PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF INTRAVITREAL INJECTIONS OF FHTR2163 IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION**
PROTOCOL NUMBER:	GR42558
VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	134632
NCT NUMBER:	*NCT04507148*
TEST PRODUCT:	FHTR2163 (RO7171009)
MEDICAL MONITOR:	[redacted], M.D., *Ph.D.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
22-Sep-2021 15:09:27	Company Signatory	[redacted]

PROTOCOL HISTORY

Version	Date Final
1	15 July 2020
2	10 October 2020
3	3 May 2021

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GR42558 has been amended primarily to include two additional treatment arms to provide safety, tolerability, pharmacokinetic, pharmacodynamic biomarker, and immunogenicity data for intravitreal administration of FHTR2163 at 10 mg.

- Two new treatment arms have been added to the study design; patients assigned to these arms will receive either 10 mg of FHTR2163 every 4 weeks (Q4W) or 10 mg of FHTR2163 every 8 weeks (Q8W), respectively. Upon implementation of protocol Version 4, newly enrolling patients from the sham control arms of parent study GR40973 (hereafter referred to as the parent study) will be assigned to the new 10 mg treatment arm that corresponds to the dosing frequency of each patient's original dosing schedule in the parent study (i.e., Q4W or Q8W). No changes will be made to the dosing regimens of patients currently enrolled in Study GR42558 (Sections 3.1, 3.4.1, 4.3.2, 6.2, 6.3, 6.5, and 6.6; Figure 1).
- Given that the changes in the study design could potentially unmask the parent study, an Internal Monitoring Committee has been added to monitor safety and study conduct during the masked period of the current study, which extends until database lock of the parent study (Sections 3.2, 4.2.2, and 5.1).
- Additional aqueous humor sample collections have been added at Week 24 and Week 72 to assess if sufficient HtrA1 target inhibition is achieved at the 10 mg of FHTR2163 dose level, and additional serum pharmacokinetic (PK) and anti-drug antibody samples have been added at Week 24 and Week 72 to enable assessment of immunogenicity at the 10 mg of FHTR2163 dose level. These sample collections have been added for all treatment arms to maintain masking (Appendix 1 and Appendix 2).

Other changes made to the protocol are as follows:

- Language around pre-injection prophylactic paracentesis procedures being performed outside of pre-specified aqueous humor collection visits has been added to the exclusion criteria, prohibited therapy criteria, and treatment interruption criteria. Specifically, given that such pre-injection prophylactic paracentesis procedures are not pre-specified procedures in the Informed Consent Form and procedure sequelae could confound the interpretation of the study outcomes, pre-injection prophylactic paracentesis procedures have been added as an exclusionary criterion and as a prohibited therapy. Treatment interruption criteria have been amended to indicate that if an enrolled patient is deemed to require a prophylactic paracentesis prior to study treatment administration, study treatment must be interrupted and may be resumed as determined by the investigator with consultation from the Medical Monitor. In addition, permitted therapy criteria have been clarified to allow for post-injection paracentesis as per clinical judgment.

Furthermore, treatment interruption criteria have been amended to indicate that if an enrolled patient has had three consecutive post-injection paracentesis procedures performed in the study eye for treatment of adverse events, study drug must be interrupted. Study treatment may be resumed as determined by the investigator with consultation from the Medical Monitor (Sections 4.1.2, 4.4.1, 4.4.2, and 5.1.5; Table 1).

- Guidelines for permitted therapy have been updated to clarify that in the event the non-study eye requires treatment for neovascular age-related macular degeneration (nAMD), treatment with any FDA-approved intravitreal anti–vascular endothelial growth factor (anti-VEGF) treatment for nAMD may be administered (Section 4.4.1).
- References to inclusion of caregiver reporting of patient health data has been removed for consistency with the Informed Consent Form (Sections 4.5.6 and 5.1.1; Appendix 1 and Appendix 2).
- The Medical Monitor has been changed; applicable study summary pages and emergency medical contact information (Section 5.4.1) have been updated accordingly.
- Guidelines for dose interruption and treatment discontinuation in the event of intraocular inflammation have been updated (Section 5.1.5; Appendix 1 and Appendix 2).
- A footnote has been added for aqueous humor and serum PK sample collections to clarify that these samples should be collected on Day 1 of the current study if the Day 1 visit does not coincide with the Week 76 visit in the parent study and these samples were not collected on Week 76 in accordance with the parent study (Appendix 1 and Appendix 2).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF INTRAVITREAL INJECTIONS OF FHTR2163 IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION**
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SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by PPD.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF INTRAVITREAL INJECTIONS OF FHTR2163 IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION**
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VERSION NUMBER:	4
EUDRACT NUMBER:	Not applicable
IND NUMBER:	134632
NCT NUMBER:	*NCT04507148*
TEST PRODUCT:	FHTR2163 (RO7171009)
PHASE:	II
INDICATION:	Geographic atrophy secondary to age-related macular degeneration
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

The primary objective of this open-label extension (OLE) study is to evaluate the long-term safety and tolerability of intravitreal (ITV) injections of 20 mg of FHTR2163 *and ITV injections of 10 mg of FHTR2163* administered every 4 weeks (Q4W) or every 8 weeks (Q8W) in eligible patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) who completed Study GR40973 (hereafter referred to as the parent study). Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective (Primary Objective)

The safety objective for this study (primary objective) is to evaluate the long-term safety and tolerability of FHTR2163 on the basis of the following endpoints:

- Incidence and severity of ocular adverse events
- Incidence and severity of systemic (non-ocular) adverse events

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is to evaluate the observed trough concentration following 20 mg of FHTR2163 *and 10 mg of FHTR2163* administered by ITV injection Q4W or Q8W on the basis of the following endpoint:

- Serum and aqueous humor concentration of FHTR2163 at specified timepoints

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the safety of FHTR2163 on the basis of the following endpoint:

- Relationship between serum and/or aqueous humor concentration for FHTR2163 and clinically relevant safety endpoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to FHTR2163 on the basis of the following endpoint:

- Prevalence of serum anti-drug antibodies (ADAs) at baseline and incidence of serum ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and safety or PK endpoints

Biomarker Objectives

The exploratory imaging biomarker objective for this study is to evaluate GA disease status, in the study population and in subgroups based on *HTRA1* risk-variant carrier status as determined in the parent study, on the basis of the following endpoint:

- Change in GA area from parent study baseline and from OLE study baseline, as measured by fundus autofluorescence (FAF) imaging and determined by a central reading center consisting of graders and ophthalmologists experienced in the conduct of clinical trials

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to FHTR2163, are associated with rate of progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of FHTR2163 activity, or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma and aqueous humor and safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between retinal imaging metrics (e.g., metrics from FAF, spectral domain optical coherence tomography, optical coherence tomography angiography) and safety, PK, immunogenicity, or other biomarker endpoints

STUDY DESIGN

Description of Study

Study GR42558 is a multicenter, OLE study to evaluate the long-term safety and tolerability of ITV injections of FHTR2163 in patients with GA who completed the parent study. Patients who discontinued from the parent study or discontinued from study treatment prior to completion of the final (Week 76) visit are not eligible for enrollment in this OLE study.

Patients who consent to participate in the OLE study will be screened for eligibility upon completion of the parent study (i.e., Week 76 visit). The Week 76 visit will serve as the final visit for the parent study and the first (Day 1) visit for the OLE study (i.e., the two visits are to be conducted on the same day), and all Week 76 assessments must be completed prior to conducting Day 1 assessments. If all assessments for the Day 1 visit cannot be completed on the same day as the Week 76 visit, patients may return to the clinic within 28 days to complete the Day 1 visit. If a patient is not able to complete the Day 1 visit within 28 days, the investigator must contact the Medical Monitor for further discussion prior to scheduling the Day 1 visit.

Patients will receive 20 mg of FHTR2163 *or 10 mg of FHTR2163* by ITV injection in the same eye selected for injections in the parent study (referred to as the "study eye") Q4W or Q8W for approximately 144 weeks. Dosing frequency will remain consistent with each patient's original dosing schedule in the parent study (i.e., Q4W or Q8W). *Upon implementation of protocol Version 4, all eligible patients in the sham control arms of the parent study that are newly enrolling in the OLE study will receive 10 mg of FHTR2163 (Q4W or Q8W). Patients currently enrolled in the OLE study (i.e. enrolled prior to implementation of protocol Version 4) will continue receiving their current dosing regimen for the remainder of the study.*

Number of Patients

Approximately 360 patients are expected to participate in the OLE study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Completion of the parent study (GR40973) through the Week 76 visit without early treatment discontinuation

- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit acceptable fundus imaging
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 28 days after the final dose of FHTR2163.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Ocular Inclusion Criteria: Study Eye

- If the study eye best corrected visual acuity (BCVA) letter score is ≥69 letters (Snellen equivalent of 20/40 or better), the non-study eye must have a BCVA letter score of ≥44 letters (Snellen equivalent of 20/125 or better) on visit Day 1 OLE/Week 76 of parent study.

Ocular Inclusion Criteria: Non-Study Eye

- The non-study eye must have a BCVA letter score of ≥44 letters (Snellen equivalent of 20/125 or better) if the study eye BCVA letter score is ≥69 letters (Snellen equivalent of 20/40 or better) on visit Day 1 OLE/Week 76 of parent study.

Exclusion Criteria

Ocular Exclusion Criteria

Patients who meet any of the following ocular criteria will be excluded from study entry:

- Active uveitis and/or vitritis (grade trace or above) in either eye
- Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Active or history of choroidal neovascularization in study eye that requires anti-VEGF treatment
- Active or recent history (i.e., since enrollment in parent study) of optic neuritis in either eye
- Retinal pigment epithelium tear that involves the macula in either eye
- Moderate or severe non-proliferative diabetic retinopathy in either eye
- Proliferative diabetic retinopathy in either eye
- Central serous retinopathy in either eye
- Recent history of recurrent infectious or inflammatory ocular disease in either eye
- Recent history of idiopathic or autoimmune-associated uveitis in either eye

- Any concurrent ocular or intraocular condition in the study eye that contraindicates the use of an investigational drug or may affect interpretation of the study results or may render the patient at high risk for treatment complications

  Note that medical history (e.g., clinically significant increased intraocular pressure meeting sight-threatening criteria) that will require the patient to receive pre-injection prophylactic paracentesis prior to the study treatment administration in the study eye is exclusionary.

Concurrent Condition Exclusion Criteria

Patients who meet any of the following concurrent condition criteria will be excluded from study entry:

- Recent history of any disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or condition that contraindicates the use of FHTR2163, that might affect interpretation of the results of the study, or that renders the patient at high risk of treatment complications
- Recent history of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the investigational drug
- Requirement for continuous use of any medication or treatment indicated as a prohibited therapy in this study
- Medical condition that may be associated with a clinically significant risk for bleeding
- Recent history of cerebral vascular accident or transient ischemic attack
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of FHTR2163

  Women of childbearing potential must have a negative urine pregnancy test result at the Day 1 visit, prior to initiation of study drug.

- Active systemic or localized infection requiring medical treatment that, in the opinion of the investigator, could interfere with study conduct

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 144 weeks after the last patient is enrolled in the study.

INVESTIGATIONAL MEDICINAL PRODUCTS

Patients will receive 20 mg of FHTR2163 *or 10 mg of FHTR2163* by ITV injection in the study eye at a dosing frequency that is consistent with the patient's original dosing schedule in the parent study (i.e., Q4W or Q8W).

STATISTICAL METHODS

Primary Analysis

The safety analysis population will consist of all patients enrolled in this study who received at least one dose of study drug.

Safety will be assessed through descriptive summaries of adverse events, ocular assessments (e.g., inflammation, intraocular pressure, best corrected visual acuity), clinical laboratory evaluations, ocular imaging, and immunogenicity against FHTR2163.

Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade (severity) if applicable.

Determination of Sample Size

This study is open to all patients who completed FHTR2163 treatment and follow-up through the final (Week 76) visit of the parent study and meet the eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
CARASIL	cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy
CFP	color fundus photograph
CNV	choroidal neovascularization
CRO	contract research organization
DKK3	Dickkopf-related protein 3
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAF	fundus autofluorescence
GA	geographic atrophy
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HRB	hyperreflective band
HtrA1	high-temperature requirement A1
ICH	International Council for Harmonisation
IMC	*Internal Monitoring Committee*
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IOI	intraocular inflammation
IOP	intraocular pressure
IRB	Institutional Review Board
ITV	intravitreal
IWRS	interactive web-based response system
LPLV	last patient, last visit
MD	multiple-dose
nAMD	*neovascular AMD*
NI	near infrared (images)
OCT-A	optical coherence tomography angiography
OLE	open-label extension
PD	pharmacodynamic

Abbreviation	Definition
PK	pharmacokinetic
Q4W	every 4 weeks
Q8W	every 8 weeks
RBR	Research Biosample Repository
RPE	retinal pigment epithelium
SAD	single ascending dose
SD-OCT	spectral domain optical coherence tomography
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor
WES	whole exome sequencing
WGS	whole genome sequencing
YAG	yttrium aluminum garnet

1. BACKGROUND

1.1 BACKGROUND ON GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in people aged 50 years or older in the developed world (Friedman et al. 2004). The majority of the visual loss occurs in the advanced stage of AMD, which has two clinical forms: 1) a non-exudative form, geographic atrophy (GA), which is characterized by loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris; and 2) an exudative or wet form, known as neovascular AMD (nAMD), which is characterized by choroidal neovascularization (CNV) (Sunness et al. 1999; Lindblad et al. 2009). The prevalence of GA increases exponentially with age and approximately quadruples per decade beyond 50 years of age (Rudnicka et al. 2012). The estimated prevalence of GA in populations of European ancestry at 70 years of age is 0.70%, rising to 2.91% at 80 years of age and 11.29% at 90 years of age (Rudnicka et al. 2012).

In the early stages of GA, patients typically show minimal changes in central visual acuity (VA). However, while central VA may not yet be affected, patients often still experience significant symptoms from visual dysfunction, such as dense parafoveal scotomas (e.g., leading to difficulties with face recognition), delayed dark adaptation, reduced contrast sensitivity, and a decrease in reading rate (Sunness et al. 1995, 1996, 1999). In the later stages, as the GA lesion expands into the fovea, a profound decrease in central VA occurs with a decline in activities of daily living (Lindblad and Clemons 2005). Moreover, GA is bilateral in most patients with advanced AMD (Sunness et al. 1999; Lindblad et al. 2009). As such, GA is a significant cause of both moderate and severe central visual loss.

Currently, there are no approved treatments for GA secondary to AMD, and a significant unmet medical need exists for treatment of this serious condition. In Chroma (Study GX29176) and Spectri (Study GX29185), the largest Phase III studies of GA conducted to date, lampalizumab (anti–complement factor D) did not result in a reduction of GA lesion area versus sham during 48 weeks of treatment (Holz et al. 2018). Other more recent Phase II studies have reported positive results: the BEACON study evaluating the brimonidine drug delivery system (Allergan), the FILLY study evaluating APL-2, a synthetic cyclic peptide conjugated to a polyethylene glycol polymer that binds specifically to C3 and C3b (Apellis 2018), and the GATHER1 study evaluating avacincaptad pegol, an inhibitor of the cleavage of C5 and formation of terminal fragments C5a and C5b (Jaffe et al. 2020).

1.2 BACKGROUND ON HTRA1

The *HTRA1* gene, located in chromosomal region 10q26, was one of the first AMD genetic loci identified, and this finding has been replicated in multiple studies employing linkage analysis or genome-wide association (Weeks et al. 2001; Fritsche et al. 2016). A single nucleotide polymorphism (rs10490924) in the promoter region of *HTRA1* is the most likely causal variant, or tags the causal variant, for AMD at 10q26 (DeWan et al. 2006; Yang et al. 2006) and is estimated to confer a population attributable risk of 49.3% (Yang et al. 2006). Transcription of *HTRA1* has been shown to be increased in association with the risk allele (Yang et al. 2006).

HtrA1 is a member of the mammalian HtrA serine protease family (Clausen et al. 2002). HtrA1 has been shown to cleave a large number of potential substrates, many of which are extracellular matrix proteins (Grau et al. 2006). In transgenic mice, overexpression of HtrA1 in RPE cells recapitulated cardinal features associated with advanced AMD, including choroidal vasculopathy and severe degeneration of elastic laminae of the Bruch's membrane (Jones et al. 2011; Kumar et al. 2014). At the molecular level, this phenotype appears to result from HtrA1-induced breakdown of extracellular matrix protein associated with RPE, Bruch's membrane, and choroid (Jones et al. 2011; Vierkotten et al. 2011; Kumar et al. 2014). In the human retina, HtrA1 is expressed by RPE cells (DeWan et al. 2006; Yang et al. 2006), and unpublished studies conducted by Genentech revealed that its expression is increased in the area peri-lesional to the GA.

1.3 BACKGROUND ON FHTR2163

FHTR2163 (RO7171009) is a Fab of a humanized monoclonal antibody directed against the HtrA1 protein (Tom et al. 2020). FHTR2163 was shown to bind with an equilibrium dissociation constant of 0.13 nM to human HtrA1. The HtrA1 protease is functional only as a trimer. Full inhibition of the enzymatic activity of trimeric HtrA1 requires three separate anti-HtrA1 Fabs to bind each HtrA1 subunit (Ciferri et al. 2015). By inhibiting HtrA1 protease activity, treatment with FHTR2163 may represent a novel therapeutic option for the treatment of GA.

1.3.1 Summary of Nonclinical Studies of FHTR2163

In Good Laboratory Practice (GLP) repeat-dose toxicity studies, FHTR2163 was generally well tolerated in cynomolgus monkeys following bilateral intravitreal (ITV) doses every 2 weeks in studies of up to 6 months in duration at doses of up to 12.5 mg/eye in a 750 mOsm/kg formulation. Hyperreflective bands (HRBs) were noted on spectral domain optical coherence tomography (SD-OCT) imaging in the fovea of some eyes that were dosed with vehicle or FHTR2163. HRBs were transient, confined to the fovea, and not correlated with functional (full-field electroretinography) or histopathologic abnormalities. These findings suggest that HRBs may be related to the volume and/or number of ITV injections, and are not due to FHTR2163 (Booler et al. 2019; Covance Laboratories Inc. report 2018 [available upon request]). Ocular effects associated with FHTR2163 were limited to ocular inflammation, which was considered to

be procedure related and/or secondary to specific immune-mediated response to a humanized protein. Ocular inflammation was associated with the presence of systemic anti-drug antibodies (ADAs), was not considered to be related to the pharmacologic action of FHTR2163, and showed reversibility by the end of the 1-month recovery period. No systemic effects were observed in evaluated parameters, including safety pharmacology endpoints (cardiovascular, respiratory, or behavioral). The no-observed-adverse-effect level in the 6-month GLP repeat-dose toxicity study was considered to be 12.5 mg/eye in a 750 mOsm/kg formulation administered as a single 50-µL ITV injection every 2 weeks.

Overall, the nonclinical studies demonstrated that FHTR2163 has an acceptable pharmacokinetic (PK) and safety profile to support long-term dosing in humans. Refer to the FHTR2163 Investigator's Brochure for details on nonclinical studies.

1.3.2 Summary of Clinical Studies of FHTR2163

Clinical studies of FHTR2163 to date consist of one completed Phase I study (GR39821) and one ongoing Phase II study (GR40973 [GAllego]).

Study GR39821 is a completed, Phase I, open-label, first-in-human study that investigated the ocular and systemic safety, tolerability, pharmacokinetics, and immunogenicity of FHTR2163 in patients with GA secondary to AMD. A total of 28 patients were enrolled in the study: 15 patients during the single ascending dose (SAD) stage and 13 patients during the multiple-dose (MD) stage. During the SAD stage, patients received single ITV injections of FHTR2163 at doses ranging from 1 to 20 mg. During the MD stage, patients received up to three ITV injections of FHTR2163 at a dose of 20 mg (maximum dose tested in the SAD stage) and a frequency of one injection every 4 weeks (Q4W). FHTR2163 was well tolerated during the study. There were no observed dose-limiting toxicities or ocular serious adverse events, and there were no observed systemic or ocular adverse events assessed as related to study drug. Following single or multiple ITV injections, FHTR2163 exhibited flip-flop kinetics, with serum concentrations low relative to aqueous humor concentrations. The apparent serum and aqueous humor half-life had a range of 3.06–8.67 days across all individuals, which is consistent with other Fabs administered by ITV injection. Pharmacodynamic (PD) changes were assessed in aqueous humor by measuring levels of cleaved DKK3, an endogenous substrate of HtrA1, as a PD biomarker of FHTR2163 inhibition of HtrA1 protease activity (Tom et al. 2020). Dose-dependent inhibition of DKK3 cleavage by FHTR2163 was observed in the SAD cohorts. Higher doses of FHTR2163 yielded longer duration of HtrA1 inhibition, and at the 20-mg dose, inhibition of DKK3 cleavage was sustained for at least 8 weeks after a single ITV administration. In the MD stage, DKK3 cleavage remained inhibited throughout the treatment period with FHTR2163. Following the final dose at Week 8, inhibition was maintained through Day 112 (Week 16; 8 weeks after the final dose), with an upward trend towards baseline levels of DKK3 cleavage by Day 133 (Week 19; 11 weeks after the final dose). The DKK3

cleavage results provided information on the duration of target coverage by FHTR2163 and supported administration of FHTR2163 Q4W or every 8 weeks (Q8W) in the Phase II study.

Refer to the FHTR2163 Investigator's Brochure for further details on clinical studies.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This open-label extension (OLE) study will evaluate the long-term safety and tolerability of ITV injections of FHTR2163 in patients with GA secondary to AMD. Currently, there are no approved treatments to slow or stop the progression of GA secondary to AMD and associated vision loss. FHTR2163 is a first-in-class inhibitor of HtrA1 in clinical development, and as such there are no published data on the clinical benefit of this mechanism for the treatment of GA secondary to AMD.

The clinical experience with FHTR2163 consists of data from the Phase I first-in-human study (GR39821) and emerging data from the ongoing Phase II study (GR40973), as described in Section 1.3.2 and the FHTR2163 Investigator's Brochure. Given the early phase of development, the safety profile of FHTR2163 in humans is not fully understood at this time. This OLE study will complement the Phase II parent study (GR40973), permitting the evaluation of long-term safety and tolerability of FHTR2163 in patients who have completed that study. In addition, this OLE study will provide an opportunity for eligible patients undergoing sham injections in Study GR40973 to receive FHTR2163.

Data from completed nonclinical pharmacology, PK, and toxicology studies, data from the completed Phase I study (GR39821), and emerging safety data from the ongoing Phase II study (GR40973) support the continued clinical development of FHTR2163 in patients with GA secondary to AMD (see Sections 1.3.1 and 1.3.2). There are no identified risks for FHTR2163 to date. Potential risks are described in Section 5.1.1. Several measures are being taken in this study to mitigate possible safety concerns, including strict inclusion and exclusion criteria (see Section 4.1), physical examinations (see Section 4.5.2), regular ocular assessments (see Section 4.5.4), and regular ocular imaging (see Section 4.5.5). Because of the high unmet medical need for new treatments for GA secondary to AMD and the safety profile of FHTR2163 observed in both nonclinical and clinical studies to date, the benefit–risk of FHTR2163 is favorable and supportive of its continued use in this OLE study.

2. OBJECTIVES AND ENDPOINTS

The primary objective of this study is to evaluate the long-term safety and tolerability of ITV injections of 20 mg of FHTR2163 *and ITV injections of 10 mg of FHTR2163* administered Q4W or Q8W in eligible patients with GA secondary to AMD who completed Study GR40973 (hereafter referred to as the parent study). Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE (PRIMARY OBJECTIVE)

The safety objective for this study (primary objective) is to evaluate the long-term safety and tolerability of FHTR2163 on the basis of the following endpoints:

- Incidence and severity of ocular adverse events, with severity determined according to the scale in Section 5.3.3
- Incidence and severity of systemic (non-ocular) adverse events, with severity determined according to the WHO toxicity scale (or the alternative scale in Section 5.3.3, if appropriate)

2.2 PHARMACOKINETIC OBJECTIVES

The PK objective for this study is to evaluate the observed trough concentration following 20 mg of FHTR2163 *and 10 mg of FHTR2163* administered by ITV injection Q4W or Q8W on the basis of the following endpoint:

- Serum and aqueous humor concentration of FHTR2163 at specified timepoints

The exploratory PK objective for this study is to evaluate potential relationships between drug exposure and the safety of FHTR2163 on the basis of the following endpoint:

- Relationship between serum and/or aqueous humor concentration for FHTR2163 and clinically relevant safety endpoints

2.3 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to FHTR2163 on the basis of the following endpoint:

- Prevalence of serum ADAs at baseline and incidence of serum ADAs during the study

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and safety or PK endpoints

2.4 BIOMARKER OBJECTIVES

The exploratory imaging biomarker objective for this study is to evaluate GA disease status, in the study population and in subgroups based on *HTRA1* risk-variant carrier status as determined in the parent study, on the basis of the following endpoint:

- Change in GA area from parent study baseline and from OLE study baseline, as measured by fundus autofluorescence (FAF) imaging and determined by a central reading center consisting of graders and ophthalmologists experienced in the conduct of clinical trials

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that are predictive of response to FHTR2163, are associated with rate of progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of FHTR2163 activity, or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in plasma and aqueous humor (listed in Section 4.5.7) and safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between retinal imaging metrics (e.g., metrics from FAF, SD-OCT, optical coherence tomography angiography [OCT-A]) and safety, PK, immunogenicity, or other biomarker endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

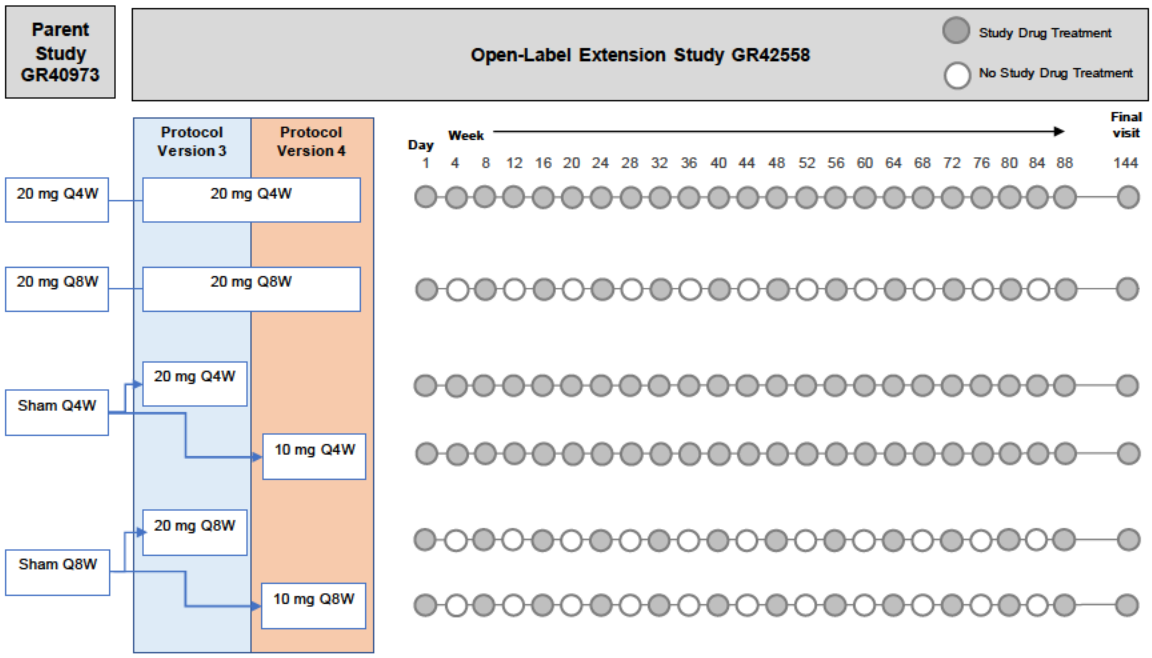
Study GR42558 is a multicenter, OLE study to evaluate the long-term safety and tolerability of ITV injections of FHTR2163 in patients with GA who completed the parent study. Patients who discontinued from the parent study or discontinued from study treatment prior to completion of the final (Week 76) visit are not eligible for enrollment in this OLE study. Approximately 360 patients are expected to participate in the OLE study.

Patients who consent to participate in the OLE study will be screened for eligibility upon completion of the parent study (i.e., Week 76 visit). The Week 76 visit will serve as the final visit for the parent study and the first (Day 1) visit for the OLE study (i.e., the two visits are to be conducted on the same day), and all Week 76 assessments must be completed prior to conducting Day 1 assessments. If all assessments for the Day 1 visit cannot be completed on the same day as the Week 76 visit, patients may return to the clinic within 28 days to complete the Day 1 visit. If a patient is not able to complete the Day 1 visit within 28 days, the investigator must contact the Medical Monitor for further discussion prior to scheduling the Day 1 visit.

Patients will receive 20 mg of FHTR2163 *or 10 mg of FHTR2163* by ITV injection in the same eye selected for injections in the parent study (referred to as the "study eye") Q4W or Q8W for approximately 144 weeks. Dosing frequency will remain consistent with each patient's original dosing schedule in the parent study (i.e., Q4W or Q8W). *Upon implementation of protocol Version 4, all eligible patients in the sham control arms of the parent study that are newly enrolling in the OLE study will receive 10 mg of FHTR2163 (Q4W or Q8W; see Figure 1). Patients currently enrolled in the OLE study (i.e. enrolled prior to implementation of protocol Version 4) will continue receiving their current dosing regimen for the remainder of the study.*

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



Q4W = every 4 weeks; Q8W = every 8 weeks.

3.2 *INTERNAL MONITORING COMMITTEE*

Because the Sponsor will be masked to treatment assignment (10 mg of FHTR2163 or 20 mg of FHTR2163) until database lock of the parent study (see Section 4.2.3), an Internal Monitoring Committee (IMC) will monitor safety and study conduct in the OLE study until the database lock of the parent study.

Members of the IMC will be unmasked to treatment allocation and will include Sponsor representatives from multiple functions who are not involved in the conduct of the study. The IMC may request that additional Sponsor scientists or other external scientists participate in the data analyses and review. The IMC members will not have direct contact with investigational staff or site monitors. Further details regarding roles and responsibilities are outlined in the IMC Charter.

3.3 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 144 weeks after the last patient is enrolled in the study. In addition, the Sponsor may decide to terminate the study at any time.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for FHTR2163 Dose and Schedule

In the MD stage of the Phase I study (GR39821), patients received three 20-mg doses of FHTR2163 (maximum dose tested) by ITV injection Q4W. The 20-mg dose and the Q4W interval were found to be well tolerated (see the FHTR2163 Investigator's Brochure). The Phase II parent study is evaluating the 20-mg FHTR2163 dose at both a Q4W interval and a Q8W interval, to assess the relationship between dosing interval and efficacy, and potentially enable a longer dosing interval, which is a major priority for patients, caregivers, and physicians in this disease indication.

On the basis of the observed serum and aqueous PK data, estimated vitreal drug concentrations for a typical patient treated with 20 mg of FHTR2163 Q8W are maintained above the 50% inhibitory concentration of 3.58 nM established in a cynomolgus monkey PK/PD study (16-0265). In addition, the Q8W dosing interval is supported by the observed PD biomarker data from aqueous humor samples collected during the Phase I study (GR39821), which suggest inhibition of HtrA1 activity through at least 8 weeks following a 20-mg dose (see Section 1.3.2).

All patients will receive *either* 20 mg of FHTR2163 *or 10 mg of FHTR2163* and will continue on the same dosing schedule as they were assigned in the parent study (Q4W or Q8W). *Upon implementation of protocol Version 4, all eligible patients in the sham control arms of the parent study that are newly enrolling in the OLE study will receive 10 mg of FHTR2163 (Q4W or Q8W; see Figure 1). This approach will provide safety, tolerability, pharmacokinetic, pharmacodynamic biomarker, and immunogenicity data for ITV administration of 10 mg of FHTR2163 at* two different treatment regimens *(i.e., Q4W and Q8W).*

The 10 mg of FHTR2163 dose level (Q4W or Q8W) proposed for the alternative dosing regimen is supported by the observed serum and aqueous PK data from the Phase I study, as the estimated vitreal drug concentrations for a typical patient treated with 10 mg of FHTR2163 are also maintained above the 50% inhibitory concentration of 3.58 nM established in the cynomolgus monkey PK/PD study. The observed PD biomarker data from aqueous humor samples collected during the Phase I study also suggest inhibition of HtrA1 activity through at least 8 weeks following a 10-mg dose.

3.4.2 Rationale for Biomarker Assessments

AMD is a heterogeneous disease, and HtrA1 expression, as well as associated downstream activity, may vary among patients. Therefore, all patients may not respond similarly to treatment with FHTR2163. Plasma biomarker samples collected at baseline and during the treatment period will be analyzed to evaluate response to FHTR2163 and to identify patients who may be more likely to respond to FHTR2163 for future studies.

Biomarkers in aqueous humor may reflect aspects of pathology or treatment response that cannot be detected in blood (Kersten et al. 2018). In nonclinical models and in the Phase I study (GR39821), FHTR2163 reduced levels of cleaved DKK3, an aqueous humor biomarker related to HtrA1 activity (Tom et al. 2020). Aqueous humor samples will be collected to measure levels of FHTR2163 and biomarkers related to HtrA1, GA, and/or AMD to support the evaluation of PK and PD effects. The method for aqueous humor sample collection in patients receiving ITV injection of therapeutic products has been shown to be generally safe and well tolerated when performed by experienced ophthalmologists (Van der Lelij and Rothova 1997; Trivedi et al. 2011; Kitazawa et al. 2017). Complication rates were less than 1% with no long-term sequelae and no effect on VA.

Aqueous humor and plasma biomarker data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. This aggregate analysis may increase the knowledge and understanding of GA and inform the development of new therapeutic targets.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 360 patients with GA secondary to AMD who completed study treatment and the Week 76 visit in the parent study will be enrolled at approximately 75 investigative sites located in the United States in this OLE study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Completion of the parent study (GR40973) through the Week 76 visit without early treatment discontinuation
- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit acceptable fundus imaging
- Ability to comply with the study protocol
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 28 days after the final dose of FHTR2163.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

Ocular Inclusion Criteria: Study Eye

- If the study eye best corrected visual acuity (BCVA) letter score is ≥69 letters (Snellen equivalent of 20/40 or better), the non-study eye must have a BCVA letter score of ≥44 letters (Snellen equivalent of 20/125 or better) on visit Day 1 OLE/Week 76 of parent study.

Ocular Inclusion Criteria: Non-Study Eye

- The non-study eye must have a BCVA letter score of ≥44 letters (Snellen equivalent of 20/125 or better) if the study eye BCVA letter score is ≥69 letters (Snellen equivalent of 20/40 or better) on visit Day 1 OLE/Week 76 of parent study.

4.1.2 Exclusion Criteria

4.1.2.1 Ocular Exclusion Criteria

Patients who meet any of the following ocular criteria will be excluded from study entry:

- Active uveitis and/or vitritis (grade trace or above) in either eye
- Active, infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Active or history of CNV in study eye that requires anti-VEGF treatment
- Active or recent history (i.e., since enrollment in parent study) of optic neuritis in either eye
- RPE tear that involves the macula in either eye
- Moderate or severe non-proliferative diabetic retinopathy in either eye
- Proliferative diabetic retinopathy in either eye
- Central serous retinopathy in either eye
- Recent history of recurrent infectious or inflammatory ocular disease in either eye

- Recent history of idiopathic or autoimmune-associated uveitis in either eye
- Any concurrent ocular or intraocular condition in the study eye that contraindicates the use of an investigational drug or may affect interpretation of the study results or may render the patient at high risk for treatment complications

  Note that medical history (e.g., clinically significant increased intraocular pressure meeting sight-threatening criteria) that will require the patient to receive pre-injection prophylactic paracentesis prior to the study treatment administration in the study eye is exclusionary.

4.1.2.2 Concurrent Condition Exclusion Criteria

Patients who meet any of the following concurrent condition criteria will be excluded from study entry:

- Recent history of any disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that gives reasonable suspicion of a disease or condition that contraindicates the use of FHTR2163, that might affect interpretation of the results of the study, or that renders the patient at high risk of treatment complications
- Recent history of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the investigational drug
- Requirement for continuous use of any medication or treatment indicated as a prohibited therapy in this study (see Section 4.4.2)
- Medical condition that may be associated with a clinically significant risk for bleeding
- Recent history of cerebral vascular accident or transient ischemic attack
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the final dose of FHTR2163

  Women of childbearing potential must have a negative urine pregnancy test result at the Day 1 visit, prior to initiation of study drug.
- Active systemic or localized infection requiring medical treatment that, in the opinion of the investigator, could interfere with study conduct

4.2 METHOD OF TREATMENT ASSIGNMENT AND MASKING

4.2.1 Treatment Assignment

This is a non-randomized study. After initial written informed consent has been obtained and eligibility has been established for a patient, the *site will obtain the patient's treatment assignment from* an interactive web-based response system (IWRS). Patients will retain the same patient number that was assigned in the parent study.

Patients will receive either 20 mg of FHTR2163 or 10 mg of FHTR2163 by ITV injection in the same study eye selected for injections in the parent study and at a dosing frequency that is consistent with the patient's original dosing schedule in the parent study (i.e., Q4W or Q8W).

4.2.2 Masking *Throughout the Study*

The best corrected visual acuity (BCVA) examiner will be masked to study eye assignment *throughout the study*. The BCVA examiner will be permitted to perform only the refraction and the following study assessments: BCVA, low-luminance BCVA, and pretreatment intraocular pressure (IOP). The BCVA examiner will also be masked to the BCVA scores from the patient's previous visits and will only have access to a patient's refraction data from previous visits. Other site study staff will not be masked to study eye assignment *or patient treatment assignment*.

4.2.3 *Masking During the Masked Period of the Study*

The study will be masked until database lock of the parent study. After the masked period, the study will follow an open-label design.

The central reading center review team, consisting of graders and ophthalmologists experienced in the conduct of clinical trials, will be masked to patient treatment assignment during the masked period of the study. The central reading center will conduct masked independent review of CFP, FAF, NI, SD-OCT, and OCT-A images to provide an objective assessment of image evaluations. Contract research organization personnel, including clinical research associates, will not be masked to patient treatment assignment.

Patients will be masked to their treatment assignment (10 mg of FHTR2163 or 20 mg of FHTR2163). Sponsor personnel (except for IMC members) will be masked to treatment assignment until after database lock of the parent study, unless there is a need to unmask as determined by the IMC. Personnel responsible for PK/PD sample management, assays, and analysis may be unmasked as needed (i.e., to evaluate PK relationship to an adverse event).

For regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is FHTR2163.

4.3.1 Study Treatment Formulation and Packaging

FHTR2163 will be supplied by the Sponsor. Information on the formulation and packaging are provided in the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

Patients will receive 20 mg of FHTR2163 *or 10 mg of FHTR2163* by ITV injection in the study eye at a dosing frequency that is consistent with the patient's original dosing schedule in the parent study (i.e., Q4W or Q8W).

Upon implementation of protocol Version 4, all eligible patients in the sham control arms of the parent study that are newly enrolling in the OLE study will receive 10 mg of FHTR2163 (Q4W or Q8W; see Figure 1). Patients currently enrolled in the OLE study (i.e. enrolled prior to implementation of protocol Version 4) will continue receiving their current dosing regimen for the remainder of the study.

Refer to the pharmacy manual for detailed instructions on drug preparation and administration.

Details on treatment administration (e.g., *frequency of* dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.14.

Patients will be monitored before and after injections as outlined in Section 5.1.4. Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.5.

4.3.3 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor per agreed method (i.e., returning the appropriate documentation form or updating IWRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed

to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the FHTR2163 Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to FHTR2163

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (FHTR2163) or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing FHTR2163 in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs) other than protocol-specified procedural medications (e.g., dilating drops, proparacaine) used by a patient in addition to protocol-mandated treatment through the final visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

In general, investigators may manage patients' preexisting conditions or new-onset conditions as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 4.4.2. Of note, the following are some common therapies that are permitted:

- Treatments as clinically indicated for onset of ocular hypertension or glaucoma are permitted in either eye during study participation
- Treatments as clinically indicated for onset of cataract or posterior capsular opacification are permitted in either eye during study participation

  Treatment interruption criteria may apply with cataract surgery (see Section 5.1.5).
- Corticosteroids (ITV, subtenon, topical, device implant, oral, or IV)
- Patients who use hormone-replacement therapy or other maintenance therapy should continue their use

- *Anti-VEGF treatment in the non-study eye is permitted*

  Intravitreal administration of FDA-approved anti-VEGF agents is permitted at the discretion of the evaluating investigator if a patient's non-study eye requires treatment for nAMD. Treatment in the non-study eye may be administered at the same visit as the study eye treatment; however, all study assessments and study eye treatment per protocol should be completed prior to anti-VEGF administration in the non-study eye. Individual trays and sterile preparation must be separately prepared for each eye treatment.

- *Paracentesis in the study eye after study drug administration is permitted per clinical judgment for treatment of adverse events*

  For patients with a history of repeated paracentesis after study drug administration, refer to treatment interruption criteria (see Table 1).

4.4.2 Prohibited Therapy

The following medications and therapies are prohibited during the study, and patients who receive any of the following therapies may have study treatment interrupted or discontinued and/or may be discontinued from the study (see Section 5.1.5):

- Systemic anti-VEGF agents
- ITV anti-VEGF agents in the study eye
- *Concurrent non-study eye treatment with unapproved anti-VEGF therapy for nAMD*
- Systemic or IV immunomodulatory therapy (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, anti-tumor necrosis factor agents, eculizumab, tocilizumab)
- Treatment with photodynamic therapy in either eye
- Other experimental therapies, including, but not limited to, stem-cell treatments, gene therapy, and long-acting delivery platforms or formulations
- *Prophylactic paracentesis in the study eye prior to study treatment administration (not including anterior chamber paracentesis to enable collection of aqueous humor samples)*

  For patients that require prophylactic paracentesis prior to study drug administration, refer to treatment interruption criteria (see Table 1).

4.5 STUDY ASSESSMENTS

Schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities should be performed and documented for each patient.

4.5.1 Informed Consent Forms

Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Week 76 evaluations in the parent study must be completed and reviewed to confirm that patients meet all eligibility criteria prior to enrollment at the Day 1 visit in this extension study. The investigator will maintain a log to record details of all patients who sign the Informed Consent Form to document each patient's eligibility or ineligibility to be enrolled in the study, as applicable.

4.5.2 Physical Examinations

A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. The patient's weight will be measured as well. Any abnormality identified at Day 1 (screening) should be recorded on the General Medical History and Baseline Conditions eCRF. If any abnormalities are noted during the study, the patient may be referred to their primary care physician or an appropriate specialist for further evaluation. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.3 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for 5 minutes, and temperature.

4.5.4 Ocular Assessments

Ocular assessments will include the following, to be performed on both eyes (with the exception of post-injection safety assessments) at timepoints specified in the schedules of activities (see Appendix 1 and Appendix 2). A detailed examination to evaluate for signs of intraocular inflammation (IOI) should be performed prior to any study drug administration.

- BCVA assessment as determined by Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 m

  Perform assessment prior to dilating eyes. Refer to Appendix 3 and the Clinical Edge Visual Acuity Certification Procedure Manual for more information on BCVA assessments.

- Low-luminance BCVA assessment as determined by ETDRS chart at a starting distance of 4 m under low-luminance conditions

  Perform assessment prior to dilating eyes. Refer to Appendix 4 and the Clinical Edge Visual Acuity Certification Procedure Manual for more information on low-luminance BCVA assessments.

- Pre-injection IOP measurement

  Perform assessment prior to dilating eyes. The method of IOP measurement used for a patient must remain consistent throughout the study.

- Slit-lamp examination

  Perform examination prior to dilating eyes. Refer to Appendix 5 for grading scales for anterior chamber flare or cells and vitreous cells.

- Dilated binocular indirect high-magnification ophthalmoscopy examination
- Finger-counting test, followed by hand motion and light perception tests when necessary, performed for the study eye within 15 minutes after study drug injection (see Appendix 6)
- Post-injection IOP measurement in the study eye between 30 and 50 minutes after injection on study treatment visit days

  If there are no safety concerns, the patient will be discharged from the clinic. If the IOP is increased by ≥ 10 mmHg compared with the pre-injection measurement or is of concern to the investigator, the IOP will be measured again at 60–80 minutes after injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary in accordance with the investigator's clinical judgment prior to the patient's discharge (see Section 5.3.5.2 for guidance on recording adverse events of increased IOP).

  The method of IOP measurement used for a patient must remain consistent throughout the study.

4.5.5 Ocular Imaging

Ocular images to be obtained during the study include the following:

- Digital color fundus photographs (CFPs) of both eyes (see Appendix 7)
- FAF images of both eyes (see Appendix 8)
- Near infrared (NI) images of both eyes (see Appendix 9)
- SD-OCT images of both eyes (see Appendix 10)
- OCT-A images of both eyes (for sites with OCT-A capabilities) (see Appendix 11)

Both eyes will be dilated prior to ocular imaging. Additional details on obtaining these images are included in the Central Reading Center Manual.

4.5.6 Follow-Up Calls

After each study treatment visit, the site must contact the patient 14 (±5) days after each treatment visit and query for adverse events; particularly any signs or symptoms of decreased visual acuity and/or inflammation (e.g., painful red eye, floaters, scotoma, pain). If the patient reports any concerning signs and/or symptoms, the patient must be evaluated by the investigator as soon as possible.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Fasting is not required prior to specimen collection. The specimens will be sent to a central laboratory. The central laboratory will either perform the analysis or send the samples to the Sponsor or a designee for analysis and/or storage.

Samples will be collected for the following analyses:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum): sodium, potassium, glucose, BUN or urea, creatinine, total protein, albumin, total and direct bilirubin, ALP, ALT, and AST
- Coagulation: INR, aPTT, and PT
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Pregnancy test

  All women of childbearing potential will have a urine pregnancy test prior to each study drug injection. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- PK analysis (serum and aqueous humor)
- Immunogenicity analysis (serum)
- Exploratory biomarker research (plasma and aqueous humor)

  Exploratory biomarker research may include, but will not be limited to, cleaved DKK3 and other biomarkers associated with HtrA1, GA, and/or AMD. Research may involve extraction of cell-free DNA.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.8), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum and aqueous humor samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood and aqueous humor samples collected for biomarker research and biomarker assay development will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

However, the storage period will be in accordance with the Institutional Review Board or Ethics Committee (IRB/EC)–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.8 Optional Samples for Research Biosample Repository

4.5.8.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to FHTR2163, diseases, or drug safety:

- Leftover blood, serum, plasma, and aqueous humor samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.8.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.8.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.8.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his

or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.8.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Unacceptable toxicity
- Any event that meets treatment discontinuation criteria defined in Table 1 in Section 5.1.5.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced and will not be allowed to resume study treatment. However, they should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

Patients who discontinue from the study prematurely will return to the clinic for an early termination visit after at least 30 days have lapsed following the final dose of study treatment (see Appendix 1 and Appendix 2).

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

FHTR2163 is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on nonclinical studies, the anticipated mechanism of action, clinical experience with the completed Phase I study (GR39821), and emerging safety data from the ongoing Phase II study (GR40973). Nonclinical toxicology and safety studies revealed minimal ocular inflammation that demonstrated complete or partial recovery, and no systemic adverse effects were observed. In addition, FHTR2163 was well tolerated in the Phase I study (GR39821), with no ocular serious adverse events, dose-limiting toxicities, or adverse events of special interest reported. The anticipated important safety risks for FHTR2163 are outlined in Section 5.1.1. Refer to the FHTR2163 Investigator's Brochure for further details. Risks associated with ITV injections and aqueous humor sampling are described in Section 5.1.2 and Section 5.1.3, respectively.

Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. *Review of unmasked safety data will be performed by an IMC (see Section 3.2).* Patients will be instructed to contact the investigator at any time if they have any health-related concerns. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 1 and Appendix 2). In addition, guidelines for managing adverse events, including guidelines for treatment interruption or discontinuation, are provided in Sections 5.1.4 and 5.1.5. Adverse events should be reported to the Sponsor in accordance with instructions provided in Section 5.2 –5.6.

5.1.1 Potential Risks Associated with FHTR2163

5.1.1.1 Potential Ocular Risks

Ocular Inflammation

In repeat-dose, GLP toxicology studies of up to 6 months in duration in cynomolgus monkeys, an anterior and posterior intraocular inflammatory response was observed in animals treated with FHTR2163. The observed inflammation was consistent with a generalized non-specific immune response to a heterologous protein, rather than direct effects of FHTR2163, because of the character and localization of the inflammation and because the incidence and/or severity of inflammation generally lacked a relationship to dose. The inflammation noted during optical coherence tomography, ophthalmic examinations, or microscopic examinations also showed complete or partial recovery.

In the Phase I clinical study (GR39821) there was one patient with 2 non-serious Grade 1 iritis events. Both events resolved with topical treatment and the patient completed the study with no changes in study drug administration.

In the ongoing Phase II clinical study GR40973, there have been reports of inflammation of the anterior chamber only, posterior chamber only, as well as combined anterior and posterior chamber. These include two serious cases of vitritis, and one serious case of uveitis; and non-serious recurrent vitritis events that lead to study discontinuation. The mechanism is not fully understood at this point.

As of 26 March 2021, there have been no reports of IOI in the ongoing Phase II study GR42558.

Refer to the FHTR2163 Investigator's Brochure for more details on ocular inflammation events in the completed and ongoing clinical studies.

The safety plan includes detailed ocular examinations, including BCVA testing, slit-lamp examinations, indirect ophthalmoscopy, and SD-OCT imaging at regular intervals throughout the study to evaluate for potential ocular adverse events. A follow-up call 14 (±5) days after all study drug administrations is required to query for adverse events; particularly any signs or symptoms of decreased visual acuity and/or inflammation (e.g., painful red eye, floaters, scotoma, pain); if the patient reports any concerning signs and/or symptoms, the patient must be evaluated by the investigator as soon as possible.

In case of non-infectious IOI, consider performing CFP/FA (widefield CFP/FA or standard CFP/FA with peripheral sweeps is preferred) and SD-OCT. A uveitis lab workup, as per clinical judgment, should also be considered. Additionally, consider treatment with corticosteroids if appropriate, based on the individual patient presentation and comorbidities (e.g., diabetes, systemic hypertension), *and consider referring patient to a uveitis specialist and/or rheumatologist, per clinical judgment*.

Management guidelines and treatment interruption and treatment discontinuation criteria for ocular inflammation are presented in Section 5.1.5 (see Table 1).

IOI-Associated Retinal Vasculitis

In the ongoing clinical study GR40973, there have been two investigator-reported cases of IOI-associated retinal vasculitis as of 23 March 2021. One case reported IOI with associated retinal sheathing of the arteries, with an initial decrease in visual acuity that is subsequently recovering with corticosteroid treatment. The other case reported uveitis with mild vasculitis (retinal venous) and optic nerve head leakage seen on FA, with no impact on visual acuity. These events occurred after administration of a single and of two doses of masked study drug, respectively, and were treated with corticosteroids.

IOI has been reported with other FDA-approved intravitreal agents for the treatment of wet AMD; it is typically mild, sterile and resolves with corticosteroid eye drops. Brolucizumab was the first approved anti-VEGF therapy associated with non-infectious retinal vasculitis after intravitreal therapy. These events have been reported up to 8 weeks after the first brolucizumab injection, making a direct toxic or infectious cause unlikely, and suggesting an immune-mediated mechanism, potentially autoimmunity (Baumal et al. 2020).

It is important to recognize and diagnose IOI-associated retinal vasculitis and to distinguish it from other causes of uveitis, endophthalmitis, and embolic causes of retinal artery occlusion. Patients with IOI should be followed up closely, and treated appropriately, realizing that some may progress and potentially show signs of retinal vasculitis (Baumal et al. 2020).

The safety plan is described above for ocular inflammation.

Management guidelines and treatment interruption and treatment discontinuation criteria IOI-associated retinal vasculitis are presented in Section 5.1.5 (Table 1).

5.1.1.2 Potential Systemic Risks

Systemic side effects of FHTR2163 are not anticipated, according to data from the nonclinical studies and the Phase I clinical study. Observed systemic levels of FHTR2163 following multiple ITV administrations of 20 mg in the Phase I study (GR39821) were less than 0.2 μg/mL on average at maximum concentration and are estimated to be at least 7,500-fold lower than vitreal FHTR2163 concentrations. On the basis of the binding affinity of FHTR2163, baseline systemic HtrA1 levels, and systemic concentrations of FHTR2163 following ITV administration at the 20-mg dose, complete inhibition of systemic HtrA1 is not expected.

There is a rare human disease called cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) that is characterized by complete loss of HtrA1 activity due to a loss-of-function mutation in the *HTRA1* gene. The main clinical manifestations of CARASIL are ischemic stroke or stepwise deterioration in brain function, progressive dementia, premature baldness, and onset of severe low back pain, spondylosis deformans, or disc herniations. Even with complete loss of HtrA1 activity from birth, the onset of clinical signs and symptoms do not manifest until 20 to 45 years of age (Hara et al. 2009; Fukutake 2011).

On the basis of the extended time course for the onset of CARASIL as well as the expectation that systemic exposures of FHTR2163 after ITV administration will not result in complete inhibition of systemic HtrA1, it is highly unlikely that patients will exhibit signs and/or symptoms of CARASIL after ITV administration of FHTR2163.

5.1.2 Risks Associated with Intravitreal Route of Administration

Potential ocular safety issues currently thought to be associated with the ITV route of administration include decreased BCVA, conjunctival hemorrhage, ocular inflammation (see Appendix 5 for grading scales for anterior chamber flare or cells and vitreous cells), intraocular infection (endophthalmitis), transient and/or sustained elevation of IOP, transient vision loss, cataract development or progression, retinal or vitreous hemorrhage, and retinal break or detachment. Section 5.1.4 provides details on monitoring for adverse events associated with ITV injections, and Section 5.1.5 provides management guidelines and treatment interruption and treatment discontinuation criteria.

5.1.3 Risks Associated with Aqueous Humor Sampling through Anterior Chamber Paracentesis

Patients will undergo anterior chamber paracentesis to enable collection of aqueous humor samples for analysis of ocular FHTR2163 pharmacokinetics and for exploratory biomarker research. Potential ocular safety issues may include cataract development or progression, anterior chamber hemorrhage, decreased IOP and/or hypotony, and decreased BCVA. There have also been rare reports of serious complications, including endophthalmitis and corneal abscess.

The procedure will be performed by experienced ophthalmologists familiar with aqueous humor sampling through anterior chamber paracentesis (see Appendix 13 for sampling procedures), and patients will be monitored closely for occurrence of potential adverse events associated with the procedure.

5.1.4 Management of Patients Who Experience Adverse Events Associated with Intravitreal Injection

Patients will remain at the clinic for at least 30 minutes after each FHTR2163 injection. IOP will be measured in both eyes before injection and in the study eye 30–50 minutes after injection. If there are no safety concerns, the patient will be discharged from the clinic. If the IOP is increased by ≥10 mmHg compared with the pre-injection measurement or is of concern to the investigator, the IOP will be measured again at 60–80 minutes post-injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary, in accordance with investigator's clinical judgment, prior to the patient's discharge. See Section 5.3.5.2 for guidance on adverse event reporting. In the study eye, a finger-counting test, followed by hand motion and light perception tests when necessary, will be performed by the investigator within 15 minutes after each FHTR2163 injection.

In addition, patients will be instructed by study site personnel about warning signs and symptoms, including decrease in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye. If warranted, patients will be asked to return to the clinic as soon as possible for an unscheduled safety assessment visit (see Appendix 1

and Appendix 2) and will be instructed to contact the investigator at any time should they have any health-related concerns. Please see Section 5.1.5 for management guidelines and treatment interruption and treatment discontinuation criteria, and management of IOI.

5.1.5 Management Guidelines and Treatment Interruption and Treatment Discontinuation Criteria

Treatment interruption and patient discontinuation from study treatment for adverse events will be determined on the basis of criteria listed in Table 1. If treatment is interrupted, treatment will not be resumed earlier than the next scheduled study visit. The reason for study treatment interruption or discontinuation should be recorded on the appropriate eCRF and, if applicable, on the Adverse Event eCRF (see Section 5.2.1 for definition of an adverse event). Adverse events should be reported to the Sponsor in accordance with instructions provided in Section 5.2 –5.6.

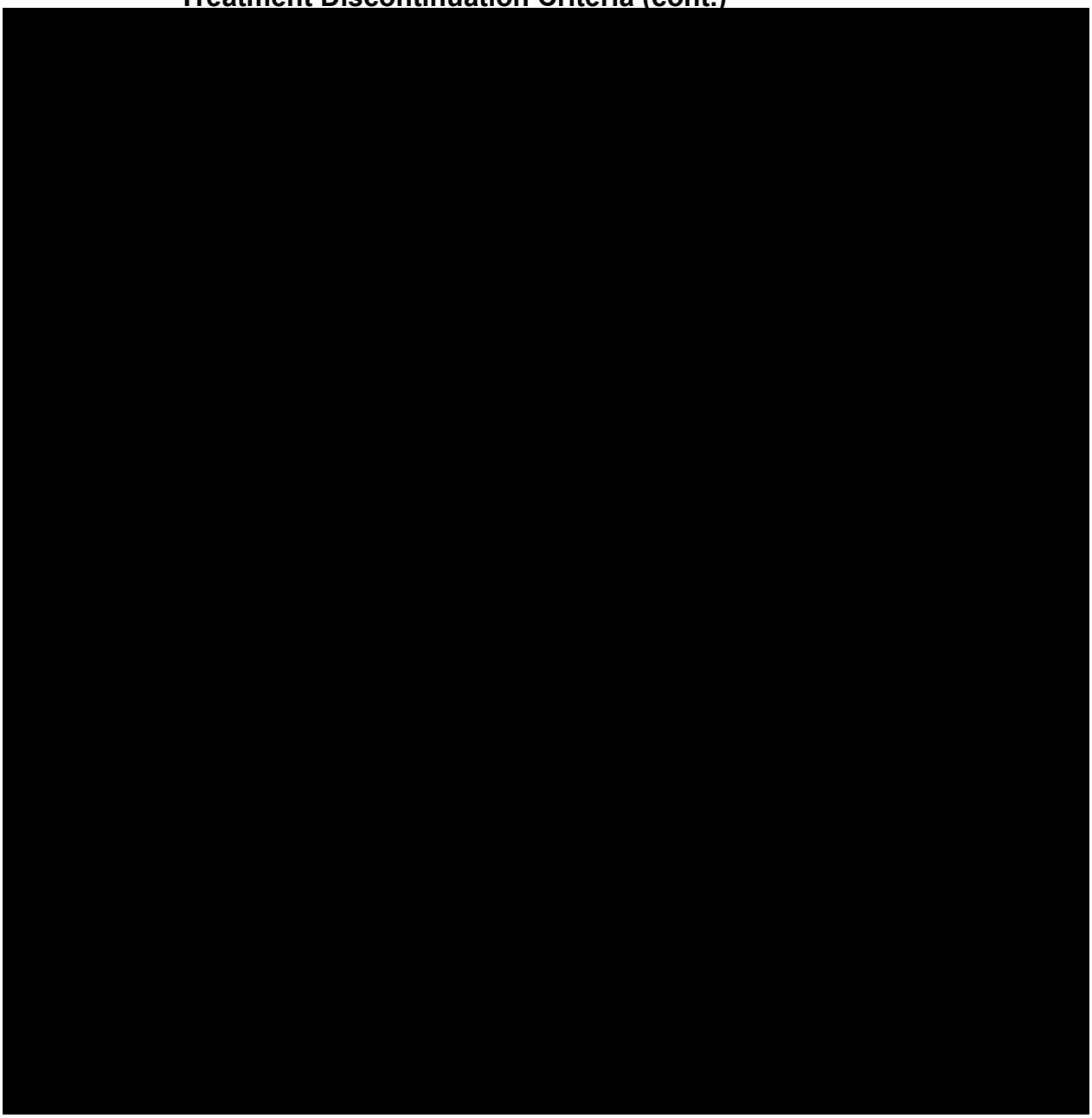
In addition, for any patient who develops any of the exclusion criteria (see Section 4.1.2) after study onset, treatment may be interrupted or the patient may be discontinued from study treatment, after discussion with the Medical Monitor.

Additionally, patients who receive any of the prohibited therapies (Section 4.4.2) may have study treatment interrupted or discontinued and/or may be discontinued from the study.

Table 1 Management Guidelines and Treatment Interruption and Treatment Discontinuation Criteria

[redacted]

Table 1 Management Guidelines and Treatment Interruption and Treatment Discontinuation Criteria (cont.)



5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.11 and 5.3.5.12 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.13)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.9)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Adverse events resulting from medication error (see Section 5.3.5.14)

  Examples of medication errors include, but are not limited to, overdose, incorrect dose, incorrect route, incorrect drug, incorrect administration, or incorrect kit.
- Sight-threatening adverse events

  All sight-threatening adverse events listed below should be reported as serious adverse events, with the underlying cause of the event (if known) listed as the primary event term.

  An adverse event is considered to be sight threatening and should be reported expeditiously if it meets one or more of the following criteria:

  – It causes a decrease in BCVA of $\geq$30 letters, compared with the most recent prior BCVA assessment, that lasts more than 1 hour and is attributable to study drug.

- It requires surgical intervention (i.e., conventional surgery, vitreous tap, or biopsy with ITV injection of an anti-infective compound; or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- It is associated with severe (Grade 4 +) IOI and/or IOI-associated retinal vasculitis as defined in Section 5.3.5.1 (see Section 5.1.1.1 for further details on potential ocular risks, Section 5.1.5, Table 1 for management guidelines and treatment interruption and treatment discontinuation criteria, and Appendix 5 for IOI grading scales).
  - An additional serum ADA and PK sample should be collected as close as possible to the time of diagnosis (see Section 5.1.5 and Appendix 1 and Appendix 2).
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight.

5.2.4 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- CNV conversion requiring treatment for either the study eye or non-study eye
- Any clinically significant ocular imaging finding

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 – 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. After the 28-day period, only serious adverse events (1) caused by a protocol-mandated intervention (e.g., invasive procedures such as aqueous humor sample), or (2) believed to be related to prior study drug treatment (see Section 5.6) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 14) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

For adverse events of IOI, severity assessment ideally should be aligned with the grading scale for assessment of anterior chamber flare or cells and vitreous chamber (see Appendix 5).

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Adverse Events of Ocular Infection and Inflammation

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

- Iritis: presence of inflammatory cells in the anterior chamber

  The presence of aqueous flare alone will not constitute iritis but should be documented as an anterior chamber flare for adverse event reporting purposes.

- Iridocyclitis: presence of inflammatory cells in both the aqueous and vitreous
- Vitritis: presence of active inflammation in the vitreous, demonstrated by the presence of inflammatory cells (trace or greater)

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

- IOI-associated retinal vasculitis: ocular inflammation and retinal vascular changes (i.e., perivascular sheathing and vascular leakage or occlusion on fluorescein angiogram), as defined by the Standardization of Uveitis Nomenclature Working Group (Jabs et al. 2005).

  The presence of occlusive retinal vasculopathy, in the absence of visible inflammation, should not be considered IOI-associated retinal vasculitis.

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

  A culture is required prior to initiating antibiotic treatment for presumed endophthalmitis. Results of bacterial or fungal cultures, treatment given, and final ophthalmologic outcome must be provided in the details section of the Adverse Event eCRF.

Note: Trace benign, aqueous pigmented cells visible on slit-lamp examination that are caused by the dilation process and are not RBCs, WBCs, or the result of any ocular disorder should not be recorded as an adverse event.

5.3.5.2 Increased Intraocular Pressure Values

In general, the observation of elevated IOP values measured 30–50 minutes post-injection should not be reported as an adverse event. Elevated IOP values measured 30–50 minutes post-injection should be reassessed at 60–80 minutes post-injection prior to reporting as an adverse event. Medical and scientific judgment should be exercised in deciding if an elevated IOP 30–50 minutes post-injection that remains elevated at the follow-up 60- to 80-minute assessment is clinically significant and qualifies to be reported as an adverse event.

5.3.5.3 Abnormal Findings on Ocular Imaging

Not every abnormal imaging finding on ocular imaging qualifies as an adverse event. An abnormal finding on ocular imaging must be reported as an adverse event if it meets any of the following criteria:

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

It is the investigator's responsibility to review all ocular images. Medical and scientific judgment should be exercised in deciding whether an isolated imaging abnormality should be classified as an adverse event.

If a clinically significant abnormal image finding is a sign of a disease or syndrome (e.g., retinal edema), only the diagnosis (e.g., CNV) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant abnormal image finding from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.6 for details on recording persistent adverse events).

5.3.5.4 Diagnosis versus Signs and Symptoms

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

5.3.5.5 Adverse Events That Are Secondary to Other Events

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

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

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.6 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.7 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (e.g., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.6 for details on recording persistent adverse events).

5.3.5.8 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.6 for details on recording persistent adverse events).

5.3.5.9 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.3) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.10 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.11 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening (Day 1) visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.12 Worsening of Geographic Atrophy in Study Eye

Medical occurrences or symptoms of deterioration that are anticipated as part of the normal progression of GA secondary to AMD of the study eye should be recorded as an adverse event only if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of study eye GA secondary to AMD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated geographic atrophy”). The expedited reporting requirements for sight-threatening events (listed in Section 5.2.3) apply to these unexpected changes in study eye GA secondary to AMD.

5.3.5.13 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.14 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For FHTR2163, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with FHTR2163, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D., Ph.D. (Primary)
Telephone No.: [redacted] (mobile)
Email address: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

These events should be reported to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest should be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 28 days after the final dose of study drug are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the

Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment or to a protocol-mandated intervention (see Section 5.3.1). These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
FHTR2163	FHTR2163 Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Data collected from the Week 72 or Week 76 visit of the parent study or the Day 1 visit of the OLE study will serve as baseline data for the OLE study.

6.1 DETERMINATION OF SAMPLE SIZE

This study is open to all patients who completed FHTR2163 treatment and follow-up through the final (Week 76) visit of the parent study and meet the eligibility criteria outlined in Sections 4.1.1 and 4.1.2). Accordingly, the sample size for this study is not based on a formal sample size calculation.

6.2 SUMMARIES OF CONDUCT OF STUDY

The clinical database will be used to assess study conduct. The numbers of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study treatment discontinuation and study discontinuation will be listed and summarized. Patient exposure to study drug (number of study treatments and duration of treatment) will be summarized for all patients and by treatment group. Eligibility criteria deviation and other major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data, OLE baseline safety data (e.g., vital signs and laboratory test results), and OLE baseline disease characteristics (e.g., GA area, BCVA, annualized GA growth rate) will be summarized for all patients and by treatment group through use of descriptive statistics.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all patients enrolled in this study who received at least one dose of study drug.

Safety will be assessed through descriptive summaries of adverse events, ocular assessments (e.g., inflammation, IOP, BCVA), clinical laboratory evaluations, ocular imaging, and immunogenicity against FHTR2163.

Verbatim descriptions of adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade (severity) if applicable (see Section 5.3.3).

6.5 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of all patients enrolled in this study who have at least one FHTR2163 serum or aqueous humor sample. Serum and aqueous humor concentrations of FHTR2163 will be summarized descriptively by treatment arm (with patients grouped according to treatment actually received) and/or by treatment regimen (Q4W or Q8W).

Concentrations of FHTR2163 in serum and aqueous humor may be pooled and analyzed with data from other studies as appropriate.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients enrolled in this study who have at least one serum ADA assessment. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) as well as after drug administration (postbaseline incidence) will be summarized by treatment arm (with patients grouped according to treatment actually received) and/or by treatment regimen (Q4W or Q8W).

The relationship between serum ADA status and safety and PK endpoints may be analyzed and reported via descriptive statistics.

6.7 BIOMARKER ANALYSES

Mean change in GA area from parent study baseline and OLE study baseline, as measured by FAF imaging and determined by a central reading center, will be summarized by descriptive statistics. The relationship between change in GA area and *HTRA1* risk-variant status (i.e., carriers versus non-carriers of the *HTRA1* AMD risk variant, rs10490924) will be explored. Biomarkers will be analyzed together with PK data to explore PK/PD relationships. Additional analyses will be performed to identify biomarkers that are predictive of response to FHTR2163, are associated with rate of progression to a more severe disease state, are associated with susceptibility to developing adverse events, can provide evidence of FHTR2163 activity, or can increase the knowledge and understanding of disease biology and drug safety.

6.8 INTERIM ANALYSES

No formal interim analysis is planned since all patients will receive active FHTR2163 treatment. Exploratory safety analyses may be performed with interim data (e.g., to support regulatory submissions).

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of

discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The designated Functional Service Provider will be responsible for discrepancy management.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and ocular imaging will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

The Sponsor will supply eCRF specifications for this study.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, images, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative

must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.3).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will maintain the medical, safety, data management, statistical programming, statistical analysis, and oversight of selected vendors during the study. A contract research organization (CRO) will manage the study, site monitoring, and selected vendors. Genentech will oversee the CRO.

An IWRS will be used for patient enrollment and management of study drug requests and shipments.

A central laboratory will be used for most laboratory assessments and for storage of other laboratory samples prior to being shipped to Sponsor or its designee for analysis. Data will be recorded on eCRFs through use of an EDC system or will be forwarded to the Sponsor electronically (e.g., safety lab data). A central reading center will conduct independent analyses of ocular images (e.g., FAF, NI, CFP, OCT-A, and SD-OCT) as needed.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon

request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

[Apellis] Apellis Pharmaceuticals, Inc. Data supports biologic activity of APL-2 in reducing the growth rate of geographic atrophy [resource on the Internet]. 2018 [updated: 22 February 2018; cited 7 December 2018]. Available from: http://investors.apellis.com/news-releases/news-release-details/apellis-pharmaceuticals-announces-18-month-results-phase-2-study.

Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology 2020;127:1345–59.

Booler H, Kusi AM, Tassew N, et al. Functional and ultrastructural assessment of novel OCT findings in the cynomolgus monkey. Invest Ophthalmol Vis Sci 2019;60:186.

Ciferri C, Lipari MT, Liang W-C, et al. The trimeric serine protease HtrA1 forms a cage-like inhibition complex with an anti-HtrA1 antibody. Biochem J 2015;472:169–81.

Clausen T, Southan C, Ehrmann M. The HtrA family of proteases: review implications for protein composition and cell fate. Mol Cell 2002;10:443–55.

DeWan A, Liu M, Hartman S, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. Science 2006;314:989–92.

Friedman DS, O'Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–72.

Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet 2016;48:134–43.

Fukutake T. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): from discovery to gene identification. J Stroke and Cerebrovasc Dis 2011;20:85–93.

Grau S, Richards PJ, Kerr B, et al. The role of human HtrA1 in arthritic disease. J Biol Chem 2006;281:6124–9.

Hara K, Shiga A, Fukutake T, et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. N Engl J Med 2009;360:1729–39.

Holz FG, Sadda SR, Busbee B, et al. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: Chroma and Spectri Phase 3 randomized clinical trials. JAMA Ophthalmol 2018;136:666–77.

Jabs DA, Nussenblatt RB, Rosenbaum JT, et al. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509–16.

Jaffe GJ, Westby K, Csaky KJ, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal Phase 2/3 trial. Ophthalmology 2020;20:30845–9.

Jones A, Kumar S, Zhang N, et al. Increased expression of multifunctional serine protease, HTRA1, in retinal pigment epithelium induces polypoidal choroidal vasculopathy in mice. Proc Natl Acad Sci 2011;108:14578–83.

Kersten E, Paun CC, Schellevis RL, et al. Systemic and ocular fluid compounds as potential biomarkers in age-related macular degeneration. Surv Ophthalmol 2018;63:9–39.

Kitazawa K, Sotozono C, Koizumi N, et al. Safety of anterior chamber paracentesis using a 30-gauge needle integrated with a specially designed disposable pipette. Br J Ophthalmol 2017;101:548–50.

Kumar S, Berriochoa Z, Ambati BK, et al. Angiographic features of transgenic mice with increased expression of human serine protease HTRA1 in retinal pigment epithelium. Invest Ophthalmol Vis Sci 2014;55:3842–50.

Lindblad AS, Clemons TE. Responsiveness of the National Eye Institute Visual Function Questionnaire to progression to advanced age-related macular degeneration, vision loss, and lens opacity. AREDS report number 14. Arch Ophthalmol 2005;123:1207–14.

Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of geographic atrophy in the Age-Related Eye Disease Study. AREDS report number 26. Arch Ophthalmol 2009;127:1168–74.

Rudnicka AR, Jarrar Z, Wormald R, et al. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology 2012;119:571–80.

Sunness JS, Applegate CA, Haselwood D, et al. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. Ophthalmology 1996;103:1458–66.

Sunness JS, Bressler NM, Maguire MG. Scanning laser ophthalmoscopic analysis of the pattern of visual loss in age-related geographic atrophy of the macula. Am J Ophthalmol 1995;119:143–51.

Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:1768–79.

Tom I, Pham VC, Katschke KJ, et al. Development of a therapeutic anti-HtrA1 antibody and the identification of DKK3 as a pharmacodynamic biomarker in geographic atrophy. Proc Natl Acad Sci U S A 2020;117;9952–63.

Trivedi D, Denniston AK, Murray PI. Safety profile of anterior chamber paracentesis performed at the slit lamp. Clin Exp Ophthal 2011;39:725–8.

Van der Lelij A, Rothova A. Diagnostic anterior chamber paracentesis in uveitis: a safe procedure. Br J Ophthalmol 1997;81:976–9.

Vierkotten S, Muether PS, Fauser S. Overexpression of HTRA1 leads to ultrastructural changes in the elastic layer of Bruch's membrane via cleavage of extracellular matrix components. PloS One 2011;6:e22959.

Weeks DE, Conley YP, Tsai H-J, et al. Age-related maculopathy: an expanded genome-wide scan with evidence of susceptibility loci within the 1q31 and 17q25 regions. Am J Ophthal 2001;132:682–92.

Yang Z, Camp NJ, Sun H, et al. A variant of the HTRA1 gene increases susceptibility to age-related macular degeneration. Science 2006;314:992–3.

Appendix 1
Schedule of Activities for Q4W Arms
Day 1–Week 96

	Day 1 [a]		Week (±5 days)																									
			Treatment Period Visits																									
	PS [b]	OLE	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	UV	ET [c]
Written informed consent		x [d]																										
Review inclusion and exclusion criteria		x																										
Medical and surgical history, including tobacco history	Ex																											
Review medical and surgical history, including tobacco history		x																										
Demographic information	Ex																											
Physical examination [e]		x																									x [f]	x
Vital signs [g]		x																									x [f]	x
Hematology, coagulation, lipids, serum chemistry (central laboratory) [h]	Ex													x												x	x [f]	x
Urine pregnancy test [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [f]	
Enrollment (IWRS)		x																										
Plasma sample for biomarkers	Ex													x												x	x [f]	x
Serum ADA sample [j]	Ex							*x*						x						*x*						x	x [f, j]	x
Serum PK sample for drug concentration [j, n]	Ex							*x*						x						*x*						x	x [f, j]	x
BCVA testing (starting at 4 m) [k]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities for Q4W Arms

Day 1–Week 96

	Day 1 [a]		Week (±5 days)																									
			Treatment Period Visits																									
	PS [b]	OLE	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	UV	ET [c]
LL BCVA testing (starting at 4 m) [k]	Ex							x						x						x						x	x [f]	x
IOP measurement [k]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Slit-lamp examination [l]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Aqueous humor sample [m, n]	Ex [n]							*x*						x						*x*						x	x [f]	
Dilated binocular indirect ophthalmoscopy	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [f]	x
FAF [o]	Ex							x						x						x						x	x [f]	x
SD-OCT [o]		x		x		x		x		x		x		x		x		x		x		x		x		x	x [f, j]	x
OCT-A [o, p]	Ex							x						x						x						x	x [f]	x
NI images [o]	Ex							x						x						x						x	x [f]	x
Color fundus photography [o]	Ex													x												x	x [f, j]	x
Administration of study drug to study eye [q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Post-treatment finger counting and IOP measurement [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications [s]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [t]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [u]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Follow-up call [v]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		

Appendix 1: Schedule of Activities for Q4W Arms

Day 1–Week 96

ADA = anti-drug antibody; BCVA = best corrected visual acuity; CFP = color fundus photograph; ET = early termination; Ex = extracted data (from PS); FA = fluorescein angiography; FAF = fundus autofluorescence; FU = follow-up; IOP = intraocular pressure; IWRS = interactive web-based response system; LL BCVA = low-luminance BCVA; NI = near infrared; OCT-A = optical coherence tomography angiography; OLE = open-label extension; PK = pharmacokinetic; PS = parent study; Q4W = every 4 weeks; SD-OCT = spectral domain optical coherence tomography; UV = unscheduled visit.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise.

On treatment days, all assessments and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

Patients who discontinue study drug prematurely should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible.

[a] The Day 1 visit for the OLE should be performed on the same day as the Week 76 visit for the PS, and all Week 76 assessments must be completed prior to conducting Day 1 assessments. If all assessments for the Day 1 visit cannot be completed on the same day as the Week 76 visit, patients may return to the clinic within 28 days to complete the Day 1 visit. If a patient is not able to complete the Day 1 visit within 28 days, the investigator must contact the Medical Monitor for further discussion prior to scheduling the Day 1 visit.

[b] Data from the PS will be extracted for use in the OLE study.

[c] For patients who discontinue early from the study, early termination assessments will be performed after at least 30 days have lapsed following the final dose of study drug.

[d] Informed consent must be documented before any study-specific procedure is performed.

[e] Includes weight and an evaluation of the head, eyes, ears, nose, throat, and cranial nerves.

[f] To be performed if clinically indicated.

[g] Vital signs consist of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position after resting for 5 minutes, and temperature.

[h] For a detailed description of sample collection, see the laboratory manual.

[i] Collect and perform urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect a serum pregnancy sample and forward it to central laboratory for testing; if the serum pregnancy test is positive, do not administer study drug.

Day 1–Week 96

[j] In case of Grade > 0 non-infectious intraocular inflammation, contact the Medical Monitor to discuss case. An additional serum ADA and PK sample should be collected as close as possible to the time of diagnosis. Consider performing CFP/FA (Appendix 12; widefield CFP/FA or standard CFP/FA with peripheral sweeps is preferred), SD-OCT, and uveitis lab workup as clinically indicated. Additionally, consider treatment with corticosteroids if appropriate, based on the individual patient presentation and comorbidities (e.g., diabetes, systemic hypertension), *and consider referring patient to a uveitis specialist and/or rheumatologist, per clinical judgment.*

[k] Perform assessment prior to dilating the eyes.

[l] Perform slit-lamp examination prior to dilating eyes; for grading scales for anterior chamber flare or cells and vitreous cells, see Appendix 5.

[m] Aqueous humor sample must be collected from the study eye after pretreatment IOP measurement, but prior to study drug administration. For a detailed description of the anterior chamber paracentesis and aqueous humor sample collection procedures, see Appendix 13 and the laboratory manual.

[n] *If the Day 1 visit for the OLE is not performed on the same day as the Week 76 visit for the parent study, and serum PK and aqueous humor samples were not collected on Week 76, these samples should be collected on Day 1 of OLE study.*

[o] Both eyes will be dilated prior to ocular imaging. FAF, SD-OCT, OCT-A (as applicable), NI images, and color fundus photographs will be obtained from both eyes and will be forwarded to the central reading center. If a patient misses a study visit where ocular images were scheduled to be obtained, the images should be obtained at the next scheduled visit.

[p] OCT-A is mandatory for sites that have the capability.

[q] All assessments (including a detailed examination to evaluate for signs of intraocular inflammation) and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

[r] After study drug administration in the study eye only, a finger-counting test, followed by hand motion and light perception tests when necessary, will be performed by the investigator within 15 minutes post-study drug injection, followed by an IOP measurement that will be obtained 30–50 minutes post-study drug injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased by ≥ 10 mmHg compared with the pre-injection measurement, the IOP will be measured again 60–80 minutes post-study drug injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary, in accordance with the investigator's clinical judgment, prior to discharge. For guidance on adverse event reporting, see Section 5.3.5.2.

[s] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs) other than protocol-specified procedural medications (e.g., dilating drops, proparacaine) used by a patient in addition to protocol-mandated treatment.

Day 1–Week 96

[t] Any adverse events ongoing after the Week 76 visit from the PS has been completed should be transcribed to the OLE Adverse Event eCRF. After informed consent has been obtained for the OLE study but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. Adverse events will be recorded starting on Day 1 after study treatment until 28 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse events caused by a protocol-mandated intervention or believed to be related to prior study drug treatment (see Section 5.6) and should be reported (see Sections 5.3.1 and 5.4.2 for instructions for reporting serious adverse events). Adverse events assessed by the investigator as related to study drug should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has ended.

[u] Record all concurrent ocular procedures performed on the study or non-study eye.

[v] After each study treatment visit, the site must contact the patient 14 (±5) days after each treatment visit and query for adverse events; particularly any signs or symptoms of decreased visual acuity and/or inflammation (e.g., painful red eye, floaters, scotoma, pain); if the patient reports any concerning signs and/or symptoms, the patient must be evaluated by the investigator as soon as possible.

Appendix 1
Schedule of Activities for Q4W Arms
Weeks 100–148

	Week (±5 days)														
	Treatment Period Visits												FU Call		
	100	104	108	112	116	120	124	128	132	136	140	144	148	UV	ET [a]
Physical examination [b]														x [c]	x
Vital signs [d]														x [c]	x
Hematology, coagulation, lipids, serum chemistry (central laboratory) [e]												x		x [c]	x
Urine pregnancy test [f]	x	x	x	x	x	x	x	x	x	x	x	x		x [c]	
Plasma sample for biomarkers												x		x [c]	x
Serum ADA sample [g]												x		x [c, g]	x
Serum PK sample for drug concentration [g]												x		x [c, g]	x
BCVA testing (starting at 4 m) [h]	x	x	x	x	x	x	x	x	x	x	x	x		x	x
LL BCVA testing (starting at 4 m) [h]						x						x		x [c]	x
IOP measurement [h]	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Slit-lamp examination [i]	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Aqueous humor sample [j]												x		x [c]	
Dilated binocular indirect ophthalmoscopy	x	x	x	x	x	x	x	x	x	x	x	x		x [c]	x
FAF [k]						x						x		x [c]	x
SD-OCT [k]		x		x		x		x		x		x		x [c, g]	x
OCT-A [k, l]						x						x		x [c]	x
NI images [k]						x						x		x [c]	x

Appendix 1: Schedule of Activities for Q4W Arms

Weeks 100–148

	Week (±5 days)														
	Treatment Period Visits												FU Call		
	100	104	108	112	116	120	124	128	132	136	140	144	148	UV	ET [a]
Color fundus photography [k]												x		x [c, g]	x
Administration of study drug to study eye [m]	x	x	x	x	x	x	x	x	x	x	x	x			
Post-treatment finger counting and IOP measurement [n]	x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant medications [o]	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [p]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [q]	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Follow-up call [r]	x	x	x	x	x	x	x	x	x	x	x	x			

ADA = anti-drug antibody; BCVA = best corrected visual acuity; CFP = color fundus photograph; ET = early termination; FA = fluorescein angiography; FAF = fundus autofluorescence; FU = follow-up; IOP = intraocular pressure; LL BCVA = low-luminance BCVA; NI = near infrared; OCT-A = optical coherence tomography angiography; OLE = open-label extension; PK = pharmacokinetic; Q4W = every 4 weeks; SD-OCT = spectral domain optical coherence tomography; UV = unscheduled visit.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise.

On treatment days, all assessments and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

Patients who discontinue study drug prematurely should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible.

[a] For patients who discontinue early from the study, early termination assessments will be performed after at least 30 days have lapsed following the final dose of study drug.

[b] Includes weight and an evaluation of the head, eyes, ears, nose, throat, and cranial nerves.

[c] To be performed if clinically indicated.

Weeks 100–148

[d] Vital signs consist of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position after resting for 5 minutes, and temperature.

[e] For a detailed description of sample collection, see the laboratory manual.

[f] Collect and perform urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect a serum pregnancy sample and forward it to central laboratory for testing; if the serum pregnancy test is positive, do not administer study drug.

[g] In case of Grade > 0 non-infectious intraocular inflammation, contact the Medical Monitor to discuss case. An additional serum ADA and PK sample should be collected as close as possible to the time of diagnosis. Consider performing CFP/FA Appendix 12; widefield CFP/FA or standard CFP/FA with peripheral sweeps is preferred), SD-OCT, and uveitis lab workup as clinically indicated. Additionally, consider treatment with corticosteroids if appropriate, based on the individual patient presentation and comorbidities (e.g., diabetes, systemic hypertension), *and consider referring patient to a uveitis specialist and/or rheumatologist, per clinical judgment.*

[h] Perform assessment prior to dilating the eyes.

[i] Perform slit-lamp examination prior to dilating eyes; for grading scales for anterior chamber flare or cells and vitreous cells, see Appendix 5.

[j] Aqueous humor sample must be collected from the study eye after pretreatment IOP measurement, but prior to study drug administration. For a detailed description of the anterior chamber paracentesis and aqueous humor sample collection procedures, see Appendix 13 and the laboratory manual.

[k] Both eyes will be dilated prior to ocular imaging. FAF, SD-OCT, OCT-A (as applicable), NI images, and color fundus photographs will be obtained from both eyes and will be forwarded to the central reading center. If a patient misses a study visit where ocular images were scheduled to be obtained, the images should be obtained at the next scheduled visit.

[l] OCT-A is mandatory for sites that have the capability.

[m] All assessments (including a detailed examination to evaluate for signs of intraocular inflammation) and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

Weeks 100–148

[n] After study drug administration in the study eye only, a finger-counting test, followed by hand motion and light perception tests when necessary, will be performed by the investigator within 15 minutes post-study drug injection, followed by an IOP measurement that will be obtained 30–50 minutes after study drug injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased by ≥ 10 mmHg compared with the pre-injection measurement, the IOP will be measured again 60–80 minutes post-study drug injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary, in accordance with the investigator's clinical judgment, prior to discharge. For guidance on adverse event reporting, see Section 5.3.5.2.

[o] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs) other than protocol-specified procedural medications (e.g., dilating drops, proparacaine) used by a patient in addition to protocol-mandated treatment.

[p] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. Adverse events will be recorded starting on Day 1 until 28 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse events caused by a protocol-mandated intervention or believed to be related to prior study drug treatment (see Section 5.6) and should be reported (see Sections 5.3.1 and 5.4.2 for instructions for reporting serious adverse events). Adverse events assessed by the investigator as related to study drug should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has ended.

[q] Record all concurrent ocular procedures performed on the study or non-study eye.

[r] After each study treatment visit, the site must contact the patient 14 (±5) days after each treatment visit and query for adverse events; particularly any signs or symptoms of decreased visual acuity and/or inflammation (e.g., painful red eye, floaters, scotoma, pain); if the patient reports any concerning signs and/or symptoms, the patient must be evaluated by the investigator as soon as possible.

Appendix 2
Schedule of Activities for Q8W Arms

	Day 1 [a]		Week (±5 days)																				
			Treatment Period Visits																		FU Call		
	PS [b]	OLE	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	148	UV	ET [c]
Written informed consent		x [d]																					
Review inclusion and exclusion criteria		x																					
Medical and surgical history, including tobacco history	Ex																						
Review medical and surgical history including tobacco history		x																					
Demographic information	Ex																						
Physical examination [e]		x																				x [f]	x
Vital signs [g]		x																				x [f]	x
Hematology, coagulation, lipids, serum chemistry (central laboratory) [h]	Ex							x						x						x		x [f]	x
Urine pregnancy test [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x [f]	
Enrollment (IWRS)		x																					
Plasma sample for biomarkers	Ex							x						x						x		x [f]	x
Serum ADA sample [j]	Ex				*x*			x			*x*			x						x		x [f, j]	x
Serum PK sample for drug concentration [j, n]	Ex				*x*			x			*x*			x						x		x [f, j]	x
BCVA testing (starting at 4 m) [k]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
LL BCVA testing (starting at 4 m) [k]	Ex				x			x			x			x			x			x		x [f]	x

Appendix 2: Schedule of Activities for Q8W Arms

	Day 1 [a]		Week (±5 days)																				
			Treatment Period Visits																		FU Call		
	PS [b]	OLE	8	16	24	32	40	48	56	64	72	80	88	96	104	112	120	128	136	144	148	UV	ET [c]
IOP measurement [k]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Slit-lamp examination [l]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Aqueous humor sample [m, n]	Ex [n]				*x*			x			*x*			x						x		x [f]	
Dilated binocular indirect ophthalmoscopy	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x [f]	x
FAF [o]	Ex				x			x			x			x			x			x		x [f]	x
SD-OCT [o]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x [f, j]	x
OCT-A [o, p]	Ex				x			x			x			x			x			x		x [f]	x
NI [n]	Ex				x			x			x			x			x			x		x [f]	x
Color fundus photography [o]	Ex							x						x						x		x [f, j]	x
Administration of study drug to study eye [q]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Post-treatment finger counting and IOP measurement [r]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant medications [s]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Adverse events [t]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concurrent ocular procedures [u]	Ex		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Follow-up call [v]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			

ADA = anti-drug antibody; BCVA = best corrected visual acuity; CFP = color fundus photograph; ET = early termination; Ex = extracted data (from PS); FA = fluorescein angiography; FAF = fundus autofluorescence; FU = follow-up; IOP = intraocular pressure; IWRS = interactive web-based response system; LL BCVA = low-luminance BCVA; NI = near infrared; OCT-A = optical coherence tomography angiography; OLE = open-label extension; PK = pharmacokinetic; PS = parent study; Q8W = every 8 weeks; SD-OCT = spectral domain optical coherence tomography; UV = unscheduled visit.

Notes: All ocular assessments are to be performed for both eyes unless noted otherwise.

Appendix 2: Schedule of Activities for Q8W Arms

On treatment days, all assessments and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

Patients who discontinue study drug prematurely should be strongly encouraged to stay in the study and undergo as many scheduled visits as possible.

[a] The Day 1 visit for the OLE should be performed on the same day as the Week 76 visit for the PS, and all Week 76 assessments must be completed prior to conducting Day 1 assessments. If all assessments for the Day 1 visit cannot be completed on the same day as the Week 76 visit, patients may return to the clinic within 28 days to complete the Day 1 visit. If a patient is not able to complete the Day 1 visit within 28 days, the investigator must contact the Medical Monitor for further discussion prior to scheduling the Day 1 visit.

[b] Data from the PS will be extracted for use in the OLE study.

[c] For patients who discontinue early from the study, early termination assessments will be performed after at least 30 days have lapsed following the final dose of study drug.

[d] Informed consent must be documented before any study-specific procedure is performed.

[e] Includes weight and an evaluation of the head, eyes, ears, nose, throat, and cranial nerves.

[f] To be performed if clinically indicated.

[g] Vital signs consist of respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position after resting for 5 minutes, and temperature.

[h] For a detailed description of sample collection, see the laboratory manual.

[i] Collect and perform urine pregnancy test for women of childbearing potential, including those who have had tubal ligation, at each study treatment visit. If positive, collect a serum pregnancy sample and forward it to central laboratory for testing; if the serum pregnancy test is positive, do not administer study drug.

[j] In case of Grade >0 non-infectious intraocular inflammation, contact the Medical Monitor to discuss case. An additional serum ADA and PK sample should be collected as close as possible to the time of diagnosis. Consider performing CFP/FA (Appendix 12; widefield CFP/FA or standard CFP/FA with peripheral sweeps is preferred), SD-OCT, and uveitis lab workup as clinically indicated. Additionally, consider treatment with corticosteroids if appropriate, based on the individual patient presentation and comorbidities (e.g., diabetes, systemic hypertension), *and consider referring patient to a uveitis specialist and/or rheumatologist, per clinical judgment.*

[k] Perform assessment prior to dilating the eyes.

[l] Perform slit-lamp examination prior to dilating eyes; for grading scales for anterior chamber flare or cells and vitreous cells, see Appendix 5.

[m] Aqueous humor sample must be collected from the study eye after pretreatment IOP measurement, but prior to study drug administration. For a detailed description of the anterior chamber paracentesis and aqueous humor sample collection procedures, see Appendix 13 and the laboratory manual.

Appendix 2: Schedule of Activities for Q8W Arms

[n] *If the Day 1 visit for the OLE is not performed on the same day as the Week 76 visit for the parent study, and serum PK and aqueous humor samples were not collected on Week 76, these samples should be collected on Day 1 of OLE study.*

[o] Both eyes will be dilated prior to ocular imaging. FAF, SD-OCT, OCT-A (as applicable), NI images, and color fundus photographs will be obtained from both eyes and will be forwarded to the central reading center. If a patient misses a study visit where ocular images were scheduled to be obtained, the images should be obtained at the next scheduled visit.

[p] OCT-A is mandatory for sites that have the capability.

[q] All assessments (including a detailed examination to evaluate for signs of intraocular inflammation) and sample collection should be completed prior to study drug administration, except for post-treatment finger counting and IOP measurement.

[r] In the study eye only, a finger-counting test, followed by hand motion and light perception tests when necessary, will be performed by the investigator within 15 minutes after study drug injection, followed by an IOP measurement 30–50 minutes after study drug injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased by ≥ 10 mmHg compared with the pre-injection measurement, the IOP will be measured again 60–80 minutes post-study drug injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary, in accordance with the investigator's clinical judgment, prior to discharge. For guidance on adverse event reporting, see Section 5.3.5.2.

[s] Record any concomitant medications (e.g., prescription drugs, over-the-counter drugs) other than protocol-specified procedural medications (e.g., dilating drops, proparacaine) used by a patient in addition to protocol-mandated treatment.

[t] Any adverse events ongoing after the Week 76 visit from the PS has been completed should be transcribed to the OLE Adverse Event eCRF. After informed consent has been obtained for the OLE study but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. Adverse events will be recorded starting on Day 1 until 28 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse events caused by a protocol-mandated intervention or believed to be related to prior study drug treatment (see Section 5.6) and should be reported (see Sections 5.3.1 and 5.4.2 for instructions for reporting serious adverse events). Adverse events assessed by the investigator as related to study drug should be followed until the event resolves or the event is assessed as irreversible, chronic, or stable, even if patient's participation in the study has ended.

[u] Record all concurrent ocular procedures performed on the study or non-study eye.

[v] After each study treatment visit, the site must contact the patient 14 (±5) days after each treatment visit and query for adverse events; particularly any signs or symptoms of decreased visual acuity and/or inflammation (e.g., painful red eye, floaters, scotoma, pain); if the patient reports any concerning signs and/or symptoms, the patient must be evaluated by the investigator as soon as possible.

Appendix 3
Best Corrected Visual Acuity Testing

SCOPE

Best corrected visual acuity (BCVA) assessment must be conducted before pupil dilation. BCVA will be measured by trained and certified personnel at the study sites. The BCVA examiner must be masked to each patient's study (treated) eye assignment. BCVA will be measured at the intervals specified in the protocol (see Appendix 1 and Appendix 2 of the protocol and the Clinical Edge Visual Acuity Certification Procedure Manual).

EQUIPMENT

The following are needed to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances
- Standard chair with a firm back
- Set of three Precision Vision™ or Lighthouse distance acuity charts (modified Early Treatment Diabetic Retinopathy Study Charts R, 1, and 2 in the United States)
- Retro-illuminated box
- Study frame
- Study lens set

TRAINING AND CERTIFICATION

BCVA specifications document, procedure manual, and training materials will be provided to the investigational sites, and examiner certification will be obtained. The BCVA examination room also must be certified before any BCVA examinations are performed.

Appendix 4
Low-Luminance Best Corrected Visual Acuity Testing

These are the same requirements as the best corrected visual acuity described in Appendix 3; however, low-luminance visual acuity will be measured by placing a 2.0–log unit neutral density filter (Kodak Wratten 2.0 neutral density filter) over the best correction for the eye and having the participant read the standard illuminated Early Treatment Diabetic Retinopathy Study Chart.

Appendix 5
Grading Scale for Assessment of Anterior Chamber Flare or Cells and Vitreous Cells

Table 1 Grading Scale for Anterior Chamber Flare or Cells

Flare	
Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Cells	
Grade	Cells in field [a]
0	0
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	>50

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

Table 2 Grading Scale for Vitreous Cells

Grade	Number of Vitreous Cells
0	0
0.5+	1–10
1+	11–20
2+	21–30
3+	31–100
4+	>100

REFERENCES

Foster CS, Kothari S, Anesi SD, et al. The Ocular Immunology and Uveitis Foundation preferred practice patterns of uveitis management. Surv Ophthalmol 2016;61:1–17.

Appendix 6
Post-Injection Procedures for All Patients

In the study eye only, a finger-counting test, followed by hand motion and light perception tests when necessary, will be performed by the investigator within 15 minutes after study drug injection.

In the study eye only, a measurement of intraocular pressure (IOP) will be obtained 30–50 minutes after study drug injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased by ≥ 10 mmHg compared with the pre-injection measurement or is of concern to the investigator, the IOP will be measured again 60–80 minutes post-injection. If the IOP value remains a concern to the investigator, the patient will remain in the clinic and will be treated as necessary, in accordance with the investigator's clinical judgment, prior to the patient's discharge.

As per individual site investigator decision, the investigator may administer anti-microbial drops after study drug injection. The individual site investigator may also instruct patients to self-administer anti-microbial drops before and after each injection.

Appendix 7
Color Fundus Photography

SCOPE

Non-stereo color fundus photographs will be taken by trained personnel at the study sites. Fundus photography will be performed at the intervals specified in the protocol (see Appendix 1 and Appendix 2).

EQUIPMENT

Equipment used during this study is described in the Central Reading Center Manual.

PROCEDURES AND CERTIFICATION

The central reading center will provide a study manual and training materials. The fundus photographer and photography equipment will be certified by the reading center before any study images are taken. See the Central Reading Center Manual for further details.

Appendix 8
Fundus Autofluorescence

SCOPE

Fundus autofluorescence (FAF) will be performed at the study sites by trained personnel who are certified by the central reading center. FAF imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1 and Appendix 2) and will be forwarded to the central reading center.

EQUIPMENT

Equipment used during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed FAF images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide a study manual and training materials.
FAF operators, systems, and software will be certified prior to any evaluation of patients.
See the Central Reading Center Manual for further details.

Appendix 9
Near Infrared Imaging

SCOPE

Near infrared (NI) imaging will be performed at the study sites by trained personnel who are certified by the central reading center. NI imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1 and Appendix 2).

The NI images of both eyes will be obtained at protocol-specified visits and will be forwarded to the central reading center.

EQUIPMENT

Equipment used during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed NI images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. NI operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 10
Spectral Domain Optical Coherence Tomography

SCOPE

Spectral domain optical coherence tomography (SD-OCT) will be performed at the study sites by trained personnel who are certified by the central reading center. SD-OCT imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1 and Appendix 2).

The SD-OCT images of both eyes will be obtained at protocol-specified visits and will be forwarded to the central reading center.

EQUIPMENT

Equipment used during this study is described in the Central Reading Center Manual. The SD-OCT equipment used for a patient must remain consistent throughout the study. The ability to transfer images to electronically exportable digital files is required (i.e., no printed SD-OCT images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. SD-OCT operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 11
Optical Coherence Tomography Angiography

SCOPE

Optical coherence tomography angiography (OCT-A) will be performed at the study sites with this capability by trained personnel who are certified by the central reading center. OCT-A imaging will be performed for each patient at the intervals specified in the protocol (see Appendix 1 and Appendix 2).

The OCT-A images of both eyes will be obtained at protocol-specified visits and will be forwarded to the central reading center.

EQUIPMENT

Equipment used during this study is described in the Central Reading Center Manual. The ability to transfer images to electronically exportable digital files is required (i.e., no printed OCT-A images will be sent to the central reading center).

PROCEDURES AND CERTIFICATION

The central reading center will provide the study manual and training materials. OCT-A operators, systems, and software will be certified prior to any evaluation of patients.

Appendix 12
Fluorescein Angiography

SCOPE

Fluorescein angiography (FA) will be performed at the study sites by trained personnel, when non-infectious intraocular inflammation is suspected and investigator considers it as an important part of the diagnostic work-up. Analysis (if applicable) will be performed by the central reading center.

EQUIPMENT AND DIGITAL IMAGING SYSTEMS

Digital angiograms must be used while conducting an angiographic evaluation for the study. Widefield FA or standard FA with peripheral sweeps is preferred, if available.

Film-based angiography is not acceptable.

PROCEDURES

Refer to the Central Reading Center Manual for details.

Appendix 13
Anterior Chamber Paracentesis and Aqueous Humor Sampling Procedures

An aqueous humor sample will be collected from the study eye after pretreatment intraocular pressure measurement, but prior to study drug administration, as indicated in Appendix 1 and Appendix 2. The anterior chamber paracentesis will be performed by a qualified physician by placing a drop of topical anesthetic on the cornea, passing a needle through the limbus into the anterior chamber, and removing approximately 100 μL of aqueous fluid and more volume, if possible without endangering patient safety at applicable patient visits. Samples will be collected with the kit provided by the central laboratory and shipped on dry ice to the central laboratory as soon as possible after the draw.

The following procedures will be used to minimize the risk of potential adverse events associated with aqueous humor sampling (e.g., endophthalmitis, corneal abscess, hyphema, cornea, lens, iris trauma).

Aseptic technique will be performed by clinic staff involved in the aqueous humor collection tray assembly, anesthetic preparation, and aqueous humor sample collection. In addition to the procedures outlined below, any additional safety measures in adherence to specific institutional policies associated with aqueous humor sample collection will be observed.

As per individual site investigator decision, patients may self-administer anti-microbial drops prior to and after aqueous humor sample collection.

Prepare a sterile field that includes the following supplies:

- 10% povidone iodine swabs
- Sterile surgical gloves
- 4 × 4 sterile pads
- 0.5% proparacaine hydrochloride
- 5% povidone iodine ophthalmic solution
- 1-cc syringe
- 27- or 30-gauge needle, 0.5 inches in length
- Sterile saline solution
- Per individual investigator discretion:
  - Sterile cotton-tipped applicators
  - Eyelid speculum
  - Sterile ophthalmic drape
  - Surgical face mask

Appendix 13: Anterior Chamber Paracentesis and Aqueous Humor Sampling Procedures

Aqueous humor sampling should be performed using an aseptic procedure and sterile field as follows:

- Instill two drops of 0.5% proparacaine hydrochloride into the study eye
- Wait 90 seconds
- As per individual investigator discretion, instill two drops of anti-microbial drops
- Wait 5 minutes (only if anti-microbial drops are used)
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye
- Disinfect the peri-ocular skin and eyelid of the study eye

  Scrub the eyelid, lashes, and peri-orbital skin with 10% povidone-iodine swabs, starting with the eyelid and lashes and continuing with the surrounding peri-ocular skin. Ensure that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion from medial to temporal aspects.
- Instill two additional drops of 5% povidone iodine ophthalmic solution in the study eye
- After washing hands, put on sterile gloves
- Per investigator discretion, the investigator may place sterile ophthalmic drape to isolate the field and place the speculum underneath the eyelid of the study eye
- Collect the aqueous humor sample (approximately 100 μL) using the 27- or 30-gauge needle attached to the 1-cc syringe through a paracentesis inserted at the temporal paralimbal clear cornea on a horizontal angle in a plane above and parallel to the iris with the bevel of the needle facing away from the iris, paying strict attention to avoid contact with the patient's eyelashes, lens, or iris.

  NOTE: The investigator and patient should refrain from talking, coughing, or sneezing during the aqueous sample collection. A surgical face mask may be worn per investigator discretion.
- Dispense collected aqueous humor into the appropriately labeled collection tube provided and store frozen until shipped as described in the laboratory manual
- As per individual site investigator decision, patients may self-administer anti-microbial drops prior to and after aqueous humor sample collection

Appendix 14
WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5–10.5 g/dL	8.0–9.4 g/dL	6.5–7.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1000–1500/mm^3	750–999/mm^3	500–749/mm^3	<500/mm^3
Platelets	75,000–99,000/mm^3	50,000–74,999/mm^3	20,000–49,000/mm^3	<20,000/mm^3
Prothrombin Time (PT)	1.01–1.25 × ULN	1.26–1.5 × ULN	1.51–3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (aPTT)	1.01–1.66 × ULN	1.67–2.33 × ULN	2.34–3 × ULN	>3 × ULN
Fibrinogen	0.75–0.99 × LLN	0.50–0.74 × LLN	0.25–0.49 × LLN	<0.25 × LLN
Fibrin Split Product	20–40 μg/mL	41–50 μg/mL	51–60 μg/mL	>60 μg/mL
Methemoglobin	5%–9.9%	10.0%–14.9%	15.0%–19.9%	>20%
LIVER ENZYMES				
AST (SGOT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
ALT (SGPT)	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
GGT	1.25–2.5 × ULN	1.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Alkaline Phosphatase	1.25–2.5 × ULN	1.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Amylase	1.1–1.5 × ULN	1.6–2.0 × ULN	2.1–5.0 × ULN	>5.1 × ULN
CHEMISTRIES				
Hyponatremia	130–135 mEq/L	123–129 mEq/L	116–122 mEq/L	<116 or mental status changes or seizures
Hypernatremia	146–150 mEq/L	151–157 mEq/L	158–165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0–3.4 mEq/L	2.5–2.9 mEq/L	2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6–6.0 mEq/L	6.1–6.5 mEq/L	6.6–7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55–64 mg/dL	40–54 mg/dL	30–39 mg/dL	<30 mg/dL or mental status changes or coma

Appendix 14: WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES (cont.)				
Hyperglycemia (note if fasting)	116–160 mg/dL	161–250 mg/dL	251–500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4–7.8 mg/dL	7.7–7.0 mg/dL	6.9–6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6–11.5 mg/dL	11.6–12.5 mg/dL	12.6–13.5 mg/dL	>13.5 mg/dL or life-threatening arrhythmia
Hypomagnesemia	1.4–1.2 mEq/L	1.1–0.9 mEq/L	0.8–0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0–2.4 mg/dL	1.5–1.9 mg/dL or replacement Rx required	1.0–1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1–1.5 × ULN	1.6–2.5 × ULN	2.6–5 × ULN	>5 × ULN
BUN	1.25–2.5 × ULN	2.6–5 × ULN	5.1–10 × ULN	>10 × ULN
Creatinine	1.1–1.5 × ULN	1.6–3.0 × ULN	3.1–6 × ULN	>6 × ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or <0.3% or <3 g/L or 200 mg–1 g loss/day	2–3+ or 0.3%–1.0% or 3–10 g/L or 1–2 g loss/day	4+ or >1.0% or >10 g/L or 2–3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only	Gross, no clots	Gross + clots	Obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		Asymptomatic, transient signs, no Rx required	Recurrent/persistent, no Rx required	Requires treatment
Hypertension	Transient increase, >20 mm, no Rx	Recurrent, chronic, >20 mm, Rx required	Requires acute Rx, no hospitalization	Requires hospitalization
Hypotension	Transient orthostatic hypotension, no Rx	Symptoms correctable with oral fluids, Rx	Requires IV fluids, no hospitalization required	Requires hospitalization
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no Rx	Symptomatic effusion, pain, ECG changes	Tamponade, pericardiocentesis, or surgery required

Appendix 14: WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CARDIAC DYSFUNCTION (cont.)				
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss, 1–2 units transfused	Massive blood loss, >3 units transfused
RESPIRATORY				
Cough	Transient, no Rx	Treatment associated cough, local Rx	Uncontrolled	
Bronchospasm, Acute	Transient, no Rx <80%–70% FEV_1 (or peak flow)	Requires Rx, normalizes with bronchodilator, FEV_1 50%–70% (or peak Flow)	No normalization with bronchodilator, FEV_1 25%–50% (or peak flow retractions)	Cyanosis: FEV_1 <25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	Mild discomfort, no limits on activity	Some limits on eating/drinking	Eating/talking very limited	Requires IV fluids
Nausea	Mild discomfort, maintains reasonable intake	Moderate discomfort, intake decreased significantly, some activity limited	Severe discomfort, no significant intake, activities limited	Minimal fluid intake
Vomiting	Transient emesis	Occasional/moderate vomiting	Orthostatic hypotension or IV fluids required	Hypotensive shock or hospitalization required for IV fluid therapy
Constipation	Mild	Moderate	Severe	Distensions w/vomiting
Diarrhea	Transient, 3–4 loose stools/day	5–7 loose stools/day	Orthostatic hypotension or >7 loose stools/day or IV fluids required	Hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro-cerebellar	Slight incoordination, dysdiadochokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Incapacitated
Mood	Mild anxiety or depression	Moderate anxiety or depression and therapy required	Severe anxiety or depression or mania, needs assistance	Acute psychosis, incapacitated, requires hospitalization
Neuro Control	Mild difficulty concentrating, no Rx, mild confusion/agitation, ADLs unaffected	Moderate confusion/agitation, some limitation of ADLs, minimal Rx	Severe confusion/agitation, needs assistance for ADLs, therapy required	Toxic psychosis, requires hospitalization

Appendix 14: WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
NEURO & NEUROMUSCULAR (cont.)				
Muscle Strength	Subjective weakness, no objective symptoms/signs	Mild objective signs/symptoms, no decrease in function	Objective weakness, function limited	Paralysis
OTHER PARAMETERS				
Fever: Oral, > 12 hours	37.7°C–38.5°C or 100.0°F–101.5°F	38.6°C–39.5°C or 101.6°F–102.9°F	39.6°C–40.5°C or 103°F–105°F	> 40.5°C or > 105°F
Headache	Mild, no Rx therapy	Transient, moderate, Rx required	Severe, responds to initial narcotic therapy	Intractable, required repeated narcotic therapy
Fatigue	No decrease in ADLs	Normal activity decreased 25%–50%	Normal activity decreased > 50%, cannot work	Unable to care for self
Allergic Reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
Local Reaction	Tenderness or erythema	Induration < 10 cm or phlebitis or inflammation	Induration > 10 cm or ulceration	Necrosis
Mucocutaneous	Erythema, pruritus	Diffuse, maculopapular rash, dry desquamation	Vesiculation, moist desquamation, or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

ADLs = activities of daily living; FEV_1 = forced expiratory volume in 1 second; GGT = gamma-glutamyl transferase; LLN = lower limit of normal; Rx = prescription; ULN = upper limit of normal.