A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)

Protocol Number:	AKST4290-205
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IND Number:	140886
Clinical Phase:	2
Sponsor:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070
Study Agent:	AKST4290
Indications:	Neovascular Age-Related Macular Degeneration
Authorized Representative:	[redacted]
Version Number:	V3.0
Version Date:	12JUN2020
Replaces Version(s):	V2.0, 20JAN2020

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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
AMD	Age-Related Macular Degeneration
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AREDS	Age-Related Eye Disease Study
ARM	Age-Related Maculopathy
ARMS2	Age-Related Maculopathy Susceptibility 2
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
[redacted]	[redacted]
BCVA	Best Corrected Visual Acuity
b.i.d.	Twice Per Day
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
bpm	Beats Per Minute
[redacted]	[redacted]
[redacted]	[redacted]
CCR3	C-C Chemokine Receptor Type 3
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatinine Kinase
CK-MB	Creatinine Kinase-MB Test
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum Plasma Concentration
CMP	Clinical Monitoring Plan
CNV	Choroidal Neovascularization
CNVM	Choroidal Neovascular Membranes
CRO	Contract Research Organization
CST	Central Subfield Thickness
[redacted]	[redacted]
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDTA	Ethylenediaminetetraacetic Acid
EMA	European Medicines Agency
ENT	Ears, Nose, and Throat
EOS	End of Study

EOT	End of Treatment
ERG	Electroretinogram
ESC	Eosinophil Shape Change
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
Eudra CT	European Union Drug Regulatory Authorities Clinical Trials
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
IAI	Intravitreal Aflibercept Injection
ICH	International Conference of Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigation New Drug Application
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
ISF	Investigator Site File
iReST	International Reading Speed Texts
ITT	Intent-to-Treat
IVT	Intravitreal
LKM	Liver-Kidney Microsomes
LLVA	Low-Luminance Visual Acuity
LSM	Least Squares Mean
LSMD	Least Squares Mean Difference
[redacted]	[redacted]
[redacted]	[redacted]
MD	Mean Deviation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mERG	Multifocal Electroretinogram
mg	Milligram
mmHg	Millimeter of Mercury

MMRM	Mixed Effect Repeats Model Measurement
MNRead	Minnesota Low-Vision Reading Test
nAMD	Neovascular Age-Related Macular Degeneration
NEI	National Eye Institute
NEI-VFQ-39	National Eye Institute Visual Function Questionnaire-39
NOA	Not Analyzed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
[redacted]	[redacted]
[redacted]	[redacted]
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography - Angiography
[redacted]	[redacted]
[redacted]	[redacted]
pH	Potential of Hydrogen
PK	Pharmacokinetic(s)
PP	Per-Protocol
PRN	Pro re Nata
PSD	Pattern Specific Deviation
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q4w	Every 4 Weeks
q8w	Every 8 Weeks
QT	QT Interval on ECG
REML	Restricted Maximum Likelihood
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
RPED	Retinal Pigment Epithelial Detachment
SAE	Serious Adverse Event
SAP	Statistical Analytical Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	Standard of Care
SRF	Subretinal Fluid
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBR	Total Bilirubin
TEAEs	Treatment-Emergent Adverse Events
ULN	Upper Limit of Normal
VA	Visual Acuity
VCA	Vascularized Composite Allotransplantation
VEGF	Vascular Endothelial Growth Factor
WOBCP	Women of Childbearing Potential
YAG	Ytrium Aluminum Garnet

PROTOCOL APPROVAL PAGE

Study Title:	A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)
Protocol Number:	AKST4290-205
Version/Date:	V3.0_12JUN2020
Sponsor Name and Address:	Alkahest, Inc. 125 Shoreway Road, Suite D San Carlos, CA 94070

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and applicable legal and regulatory requirements.

Approved by:

[redacted]

STATEMENT OF COMPLIANCE

Protocol Title: A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)
Protocol Number: AKST4290-205
Version/Date: V3.0_12JUN2020

By my signature, I:

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment, have received the Investigator Brochure, and are thoroughly familiar with the appropriate use of the investigational agent described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Alkahest, Inc., or their designee.
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with current relevant versions of the US Food and Drug Administration (FDA) regulations, European Medicines Agency (EMA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of all source documents by Alkahest, Inc. or designee and to onsite inspection of source documents by appropriate regulatory authorities, including but not limited to the FDA, local governing regulatory bodies, and IRB/IEC inspectors.

_____ _____
Investigator's Signature Date

_____
Print Name

PROTOCOL SUMMARY

Title:	A Double-Masked, Placebo-Controlled, Dose Ranging Study to Evaluate the Efficacy of Oral AKST4290 with Loading Doses of Aflibercept in Patients with Newly Diagnosed Neovascular Age-Related Macular Degeneration (PHTHALO – 205)
Précis:	This is a Phase 2, double-masked, placebo-controlled, dose-ranging, multicenter study to assess the efficacy and safety of AKST4290 administered orally at 400 mg twice per day (b.i.d.) (total daily dosage of 800 mg) (Arm 1) or 800 mg b.i.d. (total daily dosage of 1600 mg) (Arm 2) in combination with intravitreal aflibercept injections (IAI), in subjects with newly diagnosed neovascular age-related macular degeneration (nAMD) who are naïve to treatment with anti-vascular endothelial growth factor (anti-VEGF) medications in the study eye. Subjects will be treated with AKST4290 800 mg daily (Arm 1), 1600 mg daily (Arm 2), or placebo (Arm 3) for a total of 36 weeks. All subjects will receive 3 loading doses of IAI, with the initial dose administered on Day 1 (Visit 2) followed by 2 additional doses every 4 weeks (q4w) at Visits 3 and 4. Starting at 12 weeks (Visit 5), subjects in Arms 1 and 2 will be evaluated for IAI on a pro re nata (PRN) basis per strict injection criteria q4w. Subjects in Arms 1 and 2 who do not meet PRN injection criteria will receive a sham injection for masking purposes. Starting at 12 weeks (Visit 5), subjects in Arm 3 will receive IAI every 8 weeks (q8w) (at 16, 24, and 32 weeks [Visits 6, 8, and 10]) with PRN IAI evaluations conducted at every visit for masking purposes. In Arm 3, at 12, 20, 28, and 36 weeks (Visits 5, 7, 9, and 11) subjects that do not meet PRN injection criteria will receive sham injections for masking purposes. All subjects that meet PRN injection criteria will be administered IAI. For masking purposes, all PRN IAI assessments will be performed by a masked investigator and IAI or sham injections will be performed by an unmasked injector. Treatment will be discontinued after Week 36 in all study arms, and subjects will then be followed for an additional 4 weeks. Approximately 120 subjects will be enrolled with the intent of obtaining approximately 100 evaluable subjects (i.e., subjects that complete the study through Week 36). Subjects will be randomized to active treatment in Arm 1 (approximately 33 evaluable subjects) or Arm 2 (approximately 33 evaluable subjects), or to placebo in Arm 3 (approximately 33 evaluable subjects). All subjects will be masked as to their dose of AKST4290 by using a combination of active or placebo tablets. All subjects will orally self-administer AKST4290 or placebo b.i.d. The randomization schema is 1:1:1, stratified by site and baseline BCVA group (< 55 letters read or ≥ 55 letters read). The analyses of the 2 AKST4290 treatment arms (Arm 1 and Arm 2) will be performed by treatment group as well as pooled.
Objectives:	The primary objective of the study is to evaluate the potential therapeutic effects of a 36-week, b.i.d. oral dosing regimen of AKST4290, with loading doses of IAI, by assessing the improvement in best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) method. The secondary objectives include the mean change in BCVA in Arms 1 and 2 as compared with Arm 3 (control) through Week 12, the time

to PRN injection (Arms 1 and 2 only), time to the first visit where PRN injection criteria are met median number of injections, proportion of subjects with a mean change in BCVA letter score of ≥ 15 letters, mean change in central subfield thickness (CST) compared with control through Week 12, and overall safety. The exploratory objectives include investigation of changes in visual field (as available), low-luminance visual acuity (LLVA), and reading speed. Evaluations of multifocal electroretinogram (mERG) and optical coherence tomography-angiography (OCT-A) will also be performed at select sites, as available. Morphologic changes CST, (subretinal fluid [SRF], intraretinal fluid [IRF], retinal pigment epithelial detachment [RPED] height, and choroidal neovascularization [CNV]) will be evaluated by spectral domain OCT (SD-OCT) and fundus photography (FP)/fundus autofluorescence (FAF) (FAF to be performed at select sites, as available), and fluorescein angiography (FA). Biomarker, pharmacokinetic (PK), and pharmacogenomic evaluations will be conducted on blood and plasma samples. Dose response will be investigated by assessing the mean change in BCVA and the mean number of injections in Arms 1-3 by study visit. Changes in the National Eye Institute Visual Function Questionnaire-39 (NEI-VFQ-39) will also be assessed. Optional aqueous humor testing will be conducted in select subjects.

Endpoints:

Primary Endpoint:

- Mean change from baseline in BCVA per the ETDRS testing method.

Secondary Endpoints:

- Time to PRN injection (Arms 1 and 2 only).
- Time to the first visit where PRN injection criteria are met.
- Median number of injections received beginning at Week 12.
- Proportion of subjects with BCVA change of ≥ 15 letters.
- Mean change in CST compared with control through Week 12.
- Mean change in BCVA per the ETDRS testing method as compared with control through Week 12.
- Safety as assessed by incidence and intensity of adverse events (AEs).

Exploratory Endpoints:

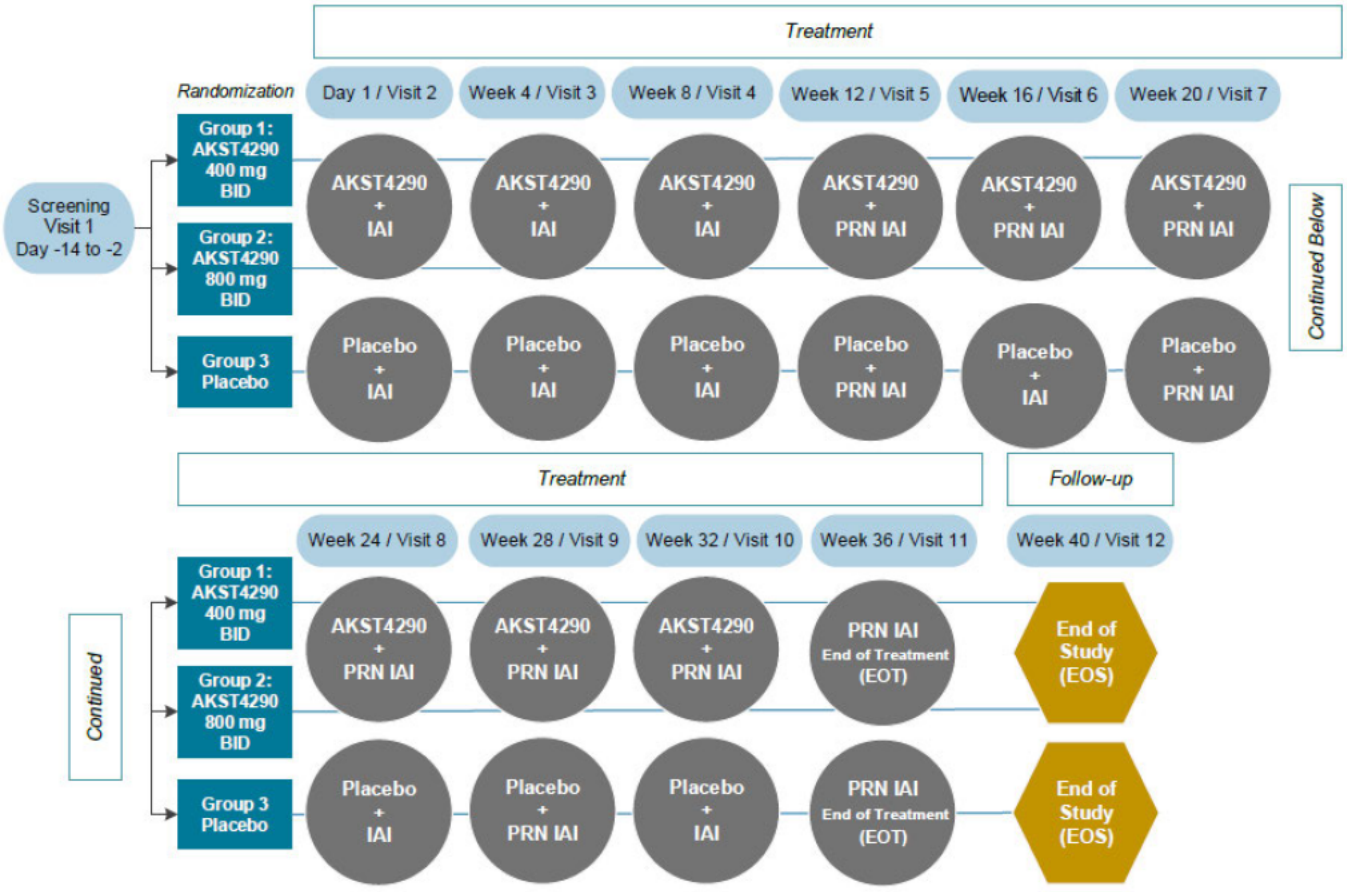
- Changes in visual field (as available), LLVA, and reading speed.
- Evaluation of mERG and OCT-A at select sites, as available.
- Changes in CST, SRF, IRF, RPED height, and CNV as measured by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA.
- Biomarker, PK, and pharmacogenomic assessments.
- Dose response as assessed by mean change in BCVA and mean number of injections by study visit.
- Changes in NEI-VFQ-39 score by study visit.
- Optional aqueous humor testing will be conducted in select subjects.

Population:

Approximately 120 subjects will be enrolled in the study with the intent of obtaining approximately 100 evaluable subjects (i.e., subjects that complete the study through Week 36) consisting of men and women, 50 years of age

	or older, with a diagnosis of nAMD who are naïve to treatment with anti-VEGF medications in the study eye.
Phase:	2
Number of Sites:	Up to 30 global sites
Description of Study Agent:	AKST4290: A small molecule antagonist of the human C-C chemokine receptor type 3 (CCR3)
Study Duration:	Approximately 24 months
Subject Participation:	Approximately 42 weeks

SCHEMATIC OF STUDY DESIGN



PRN Criteria*:
- New IRF/cystoid spaces;
- New hemorrhage;
- ≥ 5 letter loss (secondary to nAMD) compared to Week 12 AND ≥ 75 micron CST increase compared to Week 12 (applicable only starting Week 16);
- ≥ 5 letter loss (secondary to nAMD) compared to baseline**;
- ≥ 10 letter loss (secondary to nAMD) compared to maximum BCVA on study.**

*If the subject does not meet the PRN criteria, they will receive a sham injection for masking purposes.
**PRN injection based on BCVA alone requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and average of the 2 BCVA results to confirm PRN criteria.

1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

1.2 STUDY ORGANIZATION

The name and contact information of responsible parties and individuals involved with the study, including investigator(s), Sponsor's medical expert and study monitor, Sponsor's representative(s), laboratories, steering committees, and oversight committees (including IECs and IRBs), as applicable, will be maintained by the Sponsor, or their designee, and provided to the investigator.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Age-related macular degeneration (AMD) is the most common degenerative disease of the macula and the leading cause of irreversible blindness in the industrialized world in adults over 50 years of age, with a global prevalence of 170 million (Pennington 2016, Wong 2014). It is estimated that globally 196 million people will have AMD in 2020, increasing to 288 million in 2040 (Wong 2014). Approximately 10% of individuals aged 65 to 74 years and 30% of individuals aged 75 to 85 years show signs of AMD (Friedman 2004).

Early stage AMD, also termed age-related maculopathy (ARM), is associated with the accumulation of drusen and disturbances of the retinal pigment epithelium (RPE) (van Leeuwen 2003). Drusen are biochemical by-products of photoreceptor cells that accumulate in Bruch's membrane and are categorized based on their visual appearance (Bird 2010). Morphology, number, and location of drusen relative to the macula are indicative of disease progression (Jager 2008, van Leeuwen 2003). Epidemiological studies suggest that oxidative stress is associated with both the incidence and the progression of AMD. Growing evidence indicates that AMD is downstream of a chronic inflammatory condition in which activation of the immune system plays an important role (Buschini 2015). Metabolic products accumulate in the extracellular space between Bruch's membrane and the RPE, activating the complement system with a significant increase in oxidative stress, similar to what happens in atherosclerosis (Buschini 2015).

Clinically, advanced AMD is categorized into the non-exudative dry or atrophic form, and the exudative (wet) or neovascular form. Advanced dry AMD is characterized by geographic atrophy of the RPE that extends to the center of the macula (Jager 2008). Exudative, wet, or nAMD, the more aggressive and debilitating form of advanced AMD, is characterized by the growth of abnormal blood vessels from the choroid into the normally avascular sub-RPE and subretinal spaces (CNV). Fluid accumulation in the sub-RPE space from changes in the choriocapillaris, and serum and blood accumulation in the subretinal space from neovascular growth under the RPE or retina, leads to thickening in the macula. Involvement of the fovea by choroidal neovascular membrane (CNVM) growth, edema, and hemorrhage may profoundly impair visual acuity (VA) and loss of vision can be precipitous (Pennington 2016, Jager 2008). In the presence of active CNV, patients may also experience an RPED, a pathological process in which the retinal pigment epithelium separates from the underlying Bruch's membrane due to the presence of CNV, blood, and/or exudation (Pepple 2011). RPEDs are important markers of disease severity, risk for progression, and vision loss, and are seen in up to 62% of eyes with advanced nAMD (Coscas 2007). Although nAMD represents only 10 to 15% of the overall prevalence of age-related macular

AMD, it is responsible for more than 80% of cases of severe visual loss or legal blindness resulting from AMD (Ferris 1984).

Currently, blockade of vascular endothelial growth factor, a potent proangiogenic messenger, is the basis of available therapies for nAMD (Riaz 2017, Ambati 2012). Intravitreal (IVT) anti-VEGF therapies include Lucentis® (ranibizumab)(Brown 2006, Rosenfeld 2006), Avastin® (bevacizumab)(Martin 2011)(typically used as an off-label drug to treat nAMD), and Eylea® (aflibercept) (Heier 2012). These agents have become the standard of care, and have led to significant improvements in lesion morphology, reduction of the vascular leakage, and, as a consequence, improvement in central vision. However, IVT injections carry a risk to patients and a burden to both patients and caretakers. Firstly, there is the potential for complications associated with each injection, including endophthalmitis, retinal detachments, traumatic cataract, and increased intra-ocular pressure (IOP) (Falavarjani 2013). Secondly, frequent treatment and monitoring, which might continue for a patient's lifetime, is a substantial burden to patients, ophthalmologists, and the healthcare system, given the expense of the biologicals used to treat nAMD.

A clear unmet medical need exists to reduce the frequency of IVT injections (or eliminate them altogether), and extensive efforts have been undertaken to lower the injection frequency of anti-VEGF agents in nAMD (Freund 2015). The second major aspect of the unmet medical need concerns further improvement in maintenance therapy and incremental visual acuity gains over current therapies. To address these unmet clinical needs, the oral therapeutic AKST4290 was developed.

AKST4290 is a highly specific and potent small molecule antagonist of the CCR3 receptor. Results from an open-label Phase 2a study conducted by Alkahest (see Section 2.2 Rationale) demonstrated overall safety and beneficial effects of AKST4290 on BCVA in subjects with nAMD who were naïve to treatment with anti-VEGF. Alkahest is now planning to further explore the efficacy of AKST4290 administered with loading doses of aflibercept in a randomized, double-masked, placebo-controlled study.

2.2 RATIONALE

2.2.1 STUDY RATIONALE

Protocol AKST4290-205 will evaluate 400 mg and 800 mg doses of AKST4290 or placebo administered orally b.i.d. for a period of 36 weeks administered with loading doses of IAI. While the consequences of CCR3 activation in nAMD are not completely understood, CCR3 is known to be specifically expressed in CNV endothelial cells in humans with AMD. Eotaxin and CCR3 recruit systemic immune cells causing inflammation and increased hypoxic stress. CCR3-mediated migration of cells through Bruch membrane further degrades the RPE and potentially upregulates expression of vascular endothelial growth factor (VEGF), resulting in angiogenesis. Blocking the CCR3 receptor with AKST4290 may reduce inflammation, improve vascular perfusion, and interrupt endothelial cell migration, thereby reducing the morphological changes (e.g., edema and bleeding) attributed to pathologic CNV (Takeda 2009).

Expanding upon the published data regarding the role of CCR3 in nAMD (Ambati 2012, Takeda 2009), it may be that blocking the CCR3 receptor inhibits new neovascularization and therefore prevents any new structural damage. By preventing further damage, this down-regulates the expression of VEGF and may enable healing to occur within the macula, ultimately improving vision, though measurable changes in morphology may take longer to occur. This mechanism supports the trend in maintenance of morphological endpoints reported in the Phase 2a studies (ALK4290-201, ALK4290-202). Based on this mechanism, AKST4290 treatment may potentially stabilize the structural damage from the disease and allow for improved BCVA, with likely slower rate of improvement in morphology when used as monotherapy. The use of AKST4290 concurrently with IAI in a Phase 2 study may provide synergistic and orthogonal mechanistic action to either initiate morphological improvement or support stabilization of morphology over a longer treatment duration (Wang 2011).

2.2.2 DOSE RATIONALE

Oral administration of AKST4290 at doses up to 800 mg b.i.d. (1600 mg/day) for 14 days in healthy elderly volunteers (ALK4290-101), and 400 mg b.i.d. (800 mg/day) for 6 weeks in subjects with AMD (ALK4290-201 and ALK4290-202), is safe and well-tolerated.

A pharmacological assumption for dose selection is that inhibition of the CCR3 receptor activity on eosinophils closely matches a pharmacodynamic response and clinical improvement. Eosinophil shape change (ESC) and CCR3 receptor internalization assays have been used to characterize the PK-pharmacodynamic relationship in humans. The PK data in healthy elderly volunteers (ALK4290-101) demonstrated nearly dose-proportional exposure (maximum plasma concentration [C_{max}] and area under the curve [AUC]) after either single or 10 days of b.i.d. dosing of 800 mg/day or 1600 mg/day. The steady-state concentrations of AKST4290 after the proposed clinical dose of 400 mg b.i.d. (800 mg/day) are expected to provide inhibition of the CCR3 receptor sufficient to elicit a pharmacodynamic response. At trough (12 hours), the 400 mg b.i.d. dose achieves 65% inhibition in the ESC assay and 40% inhibition of CCR3 internalization. A higher dose of 800 mg b.i.d. (1600 mg/day) is being evaluated in this study to assess safety and investigate potential efficacy of this higher dose in the specific disease state of nAMD.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Clinical experience in humans with AKST4290 to date has not identified any exposure-related safety signals with doses up to 400 mg b.i.d. for 6 weeks and [redacted] ALK4290-101, ALK4290-201, ALK4290-202). Administration of 400 mg b.i.d. and 800 mg b.i.d. for 10 days in healthy elderly subjects (ALK4290-101) was well tolerated with no serious adverse events (SAEs) reported. Administration of 400 mg b.i.d. for 6 weeks in 56 subjects with nAMD (ALK4290-201, ALK4290-202, [redacted]) was also well tolerated with no SAEs.

[redacted] AKST4290 was considered safe and well tolerated by the elderly subjects within these trials.

2.3.2 KNOWN POTENTIAL BENEFITS

In the ALK4290-201 and ALK4290-202 studies, the 400 mg b.i.d. dose demonstrated positive therapeutic effects in both the naïve and refractory nAMD subject populations. In the naïve study (ALK4290-201), 83% of subjects maintained or had improvements in BCVA (≥ 0 letters; N=29) at 6 weeks, with a mean of +7 letters gained. There were 16 subjects (55%) who gained ≥ 5 letters, and 6 subjects (21%) who gained ≥ 15 letters (Table 1). In the refractory study (ALK4290-202), 72% of subjects maintained or improved BCVA at 6 weeks and 10 subjects (40%) gained ≥ 5 letters, with a mean change of +2 letters overall.

Table 1 Phase 2a BCVA Results (Change from Baseline) for Naïve and Refractory nAMD Subjects

	Naïve Population (ALK4290-201)	Refractory Population (ALK4290-202)
Number of Subjects (N)	**29**	**25**
≥ 15 Letters	**6 (21%)**	**0 (0%)**
≥ 5 Letters	**16 (55%)**	**10 (40%)**
< 5 to ≥ 0 Letters	**8 (28%)**	**8 (32%)**
≥ 0 Letters	**24 (83%)**	**18 (72%)**
< 0 Letters	**5 (17%)**	**7 (28%)**
Mean Change (Median) from Baseline	**+7.0 (+8)**	**+2.0 (+2)**

Sources: ALK4290-201, ALK4290-202
Abbreviations: BCVA=best corrected visual acuity; AMD=age-related macular degeneration; N=number of subjects

3 OBJECTIVES AND PURPOSE

The primary objective of the study is to evaluate the potential therapeutic effects of a 36-week, b.i.d. oral dosing regimen of AKST4290, with loading doses of IAI, by assessing the improvement in BCVA using ETDRS method.

The secondary objectives include the time to PRN injection (Arms 1 and 2 only), time to the first visit where PRN injection criteria are met, median number of injections received beginning at Week 12, proportion of subjects with a mean change in BCVA letter score of ≥ 15 letters, mean change in CST compared with control through Week 12, mean change in BCVA compared with control through Week 12, and overall safety.

The exploratory objectives include investigation of the changes in visual field (as available), LLVA, and reading speed. Evaluations of mERG and OCT-A will also be performed at select sites, as available. Morphologic changes (CST, SRF, IRF, RPED height, and CNV) will be evaluated by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA. Biomarker, PK, and pharmacogenomic evaluations will be conducted on blood and plasma samples. Dose response will be investigated by assessing the mean change in BCVA and the number of injections by study visit. Changes in the NEI-VFQ-39 will also be assessed. Optional aqueous humor testing will be conducted in select subjects.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is a double-masked, placebo-controlled, dose-ranging, multicenter study to assess the efficacy and safety of AKST4290 administered orally at 400 mg b.i.d. (total daily dosage of 800 mg) (Arm 1) or 800 mg b.i.d. (total daily dosage of 1600 mg) (Arm 2) for 36 weeks, with loading doses of IAI, in subjects with newly diagnosed nAMD who are naïve to treatment with anti-VEGF medications in the study eye. Only 1 eye per subject is permitted in the study. If the subject has bilateral nAMD, treatment in the fellow eye is solely at the discretion of the investigator and is not dictated by the study protocol. Subjects will be treated with AKST4290 400 mg b.i.d. (800 mg/day) (Arm 1), 800 mg b.i.d. (1600 mg/day) (Arm 2), or placebo (Arm 3) for a total of 36 weeks. All subjects will receive 3 loading doses of IAI, with the initial dose administered on Day 1 (Visit 2) followed by 2 additional doses q4w at Visits 3 and 4. Starting at 12 weeks (Visit 5), subjects in Arms 1 and 2 will be evaluated

for IAI on a PRN basis per strict injection criteria q4w. Subjects in Arms 1 and 2 who do not meet PRN injection criteria will receive a sham injection for masking purposes. Starting at 12 weeks (Visit 5), subjects in Arm 3 will receive IAI q8w (at 16, 24, and 32 weeks [Visits 6, 8, and 10]) with PRN IAI evaluations conducted at every visit for masking purposes. At 12, 20, 28, and 36 weeks (Visits 5, 7, 9, and 11) subjects in Arm 3 that do not meet PRN injection criteria will receive sham injections for masking purposes. All subjects that meet PRN injection criteria will be administered IAI. For masking purposes, all PRN IAI assessments will be performed by a masked investigator and IAI or sham injections will be performed by an unmasked injector. Treatment will be discontinued after Week 36 in all study arms, and subjects will then be followed for an additional 4 weeks.

PRN injection criteria include any of the following:

1) New IRF/cystoid spaces;
2) New hemorrhage;
3) ≥ 5 letter loss (secondary to nAMD) compared to Week 12 AND ≥ 75 micron CST increase compared to Week 12 (applicable only starting Week 16);
4) ≥ 5 letter loss (secondary to nAMD) compared to baseline;
5) ≥ 10 letter loss (secondary to nAMD) compared to maximum BCVA on study.

Note: PRN injection based on BCVA alone requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and an average of the 2 BCVA results to confirm PRN criteria.

This study will enroll approximately 120 subjects with the intent of obtaining approximately 100 evaluable subjects (i.e., subjects that complete the study through Week 36) who will be randomized to active treatment in Arm 1 (approximately 33 evaluable subjects), Arm 2 (approximately 33 evaluable subjects), or placebo in Arm 3 (approximately 33 evaluable subjects). The randomization schema is 1:1:1, stratified by site and baseline BCVA group (< 55 letters read or ≥ 55 letters read). The AKST4290 treatment arms (Arms 1 and 2) will be assessed separately for the analyses in comparison with the control arm (Arm 3). Subjects will orally self-administer AKST4290 or placebo b.i.d. Subjects in all treatment arms will be masked as to dose by using a standardized combination of active/placebo tablets.

Specific safety, tolerability, and efficacy assessments will occur at every visit (see Section 15, Schedule of Events). Extended ophthalmoscopy, IOP measurement, BCVA testing using the ETDRS, SD-OCT, visual field (as available), reading speed, LLVA, and slit lamp examinations for both study and fellow eye, will be performed by the evaluating physician prior to injection. IOP will be performed at every visit after IAI/sham injection. FP/FAF and FA will be performed at baseline and at end of treatment (EOT) in the study eye and fellow eye. A final FP/FAF will be performed at the end of study (EOS). OCT-A and mERG will be performed in the study eye and fellow eye at select sites, as available. The NEI-VFQ-39 will be performed at specific visits during the treatment period. A central reader will be responsible for assessing all SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA images to confirm eligibility, quantify morphological response, and evaluate CST parameters/presence of new hemorrhage at Visits 5-11 prior to PRN injection/sham injection. Biomarker, PK, and pharmacogenomic evaluations will be conducted on blood and plasma samples. Optional aqueous humor testing will be evaluated in select subjects. For a complete listing of study events, please see Section 15, Schedule of Events.

The study will be conducted at up to 30 global sites. The overall duration of the study/recruitment period is approximately 24 months from study initiation (i.e., following consent of first subject) to study completion (i.e., last subject, last visit). The subject participation period is approximately 42 weeks from screening through end of study, unless prematurely discontinued.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

Primary Endpoint:
Mean change from baseline in BCVA per the ETDRS testing method.

4.2.2 SECONDARY ENDPOINTS

Secondary Endpoints:
- Time to PRN injection (Arms 1 and 2 only).
- Time to first visit where PRN injection criteria are met.
- Median number of injections received beginning at Week 12.
- Proportion of subjects with BCVA change of ≥ 15 letters.
- Mean change in CST compared with control through Week 12.
- Mean change in BCVA per the ETDRS testing method compared with control through Week 12.
- Safety as assessed by incidence and intensity of AEs.

4.2.3 EXPLORATORY ENDPOINTS

Exploratory Endpoints:
- Changes in visual field (as available), LLVA, and reading speed.
- Evaluation of mERG and OCT-A in select subjects, as available.
- Changes in CST, SRF, IRF, RPED height, and CNV as measured by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA.
- Biomarker, PK, and pharmacogenomic assessments.
- Dose response as assessed by mean change in BCVA and number of injections by study visit.
- Changes in NEI-VFQ-39 by study visit.
- Optional aqueous humor testing will be conducted in select subjects.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

In order to be eligible for inclusion, all subjects must meet the following criteria:

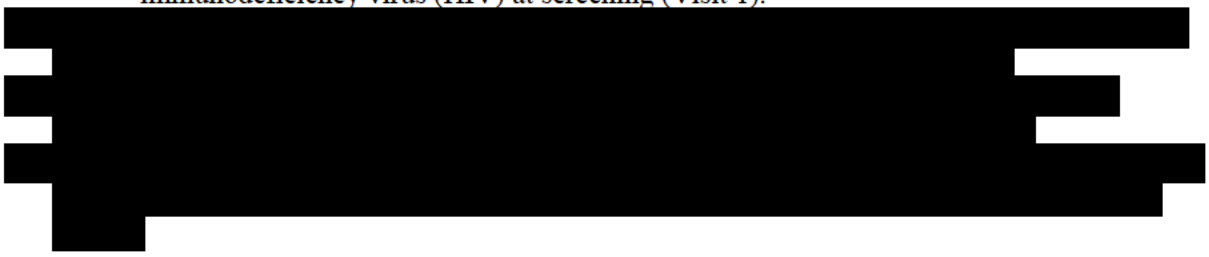
1. Men and women with newly diagnosed active CNV secondary to AMD, diagnosed by a retinal specialist with all the following characteristics and ophthalmic inclusion criteria applied to the study eye, as assessed by a central reader.
    a. Has been examined by a retinal specialist and found to be eligible to receive IAI in the study eye.
    b. No prior treatment for nAMD in the study eye.
    c. Study eye has not undergone pars plana vitrectomy or glaucoma filtering surgery.
    d. Participation in studies of investigational drugs must have been discontinued within 30 days or 5 half-lives of the drug (whichever was longer) prior to screening (Visit 1).
    e. CST thickness ≥ 250 microns on SD-OCT (exclusive of subretinal pigment epithelial fluid, inclusive of SRF).
    f. Presence of SRF and/or IRF on SD-OCT.
    g. Total lesion size not greater than 12 disc areas (30.48 mm^2) (1 disc area = 2.54 mm^2) on FA.
    h. If present, subretinal hemorrhage must comprise < 50% of the total lesion area on FA, SD-OCT, or FP/FAF.
    i. No subfoveal fibrosis or atrophy on FA, SD-OCT, or FP/FAF.
    j. Active CNV membranes with subfoveal leakage or juxtafoveal leakage too close for laser photocoagulation.

2. BCVA in the study eye between 70 and 24 letters inclusive.
3. Subjects 50 years of age or older at screening (Visit 1).
4. Body mass index (BMI) between 18 and ≤ 40 at screening (Visit 1).
5. Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions.

5.2 EXCLUSION CRITERIA

An individual will not be eligible for inclusion if any of the following criteria apply:

1. Participation in studies of investigational drugs within 30 days or 5 half-lives of the drug (whichever was longer) prior to screening (Visit 1).
2. Known hypersensitivity to the active substance or any of the excipients of AKST4290 or aflibercept.
3. Active or suspected ocular or periocular infection and/or active, severe intraocular inflammation.
4. Any form of macular degeneration that is not age-related (e.g., Best's disease, Stargardt's disease, Sorsby's disease).
5. Additional disease in the study eye that could compromise BCVA (i.e., uncontrolled glaucoma (IOP > 24) with visual field loss, clinically significant diabetic macular edema, history of ischemic optic neuropathy or retinal vascular occlusion, vitreomacular traction, high myopia > 6 diopters, or genetic disorders such as retinitis pigmentosa).
6. Presence of RPE tears or rips in the study eye.
7. Anterior segment and vitreous abnormalities in the study eye that would preclude adequate visualization with FP/FAF, FA, or SD-OCT.
8. Intraocular surgery in the study eye within 3 months prior to screening (Visit 1).
9. Aphakia or total absence of the posterior capsule (yttrium aluminum garnet [YAG] laser capsulotomy permitted in an eye with a posterior chamber intraocular lens if performed a minimum of 1 month prior to enrollment) in the study eye.
10. Known allergy to fluorescein sodium.
11. Women of childbearing potential (WOCBP). A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause).
12. Current or planned use of medications known to be toxic to the retina, lens, or optic nerve. (e.g., desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, ethambutol).
13. Medical history or condition:
    a. Uncontrolled diabetes mellitus, with hemoglobin A1c (HbA1c) > 8%.
    b. Myocardial infarction or stroke within 12 months of screening (Visit 1).
    c. Active bleeding disorder.
    d. Major surgery within 1 month of screening (Visit 1) or planned within the study period.
    e. Current, active liver disease: > 3-fold elevation of liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] over upper limit of normal [ULN]).
    f. Uncontrolled high blood pressure (systolic blood pressure of 160 mm Hg or higher and/or diastolic blood pressure of 100 mm Hg or higher) despite adequate treatment during the 3 months prior to dosing.
    g. Positive test result for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) at screening (Visit 1).



[redacted]

23. Use of systemic corticosteroids (> 10 mg prednisone or equivalent/day) within 14 days of first dose of study agent or known diseases which could require the use of systemic corticosteroids within the study period.
24. Use of intravitreal or implanted corticosteroids:
    a. Dexamethasone (Ozurdex) or triamcinolone within 6 months prior to screening (Visit 1).
    b. Fluocinolone (Retisert or Iluvien) within 48 months prior to screening (Visit 1).
25. Subjects with clinically relevant, abnormal screening hematology, blood chemistry, or urinalysis, if the abnormality defines a significant disease as defined in other exclusion criteria (e.g., AST or ALT > 3.0-fold the ULN; total bilirubin (TBR) or prothrombin time (PT) > 1.5 times the ULN). Laboratory testing may be repeated once during the screening phase.
26. Significant alcohol or drug abuse within the past 2 years.

[redacted]

28. Significant disease or other medical conditions, as determined by medical history, examination, and clinical investigations at screening (Visit 1), that may, in the opinion of the investigator, result in the any of the following:
    a. Put the subject at risk because of participation in the study.
    b. Influence the results of the study.
    c. Cause concern regarding the patient's ability to participate in the study.
29. Patients with malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

The Sponsor does not anticipate any specific challenges in meeting recruitment goals of enrolling and retaining a total of approximately 100 subjects in this study. Subjects will be recruited continuously until the planned sample size is achieved. Subjects who withdraw or are withdrawn during screening, as well as subjects who discontinue,

may be replaced (see Section 5.4.2 Handling of Participant Withdrawals).

The expected length of participation in the study of approximately 40 weeks is not expected to be challenging to subjects. Financial support for meals and miscellaneous expenses will be available during the study, as appropriate and based on local regulations and guidelines. Use of visit transport services may also be incorporated into the trial to support the subject in maintaining study visit compliance. A description of the study will be included in local clinical trial databases, as required.

5.4 SUBJECT WITHDRAWAL

5.4.1 REASONS FOR WITHDRAWAL

A subject may be withdrawn from study treatment for the following medical or administrative reasons:

- Occurrence of an AE that represents an unacceptable risk to the subject and when continued participation in the investigational study is not warranted, in the judgment of the investigator, Sponsor, or medical monitor. The investigator must follow the subject until the AE resolves or is stable unless the subject is lost to follow up.
- Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator.
- Subject noncompliance, defined as refusal or inability to adhere to the trial schedule or procedures.
- At the request of the subject (e.g., subject withdraws consent), investigator, Sponsor, or regulatory authority.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS

Subjects will be encouraged to complete the study and all assessments. Subjects may voluntarily withdraw at any time, and the investigator may discontinue individual subjects from the study at any time.

Approximately 120 subjects will be enrolled in the study with the intent of obtaining approximately 100 evaluable subjects (i.e., subjects that complete the study through Week 36; approximately 33 evaluable subjects per arm). Subjects who discontinue or are unmasked prior to Visit 8 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced. Subjects who withdraw or are withdrawn due to AEs or adverse reactions based on study procedures will not be replaced.

Subjects who have received at least 1 tablet of study drug but are withdrawn or withdraw from the study will be encouraged to complete the EOT procedures. The primary reason for study discontinuation will be documented on the electronic case report form (eCRF).

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor and/or their representatives arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the investigator will continue to protect the subjects' privacy and identity as required by relevant statues and regulations.

Alkahest, Inc. has the right to terminate a study site from participating in the study at any time. Reasons for study or site termination may include, but are not limited to:

- Immediate risk to subject safety.
- Unsatisfactory subject enrollment.
- Unacceptable protocol deviations/violations as assessed by the medical monitor.
- Inaccurate or incomplete data entry and recording/fabricated data.
- Investigational site non-compliance with ICH/GCP.

- Unacceptable emergent safety profile.

6 STUDY AGENT, CONTROL, AND CO-ADMINISTERED AGENT

6.1 STUDY AGENT, CONTROL, AND CO-ADMINISTERED AGENT DESCRIPTION

6.1.1 ACQUISITION

The study agent (AKST4290) and placebo will be manufactured, labeled, packaged, and distributed by Alkahest, Inc. The co-administered agent, Eylea® (aflibercept) is a commercially available product with global marketing approval. It will be supplied by Alkahest, Inc., and administered in the trial without modification.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

[redacted] The study agent (AKST4290) and matching placebo will be delivered to the site and labeled for investigational use only according to the relevant regulatory requirements for clinical studies.

For further details and information on AKST4290, including packaging and labeling, see the [redacted]

Eylea® (active ingredient: aflibercept) is a commercially available product from Bayer AG in EU and Regeneron in the US, presented as a 40 mg/mL solution for injection in a single package size. The excipients include polysorbate 20, sodium dihydrogen phosphate, monohydrate (for pH adjustment), disodium hydrogen phosphate, heptahydrate (for pH adjustment), sodium chloride, sucrose, and water for injection.

The co-administered agent, aflibercept, will be re-labelled for local use only in order to meet the requirements as outlined in EU Guidelines to Good Manufacturing Practice (GMP), Annex 13.

6.1.3 PRODUCT STORAGE AND STABILITY

[redacted] temperature log must be maintained to make certain the study agent is stored at the correct temperature. If the storage conditions are found to be outside the specified range, the site must immediately notify the sponsor or designee.

The co-administered agent, aflibercept, will be stored in its original packaging protected from light in refrigerator (2°C to 8°C). A temperature log must be maintained to make certain the study agent is stored at the correct temperature. If the storage conditions are found to be outside the specified range, the site must immediately notify the sponsor or designee.

6.1.4 DOSING AND ADMINISTRATION

The study drug will be self-administered orally b.i.d., approximately 12 hours apart, for a total daily dose of 800 mg (400 mg b.i.d.) or 1600 mg (800 mg b.i.d.). AKST4290 should be taken 1 hour before meals or 2 hours following a meal. Training on study drug administration will be conducted prior to administration of the initial dose. During the treatment period (Visits 2-10), subjects will be instructed to wait to administer their first daily dose until they are asked to do so by study personnel for documentation of precise administration times (following PK testing).

6.1.4.1 Injection Procedure

IAI are performed in a sterile manner. Local anesthesia is achieved by administering 0.5% proparacaine hydrochloride drops followed by 4% lidocaine-soaked cotton swabs applied to the conjunctival injection site 3 to 4 mm posterior to the limbus for 30 seconds. One drop of povidone-iodine 5% or povidone-iodine 10% diluted to a 5% concentration should be applied to the conjunctiva and allowed to coat the eye for at least 30 seconds. Povidone-iodine prepping of the eyelids and skin, and draping of the eyes may be performed at the discretion of the injecting investigator. A sterile eyelid speculum is placed to keep both the eyelashes and eyelids away from the needle. Aflibercept (2 mg/0.05 mL) should be drawn into a 1mL syringe and injected through a 30 or 32 gauge needle, 3 to 4 mm posterior to the limbus. Neither pre-injection nor post-injection antibiotic drops are indicated, but are at the discretion of the investigator. Pre and post-injection intraocular pressure (IOP) will be performed for every IAI/sham injection at every visit for all subjects.

Eyes are prepared in a similar manner for the administration of a sham injection. Instead of using a needle, the hub of the syringe should be pressed firmly against the sclera for 2 seconds to simulate the injection.

Masking of treatment assignment requires at least 2 investigators per study site: an evaluating physician (masked to treatment assignment) and an injecting physician (unmasked regarding aflibercept or sham treatment). All other study site personnel will be masked to treatment assignment.

6.1.5 ROUTE OF ADMINISTRATION

AKST4290 will be administered orally. For administration of aflibercept, see Section 6.1.4.

6.2 STUDY AGENT, CONTROL, AND CO-ADMINISTERED AGENT ACCOUNTABILITY

The investigator and/or pharmacist will receive the study agent, placebo, and co-administered agent delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol and informed consent by the IRB or IEC.
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site.
- Approval/notification of the appropriate regulatory authority.
- Availability of the curriculum vitae of the principal investigator.
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol.

The investigator and/or pharmacist must maintain records of the delivery of the study agent, placebo, and co-administered agent to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused study agent, placebo, and co-administered agent.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study agent, placebo, co-administered agent, and study subjects. The investigator/pharmacist will maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study agent, placebo, and co-administered agent received from the sponsor. At the time of final study agent, placebo, and co-administered agent reconciliation, the investigator/pharmacist must verify that all unused or partially used portion of study agent, placebo, and co-administered agent have been returned by the clinical trial subject and that no remaining study agent, placebo, and/or co-administered agent are retained by the investigator.

Accountability records must be maintained and readily available for monitoring and auditing purposes by representatives of Alkahest, Inc., or their designee and are open to inspection by regulatory authorities at any time. The accounts of any study agent, placebo, or co-administered agent accidentally wasted or intentionally disposed of must be maintained.

The disposal of used, partially used, or wasted study agent, placebo, and/or co-administered agent must be performed in accordance with the institution's drug disposal policy. At study initiation, the clinical study monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure it complies with study requirements. At the end of the study, following final study agent, placebo, and co-administered agent reconciliation by the monitor, the study site will be instructed by the sponsor to return or destroy all unused study agent, placebo, and co-administered agent. A copy of the institution's drug disposal policy should be maintained or referenced in the Investigator Site File (ISF), if applicable.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

7.1.1.1 Screening Procedures

During screening, the following will be performed:

- All ophthalmological evaluations: BCVA (as assessed by ETDRS and LLVA), SD-OCT, FP/FAF (FAF to be performed at select sites, as available), FA, slit lamp examination, extended ophthalmoscopy, and IOP.
- Medical history
- Demographics
- Review of medications
- Vital signs
- Physical examination (full)
- 12-Lead ECG
- Blood and urine collection for laboratory evaluations

Detailed descriptions of each of these procedures are provided in the sections immediately following. Information pertaining to all study activities performed during screening, and the sequence of events, is provided in Section 7.3.1 Screening.

7.1.1.1.1 Best Corrected Visual Acuity: Early Treatment Diabetic Retinopathy Study Method

BCVA will be assessed using ETDRS charts at 4 meters initial testing distance and assessed in both eyes. The trained technician measuring the BCVA using ETDRS should be the same throughout the study period. A detailed manual for performing refractions and measuring BCVA using the ETDRS testing method will be provided to investigators.

7.1.1.1.2 Low Luminance Visual Acuity

LLVA is performed for both eyes prior to dilating the eyes, and is measured by placing a 2.0-log-unit neutral density filter over the best correction and having the subject read the normally illuminated ETDRS chart. Changes in LLVA will be measured in both the experimental and control arms.

7.1.1.1.3 Optical Coherence Tomography

The retinal layers of both eyes will be visualized, and thickness measured by SD-OCT and, if available at select sites, additional scans using OCT-A will be obtained. The study eye will be investigated by a trained technician using only specified SD-OCT equipment. A detailed manual for SD-OCT and OCT-A image acquisition and data transmission will be provided in the ISF. The reported CST will be exclusive of the sub-RPE fluid.

7.1.1.1.4 Fundus Photography/Fundus Autofluorescence and Fluorescein Angiography

The retinal vasculature of both eyes will be imaged by FP/FAF (FAF will be performed at select sites, as available) and FA. The study eye will be investigated by a trained technician and evaluated by the investigator. A detailed manual for FP/FAF and FA will be provided in the ISF.

7.1.1.1.5 Slit Lamp Examination, Extended Ophthalmoscopy, and Intraocular Pressure Measurement

The slit lamp examination and extended ophthalmoscopy are to be performed in both eyes. The anterior and posterior segments of the eye should be assessed. Extended ophthalmoscopy is an assessment of the peripheral retina, usually performed with a 20 diopter lens and an indirect ophthalmoscope, to examine for retinal abnormalities such as retinal tears/detachment/hemorrhage, retinal artery perfusion before and after the IAI, etc. IOP will be measured using applanation Goldmann tonometry in both eyes during each visit before and after IAI/sham injections.

7.1.1.1.6 Medical History

The investigator or designee will obtain a detailed medical history by interviewing the subject during screening. The medical history should focus on recent history, with an emphasis on the history of nAMD and any associated ocular procedures and/or medications. Additionally, the medical history should include:

- Current/past illnesses and conditions.
- Current symptoms of any active medical condition.
- Surgeries and procedures.
- Allergies.
- Social history (e.g., smoking, alcohol, illegal substances).

7.1.1.1.7 Demographics

Demographic information such as the subject's age, ethnicity, and race will be collected by interview with the subject at screening.

7.1.1.1.8 Review of Medications

The investigator or designee should obtain a complete list of the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject in the past 3 months. Assessment of eligibility should include a review of permitted and prohibited medications. Any additions, discontinuations, or dosage changes in medication during the course of the study will be recorded.

7.1.1.1.9 Vital Signs

Vital signs will include seated systolic and diastolic blood pressure (mm Hg), heart rate (beats per minute [bpm]), respiration rate (breaths per minute), and body temperature. Vital signs will be measured after the subject has been seated for 5 minutes.

7.1.1.1.10 Full Physical Examination

A full physical examination will be performed to assess the following organ systems: skin, ENT (ears, nose, and throat), head, eyes, lungs/chest, heart, abdomen, musculoskeletal, extremities, and lymphatic systems. Height and weight will be measured.

7.1.1.1.11 12-Lead ECG

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph. A 12-lead ECG will be performed after the subject has rested quietly for at least 5 minutes in a supine position. In some cases, it may be appropriate to repeat abnormal ECGs to rule out technical factors contributing to ECG artifacts or abnormality. It is important that leads are placed in the same positions each time for consistency. The final interpretation of the ECGs will be recorded on the appropriate eCRF. The interpretation of the ECGs will be recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant. Corrected QTc interval will be calculated using Fridericia's correction formula.

7.1.1.1.12 Screening Biological Specimen Collection

For screening evaluations, blood will be drawn by a qualified medical provider, and urine specimens will also be collected. For additional information regarding laboratory tests, see Section 7.1.1.2.6.

7.1.1.2 Procedures to Assess Safety

Subjects enrolled in the trial will be monitored closely to assess safety and tolerability of the study agent, IAI, and interventional assessments. Study-specific procedures that will be used for this purpose are summarized below. Information regarding the timing and frequency of these procedures is provided in the Schedule of Events.

- Review of AEs.
- Review of medications.
- Vital signs.
- 12-Lead ECGs.
- Targeted physical examinations and measurement of weight.
- Blood and urine sample collection for laboratory evaluations.
- Slit lamp examination, extended ophthalmoscopy, and IOP.

7.1.1.2.1 Review of Adverse Events

AEs will be reviewed, documented, and reported as required at each visit, beginning at screening. For definitions, guidance, and additional information regarding AEs, refer to Section 8.

7.1.1.2.2 Review of Medications

The investigator or designee should review the subject's current medications, including over-the-counter drugs, herbal supplements and/or vitamins, as well as those taken by the subject since the last visit. Changes to the subject's list of medications should be reviewed and recorded. Review of medications should occur at every visit.

7.1.1.2.3 Vital Signs

Refer to Section 7.1.1.1.9 for a description of vital signs. Vital signs will be collected at every visit.

7.1.1.2.4 12-Lead ECG

Refer to Section 7.1.1.1.11 for information pertaining to 12-Lead ECGs.

7.1.1.2.5 Targeted Physical Examination

During the study period, a targeted physical examination, including auscultation of the heart and measurement of weight as well as review of any previous abnormalities identified during the full physical examination.

7.1.1.2.6 Blood and Urine Collection for Laboratory Evaluations

Blood samples and urine will be collected according to the Schedule of Events. Laboratory tests will include hematology, chemistry, serology, coagulation, and qualitative urinalysis.

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (including eosinophil count), platelets.
- Chemistry: glucose, sodium, potassium, calcium, inorganic phosphate, chloride, bicarbonate, magnesium, creatinine, AST, ALT, alkaline phosphatase (ALP), lactate dehydrogenase, direct and indirect bilirubin, blood urea nitrogen, total protein, albumin.
- Serology: HBV, HCV, and HIV (at screening Visit 1).
- Coagulation: partial thromboplastin time (PTT), PT.
- Urinalysis: pH, glucose, erythrocytes, leukocytes, protein, nitrites.

Additional laboratory parameters may be reported as detailed in the laboratory manual. Glomerular

filtration rate (GFR) will be estimated by the Modification of Diet in Renal Disease (MDRD) Formula utilizing serum creatinine (see Section 17.1). All safety laboratory measurements will be performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. Investigators will receive guidance and instructions on laboratory sampling and processing through a separate laboratory manual provided by the central laboratory.

The investigator is responsible for reviewing all laboratory results and determining and documenting if out-of-range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the eCRF and followed until resolution. Once resolved, the appropriate eCRF page(s) will be updated.

Samples may be used for re-testing, further evaluation of an AE and/or assessment, and follow-up of other exploratory endpoints. Samples that remain after study testing is complete will be stored in the event additional testing (e.g., further evaluation of an AE or assessment of effect) is required. Samples will be stored in a deidentified coded form. Subjects can opt out of storage of samples for future analysis.

7.1.1.2.7 Slit Lamp Examination, Extended Ophthalmoscopy, and Intraocular Pressure Measurement

Refer to Section 7.1.1.1.5 for information pertaining to slit lamp examination, extended ophthalmoscopy, and IOP.

7.1.1.3 Procedures to Assess Efficacy

7.1.1.3.1 Best Corrected Visual Acuity: Early Treatment Diabetic Retinopathy Study Method

Refer to Section 7.1.1.1.1 for information pertaining to BCVA as measured by ETDRS.

7.1.1.3.2 Ophthalmic Evaluations

The ophthalmic endpoints described below will be measured. SD-OCT and OCT-A (the latter, only if available) will be used to investigate the extent, onset, and duration of action of the study agent(s) without specific inferential testing at any time point. The same is valid for endpoints described as change from baseline.

- CST as measured by SD-OCT, absolute, and as change from baseline.
- Presence and height of IRF by SD-OCT over time, absolute, and as change from baseline.
- Presence and height of SRF by SD-OCT over time, absolute, and as change from baseline.
- Presence and height of RPED by SD-OCT over time, absolute, and as change from baseline.
- Vascular area measured by OCT-A (in select subjects) and FA, absolute and as change from baseline.
- CNV leakage as demonstrated by FA, absolute, and as change from baseline.
- Changes in visual field (as available), LLVA, and reading speed.
- Evaluation of mERG in select subjects (as available).
- Changes in NEI-VFQ-39.
- Optional aqueous humor testing will be conducted in select subjects.

7.1.1.3.2.1 Optical Coherence Tomography

Refer to Section 7.1.1.1.3 for information pertaining to OCT.

7.1.1.3.2.2 Fundus Photography/Fundus Autofluorescence and Fluorescein Angiography

Refer to Section 7.1.1.1.4 for information pertaining to FP/FAF and FA.

7.1.1.3.2.3 Slit Lamp Examination, Extended Ophthalmoscopy, and Intraocular Pressure Measurement

Refer to Section 7.1.1.1.5 for information pertaining to slit lamp examination, extended ophthalmoscopy, and IOP.

7.1.1.3.2.4 Low Luminance Visual Acuity, Visual Field, and Reading Speed
Refer to Section 7.1.1.1.2 for information pertaining to LLVA.

Visual field testing will be performed with the Humphrey threshold visual field machine, as available. In order to establish macular sensitivity, the 10-2 protocol will be used. Changes in both mean deviation (MD) and pattern specific deviation (PSD) in both the experimental and control arms will be calculated and compared.

Reading speed is an objective measure of reading performance that correlates with visual acuity. Standardized assessment of reading performance is necessary with the option of repeated measurements based on different, but equivalent, texts within one language. The following tests will be utilized based on the needs of each global site:

- The International Reading Speed Texts (iReST) consist of paragraphs of text (approximately 130 words per paragraph) and are available in several different languages.
- The Radner Test is also used for the assessment of reading speed and performance, and consists of variable reading acuity charts.
- The Minnesota Low-Vision Reading Test (MNRead) consists of continuous reading acuity cards suitable for measuring the reading speed of normal and low vision subjects.

7.1.1.3.2.5 Multifocal Electroretinography
An mERG provides the electrical activity of the cones of the central retina. The mERG technique was developed to provide a functional measure of retinal activity in the macula.

7.1.1.3.2.6 National Eye Institute Visual Function Questionnaire-39
The National Eye Institute (NEI) sponsored the development of the original visual function questionnaire- (NEI-VFQ-25) with the goal of creating a survey that would measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases, including nAMD (Mangione 2001). Due to increasing attention to the assessment of health-related quality-of-life outcomes, the NEI-VFQ-25 was expanded for use in the Age-Related Eye Disease Study (AREDS) (Clemons 2003) to include 39 items and 12 domains or subscales. The subscale scores, ranging from 0 to 100 include overall health, overall vision, difficulty with near-vision activities, pain or discomfort in around the eyes, difficulty with distance activities, driving difficulties, limitations with peripheral color vision, and limitations in social functioning, role limitations, dependency, and health symptoms related to vision (Clemons 2003). The NEI--VFQ-39 takes approximately 10 minutes on average to administer in the interviewer format.

7.1.1.3.2.7 Aqueous Humor Testing
In consenting subjects, one aqueous humor sample will be drawn immediately before IAI or sham injections as indicated in the Schedule of Events to evaluate potential biomarkers of inflammation, pathogenesis, and disease progression. Participation in aqueous humor sampling is completely voluntary.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Biological samples (e.g., whole blood, serum, urine) will be collected for laboratory evaluations in accordance with the Schedule of Events (also see Section 7.1.1.2.6). Refer to the study's laboratory manual for complete information regarding all laboratory evaluations to be performed, sample collection procedures, and related requirements.

The investigator is responsible for determining and documenting whether out of range laboratory values are clinically significant. All clinically significant values will be recorded as AEs in the eCRF and followed until determined to be stable or resolved unless the subject is lost to follow-up. Once resolved, the appropriate eCRF page(s) will be updated.

7.2.2 OTHER TESTS OR PROCEDURES

7.2.2.1 Study Agent Concentration and Pharmacokinetics

Plasma concentration measurements of AKST4290 and its major metabolite will be collected to assess systemic exposure to the study agent. For sampling time points and further details, please refer to Section 17.4.

7.2.2.1.1 Pharmacokinetic Endpoints

As far as feasible, the following PK parameter will be summarized descriptively:

- $C_{pre,ss,N}$ Pre-dose concentration of AKST4290 in plasma immediately before administration of the Nth dose

7.2.2.1.2 Methods of Sample Collections

For quantification of plasma concentrations of AKST4290 and its major metabolite, and for biomarker investigations (see Section 7.2.2.2), one blood sample of approximately 6 mL per sampling time point (see Section 17.4) will be taken from an antecubital or forearm vein into a potassium EDTA-anticoagulant blood drawing tube.

The EDTA-anticoagulated blood samples will be centrifuged to collect plasma. For PK samples only, the obtained plasma will be split into 2 aliquots and stored in polypropylene tubes. At the selected time points with additional biomarker determinations, 5 instead of 2 aliquots of at least 0.5 mL plasma each will be prepared from the blood sample. The time from blood collection until the transfer of plasma aliquots into the freezer should not exceed 60 minutes, with interim sample storage on wet ice whenever possible. Samples will be positioned upright and will be frozen at approximately -20°C or below until shipment. These aliquots will be processed by the central laboratory. Details of plasma collection, sample handling, and shipment instructions will be provided in the laboratory manual.

7.2.2.2 Plasma Biomarkers

Measurement of biomarkers is exploratory. [redacted] fter completion of the study, any remaining samples may be used for further methodological and/or other, non-genetic biomarker investigations either by the sponsor, or designee. The study samples will be discarded after completion of the additional investigations, but not later than 3 years after the final study report has been archived. The exploratory biomarker measurements will be conducted either at the sponsor's laboratories or at external contract research organizations (CROs) using appropriate methodology (e.g., immunoassays, multiplex technology). A laboratory manual will describe the handling of the samples.

7.2.2.3 Pharmacogenomic Evaluations

Pharmacogenetic analysis of prespecified genes is mandatory and a prerequisite for participation in this study. [redacted]

[redacted]

Prespecified analyses will be performed at the end of the trial and the data will be part of the report. All remaining samples will be destroyed after the end of the trial.

[redacted]

7.2.2.3.1 Methods of Sample Collections

One blood sample of 3 mL blood for prespecified pharmacogenomic testing will be obtained at Visit 2 in a potassium EDTA-anticoagulant blood drawing tube. [redacted]

The sample will be taken from an antecubital or forearm vein into a potassium EDTA-anticoagulant blood drawing tube. Details of sample collection, sample handling, and shipment instructions will be provided in the laboratory manual.

7.3 STUDY SCHEDULE

7.3.1 SCHEDULE OF EVENTS TABLE

A tabular summary of all procedures that will be accomplished at each study visit can be found in the Schedule of Events.

7.3.2 EARLY WITHDRAWAL

In cases of early withdrawal, if a subject has received at least 1 tablet of AKST4290 or placebo, the site should try to perform all assessments scheduled at the Visit 11 - EOT visit as well as the subsequent follow-up visit unless the subject has withdrawn consent (see Section 5.4).

7.3.3 STUDY COMPLETION AND END OF TRIAL

Study completion or end of study (EOS) is defined as the end of participation for each enrolled subject. This will occur at Visit 12 unless a subject withdraws or is withdrawn (see Section 7.3.2). If a subject has withdrawn consent, study completion will be at the time of consent withdrawal and no further procedures will be performed.

The end of trial will occur following the last subject's last visit. The approximate duration to conduct the trial to support full recruitment is approximately 24 months.

7.4 CONCOMITANT MEDICATIONS

All prescription, over-the-counter, and non-prescription medications (including herbal therapies and supplements) must be documented in the source documents and eCRFs. All subjects should be maintained on the same

medications at the same dosage and administration throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Any changes in medications (additions, deletions, dosage changes) should be documented in the eCRF with reason for change (e.g., AEs).

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

[redacted] In addition, use of medications known to be toxic to the retina, lens, or optic nerve. (e.g., desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, ethambutol) are prohibited.

The use of oral corticosteroids or high-potency topical steroids (i.e., with systemic exposure) are restricted during the screening and treatment period of the study. The use of inhaled corticosteroids will be allowed if the subject has been stably treated for 4 weeks prior to screening without a dose adjustment and is not anticipated to require a dose adjustment during the study treatment period. The use of low-potency topical corticosteroids (other than those intended for ocular application) will be allowed.

Primarily, no changes in concomitant therapy will be allowed except for treatments permitted according to Section 7.4 above. However, in case of AEs in need of treatment, symptomatic therapy according to the judgement of the investigator will be permitted. All concomitant therapies and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

Grapefruits, Seville oranges (including Bergamot and its peel found in Earl Gray tea) and their juices, herbal products where the type of herb or the amount of herb is unclear, and St. John's wort are not permitted from 7 days before start of study agent administration. Subjects should be advised to avoid alcoholic beverages from 48 hours before study agent administration and until the end-of-study examination.

8 ASSESSMENT OF SAFETY

Assessment of safety will be conducted by masked study personnel except in extraordinary circumstances where knowledge of whether AKST4290 or placebo was received by a subject is essential. Any instances of unmasking will be managed as indicated in Section 10.6.3 Breaking the Study Mask/Subject Code.

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS

Per 21 Code of Federal Regulations (CFR) 312.32(a) an AE is any untoward (unfavorable, harmful, or pathologic) medical occurrence in a subject administered a pharmaceutical (investigational) product even if the event does not necessarily have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding that is deemed clinically significant), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product.

An AE does include any:

- Exacerbation of a pre-existing illness.
- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study (unless it can be demonstrated by medical record review that the onset of the event preceded the date/time of informed consent).
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study.
- Symptoms associated with disease not previously reported by the subject.
- Untoward medical occurrences considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments (e.g., change on physical examination, ECG findings), if they represent a clinically significant finding, that were not present at baseline or worsened during the course of the study.
- Laboratory test abnormalities, if they represent a clinically significant finding, symptomatic or not, which were not present at baseline or worsened during the course of the study.

An AE DOES NOT include a/an:

- Elective medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion).
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery, social and/or convenience admissions).
- Overdose of either study drug or concurrent medication without any signs or symptoms.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Note: if either the investigator or the Sponsor believes that the event is serious, the event must be considered serious and evaluated for expedited reporting.

Note: the terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE. “Serious” is a regulatory definition.

A serious adverse event (experience) or reaction is an untoward medical occurrence that, at any dose, fulfills one or more of the following criteria:

a. Results in death (i.e., the AE actually causes or leads to death).
b. Is life-threatening.
   - An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death; it does not include AEs which, had it occurred in a more severe form, might have caused death.
c. Results in inpatient hospitalization or prolongation of existing hospitalization.
   - Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an AE; hospitalization for participating in this study is not considered an AE.
   - Complications that occur during hospitalization are AEs; if a complication prolongs hospitalization, the event is an SAE.
   - "Inpatient" hospitalization means the subject has been formally admitted to a hospital for medical reasons that may or may not be overnight; it does not include presentation at a casualty or emergency room unless the event meets the definition of an Important Medical Event (in the opinion of the Investigator or Sponsor).
d. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
   - 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, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
e. Results in a congenital anomaly in the offspring of a subject who received drug.
f. Results in an Important Medical Event. Important Medical Events are events that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition; examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
   - Medical and scientific judgment should be used in deciding whether prompt reporting is appropriate in this situation.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Each AE or suspected adverse reaction must be assessed for its seriousness and severity. Severity will be assessed by the investigator or designee using the following definitions:

SEVERITY	DEFINITION
MILD	Aware of sign or symptom, but easily tolerated
MODERATE	Discomfort enough to cause interference with usual activity
SEVERE	Incapacitating with inability to work or do usual activity

Outcome will be assessed using the following categories: recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, fatal, or unknown.

8.2.2 RELATIONSHIP TO STUDY AGENT AND/OR CO-ADMINISTERED AGENT

Investigators are required to assess the causal relationship (i.e., whether there is reasonable possibility that the study drug or co-administered agent caused the event) using the following definitions:

- Unrelated: another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the study agent and/or co-administered agent; or a causal relationship is considered biologically implausible.
- Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the study agent and/or co-administered agent, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the study agent and/or co-administered agent is one or several biologically plausible adverse event causes.
- Definitely Related: The AE is clearly related to use of the study agent and/or co-administered agent.

If either the investigator or the Sponsor considers the event related, then the event will be considered related for reporting purposes.

8.2.3 EXPECTEDNESS

The Sponsor or designee will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the Reference Safety Information described in the Investigator's Brochure.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected" as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the Investigator's Brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered unexpected for reporting purposes (FDA 2012).

This definition of "unexpected" relies entirely on the Reference Safety Information in the Investigator's Brochure as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is unexpected. The suspected adverse reactions listed in the Investigator's Brochure (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed.

Sponsor assessment of expectedness and relationship to study drug/causality will determine the need for expedited reporting of AEs.

8.3 TIME PERIOD/FREQUENCY FOR EVENT ASSESSMENT/FOLLOW-UP

At every clinic visit, subjects who have given informed consent will be assessed for AEs and SAEs. After the subject has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking a non-leading question such as the following:

1. "How are you feeling?"

2. "Have you had any changes since your last assessment/visit?"
3. "Have you taken any new medicines since your last assessment/visit?"

8.3.1 POST-STUDY AE AND SAE

The investigator is not obligated to actively seek SAE information in former study subjects, but the investigator is encouraged to notify Alkahest, Inc. or their designee of any AE or SAE occurring within 30 days after a subject completes the study (or has their last visit) that the investigator judges may be possibly related to study treatment or study participation.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All subjects who have given informed consent will be evaluated for AEs. All AEs that occur after the time of treatment with the study drug and/or co-administered agent will be considered TEAEs. Subjects with TEAEs must be followed until the AE is resolved or is stable, unless the subject is lost to follow up.

Each AE or suspected adverse reaction must be described as follows: the date of onset, date of resolution, severity (mild, moderate, severe), frequency of the event (single episode, intermittent, continuous), action taken with study treatment (no action taken, treatment held, treatment discontinued), outcome, causality* (unrelated, possibly related, definitely related), and seriousness criteria. Each AE or suspected adverse reaction must be recorded separately.

***Note**: Causality assessment will be made only when the AE occurs after the subject has initiated at least 1 dose of the study agent and/or co-administered agent. An AE occurring before the subject's exposure to study agent will always be labeled as "unrelated".

Any AE occurring during the study must be documented in the subject's medical records and as an AE in the eCRF. Any SAE occurring during the study must be documented in the subject's medical records and as an SAE in the eCRF.

A separate set of SAE pages should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE page.

The investigator should attempt to establish a diagnosis of the event (that meets the definition of an AE or SAE) based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs or symptoms. The diagnosis will become the basis for the verbatim term as reported by the investigator. If no diagnosis is known and clinical signs and symptoms are not present, the abnormal finding should be recorded.

In addition to the investigator's own description of the AE, each AE will be encoded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The investigator will take all appropriate and necessary therapeutic measures required for resolution of the AE. Any medication necessary for the treatment of an AE must be recorded on the concomitant medication eCRF.

The SAE pages of the eCRF should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the study CRO. It is very important that the investigator provide his/her assessment of causality to study drug as well as an applicable diagnosis at the time of the initial SAE report.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

8.4.2.1 Timeframes for Reporting SAEs

Under 21 CFR 312.32(c), the Sponsor is required to notify the FDA, EMA, and all participating investigators in a safety report of potentially serious risks from clinical trials [i.e., suspected unexpected serious adverse reaction [SUSAR]), as soon as possible after the Sponsor receives the safety information and determines that the information qualifies for reporting:

- No later than 7 calendar days for events that are life threatening (in the opinion of the investigator or the Sponsor) or that involve death as an outcome.
- No later than 15 calendar days for all other SUSAR.

As such, prompt notification of the Sponsor, and/or the Sponsor's representatives, and promptly providing requested follow-up information regarding SAEs is essential so that ethical and regulatory responsibilities and legal obligations can be satisfied. Investigators are responsible for reporting SAEs according to the following timeframes:

- All SAEs occurring during the study should be reported immediately.
- The SAE Report Form and relevant source documents, if applicable, must be completed and emailed to safety@gctrials.com within 24 hours of observation or learning of the event.
- Follow-up information must be sent to the CRO within 24 hours of receipt of information by the investigational site.

SAEs will be followed until resolution, the condition stabilizes, the event is otherwise explained or is judged by the investigator to be no longer clinically significant, or until the subject is lost to follow up.

8.4.2.2 SAE Information to Report

All information available regarding an SAE must be submitted in the timeframes indicated. At a minimum, SAE reports must contain the subject identification (ID), the SAE verbatim term, onset date, relationship to study drug and/or co-administered agent/causality, and a brief narrative of the event. Please note that **relationship to study drug and/or co-administered agent/causality as well as the reported verbatim term are very important** and should be included in the initial report as it may impact expedited regulatory reporting requirements for the event. The date of SAE discovery by the site staff should be documented in the source documents.

The investigator must record all relevant information regarding an AE/SAE in the applicable sections of the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when copies of medical records for certain cases are requested by the CRO and/or the Sponsor. If medical records are submitted to the CRO then all subject personal identifiers must be completely and thoroughly redacted prior to submission.

A blank SAE Report Form and instructions for SAE reporting will be provided to the site and will be maintained in the investigator's study file. The SAE Report Form must be completed and emailed to safety@gctrials.com according to the timeframes specified in Section 8.4.2.1. The SAE Report Form should include copies of relevant source documents, if applicable. Reconciliation of any discrepancy noted during monitoring and amending the eCRF is required.

If new information about an SAE is received or corrections to data are needed, the investigator should complete a new SAE Report Form and check the "follow-up" box on the form. This follow-up SAE Report Form should be submitted within 24 hours of learning of the information, especially if the new information concerns seriousness, relatedness, or the event term of an AE.

Sites acting under their local IRB/IEC should submit all applicable events, unanticipated problems, and safety reports to the site's local IRB/IEC, if applicable. All safety reporting deviations should also be submitted to their local IRB/IEC, if applicable.

8.5 STUDY HALTING RULES

If any of the following safety events occur, a Safety Evaluation Meeting (defined below) will be triggered:

- Three or more SAEs in the same system organ class that are assessed as possibly or definitely related to the study agent and/or co-administered agent by an investigator and confirmed as such by the Sponsor (see Section 8.2.2).
- Within or between any of the dosing arms: an overall pattern of symptomatic, clinical, or laboratory events associated with the study agent and/or co-administered agent that the Sponsor's Program Physician or designee consider a serious potential safety concern (e.g., suspicious overall pattern).

Events that are more likely related to a specific study procedure (other than IAI), will not be considered "drug related" and will not contribute to the count of definitely-related SAEs that would trigger a Safety Evaluation Meeting.

Safety Evaluation Meeting

If safety events of potential concern occur during the trial (i.e., 3 related events in the same system organ class or a suspicious overall pattern, as defined above) a Safety Evaluation Meeting will be triggered, and dosing may be temporarily halted based on the observations. The Sponsor will inform investigators and the appropriate Regulatory Authorities in the event of any temporary halt in dosing at any time during the conduct of the study. The purpose of the meeting is for investigators, the Sponsor, and the CRO Medical Monitor(s) to discuss and evaluate the safety of the subjects using available aggregated safety data and without compromising study masking, unless the Sponsor deems unmasking necessary for safety evaluation.

Attendants at the Safety Evaluation Meeting will include the Program Physician of Alkahest (or his/her designee), the CRO medical monitor(s), and available active investigators participating in the trial. After sufficient data review the Sponsor will choose one of the following courses of action:

1. Continue dosing with no change to protocol.
2. Halt dosing in all arms and stop the study.
3. Continue with a modified protocol design and amend the protocol as appropriate.

8.6 SAFETY OVERSIGHT

Safety oversight will be provided by the Sponsor's Program Physician or his or her designee and the CRO's Medical Monitor(s) in concert with the site investigators. There will be no formal Data Safety Monitoring Board established. As needed, Safety Evaluation Meetings will be convened as described in Section 8.5 to monitor the ongoing safety of the study. The Sponsor's Program Physician or designee is the final authority for safety oversight in the study.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the study CRO in accordance with the Clinical Monitoring Plan (CMP).
- A mix of on-site and centralized risk-based monitoring will be performed to ensure the safety of clinical subjects and the accuracy and completeness of study data.
- The Sponsor will be provided with copies of monitoring reports per the timelines specified within the CMP.
- Details of clinical site monitoring tasks and scope are documented in the study's CMP. The CMP describes in detail who will conduct monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits may be conducted by the Sponsor in accordance with a study-specific Quality Assurance Plan to ensure monitoring practices are performed consistently across all participating sites, that monitors are following the CMP and sites conduct the study according to the protocol, GCP, and applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL DESIGN MODEL AND ANALYTICAL PLANS

A Statistical Analysis Plan (SAP) with analytical details and assumptions will be developed and finalized before database lock and unmasking of the study data.

10.2 STATISTICAL HYPOTHESES

The primary efficacy analysis objective is to observe an improvement in the mean number of letters read from baseline to Week 36 within each of the AKST4290 treatment groups of at least 7 letters. The null and alternative hypotheses for change from baseline in BCVA ETDRS letters read at Week 36 are:

$$H_0: \mu_A = 0 \text{ vs. } H_1: \mu_A > 7$$

10.3 ANALYSIS DATASETS

Study data will be analyzed in one of the following analysis sets:

- **Intent-to-Treat (ITT)** set will include all randomized subjects.
- **Safety Evaluable** set (Safety Population) will include all randomized subjects who receive at least 1 dose of the study agent.
- **Per-Protocol (PP)** set is a subset of ITT subjects who receive at least one dose of the study agent and who follow the protocol without any major deviation(s) that interfere with the assessment of efficacy.

A detailed description of the reasons for exclusion from the PP population will be included in the SAP.

Subjects will be analyzed in the treatment arm assigned at randomization for the ITT and PP sets. For the Safety Evaluable set, subjects will be grouped according to actual treatment received.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The ITT Population will include all randomized subjects. The ITT Population will be the primary population used for efficacy analyses. Treatment assignment will be based on the randomized treatment. The Safety Population will include all subjects who receive at least one dose of study drug. The Safety Population will be the primary population used for the safety analyses. Treatment assignment will be based on the treatment actually received.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

The primary estimand is the mean change from baseline to Week 36 in BCVA ETDRS letters read for each AKST4290 group for subjects in the ITT Population. The primary analysis will consider all BCVA data collected regardless of number of PRN injections received. The mean change from baseline to Week 36 will be summarized separately for each treatment group and for the combined AKST4290 group using descriptive statistics.

Within each treatment group and for the AKST4290 combined groups, a restricted maximum likelihood (REML)-based mixed effect repeat model measurement (MMRM) analysis will be performed for the mean change from baseline in BCVA ETDRS letters read. Because model convergence is questionable with this sample size and all post-baseline visits are included, the model will include data beginning at Week 4 and collected at visits scheduled every 8 weeks thereafter up to the visit at Week 25 (i.e., Weeks 4, 12, 20, 28, and 36). The model will include visit as a fixed effect, patient as a random effect, and the baseline letters read as a covariate. An appropriate covariance structure will be selected and the Kenward Rogers method will be used to calculate the denominator degrees of freedom for the test of fixed effects. Within each AKST4290 treatment group, the mean change from baseline to Week 36 in letters read will be tested against the null value of 7 letters gained based on a one-sided alpha = 0.025. To control the Type 1 error associated with the within-group testing of two treatment groups, the tests will be performed in sequence as described in Section 10.4.6. Within each treatment group, the least-squares mean (LSM) and associated 95% confidence interval (CI) will be presented for the observed change from baseline values.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

A key secondary endpoint will be derived from the primary endpoint using a model to compare each AKST4290 treatment group and the pooled AKST4290 groups to control using an REML-based MMRM to include fixed effects for treatment group, categorical visit, and the treatment group by visit interaction; with the baseline letters read as a covariate. Estimates for the least-squares mean differences (LSMD), 95% CI of the LSMD, and the associated p-value to test for a difference between groups will be presented. A descriptive assessment of non-inferiority between the AKST4290 treatment groups and Arm 3 (control) for the BCVA mean change from baseline to Week 36 will be considered a secondary analysis. This assessment will be made by commuting the two-sided 95% CI for the difference in LSMs between each AKST4290 group and control, and the pooled AKST4290 group and control.

Other secondary endpoints will include:

- Time (weeks) to first use of PRN injection (Arms 1 and 2);

- Time (weeks) to first visit where PRN injection criteria are met;
- Median number of injections received beginning at Week 12;
- Proportion of subjects with BCVA change from baseline of ≥ 15 letters gained at Week 36;
- Mean change in CST compared with control through Week 12; andand
- Safety as assessed by incidence and severity of AEs.

Secondary endpoints will be evaluated both within treatment group for data collected through the end of treatment, Week 36, and as a comparison across treatment groups for data collected up to Week 12. The percent of subjects with a ≥ 15 letter gain from baseline to Week 36 will be summarized by treatment group, and for the pooled AKST4290 groups. Subjects with missing data at the Week 36 visit will be considered to have not achieved a 15-letter gain. Within each group, the exact 95% CI (Clopper-Pearson) will be presented for the proportion of subjects with 15-letter gains. The proportion of subjects with ≥ 15 letters gained will be further evaluated at Week 12 for a difference in proportions between each AKST4290 treatment group and the pooled AKST4290 groups against control (Arm 3), using the Fisher's exact test. A descriptive assessment of non-inferiority between the groups at each of these time points will be based on an interpretation of the CIs.

Time to the first PRN injection will be calculated in weeks for subjects assigned to the AKST4290 treatment groups (Arm 1 and Arm 2) as the date of first PRN injection (i.e., rescue) minus the first dose of study drug plus 1, divided by 7. Time to the first visit where PRN injection criteria are met starting at Week 12 will be calculated in weeks as the first date where PRN injection criteria are first met minus the date of first dose of study drug plus 1, divided by 7. Subjects who do not experience the event of interest (i.e., receive a PRN injection, meet the criteria for PRN IAI) while on the study will be censored at their last visit completed. Kaplan-Meier estimates of the distribution of time-to-event will be tabulated and plotted by treatment group, and for the combined AKST4290 groups. The tabulation will include the Kaplan-Meier estimate of the median, 25th, and 75th quartiles, and 95% CIs (if estimable). The number and percent of subjects with events and number and percent of subjects censored will be presented. In the analysis of time to first visit where PRN injection criteria are met, each AKST4290 treatment group and the pooled AKST4290 groups will be compared to control using a log rank test.

Additional secondary efficacy endpoints for median number of injections received during the treatment period and mean change in CST compared with control will be summarized similar to the primary efficacy endpoint.

Safety will be assessed through summaries of AEs, changes in laboratory test results, and changes in vital signs. In addition, all SAEs, including deaths, will be listed and summarized separately.

10.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINTS

Exploratory efficacy analyses will include the evaluation of the primary and secondary endpoints at all post-baseline time points leading up to Week 36. Exploratory analyses may not be performed in all subjects. For additional details please see the SAP.

Exploratory efficacy endpoints include changes in biomarkers in blood and plasma, changes in LLVA, changes in visual field, changes in reading speed, changes in the NEI-VFQ-39 as well as evaluation of mERG, OCT-A, and aqueous humor in select subjects, as available. Continuous endpoints, such as mean changes in BCVA at each visit, number of PRN IAI, and dose response will be summarized similar to the primary efficacy endpoint. Categorical dichotomous endpoints will be summarized similar to the secondary efficacy endpoints. These data will be summarized descriptively and included in subject data listings.

10.4.5 PLANNED INTERIM ANALYSES

Safety will be monitored on an ongoing basis. If a Safety Evaluation Meeting is triggered (see Section 8.5), an

ad hoc interim safety analysis will be performed. If such an ad hoc safety interim analysis is conducted, the treatment assignment will remain masked, unless unmasking is deemed necessary by the Sponsor for safety evaluation.

An interim analysis of primary and key secondary efficacy endpoint data is planned to be performed in December 2020, with all available data collected up to an appropriate prior data cut date included. Results of the interim analysis will be utilized to assist in making decisions for more advanced studies on subjects with nAMD (e.g., a Phase 3 program), and to assess further clinical development in AKST4290 in other indications.

Analysis of the efficacy endpoints described in Section 10.4.1 and Section 10.4.3 will be performed in a similar manner for the interim analysis. Endpoints collected over time will be summarized at select time points where scheduled for evaluation up to the Week 40, in addition to the primary analysis time point at Week 36. Further details of specific endpoints for inclusion in the interim analysis will be described in the SAP.

Tabulated descriptive results of the efficacy data will be presented by treatment group, made available to designated Alkahest personnel. Subject-level data (e.g., listings) will not be included. Any individual unblinded to the tabulated results will not be involved in any ongoing site monitoring, data management, or data handling decision making activities following the interim analysis data review up through final database lock.

No adjustments to the current protocol are planned as a result of the interim analysis. Therefore, the overall type 1 error (alpha) in the in the final analysis will be maintained at 0.05, two sided, for the primary endpoint.

10.4.6 MULTIPLE COMPARISON/MULTIPLICITY

The primary analysis will be performed separately for each of the two AKST4290 treatment arms (Arms 1 and 2) as within-group tests for the change from baseline to Week 36 in BCVA letters read. To account for multiple within-group comparisons, Arm 1 (400 mg b.i.d.) will be evaluated first at the one-sided 2.5% level of significance. If the null hypothesis is rejected, the test will be carried out for Arm 2 (800 mg b.i.d.). Analysis of secondary endpoints will not be adjusted for multiple endpoint or treatment comparisons and will be evaluated based on a two-sided significance level of 5%. This study is exploratory in nature and analysis of secondary endpoints in a potential subsequent pivotal study will include appropriate methods for adjusting for multiple comparisons.

10.4.7 EXPLORATORY ANALYSES

Exploratory endpoints will be summarized descriptively. Treatment comparisons on exploratory endpoints, if performed, will be in the nature of hypothesis generation.

10.5 SAMPLE SIZE

The primary efficacy analysis objective is to observe an improvement in the mean number of letters read from baseline to Week 36 in the AKST4290 treatment groups of at least seven letters. A sample size of 33 subjects achieves approximately 85% power to detect a difference of -7.0 letters between the null hypothesis mean of 0.0 and the alternative hypothesis mean of 7.0 letter improvement, with an estimated standard deviation of 13 and with a significance level (alpha) of 0.025 using a one-tailed one-sample t-test. The combined power of testing each AKST4290 treatment group separately as described in Section 10.9 is approximately 72%.

To ensure a sufficient number of subjects are enrolled to effectively assess the mean change in letters read within each AKST4290 group and within the two AKST4290 groups combined, the total sample size for this study will be 100 evaluable subjects (i.e., 33 subjects in each individual treatment group).

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/RANDOMIZATION/MASKING PROCEDURES

To minimize the potential bias at the time of randomization, the study will be double-masked and randomized in a 1:1:1 ratio (active 400 mg b.i.d: active 800 mg b.i.d: placebo) based on a block randomization schema. The randomization will be web-based and stratified by site and baseline BCVA group (< 55 letters read or ≥ 55 letters read). The randomization codes will be generated by a statistician that has no involvement in the study other than generation and maintenance of the randomization codes.

10.6.2 EVALUATION OF SUCCESS OF MASKING

Success of masking will be assessed based on all occurrences (intentional or unintentional) of unmasking of masked study subjects or study personnel (e.g., investigators, medical providers, assessors, the Sponsor, or their representatives). All intentional and unintentional unmasking will be documented and reported.

10.6.3 BREAKING THE STUDY MASK/SUBJECT CODE

The study mask for either AKST4290 versus placebo or aflibercept versus sham can be broken for safety reasons if the information is required for the management of SAEs, severe AEs, or pregnancies. Before breaking the mask, every attempt should be made to discuss the need with the Sponsor Program Physician, or designee. When some degree of unmasking must occur, this should be limited to the fewest number of people on a need-to-know basis.

The Investigator can obtain the AKST4290 or placebo treatment allocation for their subject through the web-based randomization system. In the rare event the web-based system is unavailable, the following contacts should be utilized:

- Sponsor Program Physician: [redacted]
- Medical Monitor email: GCT PV E-mail: safety@gctrials.com
- Medical Monitor Fax: +42 22 6160001

The Investigator can obtain the aflibercept versus sham treatment allocation for their subject from the unmasked injector source documents at the site.

Any noted intentional or unintentional breaking of the blind should be reported to the Sponsor's Study Team Lead and Quality Group. If unintentional unblinding occurs during the study, root cause analysis will be evaluated, and corrective actions implemented.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of regulatory agencies, the IRB/IEC, the Sponsor, or the Sponsor's representatives to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies or transcriptions certified after verification as being attributable, legible, accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

It is not acceptable for the eCRF to be the only record of a subject's participation in the study. This is to ensure that anyone who would access the subject's medical record has adequate knowledge that the subject is participating in a clinical trial. Source document templates will be developed for this study.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, ICH E6 R2, 21 CFR, part 320, 1993, Retention of Bioavailability and Bioequivalence Testing Samples and the Declaration of Helsinki.

12.2 INSTITUTIONAL REVIEW BOARD

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator, or their designee, to an IRB or IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the investigator, or their designee, specifying the protocol number, protocol version, documents reviewed, and date on which the committee met and granted the approval.

All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

Any modifications or amendments to the protocol must also be submitted to the IRB/IEC for approval prior to implementation.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT FORMS

Consent forms describing in detail the study agents, study procedures, and risks are given to each subject for review, and written documentation of informed consent is required prior to any study-related procedures.

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

It is the responsibility of the investigator or designee to obtain written informed consent from each subject participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study prior to undertaking any study-related procedures.

Subjects should have the opportunity to discuss the study with their family members or other advisors and the time to consider participation in the trial carefully. The subjects may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subjects will be protected by emphasizing to them that the

quality of their medical care will not be adversely affected if they decline to participate in this study.

The investigator or designee must utilize an IRB/IEC-approved consent form that contains the elements required by ICH GCP and applicable regulatory requirements for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person obtaining consent. A copy of the signed consent form will be provided to the subject. By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw voluntarily or are withdrawn from the study for any reason.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (e.g., date of screening).

All subjects who provide consent will be assigned a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to the study subject. Once a number is assigned to a subject, that number will remain with that study subject and will not be reused.

If an individual's medical chart or results of diagnostic tests performed as part of an individual's regular medical care are going to be used for screening, written informed consent must be obtained prior to review of that information in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and local regulatory requirements.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Subject confidentiality is held in strict trust by the participating investigators, their staff, the Sponsor, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC, or government regulatory agencies may inspect documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., not names) should be recorded on non-local lab samples, requisitions, and any documents submitted to the CRO, Sponsor, and/or IRB/IEC. The investigator must keep a subject log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

12.5 FUTURE USE OF STORED SPECIMENS

With the subject's approval and as approved by local IRB/IECs, de-identified biological samples may be stored at Alkahest, or designee, for future use. These samples could be used for research and to improve treatment. Alkahest will also be provided with a code-link that will allow linking the biological specimens with the specific data from each subject, maintaining the masking of the identity of the study subject. Subjects may choose whether the Sponsor can store and use samples for further research.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological

specimens stored for future research. However, withdrawal of consent for biospecimen storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be managed by Alkahest. In the event Alkahest transfers ownership to another commercial Sponsor, ownership of the samples may be transferred as well.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. The investigator may need to request previous medical records or transfer records, depending on the trial; also, current medical records must be available.

For each subject who receives the study agent or placebo, the eCRF must be completed in a timely manner. The investigator will review and approve the eCRF for each study subject after all data have been entered, the eCRFs have been source document verified, and all queries have been resolved. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the primary reason for withdrawal must be noted on the eCRF. If a subject is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

All data collection and recordkeeping procedures must be compliant with applicable ICH GCP.

13.1.1 INVESTIGATOR RESPONSIBILITIES

The investigator will comply with the protocol (which has been approved/given favorable opinion by an IEC), ICH GCP, and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this protocol as well as in other study documents, refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

13.1.2 STUDY FILES

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (although not limited to) the following: (1) investigator's study file, and (2) subject clinical source documents.
The investigator's study file will contain the protocol/amendments, eCRF, IRB/IEC approval with correspondence, informed consents, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and study-specific manuals (e.g., laboratory manual).

Subject clinical source documents would include (although are not limited to) the following: subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiologic imaging, x-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

13.2 STUDY RECORDS RETENTION

All clinical study documents must be retained by the investigator until two years after the study is discontinued and regulatory authorities have been notified. Before the investigator destroys any material related to the clinical study, he/she must obtain approval in writing from the Sponsor.

The investigator should keep a file where the full name and address of the subject and all signed informed consents are included for at least 15 years after completion of the trial. Any original study-related information that permits verification of inclusion and exclusion criteria, including clinical history, a copy of all data collection logs, and documents on the use of the study agent, must be stored for as long a time period as permitted by the center.

Should the investigator wish to move study records to another location, arrangements must be made to store these in sealed containers so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

13.3 PROTOCOL DEVIATIONS

A Protocol Deviation is any noncompliance with the clinical trial protocol or with GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. When deviations occur, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol Deviations will be categorized as either Major or Minor and will be defined in the study-specific Protocol Deviation Plan or equivalent document.

Major Protocol Deviations are departures from the approved protocol relating to the conduct of the study that may affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Major Protocol Deviations may result in data that are not deemed evaluable for the *per protocol* analysis and/or may require that subjects are discontinued from the study. Major Protocol Deviations are Significant Clinical Issues.
Note: Observations categorized as Major may include those situations where there is a pattern of deviation, numerous Minor observations, or other significant deviation.

Minor Protocol Deviations are departures from the approved protocol relating to the conduct of a study that does not affect the rights, safety, and/or wellbeing of study participants or the study outcomes or data quality. Minor Protocol Deviations do not require review by the medical monitor. Minor Protocol Deviations would not generally preclude subject data from the *per protocol* analysis population.
NOTE: persistently missed or incomplete study procedures and/or study evaluations will be considered Major Protocol Deviations.

Coronavirus Disease 2019 (COVID-19) Protocol Deviations are departures from the approved protocol related to the COVID-19 pandemic. Window extensions and missed protocol assessments may be permitted to reduce the risk of COVID-19 exposure. Any deviation to the protocol to reduce the risk of COVID-19 will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. In addition, protocol deviations have been prospectively identified that can be implemented to reduce the risk of exposure while still maintaining appropriate safety monitoring and integrity of the study data. These prospective deviations (e.g., window extentions) are described in Section 15 Schedule of Events. These measures are temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows.

All deviations will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will serve an indicator of site performance.

It is the responsibility of the site to use continuous vigilance to identify and report deviations promptly to the study CRO and/or Sponsor. All deviations must be addressed in study source documents. Notification of Protocol Deviations must be sent to the local IRB/IEC and applicable Regulatory Authorities per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

In compliance with The International Committee of Medical Journal Editors (ICMJE) clinical trials registration policy, this study will be registered by the Sponsor in a public trials registry (e.g., Eu Clinical Trials Register, ClinicalTrials.gov, etc.).

Notwithstanding the Sponsor's requirements for registration and data sharing in a public trials registry, any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and the Sponsor. In the case of multicenter studies, it is mandatory that the first publication be made based on the totality of data obtained from all centers, analyzed as stipulated in the protocol, and presented and interpreted as documented in the final Clinical Study Report. The resulting publication will name investigators according to the policy of the chosen journal. Where it is not permitted for all investigators to be included as authors, the publication will name all investigators within the publication.

Individual investigators may publish data arising from their own subjects. The investigator will provide the Sponsor with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit the Sponsor to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the investigator, and to allow establishment of co-authorship.

Investigators participating in multicenter studies must agree not to engage in presentations based on data gathered individually or by a subgroup of centers before publication of the first main publication unless this has been agreed otherwise by all other investigators and the Sponsor. However, in the event that no publication of the overall results has been submitted after approval of the Clinical Study Report, investigators may publish results of one or more center's subjects to the same review as outlined above. The Sponsor will circulate proposed multicenter publications to all investigators for review.

Data will be reviewed by all participating investigators prior to publication. The study Sponsor will have 90 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

14 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST POLICY

A separate financial disclosure agreement will be made between each Principal Investigator and Alkahest, Inc. or its authorized representative before the study agent is shipped. Each investigator will notify Alkahest, Inc. or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed. Alkahest and the study CRO will evaluate any disclosed conflicts of interest and will establish a mechanism for their management.

15 SCHEDULE OF EVENTS

	Screening	Treatment										Follow-up
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11/EOT[12]**	**12/EOS**
Week		**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**
Day	**-14 to -2**	**1**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**
Time Window (days)[a]			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent[1]/optional consent for aqueous humor[2]	X											
[redacted]	X											
Demographics	X											
Medical history	X											
Inclusion/exclusion criteria[3]	X	X										
Physical examination	X	X[14]									X	X
Vital signs (seated)	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests[4]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	X						X				X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X
OCT-A[5]		X			X						X	
FP/FAF[5]	X										X	X[15]
FA	X										X	
Visual acuity[6]	X	X	X	X	X	X	X	X	X	X	X	X
LLVA		X			X						X	
Visual field[7]		X			X						X	
Reading speed		X			X						X	
Multifocal ERG[7]		X									X	
Slit lamp exam/extended ophthalmoscopy/IOP	X	X	X	X	X	X	X	X	X	X	X	X
NEI-VFQ-39		X			X			X			X	
Administration of study agent[8]		X	X	X	X	X	X	X	X	X	X	
Dispense study agent		X	X	X	X	X	X	X	X	X		
Administer IAI/sham injection[9]		X	X	X	X	X	X	X	X	X	X	
Assessment of IAI PRN criteria[10]					X	X	X	X	X	X	X	
Study agent accountability		X	X	X	X	X	X	X	X	X	X	
PK blood sample (for plasma extraction)[11]		X	X	X	X	X	X	X	X	X	X	
Biomarker plasma aliquots[11]		X									X	X
Pharmacogenomics blood sample [redacted]		X[2]										
Optional aqueous humor collection		X			X						X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[13]	X	X	X	X	X	X	X	X	X	X	X	X
Study completion												X

Notes a. Window extensions and missed protocol assessments may be permitted to reduce the risk of COVID-19 exposure. Any deviation to the protocol to reduce the risk of COVID-19 exposure will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. These measures are

	temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows (see Section 13.3). 1. All subjects must sign an informed consent consistent with ICH-GCP guidelines prior to any trial related procedures, which includes medication washouts and restrictions. 2. Informed consents must be obtained for [redacted] optional aqueous humor collection. [redacted] Aqueous humor will be optionally collected at Visits 2, 5, and 12. 3. A thorough review of inclusion/exclusion criteria will be performed at screening (Visit 1) after obtaining informed consents. A review of the inclusion/exclusion criteria will be repeated at baseline (Visit 2) immediately prior to randomization to confirm eligibility. 4. For a complete listing of laboratory evaluations see Section 7.1.1.2.6. 5. For select sites that have the capabilities, OCT-A may be performed in addition to SD-OCT at the specified time points, and FAF may be performed with FP at the specified time points. 6. Visual acuity assessments will include BCVA as assessed by ETDRS. 7. Visual field testing and mERG at select sites, as available. 8. Study agent will be self-administered in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-11) after any pre-dose assessments, and then self-administered at home between study visits. Training on study agent administration will be conducted prior to the initial study agent administration at Visit 2. 9. IAI will be administered to all subjects at Visits 2-4. In Arms 1 and 2, subjects will be assessed for PRN IAI at Visits 5-11. If PRN criteria are met, subjects in Arms 1 and 2 will receive IAI. If PRN criteria are not met in subjects in Arms 1 or 2, they will be given a sham injection for masking purposes. In Arm 3, IAI will be administered at Visits 6, 8, and 10. In addition, subjects in Arm 3 will be assessed for PRN IAI at Visits 5-11. If PRN criteria are not met, subjects in Arm 3 will receive sham injections at Visits 5, 7, 9, and 11 for masking purposes. Pre- and post-IAI/sham IOP measurements will be performed at every visit for all subjects. 10. Assessment of PRN criteria will be performed by a masked assessor and documented in the source and CRF. IAI will be administered by an unmasked injector. 11. The PK blood samples will be taken to be centrifuged for collection of plasma samples (for timing of samples see Section 17.4). Biomarker plasma aliquots will be obtained from the PK samples. Note: the biomarker obtained at Visit 12 will require a discrete blood sample/plasma aliquot as PK will not be tested at this visit. 12. End of Treatment (EOT) visit (Visit 11): all study-related procedures will be conducted at the conclusion of treatment on Day 252 ±3. Withdrawal of consent is allowed at any time. For early termination subjects, the EOT visit procedures should be conducted at the time of early termination, in place of the next scheduled treatment visit. For subjects who withdraw consent from the study, no additional study procedures will be performed. 13. [redacted] 14. A full physical examination will be conducted at screening (Visit 1), as described in Section 7.1.1.1.10. At all subsequent timepoints, a targeted physical examination will be performed, including auscultation of the heart, weight measurement, and review of any previous abnormalities identified during the full physical examination (see Section 7.1.1.2.5). 15. Fundus autofluorescence (FAF) will be performed (as available) with FP at Visits 1 and 11 only; FAF will not be performed at Visit 12.

16 REFERENCES

16.1 PUBLISHED REFERENCES

ALK4290-201. A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Newly Diagnosed Wet Age-Related Macular Degeneration (nAMD). Available at: https://clinicaltrials.gov/ct2/show/NCT03558061?term=alkahest&rank=5.

ALK4290-202. A Single Arm Open-Label Study to Evaluate the Therapeutic Effects and Safety of a 6-Week Treatment Regimen of ALK4290 in Patients with Refractory Wet Age-Related Macular Degeneration (nAMD). Available at: https://clinicaltrials.gov/ct2/show/NCT03558074?term=alkahest&rank=4.

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16.2 UNPUBLISHED REFERENCES

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[redacted]

17 APPENDICES

17.1 MODIFICATION OF DIET IN RENAL DISEASE FORMULA

When serum creatinine is in mg/dL (conventional units), the GFR may be estimated based on the following MDRD formula:

GFR (mL/min/1.73 m^2) = 186 × (serum creatinine)$^{-1\,154}$ × (Age)$^{-0\,203}$ × (0.742 if female) × (1.210 if African American)

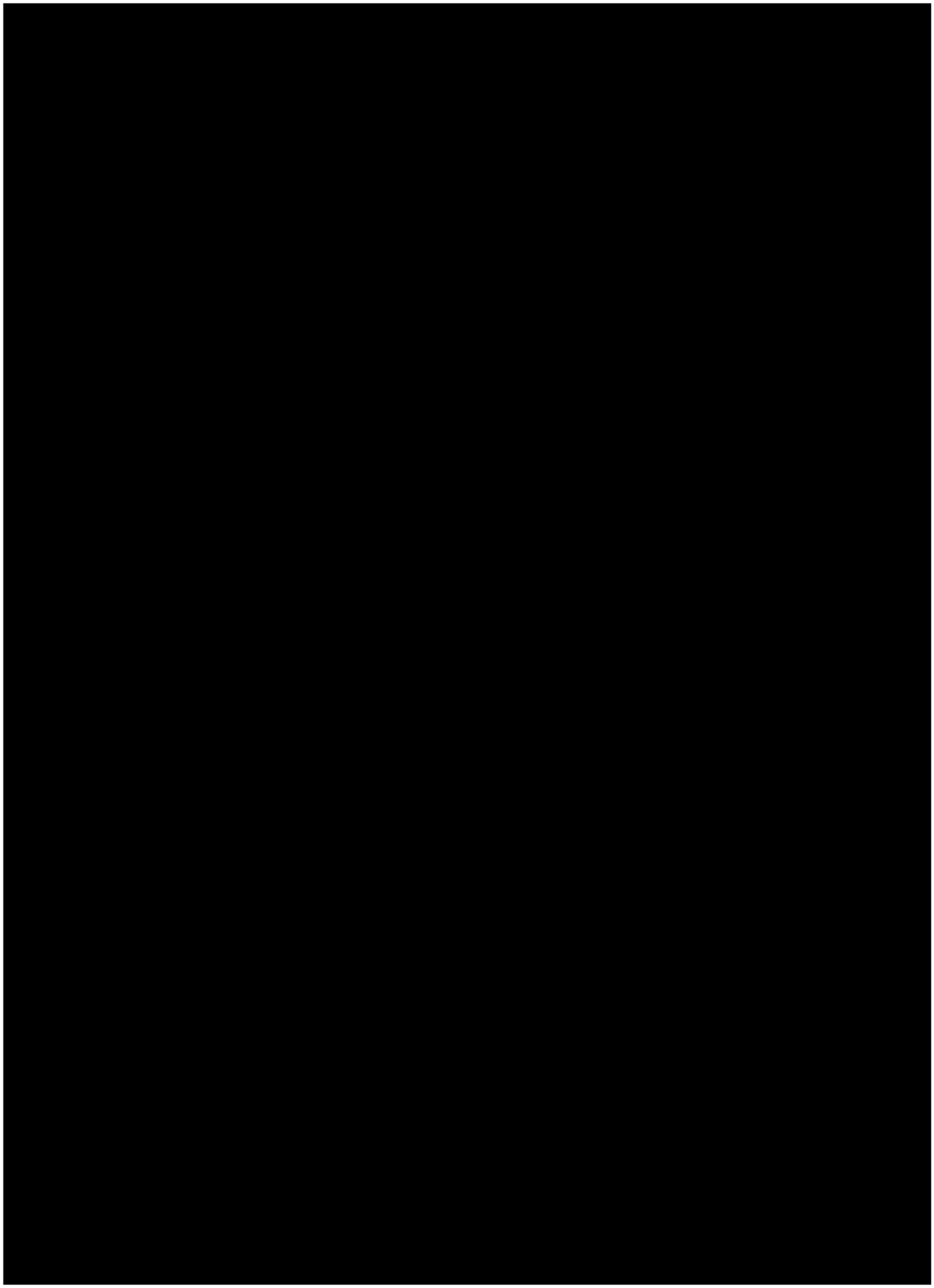
When serum creatinine is in µmol/L (SI units) the GFR may be estimated based on the following MDRD formula:

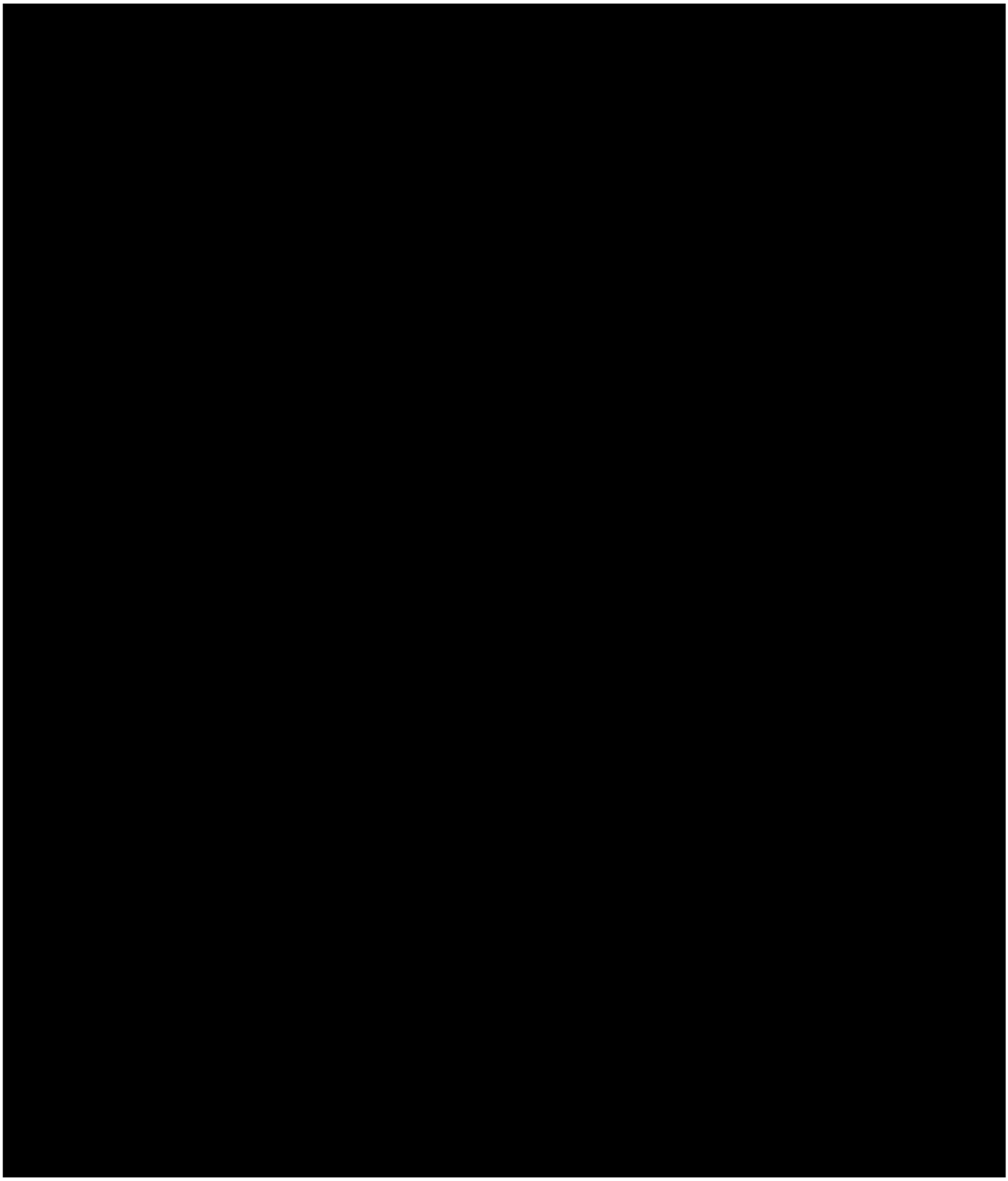
GFR (mL/min/1.73 m^2) = 186 × (serum creatinine/88.4)$^{-1\,154}$ × (Age [years])$^{-0\,203}$ × (0.742 if female) × (1.210 if African American)

17.2 LIST OF PROHIBITED MEDICATIONS AND SUBSTANCES

The table included in Section 17.2.1 presents a list of medications and substances [redacted] Of note, these tables are not exhaustive, and it remains the responsibility of the investigator to exclude further medications/substances that are not present in these tables that fall within the described criteria in Section 5.2 and Section 7.5.

[redacted]





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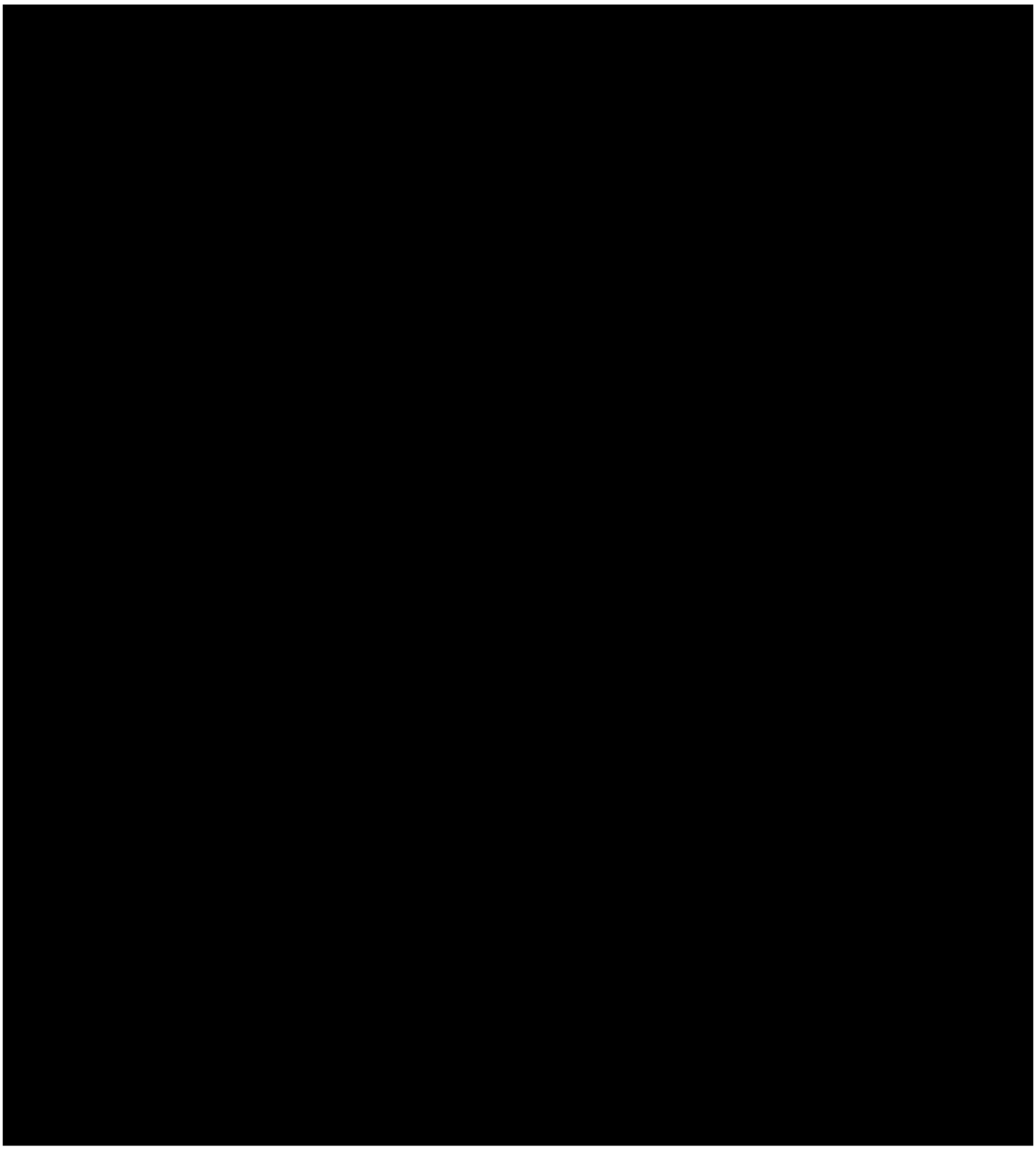

17.3 CLINICAL EVALUATION OF LIVER INJURY

17.3.1 INTRODUCTION

Alterations of liver laboratory parameters, as described in Section 8.4.3 (protocol-specified AESI), are to be further evaluated using the procedures described below.

17.3.2 PROCEDURES

[redacted]

17.3.2.1 Clinical Chemistry

- Obtain an alkaline phosphatase, albumin, PT, creatinine kinase (CK), creatinine kinase MB test (CK-MB,) ceruloplasmin, α-1 antitrypsin, transferrin amylase, lipase, fasting glucose, cholesterol, triglycerides.

17.3.2.2 Serology

- Obtain a hepatitis A (anti-immunoglobulin M [IgM], anti-IGM), hepatitis B (hepatitis B antigen, anti-HBs, DNA), HCV, ribonucleic acid (RNA) (if anti-HCV positive), hepatitis D (anti-IgM, anti-immunoglobulin G [IgG]), hepatitis E (anti-hepatitis E virus [HEV], anti-HEV IgM, RNA if anti-HEV IgM positive), anti-smooth muscle antibody (titer), anti-nuclear antibody (titer), anti-liver-kidney microsomes (LKM) antibody, antimitochondrial antibody, Epstein Barr virus (vascularized composite allotransplantation (VCA) IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

17.3.2.3 Hormones

- Thyroid-stimulating hormone

17.3.2.4 Hematology/Coagulation

- Thrombocytes, eosinophils, PTT, PT

17.3.2.5 Ultrasound

- Provide an abdominal ultrasound to rule out biliary tract, pancreatic, or intrahepatic pathology (e.g.,

[redacted]

17.4 PHARMACOKINETIC, BIOMARKER, AND PHARMACOGENOMIC SAMPLING

17.4.1 TABLE OF PHARMACOKINETIC, BIOMARKER, AND PHARMACOGENOMIC SAMPLING

Visit	Time Point	Time for Database Setup	PK Blood Sample	Extra Biomarker Aliquot from PK Blood Sample	Pharmaco-genomic Blood Sample
2	Prior to (i.e., within 15 min before study agent administration)	-0:15 h	X	X	X
	0:00 (study agent administration)	0:00 h			
	1:00 ± 10 minutes	1:00 h	X		
	2:00 ± 30 minutes	2:00 h	X		
3	-00:15 min (i.e., within 15 min before study agent administration)		X		
4	-00:15 min (i.e., within 15 min before study agent administration)		X		
5	-00:15 min (i.e., within 15 min before study agent administration)		X		
6	-00:15 min (i.e., within 15 min before study agent administration)		X		
7	-00:15 min (i.e., within 15 min before study agent administration)		X		
8	-00:15 min (i.e., within 15 min before study agent administration)		X		
9	-00:15 min (i.e., within 15 min before study agent administration)		X		
10	-00:15 min (i.e., within 15 min before study agent administration)		X		
11	-00:15 min (i.e., within 15 min before study agent administration)		X	X	
	0:00 (study agent administration)	0:00 h			

	1:00 ± 10 minutes	1:00 h	X		
	2:00 ± 30 minutes	2:00 h	X		
12	Any time during visit – preferably at the end of all visit procedures			X[a]	

[a]The biomarker obtained at Visit 12 will require a discrete blood sample/plasma aliquot as PK will not be tested at this visit.

17.5 PHARMACOKINETIC MEASURES AND EVALUATION

17.5.1 TIMING OF PHARMACOKINETIC BLOOD SAMPLING

For the time schedules of PK blood samples, please refer to Section 17.4.1.

17.5.2 PHARMACOKINETIC SAMPLE HANDLING AND SHIPMENT

Methods of PK sample collection are described in Section 7.2.2.1.2. Further instructions for sampling procedures, and for handling, storage, and shipment of the samples will be provided in the laboratory manual in the ISF.

17.5.3 PHARMACOKINETIC DATA EVALUATION

For PK analysis and displays, concentrations will be presented in the same format as reported in the bioanalytical report. Only concentrations within the validated concentration range and actual sampling times will be used for the calculation of PK parameters.

17.5.4 HANDLING OF MISSING BIOANALYTICAL DATA

In the noncompartmental analysis, concentration data identified with no sample available (NOS), no valid results (NOR), and not analyzed (NOA) will not be considered. Below the limit of quantification (BLQ) and no peak detectable (NOP) values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ and/or NOP values of the profile will be ignored. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should be excluded.

Descriptive statistics of concentrations will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the '2/3' rule is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA, NOP are included). Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available.

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 3.0 dated 12JUN2020
Replaces: Protocol Version 2.0 dated 20JAN2020

The following table describes changes from Version 2.0 (dated 20JAN2020) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V2.0_20JAN2020 ***Now reads:*** V3.0_12JUN2020	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Content updates.	Updates required to reflect revised content.
List of Abbreviations	Content updates.	Updates required to reflect revised content.
Protocol Summary, 3, 4.1, 4.2.3, 7.1.1, 7.1.1.4, 7.1.1.3.2.2	Study endpoints were updated as follows: ***Previously read:*** **Primary Endpoints** • Mean change from baseline in BCVS per the ETDRS testing method. **Secondary Endpoints** • Time to PRN injection (Arms 1 and 2 only). • Mean number of injections. • Proportion of subjects with BCVA change of ≥ 15 letters. • Mean change in CST compared with control. • Safety as assessed by incidence and intensity of adverse events. **Exploratory Endpoints** • Mean change in BCVA per the ETDRS testing method in Arms 1 and 2 as compared with Arm 3 (control). • Changes in visual field (as available), LLVA, and reading speed. • Evaluation of mERG and OCT-A in select subjects, as available. • Changes in SRF, IRF, RPED height, and CNV as measured by SD-OCT, FP/FAF, and FA. • Biomarker, PK, and pharmacogenomic assessments. • Dose response as assessed by mean change in BCVA and number of injections in Arms 1-3 by study visit. • Changes in NEI-VFQ-39. • Optional aqueous humor testing will be conducted in select subjects. ***Now reads:*** **Primary Endpoints** • Mean change from baseline in BCVS per the ETDRS testing method. **Secondary Endpoints**	Updates required for alignment with revised statistical approach and analyses (e.g., examining treatment arms separately) as well as clarity/consistency. In addition, FAF is not available at every site; therefore, it will be performed, as available.

	• Time to PRN injection (Arms 1 and 2 only). • Time to first visit where PRN injection criteria are met. • Median number of injections received beginning at Week 12. • Proportion of subjects with BCVA change of ≥ 15 letters. • Mean change in CST compared with control through Week 12. • Mean change in BCVA per the ETDRS testing method compared with control through Week 12. • Safety as assessed by incidence and intensity of adverse events. **Exploratory Endpoints** • Changes in visual field (as available), LLVA, and reading speed. • Evaluation of mERG and OCT-A in select subjects, as available. • Changes in CST, SRF, IRF, RPED height, and CNV as measured by SD-OCT, FP/FAF (FAF to be performed at select sites, as available), and FA. • Biomarker, PK, and pharmacogenomic assessments. • Dose response as assessed by mean change in BCVA and number of injections by study visit. • Changes in NEI-VFQ-39 by study visit. • Optional aqueous humor testing will be conducted in select subjects.	
Protocol Summary, 4.1, 5.4.2, 10.5	Study population was updated to include 120 enrolled subjects (previously 150) with the intent of obtaining approximately 100 evaluable subjects (previously 129) to provide approximately 33 subjects in each study arm (previously 43). Descriptive content was added following the term "evaluable subjects" to provide clarification as follows: "…100 evaluable subjects (i.e., subjects that complete the study through Week 36)"	Updates required for alignment with revised statistical analyses and sample size calculations. Revised to provide clarification of the term "evaluable subject."
Protocol Summary, 4.1, 10.6.1	Randomization remains 1:1:1, but will now also be stratified by site and baseline BCVA group (< 55 letters read or ≥ 55 letters read).	Updates required for alignment with revised statistical approach and analyses as well as clarity/consistency.
Protocol Summary, 10	The statistical analyses were extensively updated. Key revisions include examination of each treatment arm separately (previously pooled). The primary analysis was clarified to indicate all BCVA data will be included regardless of PRN injections received. Timing of data collection was also updated.	Updates required for statistical approach and analyses (e.g., examining treatment arms separately) as well as clarity/consistency.
Schematic of Study Design, 4.1	PRN Criterion #3 revised as follows: ***Previously read:*** • 3) ≥ 5 letter loss (secondary to nAMD) AND ≥ 75 micron CST increase compared to week 12; ***Now reads:*** • 3) ≥ 5 letter loss (secondary to nAMD) compared to Week 12 AND ≥ 75 micron CST increase compared to Week 12 (applicable on starting Week 16);	Revised to provide clarity and for alignment with study visit procedures.

	The "Note" was revised as follows: ***Previously read:*** • PRN injection based on BCVA alone (i.e., ≥ 10 letter loss) requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and an average of the 2 BCVA results to confirm PRN criteria. ***Now reads:*** • PRN injection based on BCVA alone requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and an average of the 2 BCVA results to confirm PRN criteria.	Revised to provide clarity and alignment with assessment criteria.
4.1, 7.1.1, 15	Indirect ophthalmoscopy was previously mentioned only in Section 4.1. This was updated to "extended ophthalmoscopy" in Section 4.1. Further additions were made to describe this assessment and include it in conjunction with slit lamp examination and IOP.	Clarification of terminology and inclusion of assessment in visit schedule.
6.1.2	Revisions made to third and fourth paragraphs as follows: ***Previously read:*** • Currently, the third and fourth paragraphs of this section read as follows: Eylea® (active ingredient: aflibercept) is a commercially available product from Bayer AG, presented as a 40 mg/mL solution for injection in a single package size. The excipients include polysorbate 20, sodium dihydrogen phosphate, monohydrate (for pH adjustment), disodium hydrogen phosphate, heptahydrate (for pH adjustment), sodium chloride, sucrose, and water for injection. The co-administered agent, aflibercept, will be re-labelled for local use only in order to meet the requirements as outlined in EU Guidelines to Good Manufacturing Practice (GMP), Annex 13. ***Now reads:*** • Eylea® (active ingredient: aflibercept) is a commercially available product from Bayer AG in EU and Regeneron in the US, presented as a 40 mg/mL solution for injection in a single package size. The excipients include polysorbate 20, sodium dihydrogen phosphate, monohydrate (for pH adjustment), disodium hydrogen phosphate, heptahydrate (for pH adjustment), sodium chloride, sucrose, and water for injection. The co-administered agent, aflibercept, will be re-labelled for local use only in order to meet the requirements as outlined in EU Guidelines to Good Manufacturing Practice (GMP), Annex 13.	Study sites may be located in EU or US; therefore, appropriate manufacturing and labelling information was added for each.
6.2	The following content was removed, "Subjects are to return all blister cards containing study agent or placebo, used or unused, to the sites at each visit for reconciliation. If the subject forgets the blister cards, they should be returned at the next visit."	This information was removed as it is duplicated in the IMP Handling Instructions.
7.1.1.3.2	OCT-A examinations were removed from bullets 1 and 3.	Optional examinations that were included along with SD-OCT in error.
7.1.1.3.5	Descriptive information for ERG was removed as it related to	Unrelated content was removed.

	full field ERG vs. mERG.	
7.2.2.1.1, 15, 17.4	Content related to evaluation of PK endpoints was updated, and additional PK collection time points have been added: • Visit 2: PK added at 2 hours ± 30 minutes • Visit 11: PK added at -15 minutes before study administration, 1 hour ± 10 minutes, and 2 hours ± 30 minutes. Study agent administration was also added to Visit 11 to enable additional PK analyses.	Additional PK assessments added to better understand and characterize the bioavailability of AKST4290.
13.3, 15	Content added re: flexibility for window extensions and missed protocol assessments related to COVID-19. Any deviation to the protocol to reduce the risk of COVID-19 will be captured as a "Protocol Deviation related to COVID-19" to categorize the anticipated increase in protocol deviations due to the pandemic. These measures are temporary, and will be repealed as soon as the situation (e.g., governmental rules, benefit/risk assessment for the trial, etc.) allows.	New content to account for potential protocol deviations related to COVID-19.
15	Additional updates to Section 15 Schedule of Events include the following: • Physical examination: Added footnote #14 to indicate that a full physical examination will be conducted at screening (Visit 1); at all subsequent timepoints, a targeted physical examination will be performed, including auscultation of the heart, weight measurement, and review of any previous abnormalities identified during the full physical examination. • OCT-A: Will only be performed at Visits 2, 5, and 11 (Visit 8 OCT-A removed). • FAF: Added a footnote #15 to indicate that FAF will be performed with FP at Visits 1 and 11 only; FAF will not be performed at Visit 12. • NEI-VFQ-39: Decreased frequency to only include assessment at Visits 2, 5, 8, and 11. • Aqueous humor: Added content to footnote #2 to indicate this assessment is optional and will only be performed after optional ICF is obtained (duplicate information removed from footnote #1).	Updates to facilitate study operations and decrease the burden on subjects.
17.2	Disease-specification medications for conditions that are excluded (e.g., HIV, certain cancers) were removed. In addition, content was added to indicate the listing of prohibited medications are "not exhaustive" and it remains the responsibility of the investigator to exclude medications that fall within described criteria.	Reduction in listings of prohibited medications by removing entries for conditions that are excluded in the study.

Protocol Version 2.0 dated 20JAN2020
Replaces: Protocol Version 1.2 dated 25AUG2019

The following table describes changes from Version 1.2 (dated 25AUG2019) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V1.2_25AUG2019	Version control.

	Now reads: V2.0 20JAN2020	
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Content updates.	Updates required to reflect revised content.
List of Abbreviations	Content updates.	Updates required to reflect revised content.
Protocol Summary, Schematic of Study Design, 4.1, 15	Study design revised to include follow-up visit at 40 weeks (was previously a follow-up call at 38 weeks); subject participation will now be approximately 42 weeks with treatment discontinued after 36 weeks.	Study extended with a final visit at 40 weeks to gather further data related to safety and efficacy.
Protocol Summary, 3, 4.1, 4.2.3, 7.1.1, 7.1.1.4, 7.1.1.3.2.2	Fundus photography (FP) will now also include fundus autofluorescence (FAF) and be performed at screening (Visit 1), week 36 (Visit 11), and week 40 (Visit 12). Fluorescein angiography (FA) will continue to be performed at screening (Visit 1) and week 36 (Visit 11) only.	FAF was added to FP as it's a noninvasive technique which assists in delineation of changes in retinal structures; FP/FAF testing was added at week 40 (Visit 12) to gather further data related to efficacy.
Protocol Summary, 3, 4.1, 4.2.3, 7.1.1.3.2, 7.1.1.3.2.7	The description of optional aqueous humor testing was modified to evaluate potential biomarkers of inflammation, pathogenesis, and disease progression (previously only included biomarkers of inflammation including TNF, IL-1, IL-6).	Provide for a broader range of testing of optional aqueous humor samples.
Protocol Summary, 4.1, 6.1.1, 7.1.1.3.2.4	Location of sites updated to read "global" rather than listing specific countries, and reading speed testing now includes, iREST, Radner Test, and MNREAD.	Revised to accommodate expansion of global study sites.
Schematic of Study Design, 4.1	PRN Criteria revised as follows: ***Previously read:*** • 1) ≥75 micron CST increase from prior visit (independent of vision loss/gain); • 2) ≥ 50 micron CST thickness increase with a corresponding > 5 letter loss from prior visit; • 3) ≥ 10 letter cumulative loss from maximum BCVA on study (independent of CST loss/gain); • 4) ≥ 10 letter loss from prior visit (independent of CST loss/gain); • 5) new hemorrhage. • Note: PRN injection based on BCVA alone (i.e., ≥ 10 letter loss) requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and an average of the 2 BCVA results to confirm PRN criteria. ***Now reads:*** • 1) New IRF/cystoid spaces; • 2) New hemorrhage; • 3) ≥ 5 letter loss (secondary to nAMD) AND ≥ 75 micron CST increase compared to week 12; • 4) ≥ 5 letter loss (secondary to nAMD) compared to baseline; • 5) ≥ 10 letter loss (secondary to nAMD) compared to maximum BCVA on study; • Note: PRN injection based on BCVA alone (i.e., ≥ 10 letter loss) requires a confirmation of a repeat BCVA within 1 week (unscheduled visit) and an average of the 2 BCVA results to confirm PRN criteria.	Revised for alignment with recent research findings and to be consistent with other recent global clinical trials in nAMD.

5.1	Updated Inclusion Criteria as follows: Inclusion Criteria #1d: ***Previously read:*** • No previous participation in any studies of investigational drugs within 1 month preceding screening (Visit 1). ***Now reads:*** • Participation in studies of investigational drugs must have been discontinued within 30 days or 5 half-lives of the drug (whichever was longer) prior to screening (Visit 1). Inclusion Criteria #1g: ***Previously read:*** • Total lesion size not greater than 12 disc areas on FA. ***Now reads:*** • Total lesion size not greater than 12 disc areas (30.48 mm^2)(1 disc area = 2.54 mm^2) on FA. Inclusion Criteria #1h: ***Previously read:*** • If present, subretinal hemorrhage must comprise < 50% of the total lesion area on FA. ***Now reads:*** • If present, subretinal hemorrhage must comprise < 50% of the total lesion area on FA, SD-OCT, or FP/FAF. Inclusion Criteria #1i: ***Previously read:*** • No subfoveal fibrosis or atrophy on FA. ***Now reads:*** • No subfoveal fibrosis or atrophy on FA, SD-OCT, or FP/FAF. Inclusion Criteria #2: ***Previously read:*** • BCVA in the study eye between 70 and 24 letters inclusive at screening (Visit 1). ***Now reads:*** • BCVA in the study eye between 70 and 24 letters inclusive.	Revised to align with global regulatory standards Size of disc area provided for clarity of measurement. Additional imaging modalities included to provide greater flexibility and accurate evaluation of criterion. Additional imaging modalities included to provide greater flexibility and accurate evaluation of criterion. Criterion updated to provide clarity regarding BCVA, which must be confirmed for eligibility through Visit 2.
5.2, 7.1.1.2.6,	Updated Exclusion Criteria as follows: • Updated Exclusion Criterion #1: ○ ***Previously read:*** Previous participation in any studies of investigational drugs within 1 month preceding screening (Visit 1). ○ ***Now reads:*** Participation in studies of investigational drugs within 30 days or 5 half-lives of the drug (whichever is longer) prior to screening (Visit 1). • Added Exclusion Criterion #2 and 3: ○ 2. Known hypersensitivity to the active substance or any of the excipients of AKST4290 or aflibercept.	Revised to align with global regulatory standards. Exclusion criterion added per global regulatory standards and to align with aflibercept labeling.

	○ 3. Active or suspected ocular or periocular infection and/or active, severe intraocular inflammation.	
	• Updated Exclusion Criterion #7: ○ ***Previously read:*** Anterior segment and vitreous abnormalities in the study eye that would preclude adequate visualization with fundus photography/FA or SD-OCT. ○ ***Now reads:*** Anterior segment and vitreous abnormalities in the study eye that would preclude adequate visualization with FP/FAF, FA, or SD-OCT.	Content revised to include FAF.
	• Updated Exclusion Criterion #13g to remove tuberculosis testing (by QuantiFERON testing) at screening.	Deleted tuberculosis testing at screening since it is not required.
	• Added cross-reference to Section 17.2.1 to Exclusion Criteria #14 and 15.	Content revised to provide cross-reference to listing of prohibited medications and substances.
	• [redacted]	[redacted]
	• [redacted]	[redacted]
	• [redacted]	[redacted]

	• [redacted] • Previous Exclusion Criteria renumbered and appropriate cross-reference were added.	[redacted] Criteria renumbered and cross-references were added, as appropriate.
5.4.2	Sentence added at the end of the second paragraph, "Subjects who withdraw or are withdrawn due to AEs or adverse reactions based on study procedures will not be replaced."	Clarification of participant replacement when withdrawn due to AEs or adverse reactions based on study procedures.
7.1.1.2.5	Content added/revised to the describe the Target Physical Examination procedure to ensure all prior abnormalities identified during the prior full examination will be reviewed.	Content revised to provide additional clarity.
7.1.1.3.2.4	Content added/revised to incorporate the expansion to global sites and to add MNREAD as a method for assessing reading speed.	Content revised to include additional reading speed method that is available in expanded global sites.
7.3.3	New section added "Study Completion and End of Trial".	Content added to provide clarity and definition of study completion and end of trial.
7.5, 17.2, 17.2.1, 17.2.2, 17.2.3	Content added/revised related to prohibited medications as well as medications that should be administered with caution.	Protocol updated to align with revised content related to potential drug-drug interactions detailed in the updated AKST4290 Investigator's Brochure V4.0.
10.4.4	Sentence added, "Exploratory analyses may not be performed in all subjects. For additional details, please see the SAP."	Exploratory testing may not be available at all sites or appropriate for all subjects.
10.6.1	Randomization will no longer be stratified by sex.	To facilitate efficient randomization, it will no longer be stratified by sex.
10.6.3	Content revised to include additional details related to	Provision of detailed procedures and

	procedures and contact information for breaking of the study mask, if required, for the management of SAEs, severe AEs, or pregnancies. Per the revised content, every attempt should be made to discuss the need for breaking the study mask with the Sponsor Program Physician, or designee. When some degree of unmasking must occur, this should be limited to the fewest number of people on a need-to-know basis.	contact information when breaking the study mask is required.
15, 17.4.1	• Revised the Schedule of Events to reduce the number of exploratory efficacy evaluations including, OCT-A, LLVA, visual field, and reading speed. • The mid-study acquisition of optional aqueous humor was moved from Visit 6 (Week 16) to Visit 5 (Week 12). • Addition of biomarker acquisition at Visit 12 which will require a discrete blood sample at PK will not be tested at this visit (see Note #11).	Reduce burden on subjects and sites. Revised to align with collection time point of other exploratory endpoints. Added acquisition of biomarker to new Visit 12 to align with collection time point of other exploratory endpoints.

Protocol Version 1.2 dated 25AUG2019
Replaces: Protocol Version 1.1 dated 16JUL2019

The following table describes changes from Version 1.1 (dated 16JUL2019) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read***: V1.1_16JUL2019 ***Now reads***: V1.2_25AUG2019	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Throughout	Change to study title.	Title updated to reflect new study design.
Table of Contents	Content updates.	Updates required to reflect revised content.
List of Abbreviations	Content updates.	Updates required to reflect revised content.
Protocol Summary, Schematic of Study Design, 2.2.1, 2.2.2, 3, 4.1, 4.2, 10, 15	Major revisions to reflect extension of study to 36 weeks (previously 20 weeks) with additional IAI loading doses. Study objectives, and endpoints were also revised throughout.	Study extended to 36 weeks to gather further data and facilitate additional IAI loading doses per standard of care; study objectives and endpoints were revised to provide robust outcomes data.
5.1	Updated Inclusion Criteria as follows: • Inclusion Criterion #9g removed ("Presence of RPE tears or rips in the study eye.") • Inclusion Criterion #9h removed ("Any active CNV with subfoveal leakage as determined by FA.")	 Criterion moved to Section 5.2. Criterion not required.

	• Inclusion Criterion #5 removed stating, 'Female subjects must not be pregnant or breastfeeding…"	Criterion removed as WOCBP are now excluded from the trial per Section 5.2.
5.2, 8.4.4	Updated Exclusion Criteria as follows: • Exclusion Criterion #9 added ("Women of childbearing potential (WOCBP). A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 year without alternative cause).")	Criterion added to exclude WOCBP; therefore, pregnancy testing, withdrawal for pregnancy, and reporting of pregnancy have also been removed from the protocol.
7.2.2.3, 17.4	Pharmacogenomics evaluation added.	Sponsor will evaluate inherited genetic traits that potentially influence response to AKST4290.
7.3	Study Schedule modified to only include link to Section 15, Schedule of Events.	Based on current industry standards, the duplication (in text) of the Study Schedule has been eliminated to prevent errors/confusion, reduce protocol size, and provide only one (consistent) area where all study procedures are listed.

Protocol Version 1.1 dated 16JUL2019
Replaces: Protocol Version 1.0 dated 27JUN2019

The following table describes changes from Version 1.0 (dated 27JUN2019) with justifications provided.

Section(s)	Description	Justification
Throughout	Protocol version update. ***Previously read:*** V1.0_27JUN2019 ***Now reads:*** V1.1_16JUL2019	Version control.
Throughout	Minor grammar and content updates.	Minor grammar/content updates for clarity/accuracy of content.
Table of Contents	Minor content updates.	Minor updates required to reflect revised content.
List of Abbreviations	Removed "MNRead: Minnesota Low-Vision Reading Test" and added, "iReST: International Reading Speed Texts."	MNRead removed and replaced with iReST as MNRead was not available in required languages.
Protocol Summary, 4.1, 7.1.1.3.2.4	Updated content to indicate that visual field testing is only required "as available."	Some sites may not have the equipment required for visual field testing.
4.1, 4.2.3, 7.1.1.1.5, 7.3.2.1, 7.3.2.2, 7.3.3.3, 15	Added content (text, footnote) indicating that IOP will be performed before/after IAI/sham injections at each visit.	IOP measurements now required before and after IAI/sham injections for safety/data assessment purposes.
5.2	Updated Exclusion Criteria as follows:	

	• [redacted] • [redacted] • Exclusion Criterion #9f: ***Previously (#9g) read:*** • Uncontrolled systemic hypertension. ***Now (#9f) reads:*** • Uncontrolled high blood pressure (systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 100 mmHg or higher) despite adequate treatment during the 3 months prior to dosing. • [redacted] • [redacted] • [redacted]	[redacted] Criterion clarified with additional, descriptive content. [redacted] [redacted] [redacted]

	[redacted]	[redacted]
7.1.1.3.2.4	Reading speed assessment was changed from MNRead to iReST in Poland and Germany, and the Radner Test in Hungary. Brief descriptive information as provided for both assessments and descriptive text for MNRead was removed.	The MNRead assessment was not available in required languages, so it was substituted with similar reading speed assessments available in Polish, German, and Hungarian.
7.5	Content updates made to ensure that all prohibited medications, per the Exclusion Criteria, were described.	Further clarification of prohibited medications.
17.1	Revised MDRD formula content to include equations to calculate estimated GFR in conventional and SI units.	Clarification of approved MDRD formulas.
[redacted]	[redacted]	[redacted]