Study Title	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 (wAMD)
NCT Number	NCT03558074
Document Description	Protocol (Version 3.0)
Document Date	15 May 2018

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 (wAMD)

Protocol Number:	ALK4290-202
Clinical Phase:	2
Sponsor:	Alkahest, Inc. 75 Shoreway Road, Suite D San Carlos, CA 94070
Investigational Drug:	ALK4290
Indication:	Wet Age-Related Macular Degeneration (wAMD)
Authorized Representative:	[redacted] 75 Shoreway Road, Suite D San Carlos, CA 94070 [redacted]
Principal Investigator:	[redacted]
Version Number:	V3.0
Version Date:	15MAY2018

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Amino Transferase
AM	Ante Meridiem
AMD	Age-Related Macular Degeneration
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ARM	Age-Related Maculopathy
ARMS2	Age-Related Maculopathy Susceptibility 2 AST
AST	Aspartate Amino Transferase
AUC	Area under the Curve
BCVA	Best Corrected Visual Acuity
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
[redacted]	[redacted]
CCR3	C-C Chemokine Receptor Type 3
[redacted]	[redacted]
CK	Creatinine Kinase
CK-MB	Creatinine Kinase-MB Test
C_{max}	Maximum Plasma Concentration
CMP	Clinical Monitoring Plan
CNV	Choroidal Neovascularization
CNVM	Choroidal Neovascular Membranes
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Central Retinal Thickness
CST	Central Subfield Thickness
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EMA	European Medicines Agency
EOT	End of Treatment
ESC	Eosinophil Shape Change
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FU	Follow-up

GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCV	Hepatitis C Virus Test
HEV	Hepatitis E Virus Test
HPLC-MS/MS	High Performance Liquid Chromatography, Tandem Mass Spectrometry
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRF	Intraretinal Fluid
ISF	Investigator Site File
IVT	Intravitreal
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Drug Regulatory Activities
NOA	Not Analyzed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
OCT	Optical Coherence Tomography
PED	Pigment Epithelial Detachment
[redacted]	[redacted]
pH	Potential of Hydrogen
PK	Pharmacokinetics
PP	Polypropylene
PT	Prothrombin Time
QRS	QRS Interval on ECG
QT	QT Interval on ECG
RBC	Red Blood Cell Count
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analytical Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SRF	Subretinal Fluid
Tdp	Torsade de Pointes
ULN	Upper Limit of Normal
VA	Visual Acuity
VCA	Vascularized Composite Allotransplantation
VEGF	Vascular Endothelial Growth Factor
wAMD	wet Age-Related Macular Degeneration
WBC	White Blood Cell Count
YAG	Yttrium Aluminum Garnet

PROTOCOL APPROVAL PAGE

Study Title:	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 (wAMD)
Protocol Number:	ALK4290-202
Version/Date:	V3.0_15MAY2018
Sponsor Name and Address:	Alkahest, Inc. 75 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:

Sponsor Representative (print)	Signature	Date

STATEMENT OF COMPLIANCE

Protocol Title:	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 (wAMD)
Protocol Number:	ALK4290-202 Protocol Version V3.0_15MAY2018

By my signature, I have thoroughly read this study protocol and have understood the requirements as well as the conditions of this study protocol. I agree to the following points:

- To perform the clinical study according to this protocol and all applicable laws and regulations including, but not limited to, current and relevant versions of the European Medicines Agency (EMA) regulations, the local (Polish/Hungarian) Drug Laws, the International Conference on Harmonization - Good Clinical Practice guideline (ICH-GCP), and the ethical principles that have their origins in the Declaration of Helsinki.
- 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).
- To record accurately all required data on the electronic case report forms (eCRFs).
- To provide direct access to source data/documents (source document verification).
- To use all study material only as specified in this protocol.
- To report within 24 hours any adverse event that is serious, whether it is considered treatment-related or not.
- To instruct and train all delegates in my institution who will take over tasks within this clinical study.
- To onsite monitoring of all source documents by Alkahest, Inc. or designee and to on-site inspection of source documents by appropriate regulatory authorities, including but not limited to the EMA, local governing regulatory bodies, and IRB/IEC inspectors.

_____ _____

Investigator's Signature Date

_____

Print Name

PROTOCOL SUMMARY

Title:

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 (wAMD)

Précis:

This study is designed to evaluate the therapeutic effects and safety of oral ALK4290 administered at 800 mg daily over a 6-week dosing period in subjects with refractory wAMD following treatment with intravitreal (IVT) anti-vascular endothelial growth factor (anti-VEGF). The study agent will be self-administered orally. Training on study agent administration will be conducted prior to initial study agent administration (at Visit 2) under the supervision of study personnel. All study agent administrations at the study site will be done under the direct supervision of the study personnel for documentation of precise administration times.

All subjects will undergo a screening visit, baseline/treatment visit(s), an end of study/early termination visit, and follow-up visits, as applicable. Visits will include safety and tolerability assessments, best corrected visual acuity (BCVA) as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) testing method, and morphological evaluations utilizing spectral domain optical coherence tomography (SD-OCT) and fundus photography/fluorescein angiography (FA). For a complete listing of study events, please see Section 15.1, Schedule of Events Table.

Objectives:

The primary objective of the study is to investigate the potential therapeutic effects of a 6-week, twice daily oral dosing regimen of ALK4290 on BCVA, as measured by ETDRS, in subjects with refractory wAMD following treatment with IVT anti-VEGF. As a secondary objective, the study will assess the safety of the proposed dosing regimen. The exploratory objectives are to investigate the potential pharmacokinetic and ocular morphological effects related to twice daily treatment of ALK4290 in refractory subjects with wAMD by measuring changes in concentrations of ALK4290 in plasma at various time points as well as central subfield thickness (CST), intraretinal fluid (IRF), subretinal fluid (SRF), and pigment epithelial detachment (PED) identified by SD-OCT and fundus photography/FA. Additionally, pharmacogenomic and biomarker evaluations will be conducted on blood and plasma samples.

Endpoints:

Primary Endpoint:

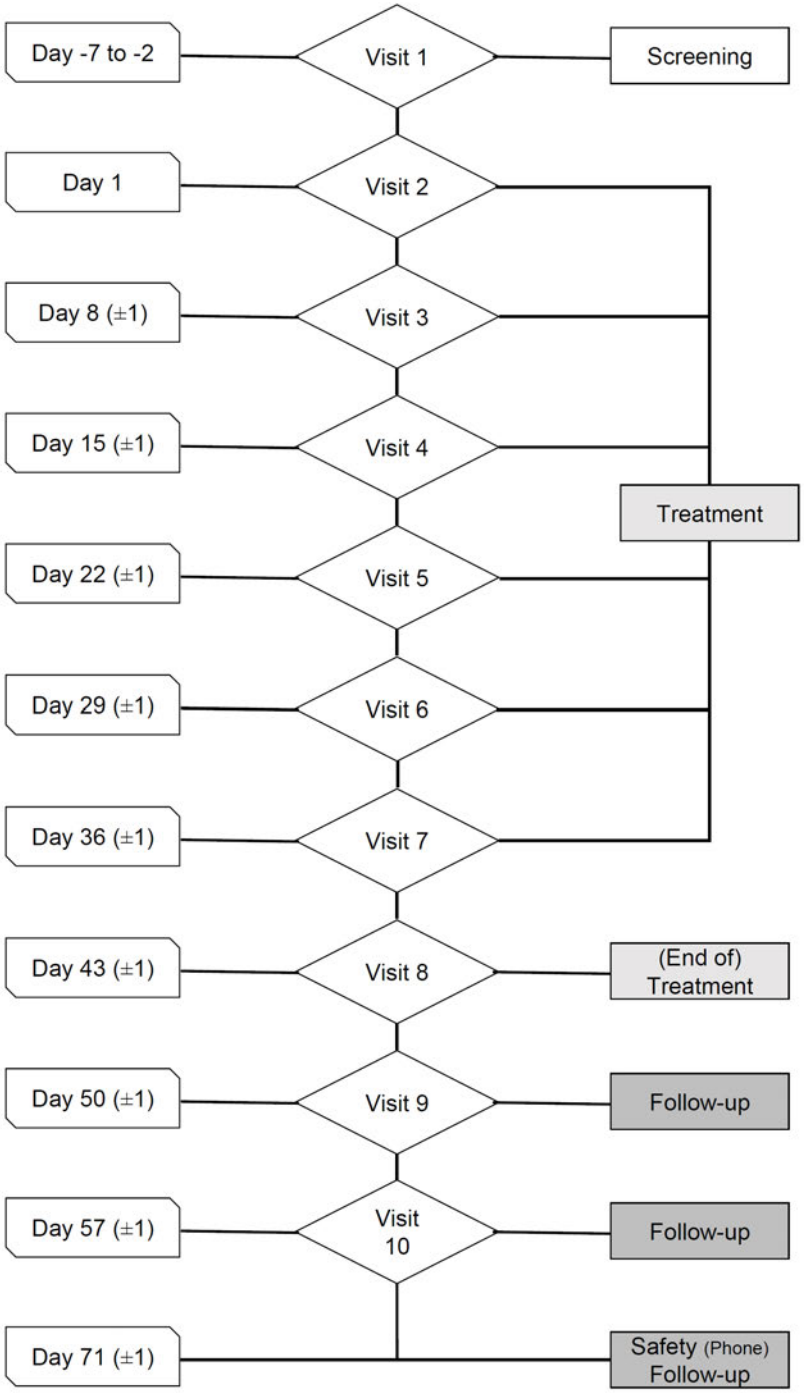
- Mean change in BCVA letter score as measured by the ETDRS testing method

Secondary Endpoint:

- Safety as assessed by incidence, seriousness, and severity of adverse events

	Exploratory Endpoints: • Changes in concentrations of ALK4290 in plasma at various time points • Changes in CST, IRF, SRF, and PED as measured by SD-OCT and fundus photography/FA • Evaluation of pharmacogenomic characteristics and biomarkers in blood and plasma samples
Population:	Approximately 30 subjects, 50 years of age or older, with a diagnosis of refractory wAMD
Phase:	2
Number of Sites:	Up to 12 sites
Description of Study Agent:	ALK4290: A small molecule antagonist of the human C-C chemokine receptor type 3 (CCR3)
Study Duration:	10 months
Participant Duration:	10 weeks (6-week treatment plus 4-week follow-up)

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

1.1 AUTHORIZED REPRESENTATIVE (SIGNATORY) / RESPONSIBLE PARTY

[redacted]
Alkahest, Inc.
75 Shoreway Road, Suite D
San Carlos, CA 94070
[redacted]

1.2 STUDY ORGANIZATION

The name and contact information of the responsible party and individuals involved with the study (e.g., investigator(s), sponsor's medical expert and study monitor, sponsor's representative(s), laboratories, steering committees, and oversight committees [including independent ethics committees (IECs) and Institutional Review Boards (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, with a global prevalence of 170 million (Pennington 2016, Wong 2014). It is estimated that 196 million people worldwide 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 the 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 wherein 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 or Alzheimer's disease (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 drusen and geographic atrophy extending to the center of the macula (Jager 2008). Exudative or wet AMD (wAMD), arises from the growth of abnormal blood vessels from the choroid into the normally avascular sub-RPE and subretinal regions (choroidal neovascularization (CNV). Fluid accumulation in the sub-RPE spaces, derived from the abnormal choriocapillaris changes and growth under the RPE or retina causing serum and blood accumulation into subretinal spaces, leads to retinal thickening, mostly at the macular area. 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 pigment epithelial detachment (PED), a pathological process in which the retinal pigment epithelium separates from the underlying Bruch's membrane due to the presence of blood, SRF and/or IRF (Pepple 2011). PEDs are important markers of disease severity, risk for progression, and vision loss, and are seen in up to 62% of eyes with advanced wAMD (Coscas 2007). Although wAMD 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 wAMD (Riaz 2017, Ambati 2012). Intravitreally administered anti-VEGF therapies include Lucentis® (ranibizumab)(Brown 2006, Rosenfeld 2006), Avastin® (bevacizumab)(Martin 2011)(typically used as an off-label drug to treat wAMD), 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.

Although anti-VEGF agents are a key foundation in wAMD treatment, some patients have a poor response or a nonresponse to IVT anti-VEGF therapy. In these patients, persistent fluid remains or recurs following treatment. In the randomized Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), investigators assessed the efficacy of IVT Lucentis® or Avastin® in both monthly and in as-needed regimens (Martin 2012). Despite monthly treatments with these anti-VEGF agents for 2 years, 51.5% of patients receiving Lucentis®, and 67.4% of patients treated with Avastin®, had evidence of persistent fluid on OCT. A similar study of IVT administration of Eylea® reported that 19.7–36.6% of patients had active exudation on either FA or OCT after 1 year of regular therapy (given monthly or every 2 months) (Heier 2012).

Researchers have used various terms to describe these patients including "incomplete responders," "poor responders," "nonresponders," "unresponsive," "treatment resistant," "refractory," etc. We have chosen the term, "refractory" to describe and classify the group of patients with persistent SRF, IRF, and absence of improvement in visual acuity after at least 3 consecutive (approximately 4-6 weeks apart) IVT anti-VEGF injections. A clear unmet medical need exists to provide an appropriate therapeutic option for this subset of patients. Therefore, to address this clinical need, the oral therapeutic ALK4290 was developed.

2.2 RATIONALE

Alkahest study ALK4290-202 will evaluate 400 mg of ALK4290 administered orally twice a day for a total daily dose of 800 mg. ALK4290 is a highly specific and potent small molecule antagonist of the human C-C chemokine receptor type 3 (CCR3). The CCR3/eotaxin axis is a key chemotactic factor for eosinophils, mast cells, and, in the context of wAMD, endothelial cells. Inhibiting CCR3 interrupts endothelial cell migration, thereby reducing the morphological changes (e.g., central retinal thickness (CRT), edema, and blood leakage) attributed to pathologic CNV (Nagai 2015). The anticipated clinical results from an orally administered CCR3 antagonist therapy would be to maintain or, potentially, improve visual acuity, enhance quality of life, and provide a clinical option for patients who are refractory to IVT anti-VEGF therapy.

Although a significant amount of preclinical data exists for CCR3 blockade in wAMD, there is no published clinical data supporting the therapeutic use of CCR3 in wAMD (Nagai 2015, Wang 2016, Wang 2011)(for further details and information, see the [redacted] for ALK4290). This study is designed to evaluate potential therapeutic effects of ALK4290 on BCVA in wAMD subjects. Without treatment, patients with wAMD lose an average of 10 ETDRS letters within 1 year and eventually most patients become legally blind. The current standard of care for wAMD is IVT anti-VEGF therapy which usually maintains and improves BCVA. However, for the subset of patients

who do not respond to this treatment (see Section 2.1 above), the therapeutic choices are severely limited.

Hence, an effective oral treatment, or an oral treatment that provides incremental improvement in BCVA, would be considered a substantial medical advance for refractory patients. The aim of this 6-week trial is to investigate whether orally administered ALK4290 has the potential to maintain or increase BCVA as measured by ETDRS in subjects who have proven to be refractory to IVT anti-VEGF therapy. If a favorable effect on BCVA is observed, this study would potentially provide the basis for longer-term evaluation of the effects of ALK4290 to further assess functional and morphological benefits.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

[redacted] ALK4290 was considered safe and well tolerated by the subjects with wAMD in the trial. Potential risks associated with the study design include those related to the study procedures and methodology, most notably the potential risks associated with FA including allergic reactions and renal/ thyroid complications.

2.3.2 KNOWN POTENTIAL BENEFITS

The primary aim of this study is to determine if inhibition of CCR3 with ALK4290 has beneficial functional effects related to BCVA as measured by ETDRS. An effective oral maintenance treatment, or an oral treatment that provides incremental improvement in BCVA, would be considered a substantial medical advance and provide a therapeutic option for those patients who are refractory (poor- or non-responders) to IVT anti-VEGF therapy. A specific aim of the current study is to investigate whether orally administered ALK4290 has the potential to improve BCVA. If a favorable effect is observed, this study could potentially provide the basis for longer term studies to evaluate BCVA as well as associated beneficial morphological endpoints.

[redacted]

[redacted]

Hence, the current risk benefit supports administration in modest subject numbers up to an exposure of 6 weeks in duration to further investigate therapeutic effects, safety, pharmacokinetics, and morphological outcomes related to treatment with ALK4290 in subjects with wAMD.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to investigate the potential therapeutic effects of a 6-week, twice daily oral dosing regimen of ALK4290 on BCVA in subjects with refractory wAMD (i.e., following 3 consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections in the study eye). Secondarily, this study aims to assess the safety of the study agent. Exploratory objectives include measuring changes in concentrations of ALK4290 in plasma at various time points as well as CST, IRF, SRT, and PED identified by SD-OCT and fundus photography/FA. Additionally, pharmacogenomic and biomarker evaluations will be conducted on blood and plasma samples.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This will be a single arm, open-label, study to evaluate the therapeutic effects and safety of a 6-week treatment regimen of ALK4290 in subjects with refractory wAMD.

This study enrolls subjects with refractory CNV secondary to AMD who have received at least 3 consecutive (approximately 4-6 weeks) IVT anti-VEGF injections prior to screening. At every visit, safety and tolerability assessments will occur. At specified visits, BCVA will be measured by ETDRS and morphological evaluations will be conducted utilizing SD-OCT and fundus photography/FA. For a complete listing of study events, please see Section 15.1, Schedule of Events Table.

The overall duration of the study is approximately 10 months from study initiation (i.e., first subject enrolled) to study completion (i.e., last subject last visit) with a targeted recruitment of 30 subjects over the accrual period. The subject participation period is 10 weeks (6-week treatment plus 4-week follow-up), unless prematurely discontinued.

4.2 STUDY ENDPOINTS

The endpoints in this study pertain to the therapeutic efficacy, safety, and pharmacokinetic/pharmacodynamic effects of a total daily dosage of 800 mg of ALK4290 administered orally twice a day as 400 mg tablets for 6 weeks.

Primary Endpoint:

- Mean changes in BCVA as measured by the ETDRS testing method (see Section 7.1)(Ferris 1982)

Secondary Endpoint:

- Safety as assessed by incidence, seriousness, and severity of adverse events

Exploratory Endpoints:

- Changes in concentrations of ALK4290 in plasma at various time points
- Changes in CST, IRF, SRF, and PED as measured by SD-OCT and fundus photography/FA
- Evaluation of pharmacogenomic characteristics and biomarkers in blood and plasma samples

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 INCLUSION CRITERIA

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

- Men and women with refractory active CNV secondary to AMD, diagnosed by a retinal specialist with all the following characteristics and ophthalmic inclusion criteria applied to the study eye:
  - Persistent exudation of SRF and IRF as documented by SD-OCT and absence of improvement in visual acuity following 3 consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections; subject must have received their last IVT anti-VEGF injection 30 to 90 days prior to the initial screening visit
  - CST ≥ 250 microns on SD-OCT (exclusive of subretinal pigment epithelial fluid, inclusive of SRF)
  - Total lesion size not greater than 12 disc areas on FA
  - If present, subretinal hemorrhage must comprise < 50% of the total lesion area on FA
  - No subfoveal fibrosis or atrophy on FA
- BCVA letter score, as measured by ETDRS in the study eye, between 70 and 24 letters, inclusive, at screening
- Patients 50 years of age or older at screening visit 1
- Body mass index (BMI) between18 and ≤ 40 at screening visit 1
- **Hungary:** Female subjects must not be pregnant or breastfeeding. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately.
  Poland: Female subjects must not be pregnant or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test at screening/visit 1, the first treatment visit, and the last treatment visit. Women of childbearing potential and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately.
- 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

A subject will not be eligible for inclusion if any of the following criteria apply:

- Treatment with IVT anti-VEGF therapy within 30 days preceding screening visit (Visit 1) in the study eye and/or planned concomitant IVT anti-VEGF treatment in the fellow eye during the study period
- Previous participation in any studies of investigational drugs within 1 month preceding screening visit (Visit 1)
- Any form of macular degeneration that is not age-related (e.g., Best's disease, Stargardt's disease, Sorsby's disease, etc.)
- Additional eye disease in the study eye that could compromise BCVA (i.e., uncontrolled glaucoma (intra-ocular pressure > 24) with visual field loss, clinically significant diabetic maculopathy, history of ischemic optic neuropathy or retinal vascular occlusion, vitreomacular traction, monocular vision, or genetic disorders such as retinitis pigmentosa; high myopia > 8 diopters)
- Anterior segment and vitreous abnormalities in the study eye that would preclude adequate observation with fundus photography/FA or SD-OCT

- Intraocular surgery in the study eye within 3 months prior to screening
- Aphakia or total absence of the posterior capsule (yttrium aluminum garnet (YAG) laser capsulotomy permitted, a minimum of 1 month prior to enrollment) in the study eye
- Known allergy to fluorescein sodium for injection in FA
- 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, and ethambutol)
- Medical history or condition:
    - Uncontrolled diabetes mellitus, with hemoglobin A1c (HbA1c) > 8%
    - Myocardial infarction or stroke within 12 months of screening
    - Active bleeding disorder
    - Concomitant use of warfarin or anticoagulation therapy
    - Major surgery within 1 month of screening or planned within the study period
    - Hepatic impairment
    - Uncontrolled hypertension
    - Positive screening for Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV)
- [redacted]
- Use of systemic steroids (>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 steroids within the study period
- Use of intravitreal steroids:
    - Dexamethasone (Ozurdex) or triamcinolone within 6 months prior to screening
    - Flucinolon (Retisert or Iluvien) within 48 months prior to screening
- Patients with a clinically relevant abnormal screening hematology, blood chemistry, or urinalysis, if the abnormality defines a significant disease as defined in other exclusion criteria (e.g., aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2.0-fold the upper limit of normal at screening; total bilirubin or prothrombin time (INR) > 1.5 times the upper limit of normal at screening). Laboratory testing may be repeated once during the screening phase
- Patients with impaired renal function defined as calculated glomerular filtration rate (GFR) < 30 mL/min
- Significant alcohol or drug abuse within past 2 years
- Based on electrocardiogram (ECG) reading, patients with a risk of prolonged QT interval effects including:
    - A marked baseline prolongation of QTc (using Bazett's formula: ≥ 430 ms in men and ≥ 450 ms in women) with confirmation on a repeat ECG)
    - A history of additional risk factors for Torsade de Pointes (TdP) (e.g., heart failure, hypokalemia, family, history of Long QT Syndrome, etc.)
    - The use of concomitant medications known to prolong the QT/QTc interval
- Significant disease or other medical conditions (as determined by medical history, examination, and clinical investigations at screening) that may, in the opinion of the investigator, result in the any of the following:
    - Put the patient at risk because of participation in the study
    - Influence the results of the study
    - Cause concern regarding the patient's ability to participate in the study
- 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 SUBJECT WITHDRAWAL OR TERMINATION

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

A subject will be withdrawn from the study 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
- 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 or the subject's legally authorized representative (e.g., subject withdraws consent), investigator, sponsor or regulatory authority
- Pregnancy

5.3.2 HANDLING OF PARTICPANT WITHDRAWALS OR TERMINATION

Approximately 30 subjects will be enrolled in the study. Subjects will be encouraged to complete the study and all assessments. However, subjects may voluntarily withdraw at any time, and the investigator may discontinue individual subjects from the study at any time. For subjects who withdraw consent from the study, no study procedures will be done thereafter. For those that withdraw from receiving the study agent, follow-up visits and the safety phone follow-up, are to occur per the protocol. Excluding cases of medical emergency but prior to the discontinuation of a subject from the clinical study for disease worsening, the study investigator should discuss each case of discontinuation with the sponsor and/or the medical monitor.

The subject withdrawal criterion below should be used to assess worsening or disease progression. In such cases, a documented assessment by the principal investigator is required, and subjects with clinically significant disease progression should be considered for withdrawal from the study and subsequent initiation of standard of care:

- A BCVA loss of ≥ 5 letters from baseline
- New macular subretinal hemorrhage
- Investigator discretion based on acute worsening of underlying disease or substantial risk to further participation in the study

5.4 PREMATURE TERMINATION OR SUSPENSION OF STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will 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:

- Unsatisfactory subject enrollment (i.e., < 2 subjects enrolled within a 6-month period)
- Unacceptable protocol deviations/violations as assessed by the medical monitor
- Inaccurate or incomplete data entry and recording

- Investigational site non-compliance with ICH/GCP
- Unacceptable emergent safety profile

6 TREATMENTS

6.1 STUDY AGENT DESCRIPTION

6.1.1 ACQUISITION

The study agent will be formulated, tableted, labeled, packaged, and distributed by Alkahest, Inc.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

[redacted] The subjects will be provided with 1 bottle at each treatment visit so that the time windows between visits (see Section 15.1, Schedule of Events Table) will be covered. The study agent will be delivered to the sites immediately prior to site activation and thereafter upon request. The product will be labeled for investigational use according to the relevant regulatory requirements for clinical studies.

For further details and information on ALK4290, including packaging and labeling, see the [redacted]

6.1.3 PRODUCT STORAGE AND STABILITY

[redacted] 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 agent will be self-administered orally twice daily for a total daily dose of 800 mg. Training on study agent administration will be conducted prior to initial study agent administration (at Visit 2) under the supervision of study personnel. All study agent administrations at the study site will be done under the direct supervision of the study personnel for documentation of precise administration times.

6.2 STUDY AGENT ACCOUNTABILITY

The investigator and/or pharmacist will receive the study 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 study agent's delivery 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.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study agent and trial 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 received from the sponsor. At the time of final study agent reconciliation, the investigator/pharmacist must verify that all unused or partially used portion of study agent have been returned by the clinical trial subject and that no remaining study agent is retained by the investigator.

Accountability records must be maintained and readily available for inspection 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 accidentally wasted or intentionally disposed of must be maintained.

The disposal of used, partially used, or wasted study agent materials 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 reconciliation by the monitor, the study site will be instructed by the sponsor to return or destroy all unused study agent supplies, including empty containers. A copy of the institution's drug disposal policy should be maintained or referenced in the ISF.

6.3 CONCOMITANT MEDICATIONS AND TREATMENTS

All prescription, over-the-counter, and non-prescription medications (including herbal therapies and supplements) must be documented in the source documents and electronic Case Report Forms (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 should be documented in the eCRF with reason for change (e.g., adverse event, etc.).

6.4 PROHIBITED TREATMENTS, MEDICATIONS, AND PROCEDURES

[redacted]

No other interventional therapy for wAMD is concomitantly allowed.

The use of oral corticosteroids or high potency topical steroids (e.g. with systemic exposure) are restricted during the screening and treatment period of the study. The use of inhaled corticosteroids will be allowed if stably treated for 4 weeks prior to screening without a dose adjustment and 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 6.3 above. However, in case of adverse events 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.

[redacted]

7 VARIABLES AND THEIR ASSESSMENT

For the following endpoints, baseline is the value from Visit 2 (if not measured at Visit 2, then is the value from Visit 1). Detailed information on the methodology used with the following will be included in a Statistical Analytical Plan (SAP).

7.1 THERAPEUTIC EFFECT

BCVA will be assessed using ETDRS charts at 4 meters initial testing distance. The trained technicians 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.

7.2 SAFETY AND EXPLORATORY OUTCOMES

Safety will be assessed by the incidence, seriousness, and severity of adverse events (AEs) (see Section 7.2.1). Changes in laboratory test results, vital signs, ECG, physical examination, and/or ocular morphologic investigations will be recorded as AEs/serious adverse events (SAEs) in the eCRF if they are judged clinically relevant by the investigator.

7.2.1 ASSESSMENT OF ADVERSE EVENTS

7.2.1.1 Terminology to Use for Adverse Event Descriptions

When reporting an adverse event, the event description should use the best matching terminology describing the event as found in the Common Terminology Criteria for Adverse Events (CTCAE v4.03). If an available CTCAE term fits the event well, no additional descriptors may be needed. However, necessary descriptions should be added in order to clarify the event or to place it in an appropriate context. The adverse event name should ideally be 1-3 words in length with additional description provided elsewhere on the adverse event report. A copy of the CTCAE is provided in the ISF. Standardized terms from the CTCAE will be used by the sponsor and the Contract Research Organization (CRO) to categorize events for reporting to regulatory authorities using the Medical Dictionary for Regulatory Activities (MedDRA, v. 20.1). In most cases, the CTCAE terms match MedDRA coding terminology. If an appropriate term matching the adverse event cannot be found in the CTCAE and the preferred MedDRA term is unknown, the AE description should include a diagnosis, sign, or symptom with additional information to facilitate subsequent categorization into MedDRA coding terms.

7.2.1.2 Definition of Adverse Events

7.2.1.2.1 Adverse Event

An AE is defined in the ICH E2D as "any unfavorable or unintended sign, symptom, or disease temporarily associated with the use of a medicinal product whether or not considered related to the product." Progression or worsening of the medical condition under study, by itself, does not necessarily constitute an adverse event unless the change can be reasonably attributed to an action of the study agent and not only to its lack of efficacy. Simply defining an adverse event does not imply a causal relationship; relatedness to the study agent is defined in Section 7.2.1.2.4.

7.2.1.2.2 Serious Adverse Event

An SAE is defined for this protocol as any AE that meets one or more of the following criteria:

A. A death (CTCAE Grade 5 event) occurring during the study, whether or not considered treatment-related;
B. A life-threatening event (CTCAE Grade 4);
C. An event requiring inpatient hospitalization or prolonged hospitalization due to the adverse event;
D. An adverse event resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the participant's body function or structure, physical activities or quality of life;
E. An event that otherwise required a medical or surgical intervention to preclude permanent impairment or damage (excluding unrelated elective or cosmetic procedures).

7.2.1.2.3 Grading Severity of Adverse Events

The investigator must grade the severity of all reported adverse events into one of the following five (5) categories:

- Grade 1 (Mild)
- Grade 2 (Moderate)
- Grade 3 (Severe)
- Grade 4 (Life-Threatening)
- Grade 5 (Death)

The standardized CTCAE severity grading scales for the specific type of adverse event reported must be used when a matching CTCAE term is available. The highest severity grade experienced for the event should be reported. The initial severity grading may be updated in follow-up reports if the maximum grade changes to a higher level. The CTCAE grading scale should be used according the following guidelines.

Grade 1 (Mild)

Transient (< 48 hours) or mild discomforts, no or minimal medical therapy or intervention required, hospitalization not necessary, no or little limitation in normal activities, nonprescription or single-use prescription therapy may be employed to relieve symptoms (e.g., aspirin for simple headache, acetaminophen with codeine for post-surgical pain). Mild adverse events may be listed as expected consequences of the therapy for any given protocol, and standard supportive measures for such an expected event do not necessarily elevate the event to a higher grade.

Grade 2 (Moderate)

Mild to moderate limitation in activity, some assistance may be needed; possibly none but usually minimal intervention/therapy required, hospitalization possible.

Grade 3 (Severe)

Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalization possible or likely.

Grade 4 (Life-Threatening)

Extreme limitation in activity, significant and immediate assistance required; significant medical/therapy intervention required to prevent loss of life; hospitalization, emergency treatment or hospice care probable. This grade is used when the subject was, in the view of the investigator, at substantial risk of dying at the time of the adverse event or it was suspected that use or continued use of the study agent would have resulted in the subject's death.

Grade 5 (Death)

Death related to AE.

7.2.1.2.4 Relatedness of Study Agent to Adverse Event

The investigator (or an authorized study physician) or sponsor must submit an attribution for the relatedness of the reported AE to the study agent. The attribution should take into account both the temporal association and any known physical, physiological, or toxicological information regarding the study agent that could reasonably infer causality. The three attribution categories are:

- **Definite** - Clearly related to the study agent. An adverse event that follows a temporal sequence from administration of the study agent; follows a known response pattern to study agent; and, when appropriate to the protocol, is confirmed by improvement after stopping the study agent (positive rechallenge; and by reappearance of the reaction after repeat exposure (positive rechallenge)); and cannot be reasonably explained by known characteristics of the subject's clinical state or by other therapies.
- **Possibly** - May be related to the study agent. An adverse event that follows a reasonable temporal sequence from administration of study agent and follows a known response pattern to the study agent, but could have been produced by the subject' clinical state or by other therapies.
- **Unrelated** - Clearly NOT related to the study agent. An adverse event that does not follow a reasonable temporal sequence after administration of the study agent and most likely is explained by the subject's clinical disease state or by other therapies. In addition, a negative rechallenge to the study agent would support an unrelated relationship.

7.2.1.2.5 Worsening of Underlying Disease and/or Other Pre-Existing Conditions

Worsening of the underlying disease and/or of other pre-existing conditions will be recorded as an AE/SAE in the eCRF.

7.2.1.2.6 Changes in Safety Evaluations

Changes in vital signs, ECG, physical examination, laboratory test results, and ophthalmic evaluations will be recorded as an AE/SAE in the eCRF if they are judged clinically relevant by the investigator.

7.2.1.2.7 Adverse Events of Special Interest

The following are considered adverse events of special interest (AESI):

- Hepatic injury defined by the following alterations of liver parameters:
  For subjects with normal liver function at baseline an elevation of AST and/or ALT ≥ 3-fold ULN combined with an elevation of total bilirubin ≥ 2-fold upper limit of normal (ULN) measured in the same blood draw sample. Subjects showing these lab abnormalities need to be followed up according to Section 17.1.2.
- Abrupt decrease (> 15 letters lost from baseline) of BCVA
- QTc prolongation (> +50 ms from baseline and > 450 ms)

Protocol-specific AESIs are to be reported in an expedited manner similar to SAEs even if they do not meet any of the criteria for an SAE (see Section 7.2.1.2.2).

7.2.1.3 Adverse Event and Serious Adverse Event Reporting

All AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent through the follow-up period) will be collected, documented, and reported to the sponsor by the investigator on the appropriate eCRF and SAE reporting forms.

For each AE, the investigator will provide the onset date, end date, seriousness, grade, relatedness, treatment required, outcome, and action taken with the study agent. The investigator will determine the grade as defined in Section 7.2.1.2.3 and the causal relationship to the study agent (relatedness) as defined in Section 7.2.1.2.4.

The investigator must report the following events immediately (within 24 hours or the next business day whichever is shorter) to the sponsor or designee (refer to the Lab Manual/ISF for specific instructions): SAEs and non-serious AEs relevant to the reported SAE and protocol-specified AESI.

The investigator does not need to actively monitor subjects for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the subject has completed the clinical trial, it should be reported by the investigator to the sponsor if considered relevant by the investigator.

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 SAE report 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 report.

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.

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 case report form.

The SAE report(s) should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to the sponsor or designee (e.g., study CRO). It is very important that the investigator provide his/her assessment of relatedness to the study agent as well as an applicable diagnosis at the time of the initial SAE report.

7.2.2 SAFETY LABORATORY EVALUATIONS

Blood samples and urine must be collected at every visit. Safety laboratory examinations will include hematology, biochemistry, coagulation and qualitative urine analysis.

- Hematology: hemoglobin, red blood cell count (RBC), white blood cell count (WBC) with differential, platelets
- Biochemistry: glucose, sodium, potassium, calcium, inorganic phosphate, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), lactate dehydrogenase (LDH), total bilirubin (if elevated provide direct bilirubin), urea, total protein, albumin, uric acid
- Coagulation: activated partial thromboplastic time (aPTT), prothrombin time (PT)/international normalized ration (INR)
- Urine: potential of hydrogen (pH), glucose, erythrocytes, leukocytes, protein, nitrite

Glomerular filtration rate (GFR) will be estimated by the Cockroft Gault Formula utilizing serum creatinine (see Section 17.5). All safety laboratory measurements will be performed by a central laboratory. Investigators will get guidance and instructions on laboratory sampling and processing through a separate Lab Manual provided by the central laboratory.

The investigator is responsible for determining and documenting if out of range laboratory values are clinically significant or not. 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.

7.2.3 ELECTROCARDIOGRAM

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph. The ECGs will be recorded for a 10-second duration after the subjects have rested for at least 5 minutes in a supine position (see Section 15.1, Schedule of Events Table, for time points). ECGs will be stored in the subject's medical records. ECGs may be repeated for quality reasons and the repeat ECG will be used for analysis. Additional ECGs may be collected by the investigator for safety reasons. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) in the eCRF.

7.2.4 VITAL SIGNS AND PHYSICAL EXAMINATION

7.2.4.1 Vital Signs

Vital signs (blood pressure, pulse rate and respirations) and temperature will be recorded according to Section 15.1, Schedule of Events Table.

7.2.4.2 Physical Examination

A general physical examination including height (measured only at screening) and weight will be performed according to the time points in Section 15.1, Schedule of Events Table. Whenever possible, the same health care practitioner should perform this examination.

7.2.5 OTHER OPHTHALMIC EXPLORATORY ENDPOINTS AND EVALUATIONS

The ophthalmic endpoints described below as being evaluated over time will be measured in an exploratory manner to investigate the extent, onset, and duration of action 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 PED by SD-OCT over time, absolute and as change from baseline
- Neovascular leakage as demonstrated by fundus photography/FA, absolute and as change from baseline
- Vascular area measured by SD-OCT and fundus photography/FA, absolute and as change from baseline

7.2.5.1 Optical Coherence Tomography

The retinal layers and thickness can be visualized and measured by OCT. The study eye will be investigated by a trained person using only specified OCT equipment. A detailed manual for OCT image acquisition and data transmission will be provided in the ISF. The reported CST will be exclusive of the sub-RPE layer fluid.

7.2.5.2 Fundus Photography/Fluorescein Angiography

The retinal vasculature of the study eye will be evaluated and imaged by fundus photography/FA. A detailed manual for fundus photography/FA will be provided in the ISF.

7.2.5.3 Slit Lamp and Intraocular Pressure Measurement

The slit lamp examination is to be performed in both eyes. The anterior and posterior segment of the eye should be assessed. The results will be entered in the eCRF. IOP will be measured using applanation Goldmann tonometry in both eyes during each visit. The results will also be entered in the eCRF.

7.2.6 STUDY AGENT CONCENTRATION AND PHARMACOKINETICS

Plasma concentration measurements of ALK4290 will be collected to assess systemic exposure to the study agent. For sampling time points and further details, please refer to Section 17.3.

7.2.6.1 Pharmacokinetic Endpoints

As far as feasible, the following pharmacokinetic parameters will be derived by noncompartmental methods:

- C_{max} Maximum concentration of ALK4290 in plasma after single dose
- t_{max} Time of C_{max} relative to last dosing
- $t_{max,ss}$ Time of $C_{max,ss}$ relative to last dosing
- $C_{pre,ss,N}$ Pre-dose concentration of ALK4290 in plasma immediately before administration of the Nth dose

In addition, the average pre-dose concentration in plasma at steady state will be calculated as the geometric mean of $C_{pre,ss,N}$ values.

7.2.6.2 Methods of Sample Collections

For quantification of ALK4290 plasma concentrations and for biomarker investigations (see Section 7.2.8), one blood sample of approximately 6 mL per sampling time point (see Section 17.2.1, Table of Pharmacokinetic, Biomarker, and Pharmacogenomic Sampling) will be taken from an antecubital or forearm vein into a potassium ethylenediaminetetraacetic acid (EDTA)-anticoagulant blood drawing tube.

The EDTA-anticoagulated blood samples will be centrifuged to collect plasma. For pharmacokinetic 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 Lab Manual/ISF.

7.2.6.3 Analytical Determinations

Concentrations of ALK4290 and metabolites (if feasible) in plasma samples will be determined by a validated high performance liquid chromatography, tandem mass spectrometry (HPLC-MS/MS) assay. Leftover samples will be used for exploratory biomarker assessment (see Section 7.2.8).

7.2.7 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]

7.2.7.1 Methods and Timing of Sample Collection

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] For additional information, see Section 17.2.1, Table of Pharmacokinetic, Biomarker, and Pharmacogenomic Sampling and in the Lab Manual/ISF.

The PAXgene Blood DNA tubes and EDTA containing blood sampling tubes can be stored and shipped at room temperature within 14 days. If a longer storage and shipment period for PAXgene Blood DNA tubes is necessary, these blood samples should be stored at a temperature of -20°C or below. Once frozen, thawing of the samples should be avoided.

7.2.7.2 Analytical Determinations

DNA will be extracted from blood samples according to standard molecular genetics methods and analyzed by standard genotyping and gene expression technologies.

Detailed instructions for pharmacogenomic sampling, handling and shipment of samples are provided in the Lab Manual/ISF.

7.2.8 BIOMARKERS

Measurement of biomarkers is exploratory. [redacted]

[redacted] After completion of the study, leftover 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.

7.2.8.1 Method of Sample Collection

For quantification of ALK4290 plasma concentrations (see Section 7.2.6) and for biomarker investigations, one blood sample of approximately 6 mL per sampling time point (see Section 17.2.1, Table of Pharmacokinetic, Biomarker, and Pharmacogenomic Sampling and Section 15.1 Schedule of Events Table) 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 pharmacokinetic studies 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 collected by the central laboratory. Details of plasma collection, sample handling, and shipment instructions will be given in the Lab Manual in the ISF.

7.2.8.1 Analytical Determinations

The exploratory biomarker measurements will be conducted either at the sponsor's labs or at external CROs using appropriate methodology (e.g., immunoassays, multiplex technology). A Lab Manual/ISF will describe the handling of the samples.

8 INVESTIGATIONAL PLAN

8.1 VISIT SCHEDULE

All study agent administrations at the study site will be done under the direct supervision of the study personnel for documentation of precise administration times. In case a visit is delayed beyond the window detailed in Section 15.1, Schedule of Events Table, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. The next visit should still take place at the time it was originally scheduled in this treatment course. Any delays in visit dates, outside of the defined criteria in the Schedule of Events Table, will be reported as a protocol deviation.

8.2 VISIT PROCEDURES

The investigations as outlined in Section 15.1, Schedule of Events Table will be performed at the respective visits as described in detail in the following sections.

8.2.1 SCREENING AND RUN-IN PERIOD

The screening period (Visit 1), i.e. the phase after informed consent and before the first administration of the study agent, may be as long as 6 days (day -7 to -2). However, a pretrial fundus photography/FA examination performed within 14 days prior to Visit 1 can be used as the screening ophthalmologic examination. In special cases where it is not logistically possible to meet the protocol defined screening period, the screening can be extended by an additional 7 days (day -14) without repeating the screening assessment.

The medical history and medication history within 3 months prior to Visit 1, as well as baseline condition of the subject, will be captured in the eCRF.

8.2.1.1 Visit 1

At Visit 1, the following procedures and assessments are performed:

- Signing of all applicable Informed Consents
- Potential study subject eligibility based on all study-specific inclusion and exclusion criteria (see Sections 5.1 and 5.2)
- Demographics and medical history
- All ophthalmological evaluations: BCVA, SD-OCT, fundus photography/FA, slit lamp, and IOP (see Sections 7.1 and 7.2.5)
- Vital signs, physical examination, safety laboratory tests, **Poland only**: serum pregnancy test (in women of childbearing potential), and 12-lead ECG, (see Sections 7.2.2, 7.2.3 and 7.2.4)
- Review of concomitant medications (see Sections 6.3 and 6.4)
- AE reporting and evaluation according to Section 7.2.1

8.2.2 TREATMENT PERIOD

All ophthalmic examinations and other assessments will be performed before intake of the study agent on the respective day. The examinations of each visit are specified in Section 15.1, Schedule of Events Table. In addition, please see Section 17.2.1, Table of Pharmacokinetic, Biomarker, and Pharmacogenomic Sampling for detailed information regarding these evaluations.

8.2.2.1 Visit 2

At Visit 2, the following procedures and assessments are performed:

- Pharmacokinetic and biomarker samples are taken (see Sections 7.2.6 and 7.2.8)
- Pharmacogenomic samples are taken (see Section 7.2.7)
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs, physical examination, safety laboratory tests, and **Poland only**: serum pregnancy test (in women of childbearing potential)
- Review of concomitant medications

- AE reporting and evaluation
- Study agent administration training and study agent dispensing/administration
- Study agent accountability

8.2.2.2 Visit 3

At Visit 3, the following procedures and assessments are performed:

- Pharmacokinetic samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs, safety laboratory tests, and 12-lead ECG
- Review of concomitant medications
- AE reporting and evaluation
- Study agent dispensing/administration
- Study agent accountability

8.2.2.3 Visit 4

At Visit 4, the following procedures and assessments are performed:

- Pharmacokinetic samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs, physical examination and safety laboratory tests
- Review of concomitant medications
- AE reporting and evaluation
- Study agent dispensing/administration
- Study agent accountability

8.2.2.4 Visit 5

At Visit 5, the following procedures and assessments are performed:

- Pharmacokinetic samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs and safety laboratory tests
- Review of concomitant medications
- AE reporting and evaluation
- Study agent dispensing/administration
- Study agent accountability

8.2.2.5 Visit 6

At Visit 6, the following procedures and assessments are performed:

- Pharmacokinetic and biomarker samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit-lamp, and IOP
- Vital signs, physical examination, safety laboratory tests, and 12-lead ECG
- Review of concomitant medications
- AE reporting and evaluation
- Study agent dispensing/administration
- Study agent accountability

8.2.2.6 Visit 7

At Visit 7, the following procedures and assessments are performed:

- Pharmacokinetic samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs and safety laboratory tests
- Review of concomitant medications
- AE reporting and evaluation
- Study agent dispensing/administration
- Study agent accountability

8.2.3 END OF TREATMENT

All end of treatment (EOT) study-related procedures will be conducted at the conclusion of 6 weeks of treatment on Day 43 ±1. However, for subjects who withdraw consent from the study, no study procedures will be done thereafter. For subjects that withdraw from the study agent, EOT procedures and follow-up visits are to occur as per the protocol. Excluding cases of medical emergency, but prior to the discontinuation of a subject from the clinical study for disease worsening, the study investigator should discuss each case of discontinuation with the sponsor.

8.2.3.1 Visit 8

At Visit 8, the following procedures and assessments are performed:

- Pharmacokinetic and biomarker samples are taken
- All ophthalmological assessments: BCVA, SD-OCT, fundus photography/FA, slit lamp, and IOP
- Vital signs, physical examination, safety laboratory tests, **Poland only**: serum pregnancy test (in women of childbearing potential), and 12-lead ECG

- Review of concomitant medications
- AE reporting and evaluation

8.2.4 FOLLOW-UP VISITS

Follow-up visits will be performed after Visit 8 for all subjects who had at least one dose of trial treatment. Follow-up visits will not be performed if:

- The subject is lost to follow-up
- The subject withdraws consent from the study
- The investigator and sponsor agree not to pursue further follow-up visits with the subject
- The subject dies

In these cases, the trial completion page of the eCRF must be filled out.

8.2.4.1 Visit 9

At Visit 9, the following procedures and assessments are performed:

- Pharmacokinetic and biomarker samples are taken
- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs and safety laboratory tests
- Review of concomitant medications
- AE reporting and evaluation

8.2.4.2 Visit 10

At Visit 10, the following procedures and assessments are performed:

- Specified ophthalmological assessments: BCVA, SD-OCT, slit lamp, and IOP
- Vital signs, physical examination, and safety laboratory tests
- Review of current medications
- AE reporting and evaluation

8.2.4.3 Safety Follow-up: Documented Phone Call

At Day 71 (28 days after end of treatment), the following assessments are performed by phone:

- Review of current medications
- AE reporting and evaluation

In addition, the Trial Completion page must be finalized and entered in the eCRF.

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 the Clinical Quality Oversight Plan to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL DESIGN MODEL AND ANALYTICAL PLANS

The therapeutic effect of the treatment will be investigated in one single group of subjects, with no control group. The observed mean effect will be compared with 0 as reference value. Overall baseline and demographic data will be summarized using descriptive statistics.

Subject disposition (e.g., the number of subjects enrolled, completed, and discontinued) will be summarized and medical history data will be listed. Prior and concomitant medications taken from screening and during the study will be categorized by World Health Organization (WHO) classification for therapeutic class and drug name, listed and summarized by number and percentage of subjects.

Final analyses are not limited to the summaries described herein. Analytical details and assumptions will be fully presented in the SAP.

10.2 STATISTICAL HYPOTHESES

The null and alternative hypothesis for change from baseline in BCVA letter score as measured by ETDRS testing method are:

H_0: Change from baseline in BCVA letter score = 0

H_1: Change from baseline in BCVA letter score $\neq$ 0 with α_1= 0.20

10.3 ANALYSIS DATASETS

Four analysis datasets are possible; however, analyses may not necessarily be conducted with all four:

- **Intention-to-Treat (ITT) Dataset**: all enrolled subjects
- **Safety Dataset**: all subjects who received at least 1 dose of the study agent
- **Evaluable Dataset:** all subjects who complete at least 3 weeks of treatment during the 6-week treatment period
- **Per Protocol Dataset:** a subset of the Evaluable Dataset comprised of subjects who have no major protocol violations

The presentation of baseline characteristics will be based on the ITT dataset. All safety analyses will be performed for the Safety Dataset. Analyses of the primary and exploratory endpoints will focus on the Evaluable and/or Per Protocol Datasets.

10.4 PLANNED ANALYSES

10.4.1 ANALYSIS OF THE PRIMARY ENDPOINT

The therapeutic effect of the treatment will be investigated in one single group of subjects, with no control group. The changes from baseline in BCVA will be compared with 0 as reference value. The study is not designed to detect significant changes in BCVA over time. However, using available data, including changes in BCVA from baseline, descriptive summarization will be developed. Of particular interest will be the within-subject changes in BCVA from baseline and their distribution around a null value of zero.

10.4.2 ANALYSIS OF THE SECONDARY ENPOINT

Safety will be assessed for the following endpoints:

- Incidence, seriousness, and severity of adverse events
- Changes from baseline in clinical laboratory values
- Changes from baseline in physical examination
- Changes from baseline in vital signs

All treated subjects (i.e., all subjects who received at least 1 dose of the study agent) will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on accepted standards.

Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to evaluate continuous (quantitative) data.

10.4.3 EXPLORATORY ANALYSES

Observed values as well as changes from baseline in CST, IRF, SRF, and PED as measured by SD-OCT and fundus photography/FA will be summarized using descriptive statistics. Pharmacokinetic, biomarker, and pharmacogenomic analyses will be carried out using an exploratory approach to investigate the potential influence on the therapeutic response of ALK4290.

10.4.4 PLANNED INTERIM ANALYSES

Continuous data monitoring will be performed. One interim analysis will be performed when 2/3 of all entered subjects have reached Day 15 (Visit 4). It will include only the primary and a subset of the secondary endpoints, (i.e., mean change in BCVA as measured by ETDRS and the accumulated AE information). Recruitment into the trial will be stopped if the interim analysis shows relevant safety problems with ALK4290. No formal futility analysis will be conducted.

10.5 SAMPLE SIZE

A total of 30 subjects will be enrolled in the study with the intent of obtaining ~25 evaluable subjects who have completed at least 3 weeks of treatment and evaluations through Visit 4. Subjects who discontinue prior to Visit 4 may be replaced. Subjects who withdraw or are withdrawn during screening will be replaced. The study is not powered for detecting statistically significant differences in therapeutic parameters in subjects with wAMD receiving ALK4290. However, the proposed sample size may be sufficient to identify trends in the effects of ALK4290 and in the relationship between dose and response.

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 participants. 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, participant'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 accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant 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 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 study will be conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki, and in accordance with the ICH Harmonized Tripartite Guideline for GCP.

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 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 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 approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Any modifications or amendment 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 agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any invasive study 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 and/or their legally authorized representative after adequate explanation of the aims, methods, objectives, and potential hazards of the study and 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 participants may withdraw consent at any time throughout the course of the trial. The rights and welfare of the participants 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/or their legally authorized representative and the person obtaining consent. A copy of the signed consent form will be provided to the subject and/or their legally authorized representative. By signing the informed consent form, all parties agree they will complete the evaluations required by the study, unless they withdraw voluntarily or are terminated 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.

12.4 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 participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the 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 participants in this study. The clinical study site will permit the study monitor to 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 subject initials and 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 participant'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 (or the subject's legally authorized representative'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.

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 will 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.

12.6 EXPEDITED REPORTING OF ADVERSE EVENTS

Expedited reporting of serious adverse events to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

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, 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 reason 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 IRB/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., Lab 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 NONCOMPLIANCE: DEVIATIONS AND VIOLATIONS

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 are instances of protocol noncompliance that DO NOT have the potential to affect the safety of subjects. Protocol Deviations do not require review by the medical monitor.

- *5.20 Noncompliance, sections 5.20.1, and 5.20.2.* **Violations** are instances of protocol noncompliance that DO have the potential to affect the safety of subjects. Violations are a subset of Protocol Deviations.

All instances of protocol noncompliance will be logged and tracked by the site and CRO. Periodic review of Protocol Deviations will inform assessment 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. Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site investigator/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

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 (CSR). 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 CSR, 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 60 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

Sponsor reserves final approval and editing rights for all publications or abstracts that consider aggregated data from more than one individual site.

13.5 COMPLETION OF TRIAL

The EMA/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject out) or early termination of the trial.

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

15.1 SCHEDULE OF EVENTS TABLE

	Screening	Treatment Period							Follow-Up		
Visit Number **Day** **Time Window (days)**	**1** **-7 to -2**	**2** **1**	**3** **8** **±1**	**4** **15** **±1**	**5** **22** **±1**	**6** **29** **±1**	**7** **36** **±1**	**8/EOT[7]** **43** **±1**	**9/FU** **50** **±1**	**10/FU** **57** **±1**	**Phone/FU** **71** **±1**
Informed Consent[1]	X										
Informed Consent for Pharmacogenomics[2]	X										
[redacted]	[redacted]										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria[3]	X	X									
Physical examination	X	X		X		X		X[7]		X	
Vital signs (seated)	X	X	X	X	X	X	X	X[7]	X	X	
Pregnancy test (as applicable)[9]	X	X						X			
Laboratory tests	X	X	X	X	X	X	X	X[7]	X	X	
12-lead ECG	X		X			X		X[7]			
SD-OCT	X	X	X	X	X	X	X	X[7]	X	X	
Fundus photography/FA	X							X[7]			
Visual acuity	X	X	X	X	X	X	X	X[7]	X	X	
Slit lamp	X	X	X	X	X	X	X	X[7]	X	X	
IOP	X	X	X	X	X	X	X	X[7]	X	X	
Administration of study agent[4]		X	X	X	X	X	X	X[7]			
Dispense study agent		X	X	X	X	X	X				
Study agent accountability		X	X	X	X	X	X	X[7]			
Pharmacokinetics blood sample (for plasma extraction)		X[5]	X[6]	X[6]	X[6]	X[6]	X[6]	X[5,7]	X		
Biomarker plasma aliquots		X[5]				X[5]		X[5,7]	X[5]		
Pharmacogenomics blood sample [redacted]		X[2]									
Adverse events[8]	X	X	X	X	X	X	X	X[7]	X	X	X
Concomitant/current medications[8]	X	X	X	X	X	X	X	X[7]	X	X	X
Trial completion											X

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 pharmacogenomic sampling [redacted]. Pharmacogenomics sampling will be performed at enrollment/baseline (Visit 2). [redacted].
3. A preliminary check of inclusion/exclusion criteria will be performed at screening (Visit 1) after obtaining informed consents.
4. Study agent will be self-administered in the clinic under supervision of study personnel during every visit of the treatment period (Visits 2-8) following all safety and ophthalmic assessments. Training on study agent administration will be conducted prior to the initial study agent administration at Visit 2.
5. A pre-dose pharmacokinetic (PK) blood sample will be taken to be centrifuged for collection of plasma samples. Biomarker plasma aliquots will be obtained from the pharmacokinetic (PK) samples. At Visit 2 only, four post-dose pharmacokinetic blood samples will be taken.
6. A pre-dose PK blood sample will be taken to be centrifuged for collection of plasma samples.
7. End of Treatment (EOT) visit (Visit 8): all study related procedures will be conducted at the conclusion of 6 weeks of treatment on Day 43 ±1. Withdrawal of consent is allowed at any time. For subjects who withdraw consent from the study, no study procedures will be done thereafter. For those that withdraw from the study agent, follow-up visits are to occur as per the protocol. Excluding cases of medical emergency, but prior to the discontinuation of a subject from the clinical study for disease worsening, the study investigator should discuss each case of discontinuation with the sponsor.
8. Adverse events and concomitant medications will be assessed at every study visit as well as recorded at any unscheduled subject contact (e.g., unscheduled phone calls, etc.). Following completion of study agent treatment (Visits 2-8), all current medications will be assessed in the follow-up period.
9. Pregnancy test required in **Poland only** per Inclusion Criteria.

16 REFERENCES

16.1 PUBLISHED REFERENCES

Ambati J, Fowler BJ. Mechanisms of age-related macular degeneration. Neuron. 2012;75:26-39.

Bird AC. Therapeutic targets in age-related macular disease. J Clin Investig. 2010;120:3033-3041.

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1432-1444.

Buschini E, Fea AM, Lavia CA, Nassisi M, Pignata G, Zola M, et al. Recent developments in the management of dry age-related macular degeneration. Clin Ophthalmol. 2015;9:563-574.

Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. Version 2014-09-15:1-13.

Coscas F, Coscas G, Souied E, Tick S, Soubrane G. Optical coherence tomography identification of occult choroidal neovascularization in age-related macular degeneration. Am J Ophthalmol. 2007;144:592-599.

Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol. 1984;102:1640-1642.

Ferris FL, Kasoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982;94:91-96.

Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, de Jong P, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564-572.

Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. Ophthalmology. 2012;119:2537-2548.

Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med. 2008;358:2606-2617.

Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration: two-year results. Ophthalmology. 2012;119:1388-1398.

Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364:1897-1908.

Nagai N, Ju M, Izumi-Nagai K, Robbie SJ, Bainbridge JW, Gale DC, et al. Novel CCR3 antagonists are effective mono- and combination inhibitors of choroidal neovascular growth and vascular permeability. Am J Pathol. 2015;185:2534-2549.

Pennington KL, DeAngelis MM. Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors. Eye Vis. 2016;3:1-20.

Pepple K, Mruthyunjaya P. Retinal pigment epithelial detachments in age-related macular degeneration: classification and therapeutic options. Semin Ophthalmol. 2011;26:198-208.

Riaz M, Baird PN. Recent advances and future directions for the pharmacogenetic basis of anti-VEGF treatment response in neovascular age-related macular degeneration. Neural Regen Res. 2017;12:584-585.

Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355:1419-1431.

van Leeuwen R, Klaver CC, Vingerling JR, Hofman A, de Jong P. The risk and natural course of age-related maculopathy. Arch Ophthalmol. 2003;121:519-526.

Wang H, Han X, Gambhir D, Becker S, Kunz E, Liu AJ, et al. Retinal inhibition of CCR3 induces retinal cell death in a murine model of choroidal neovascularization. PLoS One. 2016;11(6):e0157748.

Wang J, Wittchen ES, Jiang Y, Ambati B, Grossniklaus HE, Hartnett ME. Upregulation of CCRS by age-related stresses promotes choroidal endothelial cell migration via VEGF-dependent and -independent signaling. Invest Ophthalmol Vis Sci. 2011;52:8271-8277.

Wong WL, Su X, Li X, Mong C, Cheung CMG, Klein R, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:e106-116.

16.2 UNPUBLISHED REFERENCES

[redacted]

17 APPENDICES

17.1 CLINICAL EVALUATION OF LIVER INJURY

17.1.1 INTRODUCTION

Alterations of liver laboratory parameters, as described in Section 7.2.1.1.7 (protocol-specified AESI), are to be further evaluated using the procedures described below.

17.1.2 PROCEDURES

[redacted]

17.1.2.1 Clinical Chemistry

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

17.1.2.2 Serology

- Obtain a hepatitis A (anti-immunoglobulin M(IgM), anti-IGM)), hepatitis B (hepatitis B antigen, anti-HBs, DNA), hepatitis C (anti-hepatitis C virus (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)

17.1.2.3 Hormones

- Thyroid-stimulating hormone

17.1.2.4 Hematology

- Thrombocytes, eosinophils

17.1.2.5 Ultrasound

- Provide an abdominal ultrasound to rule out biliary tract, pancreatic, or intrahepatic pathology (e.g., bile duct stones or neoplasm)

17.1.2.6 Observation/Repeat Testing

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgment and GCP.

17.2 PHARMACOKINETIC, BIOMARKER, AND PHARMACOGENOMIC SAMPLING

17.2.1 TABLE OF PHARMACOKINETIC (PK), BIOMARKER, AND PHARMACOGENOMIC (PGX) SAMPLING

Visit	Day	Time Point	Time for Database Setup	PK Blood	Extra Biomarker Aliquot from PK Blood Sample	PGX Blood
2	1	Prior to (i.e., within 15 min before study agent administration)	-0:15 h	X	X	**X**
		0:00	0:00 h	Study agent administration		
		0:15 ± 5 minutes	0:15 h	X		
		0:30 ± 5 minutes	0:30 h	X		
		1:30 ± 20 minutes	1:30 h	X	X	
		3:00 or later (preferably at the end of all visit procedures)	3:00 h	X		
3	8 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	167:45 h	X		
4	15 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	335:45 h	X		

5	22 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	503:45 h	X		
6	29 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	671:45 h	X	X	
7	36 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	839:45 h	X		
8	43 (±1)	-00:15 min (i.e., within 15 min before study agent administration)	1,007:45 h	X	X	
9	50 (±1)	Any time during visit – preferably at the end of all visit procedures	1,179:00 h	X	X	

17.3 PHARMACOKINETIC MEASURES AND EVALUATION

17.3.1 TIMING OF PHARMACOKINETIC BLOOD SAMPLING

For the time schedules of pharmacokinetic blood samples, please refer to Section 17.2.1. PK samples will be taken from all subjects at Visits 2-9.

17.3.2 PHARMACOKINETIC SAMPLE HANDLING AND SHIPMENT

Methods of pharmacokinetic sample collection are described in Section 7.2.6.2. Further instructions for sampling procedures, and for handling, storage and shipment of the samples will be provided in the Lab Manual in the ISF.

17.3.3 PHARMACOKINETIC DATA EVALUATION

For pharmacokinetic 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 pharmacokinetic parameters.

Noncompartmental pharmacokinetic analyses of the plasma concentration-time data will be performed using a validated software program and for this purpose the actual sampling time for pre-dose samples will be set to zero. Plasma concentrations will be plotted graphically versus time for all subjects as listed in the plasma concentration-time tables. For the presentation of mean profiles, the arithmetic and geometric mean and the planned blood sampling times will be used.

Individual $t_{max(,ss)}$ values will be directly determined from the plasma concentration time profiles of each subject.

The following descriptive statistics will be calculated for concentration data and PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, 10^{th}, 25^{th}, 75^{th}, and 90^{th} percentiles, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. Individual concentration values/PK parameters may be excluded from calculation of descriptive statistics and graphical displays, e.g. due to relevant deviation of actual versus planned sampling time. Such data however will be listed associated with an appropriate flag.

17.3.4 HANDLING OF MISSING DATA

In the noncompartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. Values that are below the limit of quantification (BLQ) and with no peak detectable (NOP) in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first timepoint 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 by 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.

17.4 LIST OF [redacted]

The table included in Section 10.4.1 presents a list of [redacted]

[redacted]

17.5 COCKCROFT-GAULT FORMULA

Glomerular filtration rate (GFR) may be estimated based on the commonly used and accepted formula, the Cockcroft-Gault formula:

$$GFR = \frac{(140 - age) \times weight \times F_S}{Serum\ Creatinine \times 72}$$

Units: GFR [ml/min], age [years], weight [kg], serum creatinine [mg/dl], FS is a correction Factor for Sex: in males FS = 1, in females FS = 0.85

18 REVISION HISTORY

18.1 SUMMARY OF CHANGES

Protocol Version 3.0 dated 15MAY2018
Replaces: Protocol Version 2.0 dated 22JAN2018 [Hungary]
Replaces: Protocol Version 2.0 dated 19MAR2018 [Poland]

The following table describes changes from Version 2.0 (dated 22JAN2018 [Hungary]) and Version 2.0 (dated 19MAR2018 [Poland]) with justifications provided. In Version 3.0, the two former country-specific protocols were combined into a single protocol for global standardization and compliance.

Section	Description	Country	Justification
Title Page	Change in Authorized Representative	• Hungary • Poland	Due to staffing assignment changes within Alkahest, the Authorized Representative has been changed from [redacted]
Throughout	The exploratory endpoint of central retinal thickness (CRT) was changed to central subfield thickness (CST)	• Hungary • Poland	• Measurement of central retinal thickness (CRT) includes multiple subfields and must be performed by a central reader, which was not utilized in this study. • Determination of central subfield thickness (CST) is a specific measurement of retinal thickness that is limited to a circular area of diameter of 1 mm from the center point of the retina that can be measured by investigators without the need for a central reader.
Throughout	Minor changes to grammar and formatting	• Hungary • Poland	Grammar and formatting standardization.
List of Abbreviations	• Added "CST: Central Subfield Thickness" • Removed "OPU: Operative Unit"	• Hungary • Poland	• Abbreviation added to accommodate clarified exploratory endpoint measurement. • Abbreviation removed – not required in Protocol.
1.1	Change in Authorized Representative (Signatory) / Responsible Party	• Hungary • Poland	Due to staffing assignment changes within Alkahest, the Authorized Representative (Signatory) / Responsible Party has been changed from [redacted] The email address has also been updated to reflect this change.
5.1 and Throughout	Inclusion Criteria in bullet 1/sub-bullet 1: was updated to read as follows: "Persistent exudation of SRF and IRF as	Hungary	• The term "monthly" lacks specificity and should be regarded as a period of 4 to 6 weeks between each IVT injection for the purposes of this protocol. • In addition to Section 5.1, the statement "monthly IVT anti-VEGF therapy" is also used throughout the protocol. Per the revision, this statement should now be

	documented by SD-OCT and absence of improvement in visual acuity following 3 consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections, subject must have received their last injection 30 to 90 days prior to the initial screening visit"		interpreted as "consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections." • Information was previously communicated to Principal Investigators and Study Coordinators in a Clarification Memorandum dated April 9, 2018.
5.1 and Throughout	Inclusion Criteria in bullet 1/sub-bullet 1: was updated to read as follows: "Persistent exudation of SRF and IRF as documented by SD-OCT and absence of improvement in visual acuity following 3 consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections, subject must have received their last injection 30 to 90 days prior to the initial screening visit"	Poland	• The term "monthly" lacks specificity and should be regarded as a period of 4 to 6 weeks between each IVT injection for the purposes of this protocol. • In addition to Section 5.1, the statement "monthly IVT anti-VEGF therapy" is also used throughout the protocol. Per the revision, this statement should now be interpreted as "consecutive (approximately 4 to 6 weeks apart) IVT anti-VEGF injections." • To shorten the time period from receipt of last IVT anti-VEGF injection relative to screening, the study will only include subjects who received their last IVT anti-VEGF injection within 30 to 90 days prior to the initial screening visit. o Previously incorporated into ALK4290-202 V2.0 in Hungary.
5.1	Inclusion Criteria in bullet 1/sub-bullet 2: Changed "Central subfield retinal thickness to CST"	• Hungary • Poland	Standardized nomenclature to align with clarified abbreviation.
5.1	• Inclusion Criteria in bullet 5 revised to designate country-specific requirements related to	• Hungary • Poland	Bullet 5 now includes the following country-specific requirements: • **Hungary:** Female subjects must not be pregnant or breastfeeding. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study

	pregnancy and pregnancy testing • The requirements have not changed in either country from V2.0 to V3.0 other than being combined to create a single protocol		entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately • **Poland:** Female subjects must not be pregnant or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test at screening/visit 1, the first treatment visit, and the last treatment visit. Women of childbearing potential and men must agree to use highly effective contraception (Clinical Trial Facilitation Group 2014) prior to study entry. A woman is considered of childbearing potential following menarche and until becoming postmenopausal (no menses for at least 2 years without an alternative cause). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in the study, she should inform her treating physician immediately
7.2.5.1	Removed the following sentence: "As a further endpoint, the total retinal thickness, inclusive of the sub-RPE layer, will be measured."	• Hungary • Poland	Measurement of total retinal thickness includes multiple subfields and must be performed by a central reader, which was not utilized in this study.
8.2.1.1	Serum pregnancy test required in Poland only added to bullet 5	Hungary	Per request from the Polish Department of Clinical Trials for Medicinal Products, added the following: "**Poland only**: serum pregnancy test (in women of childbearing potential)."
8.2.1.1	Serum pregnancy test required in Poland only	Poland	Added "**Poland only:**" to indicate that serum pregnancy testing is not required in Hungary.
8.2.2.1	Serum pregnancy test required in Poland only added to bullet 4	Hungary	Per request from the Polish Department of Clinical Trials for Medicinal Products, added the following: "**Poland only**: serum pregnancy test (in women of childbearing potential)."
8.2.2.1	Serum pregnancy test required in Poland only	Poland	Added "**Poland only:**" to indicate that serum pregnancy testing is not required in Hungary.
8.2.3.1	Serum pregnancy test required in Poland only added to bullet 3	Hungary	Per request from the Polish Department of Clinical Trials for Medicinal Products, added the following: "**Poland only**: serum pregnancy test (in women of childbearing potential)."
8.2.3.1	Serum pregnancy test required in Poland only	Poland	Added "**Poland only:**" to indicate that serum pregnancy testing is not required in Hungary.

10.2	• H_0 updated to "Change from baseline in BCVA letter score = 0" was previously "Change from baseline in BCVA letter score > 0" • H_1 updated to "Change from baseline in BCVA letter score ≠ 0 with α_1= 0.20" was previously "Change from baseline in BCVA letter score < 0 with α_1= 0.025"	• Hungary • Poland	Statistical analyses updated to two-sided alpha between 0.05 and 0.20 versus one-sided approach used in previous version.
15.1	Removed superscript "5" from "Pharmacokinetics blood sample (for plasma extraction)" at Visit 9	• Hungary • Poland	No treatment is administered at Visit 9. Thus, the sample can be performed at any time during visit – preferably at the end of all visit procedures.
15.1	Pregnancy test screening/visit 1, first treatment visit, and final treatment visit for subjects in Poland	Hungary	Per request from the Polish Department of Clinical Trials for Medicinal Products, added pregnancy test (as applicable per Inclusion Criteria in Poland) at screening/visit 1, first treatment visit, and final treatment visit.
15.1	Added superscript "9" and footnote to Pregnancy test indicating it is required in Poland only	• Hungary • Poland	Superscript/footnote required to indicate this test is required in **Poland only**.
16.1	Added reference to define "highly effective" contraception	Hungary	Clinical Trial Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. Version 2014-09-15:1-13.