delay to facilitate early diagnosis and treatment (Section 6.1.11.9). Intraocular pressure and the perfusion of the optic nerve head will also be monitored and managed (Section 6.1.4). Subjects with active ocular infection or inflammation in either eye (e.g., blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis) are excluded from this study (Section 3.1.2.1).

Abbreviations: ATE = arterial thromboembolic event; IB = Investigator's Brochure; SAE = serious adverse event; VEGF = vascular endothelial growth factor.

1.3.2.1 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 subjects are carefully considered and will be documented on an ongoing basis. In wAMD, both earlier diagnosis and earlier initiation of treatment with intravitreal anti-VEGF therapy are associated with better functional outcomes (Chew 2014). Moreover, intravitreal anti-VEGF treatment is recognized as an essential healthcare service during the pandemic by ophthalmology physician societies worldwide. This trial affords all subjects the opportunity to receive anti-VEGF therapy for their wAMD. Measures that prioritize trial subject safety and data integrity have been developed in consideration of local guidelines.

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

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 the course of this trial and local circumstances lead to a local change in risk assessment, additional measures may be implemented. In this case, an Investigator-driven risk assessment will be conducted and documented in the Investigator's site master file and communicated to the Sponsor.

1.3.3 Overall Benefit/Risk Conclusion

The potential benefits of treatment of wAMD with KSI-301 (longer treatment intervals) have been considered against both the risks associated with KSI-301 treatment and the COVID-19 pandemic. Subjects in this study will be carefully monitored with special attention to known and potential risks and managed as appropriate. Exclusion criteria restrict enrollment of subjects at higher risk, and routine monitoring and follow-up evaluations will be conducted for early detection of any AEs, as noted in Section 6.1.11. Reassessment of the risks will continue as the COVID-19 situation develops and any changes to this approach will be documented accordingly.

In wAMD, both earlier diagnosis and earlier initiation of treatment with intravitreal anti-VEGF therapy are associated with better functional outcomes (Chew 2014). Moreover, intravitreal anti-VEGF treatment is recognized as an essential healthcare service during the pandemic by the World Health Organization and physician groups worldwide. Therefore, based upon the well-known, clinically demonstrated mechanism of action (Homayouni 2009); favorable nonclinical and Phase 1/1b 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.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in BCVA from Day 1 to Year 1. Year 1 is defined as the mean of the Week 48 and 52 measurements.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of KSI-301 5 mg compared to aflibercept 2 mg from Day 1 to Week 96 by assessing visual and anatomical parameters.
- To evaluate the proportion of subjects maintained on a Q12W, Q16W, or Q20W dosing regimen of KSI-301 over the duration of the first 52 weeks.

- To evaluate the safety and tolerability of KSI-301 5 mg compared to aflibercept 2 mg.
- To assess the systemic pharmacokinetics and immunogenicity of KSI-301.

3.0 SUBJECT SELECTION

Approximately 550 subjects will be enrolled (275 per treatment group). Subjects will be assigned to study treatment 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 subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

3.1.1 Inclusion Criteria

Each subject must meet all the criteria outlined below to be enrolled in this study.

3.1.1.1 Ocular Inclusion Criteria

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

1. Active, treatment-naïve choroidal neovascularization (CNV) secondary to AMD, including subfoveal, juxtafoveal and extrafoveal lesions or retinal angiomatous proliferations (RAP) lesions with a CNV component that affect the central subfield as evidenced by FA or OCT in the Study Eye at Screening.
2. The CNV area in the Study Eye must be at least 50% of total lesion size at Screening.
3. A lesion area <30 mm2 (12-disc areas) of any CNV lesion subtype in the Study Eye.
4. Intra and/or subretinal fluid and/or SHRM (subretinal hyperreflective material) affecting the central subfield of the Study Eye on OCT at Screening.
5. BCVA ETDRS score between 80 and 25 letters (20/25 to 20/320 Snellen equivalent), inclusive, in the Study Eye at screening and reconfirmed at Day 1.
6. Decrease in vision in the Study Eye determined by the Investigator to be primarily the result of wAMD.

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

3.1.1.2 General Inclusion Criteria

7. Capable of understanding the informed consent, provides signed and dated informed consent, and agrees to comply with protocol requirements.
8. Male or female ≥50 years of age.
9. For women of childbearing potential: agreement to remain as abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period [redacted].
    - A woman is considered of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    - 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.
    - 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.
    - 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 subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
10. For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period [redacted] after the last dose of study drug. Men must refrain from donating sperm during this same time period.
11. Ability and willingness to undertake all the scheduled visits and assessments.

3.1.2 Exclusion Criteria

Subjects meeting any of the criteria outlined below will be excluded from the study.

3.1.2.1 Ocular Exclusion Criteria

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

1. BCVA of hand motion or worse in the non-Study Eye or non-physical presence of a non-Study Eye (i.e., monocular).
2. Active or suspected ocular or periocular infection or inflammation in either eye at Day 1.
3. CNV secondary to other causes in the Study Eye, including pathologic myopia, angioid streaks, prior trauma, ocular histoplasmosis, or others.
4. Any history of macular pathology unrelated to AMD but affecting vision or contributing to subretinal or intraretinal fluid, such as central serous chorioretinopathy.
5. Fibrosis or atrophy of >50% of the lesion size and/or involving the foveal center of the Study Eye at Screening.
6. Subretinal blood affecting the foveal center of the Study Eye and/or more than 50% of the lesion size at Screening.
7. Retinal pigment epithelium tear or rip in the Study Eye at Screening.
8. Any approved or investigational treatment for neovascular AMD (other than oral vitamin supplements) in the Study Eye at any time.
9. Prior macular laser (e.g., thermal laser or photodynamic therapy laser) in the Study Eye.
10. Any history or evidence of a concurrent intraocular condition in the Study Eye that, in the judgment of the Investigator, could require either medical or surgical intervention during the study to prevent or treat visual loss.
11. Prior intraocular or periocular steroids in the Study Eye.
12. Current vitreous hemorrhage or history of vitreous hemorrhage in the Study Eye within 3 months of Screening.
13. Prior vitrectomy surgery in the Study Eye.
14. Intraocular surgery other than uncomplicated cataract surgery (i.e., retinal detachment surgery) within 3 months of Day 1, or uncomplicated cataract surgery within 1 month of Day 1 in the Study Eye.
15. Uncontrolled glaucoma in the Study Eye defined as IOP >25 mmHg on medication at Screening or Day 1.
16. History of glaucoma-filtering surgery in the Study Eye.
17. History of corneal transplant in the Study Eye.
18. History of autoimmune or idiopathic uveitis in either eye.
19. Aphakia in the Study Eye.

3.1.2.2 General Exclusion Criteria

20. 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.
21. 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.
22. History of hypersensitivity to any component of KSI-301, aflibercept, ophthalmic dye (fluorescein), dilating drops, or any of the anesthetic or antimicrobial preparations used during the study, as assessed by the Investigator.
23. Women who are pregnant or lactating or intending to become pregnant during the study.
24. Women of childbearing potential must have a negative urine pregnancy test result within 28 days prior to Day 1. If the urine pregnancy test is positive, it must be confirmed with a serum pregnancy test.
25. Participation in an investigational study within 30 days prior to the screening visit that involved treatment with any drug (excluding vitamins and minerals) or device.
26. Treatment with systemic anti-VEGF therapeutics within 90 days prior to Screening.
27. Stroke or myocardial infarction in the 6-month period prior to Day 1.
28. 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 subject's initial blood pressure measurement exceeds these values, a second reading may be taken later on the same day or a different day during the screening period. If the subject's blood pressure is controlled by antihypertensive medications, the subject should be on a stable medication regimen continuously for 30 days prior to Day 1.

4.0 INVESTIGATIONAL PLAN

4.1 Study Design

This is a Phase 2b/3, prospective, randomized, double-masked, active comparator controlled, multi-center study evaluating the efficacy and safety of repeated dosing of 5 mg KSI-301 administered by intravitreal injections in treatment-naïve subjects with wAMD.

The overall duration of the study is approximately 2 years after the last subject is randomized to the study. The study will consist of a screening period of up to 21 days (-21 to -1) and a treatment period of approximately 2 years (Day 1 to Week 92), followed by the final study visit at Week 96. The duration of the study is defined for each subject as the date a signed written

informed consent is provided through the last follow-up visit at Week 96. A single eye per subject will be designated as the Study Eye. If both eyes are eligible to become the Study Eye, the eye with worse visual BCVA at Screening will be selected as the Study Eye. If both eyes have the same BCVA, the decision of which eye to select as the Study Eye will be made by the Investigator. Only one eye per subject can participate in the study.

Subjects will be randomized 1:1 into one of the following dose groups:

- KSI-301 5 mg; or
- Aflibercept 2 mg.

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

4.2 Screening Period

Subjects 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 subject's standard care. After providing informed consent, subjects will be evaluated for entry criteria during the screening period within 21 days before administration of study drug(s). Re-screening after screen failure will be allowed.

4.3 Screening Failure

Screen failures are defined as subjects who consent to participate in this study and are not randomized. To ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, the IRT system will collect information on screen failures, including the date of consent and reason(s) for screen failure.

This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (i.e. re-screening is allowed during the screening period). When re-screening, the subject must be re-consented if more than 30 days have elapsed since the date of the last informed consent and meet all eligibility criteria.

4.4 Treatment Period

Subjects in this study will be treated until Week 92, 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 4.8.1 are met.

4.4.1 Administration of Study Drug

Study Year 1 (Day 1 Visit through Week 52 Visit):

As shown in Table 4, all subjects will receive 3 initial injections of either KSI-301 or aflibercept, at Day 1, Week 4, and Week 8. The minimum interval between doses is 21 days.

KSI-301 Arm:

Following the 3 initial injections, the dosing regimen will be based on Disease Activity Assessments and may vary between Q12W to Q20W.

Year 1 Disease Activity Assessments:

- At Week 20 (12 weeks after the Week 8 dose), subjects that meet the Disease Activity Criteria will be dosed with KSI-301 and assigned to a Q12W dosing regimen through the remaining duration of the first year.
- Subjects that do not meet the Disease Activity criteria at Week 20 will not be dosed with KSI-301 at Week 20 and will be reassessed at Week 24.
- At Week 24 (16 weeks after the Week 8 dose), subjects that meet the Disease Activity criteria will be dosed with KSI-301 and assigned to a Q16W dosing regimen.
- Subjects that do not meet the Disease Activity criteria at Week 24 will not be dosed with KSI-301, will be assigned to a Q20W dosing regimen and dosed with KSI-301 at Week 28.
- At Week 36 (12 weeks after the Week 24 dose), subjects in the Q16W dosing regimen that meet the Disease Activity criteria will be adjusted to the Q12W dosing regimen, dosed with KSI-301 and maintained on this dosing interval through the remaining duration of the first year.
- Subjects who do not meet the Disease Activity criteria at Week 36 will continue their designated Q16W dosing regimen, with the next KSI-301 dosing at Week 40.
- At Week 40 (12 weeks after the Week 28 dose), subjects in the Q20W dosing regimen that meet the Disease Activity criteria will be adjusted to the Q12W dosing regimen and dosed with KSI-301.
- Subjects that do not meet the Disease Activity criteria at Week 40 will not be dosed with KSI-301 at Week 40 and will be reassessed at Week 44.
- At Week 44 (16 weeks after the Week 28 dose), subjects in the Q20W dosing regimen that meet the Disease Activity criteria will be adjusted to the Q16W dosing regimen and dosed with KSI-301.
- Subjects who do not meet the Disease Activity criteria at Week 44 will continue their designated Q20W dosing regimen through the remainder of the first year.

Year 1 Disease Activity Criteria:

- Decrease in BCVA of ≥ 5 letters compared to Week 12 and an increase in Optical Coherence Tomography (OCT) central subfield Thickness (CST) ≥50 µm compared to Week 12.
- Increase in OCT CST ≥75 µm compared to Week 12.
- Decrease in BCVA of ≥ 10 letters compared to the highest BCVA since Day 1 (inclusive) due to wAMD disease activity (e.g. increased intraretinal fluid, increased subretinal fluid, new intraretinal hemorrhage, new subretinal hemorrhage).
- New macular hemorrhage (documented with color fundus photograph).

Disease Activity Assessments will be conducted by the masked Investigator.

The IRT system will make the adjustments to the dosing schedule based on disease activity data from the study site.

Aflibercept Arm:

Following the 3 initial monthly injections, subjects randomized to aflibercept will be dosed at a fixed Q8W dosing regimen for the duration of the first year.

Second Year of the Study (Week 52 Visit through Week 96 Visit):

KSI-301 Arm:

As shown in Table 5, in the second year, dosing regimen adjustments in the KSI-301 group will also be based on Disease Activity Assessments, but the dosing regimens can be adjusted to both reduce or extend the treatment interval in increments of Q4W per dosing cycle, although adjustment of Q20W to Q12W is also allowed when needed. The minimum dosing interval is Q12W and the maximum dosing interval is Q20W.

[redacted]

Subjects that do not meet the Disease Stability/Extension Adjustment Criteria will be dosed with KSI-301 at their Scheduled Dosing Visit.

Year 2 Disease Activity Criteria:

Reduce Adjustment

Identical to Year 1 Disease Activity Criteria

[redacted]

Disease Activity Assessments will be conducted by the masked Investigator. The IRT system will make the adjustments to the dosing schedule based on disease activity data from the study site.

Aflibercept Arm:

At Week 52 subjects originally assigned to the aflibercept arm will be [redacted]

[redacted]

[redacted]

Masking: To maintain masking, all subjects will be treated with randomized study treatment or sham injections at all planned monthly study visits except for the Week 12 visit as the study dosing schedules of KSI-301 and aflibercept do not require dosing at that timepoint.

Table 4. Protocol KSI-CL-102: Year 1 Dosing Schedules in the KSI-301 and Aflibercept Treatment Groups

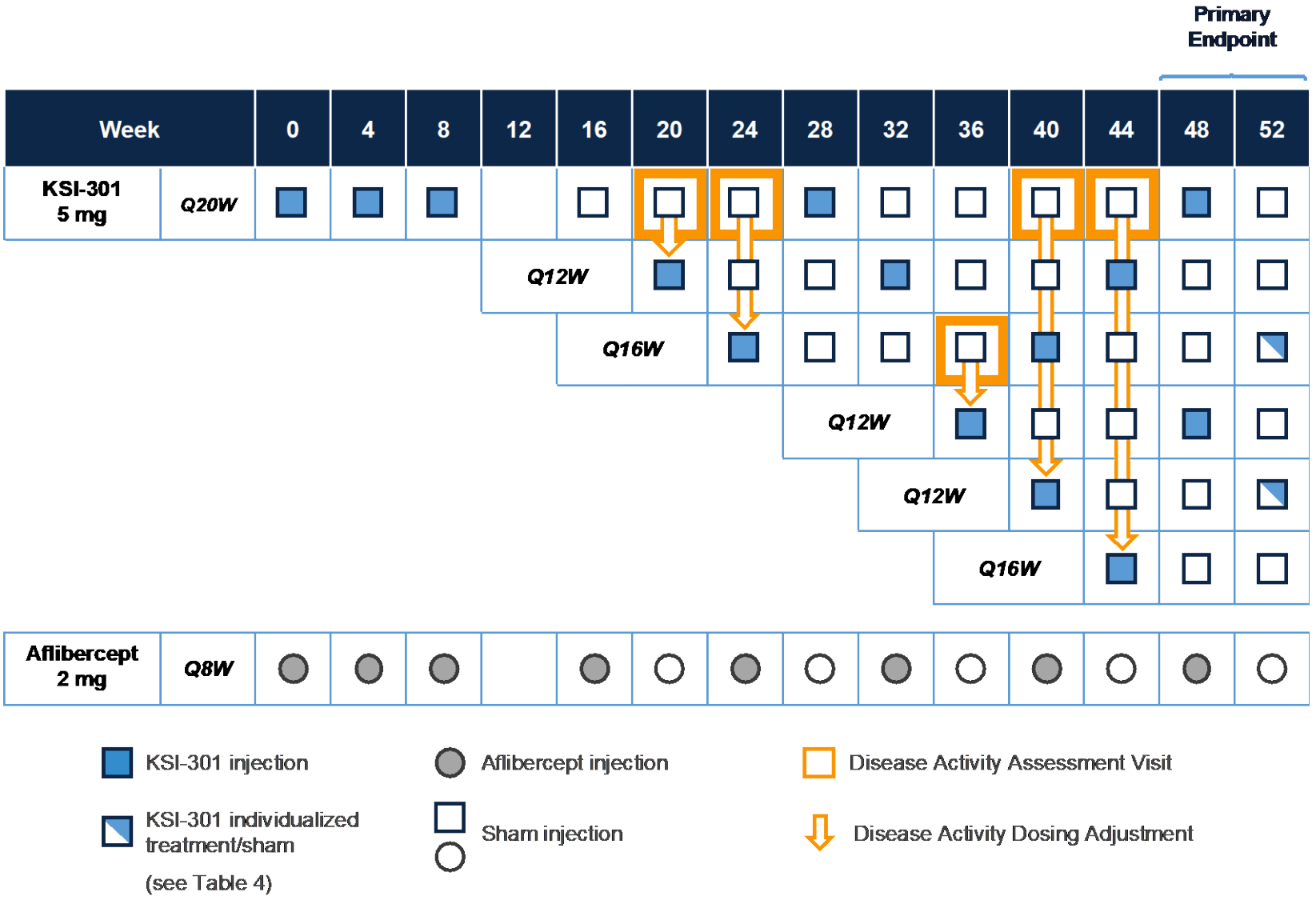
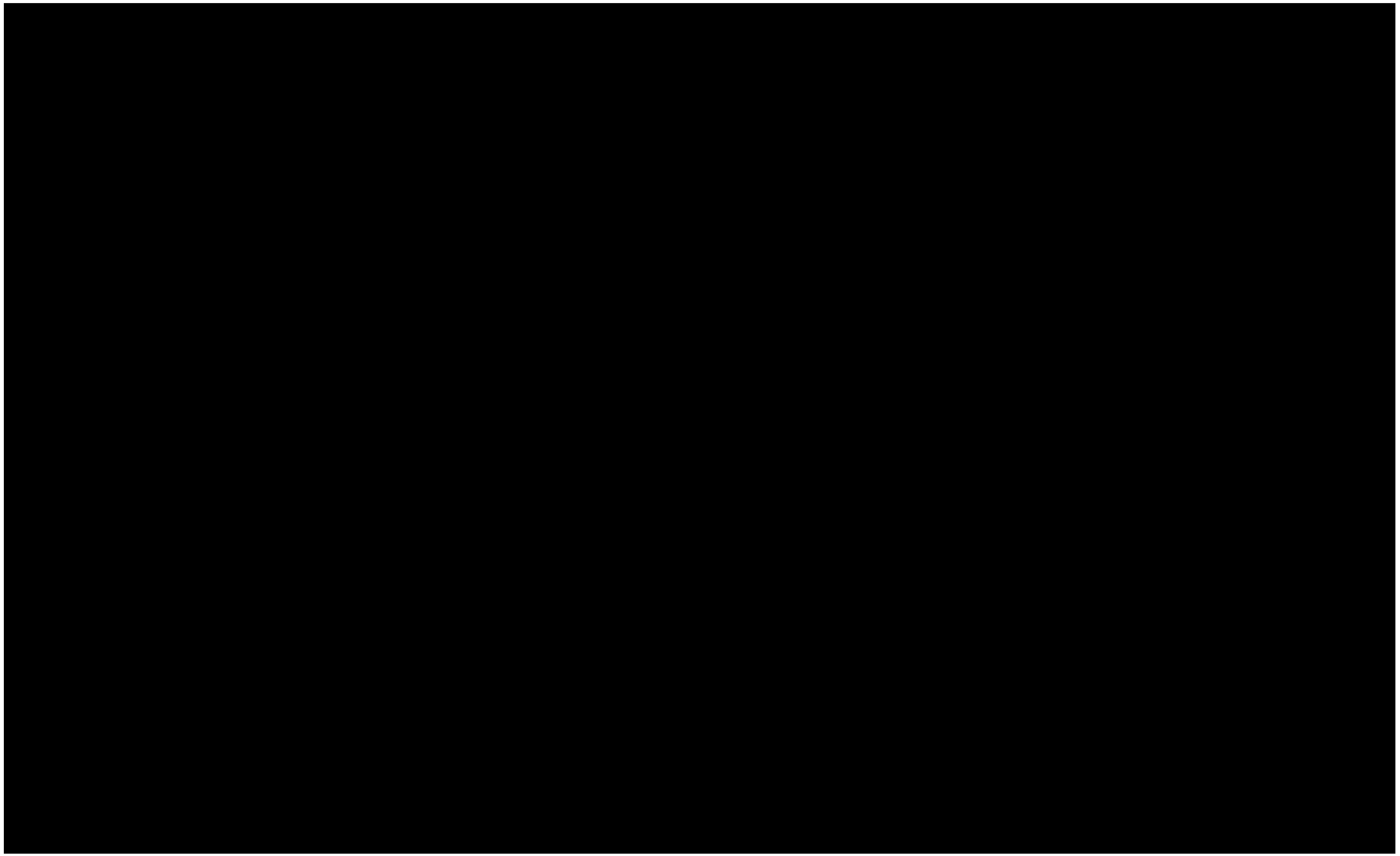


Table 5. **Protocol KSI-CL-102: Year 2 Dosing Schedules in the KSI-301 and Aflibercept Treatment Groups**



4.5 Missed Visits

Every attempt should be made to avoid missed visits.

The IRT will adjust the dosing schedule in consideration of missed visits, out of window visits and missing data during a visit.

4.6 Rescue Treatment

Subjects with active wAMD who experience severe visual acuity loss as defined below shall be eligible to be treated with standard of care if they meet this criterion at any time during the study:

- Loss of ≥ 15 BCVA ETDRS letters compared to Day 1.

Institution of rescue therapy for subjects who meet this criterion is at the discretion of the Investigator. Subjects who discontinue study drug to receive rescue treatment should NOT be considered withdrawn from the study. Unless they withdraw consent or there is additional risk to the subject, subjects 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, Week 52 and Week 96 (primary and secondary endpoint) visits. The Sponsor will not provide rescue treatment. All procedures in the Early Termination visit should be completed prior to administration of the rescue treatment.

4.6.1 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. At least one investigator will be designated as the evaluating physician who will be masked to subjects' treatment assignments and will evaluate all ocular assessments. At least one other investigator (and designated unmasked assistants, as needed) will be designated as the treating (injecting) physician who will be unmasked to subjects' treatment assignments and will administer injections (KSI-301, aflibercept and sham) as well as the immediate post-injection assessments and tonometry. The post-injection tonometry exams can also be performed by an unmasked assistant. The unmasked treating physician and unmasked staff must not divulge treatment assignment to anyone.

Subjects, study site personnel (except for the treating physician(s), unmasked 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, and low luminance examinations) will be masked to the subject treatment assignment. The BCVA examiner will have no access to the VA scores of a subject's previous visits and may have access only to a subject's refraction data from previous visits.

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. Emergency code break is available to the Investigator on-line in the IRT. If unmasking is necessary for subject management (for example, in the case of a serious adverse event (SAE) for which subject management might be affected by knowledge of the treatment assignment), the Investigator will be able to break the treatment code by accessing the IRT. Treatment codes must not be broken except in emergency situations. If the Investigator wishes to know a subject'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, CRO pharmacovigilance personnel) will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the Investigator or Sponsor to be related to study drug. The subject may continue to receive treatment, and the Investigator, subject, and Sponsor or CRO personnel, except for the pharmacovigilance personnel who must have access to subject treatment assignments to fulfill their roles, will remain masked to treatment assignments.

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

4.7 Treatment Compliance

Only subjects 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 and aflibercept and for administering sham, according to the study protocol.

4.8 End of Treatment

Subjects 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 subjects in the study. The end-of-treatment visit should occur 28 +/- 7 days after study treatment is discontinued or before a new treatment regimen begins.

Subjects who discontinue study drug should NOT be considered withdrawn from the study. Unless they withdraw consent or there is additional risk to the subject, subjects 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, Week 52 and Week 96 (primary and secondary endpoint) visits.

The reasons for study treatment discontinuation and/or withdrawal from the study (study discontinuation) will be recorded on the appropriate eCRF.

4.8.1 Reasons for Withdrawal/Discontinuation

The reasons for study treatment discontinuation and/or withdrawal from the study (study discontinuation) will be recorded on the appropriate eCRF. A subject may be withdrawn from the study for any of the following reasons:

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

The Investigator will also withdraw a subject if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a subject 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 subject may withdraw his or her consent at any time.

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

Study treatment interruption and/or subject discontinuation from the study treatment due to certain AEs or concomitant procedures in the Study Eye will be determined using the criteria provided in Table 6. If any of these are met, treatment will be interrupted (or discontinued if applicable). Treatment may be resumed after resolution of the AE(s) 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 6. Protocol KSI-CL-102: Study Treatment Interruption/Subject Discontinuation Criteria

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

4.8.3 Handling of Study Treatment Discontinuation and Withdrawals

Subjects should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible, with emphasis on the Week 48, Week 52, and Week 96 visits. However, subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject 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 on the relevant page of the electronic case report form (eCRF). Whenever possible, all subjects who discontinue study treatment or withdraw from the study prematurely will undergo an Early Termination visit. Subjects who fail to return for final assessments must be contacted by the site by phone and in writing to obtain follow-up.

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

It is vital to obtain follow-up data on any subject withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety follow-up procedures.

4.8.4 Replacements

Subjects who discontinue study drug treatment will not be replaced or allowed to re-start the study treatment.

4.9 End of Study

The end of the study according to the protocol is defined as the last follow-up visit of the last subject enrolled or a Sponsor decision to terminate the study, whichever comes first.

Study data may be collected beyond the end of the study.

4.10 Treatment After End of Study

After subjects complete their final follow-up visit or discontinue from the study prematurely, all subjects 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 subject's study treatment period.

4.11 Non-protocol-specified Treatments

4.11.1 Concomitant Therapy

Use of all concomitant medications will be recorded in the subject's eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, and over the counter (OTC) medications. Any changes in concomitant medications also will be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

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

In case the non-Study Eye requires anti-VEGF treatment during the conduct of the study for the treatment of wAMD, the subject may be treated at the discretion of the Investigator and according to the standard of care in the respective country. The treatment of the non-Study Eye may be implemented at any time once the Day 1 injection has been administered. Non-Study Eye anti-VEGF treatment must be documented on the appropriate eCRF. If the non-Study Eye requires treatment at the same visit as the Study Eye, all Study Eye assessments and Study Eye treatment administration should be completed before treating the non-Study Eye, and the non-Study Eye should be treated by the unmasked physician to preserve masking.

4.11.2 Prohibited Therapy

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

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

Subjects whose medical care requires use of a prohibited therapy must have study treatment interrupted in order to receive that therapy. After discussion with the Sponsor's Medical Monitor, subjects whose study treatment has been interrupted but no longer need a prohibited therapy may resume study treatment.

5.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUG

5.1 KSI-301

5.1.1 Drug Description and Formulation

KSI-301 is an antibody biopolymer conjugate consisting of a recombinant, mammalian cell expressed full-length humanized anti-VEGF monoclonal antibody that is covalently conjugated to a branched high molecular weight phosphorylcholine-based biopolymer.

KSI-301 will be supplied by the Sponsor as a sterile liquid aqueous solution at [redacted] mg/ml (based on antibody mass) and filled into single-use vials.

5.1.2 Drug Packaging and Labeling

KSI-301 will be packaged and labeled according to current good manufacturing practices. Each vial will be labeled with the study drug number/name, strength, name of the Sponsor, lot number and the required cautionary statement(s).

5.1.3 Drug Reconstitution and Handling

KSI-301 drug product is an aqueous solution that is that is provided in vials and filled into syringes by unmasked site personnel without reconstitution or dilution.

The instructions for administration of KSI-301 drug product are described in the Pharmacy Manual.

5.1.4 Drug Storage

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 Pharmacy Manual for additional instructions.

5.2 Aflibercept

Aflibercept will be supplied by the Sponsor as a sterile liquid for intravitreal injection in single-use glass vials. Refer to the Pharmacy Manual for additional details. For information regarding the administration of aflibercept, refer to the country-specific approved prescribing information for aflibercept, such as the Summary of Product Characteristics (SmPC).

5.3 Sham Formulation

The sham vial is an empty glass vial which will remain empty throughout the sham treatment procedure (full details of the sham procedure are in the Pharmacy Manual). A sham injection is used for masking purposes and mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe, without a needle, against an anesthetized eye. A sham vial is provided to help maintain masking of the study.

5.4 Study Drug Accountability and Reconciliation

Study drug packaging will be overseen by Kodiak Sciences Inc. or their CRO partner 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 drug, to confirm the shipment condition and content. Any damaged shipments will be replaced. Upon arrival of the study drug at the site, site personnel will complete the following:

- Check the drug shipment for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Sponsor or their delegate upon discovery.

The Investigator or delegate 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.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

Remaining study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site must obtain written authorization from the Sponsor before any study drug is destroyed, and study drug destruction must be documented on the appropriate form.

6.0 STUDY ASSESSMENTS AND PROCEDURES

Before undertaking any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the subject. The Investigator or designee will also sign the ICF.

Study procedures and their timing are summarized in the Schedule of Activities (SoA) for Year 1 (Table 1) and Year 2 (Table 2). Assessments performed in the event of an unscheduled safety visit (Section 13.1) 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.

6.1 Study Assessments

6.1.1 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 medications, herbal or homeopathic remedies, nutritional supplements) used by the subject regularly or within 30 days preceding Day 1 must be recorded. A full ocular history including prior ocular treatments will be noted. Demographic data will include age, sex, and self-reported race, ethnicity and smoking status.

6.1.2 Ophthalmic Exams

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

Slit-lamp examination which will include:

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

Dilated indirect ophthalmoscopy will include examination of the peripheral retina.

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

Subjects will be instructed to report any signs or symptoms of intraocular inflammation (uveitis) or endophthalmitis that may be a clinical sign and include symptoms such as pain, photophobia, redness, or reduced vision.

6.1.3 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 IVT injections. Aseptic technique must be observed by clinic staff involved in the assembly of the injection tray, study drug preparation, anesthetic preparation, and study treatment administration. To minimize the risk of infection the periocular skin and eyelid of the Study Eye must be disinfected with 10% povidone iodine swabs and 5% povidone iodine must be applied to the bulbar conjunctiva directly over and surrounding the injection site.

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

Please refer to Syringe Preparation and Injection Procedure Guidelines found in the Pharmacy Manual for additional instructions.

6.1.4 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 subject will be permitted to leave the clinic. If the IOP value is of concern to the Investigator, the subject 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 remain the same throughout the study for each subject.

6.1.5 Best Corrected Visual Acuity (BCVA) and Low Luminance BCVA

6.1.5.1 BCVA

BCVA will be measured utilizing the ETDRS method by qualified, 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.

[redacted]

A BCVA and [redacted] Testing Procedure Manual and training materials will be provided to all sites by the third-party VA Examiner certification vendor.

6.1.6 Fundus Photography (FP)

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

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

6.1.7 Spectral Domain Optical Coherence Tomography (SD-OCT)

SD-OCT will be performed at the study sites by qualified 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.

6.1.8 Fluorescein Angiography (FA)

Two-field FA will be performed at all the study sites by qualified personnel. It is mandatory that the same model of device is used for the entire duration of the study.

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

6.1.9 Disease Activity Assessments

The IRT will make the necessary adjustments to the dosing schedule based on disease activity data from the study site. Details of the Disease Activity Assessments are described in Section 4.4.1.

6.1.10 Vital Signs

The following vital signs will be assessed taken with the subject in a seated position after resting for 5 minutes: blood pressure, pulse rate, and body temperature, in addition to height and weight at Screening.

6.1.11 Adverse Events

The following definitions, based on the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical trial.

6.1.11.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject enrolled in the study, regardless of treatment assignment that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including, for example, an abnormal laboratory finding), symptom, syndrome, disease, or increase in severity of a pre-existing abnormality, whether or not considered related to the study drug.

Examples of AEs include the following:

- Any treatment-emergent signs and symptoms (events that are a change from the subject's baseline conditions, including an increase in frequency or severity).
- Clinically significant laboratory findings as judged by the Investigator.
- Disease-related (indication) signs and symptoms not present at baseline.
- Reactions from the investigational treatment, including method of administration.

- Injury or accidents.
- Any other event or finding that the Investigator feels is clinically significant.

Disease-related signs and symptoms present at Screening should not be recorded as AEs.

Adverse events will be recorded starting after the first dose of trial drug [treatment emergent AEs (TEAEs)] and continuing until 4 weeks after the last dose or until the last follow-up visit required by the protocol, whichever comes later.

Events that are not considered AEs include the following:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject'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 subject'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.

6.1.11.2 Monitoring Adverse Events

Adverse events will be assessed starting after the first dose of trial drug (TEAEs) and up to 4 weeks after the last dose of study drug. Serious AEs that occur more than 4 weeks after the last dose of study drug need not be reported unless the Investigator considers them related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They 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 subject 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 subject safety will be documented on the AE page in the eCRF.

6.1.11.3 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	These events require minimal or no treatment and do not interfere with the subject's daily activities in a significant manner – it may be an annoyance.
Moderate:	These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning, but it is not hazardous to the subject's health.
Severe:	These events produce significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

The evaluation of severity is distinguished from "seriousness." A severe event might not meet the criteria for seriousness and a serious event might be evaluated as mild or moderate in intensity. For example, a subject might have a severe headache that does not require hospitalization and is consequently not serious; or a subject might have a mild myocardial infarction that requires hospitalization and is, therefore, serious.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent do not require documentation of onset and duration of each episode.

6.1.11.4 Assessment of Causality

The causality of each AE must be assessed by the masked Investigator. The masked Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IP and the AE.

The following considerations should be assessed by the Investigator to guide determination of causality:

- Temporal association between the study treatments (injection procedure and study drug) and the event;
- Cessation or re-challenge (e.g., of a suspected concomitant medication);
- Compatibility with known effects of the study treatments;
- Known effects of concomitant medications;

- Pre-existing risk factors; and/ or
- A plausible mechanism.

The relationship to the intravitreal injection procedure or to study drug 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 drug.
- **Related** - There is a reasonable possibility that the AE is related to the injection procedure or to the study drug.

6.1.11.5 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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)

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

- Endophthalmitis: diffuse intraocular inflammation predominantly involving the vitreous cavity but also involving the anterior chamber, implying a suspected underlying infectious cause

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.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

6.1.11.6 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (at the time of the event);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
    - In general, hospitalization signifies that the subject 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.
- 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.

- Is a congenital anomaly/birth defect (in an offspring); and/or
- Is an important medical event.
    - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment by the Investigator or Sponsor, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For this study, scheduled hospitalizations for administration of the IP, elective surgery, or for scheduled study procedures, are not to be reported as SAEs.

6.1.11.7 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.1.10.6) must be reported to the Sponsor or its designee immediately (i.e., within 24 hours) after the time site personnel first learn about the event. SAE reporting instructions are outlined in the Site Binder.

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.

6.1.11.8 Definition of Adverse Events of Special Interest (AESI)

An AE 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 AEs may be serious or non-serious. Applicable AEs 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.

6.1.11.9 Reporting Adverse Events of Special Interest (AESI)

These AESIs must be reported by the Investigator using the same mechanism (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:

- Cases of potential liver injury (see Section 6.4.2).
- AEs resulting from medication error, including overdose, incorrect dose, incorrect drug, incorrect administration or incorrect kit.
- AEs with sight-threatening potential, meeting one or more of the following criteria:

- Causes a decrease ≥ 30 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 Section 13.2 for grading scales).
- Requires surgical intervention to prevent permanent loss of sight.

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

6.1.11.10 Immediate Reporting Requirements from Investigator to Sponsor

The Investigator must report certain events to the Sponsor or its CRO partner to allow for appropriate measures to be taken to manage potential new risks in a clinical study. These events should be reported immediately to the Sponsor, and in all cases within 24 hours of learning from the event. The following events should be immediately reported, regardless of relationship to study drug:

- SAEs
- Non-serious AESIs
- Pregnancies

In addition, the Investigator must report new significant follow-up information for these events immediately (within 24 hours). New significant information includes:

- New signs or symptoms of a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the outcome of the event, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and the IRB/IEC.

6.1.11.11 Expedited Reporting to Regulatory Authorities, Investigators, Institutional Review Boards and Ethics Committees

The Sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) and serious and non-serious AESIs against cumulative product experience to identify possible new safety findings. Expectedness of these events will be assessed using the following reference documents:

- KSI-301 Investigator's Brochure; and
- Aflibercept (Eylea®) European Medicines Agency (EMA) Summary of Product Characteristics.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

All cases will be reported to the IRB/IEC in accordance with the standard operating procedures (SOPs) and policies of the IRB/IEC and reported to regulatory authorities, per local regulations such that:

- All fatal or life-threatening AEs will be reported immediately after the Sponsor receives the initial report from the Investigator; and
- All nonfatal or non-life-threatening cases will be reported within a maximum of 15 days after the initial Investigator's report.

6.1.11.12 Diagnosis Versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

6.1.11.13 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If vitreous hemorrhage results in VA decrease only the vitreous hemorrhage should be reported.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

6.1.11.14 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

6.1.11.15 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial

severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

6.1.11.16 Deaths

All deaths that occur during the protocol-specified AE reporting period regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

6.1.11.17 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the Medical History eCRF.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the eCRF, it is important to clearly inform the concept that the pre-existing condition has changed by including the characteristics of the change.

6.1.11.18 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatments is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the eCRF and should be reported to the Sponsor immediately (no more than 24 hours after the event is recognized).

6.1.11.19 Follow-Up of Subjects Reporting Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the subject is considered stable.

6.2 Safety 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.

6.3 Pregnancy

Samples for pregnancy testing will be taken at the Screening and Day 1 visits and then monthly, as specified in the SoA for Year 1 (Table 1) and Year 2 (Table 2).

Prior to enrollment in the study, female subjects of childbearing potential and male subjects 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.

During the study, female and male subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant or if their partner becomes pregnant, respectively. 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 in a Sponsor prepared form. To ensure subject 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 subject 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 subject has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported to the Sponsor.

6.4 Laboratory Analyses

Blood samples for the following laboratory assessments will be at taken as specified in the SoA for Year 1 (Table 1) and Year 2 (Table 2):

- Hematology: hemoglobin, platelet count, white blood cell (WBC) and differential;

- Renal function: serum creatinine and blood urea nitrogen (BUN);
- Hepatic function: serum bilirubin, alkaline phosphatase, gamma-glutamyl-transferase (GGT), serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT); and
- Electrolytes: sodium, potassium, chloride, bicarbonate, calcium and phosphate.

If the Investigator judges a laboratory value outside of the normal range as clinically significant, the Investigator may at their discretion repeat the laboratory determination as judged appropriate to ensure the validity of the abnormal result.

6.4.1 Abnormal Laboratory Values

Any abnormal laboratory test results (hematology or clinical chemistry) or other abnormal diagnostic findings (e.g., ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Not every laboratory abnormal value qualifies as an AE. An abnormal laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., treatment discontinuation or interruption).
- Results in a medical intervention.
- Clinically significant in the Investigator's judgment.

It is the responsibility of the Investigator to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated abnormal laboratory result should be classified as an AE.

If a clinically significant laboratory value abnormality is a sign of a disease or syndrome, only the diagnosis should be recorded on as an AE in the eCRF. If it is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE in the eCRF, describing if the value is above or below the normal range (e.g., "elevated sodium", instead of "abnormal sodium").

In case the same clinically significant laboratory abnormality is observed in subsequent visits it should not be recorded repeatedly as an AE in the eCRF, unless the etiology changes. The initial severity of the event should be recorded and updated in case the event worsens.

6.4.2 Abnormal Liver Function Tests

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); and
- 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.

6.5 Pharmacokinetic, Biomarker, and Immunogenicity Assessments

Blood samples (4 mL) for systemic pharmacokinetic, systemic biomarker, and systemic immunogenicity testing will be taken at the timepoints specified in the SoA for Year 1 (Table 1) and Year 2 (Table 2). Supplementary testing of samples may be used for exploratory evaluation of the bioanalytical method.

To understand the systemic PK of the study drug following intravitreal injection, plasma concentration of KSI-301 will be measured. For exploratory purposes, plasma VEGF levels or other blood factors may be evaluated as systemic biomarkers. Plasma samples of comparator may also be analyzed for systemic PK and systemic biomarkers.

As with all therapeutic proteins, there is the potential for an immune response in subjects treated with KSI-301. The detection of anti-drug antibodies (ADAs), or anti-KSI-301 antibodies in subject plasma samples will be assessed. Additional immunogenicity testing of samples may be performed to further characterize the ADA response for specificity and/or neutralizing antibodies (NAB).

Details on sampling procedures, sample storage and shipment will be provided by the central laboratory.

7.0 STATISTICAL AND ANALYTICAL PLAN

Analysis of the primary (Year 1) data will be performed when all subjects have either completed the Week 52 visit or have discontinued from the study prior to the Week 52 visit, whichever comes later, and all data up to and including the Week 52 visit have been entered into the database, cleaned and verified as appropriate, and the database for the primary analysis locked. Analysis of data for Year 2 of the study will be performed when all subjects have either completed the Week 96 visit or have discontinued from the study, and all data have been entered into the database, cleaned and verified as appropriate, and the database locked.

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

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

7.1 Primary Efficacy Endpoint

The primary endpoint of this study will be the mean change in BCVA from Day 1 to Year 1, comparing subjects receiving KSI-301 to aflibercept at a non-inferiority margin of 4 letters. Year 1 is defined as the mean BCVA at Weeks 48 and 52.

7.2 Secondary Efficacy Endpoints

<u>At Year 1:</u>

- Proportion of subjects on a Q12W, Q16W or Q20W dosing regimen of KSI-301 at Week 52
- Proportion of subjects who gain ≥ 5, ≥10 and ≥15 letters from baseline over time
- Proportion of subjects who lose ≥ 5, ≥10 and ≥15 letters from baseline over time
- Mean change from baseline in BCVA from baseline to Week 12, Week 16, and over time
- Proportion of subjects with BCVA Snellen equivalent of 20/40 or better from baseline over time
- Proportion of subjects with BCVA Snellen equivalent of 20/200 or worse from baseline over time
- Mean change in OCT CST from baseline to Week 12, Week 16, and over time
- Mean change in OCT intraretinal fluid volume from baseline to Week 12, Week 16, and over time
- Mean change in OCT subretinal fluid volume from baseline to Week 12, Week 16, and over time
- Proportion of subjects without intraretinal fluid on OCT from baseline to Week 12, Week 16 and over time
- Proportion of subjects without subretinal fluid on OCT from baseline to Week 12, Week 16 and over time

- Proportion of subjects without pigment epithelial detachments on OCT from baseline over time
- Mean change in CNV total lesion area on FA from baseline at Year 1
- Mean chance in area of leakage on FA from baseline at Year 1
- Number of study drug injections received in the KSI-301 and aflibercept groups through Year 1
- For the KSI-301 group, the predictability of being on Q12W, Q16W, or Q20W dosing at the end of Year 1 on the basis of the first set of Disease Activity Assessments (at Weeks 20 and 24).

At Year 2:

- Proportion of subjects who gain ≥ 5, ≥10 and ≥15 letters from baseline over time
- Proportion of subjects who lose ≥ 5, ≥10 and ≥15 letters from baseline over time
- Mean change from baseline in BCVA from baseline over time
- Proportion of subjects with BCVA Snellen equivalent of 20/40 or better from baseline over time
- Proportion of subjects with BCVA Snellen equivalent of 20/200 or worse from baseline over time
- Mean change in OCT CST from baseline over time
- Mean change in OCT intraretinal fluid volume from baseline to Week 12, Week 16, and over time
- Mean change in OCT subretinal fluid volume from baseline to Week 12, Week 16, and over time
- Proportion of subjects without intraretinal fluid on OCT from baseline over time
- Proportion of subjects without subretinal fluid on OCT from baseline over time
- Proportion of subjects without pigment epithelial detachments on OCT from baseline over time
- Mean change in CNV total lesion area on FA from baseline at Year 2
- Mean chance in area of leakage on FA from baseline at Year 2

For BCVA and OCT, Year 1 is defined as the average measurement at Weeks 48 and 52 and Year 2 is defined as the average measurement at Weeks 92 and 96.

A full list of secondary endpoints, including the delineation of key versus additional secondary endpoints, will be outlined in the SAP.

7.3 Sample Size Calculations

Subjects will be randomized in a 1:1 ratio to KSI-301 or the active comparator, aflibercept. The sample size for the comparison between the KSI-301 and aflibercept groups at Year 1 is based on a non-inferiority approach. The following assumptions were made to calculate the sample size:

- Overall Type I error rate of 0.025. Testing at the 0.025 level corresponds to setting 95% confidence intervals.
- Statistical power of ≥90%.
- Standard deviation of the distribution of change in visual acuity from baseline of [redacted] letters (averaged over Weeks 48 and 52).
- The maximum clinically-acceptable true difference for KSI-301 to be considered non-inferior, or the "non-inferiority margin," [redacted]
- The anticipated true difference in mean change from baseline in BCVA between treatment groups is 0. That is, both treatment arms are expected to have the same efficacy.
- The statistical test used to compare the two treatment groups at Week 52 is an independent t-test on the mean change in visual acuity from baseline.
- Lost to follow-up rate [redacted]

The sample size calculated using the above assumptions is 550 subjects (275 per treatment group).

Confidence intervals will be 100(1-2 α) or 95% confidence intervals. If the null hypothesis of inferiority is rejected, testing for superiority will be performed. That is, if the lower confidence limit for the difference in mean BCVA lies within (-4, ∞), the null hypothesis of inferiority will be rejected, and the non-inferiority will be established. Furthermore, if the lower confidence limit lies within (0, ∞), superiority will be established.

[redacted]

7.4 Analysis Sets

Full details and definitions of analysis sets will be provided in the SAP. The following analysis sets will be used in the statistical analyses:

- Intent to treat set (ITT) will be comprised of all subjects who were randomized in the study. For analyses based on this population, subjects will be grouped according to the treatment assigned at randomization.
- Per-protocol set (PPS): The PPS will consist of all ITT subjects 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 subjects according to treatment actually received.
- Safety set: The safety set will consist of all subjects who received any study drug. All analyses using the safety set will group subjects according to treatment actually received.
- Systemic pharmacokinetic (PK)/biomarker/ADA set: The PK/biomarker data set will consist of all subjects with at least one post Day 1 data point. The ADA data set will consist of all subjects with pre-dose sample on Day 1 and at least one post Day 1 data point.

7.5 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later.

Results from this study will be reported using descriptive statistics-number of subjects (N), mean, standard deviation or standard error of the mean, median, maximum and minimum for continuous outcomes and frequency and percentage for categorical variables. Data will be listed in data listings.

Details of all analyses, including imputation approaches for handling of missing data, will be included in the SAP. The results of all analyses detailed in the SAP will appear in the final clinical study report.

7.5.1 Analysis of Primary Efficacy Endpoint

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

The primary endpoint is defined as the mean change in ETDRS BCVA from Day 1 to Year 1. Year 1 is defined as the mean BCVA at Weeks 48 and 52. The primary assessment of efficacy will be based on a pairwise comparison in mean change in BCVA between the two treatment groups. If there are no imbalances on important prognostic factors at baseline, a simple independent t-test and corresponding confidence intervals will be used for evaluation of treatment differences. If there are imbalances in key prognostic factors at baseline (e.g., BCVA) generalized linear models or other statistical models (such as mixed effects models) will be used to estimate the difference in mean change in VA between treatment groups and confidence intervals derived from the corresponding standard error of the estimate. These models will also include indicator variables for stratification variables. An alpha level of 0.025 will be used for hypothesis testing and confidence intervals will be 100(1-2α) or 95% confidence intervals. If the null hypothesis of inferiority is rejected, testing for superiority will be performed.

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

7.5.2 Analysis of Key Secondary Efficacy Endpoints

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 timepoint 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 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.

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.

Full details will be provided in the SAP.

7.5.3 Analyses of Additional Secondary Efficacy Endpoints

Continuous and categorical secondary efficacy endpoints will be analyzed as described in the SAP.

7.5.4 Pharmacokinetic Analyses

PK Analyses will be outlined in the PK Analysis Plan.

7.5.5 Safety Analyses

The safety analysis (using the safety set as described in Section 7.4) will use outcomes of all subjects 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 AEs 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 AEs, per-injection rates will also be described.

7.5.6 Interim Analyses

[redacted]

Full details regarding interim analyses will be provided in the SAP.

8.0 DATA QUALITY ASSURANCE

This study will be conducted according to the ICH E6 guideline for GCP for all risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include ophthalmic clinical images, laboratory reports, among others.

The Sponsor or a designated CRO will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the eCRF via the EDC system. Data entered manually will be collected via EDC using eCRFs. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data). In the event of discrepancies in the data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The audit trail of the EDC system

will keep records of the eCRFs and the correction documents. The Sponsor will supply eCRF specifications for this study.

Clinical data management will be performed in accordance with all applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. AE terms will be coded using the MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG).

9.0 ETHICS

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6 Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

Any changes to the protocol, ICF, advertisements (if applicable), and any other written information provided to the subjects can only be made by the Sponsor and must be reviewed and approved by the IRB/IEC.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must promptly supply the Sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, ICH and GCP guidelines, and in accordance with the ethical principles for medical research involving human subjects as stated in the Declaration of Helsinki.

9.3 Subject Information and Consent

A written informed consent in compliance with all applicable regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject.

The Principal Investigator (PI) will ensure that the nature, purpose, procedures, duration, potential risks and potential benefits of participation in the study are explained to each subject. The subject will be provided with the IRB approved ICF, written in a language in which they understand, and given sufficient time to ask questions and to consider all information provided and the risks associated with participation. Subjects will be explained about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject will be informed that they have the right to withdraw from the study at any time without any disadvantage.

Once the Investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The Investigator shall retain the signed original ICF and give a copy of the signed original form to the subject or legal guardian.

10.0 INVESTIGATOR'S OBLIGATIONS

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Study Monitoring Requirements

The PI/institution(s) will permit trial-related monitoring, audits, IRB review and regulatory inspections, and will provide direct access to source data/documentation.

Site visits will be conducted in accordance with the monitoring plan to evaluate study data, subject's medical records, source document worksheets, and eCRFs in accordance with current ICH-GCP guidelines. During these site visits, source documents will be reviewed to confirm the study is being conducted according to the protocol and that subject safety is being maintained. Additionally, source data verification (SDV) will be conducted for accuracy of data entered into the EDC system.

Regularly scheduled site visits to monitor proper conduct of the study will be conducted by Sponsor and/or contract research organization (CRO) representatives. During these visits,

essential study documents, subject medical records, trial-related activities and protocol adherence, completed source document worksheets, eCRFs, and any data pertinent to the study will be reviewed with the site personnel. If necessary, the site monitor will conduct re-training of study site personnel to ensure compliance with the protocol and applicable regulation.

The monitor is responsible for inspecting the eCRFs throughout the study to verify adherence to the protocol as well as completeness, accuracy, and consistency of the data. The monitor will also ensure adherence to local regulations on the conduct of clinical research. The monitor should have direct access to subject medical records and other study related records needed to verify the accuracy of the entries on the eCRFs.

The PI agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with the International Conference on Harmonization Guidance on GCP and the Sponsor's audit plans, study sites may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study related records will occur to evaluate the study conduct and compliance with the protocol, International Conference on Harmonization, GCP and applicable regulatory requirements.

The PI will also permit the local regulatory authorities to inspect facilities and records relevant to this study. The PI is to ensure that the Sponsor is notified immediately of any notice or conduct of such inspection.

10.2 Confidentiality

The confidentiality of the subjects will be maintained by coding each subject enrolled in the study through assignment of a unique identification number. Subject identifiers including names are not included in any data set provided to the Sponsor.

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

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

Subject 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 subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be

released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the US Food and Drug Administration (FDA) or other governmental health authorities, or the IRB/IEC.

The PI must ensure that any subject data or records that are transmitted are de-identified. Subjects will be identified by an anonymized subject number on the eCRFs or other study related documents. Other study related documents (e.g., signed ICFs) should be kept in strict confidence by the PI.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the regulatory authority, national and local health authorities, the Sponsor, and the investigative site's IRB.

The Investigator and all employees and coworkers 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.

10.3 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator 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 subject's disease.

10.4 Study Conduct

The Investigator agrees that the study will be conducted as outlined in this protocol and according to the principles of ICH E6. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers.

10.5 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to the Sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.6 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

10.7 Records Retention

The PI must ensure that adequate records are maintained for the study including the protocol, protocol amendments, source document worksheets and DVDs of electronic case record books, source documents, signed ICFs, drug accountability records, AE reports, screening logs, records of drug accountability, subject charts and records, laboratory reports, IRB approvals, correspondence with IRB, correspondence with Sponsor, all documents submitted to Sponsor, all documents submitted to regulatory and government authorities, other source documents, other pertinent data and all study communications, whether written, telephonic, or electronic.

These files must be available for audit or inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities.

None of the required documents may be destroyed or transferred to the control of another party without the written approval of the Sponsor. Subject medical records may be archived in accordance with the archiving regulations or facilities of the investigational sites.

As required by 21CFR 312.62, Investigators must retain essential documents for a period of 2 years following approval to market of the product in the same indication or for a period of 2 years from the time the FDA is notified that development in the same indication has been discontinued.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will inform the PI/institution in writing of the need for record retention and will notify the PI/institution in writing when the trial related records no longer need to be retained.

10.8 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel, following the same ICMJE guidelines and requirements.

Any inventions and resulting patents or improvements originating from the use of data from this study will become and remain exclusive and unburdened property of the Sponsor.

11.0 STUDY MANAGEMENT

11.1 Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities of the termination/ suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons. The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause.

Reasons for the closure of an investigational site or termination of a study may include:

- Unsatisfactory subject enrollment;
- The Investigator fails to comply with the protocol or GCP guidelines;
- Incidence or severity of AEs indicate a potential safety concern; and/or
- Sufficient data suggesting lack of efficacy.

If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s) by telephone and subsequently will provide written confirmation of and instructions for study termination. The Investigator may be informed of additional procedures to

be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing the IRBs/IECs of the early termination of the trial.

11.2 Protocol Amendments

Modification of the protocol, except as necessary to remove an apparent, immediate hazard to the subject, is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB and regulatory authorities prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

11.3 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH Guideline E3: *Structure and Content of Clinical Study Reports*.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the Sponsor will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registries.

12.0 APPENDICES

Appendix 1: Unscheduled Safety Assessment Visits

Appendix 2: Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreous Hemorrhage Density, and Vitreous Haze

Appendix 3: Protocol Amendment History

12.1 Appendix 1: Unscheduled Safety Assessment Visits

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

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

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

12.2 Appendix 2: Grading Scale for Assessment of Anterior Chamber Flare or Cells, Vitreous Hemorrhage Density, and Vitreous Haze

12.2.1 Grading Scales for Anterior Chamber Cells or Flare

The SUN Working Group Grading Scale for Anterior Chamber Cells

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

Abbreviations: SUN = Standardization of uveitis nomenclature.

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

Source: Jabs 2005

The SUN Working Group Grading Scale for Anterior Chamber Flare

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

Abbreviations: SUN = Standardization of uveitis nomenclature.

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

Source: Jabs 2005

12.2.2 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 2002

12.2.3 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

12.3 Appendix 3: Protocol Amendment History

The amendment history for Protocol KSI-CL-102 is provided in Table 7.

Table 7: Protocol KSI-CL-102: Amendment History

Version	Version Date	Description
3.0	02 June 2021	Changes from version 2.0 to version 3.0 include the following: • Minor editorial and administrative revisions; and • Addition of Appendix 3: Protocol Amendment History.
2.0	03 August 2020	Changes from version 1.0 to version 2.0 include the following: • Minor editorial and administrative revisions; • [redacted] • The KSI-301 benefit/risk assessment was re-evaluated in consideration of protocol development for the planned Phase 3 studies in retinal diseases and the Coronavirus disease (COVID-19) pandemic caused by the virus SARS-CoV-2 and the impact it may have on clinical trials. The benefit/risk assessment was also harmonized across the Investigator's Brochure and other Phase 3 protocols.
1.0	15 April 2019	Original protocol

13.0 REFERENCE LIST

1. Brown DM, Kaiser PK, Michels M, *et al.,* (2006). ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration N Engl J Med.;355(14):1432-44.
2. Campochiaro PA at al, (2015). Molecular pathogenesis of retinal and choroidal vascular diseases. Prog Retin Eye Res;49:67-81.
3. Cheung N, Mitchell P, Wong TY *et al.,* (2010) Diabetic retinopathy. Lancet; 376(9735):124-36
4. Chew EY, Clemons TE, Agron E, *et al.,* (2014). Ten-year follow-up of age-related macular degeneration in the age-related eye disease study. AREDS Report No. 36. JAMA Ophthalmol132(3):272-277.
5. Chew EY, Clemons TE, Bressler SB*, et al.* (2014). Randomized trial of a home monitoring system for early detection of choroidal neovascularization home monitoring of the Eye (HOME) study. Ophthalmology, 121: 535-44.
6. Chong V. (2016) Ranibizumab for the treatment of wet AMD: a summary of real-world studies. Eye (Lond);30(2):270-86.
7. Flaxel CJ, Adelman RA, Bailey ST*, et al.* (2020). Diabetic Retinopathy Preferred Practice Pattern®. Ophthalmology, 127: P66-P145.
8. Foster CS, Vitale AT. (2002) Diagnosis and Treatment of Uveitis, JP Medical Ltd.
9. Gragoudas ES, Adamis AP, Cunningham Jr ET*, et al.* 2004. Pegaptanib for neovascular age-related macular degeneration. New England Journal of Medicine, 351: 2805-16.
10. Heier JS, Brown DM, Chong V, *et al.,* (2012). VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012 Dec;119(12):2537-48.
11. Holz FG, Sadda SR, Busbee B*, et al.* (2018). Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri phase 3 randomized clinical trials. JAMA ophthalmology, 136: 666-77.
12. Homayouni M. (2009). Vascular endothelial growth factors and their inhibitors in ocular neovascular disorders. Journal of ophthalmic & vision research, 4: 105.
13. Jabs DA, Nussenblatt RB, Rosenbaum JT (2005). Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 140(3):509-16.
14. Nguyen QD, Tatlipinar S, Shah SM, *et al.,* (2006). Vascular endothelial growth factor is a critical stimulus for diabetic macula edema. Am J Ophthalmol;142(6):961-9.

15. Nguyen QN, Brown DM, Marcus DM, *et al*., (2012) RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 Phase III randomized trials: RISE and RIDE. Ophthalmology;119(4):789–801

16. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. (1985) Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 92(4):467-71.

17. Rosenfeld PJ, Brown DM, Heier JS, *et al.,* (2006). MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med;355(14):1419-31

18. Rubio RG, Adamis AP *et al.,* (2016). Ocular Angiogenesis: Vascular Endothelial Growth Factor and Other Factors. Dev Ophthalmol.;55:28-37

19. Souied EH, Dugel PU, Ferreira A*, et al.* (2016). Severe Ocular Inflammation Following Ranibizumab or Aflibercept Injections for Age-Related Macular Degeneration: A Retrospective Claims Database Analysis. Ophthalmic Epidemiol, 23: 71-9.

20. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. (2014). The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology;121(5):1092-101.

21. Wong WL, Su X, Li X, , *et al.,* (2014). Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health.;2(2):e106-16.