**Official Title:** A PHASE II, MULTICENTER, RANDOMIZED, SINGLE-MASKED, SHAM-CONTROLLED STUDY TO ASSESS SAFETY, TOLERABILITY, AND EFFICACY OF INTRAVITREAL INJECTIONS OF FHTR2163 IN PATIENTS WITH GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION (GALLEGO)

**NCT Number:** NCT03972709

**Document Date:** Protocol Amendment Version 5: 23 October 2023

**PROTOCOL**

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| **PROTOCOL NUMBER:** | GR40973 |
| **VERSION NUMBER:** | 5 |
| **EUDRACT NUMBER:** | NA |
| **IND NUMBER:** | 134632 |
| **NCT NUMBER:** | *NCT03972709* |
| **TEST PRODUCT:** | FHTR2163 (RO7171009) |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | See electronic signature and date stamp on the final page of this document. |

## PROTOCOL HISTORY

| Version | Date Final |
|---|---|
| 1 | 18 February 2019 |
| 2 | 12 September 2020 |
| 3 | 3 May 2021 |
| 4 | 25 October 2021 |

## PROTOCOL AMENDMENT, VERSION 5:
## RATIONALE

Protocol GR40973 has been amended primarily to update the NCT number. Changes to the protocol, along with a rationale for each change, are summarized below:

- The NCT number has been corrected from NCT04507148 to NCT03972709 (front matter)

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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**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

| | |
|---|---|
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| **IND NUMBER:** | 134632 |
| **NCT NUMBER:** | *NCT03972709* |
| **TEST PRODUCT:** | FHTR2163 (RO7171009) |
| **PHASE:** | Phase II |
| **INDICATION:** | Age-related macular degeneration |
| **SPONSOR:** | Genentech, Inc. |

### OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of intravitreal (ITV) injections of 20 mg FHTR2163 administered every 4 weeks (Q4W) or every 8 weeks (Q8W) in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) compared with sham control. Specific objectives and corresponding endpoints for the study are outlined below.

#### EFFICACY OBJECTIVES

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoint:

- Mean change in the GA area from baseline to Week 72 as measured by fundus autofluorescence (FAF)

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoints:

- Mean change in best corrected visual acuity (BCVA) score from baseline to Week 72 as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart under low-luminance conditions
- Mean change in BCVA score from baseline to Week 72 as assessed by ETDRS chart

Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- To evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoint:
  - Mean rate of change in the GA area, estimated based on GA area as measured by FAF at four timepoints: baseline, Week 24, Week 48, and Week 72
- To evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with foveal-involving GA and in patients with non-foveal–involving GA compared with sham control on the basis of the following endpoints:
  - Mean change in the GA area from baseline to Week 72 as measured by FAF
  - Mean rate of change in the GA area, estimated based on GA area as measured by FAF at four timepoints: baseline, Week 24, Week 48, and Week 72

Safety Objective

The safety objective for this study is to evaluate the local and systemic safety and tolerability of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W relative to sham control on the basis of the following endpoints:

- Frequency, severity, and timing of ocular and systemic adverse events, serious adverse events, adverse events leading to study discontinuation, and adverse events of special interest
- Frequency, severity, and timing of notable findings in ocular examinations and ocular imaging, including those requiring intervention or start of anti-vascular endothelial growth factor (anti-VEGF) therapy
- Incidence of neovascular AMD diagnosed during the conduct of the study

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the FHTR2163 PK profile 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 as follows: To evaluate potential relationships between drug exposure and the safety and efficacy of FHTR2163 on the basis of the following endpoints:

- Relationship between serum and/or aqueous humor concentration or PK parameters for FHTR2163 and efficacy endpoints
- Relationship between serum and/or aqueous humor concentration or PK parameters for FHTR2163 and safety endpoints

Immunogenicity Objective

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 serum ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objectives

The exploratory diagnostic biomarker objective for this study is to evaluate the efficacy as defined in the primary efficacy objective in carriers versus non-carriers of the high-temperature requirement A1 (HtrA1) AMD risk variant rs10490924.

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, on the basis of the following endpoints:

- Relationship between biomarkers in blood and aqueous humor and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between retinal imaging measures (i.e., FAF, spectral domain optical coherence tomography [SD-OCT], optical coherence tomography angiography [OCT-A]) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

## STUDY DESIGN

### DESCRIPTION OF STUDY

This is a Phase II, multicenter, randomized, single-masked, sham-controlled study evaluating the safety, tolerability, and efficacy of 20 mg FHTR2163 dose administered Q4W or Q8W by ITV injections for approximately 76 weeks, in patients with GA secondary to AMD. Approximately 360 patients (144 patients in FHTR2163 Q4W arm, 72 patients in FHTR2163 Q8W arm, and 144 patients in pooled sham arm) will be enrolled in the study at approximately 77 investigational sites in the United States. Site investigators will be qualified ophthalmologists.

The study will consist of the following:

- Screening period of up to 120 days, divided into a prebaseline screening period (Day –120 to Day –31) and a baseline screening window (Day –30 to Day –1)
- Treatment period of up to 68 weeks (Day 1 to Week 68 for the Q4W treatment arms and Day 1 to Week 64 for the Q8W treatment arms)
- Primary analysis timepoint visit (Week 72)
- Final study visit (Week 76)

To be eligible for the study, patients must satisfy all eligibility criteria at both the screening visit(s) and the Day 1 visit (i.e., day patient is enrolled and study drug is administered). One essential eligibility criterion is that patients will be required to have two FAF images, a prebaseline image and a baseline image performed on a Heidelberg platform obtained at a minimum of ~3 months (84 days) and maximum of ~11 months (336 days) prior to the baseline screening visit.

Patients who fail screening may be eligible for rescreening up to three additional times during the enrollment period of the study. Eligible patients will be randomized in a 2:1:1:1 ratio such that approximately 144 patients will receive study drug treatment Q4W, 72 patients will receive sham-control treatment Q4W, 72 patients will receive study drug treatment Q8W, and 72 patients will receive sham-control treatment Q8W. Patients receiving Q4W dosing will receive a total of 18 treatments and patients receiving Q8W dosing will receive a total of 9 treatments.

### NUMBER OF PATIENTS

Approximately 360 patients with GA secondary to AMD will be enrolled in this study at approximately 77 investigative sites located in the United States.

### TARGET POPULATION

Inclusion Criteria

Patients must meet the following criteria for study entry:

*General Inclusion Criteria*

- Signed Informed Consent Form
- Age $\geq$60 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- 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 at least 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 ($\geq 12$ 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.
- Ability and willingness to undertake all scheduled visits and assessments

*Ocular Inclusion Criteria: Study Eye*

One eye will be designated as the study eye. If both eyes meet the following criteria, the eye with the worse visual acuity (VA) and/or least function (as determined by the investigator and patient) will be selected for study treatment (study eye). If both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye.

- Visual acuity: BCVA letter score of $\geq 24$ letters (Snellen equivalent of 20/320 or better) using ETDRS chart at starting distance of 4 m

  If the study eye BCVA letter score is $\geq 69$ letters (Snellen equivalent of 20/40 or better), the non-study eye must have a BCVA letter score of $\geq 44$ letters (Snellen equivalent of 20/125 or better).
- Well-demarcated area of GA secondary to AMD with no evidence of prior or active choroidal neovascularization (CNV)
- Prebaseline FAF image obtained via a Heidelberg platform 84–336 days prior to the screening visit that meets the following criteria:
  - Total GA lesion size must be $\geq 2.54$ mm$^2$ (approximately $\geq 1$ disc area [DA]) and $\leq 17.78$ mm$^2$ (approximately $\leq 7$ DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea)

    If GA is multifocal, at least 1 focal lesion must be $\geq 1.27$ mm$^2$ (approximately $\geq 0.5$ DA).
  - Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to GA area

    Note: Diffuse-trickling pattern is excluded.
- Baseline FAF image obtained during the baseline screening window (Day –30 to Day –1) must meet the following criteria:
  - Total GA lesion size must be $\geq 2.54$ mm$^2$ (approximately $\geq 1$ DA) and $\leq 25.4$ mm$^2$ (approximately $\leq 10$ DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea).

    If GA is multifocal, at least 1 focal lesion must be $\geq 1.27$ mm$^2$ (approximately $\geq 0.5$ DA).

- Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to GA area

  Note: Diffuse-trickling pattern is excluded.

- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging
- Ocular anatomy that would allow for safe and uneventful collection of approximately 100 μL aqueous humor sample in the opinion of the investigator

*Ocular Inclusion Criteria: Non-Study Eye*

- GA secondary to AMD with no evidence of prior or active CNV
- 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).

Exclusion Criteria

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

*GA Characteristics Exclusion Criterion*

- GA in either eye due to causes other than AMD (monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy])

*Ocular Exclusion Criteria: Study Eye*

- Absence of any hyperfluorescence pattern (none) adjacent to GA area in the study eye
- Presence of diffuse-trickling, patchy, or minimal (focal) hyperfluorescence pattern adjacent to GA area in the study eye
- Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could result in either of the following:
  - Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
  - If allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of BCVA during the study period
- Intraocular surgery, including cataract surgery, in the study eye within 3 months prior to Day 1
- Uncontrolled glaucoma in the study eye, defined as intraocular pressure ≥30 mmHg despite treatment with anti-glaucoma medication
- Current vitreous hemorrhage in the study eye
- Aphakia or absence of the posterior capsule in the study eye
- Previous laser photocoagulation or ITV anti-VEGF for CNV, diabetic macular edema, retinal vein occlusion, or proliferative diabetic retinopathy
- Prior treatment with photodynamic therapy, external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy
- Any posterior segment device or implant (e.g., any type of corticosteroid implant/device, encapsulated cell therapy, or Argus® II Retinal Prosthesis System)
- ITV, subtenon, or topical (ocular) corticosteroids within 3 months prior to randomization

  A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.
- History of vitrectomy surgery, submacular surgery, or any surgical intervention for AMD
- History of prophylactic subthreshold laser treatment for AMD
- History of glaucoma-filtering (trabeculectomy, valves, or minimally invasive glaucoma stents) surgery in the study eye

- History of corneal transplant in the study eye
- History of retinal tear in the study eye

  Patient may be permitted after appropriate treatment and subsequent determination of stability by the investigator.
- History of retinal detachment or macular hole (Stage 3 or 4) in the study eye
- Any concurrent ocular or intraocular conditions that contraindicate the use of an investigational drug, 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.
- Previous violation of the posterior capsule in the study eye unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error in the study eye demonstrating $>8$ diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia.

*Ocular Exclusion Criteria: Non-Study Eye*

- Non-functioning non-study eye defined as either:

  BCVA of hand motion or worse
  OR
  No physical presence of non-study eye (i.e., monocular)

*Ocular Exclusion Criteria: Both Eyes*

- 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 ocular melanoma in either eye
- Active or history of CNV in either eye
- Active or history 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

  Note: Mild non-proliferative diabetic retinopathy (e.g., occasional hemorrhage or microaneurysm) in either eye may be permitted at the discretion of the investigator. Moreover, a patient with the onset of mild non-proliferative diabetic retinopathy in either eye during study participation may be permitted to continue study treatment at the discretion of the investigator.
- Proliferative diabetic retinopathy in either eye
- Central serous retinopathy in either eye
- Previous participation in an interventional clinical trial for GA or dry AMD trial that tested stem cell treatments, gene therapy, long-acting delivery platforms/formulations (e.g., biodegradable/non-biodegradable implants or formulations, device implant, encapsulated cell technologies), or inhibitors/modulators of the visual cycle (e.g., fenretinide, emixustat) regardless of timing of patient participation

- Previous participation in interventional clinical trials for GA or dry AMD, except for vitamins and minerals, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months

  Note: If patient participation in an interventional clinical trial for GA or dry AMD was >6 months prior to screening, the patient may be eligible for the trial at the discretion of the investigator.
- History of recurrent infectious or inflammatory ocular disease in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye

*Concurrent Systemic Conditions Exclusion Criteria*

- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg while patient is sitting

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient can be eligible if medication is taken continuously for at least 30 days prior to Day 1.
- History of cerebral vascular accident or transient ischemic attack
- History of other diseases, 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
- Active cancer within past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the investigational drug injection
- Previous participation in any studies of investigational drugs within the last 6 months, excluding vitamins and minerals

  If patient participation in a clinical trial was >6 months prior to screening, the patient may be eligible for the study at the discretion of the investigator.
- Requirement for continuous use of any medications/treatments indicated as a prohibited therapy in this study
- Medical conditions that may be associated with a clinically significant risk for bleeding
- 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 serum pregnancy test result within 28 days 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 76 weeks after the last patient is randomized to the study. In addition, the Sponsor may decide to terminate the study at any time.

**LENGTH OF STUDY**

The duration of the study is approximately 76 weeks after the last patient is randomized to the study.

**INVESTIGATIONAL MEDICINAL PRODUCTS**

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

### TEST PRODUCT (INVESTIGATIONAL DRUG AND SHAM CONTROL)

On Day 1, patients will be randomized in a 2:1:1:1 ratio to one of the study treatment arms (FHTR2163 Q4W, sham control Q4W, FHTR2163 Q8W, or sham control Q8W). The first ITV injection of 20 mg FHTR2163 or sham control will be conducted by investigators on the same day as randomization (i.e., Day 1).

## STATISTICAL METHODS

### PRIMARY ANALYSIS

The primary efficacy analyses will be based on the modified intent-to-treat population (see Data Analysis Plan for detailed definition). Patients will be grouped according to the treatment assigned at randomization. Patients in the sham-control Q4W and sham-control Q8W groups will be pooled in the analyses.

If not otherwise specified, analyses of efficacy outcome measures will be stratified by HtrA1 risk-variant carrier status (HtrA1 risk-variant carrier vs. HtrA1 risk-variant non-carrier, as determined by the HtrA1 risk-variant genotyping assay), baseline GA lesion size ($<9.0$ mm$^2$ vs. $\geq 9.0$ mm$^2$), and annualized prebaseline GA progression rate (<1.9 mm$^2$/yr vs. $\geq$1.9 mm$^2$/yr). A data-as-observed approach with the mixed-effect model will be used to handle missing data in the primary analysis. Sensitivity analyses will be performed to evaluate the effect of missing data on the results.

### DETERMINATION OF SAMPLE SIZE

This study is designed to evaluate the efficacy of FHTR2163 administered ITV Q4W and Q8W to patients with GA secondary to AMD. The focus of the efficacy outcome analyses will be on estimation of the magnitude of the treatment effect.

The primary efficacy endpoint is the mean change in GA area from baseline to Week 72 as measured by FAF. The sample size provides reasonable precision for estimation of the treatment effect with respect to the primary endpoint.

Approximately 360 patients will be randomized in a 2:1:1:1 ratio to one of four treatment groups: FHTR2163 Q4W, sham control Q4W, FHTR2163 Q8W, or sham control Q8W. Patients in the sham control Q4W and sham control Q8W groups will be pooled in the analyses.

Assuming a 15% dropout rate by Week 72 and a standard deviation of 1.82 mm$^2$ for change from baseline in GA area at Week 72 (estimated from the lampalizumab Phase II Study CFD4870g and the Phase III Studies GX29176 and GX29185), 114 patients in the FHTR2163 Q4W arm and 114 patients in the pooled sham-control group will provide 80% power to detect a targeted difference of 0.56 mm$^2$ (20% reduction relative to sham control) in the change from baseline in GA area at Week 72 between the FHTR2163 Q4W arm and the pooled sham-control arm. Calculations were based on two-sided t-test at the significance level of 20% and resulted in a total sample size of 285. No multiplicity adjustment is planned for this study.

A total of 131 patients had enrolled in this study as of 10 April 2020. As a result of the increase in missed visits, missed dosing, and missed assessments as a consequence of the COVID-19 pandemic, up to approximately 75 patients will be enrolled in addition to the originally planned 285 patients to help mitigate the potential impact on treatment effect and data.

### OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by the unmasked internal monitoring committee (IMC) and will be interpreted by the IMC and appropriate senior management personnel. Access to treatment assignment information will follow the Sponsor's standard procedures. The details of the timing and scope of the interim analysis, if any, will be specified in the IMC Agreement.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| AMD | age-related macular degeneration |
| anti-VEGF | anti-vascular endothelial growth factor |
| 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 |
| DA | disc area |
| DAP | Data Analysis Plan |
| 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 | hyper-reflective 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 systems |
| LPLV | last patient, last visit |
| MD | multiple dose |
| NGS | next-generation sequencing |
| nAMD | neovascular AMD |
| NI | near infrared |

| Abbreviation | Definition |
|---|---|
| OCT-A | optical coherence tomography angiography |
| PD | pharmacodynamic |
| 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 |
| 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: a non-exudative form, geographic atrophy (GA), which is characterized by loss of photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris; and 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, 1999; Sunness and Applegate 1996). 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 and Spectri, 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).

The Phase II clinical development plan for FHTR2163 (Fab of a humanized monoclonal antibody directed against the high-temperature requirement A1 [HtrA1] protein) is designed to test the safety, tolerability, and efficacy in patients with GA secondary to AMD.

## 1.2 BACKGROUND ON HTRA1

The high-temperature requirement A1 (*HtrA1*) gene, located in chromosomal region 10q26, was one of the first AMD genetic loci identified and has been replicated in multiple studies with associations seen in both linkage and genome-wide association (Weeks et al. 2001; Fritsche et al. 2016). A single nucleotide polymorphism 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 FHTR2163 Nonclinical Toxicology Summary

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. Hyper-reflective 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 (Covance Laboratories Inc. report 2018 [available upon request]; Booler et al. 2019). 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 at least partial reversibility by the end of the 1-month recovery periods. 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.

The toxicology program for FHTR2163 supports both the dose regimens of 20 mg/eye every 4 weeks (Q4W) and every 8 weeks (Q8W), and the duration of this Phase II clinical trial. Refer to the FHTR2163 Investigator's Brochure for details on nonclinical GLP toxicology studies.

### 1.3.2 FHTR2163 Phase I Safety Summary and Pharmacokinetic Preliminary Data

Study GR39821 was an open-label, multicenter, Phase I, first-in-human study designed to investigate the safety, tolerability, pharmacokinetics, and immunogenicity of FHTR2163 administered intravitreally in patients with GA secondary to AMD. The study consisted of two stages: a single ascending dose (SAD) and multiple dose (MD). The SAD stage allowed escalated exposure to FHTR2163 with 5 doses (1, 3, 10, 15, and 20 mg) in 15 patients (3 patients per dose level). The MD stage evaluated the maximum tested dose in SAD (20 mg) administered every 4 weeks for 3 administrations in 10 evaluable patients. The study was completed on 20 November 2018 (last patient, last visit).

In Study GR39821, FHTR2163 was well tolerated. There were no dose-limiting toxicities and no ocular serious adverse events. Two participants, in the MD stage of the study, experienced systemic serious adverse events; none of these events were assessed as related to study drug.

In the SAD cohorts, adverse events reported in $>1$ participant were as follows: conjunctival hemorrhage ($n=5$) and conjunctival hyperemia ($n=2$). In the MD cohorts, adverse events reported in $>1$ participant were as follows: conjunctival hemorrhage ($n=2$), conjunctival hyperemia ($n=2$), skin ulcer ($n=2$), and squamous cell carcinoma ($n=2$). None of the systemic or ocular adverse events reported in the SAD or MD cohorts were assessed as related to study drug.

No adverse drug reactions related to FHTR2163 have been identified. Potential risks are discussed in Section 5.1.1.

Based on preliminary pharmacokinetic (PK) analysis, the aqueous humor and serum PK profile of FHTR2163 in humans was generally consistent with other Fabs

(e.g., Lucentis®) administered via ITV injection. The estimated ocular elimination half-life in humans was 4.9 days. The systemic FHTR2163 concentrations following ITV injection are estimated to be at least 7,500-fold lower than vitreal FHTR2163 concentrations.

Based on the results of the Phase I study (GR39821), there has been no change to the potential risks or the reference safety information for FHTR2163 as outlined in the current version of the FHTR2163 Investigator's Brochure.

### 1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

As described in Section 1.1, 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.

This Phase II study will evaluate the efficacy of FHTR2163 and will further investigate the ocular and systemic safety, tolerability, and pharmacokinetics of FHTR2163 following multiple ITV administrations in patients with GA secondary to AMD.

The clinical experience with FHTR2163 is limited to one first-in-human study (see Section 1.3.2), and the safety profile in humans is not fully understood at this time. The completed nonclinical toxicology studies for FHTR2163 support the continued development of the molecule in clinical studies in patients with GA secondary to AMD (see Section 1.3.1). There are no known 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), regular ocular assessments (see Section 4.5.5), regular ocular imaging (see Section 4.5.6), physical examinations (see Section 4.5.3), and regular safety review by an unmasked Internal Monitoring Committee (IMC) (Section 3.1.2).

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 use in this clinical study.

## 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control. Specific objectives and corresponding endpoints for the study are outlined below.

## 2.1 EFFICACY OBJECTIVES

### 2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoint:

- Mean change in the GA area from baseline to Week 72 as measured by fundus autofluorescence (FAF)

### 2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoints:

- Mean change in best corrected visual acuity (BCVA) score from baseline to Week 72 as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart under low-luminance conditions
- Mean change in BCVA score from baseline to Week 72 as assessed by ETDRS chart

### 2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- To evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with GA secondary to AMD compared with sham control on the basis of the following endpoint:
  - Mean rate of change in the GA area, estimated based on GA area as measured by FAF at four timepoints: baseline, Week 24, Week 48, and Week 72
- To evaluate the efficacy of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W in patients with foveal-involving GA and in patients with non-foveal–involving GA compared with sham control on the basis of the following endpoints:
  - Mean change in the GA area from baseline to Week 72 as measured by FAF
  - Mean rate of change in the GA area, estimated based on GA area as measured by FAF at four timepoints: baseline, Week 24, Week 48, and Week 72

## 2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the local and systemic safety and tolerability of ITV injections of 20 mg FHTR2163 administered Q4W or Q8W relative to sham control on the basis of the following endpoints:

- Frequency, severity, and timing of ocular and systemic adverse events, serious adverse events, adverse events leading to study discontinuation, and adverse events of special interest (see Sections 5.2.3 and 5.3.3)

- Frequency, severity, and timing of notable findings in ocular examinations and ocular imaging, including those requiring intervention or start of anti-vascular endothelial growth factor (anti-VEGF) therapy
- Incidence of neovascular AMD diagnosed during the conduct of the study

## 2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the FHTR2163 PK profile 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 as follows: To evaluate potential relationships between drug exposure and the safety and efficacy of FHTR2163 on the basis of the following endpoints:

- Relationship between serum and/or aqueous humor concentration or PK parameters for FHTR2163 and efficacy endpoints
- Relationship between serum and/or aqueous humor concentration or PK parameters for FHTR2163 and safety endpoints

## 2.4 IMMUNOGENICITY OBJECTIVE

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 serum ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

## 2.5 BIOMARKER OBJECTIVES

The exploratory diagnostic biomarker objective for this study is to evaluate the efficacy of FHTR2163 as defined in the primary efficacy objective (see Section 2.1.1) in carriers versus non-carriers of the HtrA1 AMD risk variant rs10490924.

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, on the basis of the following endpoints:

- Relationship between biomarkers in blood and aqueous humor (listed in Section 4.5.8) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

- Relationship between retinal imaging measures (e.g., FAF, SD-OCT, optical coherence tomography angiography [OCT-A]) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, randomized, single-masked, sham-controlled study evaluating the safety, tolerability, and efficacy of 20 mg FHTR2163 dose administered Q4W or Q8W by ITV injections for approximately 76 weeks, in patients with GA secondary to AMD. Approximately 360 patients (144 patients in FHTR2163 Q4W arm, 72 patients in FHTR2163 Q8W arm, and 144 patients in pooled sham arm) will be enrolled in the study at approximately 77 investigational sites in the United States. Site investigators will be qualified ophthalmologists.

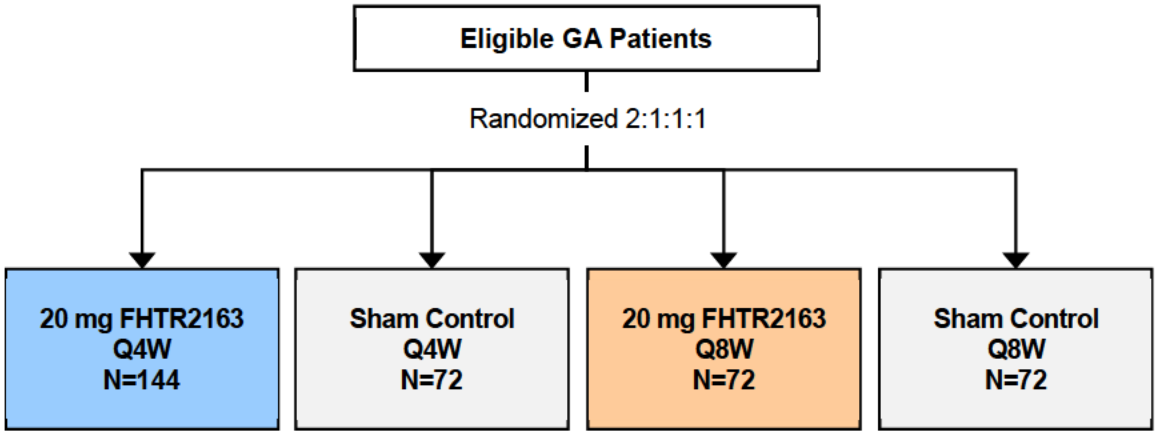
The study will consist of the following:

- Screening period of up to 120 days, divided into a prebaseline screening period (Day –120 to Day –31) and a baseline screening window (Day –30 to Day –1)
- Treatment period of up to 68 weeks (Day 1 to Week 68 for the Q4W treatment arms and Day 1 to Week 64 for the Q8W treatment arms)
- Primary analysis timepoint visit (Week 72)
- Final study visit (Week 76)

The duration of the study is approximately 76 weeks after the last patient is randomized to 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**




GA = geographic atrophy; N = number; Q4W = every 4 weeks; Q8W = every 8 weeks.

To be eligible for the study, patients must satisfy all eligibility criteria (see Section 4.1) at both the screening visit(s) and the Day 1 visit (i.e., day patient is enrolled and study drug is administered).

One essential eligibility criterion is that patients will be required to have two FAF images, a prebaseline image and a baseline image performed on a Heidelberg platform obtained at a minimum of ~3 months (84 days) and maximum of ~11 months (336 days) prior to the baseline screening visit. The prebaseline and baseline FAF images may be obtained in two different approaches as illustrated in Figure 2 and described below.

### No Preexisting FAF Image

Patients who do not have a preexisting FAF image available will have an FAF obtained along with all other prebaseline assessments listed in Appendix 1 and Appendix 2 to assess eligibility. This FAF image will be designated as the prebaseline FAF image. If the prebaseline FAF image is ungradable by the reading center, a repeat FAF image needs to be obtained within 30 days. Up to an additional 7 business days may be permitted for exceptional circumstances after consultation with and approval by the Medical Monitor. If prebaseline eligibility criteria for the FAF image (see Section 4.1) are met, the patient will enter the 90 (+30) day prebaseline screening period starting from the date the FAF image was obtained. The patient will then return to the clinic during the baseline screening window (Day –30 to Day –1) to perform the screening assessments (except for keratometry), including the baseline FAF image (see Appendix 1 and Appendix 2 and Figure 2).

### Preexisting FAF Image

Patients with a preexisting FAF image that was obtained on a Heidelberg platform and was obtained 84–336 days prior to the baseline screening visit may have the preexisting FAF image designated as the prebaseline FAF image, and the patient may proceed directly to the baseline screening window (Day –30 to Day –1) to obtain the baseline FAF image along with the other screening assessments (see Figure 2).

Any preexisting near infrared (NI) image obtained 84–336 days prior to the baseline screening visit should also be sent to the central reading center. Preexisting NI images are not necessary for eligibility and absence of a preexisting NI image(s) does not exclude a patient from screening.

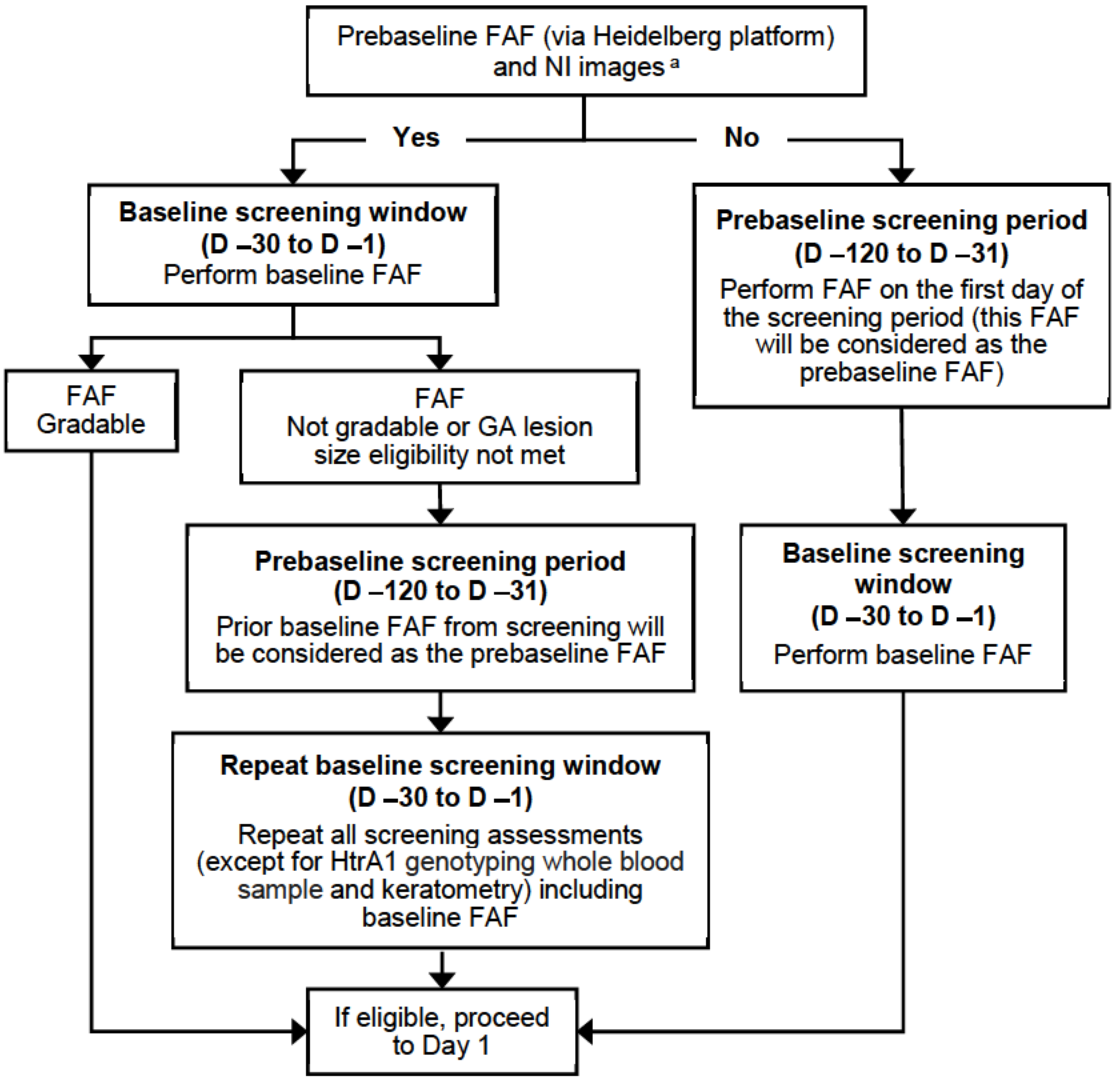
If patients have more than one preexisting FAF/NI image (obtained 84–336 days prior to the baseline screening visit), all such images should be sent to the central reading center.

In the event the preexisting FAF image is deemed not gradable by the central reading center or the measured GA lesion size is smaller than required ($< 2.54$ mm$^2$), the FAF image obtained during the baseline screening window will be considered the prebaseline image. If all other eligibility criteria are met (see Section 4.1), the patient will be allotted

an additional 90 (+30) days from the date that FAF image was obtained to return to the clinic. The patient then will repeat the baseline screening window assessments (except for HtrA1 genotyping whole blood sample and keratometry), including the baseline FAF (see Figure 2).

Prebaseline and baseline screening assessments may be completed on separate days provided that all assessments are captured within the prebaseline screening period (Day –120 to Day –30) or baseline screening window (Day –30 to Day –1), respectively. The baseline screening window may be extended for up to 7 business days for exceptional circumstances after consultation with and approval by the Medical Monitor. All prebaseline and baseline screening images (see Appendix 1 and Appendix 2 for details of images required) must be received and evaluated by the central reading center prior to the Day 1 visit.

**Figure 2 Prebaseline Image Collection Flowchart**




FAF = fundus autofluorescence; GA = geographic atrophy; HtrA1 = high-temperature requirement A1; NI = near infrared.

[a] Any preexisting NI image obtained 84–336 days prior to the baseline screening visit should also be sent to the central reading center. However, preexisting NI images are not required for eligibility.

Patients who fail screening may be eligible for rescreening up to three additional times during the enrollment period of the study. At rescreening, all screening visit assessments will be performed except for the whole blood sample for HtrA1 genotyping assay and keratometry, provided that a valid HtrA1 risk-variant carrier status result is available.

Eligible patients will be administered study drug or sham control on Day 1. Only one eye will be chosen as the study eye. If both eyes are eligible to become the study eye, the

eye with the worse visual function as determined by the investigator and the patient will be the study eye. If both eyes have the same visual function, the eye with the larger area of GA lesion will be selected as the study eye.

Eligible patients will be randomized in a 2:1:1:1 ratio such that approximately 144 patients will receive study drug treatment Q4W, 72 patients will receive sham-control treatment Q4W, 72 patients will receive study drug treatment Q8W, and 72 patients will receive sham-control treatment Q8W. Patients receiving Q4W dosing will receive a total of 18 treatments and patients receiving Q8W dosing will receive a total of 9 treatments.

Randomization will be stratified by HtrA1 risk-variant carrier status (HtrA1 risk-variant carrier vs. HtrA1 risk-variant non-carrier), baseline GA lesion size ($<$9.0 mm$^2$ vs. $\geq$9.0 mm$^2$), and annualized prebaseline GA progression rate (<1.9 mm$^2$/yr vs. $\geq$1.9 mm$^2$/yr). HtrA1 risk-variant carriers and HtrA1 risk-variant non-carriers may be enrolled in either FHTR2163 or sham-control arms.

After randomization on Day 1, patients will be administered the first ITV injection of FHTR2163 or sham control by the investigator. If a site has an unexpected issue (e.g., unable to assign the study kit), with the Medical Monitor's permission, the patient's first study treatment may be administered within 3 working days of the Day 1 visit. The following assessments will be repeated on the day of the study treatment: slit lamp examination, indirect ophthalmoscopy, and pre- and post-treatment intraocular pressure (IOP) measurement (and recorded on the Day 1 electronic Case Report Form [eCRF]).

Subsequent study treatment visits will be scheduled Q4W or Q8W relative to the Day 1 visit date. Study treatment should not occur earlier than 22 days after the previous treatment. Missed study treatments will not be made up.

At the subsequent visits, patients will have safety evaluations performed by the investigator prior to receiving study drug or sham control. Patient self-administered anti-microbials pre- and post-injection may be used at the investigator's discretion. Patients will be educated as to signs and symptoms of post-injection adverse events and instructed to contact the investigator at any time if they have any health-related concerns. All assessments for a scheduled visit will be performed on the same day, (with the exception of assessments performed during the prebaseline screening period or baseline screening window, which may be performed at any time during the 90-day or 30-day time frame, respectively). After the Day 1 visit, if a patient misses a study visit when ocular images are scheduled to be taken (see Appendix 1 and Appendix 2), the images must be obtained at the next scheduled visit.

Patients who are prematurely discontinued from study treatment (but have not withdrawn consent) will be encouraged to undergo as many scheduled visits as possible with emphasis on completing Week 72 visit.

Patients discontinued from the study prior to completion will be asked to return for an early termination visit after a minimum of 30 days have elapsed following the final study treatment for monitoring of adverse events and the early termination visit assessments. Early termination visits not completed after 6 months following the last treatment will be considered as “loss of follow-up” when appropriate.

### 3.1.1 Open-Label Extension Study and Study Follow-Up

After completing the study’s last visit (Week 76), eligible patients will have the option to enroll in an open-label extension study (GR42558) of GAllego and receive open-label FHTR2163 injections. The Week 76 visit will serve as the final visit for the GAllego study (GR40973) and the first (Day 1) visit for Study GR42558. Dosing frequency will remain consistent with each patient's dosing schedule in this study (i.e., Q4W or Q8W).

Patients who do not enter Study GR42558 will be contacted 7–10 days after the last visit by a follow-up call to elicit reports of any decrease in vision, eye pain, unusual redness, or other new ocular symptoms in the study eye.

### 3.1.2 Internal Monitoring Committee

An IMC will monitor safety and study conduct on an ongoing basis. 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 Agreement.

## 3.2 END OF STUDY AND LENGTH 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 76 weeks after the last patient is randomized to the study. In addition, the Sponsor may decide to terminate the study at any time.

## 3.3 RATIONALE FOR STUDY DESIGN

The primary efficacy objective of this Phase II study is an anatomic endpoint, specifically, the growth rate of GA lesion area based on FAF imaging (Biarnes et al. 2015). The anatomic primary endpoint provides a more sensitive, quantitative, and earlier metric of GA progression and serves as a surrogate for vision loss. The 76-week study length was designed because of the slow progressing nature of the disease and to maximize the opportunity to ascertain a treatment effect (Fleckenstein et al. 2018).

### 3.3.1 Rationale for FHTR2163 Dose and Schedule

To provide assessment of the relationship between dosing interval and efficacy, two FHTR2163 treatment arms will be evaluated in this Phase II study, a 20-mg dose administered ITV Q4W and a 20-mg dose administered ITV Q8W.

In the Phase I study (GR39821), 20 mg of FHTR2163 was the maximum dose tested and was administered ITV Q4W for three doses. The 20-mg dose and the Q4W interval were found to be well tolerated. The 20-mg dose administered Q4W allows evaluation of the highest exposure of FHTR2163.

The Q8W dosing regimen will be assessed to allow evaluation of a longer dosing interval, which is a major priority for patients, caregiver, 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 Q8W are maintained above the 50% inhibitory concentration of 3.58 nM established in a cynomolgus monkey PK/pharmacodynamic (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.

### 3.3.2 Rationale for Patient Population and Analysis Groups

Currently, there are no approved treatments to reverse, prevent, or reduce the progression of GA secondary to AMD and the associated decrease in visual function. Consequently, a significant unmet need exists for treatment of this serious condition.

This study will enroll a target population of patients with a diagnosis of GA secondary to AMD. Key eligibility criteria were selected to enrich the study population for patients with GA who may have more rapid growth of GA lesions to maximize the chances of detecting progression of disease and treatment effects over the planned study duration as well as to identify patients most likely to potentially benefit from the treatment. The key eligibility criteria and rationale for the criteria are presented below.

#### Evidence of Geographic Atrophy in Study Eye and Non-Study (Fellow) Eye

Bilateral GA represents the majority of the population (approximately 60%–67%) diagnosed with GA as reported in two natural history studies (Holz et al. 2007; Sunness et al. 2007) and has been associated with an increased rate of GA lesion growth compared with unilateral GA (Sunness et al. 2007).

#### Presence of Hyperautofluorescence Adjacent to the GA Area in the Study Eye (i.e., Banded or Diffuse Junctional Fundus Autofluorescence Patterns)

Holz et al. (2007) described four major perilesional FAF patterns (none, focal, banded, and diffuse) that were correlated with the rate of GA lesion growth in the longitudinal natural history arm of patients with GA secondary to AMD in the multicenter FAM study.

Holz reported that GA lesions with banded or diffuse junctional patterns expanded at a significantly higher rate than lesions with focal or no hyperautofluorescence. Of note, approximately 70% of the patients in the FAM study exhibited the banded or diffuse junctional perilesional FAF patterns. Furthermore, the diffuse-trickling pattern of FAF will be excluded due to a much faster progression rate relative to the other forms as well as the potential for being a distinct form of GA (Holz et al. 2007; Fleckenstein et al. 2014).

**Association between Baseline GA Lesion Size, Historical Rate of GA Progression, and Rate of GA Progression**

Sunness et al. (2007) reported that eyes with larger baseline GA area tended to have larger subsequent growth. This association was also suggested by Schmitz-Valckenberg et al. (2016). Sunness et al. (2007) also reported that the prior 2-year growth of GA was strongly correlated with the subsequent growth over 2 years. A similar correlation between prior growth rate and subsequent growth rate was also suggested in an analysis of lampalizumab Phase III Studies (GX29176 and GX29185) (unpublished data at Genentech).

### 3.3.3 Rationale for Sham-Control Group

A sham-control group will be used in this study to assess the differences in GA progression, change in clinical function measures, and safety in patients who receive FHTR2163 compared with patients who receive sham control. Patients randomized to the sham-control group will undergo the same assessments as patients randomized to the study drug ITV injection group.

Sham-control injections were chosen instead of placebo ITV injections to minimize the known risk of ITV injection-related adverse events (e.g., endophthalmitis) and because no potential patient value would be derived from an ITV injection of placebo.

### 3.3.4 Rationale for Pharmacokinetic and Pharmacodynamic Sampling Schedule

The PK sampling schedule enables characterization of the FHTR2163 concentration–time profile in serum and aqueous humor to understand both ocular and systemic PK properties after ITV administration.

The serum samples collected after dosing will characterize drug absorption from the eye as well as the subsequent elimination of FHTR2163 from the systemic circulation. Furthermore, the relationship between pharmacokinetics and pharmacodynamics will be explored in aqueous humor, and these data will be used to support selection of a recommended dose and dose regimen for future clinical trials.

The aqueous humor sampling schedule aims to characterize PD response throughout the treatment period with sampling times to assess change in PD response following multiple doses. In addition, aqueous humor sampling at Week 76 enables characterization of PD response at 8 weeks and 12 weeks following the previous dose for the Q4W and Q8W arms, respectively. See Appendix 1 and Appendix 2 for sampling schedule details.

### 3.3.5 Rationale for Biomarker Assessments

#### 3.3.5.1 Rationale for Aqueous Humor Samples

Biomarkers in aqueous humor may reflect aspects of pathology or treatment response that cannot be detected in blood (Kersten et al. 2018). In preclinical 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 and/or GA 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 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 visual acuity.

#### 3.3.5.2 Rationale for Plasma and Whole Blood Samples

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 after administration of FHTR2163 will be analyzed to evaluate response to FHTR2163. In addition, biomarker samples will be used in an effort to identify patients who may be more likely to respond to FHTR2163 for future studies.

Whole blood samples will be collected during screening for DNA extraction to enable polymerase chain reaction to identify HtrA1 risk-variant carrier status by genotyping assay (see Appendix 3). Whole blood samples will be collected at baseline to find potential genetic polymorphisms that may be predictive of response to study drug, may be associated with faster progression or progression to a more severe disease state, and may be associated with susceptibility to developing adverse events. At participating sites, this sample may also be used for next-generation sequencing (NGS) methods that may include whole genome sequencing (WGS) or whole exome sequencing (WES) (see Section 4.5.9.)

Aqueous humor, whole blood, 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.

#### 3.3.5.3 Rationale for Collection of Prebaseline FAF Images and Historical Ocular Images

In the general GA population, there is significant variability of GA growth rates. However, in the proposed study patient population, GA growth rates are approximately linear (Sunness et al. 2007; analysis of the lampalizumab Phase III Studies GX29176 and GX29185). Sunness et al. (2007) also reported that the prior 2-year growth of GA was strongly correlated with the subsequent growth over 2 years. A similar correlation between prior growth rate (3–11 month timeframe) and subsequent growth rate was also suggested in an analysis of lampalizumab Phase III Studies (GX29176 and GX29185) (unpublished data at Genentech).

On the basis of the analyses above, prebaseline GA growth rates have the potential to be used as a stratification variable to increase the confidence in study analyses by incorporating GA growth rates as a prognostic variable. The collection and analysis of prebaseline FAF will enable quantification of prebaseline GA growth rates.

Historical ocular images will be used to evaluate correlation between a prior growth rate of a duration $>$11 months to subsequent growth rate.

#### 3.3.5.4 Rationale for HtrA1 Risk-Variant Genotyping Assay

Patients will be stratified at enrollment on the basis of carrier versus non-carrier status using the HtrA1 risk-variant genotyping assay for the single nucleotide polymorphism rs10490924 (see Appendix 3). rs10490924 is established as one of the most significant genetic risk factors for advanced AMD (Fritsche et al. 2016) and the response to FHTR2163 treatment will be evaluated in carrier versus non-carrier subgroups.

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Approximately 360 patients with GA secondary to AMD will be enrolled in this study at approximately 77 investigative sites located in the United States.

#### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

**General Inclusion Criteria**

- Signed Informed Consent Form
- Age $\geq$60 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- 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 at least 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 ($\geq 12$ 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.

- Ability and willingness to undertake all scheduled visits and assessments

**Ocular Inclusion Criteria: Study Eye**

One eye will be designated as the study eye. If both eyes meet the following criteria, the eye with the worse VA and/or least function (as determined by the investigator and patient) will be selected for study treatment (study eye). If both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye.

- Visual acuity: BCVA letter score of $\geq 24$ letters (Snellen equivalent of 20/320 or better) using ETDRS chart at starting distance of 4 m

  If the study eye BCVA letter score is $\geq 69$ letters (Snellen equivalent of 20/40 or better), the non-study eye must have a BCVA letter score of $\geq 44$ letters (Snellen equivalent of 20/125 or better).

- Well-demarcated area of GA secondary to AMD with no evidence of prior or active CNV

- Prebaseline FAF image obtained via a Heidelberg platform 84–336 days prior to the screening visit that meets the following criteria:
  - Total GA lesion size must be ≥2.54 $mm^2$ (approximately ≥1 disc area [DA]) and ≤17.78 $mm^2$ (approximately ≤7 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea)

    If GA is multifocal, at least 1 focal lesion must be ≥1.27 $mm^2$ (approximately ≥0.5 DA).
  - Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to GA area

    Note: Diffuse-trickling pattern is excluded.
- Baseline FAF image obtained during the baseline screening window (Day –30 to Day –1) must meet the following criteria:
  - Total GA lesion size must be ≥2.54 $mm^2$ (approximately ≥1 DA) and ≤25.4 $mm^2$ (approximately ≤10 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea).

    If GA is multifocal, at least 1 focal lesion must be ≥1.27 $mm^2$ (approximately ≥0.5 DA).
  - Presence of hyperautofluorescence of either banded or diffuse patterns adjacent to GA area

    Note: Diffuse-trickling pattern is excluded.
- Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging
- Ocular anatomy that would allow for safe and uneventful collection of approximately 100 μL aqueous humor sample in the opinion of the investigator

**Ocular Inclusion Criteria: Non-Study Eye**

- GA secondary to AMD with no evidence of prior or active CNV
- 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).

### 4.1.2 Exclusion Criteria

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

**GA Characteristics Exclusion Criterion**

- GA in either eye due to causes other than AMD (monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy])

**Ocular Exclusion Criteria: Study Eye**

- Absence of any hyperfluorescence pattern (none) adjacent to GA area in the study eye
- Presence of diffuse-trickling, patchy, or minimal (focal) hyperfluorescence pattern adjacent to GA area in the study eye
- Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could result in either of the following:
  - Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
  - If allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of BCVA during the study period
- Intraocular surgery, including cataract surgery, in the study eye within 3 months prior to Day 1
- Uncontrolled glaucoma in the study eye, defined as IOP $\geq$30 mmHg despite treatment with anti-glaucoma medication
- Current vitreous hemorrhage in the study eye
- Aphakia or absence of the posterior capsule in the study eye
- Previous laser photocoagulation or ITV anti-VEGF for CNV, diabetic macular edema, retinal vein occlusion, or proliferative diabetic retinopathy
- Prior treatment with photodynamic therapy, external-beam radiation therapy (for intraocular conditions), or transpupillary thermotherapy
- Any posterior segment device or implant (e.g., any type of corticosteroid implant/device, encapsulated cell therapy, or Argus® II Retinal Prosthesis System)
- ITV, subtenon, or topical (ocular) corticosteroids within 3 months prior to randomization

  A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.
- History of vitrectomy surgery, submacular surgery, or any surgical intervention for AMD
- History of prophylactic subthreshold laser treatment for AMD
- History of glaucoma-filtering (trabeculectomy, valves, or minimally invasive glaucoma stents) surgery in the study eye
- History of corneal transplant in the study eye
- History of retinal tear in the study eye

  Patient may be permitted after appropriate treatment and subsequent determination of stability by the investigator.

  History of retinal detachment or macular hole (Stage 3 or 4) in the study eye

- Any concurrent ocular or intraocular conditions that contraindicate the use of an investigational drug, 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.
- Previous violation of the posterior capsule in the study eye unless it occurred as a result of yttrium aluminum garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
- Spherical equivalent of the refractive error in the study eye demonstrating $>$8 diopters of myopia
- For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 8 diopters of myopia.

**Ocular Exclusion Criteria: Non-Study Eye**

- Non-functioning non-study eye defined as either:

    BCVA of hand motion or worse
    OR
    No physical presence of non-study eye (i.e., monocular)

**Ocular Exclusion Criteria: Both Eyes**

- 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 ocular melanoma in either eye
- Active or history of CNV in either eye
- Active or history 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

    Note: Mild non-proliferative diabetic retinopathy (e.g., occasional hemorrhage or microaneurysm) in either eye may be permitted at the discretion of the investigator. Moreover, a patient with the onset of mild non-proliferative diabetic retinopathy in either eye during study participation may be permitted to continue study treatment at the discretion of the investigator.
- Proliferative diabetic retinopathy in either eye
- Central serous retinopathy in either eye

- Previous participation in an interventional clinical trial for GA or dry AMD trial that tested stem cell treatments, gene therapy, long-acting delivery platforms/formulations (e.g., biodegradable/non-biodegradable implants or formulations, device implant, encapsulated cell technologies), or inhibitors/modulators of the visual cycle (e.g., fenretinide, emixustat) regardless of timing of patient participation
- Previous participation in interventional clinical trials for GA or dry AMD, except for vitamins and minerals, regardless of the route of administration (i.e., ocular or systemic) within the last 6 months

  Note: If patient participation in an interventional clinical trial for GA or dry AMD was >6 months prior to screening, the patient may be eligible for the trial at the discretion of the investigator.
- History of recurrent infectious or inflammatory ocular disease in either eye
- History of idiopathic or autoimmune-associated uveitis in either eye

**Concurrent Systemic Conditions Exclusion Criteria**

- Uncontrolled blood pressure, defined as systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg while patient is sitting

  If a patient's initial measurement exceeds these values, a second reading may be taken 30 or more minutes later. If the patient's blood pressure must be controlled by antihypertensive medication, the patient can be eligible if medication is taken continuously for at least 30 days prior to Day 1.
- History of cerebral vascular accident or transient ischemic attack
- History of other diseases, 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
- Active cancer within past 12 months except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a Gleason score of <6 and a stable prostate-specific antigen for >12 months
- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the investigational drug injection
- Previous participation in any studies of investigational drugs within the last 6 months, excluding vitamins and minerals

  If patient participation in a clinical trial was >6 months prior to screening, the patient may be eligible for the study at the discretion of the investigator.
- Requirement for continuous use of any medications/treatments indicated as a prohibited therapy in this study (see Section 4.4.2)
- Medical conditions that may be associated with a clinically significant risk for bleeding

- 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 serum pregnancy test result within 28 days 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

After written informed consent has been obtained, all patients will receive a screening number assigned through the interactive web-based response systems (IWRS). A patient must satisfy all eligibility criteria (see Sections 4.1.1 and 4.1.2) at both the screening and the Day 1 visit (first study treatment) prior to randomization. As part of the screening process, the central reading center (masked to patient treatment assignment) will evaluate FAF, color fundus photograph (CFP), NI, SD-OCT, and OCT-A (if available) images to provide an objective assessment of patient eligibility. After all patient eligibility requirements are confirmed, site personnel will contact the IWRS during the Day 1 visit to randomize the patient. Patients will be randomized in a 2:1:1:1 ratio to one of the study treatment arms (FHTR2163 Q4W, sham control Q4W, FHTR2163 Q8W, or sham control Q8W). The study treatment kit number will also be assigned by IWRS at that time. Patients will be randomized on the same day the study treatment is to be initiated (Day 1 visit). Randomization will be stratified by HtrA1 risk-variant carrier status (HtrA1 risk-variant carrier vs. HtrA1 risk-variant non-carrier, as determined by HtrA1 risk-variant genotyping assay; see Appendix 3), baseline GA lesion size ($<9.0$ mm$^2$ vs. $\geq 9.0$ mm$^2$), and annualized prebaseline GA progression rate (<1.9 mm$^2$/yr vs. $\geq 1.9$ mm$^2$/yr).

Details of the randomization procedure will be described in the Data Analysis Plan (DAP).

### 4.2.2 Masking

This is a single-masked study with patients masked to their treatment assignment (study drug vs. sham control). The BCVA examiner will also be masked to the study eye and treatment assigned. The BCVA examiner will only be permitted to perform the refraction, BCVA assessment, and pretreatment IOP measurement. The BCVA examiner will also be masked to the BCVA scores from the patient's previous visits and may only have access to a patient's refraction data from previous visits. Other site study staff will not be masked to the patient treatment assignments.

The central reading center review team, consisting of graders and ophthalmologists experienced in the conduct of clinical trials, will be masked to patients' treatment assignment. They 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 (CRO) personnel, including clinical research associates, will not be masked to the patient treatment assignments.

Sponsor personnel (except for IMC members) will be masked to treatment assignment until after database lock, unless there is a need to unmask as determined by the IMC. Furthermore, 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). Additionally, 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.

Patients will be masked to HtrA1 risk-variant carrier status.

Patients, site study investigator and staff (study coordinators, etc.), and Sponsor personnel (except for IMC members) will be masked to prebaseline GA growth rate unless there is a need to unmask as determined by the IMC.

## 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, Packaging, and Handling

FHTR2163 will be supplied by the Sponsor as a sterile lyophilized powder for reconstitution. Detailed instructions for reconstitution and dilution are provided in the pharmacy manual.

For information on the formulation and handling of FHTR2163, see the FHTR2163 Investigator's Brochure and pharmacy manual.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

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

Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.14.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.5.

#### 4.3.2.1 FHTR2163 and Sham Control

On Day 1, patients will be randomized in a 2:1:1:1 ratio to one of the study treatment arms (FHTR2163 Q4W, sham control Q4W, FHTR2163 Q8W, or sham control Q8W). The first ITV injection of 20 mg FHTR2163 or sham control will be conducted by investigators on the same day as randomization (i.e., Day 1).

Subsequent study treatment visits will be scheduled Q4W or Q8W relative to the Day 1 visit date.

### 4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of the IMP supplied by the Sponsor per agreed method (e.g., returning the appropriate documentation form or updating IWRS) by the study team. Any damaged shipments will be replaced.

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 (if supplied by 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 (or Sponsor representative) 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 Inventory Log.

### 4.3.4 Continued Access to FHTR2163

Patients may be eligible to receive FHTR2163 as part of an open-label extension study offered by the Sponsor (Genentech, a member of the Roche Group), as described in Section 3.1.1. The Roche Global Policy on Continued Access to Investigational Medicinal Product is 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 preparations) other than protocol-specified procedural medications (e.g., dilating drops) and pre- and post-injection medications (e.g., proparacaine) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug (Day 1) to the study completion/discontinuation 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. Patients who use other maintenance therapies should continue their use. Of note, the following are some common therapies that are permitted:

- Onset of ocular hypertension or glaucoma in the study eye during study participation should be treated as clinically indicated
- Onset of cataract or posterior capsular opacification in either eye during study participation may be treated as clinically indicated

  Dose-interruption criteria (see Section 5.1.5 and Table 1) may apply with cataract surgery.
- 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 neovascular AMD (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

At the discretion of the investigator, patients may continue to receive medications and standard treatments administered for other conditions. However, the following medications/treatments 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 intravenous 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/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.

See Appendix 1 and Appendix 2 for the schedules of activities performed for Q4W and Q8W arms, respectively.

### 4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations and evaluations at Day 1 must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 4.5.2 Medical History and Demographic Data

Medical history, including clinically significant diseases, surgeries, chronic and ongoing conditions, (e.g., trauma, cancer, cardiovascular, and ophthalmic history), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment (Day 1 visit) will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

### 4.5.3 Physical Examinations

A targeted physical examination should include an evaluation of the head, eyes, ears, nose, throat, and cranial nerves. A patient's height and weight will be measured as well. Any abnormality identified at baseline 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.

### 4.5.4 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. Vital signs should be taken during visits as indicated (see Appendix 1 and Appendix 2).

### 4.5.5 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 ETDRS chart at a starting distance of 4 m (see Appendix 4)

  Perform prior to dilating eyes; please refer to instruction manual provided by Clinical Edge.

- Low-luminance BCVA assessment as determined by ETDRS chart at a starting distance of 4 m (see Appendix 5) under low-luminance conditions

  Perform prior to dilating eyes; please refer to instruction manual provided by Clinical Edge.

- Pre-injection IOP measurement of both eyes

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

- Slit lamp examination

  Perform prior to dilating eyes; for grading scales for anterior and vitreous cells, see Appendix 6.

- Dilated binocular indirect high-magnification ophthalmoscopy
- Finger-counting test followed by hand motion and light perception tests (when necessary) performed within 15 minutes post-injection for the study eye (see Appendix 7)
- At study treatment visits, post-injection IOP will be measured between 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 $\geq$10 mmHg from 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 intraocular pressure). The method of IOP measurement used for a patient must remain consistent throughout the study.

### 4.5.6 Ocular Imaging

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

- Digital CFPs of both eyes (see Appendix 8)
- FAF (with keratometry measurements) images of both eyes (see Appendix 9)
- NI images of both eyes (see Appendix 10)
- SD-OCT images of both eyes (see Appendix 11)
- OCT-A images of both eyes (for sites with OCT-A capabilities) (see Appendix 12)

Historical ocular images are defined as FAF and SD-OCT (study eye and/or non-study eye) images obtained during the 5-year period prior to the screening visit excluding those used for prebaseline FAF (see Section 3.1). Historical ocular images may be collected and submitted to the central reading center any time after enrollment into the study.

Additional details on obtaining these images are included in the Central Reading Center Manual.

### 4.5.7 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.

### 4.5.8 Laboratory, Biomarker, and Other Biological Samples

At scheduled visits, specimens should be collected prior to study eye treatment. Fasting is not required prior to specimen collection. The specimens will be forwarded to the central laboratory. The central laboratory will either perform the analysis or forward samples to Sponsor or its designee for analysis and/or storage. Instructions for obtaining, processing, storing, and shipping of all specimens are provided in the laboratory manual. Laboratory supply kits will be provided to the sites by the central laboratory. See Appendix 1 and Appendix 2 for sample collection timepoints.

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 serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Serum samples for measurement of anti-FHTR2163 antibodies (ADAs)
- Serum samples to measure FHTR2163 concentration
- Aqueous humor samples to measure FHTR2163 concentration
- Aqueous humor samples for determination of biomarkers related to HtrA1 activity and disease progression
- Plasma samples for exploratory research on biomarkers related to HtrA1 and GA
- Screening whole blood sample for polymerase chain reaction genotyping of HtrA1 risk-variant carrier status (rs10490924)
- Whole blood clinical genotyping sample for genomic research aimed at exploring inherited genome variations associated with AMD and the response to study drug. Analysis may include targeted single-nucleotide polymorphism genotyping or sequencing for rare variants. At participating sites, this sample may also be used for NGS methods that may include WGS or WES (see Section 4.5.9).

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 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples and aqueous humor collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, serum 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 (IRB)/Ethics Committee (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.

### 4.5.9 Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS, this section of the protocol (Section 4.5.9) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provide a comprehensive characterization of the genome 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 will be analyzed in the context of this study but will 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.

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

Refer to Section 4.5.8 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

### 4.5.10 Optional Samples for Research Biosample Repository

#### 4.5.10.1 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 biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens 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, adverse events, or disease progression
- To increase knowledge and understanding of disease biology

- 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

#### 4.5.10.2 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 4.5.10) will not be applicable at that site.

#### 4.5.10.3 Sample Collection and Storage Timeline

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 WGS, 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).

#### 4.5.10.4 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.

#### 4.5.10.5 Consent to Participate in the Roche 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 RBR Research Sample Informed Consent 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.

#### 4.5.10.6 Withdrawal from the Roche 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 RBR Research Sample Withdrawal of Informed Consent 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.

#### 4.5.10.7 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 withdrawn from the study prior to completion will be asked to return for an early termination evaluation after a minimum of 30 days following his or her final study treatment for monitoring of adverse events and assessments listed for the early termination visit (see Appendix 1 and Appendix 2). The reason for the discontinuation should be recorded on the appropriate eCRF. Discontinued patients will not be replaced or allowed to re-enter the study.

Patients who discontinued treatment will not be allowed to re-start the 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 discontinued or withdrawn from study will return to the clinic for a study discontinuation visit after a minimum of 30 days following his or her final study treatment (see Appendix 1 and Appendix 2).

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.

If a patient discontinued the study but has not withdrawn the informed consent, the site should make every effort to continue to follow up on serious adverse events, deaths, and adverse events of special interest in these patients.

### 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:

- 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 nonclinical toxicology and safety studies have revealed minimal ocular inflammation that demonstrated complete or partial recovery. No systemic adverse effects were observed in nonclinical studies. 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. See Section 1.3.2 and the FHTR2163 Investigator's Brochure for further details.

Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. Ongoing review of unmasked safety data will be performed by an IMC (see Section 3.1.2).

The safety plan for patients in this study is based on nonclinical studies, the anticipated mechanism of action, and clinical experience with the completed FHTR2163 Phase I study, GR39821. The anticipated important safety risks for FHTR2163 are outlined below.

### 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 FHTR2163 Phase I clinical study (GR39821), there was one patient with 2 nonserious 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 of serious case of uveitis; and nonserious 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 BCVA, detailed ocular examinations, including slit lamp examinations and indirect ophthalmoscopy, as well as SD-OCT imaging at most study visits to evaluate any potential ocular adverse event. A follow-up call 14 ($\pm$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.

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

An IMC will review unmasked data on a regular basis to assess for any imbalances in rates of ocular inflammation across different treatment arms (see Section 3.1.2 and the IMC Agreement for further details).

### 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 noninfectious 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.

Dose interruption and treatment discontinuation criteria for 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 based on 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; see Section 1.3.2) 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 the systemic concentrations of FHTR2163 following ITV administration of 20 mg, complete inhibition of systemic HtrA1 is not expected.

Furthermore, there is a rare human disease, characterized by complete loss of HtrA1 activity due to a loss of function mutation in the HTRA1 gene, called cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). The main clinical manifestations of CARASIL are ischemic stroke or stepwise deteriorations in brain functions, progressive dementia, premature baldness, and attack of severe low back pain or spondylosis deformans/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.

As part of the safety plan, masked aggregate adverse event reports will be reviewed periodically to assess for any potential systemic safety effect with specific focus on adverse events that may be related CARASIL signs and symptoms, and an IMC will review unmasked data on a regular basis to assess for any imbalances in rates of adverse events across different treatment arms (see Section 3.1.2 and the IMC Agreement for further details).

### 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 6 for anterior chamber and vitreous inflammation grading scales), 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. See Section 5.1.5 for details on management and Table 1 for instructions concerning dose-interruption and treatment discontinuation criteria.

An IMC will review unmasked data on a regular basis to assess for any imbalances in rates of adverse events due to ITV injections across different treatment arms (see Section 3.1.2 and the IMC Agreement for further details).

### 5.1.3 Risks Associated with Aqueous Humor Sampling through Anterior Chamber Paracentesis

Sampling of aqueous humor through anterior chamber paracentesis is a valuable procedure in providing samples for assessment of ocular PK and PD parameters of FHTR2163. 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 14 for anterior chamber paracentesis and aqueous humor sampling procedures), and patients will be monitored closely for occurrence of any potential adverse event associated with the procedure.

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

Following the study drug injection, patients will remain at the clinic for at least 30 minutes. 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 from 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. For guidance on adverse event reporting, see Section 5.3.5.2. During each drug administration visit, finger counting will be tested within 15 minutes after study drug injection by the investigator; hand motion and light perception will be tested when necessary.

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 Table 1 and Section 5.1.5 for instructions concerning dose-interruption and treatment discontinuation criteria, and management of IOI.

### 5.1.5 Dose-Interruption and/or Treatment Discontinuation Criteria

Study-treatment interruption and patient discontinuation from the study treatment for adverse events will be determined using the 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 Sections 5.2–5.6.

In addition, for any patient who develops any of the exclusion criteria (Section 4.1.2) after study onset, dosing may be interrupted or the patient may be discontinued from study treatment after discussion with the Medial 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 Dose Interruption and Treatment Discontinuation Criteria and Management**

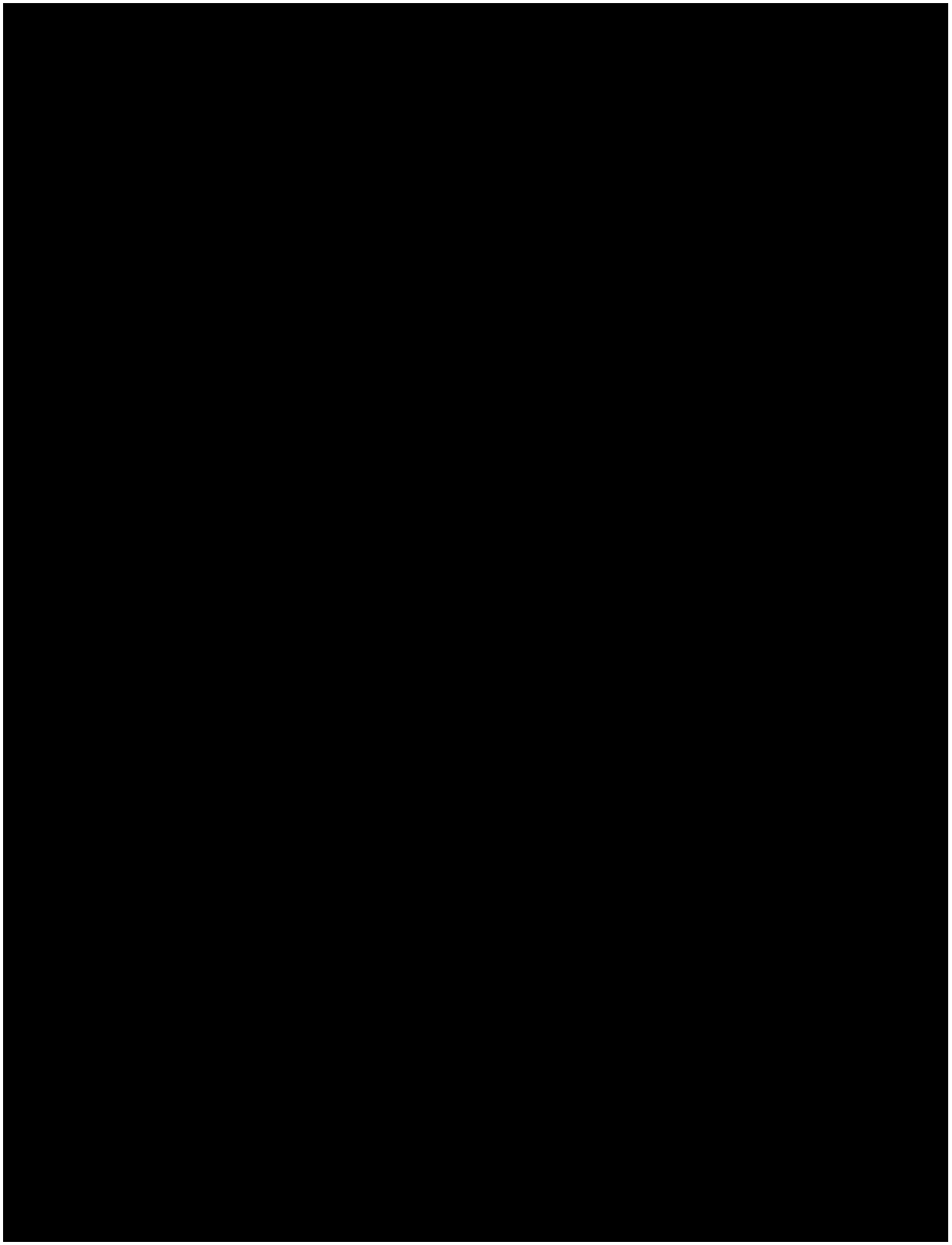
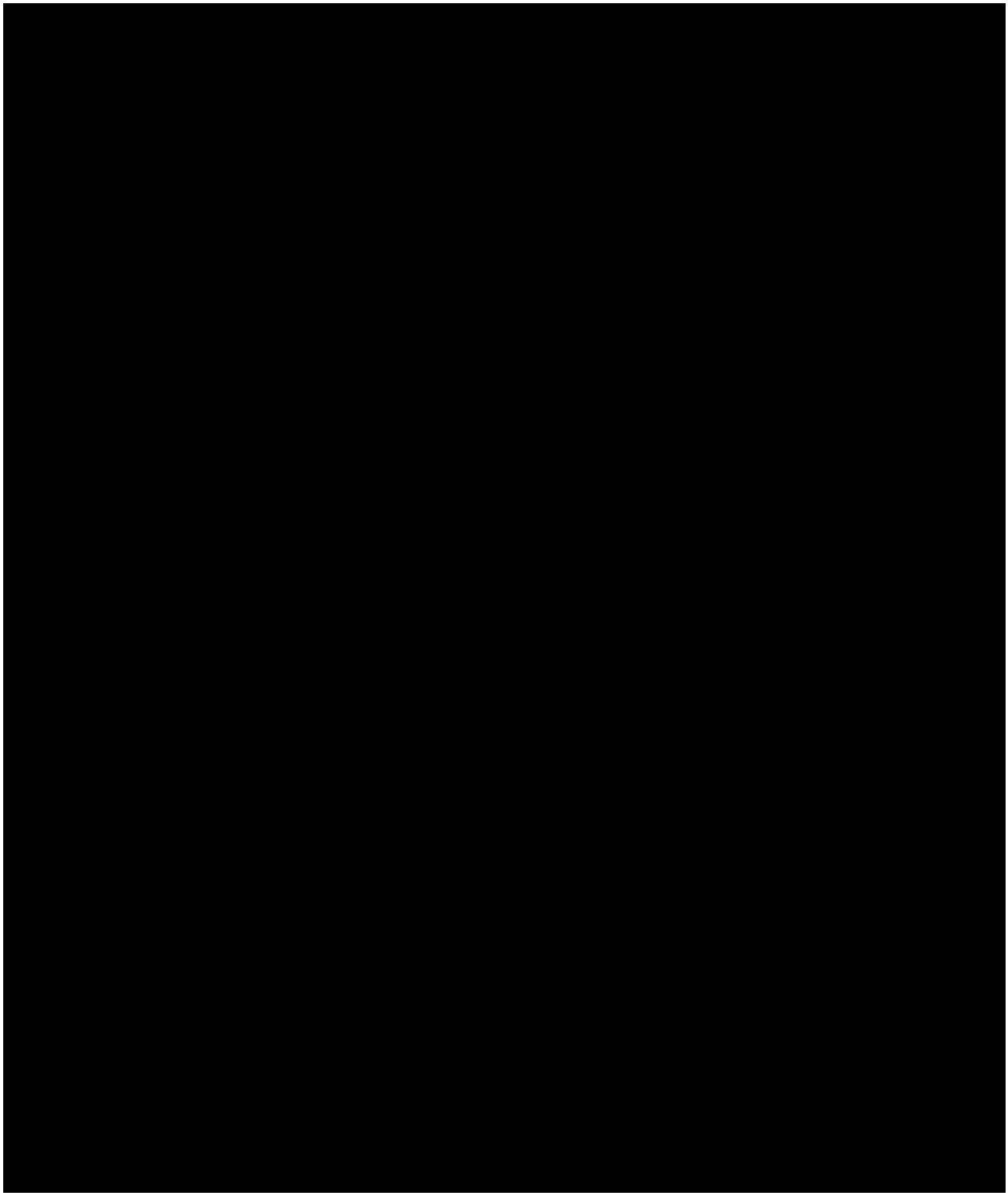


**Table 1 Dose Interruption and Treatment Discontinuation Criteria (cont.)**



## 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 patient 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 Section 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 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

### 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 patient 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 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 (if known) of the event 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 of ≥30 letters in VA score, compared with the most recent prior VA 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, Table 1 for dose-interruption and treatment-discontinuation criteria, and Appendix 6 for IOI grading scales).

  An additional 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:

- Loss of VA ≥30 letters, compared with the last assessment of VA prior to the most recent assessment, lasting more than 1 hour due to study drug treatment
- 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–Section 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 15) 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 6).

**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.<br>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: the presence of inflammatory cells in the anterior chamber

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

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

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

- 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 red blood cells, white blood cells, or the result of any ocular disorder should not be recorded as an adverse event.

#### 5.3.5.2 Increased Intraocular Pressure Values

The observation of elevated IOP values measured between 30–50 minutes post-injection, in general, should not be reported as an adverse event. Elevated IOP values measured between 30– 50 minutes post-injection should be reassessed at 60–80 minutes post-injection prior to reporting an adverse event. Medical and scientific judgment should be exercised in deciding if an elevated IOP at 30–50 minutes post-injection that remains elevated at the follow-up 60–80 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 (i.e., 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 Sections 5.2.2 and 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 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., 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 (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should 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 5.3.5.4) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event (see Section 5.2.2) or adverse event of special interest (see Section 5.2.3).

#### 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 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 the study eye GA secondary to AMD.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events.

#### 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, 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 or sham control, 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 (i.e., wrong drug), 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 administered, 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), United States of America

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 immediately (i.e., no more than 24 hours after learning of the event) on the Adverse Event eCRF and the report submitted 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 below:

| | |
|---|---|
| Email address: | RTPSafety@ppdi.com |
| Fax No.: | +1 888 529 3580 |

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events, adverse events of special interest, should be reported within 24 hours after learning of the event until the final study visit (Week 76). 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 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 in Section 5.4.2.1. 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 after the final study visit (Week 76) 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 in Section 5.4.2.1. 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 paper 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 Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided below:

Email address: us_drug.safety@gene.com

Fax No.: +1 650 225 4682

## 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 using the following reference document:

- 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

The analysis of data for the 76-week study period will be performed when all randomized patients have either completed the 76-week study period or have discontinued from the study prior to Week 76, all data from this period are in the database, all data have been cleaned and verified, and the database is locked.

Detailed specifications of the statistical methods will be described in the DAP.

## 6.1 DETERMINATION OF SAMPLE SIZE

This study is designed to evaluate the efficacy of FHTR2163 administered ITV Q4W and Q8W to patients with GA secondary to AMD. The focus of the efficacy outcome analyses will be on estimation of the magnitude of the treatment effect.

The primary efficacy endpoint is the mean change in GA area from baseline to Week 72 as measured by FAF. The sample size provides reasonable precision for estimation of the treatment effect with respect to the primary endpoint.

Approximately 360 patients will be randomized in a 2:1:1:1 ratio to one of four treatment groups: FHTR2163 Q4W, sham control Q4W, FHTR2163 Q8W, or sham control Q8W. Patients in the sham control Q4W and sham control Q8W groups will be pooled in the analyses.

Assuming a 15% dropout rate by Week 72 and a standard deviation of 1.82 $mm^2$ for change from baseline in GA area at Week 72 (estimated from the lampalizumab Phase II Study CFD4870g and the Phase III Studies GX29176 and GX29185), 114 patients in the FHTR2163 Q4W arm and 114 patients in the pooled sham-control group will provide 80% power to detect a targeted difference of 0.56 $mm^2$ (20% reduction relative to sham control) in the change from baseline in GA area at Week 72 between the FHTR2163 Q4W arm and the pooled sham-control arm. Calculations were based on two-sided t-test at the significance level of 20% and resulted in a total sample size of 285. No multiplicity adjustment is planned for this study.

A total of 131 patients had enrolled in this study as of 10 April 2020. As a result of the increase in missed visits, missed dosing, and missed assessments as a consequence of the COVID-19 pandemic, up to approximately 75 patients will be enrolled in addition to the originally planned 285 patients to help mitigate the potential impact on treatment effect and data.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The clinical database will be used to assess study conduct. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study treatment discontinuation and study discontinuation, any eligibility criteria deviation, and other major protocol deviations will also be tabulated.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (e.g., age, sex, race), baseline safety (e.g., baseline vital signs and laboratory test results), and baseline disease characteristics (e.g., baseline GA area, baseline BCVA, annualized prebaseline GA growth rate) will be summarized for all randomized patients by treatment group using descriptive statistics.

## 6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be based on the modified intent-to-treat population (see DAP for detailed definition). Patients will be grouped according to the treatment assigned at randomization. Patients in the sham control Q4W and sham control Q8W groups will be pooled in the analyses.

If not otherwise specified, analyses of efficacy outcome measures will be stratified by HtrA1 risk-variant carrier status (HtrA1 risk-variant carrier vs. HtrA1 risk-variant non-carrier, as determined by the HtrA1 risk-variant genotyping assay; see Appendix 3), baseline GA lesion size ($<9.0$ mm$^2$ vs. $\geq 9.0$ mm$^2$), and annualized prebaseline GA progression rate (<1.9 mm$^2$/yr vs. $\geq$1.9 mm$^2$/yr). A data-as-observed approach with the mixed-effect model will be used to handle missing data in the primary analysis. Sensitivity analyses will be performed to evaluate the effect of missing data on the results (see DAP for details).

### 6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change in GA area from baseline to Week 72 as measured by FAF.

Comparison of each active arm versus the pooled sham-control arm will be assessed using a linear mixed-effect model with an effect for treatment and with covariate adjustments for baseline factors such as HtrA1 risk-variant carrier status, baseline GA lesion size, and annualized prebaseline GA progression rate. The primary analysis will be based on all available data up to 72 weeks, with no imputation for missing data. Two-sided 80% confidence interval will be provided for the estimated treatment effects. Hypothesis testing will be conducted at the two-sided significance level of 20%, and no multiple-testing adjustment is planned.

Detailed specifications of the statistical methods will be described in the DAP.

### 6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Mean change in BCVA score from baseline to Week 72 as assessed by ETDRS chart under low-luminance conditions
- Mean change in BCVA score from baseline to Week 72 as assessed by ETDRS chart

The secondary endpoints will be analyzed in a similar manner as the primary endpoint, using a linear mixed-effect model. Additional details regarding the analysis of secondary and exploratory efficacy endpoints will be provided in the DAP.

## 6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one FHTR2163 injection or sham control, with patients grouped according to treatment received. Safety summaries will be presented for all treated patients.

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

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

## 6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of any patient who has at least one FHTR2163 concentration data point. Individual and mean serum and aqueous humor FHTR2163 concentration versus time data will be tabulated and plotted by treatment arm. The serum and aqueous humor pharmacokinetics of FHTR2163 will be summarized by estimating total exposure (area under the concentration–time curve), maximum concentration, and elimination rate as data allow. Estimates for these parameters will be tabulated and summarized. Interpatient variability will be evaluated. Additional PK analyses will be conducted as appropriate.

## 6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

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 group.

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

## 6.8 BIOMARKER ANALYSES

The primary efficacy analysis described in Section 6.4 will be repeated in the HtrA1 risk-variant carrier and non-carrier subgroups as an exploratory analysis. 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.

## 6.9 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed by the unmasked IMC and will be interpreted by the IMC and appropriate senior management personnel. Access to treatment assignment information will follow the Sponsor's standard procedures. The details of the timing and scope of the interim analysis, if any, will be specified in the IMC Agreement.

# 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. Food and Drug Administration 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.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. 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 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 3.2).

# 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 CRO will manage the study, site monitoring, and selected vendors. Genentech will oversee the CRO.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in

Section 4.5.8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

An IWRS will be used for patient screening and randomization and for 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 by an EDC system using eCRFs or forwarded to Sponsor electronically (e.g., safety lab data). A central reading center will be used for ocular imaging analyses (e.g., FAF, NI, CFP, OCT-A, and SD-OCT) that will be forwarded to Sponsor electronically.

## 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, provided the requirements of Roche's global policy on data sharing have been met. 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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# Appendix 1
# Schedule of Activities: Q4W Arm

| | PreBL | BL | Day | | Week Visit | | | | | | | | | | | | | | | | | | UV | Early |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Scrn [a] | Scrn [b] | 1 | 8 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 [c] | | |
| Assessment Windows (Days) | –120 to –31 | –30 to –1 | — | ±2 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | | Term [d] |
| Written informed consent [e] | x | x | | | | | | | | | | | | | | | | | | | | | | | |
| Review of inclusion and exclusion criteria | x | x | x | | | | | | | | | | | | | | | | | | | | | | |
| Medical and surgical history including tobacco history [f] | | x | | | | | | | | | | | | | | | | | | | | | | | |
| Demographic information [g] | | x | | | | | | | | | | | | | | | | | | | | | | | |
| Historical image collection [h] | | | x | | | | | | | | | | | | | | | | | | | | | | |
| PreBL FAF and NI image collection [i, j] | | x | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization (IWRS) [k] | | | x | | | | | | | | | | | | | | | | | | | | | | |
| Physical examination | | x | | | | | | | | | | | | | | | | | | | | | x [l] | x | |
| Vital signs [m] | x | x | x | | | | | | | | | | | | | | | | | | | | x [l] | x | |
| Hematology, coagulation, lipids, serum chemistry (central laboratory) [n] | | x | | | | | | | | | | x | | | | | | | | | | x | x [l] | x | |
| Urine pregnancy test [o] | | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | | | x [l] | |
| Serum pregnancy sample [p] | | x | | | | | | | | | | | | | | | | | | | | | | | |
| Whole blood sample for HtrA1 genotyping | | x | | | | | | | | | | | | | | | | | | | | | | | |
| Plasma sample for biomarker | | | x | | | | | | | | | | | | | x | | | | | | x | x | x [l] | x |

## Appendix 1: Schedule of Activities: Q4W Arms

| Assessment Windows (Days) | PreBL Scrn [a] –120 to –31 | BL Scrn [b] –30 to –1 | Day 1 — | Day 8 ±2 | Week Visit 4 ±5 | 8 ±5 | 12 ±5 | 16 ±5 | 20 ±5 | 24 ±5 | 28 ±5 | 32 ±5 | 36 ±5 | 40 ±5 | 44 ±5 | 48 ±5 | 52 ±5 | 56 ±5 | 60 ±5 | 64 ±5 | 68 ±5 | 72 ±5 | 76 [c] ±5 | UV | Early Term [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Whole blood sample for biomarkers (clinical genotyping) | | | x | | | | | | | | | | | | | | | | | | | | | | |
| Serum ADA sample | | | x | | x | | x | | | x | | | | | | x | | | | | | x | | x [l, q] | x |
| Serum PK sample for drug concentration | | | x | x | x | | x | | | x | | | | | | x | | | | | | x | x | x [l, q] | x |
| BCVA testing (starting at 4 m) [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 |
| LL BCVA testing (starting at 4 m) [r] | | x | | | | | | | | x | | | | | | x | | | | | | x | | x [l] | |
| 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 |
| Slit lamp examination [s] | 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 [t] | | | x | | x | | | | | x | | | | | | x | | | | | | | x | x [l] | |
| Dilated binocular indirect ophthalmoscopy | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x [l] | x |
| FAF [u] | x | x [k] | | | | | | | | x | | | | | | x | | | | | | x | | x [l] | x |
| Keratometry [u, v] | x | x | | | | | | | | | | | | | | | | | | | | | | | |
| SD-OCT [u] | x | x | | x | | x | | x | | x | | x | | x | | x | | x | | x | | x | | x [l, q] | x |
| OCT-A [u, w] | | x | | | | | | | | x | | | | | | x | | | | | | x | | x [l] | x |
| NI [u] | x | x | | | | | | | | x | | | | | | x | | | | | | x | | x [l] | x |
| Color fundus photography [u] | | x | | | | | | | | | | | | | | | | | | | | x | | x [l, q] | x |

## Appendix 1: Schedule of Activities: Q4W Arms

| | PreBL Scrn [a] | BL Scrn [b] | Day | | Week Visit | | | | | | | | | | | | | | | | | | UV | Early Term [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 8 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 76 [c] | | |
| Assessment Windows (Days) | –120 to –31 | –30 to –1 | — | ±2 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | | |
| Administration of study drug/sham control to study eye [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 [y] | | | x | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | | | | |
| Concomitant medications [z] | | 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 [aa] | | 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 [bb] | | | 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 [cc] | | | 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; BL = baseline; CFP = color fundus photograph; Early Term = early termination; FA = fluorescein angiography; FAF = fundus autofluorescence; GA = geographic atrophy; HtrA1 = high-temperature requirement A1; IOP = intraocular pressure; IWRS = Interactive Web Response Systems; LL BCVA = low-luminance BCVA; NI = near infrared; OCT-A = optical coherence tomography angiography; PK = pharmacokinetic; preBL = prebaseline; Q4W = every 4 weeks; Scrn = screening; SD-OCT = spectral domain optical coherence tomography; UV=unscheduled visit.

Note: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except for those at screening. **For treatment day, other than post-treatment finger counting and IOP measurement, all assessments and sample collection should be completed prior to study drug administration.**

[a] The prebaseline screening visit is only necessary for patients who do not have eligible preexisting FAF images (see Figure 2). Assessments may be completed on separate days provided that all assessments are captured within the prebaseline screening period of Day –120 to Day –30. Patients who do not have preexisting FAF will have an FAF obtained with the other prebaseline screening activities to evaluate eligibility. This FAF will be designated the prebaseline FAF. If all eligibility criteria are met in accordance to Section 4.1, the patient will return 90 (+30) days from the date of the FAF image and enter the 30-day baseline screening window (Day –30 to Day –1).

[b] Patients who have an eligible preexisting FAF image may directly enter in the 30-day baseline screening window (see Figure 2). The preexisting FAF will be considered the prebaseline FAF. See Section 4.1 for GA lesion eligibility criteria. Baseline screening activities may be completed across more than one visit if necessary.

[c] After completing the study's last visit (Week 76), eligible patients will have the option to enroll in an open-label extension study (GR42558) and receive FHTR2163 injections. The Week 76 visit will serve as the final visit for this study (GR40973; GAllego) and the first (Day 1) visit for Study GR42558. Patients who do not enter Study GR42558 will be contacted 7–10 days after the last visit by a follow-up call to elicit reports of any decrease in vision, eye pain, unusual redness, or other new ocular symptoms in the study eye.

[d] For patients who discontinue early from the study, early termination assessments will be performed after minimum of 30 days have lapsed following the final study treatment.

[e] The Informed Consent Form needs to be signed and documented only once during prebaseline screening or screening visit.

[f] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, and ophthalmic history), and tobacco use, surgeries, cancer history, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Day 1 visit.

[g] Demographic data will include age, sex, and self-reported race/ethnicity.

[h] Historical ocular images are defined as FAF and SD-OCT images of both eyes obtained up to 5 years prior to the baseline screening window, excluding those used to evaluate prebaseline FAF. Historical ocular images may be collected and submitted any time after enrollment into the study. This assessment is required only for patients who have historical images available.

[i] Prebaseline FAF and NI images from patients must have been obtained on a Heidelberg platform 84–336 days prior to screening (Day –30 to Day –1). If both eyes have the potential to be eligible for the study, FAF and NI images from both eyes should be sent to central reading center.

[j] If the preexisting FAF image is not gradable or the total GA lesion size is smaller than the required ($<2.54$ mm$^2$), the FAF image obtained during the baseline screening window will be considered as the prebaseline image. If all other eligibility criteria are met (see Section 4.1), the patient will return to clinic for a repeat screening visit 90 (+ 30) days from the date of when the prebaseline image was obtained. During the repeat 30-day baseline screening window, all screening visit assessments will be performed except for HtrA1 genotyping whole blood sample and keratometry.

[k] On Day 1, contact IWRS for study drug kit assignment after all assessments are performed.

[l] To be performed if clinically indicated.

[m] Vital signs consist of measurements 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.

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

[o] 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 to central laboratory for testing; if the serum pregnancy test is positive, do not administer the study treatment.

[p] At screening, collect serum pregnancy sample for women of childbearing potential, including those who have had tubal ligation. If positive, record the patient as a screen fail. At early termination visit, collect the serum pregnancy sample and forward to the central laboratory for testing.

[q] 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 13; 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.

[r] Perform assessment prior to dilating the eyes.

[s] Recommend the slit lamp examination be performed prior to dilating eyes; for grading scales for anterior and vitreous cells, see Appendix 6.

[t] Aqueous humor sample must be collected from the study eye after pretreatment IOP measurement, but prior to study drug administration, when applicable. For a detailed description of the anterior chamber paracentesis and aqueous humor sample collection procedures, see Appendix 14 and the laboratory manual.

[u] FAF, keratometry, 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. Note: After randomization, 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.

[v] Only one keratometry measurement on each eye (obtained at prebaseline screening or baseline screening) is required.

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

[x] 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.

[y] 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 between 30–50 minutes post-injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased ≥ 10 mmHg from pre-injection measurement, the IOP will 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 in accordance with the investigator's clinical judgment prior to discharge. For guidance on adverse event reporting, see Section 5.3.5.2.

[z] Record any concomitant medications (e.g., prescription drugs, over-the-counter preparations other than protocol-specified procedural medications [e.g., dilating drops or fluorescein dyes] and pre- and post-injection medications [e.g., proparacaine]) used by the patient from 7 days prior to Day 1 to until the study completion/discontinuation visit.

[aa] 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 after the study treatment until 28 days after the final dose of study drug. After the 28 day period, only serious adverse events caused by a protocol-mandated intervention or believed to be related to prior study drug treatment (see Section 5.6) 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.

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

[cc] 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: Q8W Arms

| Assessment Windows (Days) | PreBL Scrn [a] | Baseline Scrn [b] | Day | | Week Visit | | | | | | | | | | UV | Early Term [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 8 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 64 | 72 | 76 [c] | | |
| | –120 to –31 | –30 to –1 | — | ±2 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | | |
| Written informed consent [e] | x | x | | | | | | | | | | | | | | |
| Review of inclusion and exclusion criteria | x | x | x | | | | | | | | | | | | | |
| Medical and surgical history including tobacco history [f] | | x | | | | | | | | | | | | | | |
| Demographic information [g] | | x | | | | | | | | | | | | | | |
| Historical ocular image collection [h] | | | x | | | | | | | | | | | | | |
| PreBL FAF and NI image collection [i, j] | | x | | | | | | | | | | | | | | |
| Randomization (IWRS) [k] | | | x | | | | | | | | | | | | | |
| Physical examination | | x | | | | | | | | | | | | | x [l] | x |
| Vital signs [m] | x | x | x | | | | | | | | | | | | x [l] | x |
| Hematology, coagulation, lipids, serum chemistry (central laboratory) [n] | | x | | | | | | x | | | | | x | | x [l] | x |
| Urine pregnancy test [o] | | | x | | x | x | x | x | x | x | x | x | | | x [l] | |
| Serum pregnancy sample [p] | | x | | | | | | | | | | | | | | |
| Whole blood sample for HtrA1 genotyping | | x | | | | | | | | | | | | | | |
| Plasma sample for biomarker | | | x | | | | | | | x | | | x | x | x [l] | x |
| Whole blood sample for biomarkers (clinical genotyping) | | | x | | | | | | | | | | | | | |
| Serum ADA sample | | | x | | x | | x | | | x | | | x | | x [l, q] | x |

## Appendix 2: Schedule of Activities: Q8W Arms

| Assessment Windows (Days) | PreBL Scrn [a] | Baseline Scrn [b] | Day | | Week Visit | | | | | | | | | | UV | Early Term [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 8 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 64 | 72 | 76 [c] | | |
| | –120 to –31 | –30 to –1 | — | ±2 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | | |
| Serum PK sample for drug concentration | | | x | x | x | | x | | | x | | | x | x | x [l, q] | x |
| BCVA testing (starting at 4 m) [r] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| LL BCVA testing (starting at 4 m) [r] | | x | | | | | x | | | x | | | x | | x [l] | |
| IOP measurement [r] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Slit lamp examination [s] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Aqueous humor sample [t] | | | x | | x | | x | | | x | | | | x | x [l] | |
| Dilated binocular indirect ophthalmoscopy | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x [l] | x |
| FAF [u] | x | x [k] | | | | | x | | | x | | | x | | x [l] | x |
| Keratometry [u, v] | x | x | | | | | | | | | | | | | | |
| SD-OCT [u] | x | x | | x | x | x | x | x | x | x | x | x | x | | x [l, q] | x |
| OCT-A [u, w] | | x | | | | | x | | | x | | | x | | x [l] | x |
| NI [u] | x | x | | | | | x | | | x | | | x | | x [l] | x |
| Color fundus photography [u] | | x | | | | | | | | | | | x | | x [l, q] | x |
| Administration of study drug/sham control to study eye [x] | | | x | | x | x | x | x | x | x | x | x | | | | |
| Post-treatment finger counting and IOP measurement [y] | | | x | | x | x | x | x | x | x | x | x | | | | |
| Concomitant medications [z] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Adverse events [aa] | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

## Appendix 2: Schedule of Activities: Q8W Arms

| Assessment Windows (Days) | PreBL Scrn [a] | Baseline Scrn [b] | Day | | Week Visit | | | | | | | | | | UV | Early Term [d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 8 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 64 | 72 | 76 [c] | | |
| | –120 to –31 | –30 to –1 | — | ±2 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | ±5 | | |
| Concurrent ocular procedures [bb] | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Follow-up call [cc] | | | x | | x | x | x | x | x | x | x | x | | | | |

ADA = anti-drug antibody; BCVA = best corrected visual acuity; CFP = color fundus photograph; Early Term = early termination; FA = fluorescein angiography; FAF = fundus autofluorescence; GA = geographic atrophy; HtrA1 = high-temperature requirement A1; IOP = intraocular pressure; IWRS = Interactive Web Response Systems; LL BCVA = low-luminance BCVA; NI = near infrared imaging; OCT-A = optical coherence tomography angiography; PK = pharmacokinetic; preBL = prebaseline; Q8W = every 8 weeks; Scrn = screening; SD-OCT = spectral domain optical coherence tomography; UV=unscheduled visit.

Note: All ocular assessments are to be performed for both eyes unless noted otherwise. All assessments are to be performed on the same day, except for those at screening. **For treatment day, other than post-treatment finger counting and IOP measurement, all assessments and sample collection should be completed prior to study drug administration.**

[a] The prebaseline screening visit is only necessary for patients who do not have eligible preexisting FAF images (see Figure 2). Assessments may be completed on separate days provided that all assessments are captured within the prebaseline screening period of Day –120 to Day –30. Patients who do not have preexisting FAF will have an FAF obtained with the other prebaseline screening activities to evaluate eligibility. This FAF will be designated the prebaseline FAF. If all eligibility criteria are met in accordance to Section 4.1, the patient will return 90 (+30) days from the date of the FAF image and enter the 30-day baseline screening window (Day –30 to Day –1).

[b] Patients who have an eligible preexisting FAF image may directly enter into the 30-day baseline screening window (see Figure 2). The preexisting FAF will be considered the prebaseline FAF. See Section 4.1 for GA lesion eligibility criteria. Baseline screening activities may be completed across more than one visit if necessary.

[c] After completing the study's last visit (Week 76), eligible patients will have the option to enroll in an open-label extension study (GR42558) and receive FHTR2163 injections. The Week 76 visit will serve as the final visit for this study (GR40973; GAllego) and the first (Day 1) visit for Study GR42558. Patients who do not enter Study GR42558 will be contacted 7–10 days after the last visit by a follow-up call to elicit reports of any decrease in vision, eye pain, unusual redness, or other new ocular symptoms in the study eye.

[d] For patients who discontinue early from the study, early termination assessments will be performed after minimum of 30 days have lapsed following the final study treatment.

[e] The Informed Consent Form needs to be signed and documented only once during prebaseline screening or screening visit.

[f] Significant medical and surgical history, including chronic and ongoing conditions (e.g., trauma, cancer, cardiovascular, and ophthalmic history), and tobacco use, surgeries, cancer history, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to Day 1 visit.

[g] Demographic data will include age, sex, and self-reported race/ethnicity.

[h] Historical ocular images are defined as FAF and SD-OCT images of both eyes obtained up to 5 years prior to the baseline screening window, excluding those used to evaluate prebaseline FAF. Historical ocular images may be collected and submitted any time after enrollment into the study. This assessment is required only for patients who have historical images available.

[i] Prebaseline FAF and NI images from patients must have been obtained on a Heidelberg platform 84–336 days prior to screening (Day –30 to Day –1). If both eyes have the potential to be eligible for the study, FAF and NI images from both eyes should be sent to central reading center.

[j] If the preexisting FAF image is not gradable or the total GA lesion size is smaller than the required ($<2.54$ mm$^2$), the FAF image obtained during the baseline screening window will be considered as the prebaseline image. If all other eligibility criteria are met (see Section 4.1), the patient will return to clinic for a repeat screening visit 90 ($+30$) days from the date of when the prebaseline image was obtained. During the repeat 30-day baseline screening window, all screening visit assessments will be performed except for HtrA1 genotyping whole blood sample and keratometry.

[k] On Day 1, contact IWRS for study drug kit assignment after all assessments are performed.

[l] To be performed if clinically indicated.

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

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

[o] 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 to central laboratory for testing; if the serum pregnancy test is positive, do not administer the study treatment.

[p] At screening, collect serum pregnancy sample for women of childbearing potential, including those who have had tubal ligation. If positive, record the patient as a screen fail. At early termination visit, collect the serum pregnancy sample and forward to the central laboratory for testing.

[q] 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 13; 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.

[r] Perform assessment prior to dilating the eyes.

[s] Recommend the slit lamp examination be performed prior to dilating eyes; for grading scales for anterior and vitreous cells, see Appendix 6.

[t] Aqueous humor sample must be collected from the study eye after pretreatment IOP measurement, but prior to study drug administration, when applicable. For a detailed description of the anterior chamber paracentesis and aqueous humor sample collection procedures, see Appendix 14 and the laboratory manual.

[u] FAF, keratometry, 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. Note: After randomization, 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.

[v] Only one keratometry measurement on each eye (obtained at prebaseline screening or baseline screening) is required.

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

[x] 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.

[y] 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 between 30-50 minutes post-injection. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased ≥ 10 mmHg from pre-injection measurement the IOP will measured again at 60 to 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 in accordance with the investigator's clinical judgment prior to discharge. For guidance on adverse event reporting, see Section 5.3.5.2.

[z] Record any concomitant medications (e.g., prescription drugs, over-the-counter preparations) other than protocol-specified medications (e.g., dilating drops, proparacaine, and pre and post-injection anti-microbial drops) used by the patient from 7 days prior to Day 1 to until the study completion/discontinuation visit.

[aa] 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 after the study treatment until 28 days after the final dose of study drug. After the 28-day period, only serious adverse events caused by a protocol-mandated intervention or believed to be related to prior study drug treatment (see Section 5.6) 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.

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

## Appendix 2: Schedule of Activities: Q8W Arms

[cc] 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
# HtrA1 Risk-Variant Genotyping Assay

The genotype at the single nucleotide polymorphism [redacted] is determined using a TaqMan® polymerase chain reaction assay ([redacted]). The assay has been designed and validated by Life Technologies and is performed in a Clinical Laboratory Improvement Amendments certified lab.

Each assay contains two sequence-specific primers for amplifying and two allele specific TaqMan MGB probes (labeled with reporter dyes VIC and FAM) for detecting the alleles for the specific polymorphisms of interest. The fluorescence data are collected and analyzed using the ABI Prism® 7900HT Sequence Detection Systems software. The software uses Cycle Threshold (Ct) values for mutant and wild-type probes to determine genotype [redacted].

[redacted]

# Appendix 4
# 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 and treatment arm (study drug vs. sham control) assignment. BCVA will be measured at the intervals specified in the protocol (see Appendix 1 and Appendix 2 of the protocol and Clinical Edge Instruction 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

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

# Appendix 5
# Low-Luminance Best Corrected Visual Acuity Testing

These are the same requirements as the best corrected visual acuity described in Appendix 4; 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 6
# 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 7
# Post-Injection Procedures for All Patients

The patient will be monitored with a finger-counting test followed by hand motion and light perception tests (when necessary) within 15 minutes of the study treatment by the investigator.

A measurement of intraocular pressure (IOP) in the study eye only will be obtained 30–50 minutes after study treatment. If there are no safety concerns, the patient may be discharged from the clinic. If the IOP is increased by $\geq$10 mmHg from 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.

As per individual site investigator decision, the investigator may administer antimicrobial drops after treatment following study drug injection. The individual site investigator may also instruct patients to self-administer antimicrobial drops pre- and post-injection.

Unless country regulatory prohibits, the used study drug kit, including the used vial, should be stored until the Sponsor representative conducts the study drug accountability and the site is instructed to discard or ship to the Sponsor. Discard all syringes and needles in the sharps container.

# Appendix 8
# 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

See the Central Reading Center Manual.

## PROCEDURE

The central reading center will provide a study manual and the 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 9
# 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 the study manual and training materials.
FAF operators, systems, and software will be certified prior to any evaluation of patients.

# Appendix 10
# 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 11
# 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 12
# 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 13
# 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 14
# Anterior Chamber Paracentesis and Aqueous Humor Sampling Procedure

An aqueous humor sample will be collected before the treatment of the study eye (if applicable) 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 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 antimicrobial drops prior to treatment and after treatment following the 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 14: Anterior Chamber Paracentesis and Aqueous Humor Sampling Procedure

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 antimicrobial drops
- Wait 5 minutes (only if antimicrobial drops are used)
- Instill two drops of 5% povidone iodine ophthalmic solution in the study eye
- Disinfect the periocular skin and eyelid of the study eye

  Scrub the eyelid, lashes, and periorbital skin with 10% povidone-iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular 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 antimicrobial drops after treatment following aqueous humor sampling

# Appendix 15
# 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 15: 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 15: 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 15: 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

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