PROTOCOL TITLE:	A Phase 2a Multicenter, Randomized, Masked Study Evaluating the Pharmacodynamics of Emixustat Hydrochloride in Subjects with Macular Atrophy Secondary to Stargardt Disease
PROTOCOL NUMBER:	4429-204
NAME OF TEST ARTICLE:	Emixustat hydrochloride
[redacted]	[redacted]
INDICATION:	Stargardt Disease
DEVELOPMENT PHASE:	Phase 2a
STUDY DESIGN:	Multicenter, randomized, masked, parallel-group
SPONSOR:	Acucela Inc. 818 Stewart St., Suite 1110 Seattle, WA 98101
DATE OF PROTOCOL:	Original: 28 September 2016 Amendment 1: 13 July 2017
NCT NUMBER:	03033108

This study will be conducted in accordance with the International Council for Harmonisation guideline E6 (R1): Good Clinical Practice: Consolidated Guideline and the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects 1964, including all amendments and Notes of Clarification.

1 Sponsor Signature Page

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Approved by:

[redacted]

[redacted]

2 Key Roles and Contacts

Key roles may be updated by written notification to the clinical sites without a protocol amendment.

Sponsor:	Acucela Inc. 818 Stewart St., Suite 1110 Seattle, WA 98101 Phone: 206-805-8300
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3 Protocol Summary

Protocol Number:	4429-204
Protocol Title:	A Phase 2a Multicenter, Randomized, Masked Study Evaluating the Pharmacodynamics of Emixustat Hydrochloride in Subjects with Macular Atrophy Secondary to Stargardt Disease
Phase:	Phase 2a
Study Objectives **Primary:**	To characterize the pharmacodynamics (PD) of emixustat hydrochloride (emixustat) in subjects with macular atrophy (MA) secondary to Stargardt disease (STGD).
Secondary:	To evaluate the safety and tolerability of emixustat when administered orally for 1 month.
Study Population:	Subjects who have MA secondary to STGD.
Study Design:	This is a multicenter, randomized, masked study to evaluate the PD and safety and tolerability of emixustat in subjects with MA secondary to STGD. Subjects will be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio. Treatment arms include: • Emixustat 2.5 mg • Emixustat 5 mg • Emixustat 10 mg Subjects will take study drug once daily (QD) in the evening for 1 month.
Number of Subjects:	Approximately 30 subjects will be enrolled, with a goal of having 24 subjects (8 per treatment arm) complete the masked treatment phase of the study.
Inclusion Criteria:	Subjects who meet all of the following criteria at Screening and Baseline (unless otherwise indicated) may be eligible for inclusion in the study: 1. Males or females, age ≥ 18 years. 2. Clinical diagnosis of MA secondary to STGD in one or both eyes as determined by the Investigator and confirmed by the central image reading center. 3. At least 2 pathogenic mutations of the ABCA4 gene. If only one ABCA4 allele has a pathogenic mutation,

	the subject must have a typical STGD phenotype (ie, at least one eye has flecks at the level of the retinal pigment epithelium [RPE] typically seen in STGD) and be approved for enrollment by the Sponsor. 4. Total area of MA (definitely decreased autofluorescence plus questionably decreased autofluorescence) in the study eye equal to 1.25 - 26 mm^2 (~0.5 – 10.25 disc areas) in size as determined by the central image reading center's assessment of fundus autofluorescence (FAF) imaging at Screening. 5. The entire lesion must be completely visualized on the macula-centered image (Field 2 –Macula Image). 6. Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) of ≥ 20 letters (approximately ≥ 20/400 Snellen) in the study eye. 7. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of MA in the study eye as determined by the Investigator. 8. Able and willing to provide written informed consent before undergoing any study-related procedures. 9. Able to reliably administer oral medication by self or with available assistance.
Exclusion Criteria:	Subjects will be excluded from participation in the study if they meet any of the following criteria at Screening or Baseline (unless otherwise indicated): 1. Macular atrophy associated with a condition other than STGD in either eye. 2. Presence in either eye of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including, but not limited to, choroidal neovascularization, diabetic retinopathy, uveitis, other macular diseases, or uncontrolled glaucoma/ocular hypertension. 3. History of any intraocular or ocular surface surgery in either eye within 3 months of Screening. 4. Current or previous participation in an interventional study to treat STGD using gene therapy or stem cell therapy at any time, or participation in an

	interventional study of a vitamin A derivative ≤3 months prior to screening. 5. Known serious hypersensitivity to emixustat or any of the excipients in emixustat tablets (ie, silicified microcrystalline cellulose, pregelatinized starch, colloidal silicon dioxide, and stearic acid). 6. Prohibited medications: Systemic use of a strong inducer of, or a strong or moderate inhibitor of, cytochrome P450 2D6 (CYP2D6) beginning within 4 weeks prior to Screening or between Screening and Baseline, or planned use during the study period. 7. Any of the following laboratory abnormalities at Screening: a. Aspartate transaminase (AST)/alanine transaminase (ALT) > 2.5 × upper limit of normal (ULN). b. Total bilirubin > 1.5 × ULN. c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. d. Impaired hematologic function: hemoglobin < 10 g/dL; neutrophil count < 1.6 × 10^9/L; or platelet count < 100 × 10^9/L. Any laboratory screening test that meets the abnormality criteria stated above can be repeated once within the 30-day period from Screening to Baseline. 8. Participation in any study using an investigational drug within 5 half-lives (of the investigational drug) of Screening, or, if the half-life is not known, within 30 days of Screening. 9. Participation in any study of an investigational device within 60 days of Screening. 10. Anticipated participation during the study period in any other study using an investigational study drug or interventional device. 11. Presence of other medical or ophthalmic disease, physical examination finding, or clinical laboratory finding that in the opinion of the Investigator contraindicates the use of an investigational drug; places the subject at risk by participating in the study;

	might interfere with the evaluation of the PD or safety of emixustat; negatively impacts subject compliance with the protocol; confounds the ability to interpret data from the study; or jeopardizes the subject's ability to complete the protocol. 12. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year of Screening. 13. History of myocardial infarction, stroke, unstable ischemic heart disease, uncontrolled cardiac arrhythmia, or hospitalization for congestive heart failure within 6 months of Screening. 14. Anticipated hospitalization for a medical/surgical procedure(s) that could result in interruption/premature cessation of study treatment or participation. 15. Electrocardiogram with a clinically significant abnormal finding (eg, acute ischemia, bundle branch block) or a QT interval, corrected for heart rate by Bazett's formula (QTcB) or Fridericia's formula (QTcF), of > 460 milliseconds (msec) for men and > 470 msec for women at Screening. 16. Female subjects who are pregnant or lactating. 17. Female subjects of childbearing potential (ie, not postmenopausal for at least 2 years and not surgically sterile) who are not willing to practice a medically accepted method of birth control with their non-surgically sterile male sexual partner from Screening through 30 days after the final dose of study drug. Medically accepted methods of birth control include abstinence, hormonal contraceptives, nonhormonal intrauterine contraceptive device with spermicide, condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide. 18. Male subjects who are not surgically sterile and are not willing to practice a medically accepted method of birth control with their female partner of childbearing potential (as listed above) from Screening through 30 days after the final dose of study drug.

Study Eye Determination:	The study eye will be determined as the eye that meets all of the inclusion criteria and none of the exclusion criteria. If both eyes qualify, the eye with the larger MA lesion area will be selected as the study eye. If both eyes qualify and are equal in MA lesion area, the right eye will be selected as the study eye. The study eye will be determined by the Investigator; MA lesion characteristics will be confirmed by the central image reading center.
Test Product, Dose, and Mode of Administration:	Emixustat (2.5 mg, 5 mg, and 10 mg) tablets will be packaged in identical-appearing, tamper proof, blister packaging to maintain masking. Study drug will be taken orally QD in the evening for 1 month.
Study Procedures:	The scheduled visits include Screening (within 30 days prior to Baseline), Baseline (Day 1), and End of Treatment (Month 1). A Study Exit visit will be performed 30 days after the End of Treatment (Month 1) visit (30 days after the last dose of study drug for subjects that terminate study participation early). See Section 12 and Table 12-1 for the Schedule of Events and description of the study procedures.
Criteria for Evaluation **Variables:** **Pharmacodynamic:**	Pharmacodynamic variables will include electroretinography (ERG) rod b-wave amplitudes and the degree of suppression of the b-wave rod recovery after a photobleaching light.
Safety:	Safety variables will include adverse events (AEs), BCVA, slit-lamp biomicroscopy, intraocular pressure (IOP), dilated ophthalmoscopy, physical examination findings, vital signs, electrocardiograms (ECGs), and clinical laboratory tests.
Study Endpoints **Pharmacodynamic:**	The degree of suppression compared to baseline of the rod b-wave amplitudes after a photobleaching light.
Safety:	Safety endpoints will include: 1. Incidence, severity, and seriousness of AEs, and discontinuations due to AEs. 2. Change from baseline in laboratory values, vital signs, physical examination findings, ECGs, and ophthalmic assessments.

Statistical Analyses:	This study will enroll approximately 30 subjects with a goal of having 24 subjects (8 per treatment arm) complete the masked treatment phase of the study. This sample size is not based on statistical rationale but is considered adequate to determine the PD response of each dose of emixustat in this study population. Pharmacodynamic variables will include ERG rod b-wave amplitudes and the degree of suppression of the rod b-wave rod recovery after a photobleaching light. The degree of suppression will be determined as the percent decrease from baseline to post-treatment in the rate of recovery of the rod b-wave amplitude during the 30-minute post-bleaching period. Results will be summarized by treatment arm. Safety and tolerability will be assessed on the basis of ocular and non-ocular AEs, serious adverse events (SAEs), ophthalmic examination findings, vital signs, physical examination findings, ECG findings, and laboratory analyses. Safety assessments will be summarized descriptively.
Study Duration:	The dosing period is 1 month, and subjects will complete the study approximately 1 month after taking the last dose of study drug.

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5 Glossary of Abbreviations and Definition of Terms

ABBREVIATION	DEFINITION
11*c*RDH	11-*cis*-retinol dehydrogenase
A2E	N-retinylidene-N-retinylethanolamine
ABCA4	ATP binding cassette subfamily A member 4
AE	adverse event
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AST	aspartate aminotransferase
ATP	adenosine triphosphate
A*t*RDH	all-*trans*-retinal dehydrogenase
BCVA	best-corrected visual acuity
CFR	Code of Federal Regulations
CRA	clinical research associate
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450 (eg, CYP2D6)
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
ERG	electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FAF	fundus autofluorescence
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IND	Investigational New Drug (Application)
IOP	intraocular pressure
IRB	Institutional Review Board
IWRS	interactive web response system
LRAT	lecithin retinol acyl transferase
MA	macular atrophy
MedDRA	Medical Dictionary for Regulatory Activities
msec	milliseconds
ONL	outer nuclear layer
PD	pharmacodynamics

ABBREVIATION	DEFINITION
QD	once daily
RPE	retinal pigment epithelium
RPE65	retinal pigment epithelium 65
SA	Safety Analyses (set of subjects)
SAE	serious adverse event
STGD	Stargardt disease
STGD1	autosomal recessive STGD
ULN	upper limit of the normal range

6 Introduction

6.1 Background

Emixustat hydrochloride (emixustat) is under clinical development by Acucela Inc. (Acucela) for retinal diseases including Stargardt disease (STGD).

Stargardt disease is a rare, inherited, degenerative disease of the retina affecting approximately 1 in 8,000 to 10,000 individuals and is the most common type of hereditary macular dystrophy.[1] There are no approved treatments for STGD.

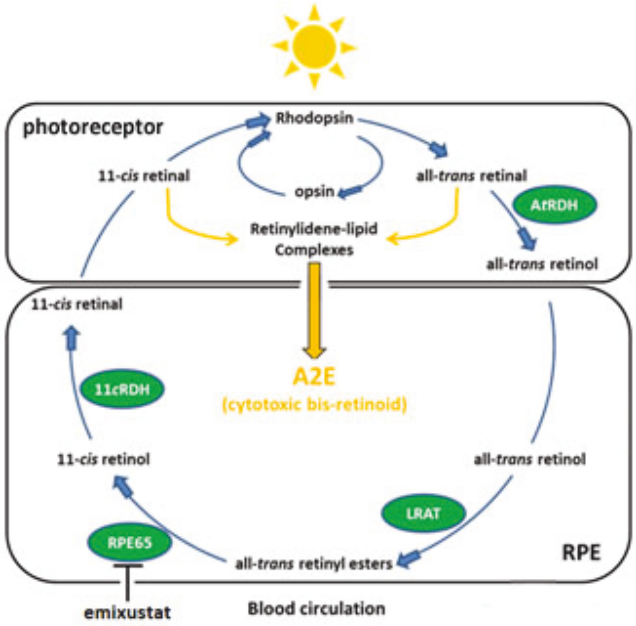
Stargardt disease is characterized by an excessive build-up of lipofuscin at the level of the retinal pigment epithelium (RPE). Lipofuscin, which normally accumulates with age, consists of lipids, proteins, and toxic bis-retinoids such as N-retinylidene-N-retinylethanolamine (A2E) that are mainly derived from incompletely digested photoreceptor outer segments. Accumulation of the toxic bis-retinoids found in lipofuscin is thought to cause RPE cell dysfunction and eventual apoptosis, which leads to photoreceptor death and loss of vision. While there are multiple sub-types of STGD, autosomal recessive STGD (STGD1) represents the vast majority (> 95%) of all cases. Autosomal recessive STGD is typically diagnosed in the first three decades of life and is caused by mutations of the adenosine triphosphate (ATP) binding cassette subfamily A member 4 (ABCA4) gene.[2] The ABCA4 gene product transports N-retinylidene-phosphatidylethanoloamine (a precursor of toxic bis-retinoids consisting of one molecule of phosphatidylethanolamine covalently bound to one molecule of 11-*cis*- or all-*trans*-retinal) from the lumen side of photoreceptor disc membranes to the cytoplasmic side, where the retinal is hydrolyzed from phosphatidylethanolamine.[3] Mutations of the ABCA4 gene result in accumulation of this precursor in disc membranes that are eventually phagocytized by RPE cells, where the precursors are converted into toxic bis-retinoids such as A2E. In addition to being a precursor to A2E, all-*trans*-retinal has also been implicated in the pathogenesis of STGD through its role in light-mediated toxicity.[4]

6.2 Rationale for the Study

The target for emixustat is the visual cycle isomerohydrolase, retinal pigment epithelium 65 (RPE65). As depicted in Figure 1, enzymatic processing within the visual cycle begins with delivery of vitamin A (all-*trans*-retinol) from the blood circulation as a ternary complex bound to retinol binding protein and transthyretin. Upon entry into the RPE, all-*trans*-retinol is converted to a retinyl ester through the activity of lecithin retinol acyl transferase (LRAT). The resulting all-*trans*-retinyl esters represent a storage form of vitamin A upon which RPE65 acts. Following conversion to 11-*cis*-retinol, an 11-*cis*-retinol dehydrogenase (11*c*RDH) catalyzes the formation of the visual chromophore, 11-*cis*-retinal. The visual chromophore is

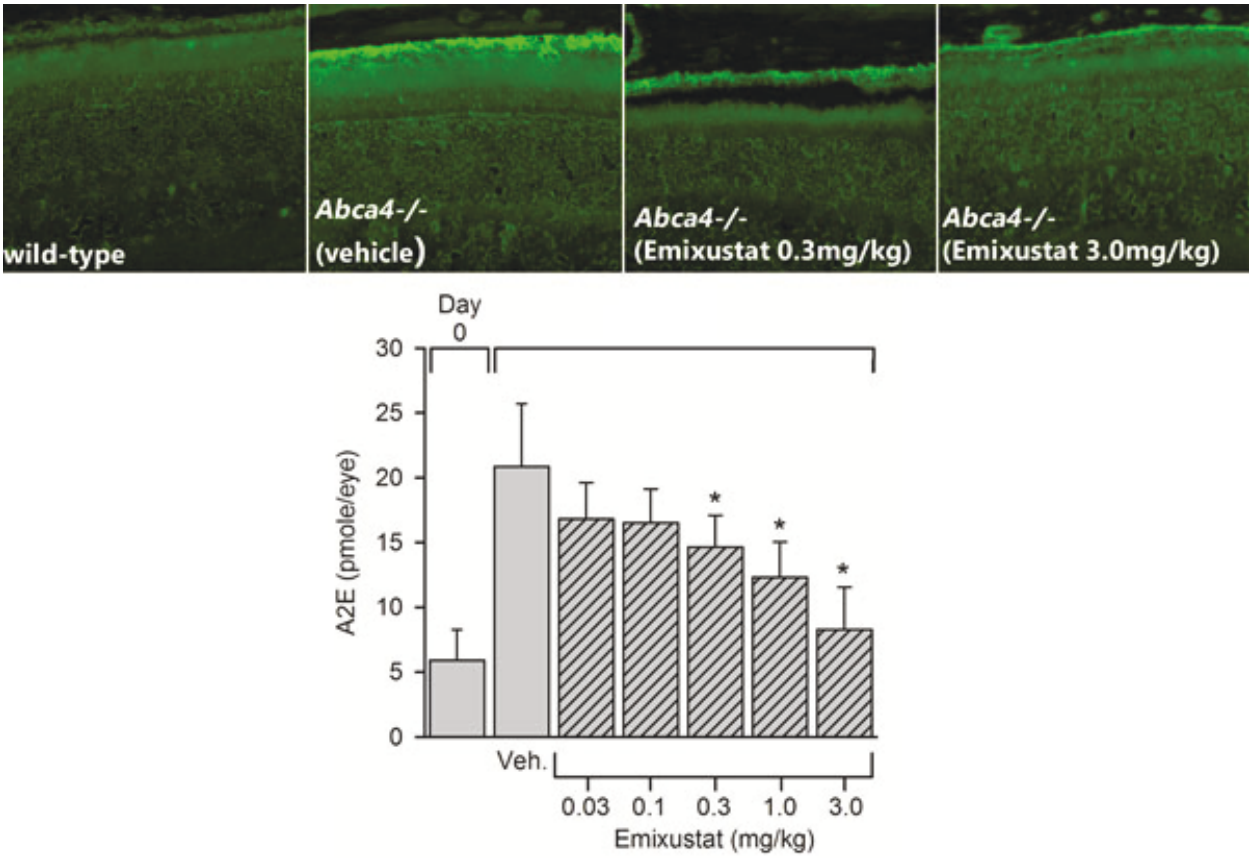
then delivered to rod and cone outer segments where it combines with opsins to form visual pigments (eg, rhodopsin). Light activation of rhodopsin initiates the process of visual transduction and liberates all-*trans*-retinal as a photoproduct. Reduction of all-*trans*-retinal, via all-*trans*-retinal dehydrogenase (A*t*RDH), produces all-*trans*-retinol which is transferred back to the RPE for recycling within the RPE.

Figure 1: Overview of the Visual Cycle and Modulation by Emixustat



Emixustat is a potent inhibitor of RPE65 isomerization activity and reduces the production of visual chromophore (11-*cis*-retinal) in a dose-dependent and reversible manner. Because 11-*cis*-retinal and its photoproduct (all-*trans*-retinal) are substrates for biosynthesis of retinoid toxins (eg, A2E), chronic treatment with emixustat retards the rate at which these toxins accumulate. In an animal model of STGD1 (ABCA4-/- mice) in which excessive A2E accumulates, chronic treatment (3 months, starting at 2 months of age) with emixustat doses ≥ 0.3 mg/kg/day produced statistically significant reductions in A2E accumulation, compared to vehicle-treated mice (Figure 2). [redacted] These data suggest that the accumulation of A2E can be reversed by emixustat treatment.[5, 6]

Figure 2: Emixustat Reduces Lipofuscin Autofluorescence and A2E in ABCA4-/- Mice



All-*trans*-retinal is known to be a key mediator of light damage. In wild-type mice, prolonged exposure to intense white light (8,000 lux for 1 hour) causes repeated photobleaching of 11-*cis*-retinal to all-*trans*-retinal which results in near complete destruction of the outer nuclear layer (ONL) of the retina. The ability of emixustat to rapidly and potently reduce the production of 11-*cis*-retinal, and thus all-*trans*-retinal, affords protection from light damage. In a mouse light toxicity model, pre-treatment with a single dose of emixustat (1.0 or 3.0 mg/kg) has been shown to provide near complete preservation of the ONL, compared to vehicle-treated mice ($p<0.01$, $ED_{50} = 0.20$ mg/kg).

These nonclinical findings suggest that, by decreasing the availability of 11-*cis*-retinal and thus all-*trans*-retinal, orally administered emixustat may slow the progression of STGD by reducing retinal pathology caused by prominent cellular stressors such as toxic retinoid by-products and light.

6.3 Rationale for Dose Selection

To characterize the pharmacodynamics (PD) of emixustat in subjects with macular atrophy (MA) secondary to STGD, doses within the range previously assessed for safety in subjects

with geographic atrophy secondary to age-related macular degeneration (AMD) have been selected.

A once-daily schedule for administration of emixustat has been chosen for this study based on the pharmacokinetic profile characterized in the Phase 1 program. Following multiple dosing in healthy subjects who received doses ranging from 5 to 40 mg of emixustat once daily (QD) for 14 days, emixustat was steadily eliminated with terminal elimination half-life values ranging from 4.6 to 7.9 hours. Pharmacokinetic values were similar on Days 1 and 14, with mean accumulation ratio for area under the concentration curve values ranging from 1.04 to 1.19 across all treatments, indicating no accumulation following QD dosing with emixustat for 14 days.[7]

7 Study Objectives

7.1 Primary Objective

The primary objective of this study is to characterize the PD of emixustat in subjects with MA secondary to STGD.

7.2 Secondary Objectives

The secondary objective of this study is to evaluate the safety and tolerability of emixustat when administered orally for 1 month.

8 Investigational Plan

8.1 Overall Study Design and Plan

This is a multicenter, randomized, masked study to characterize the PD and safety and tolerability of emixustat in subjects with MA secondary to STGD. Subjects will be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio. Treatment arms include:

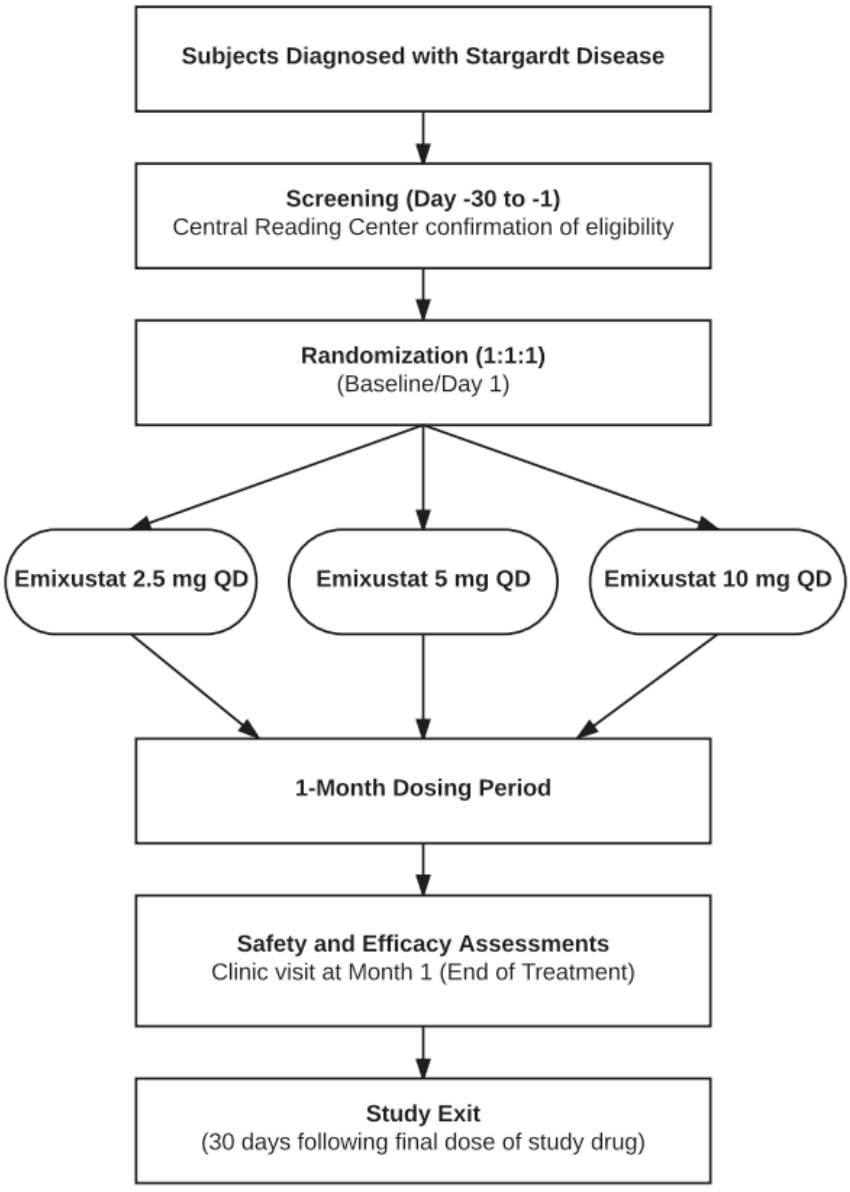
- Emixustat 2.5 mg
- Emixustat 5 mg
- Emixustat 10 mg

Subjects will self-administer study drug QD in the evening for 1 month, from the evening of the Baseline visit through the evening before the End of Treatment visit.

The scheduled visits include Screening (within 30 days prior to Baseline), Baseline (Day 1), and End of Treatment (Month 1). A Study Exit visit will be performed 30 days after the End of Treatment visit (30 days after the last dose of study drug for subjects that terminate study participation early).

The study design is presented schematically in Figure 3.

Figure 3: Study Design Schema



8.2 Number of Subjects

Approximately 30 subjects across multiple clinical sites will be enrolled (approximately 10 subjects per treatment arm) in order to obtain approximately 8 evaluable subjects per arm.

8.3 Study Sites

This study will be conducted at 4 to 6 clinical sites in the United States.

8.4 Discussion of Study Design, Including the Choice of Control Groups

Randomization and masking will be used to minimize bias in subject selection and the evaluation of subjects during the study.

Doses within the range previously assessed for safety in subjects with GA secondary to AMD have been selected, and a QD dosing regimen is based on the pharmacokinetic profile characterized in the Phase 1 program.[7]

The 1-month dosing period and sample size are expected to provide the opportunity to determine the PD response of each dose of emixustat and to evaluate safety and tolerability.

8.5 Pharmacodynamic Variables

Pharmacodynamic variables will include electroretinography (ERG) rod b-wave amplitudes and the degree of suppression of the b-wave rod recovery after a photobleaching light.

8.6 Safety Variables

Safety variables will include adverse events (AEs), best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, intraocular pressure (IOP), dilated ophthalmoscopy, physical examination findings, vital signs, electrocardiograms (ECGs), and clinical laboratory tests. Pregnancy tests will be conducted for women of childbearing potential.

9 Study Population

9.1 Target Population

The target population of this study is male or female subjects ≥ 18 years of age who have MA secondary to STGD.

9.2 Inclusion Criteria

Subjects who meet all of the following criteria at Screening and Baseline (unless otherwise indicated) may be eligible for inclusion in the study:

1. Males or females, age ≥18 years.
2. Clinical diagnosis of MA secondary to STGD in one or both eyes as determined by the Investigator and confirmed by the central image reading center.
3. At least 2 pathogenic mutations of the ABCA4 gene. If only one ABCA4 allele has a pathogenic mutation, the subject must have a typical STGD phenotype (ie, at least one eye has flecks at the level of the RPE typically seen in STGD) and be approved for enrollment by the Sponsor.
4. Total area of MA (definitely decreased autofluorescence plus questionably decreased autofluorescence) in the study eye equal to 1.25 - 26 mm^2 (~0.5 – 10.25 disc areas) in size as determined by the central image reading center's assessment of fundus autofluorescence (FAF) imaging at Screening.
5. The entire lesion must be completely visualized on the macula-centered image (Field 2 - Macula Image).
6. Early Treatment Diabetic Retinopathy Study BCVA of ≥ 20 letters (approximately ≥ 20/400 Snellen) in the study eye.
7. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of MA in the study eye as determined by the Investigator.
8. Able and willing to provide written informed consent before undergoing any study-related procedures.
9. Able to reliably administer oral medication by self or with available assistance.

9.3 Exclusion Criteria

Subjects will be excluded from participation in the study if they meet any of the following criteria at Screening or Baseline (unless otherwise indicated):

1. Macular atrophy associated with a condition other than STGD in either eye.
2. Presence in either eye of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including, but not limited to, choroidal neovascularization, diabetic retinopathy, uveitis, other macular diseases, or uncontrolled glaucoma/ocular hypertension.
3. History of any intraocular or ocular surface surgery in either eye within 3 months of Screening.

4. Current or previous participation in an interventional study to treat STGD using gene therapy or stem cell therapy at any time, or participation in an interventional study of a vitamin A derivative ≤3 months prior to screening.
5. Known serious hypersensitivity to emixustat or any of the excipients in emixustat tablets (ie, silicified microcrystalline cellulose, pregelatinized starch, colloidal silicon dioxide, and stearic acid).
6. Prohibited medications: Systemic use of a strong inducer of, or a strong or moderate inhibitor of, cytochrome P450 2D6 (CYP2D6) beginning within 4 weeks prior to Screening or between Screening and Baseline, or planned use during the study period.
7. Any of the following laboratory abnormalities at Screening:
    a. Aspartate transaminase (AST)/alanine transaminase (ALT) > 2.5 × upper limit of normal (ULN).
    b. Total bilirubin > 1.5 × ULN.
    c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.
    d. Impaired hematologic function: hemoglobin < 10 g/dL; neutrophil count < 1.6 × 10^9/L; or platelet count < 100 × 10^9/L.

    Any laboratory screening test that meets the abnormality criteria stated above can be repeated once within the 30-day period from Screening to Baseline.
8. Participation in any study using an investigational drug within 5 half-lives (of the investigational drug) of Screening, or, if the half-life is not known, within 30 days of Screening.
9. Participation in any study of an investigational device within 60 days of Screening.
10. Anticipated participation during the study period in any other study using an investigational study drug or interventional device.
11. Presence of other medical or ophthalmic disease, physical examination finding, or clinical laboratory finding that in the opinion of the Investigator contraindicates the use of an investigational drug; places the subject at risk by participating in the study; might interfere with the evaluation of the PD or safety of emixustat; negatively impacts subject compliance with the protocol; confounds the ability to interpret data from the study; or jeopardizes the subject's ability to complete the protocol.
12. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year of Screening.

13. History of myocardial infarction, stroke, unstable ischemic heart disease, uncontrolled cardiac arrhythmia, or hospitalization for congestive heart failure within 6 months of Screening.
14. Anticipated hospitalization for a medical/surgical procedure(s) that could result in interruption/premature cessation of study treatment or participation.
15. Electrocardiogram with a clinically significant abnormal finding (eg, acute ischemia, bundle branch block) or a QT interval, corrected for heart rate by Bazett's formula (QTcB) or Fridericia's formula (QTcF), of > 460 milliseconds (msec) for men and > 470 msec for women at Screening.
16. Female subjects who are pregnant or lactating.
17. Female subjects of childbearing potential (ie, not postmenopausal for at least 2 years and not surgically sterile) who are not willing to practice a medically accepted method of birth control with their non-surgically sterile male sexual partner from Screening through 30 days after the final dose of study drug. Medically accepted methods of birth control include abstinence, hormonal contraceptives, nonhormonal intrauterine contraceptive device with spermicide, condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide.
18. Male subjects who are not surgically sterile and are not willing to practice a medically accepted method of birth control with their female partner of childbearing potential (as listed above) from Screening through 30 days after the final dose of study drug.

9.4 Determination of Study Eye

The study eye will be determined as the eye that meets all of the inclusion criteria and none of the exclusion criteria. If both eyes qualify, the eye with the larger MA lesion area will be selected as the study eye. If both eyes qualify and are equal in MA lesion area, the right eye will be selected as the study eye. The study eye will be determined by the Investigator; MA lesion characteristics will be confirmed by the central image reading center.

9.5 Enrollment and Subject Identification Numbers

All subjects screened for the study who sign an informed consent form (ICF) will be assigned a screening number that will be entered in the Screening and Enrollment Log. The screening number will be the subject identification (ID) number for the remainder of the study.

9.6 Subject Withdrawal from Treatment or Study

Subjects may withdraw from treatment or the study for any reason and at any time. Subjects may also be removed from study for any of the following circumstances:

- Adverse events
- Investigator/Sponsor decision to withdraw subject from study
- Subject withdrawal of consent
- Pregnancy
- Lost to follow-up
- Death
- Study termination by Sponsor
- Other

All subjects who discontinue treatment prematurely will be withdrawn from the study.

9.6.1 Handling of Withdrawals

At the time of withdrawal, the Investigator should advise the subject of the other available options. When a subject is withdrawn from the study for any reason, the primary reason for withdrawal will be recorded in the electronic case report form (eCRF). For any subject who withdraws due to an AE, the reason for withdrawal must only be recorded as an AE (no other reason may be recorded). All subjects who withdraw from the study prematurely during the masked treatment phase will undergo assessments listed for the Early Termination visit and then complete the Study Exit visit 30 days following the last dose of study drug.

A subject who fails to return for any scheduled visit will be contacted by the site personnel in an attempt to have the subject comply with the protocol. After randomization, if a subject cannot be contacted with 3 telephone calls over a period of 2 weeks followed by a certified letter and there is no known reason for discontinuation (eg, withdrawn consent or AE), the reason for discontinuation will be recorded as "lost to follow-up." The date the certified letter was mailed will be considered the date of study withdrawal.

In the event of a subject death during the study, the date of death (as listed on the death certificate) will be used as the date of study withdrawal. It is vital to obtain follow-up data on any subject who is withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures.

The Medical Monitor should be notified promptly when a subject is withdrawn.

9.6.2 Replacements

Subjects who are withdrawn from the study will not be replaced.

9.6.3 Sponsor or Regulatory Agency Termination of the Study

Although the Sponsor intends to complete the study, the right is reserved to discontinue the study at any time for clinical or administrative reasons, or if required by the local regulatory authority.

9.7 End of Study

The end of study will be defined as the date of the last visit of the last subject. A summary of the End of Study report will be sent to Institutional Review Boards (IRBs), if required, within 12 months of the end of the study.

10 Randomization and Masking

10.1 Randomization

Randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons. Once a subject meets all qualification criteria at Screening and Baseline, they will be enrolled and randomly assigned in a masked fashion to study treatment through the use of an interactive web response system (IWRS).

At Baseline (Day 1), eligible subjects will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms:

- Emixustat 2.5 mg
- Emixustat 5 mg
- Emixustat 10 mg

Subjects will receive a randomization number when randomized at Baseline.

10.2 Masking

Study subjects and Investigators and their staff will be masked to the identity of treatment until after the final database is locked. For ERG recordings, the technician performing the ERG must ensure that the recordings will be filed and maintained in a masked fashion and will not be allowed to perform any functional assessments or assess AEs. To ensure masking, site

personnel who perform any functional assessments and/or assess AEs will not be allowed to be involved in the ERG procedure and will not be allowed access to ERG results.

The 3 dosage strengths of emixustat will be identical-appearing tablets, and each treatment will be packaged in identical, tamper-proof, blister packaging to maintain masking.

Appropriate precautions must be taken to prevent unauthorized access to the randomization scheme. The decision to unmask a subject's treatment assignment is to be made by the Investigator only if the subject's safety requires it. The treatment assignment for an individual subject may be obtained through the IWRS only in the case of a medical emergency when identity of the treatment assignment is essential for the clinical management of the subject. The Investigator must make every effort to contact the Medical Monitor before unmasking the treatment assignment. If unmasking is required for emergency subject management, the Investigator must document the medical rationale for unmasking and forward the information to the Sponsor within 24 hours of unmasking without revealing to the Sponsor personnel the treatment assignment. If emergency unmasking is required for any reason, the subject will be withdrawn from the study.

11 Study Treatments

11.1 Drug Dosage and Administration

Subjects will take 1 tablet (2.5, 5, or 10 mg) of emixustat orally QD in the evening for 1 month, from the evening of randomization until the evening before the End of Treatment (Month 1) visit. Subjects will be maintained on the randomized dose for the entire dosing period.

11.2 Supply, Packaging, Labeling, and Storage

Study drug (emixustat) will be packaged in tamper proof, blister packaging with identical labeling, except for the kit number. All study site personnel will remain masked to treatment assignment in order to allow for an unbiased assessment of study measures. The treatment assignments will remain masked until database lock and authorization of data release by the Sponsor according to standard operating procedures.

Each kit will be labeled with a single panel label clearly displaying a space for the subject ID number (to be filled in by the clinical site at the time the kit is dispensed to the subject), kit number, protocol number, contents, storage conditions, Sponsor's name and address, instructions for use, and appropriate precautionary statements.

Study drug will be stored at ambient room temperature in a securely locked cabinet or enclosure. Access should be strictly limited to the Investigators and their designees. Neither the Investigators nor any designees may provide study drug to any individual not participating in this protocol. Study drug will be dispensed by site personnel following randomization at the Baseline visit. Subjects will be instructed to store study drug at room temperature under secure conditions.

11.3 Measurement of Study Drug Adherence

Study drug will be administered orally QD in the evening for 1 month. At the End of Treatment (Month 1) visit, the subject will be queried regarding compliance with the treatment regimen. In addition, site personnel will collect the used blister pack of study drug and review subject compliance.

11.4 Study Drug Accountability

The Investigator will maintain accurate records of inventory and dates of receipt of all study drug. In addition, accurate records will be kept regarding when and how much study drug is dispensed to each subject and how much is returned by each subject. Reasons for departure from the expected dispensing regimen must also be recorded.

For regulatory requirements regarding drug accountability, all unused study drug and opened, empty blister packaging from used study drug will be reconciled by the clinical research associate (CRA). Once reconciled, study drug (both used and unused) will be returned to the Sponsor or designee according to applicable state and federal regulations.

Study drug returned by the site must be accompanied by appropriate documentation and be clearly identified by protocol number and study site on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The CRA should facilitate the return of unused study drug and opened, empty blister packaging from used study drug.

11.5 Prior and Concomitant Therapy

In addition to the exclusion criteria, the medications listed in Table 11-1 are the systemic CYP2D6 inhibitors and inducers that are prohibited during the study or within **4 weeks** prior to Screening.

Table 11-1: Prohibited CYP2D6 Inhibitors and Inducers

Prohibited CYP2D6 Inhibitors and Inducers	
Inhibitors:	
• Amiodarone • Cinacalcet • Terbinafine • Quinidine	• Bupropion • Duloxetine • Fluoxetine • Paroxetine • Sertraline
Inducers: No medications currently meet this criterion	

If elective, urgent, or emergency surgery is required at any time between randomization and End of Treatment (Month 1), the investigator will confer with the Medical Monitor, who will determine if a temporary discontinuation of masked study drug is warranted before and/or after the surgery.

For subjects who undergo ocular treatments, procedures, or surgeries (eg, retinal detachment surgery) with the potential to affect protocol assessments or disease outcomes, the Investigator should confer with the Medical Monitor to determine whether or not the subject should continue with study drug.

The Medical Monitor should be notified before prohibited medication or therapy (as listed in Section 9.3 Exclusion Criteria and in Table 11-1) is administered unless the safety of the subject requires immediate action. The decision to administer a prohibited medication or therapy should be done with the safety of the subject as the primary consideration. The Medical Monitor will determine whether or not the subject may continue with study participation. The Investigator should contact the Medical Monitor if permissibility of a specific medication or therapy is in question to discuss whether or not the subject should continue with study participation.

12 Study Visits

The Schedule of Events is presented in Table 12-1.

The scheduled visits include Screening (within 30 days prior to Baseline), Baseline (Day 1), and End of Treatment (Month 1). A Study Exit visit will be performed 30 days after the End of Treatment (Month 1) visit (30 days after the last dose of study drug for subjects that terminate study participation early).

All required ophthalmic exams should be performed on both eyes at each study time point. For each visit, all ophthalmic exams must be performed on the same day and cannot be split between 2 or more days. Best-corrected visual acuity must be completed prior to any ophthalmic exam requiring contact with the eye. Fundus autofluorescence must be performed prior to IOP measurement if IOP is to be assessed using Goldmann tonometry.

Table 12-1: Schedule of Events

Assessment	Screening[a]	Baseline	End of Treatment	Study Exit[b]	Early Termination[c]
Study Month	**-1**	**0**	**1**	**2**	
Study Day[d] ± window (days)	**-30 to -1[e]**	**1**	**30 ± 5**	**30 ± 5 days after Month 1 visit**	
Visit Number	**1**	**2**	**3**	**4**	
Informed consent	X				
Inclusion/Exclusion criteria	X	X[f]			
Demographics	X				
Medical, surgical, and ocular history	X	X			
Randomization		X			
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Abbreviated physical examination, height & weight	X[g]		X		X
Vital signs	X		X		X
12-lead ECG	X		X		X
Serum/urine pregnancy test for women of childbearing potential[h]	X	X	X	X	X
Clinical chemistry and hematology blood sample	X[i]		X	X[j]	X
ABCA4 genotype[k]	X				
BCVA[l]	X	X	X	X	X
Slit-lamp biomicroscopy[l]	X	X	X	X	X
IOP[l, m]	X		X		X
Dilated ophthalmoscopy[l]	X	X	X	X	X
Electroretinography[l]		X	X		X
Reduced-illuminance FAF[l]	X				
Dispense study drug		X			
Collect study drug and review compliance			X		X

[a] Screening must be performed ≤ 30 days before randomization.

[b] Study Exit to be completed 30 days after the last dose of study drug. If follow-up is needed after this visit, it should occur as an unscheduled visit.

[c] If the subject terminates early during the masked treatment phase, these evaluations should be performed at the time that study drug is stopped or as soon as possible after stopping study drug.

[d] Study day is based on 30 days = 1 month.

[e] If the subject is not dosed by Day 30 of the 30-day screening period, the subject may be re-screened by repeating all of the screening procedures.

[f] Review of the inclusion/exclusion criteria at Baseline must include confirmation of eligibility assessment from the central image reading center.

[g] Height will only be recorded at the Screening visit.

[h] Pregnancy test for women of childbearing potential will be via serum at Screening and via urine at all other visits.

[i] Any laboratory screening tests that meets the abnormality criteria stated in the exclusion criteria can be repeated once within the 30-day period from Screening to Baseline.

[j] Only perform if safety laboratory test results at the Month 1 or Early Termination visit were considered clinically significant by the Investigator.

[k] ABCA4 genotyping will be performed unless the subject's ABCA4 genotype is already documented.

[l] All required ophthalmic exams should be performed on both eyes at each study time point. For each visit, all ophthalmic exams must be performed on the same day and cannot be split among 2 or more days. Best-corrected visual acuity must be completed prior to any ophthalmic exam requiring contact with the eye.

[m] The site will attempt to collect IOP measurements at approximately the same time of day for a given subject. Intraocular pressure using Goldmann tonometry must be performed after FAF.

12.1 Early Termination

Subjects who discontinue from the study during the masked treatment phase will undergo an Early Termination visit when study drug is stopped, or as soon as possible after stopping study drug; they will then undergo Study Exit visit evaluations 30 days after the last study drug dose. If the Early Termination visit occurs ≥ 25 days after last study drug dose, the Early Termination and Study Exit visits may be combined.

12.2 Unscheduled Visits

Unscheduled visits may be necessary due to AEs or for other reasons. The Investigator may examine a subject as often as is medically necessary while the subject is enrolled in the study. In addition, if the Investigator believes follow-up is needed after the Study Exit or Early Termination visit, it should occur as an unscheduled visit at his/her discretion. Assessments performed at unscheduled visits are at the discretion of the Investigator.

13 Study Assessments

This section describes the study assessment procedures. For timing of study assessments, see the Schedule of Events (Table 12-1).

13.1 Informed Consent

At Screening, clinical sites will obtain a signed ICF from each subject prior to performing any study-related procedures (including any pre-treatment procedures or withdrawal from exclusionary medications). Informed consent must be obtained and documented in the subject's chart prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research.

13.2 Eligibility Assessment

At Screening, each inclusion and exclusion criterion must be checked and documented for each subject, and restricted and prohibited prior and concomitant therapy must be assessed and documented. Results of eligibility assessment from the central image reading center must be present prior to randomization.

At Baseline, eligibility requirements must be reviewed to determine if the subject is eligible to continue in the study.

13.3 Demographic Data

Demographic data, including age, sex, race, ethnicity, and iris color, will be collected at the Screening visit.

13.4 Medical, Surgical, and Ocular History

A medical, surgical, and ocular history should be obtained from each subject at Screening and updated at Baseline, and any time the Investigator learns of information that should be included in the subject's medical, surgical, or ocular history.

13.5 Prior and Concomitant Therapy

All current therapies and relevant prior therapies will be assessed at Screening and updated at Baseline. Concomitant therapies will be collected and recorded throughout the study.

13.6 Abbreviated Physical Examinations

The abbreviated physical examination will be performed by qualified study personnel. This will consist of a review of body systems and examination of the heart and lungs with a stethoscope. Based upon medical history and findings from the above portions of the exam, more detailed examinations of additional systems may be indicated including: skin, ears/nose/throat, abdomen, extremities, neurological system, and "other." Height will only be recorded at the Screening Visit. All abnormal findings will be recorded.

13.7 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, and respiratory rate) will be assessed by qualified study personnel after the subject has been resting in a sitting or supine position for at least 5 minutes.

13.8 12-Lead Electrocardiogram

Safety 12-lead ECGs will be obtained by qualified study personnel with the subject in a supine position after resting for at least 3 minutes. Electrocardiograms will be read by the Investigator or other qualified designee.

13.9 Pregnancy Testing

A serum pregnancy test will be conducted at the Screening visit, and a urine pregnancy test will be conducted at all other visits for women of childbearing potential.

13.10 Clinical Laboratory Evaluations

The laboratory assessments listed in Table 13-1 are to be performed according to the Schedule of Events (Table 12-1).

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study on the AE eCRF. All laboratory results must be reviewed promptly to evaluate the subject's safety. Prior to randomization, results must be present and evaluable for laboratory parameters associated with an exclusion criterion. With the exception of the urine pregnancy test, all laboratory assessments will be performed by a central laboratory.

Table 13-1: Clinical Laboratory Assessments Performed During the Study

Category	Parameters
Chemistry (serum)	Sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total protein, albumin, ALT, AST, total bilirubin, alkaline phosphatase, creatine phosphokinase, cholesterol, and triglycerides, uric acid, and eGFR (by the Modification of Diet in Renal Disease Study equation)
Hematology	Hematocrit, hemoglobin, red blood cell count, platelet count, and white blood cell count with automated differential (% and absolute count)
Pregnancy [a] (serum at Screening, urine at all other clinic visits)	ß-human chorionic gonadotropin

[a] Women of childbearing potential only

13.11 ABCA4 Genotype Testing

ABCA4 genotyping will be performed at Screening by a central laboratory unless the subject's ABCA4 genotype is already documented.

If only one ABCA4 allele has a pathogenic mutation, the subject must have a typical STGD phenotype (ie, at least one eye has flecks at the level of the RPE typically seen in STGD) and be approved for enrollment by the Sponsor.

13.12 Visual Acuity

Total BCVA letter score will be measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) retro-illuminated chart, the ETDRS electronic visual acuity (ETDRS-EVA) system, or the standard ETDRS wall chart in normal luminance lighting. Total BCVA letter score will be recorded as total letter score in each eye.

Visual acuity testing should precede any examination requiring contact with the eye. In order to provide standardization and well-controlled assessments of BCVA during the study, all BCVA assessments at a single site must be consistently done using the same lighting conditions during the entire study. The Investigator should also consistently use the same correction, chart type, and measurement procedure for an individual subject during the entire study.

13.13 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye prior to dilating the pupil. Magnification will be consistent with standard clinical practice. The subject will be seated during the examination. This procedure should be conducted in the same manner for all subjects and will include an assessment of each of the following as normal or abnormal:

- Eyelids
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Lens

All abnormal findings will be recorded.

13.14 Intraocular Pressure

Intraocular pressure will be measured in each eye and results will be recorded in mm Hg.

At visits where IOP is to be measured, a single measurement will be made. Contact or non-contact tonometry can be performed. The same tonometry method should be used throughout the study.

The tonometer must be calibrated for accuracy before the first subject in the study undergoes the first examination and according to manufacturer specifications during the study, until the last subject has exited the study.

The site will attempt to collect IOP measurements at approximately the same time of day for a given subject. If IOP is measured using a Goldmann tonometer, it must be performed after FAF.

13.15 Dilated Ophthalmoscopy

A dilated fundus examination will be performed for each eye in all subjects. The following will be observed for the presence of abnormalities:

- Vitreous
- Peripheral retina
- Macula
- Choroid
- Optic nerve

All abnormal findings will be recorded.

13.16 Electroretinography

Full-field electroretinography will be performed for each eye in all subjects. Electroretinography data will be sent to the central ERG reading center to be evaluated.

Electroretinography will be performed per the ERG manual. Briefly, the ERG procedure will begin with the subject's pupils being maximally dilated, followed by a period of dark adaptation that lasts for at least 30 minutes. At the end of this period, an electrode (Dawson Trick Litskow [DTL] fiber) will be placed on each eye under dim red light, and a rod response and a maximal response (mixed) ERG will be recorded. Following a single-flash cone response and 31 Hz flicker response at the end of a 10-minute period of light adaptation, subjects will undergo photobleaching for a period of 3 minutes. Rod responses will be recorded immediately after photobleaching and at 10, 20, and 30 minutes following the photobleaching.

13.17 Reduced-illuminance Fundus Autofluorescence

Reduced-illuminance FAF images will be obtained to assess lesion characteristics of each eye for all subjects. For reduced-illuminance FAF, Spectralis models must be used as described in

the central image reading center manual. Images will be sent to the central image reading center to confirm eligibility.

The study personnel who perform reduced-illuminance FAF will be trained and certified by the central image reading center prior to enrollment of subjects.

13.18 Evaluation of Adverse Events

All AEs (serious and nonserious) must be recorded in the source documents and AE eCRFs, regardless of causal relationship with study drug or procedures. AEs must be captured from the time the subject signs the ICF through the earlier of either the final study visit or 30 days after the last study drug dose. The following information will be collected about each AE: severity, onset and resolution dates and times, frequency, seriousness, relationship to study drug, action taken, outcome, location, and whether the AE caused the subject to discontinue from the study.

13.18.1 Definitions

An AE is any untoward medical occurrence in a subject administered a study drug and does not necessarily have to have a causal relationship with the study drug.

AEs may include:

- Any unfavorable sign, medical diagnosis, or symptom. Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single AE term (eg, “cough, rhinitis, and sneezing” might be grouped together as “upper respiratory tract infection”).
- An unfavorable change of a pre-existing condition that occurs during the protocol-defined reporting period.
- Clinically significant laboratory abnormalities, ophthalmic assessments, or vital signs. If possible, abnormal laboratory results or changes in vital signs that meet the definition of an AE should be reported as a clinical diagnosis, rather than the abnormal laboratory value (eg, “hypertension” rather than “blood pressure increased”).

Special considerations include:

- A medical or surgical procedure, itself, should not be captured as an AE. The Investigator should determine whether or not the medical condition or diagnosis necessitating such treatment is an AE, eg, the worsening of a pre-existing condition or a new diagnosis.

- Changes in pre-existing medical conditions, including worsening severity, frequency, or character during the protocol-defined reporting period, should be recorded as AEs.
- Death itself is not considered an AE. The cause of death should be reported as a serious adverse event (SAE).
- Pregnancy is not an AE. Pregnancy in a female subject or the partner of a male subject should be reported to the Sponsor in accordance with Section 13.18.4.

A **treatment-emergent AE** is any AE that occurs after the subject has received the first dose of study drug, whether or not it is considered causally related to the study drug.

A **serious AE** includes any event that, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death
- Life-threatening (ie, the subject was at immediate risk of death at the time of the event). It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect of offspring
- An important medical event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the subject or might require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

AE Severity:

AEs will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. The criteria can be accessed at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The term “severe” is a measure of intensity. A severe AE is not necessarily a serious AE.

Study Drug Causality:

Relationship of an AE to treatment will be assessed by the investigator as follows:

Causality	Definition
Related	There is a reasonable causal association with administration of the drug; the event is confirmed by stopping and/or restarting the drug or is not explained by any other reasonable hypothesis; there is evidence to suggest a causal relationship between the drug and the AE.
Not related	There is no causal or temporal relationship to the study drug administration; the event is related to other etiologies such as concomitant medications or conditions.

13.18.2 Adverse Event Reporting Procedures

Subjects will be instructed to report all AEs that occur during their study participation. The Investigator will assess subjects for the occurrence of AEs at all scheduled and unscheduled visits. The occurrence of AEs should be elicited by non-direct questioning of the subject at each visit, eg, "Have you had any problems since your last visit?" The Investigator may detect AEs while performing a physical examination or other assessments. All AEs (serious and nonserious) reported by the subject will be reviewed by a qualified Investigator in the study and must be recorded on the source documents and AE eCRFs.

An AE that is serious must be reported on an SAE form to the Sponsor's Drug Safety department no later than 24 hours after the Investigator becomes aware of the event.

SAE Notification

[redacted]

All SAEs occurring after the ICF is signed but before administration of study drug that are considered **related** to a protocol procedure must also be reported to Drug Safety within 24 hours after the clinical site becomes aware of the event.

For SAEs that occur before the first dose of study drug is administered and that are considered **unrelated** to any study procedure by the Investigator, record the SAE on the AE eCRF only; completion of an SAE form and reporting to Drug Safety is not required for such events.

If an ongoing SAE changes in intensity, outcome, or the relationship to study drug, a follow-up SAE report should be sent to the Sponsor within 24 hours after the clinical site becomes aware of the change in status.

13.18.3 Reporting Serious Adverse Events to Regulatory Agencies

The Sponsor will determine which SAEs qualify for expedited reporting. Reports of those SAEs that qualify for expedited reporting will be submitted to regulatory agencies in accordance with applicable local regulation (eg, 21 Code of Federal Regulations [CFR] 312.32). Expedited reports will be also distributed to Investigators, but without revealing the treatment assignment, and will be submitted to the IRB in accordance with institutional guidelines and local regulation.

13.18.4 Pregnancy

Pregnancy itself is not an AE. However, any report of pregnancy that occurs in a female subject or the partner of a male subject during study participation or within 30 days after the subject's last dose of study drug, and that becomes known to the Investigator, must be reported to the Sponsor even if the subject is withdrawn from study.

If a subject or Investigator suspects that a subject may be pregnant prior to study drug administration, the study drug administration must be withheld until the results of blood serum or urine pregnancy tests are available. If pregnancy is confirmed, the subject must not receive the study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must be withheld immediately until the result of the serum pregnancy test is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be withdrawn from the trial.

The Investigator must follow the pregnancy to conclusion and will collect data on both maternal and fetal outcome including follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Infants will be followed for a minimum of 6 months.

Pregnancy itself should be entered as an AE in the eCRF and reported to Drug Safety on the Pregnancy Report Form. Any abnormal pregnancy outcome should be reported to the Sponsor

in accordance with Section 13.18.2. This includes spontaneous abortion and any neonatal outcome that meets the seriousness criteria.

13.18.5 Overdose

Overdose is defined as any dose higher than the defined or prescribed dose of study drug. Occurrences of overdose will be documented as protocol deviations. An overdose resulting in an AE will be reported on the AE eCRF.

An overdose leading to an SAE will be reported to the Sponsor in accordance with the procedure described in Section 13.18.2.

13.18.6 Follow-up of Adverse Events

Subjects with ongoing SAEs will be followed until the event(s) is resolved, stabilized, no longer considered clinically significant by the Investigator, or the subject dies or withdraws consent.

Resolution means the subject has returned to the baseline state of health. Stabilization means the Investigator does not expect any further improvement or worsening in the subject's condition.

All nonserious AEs will be followed through the last scheduled or unscheduled visit.

For a nonserious AE that is first identified on the last scheduled contact (and with onset ≤ 30 days after the last study drug dose), the event must be recorded on the AE eCRF with the current status noted, but no further follow-up needs to be performed.

Nonserious AEs which occur > 30 days after the last study drug dose will not be recorded on the AE eCRF.

13.18.7 Follow-up of Post-study Serious Adverse Events

Any new SAE reported by the subject to the Investigator, with onset after the earlier of the final study visit or 30 days after the last study drug dose and that is determined by the Investigator to be associated with the use of study drug, should be reported to the Sponsor. The Investigator should follow these related SAEs and continue to report any significant follow-up information to the Sponsor until the events are resolved or stabilized, or the subject is lost to follow-up.

14 Data Monitoring Committee

This study will not use a Data Monitoring Committee to evaluate safety data. A Safety Review Team consisting of Sponsor staff and/or consultants will periodically review aggregate safety data.

15 Study Endpoints

15.1 Pharmacodynamic Endpoint

The PD endpoint is the percent suppression at the end of the 1-month treatment period compared to baseline of the rod b-wave amplitude recovery after a photobleaching light.

15.2 Safety Endpoints

Safety endpoints will include:

1. Incidence, severity, and seriousness of AEs, and discontinuations due to AEs.
2. Change from baseline in laboratory values, vital signs, physical examination findings, ECGs, and ophthalmic assessments.

16 Statistical Analysis and Study Variables

16.1 Determination of Sample Size

This study will enroll approximately 30 subjects with a goal of having 24 subjects (8 per treatment arm) complete the masked treatment phase of the study. This sample size is not based on statistical rationale but is considered adequate to determine the PD response of each dose of emixustat in this study population.

16.2 Data Sets to be Analyzed

The ERG variables will be analyzed using the PD set of subjects, and all safety variables will be analyzed using the Safety Analysis (SA) set of subjects. The determination of subjects included in these data sets will be made prior to locking the final database. These data sets are defined below.

16.2.1 Pharmacodynamic Set

The PD set of subjects will include all randomized subjects who have at least 1 post-baseline ERG performed while on study drug that is considered at least partially analyzable by the central ERG reading center.

16.2.2 Safety Analysis Set

The SA set of subjects will include all randomized subjects who took at least 1 dose of study drug. Subjects will be analyzed in the group according to the treatment they received, and no subjects (or data) will be excluded from this data set because of protocol deviations that occur during the study.

16.3 Subject Disposition

Subject disposition including the number of subjects randomized, treated with masked study drug, completing each study visit, and completing the study will be tabulated by treatment arm. The percentage of subjects treated and completing the study will be based on the total number randomized. Major protocol deviations will also be summarized by treatment arm. Subject discontinuations and the reasons for discontinuation will also be summarized for all randomized subjects.

16.4 Analysis of Demographic and Baseline Data

Subject demographic and baseline data will be summarized by treatment arm for all randomized subjects. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum), and categorical variables will be summarized using the count and percentage of subjects in each category.

16.5 Compliance and Exposure

Study drug will be administered orally QD in the evening for 1 month, until the evening before the Month 1 visit.

Subjects will be instructed to return all used and/or unused blister packs of study drug to the clinic at the Month 1 visit for assessment of dosing compliance. Subjects will be queried regarding compliance with the dosing regimen, and any missed doses will be documented. Compliance and total exposure information will be summarized.

16.6 Pharmacodynamic Analysis

The primary analysis of the ERG data will be performed on the data through Month 1, and will be performed after all subjects have either completed Study Exit visit or discontinued early from the study, and the study database has been cleaned, verified, and locked. It is planned that the data from all clinical sites that participate in this study will be combined, so that the target sample size will be available for analysis. Further details of the statistical methods will be included in the Statistical Analysis Plan.

Pharmacodynamic variables will include ERG rod b-wave amplitudes and the degree of suppression of the rod b-wave amplitude recovery following a photobleaching light. The degree of suppression will be determined as the percent decrease from baseline to post-treatment in the rate of recovery of the rod b-wave amplitude during the 30-minute post-bleaching period. Results will be summarized by treatment group.

16.7 Safety Analysis

All safety variables will be analyzed using the SA set of subjects. The assessment of safety will be based on the summaries of ocular and non-ocular AEs, ophthalmic examination findings, vital signs, physical examination findings, ECGs, and clinical laboratory values. Subjects will be summarized in the group according to the treatment received.

Adverse events reported during the study will have their verbatim terms mapped to the corresponding thesaurus terms from the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary. All summaries of AEs will be based on the assigned MedDRA Preferred Term and System Organ Class, and summaries will be given for each of the randomized treatment arms.

Separate summaries of AEs related to treatment (as reported by the Investigator) and by severity will be prepared. The number of SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

Other safety assessments will be presented descriptively (absolute values and changes from baseline). These will include total BCVA letter score, IOP, vital signs, clinical laboratory values, and ECG findings. Continuous variables will be summarized using descriptive statistics, and categorical variables will be summarized using the count and percentage of subjects in each category. Shift tables will be prepared by treatment arm showing all categorical changes from baseline to each study visit.

16.8 Subgroup Analysis

Because of the small number of subjects in this study, no subgroup analyses are planned.

16.9 Interim Analyses

No interim analyses are planned during this study.

17 Data Handling and Quality Assurance

17.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain an accurate eCRF and source documentation as part of the case history for each subject. Source documentation may include chart notes, laboratory reports, and ECG strips.

All requested information is to be filled in on the eCRF. If an item is not available or is not applicable, this should be indicated. Blank data fields should not be present unless otherwise directed.

Each completed eCRF must be reviewed, signed, and dated by the Investigator in a timely manner.

17.2 Monitoring of the Study

The CRA, a representative of the Sponsor, will follow the study closely. The CRA will maintain necessary email, telephone, fax, and/or mail contact with the Investigators and study site and will visit the study sites at periodic intervals. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigators and study site staff. During those visits, the CRA will compare the subject data recorded in the eCRF against source documents at the clinical site. The CRA will be masked to the identity of each subject's treatment assignment.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to the International Council for Harmonisation (ICH) guideline E6 (R1): Good Clinical Practice (GCP): Consolidated Guideline and current standard operating procedures.

17.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to all study records. The Investigator or study site may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the Food and Drug Administration (FDA), or other regulatory agency access to all study records.

The Sponsor will review eCRF data and perform electronic edit checks on the data.

The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

17.4 Study Record Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical study must be retained by the investigator. Original source documents for each subject should be included in this documentation. Study documentation should be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary. Study documentation includes records of laboratory tests, clinical notes, and subject medical records. It is the responsibility of the Sponsor to inform the Investigator/institution as to when this documentation no longer needs to be retained.

Records containing subject medical information must be handled in accordance with the requirements of the applicable privacy rules and consistent with the terms of the subject authorization contained in the ICF for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the ICF. Furthermore, eCRFs and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of subject identities. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRB with direct access to original source documents.

Essential documents should be retained until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for longer, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

18 Study Ethical Considerations

18.1 Ethical Conduct of the Study

The Investigator agrees that the study will be conducted according to the GCP principles of the ICH E6 (R1) guideline and the principles of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects 1964,

including all amendments and Notes of Clarification. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

18.2 Informed Consent

Written informed consent in compliance with Title 21 of the CFR Part 50 shall be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involves risk to the subject. An ICF template may be provided by the Sponsor or designee to investigative sites. The ICF will be submitted by the Investigator to his or her IRB for review and approval prior to the start of the study. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF should be reviewed by the Sponsor and/or its designee, if appropriate, prior to IRB submission. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the nature of the study and the action of the study drug. The subject will be informed that participation is voluntary and that they can withdraw from the study at any time. The subject will be allowed to read the approved ICF. Once the Investigator is assured that the subject agrees to participate in the study, the subject will be asked to give consent by signing the ICF.

The Investigator shall provide a copy of the signed and dated ICF to the subject. The original shall be maintained in the subject's medical records at the site. The informed consent process will be documented in the subject's medical records.

18.3 Institutional Review Board

Federal regulations and ICH guidelines require that approval be obtained from an IRB prior to participation of human subjects in research studies. Prior to the study onset at any given Investigator site, an appropriate IRB must approve the protocol, ICF, advertisements to be used for subject recruitment, and any other written information regarding this study that is to be provided to the subject. Documentation of all IRB approvals and of the IRB compliance with the ICH E6 (R1) guideline will be maintained by the site and will be available for review by the Sponsor or its designee.

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

The Investigator will supply the following to the investigative site's IRB:

- Protocol and amendments

- Informed consent form and updates
- Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB

The Investigator must provide written documentation of the following to the Sponsor or designee:

- IRB periodic (eg, quarterly, annual) re-approval of the protocol, as required by the IRB
- IRB approvals of any amendments to the protocol or revisions to the ICF
- IRB receipt of safety and SAE reports, as appropriate

19 Administrative Considerations

19.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA (or other international regulatory agency), or the IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

19.2 Modification of the Protocol

The Investigator may implement a change from the protocol without prior Sponsor and IRB approval only to eliminate an immediate hazard to a subject, in which case, Sponsor and IRB must be notified of the change within 24 hours.

Amendments to the protocol must be submitted in writing to the FDA and/or other regulatory agencies and IRB and approved prior to subjects being enrolled into an amended protocol.

19.3 Protocol Deviations

A protocol deviation occurs when the Investigator or subject has failed to adhere to protocol requirements. All significant deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment should be documented. Specific categories to be documented include but are not limited to:

- Subjects who enter the study even though they do not satisfy the entry criteria
- Subjects who develop withdrawal criteria during the study but are not withdrawn
- Subjects who receive the wrong treatment or incorrect dose
- Subjects who receive a prohibited concomitant treatment

Other protocol deviations to be considered include nonadherence to the protocol that results in a significant additional risk to the subject.

The Investigator must document and explain any protocol deviation in the subject's source documentation. The IRB should be notified of important protocol deviations in a timely manner, in accordance with IRB requirements. Protocol deviations should be reported to the IRB periodically, according to their requirements. Protocol deviations will also be documented by the clinical monitor during monitoring visits and those observations will be reviewed with the Investigator.

The Investigator is responsible for enrolling subjects who have met protocol eligibility criteria. If the Investigator has a question concerning a subject who may not meet an entry criterion, they should contact the Medical Monitor to discuss the specifics. *Waivers for protocol eligibility will not be granted in this study.*

19.4 Study Reporting Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit periodic reports to his/her IRB as appropriate.

19.5 Financial Disclosure

Principal Investigators and Sub-investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under Title 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to update this information promptly, if any relevant changes occur during the course of the investigation, at the completion of the trial, and 1 year following the completion of the study.

19.6 Financial Obligations

The Sponsor is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor is not financially responsible for further treatment of the subject's disease.

19.7 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6 (R1), Section 8.2 and Title 21 CFR by providing the following essential documents, including but not limited to:

- An Investigator-signed Investigator Agreement page of the protocol (Section 20)
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject
- IRB approval of the Investigator and protocol
- IRB acknowledgement of receipt of the Investigator's Brochure
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curricula vitae for the Principal Investigator and each Sub-investigator listed on Form FDA 1572. Current licensure must be noted on the curricula vitae or a copy of the license provided. The curricula vitae must be signed and dated by the Principal Investigators and Sub-investigators within 1 year of study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under Title 21 CFR 54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation, at the completion of the trial, and 1 year following the completion of the study.

19.8 Clinical Trial Agreement

Payments by the Sponsor to Investigators and institutions conducting the study, requirements for Investigators' insurance, and other requirements are specified in the Clinical Trial Agreement.

19.9 Policy for Publication and Presentation of Data

Following completion of the study at all sites, data may be considered for reporting at a scientific meeting and/or for publication in a scientific journal. Draft manuscripts of any public disclosure shall be provided to the Sponsor 60 days prior to presentation or publication in order to enable the Sponsor to review and comment and take any steps necessary to protect its intellectual property rights, consistent with the Clinical Trial Agreement.

20 Investigator Agreement

I agree to conduct the study as outlined in the protocol entitled, "A Phase 2a Multicenter, Randomized, Masked Study Evaluating the Pharmacodynamics of Emixustat Hydrochloride in Subjects with Macular Atrophy Secondary to Stargardt Disease," and in accordance with generally accepted standards of GCP, and all applicable guidelines and government regulations including Title 21 CFR 54. I agree to provide the Sponsor with accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by applicable regulations.

I have read and understand all sections of the protocol, including the sections on study ethical considerations (Section 18) and administrative considerations (Section 19).

_____
Principal Investigator's Name

_____ _____
Principal Investigator's Signature Date

21 References

1. Blacharski PA. Fundus flavimaculatus. In: Newsome, DA, ed. Retinal dystrophies and degenerations. New York: Raven Press, 1988:135-159.
2. Abdollahi S, Hirose T. Stargardt-fundus flavimaculatus: Recent Advancements and Treatment. Seminars in Ophthalmology, 2013; 28(5–6):372–376.
3. Molday RS. Insights into the molecular properties of ABCA4 and its role in the visual cycle and Stargardt disease. Prog Mol Biol Transl Sci. 2015;134:415-31.
4. Chen Y, Okano K, Maeda T, et al. Mechanism of all-trans-retinal toxicity with implications for Stargardt disease and age-related macular degeneration. J Biol Chem. 2012 Feb 10; 287(7):5059-69.

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6. Bavik C, Henry SH, Zhang Y, Mitts K, McGinn T, Budzynski E, et al. Visual Cycle Modulation as an Approach toward Preservation of Retinal Integrity. PLoS ONE. 2015;10(5):e0124940.
7. Kubota R, Al-fayoumi S, Mallikaarjun S, Patil S, Bavik C, Chandler JW. Phase 1, dose-ranging study of emixustat hydrochloride (ACU-4429), a novel visual cycle modulator, in healthy volunteers. Retina. 2014;34(3):603-9.

22 Appendices

22.1 Appendix A: Summary of Changes for Amendments

22.1.1 Protocol Amendment 1, Summary of Changes, dated 13 July 2017

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Title page	Acucela Inc 1301 Second Ave, Suite 4200 Seattle, WA 98101-3805	Acucela Inc 818 Stewart St, Suite 1110 Seattle, WA 98101	Sponsor address change	None
Section 2, Key Roles and Contacts	Acucela Inc 1301 Second Ave, Suite 4200 Seattle, WA 98101-3805	Acucela Inc 818 Stewart St, Suite 1110 Seattle, WA 98101	Sponsor address change	None
Section 9.2, Inclusion Criteria	4. Total area of definitely decreased autofluorescence MA in the study eye equal to 1.25 - 18 mm^2 (~0.5 – 7 disc areas) in size as determined by the central image reading center's assessment of fundus autofluorescence (FAF) imaging at Screening.	4. Total area of MA (definitely decreased autofluorescence plus questionably decreased autofluorescence) in the study eye equal to 1.25 - 26 mm^2 (~0.5 – 10.25 disc areas) in size as determined by the central image reading center's assessment of fundus autofluorescence (FAF) imaging at Screening.	Allows a broader population to be enrolled.	None