PROTOCOL TITLE:	A Multicenter, Randomized, Double-Masked, Placebo-Controlled, Pilot Study to Evaluate Effects of Emixustat Hydrochloride on Aqueous Humor Biomarkers Associated with Proliferative Diabetic Retinopathy
PROTOCOL NUMBER:	4429-203
NAME OF TEST ARTICLE:	Emixustat hydrochloride
[redacted]	[redacted]
INDICATION:	Proliferative Diabetic Retinopathy
DEVELOPMENT PHASE:	Phase 2
STUDY DESIGN:	Multicenter, randomized, double-masked, placebo-controlled, parallel-group
SPONSOR:	Acucela Inc. 1301 Second Ave, Suite 4200 Seattle, WA 98101-3805
DATE OF PROTOCOL:	05 February 2016
NCT NUMBER:	02753400

This study will be conducted in accordance with the International Conference 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

Protocol Number:	4429-203
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Approved by:

[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. 1301 Second Ave, Suite 4200 Seattle, WA 98101-3805 Phone: 206-805-8300
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3 Protocol Summary

Protocol Number:	4429-203
Protocol Title:	A Multicenter, Randomized, Double-Masked, Placebo-Controlled, Pilot Study to Evaluate Effects of Emixustat Hydrochloride on Aqueous Humor Biomarkers Associated with Proliferative Diabetic Retinopathy
Phase:	Phase 2
Study Objectives Primary:	To evaluate the effects of oral emixustat hydrochloride (emixustat) on aqueous humor biomarkers (interleukin [IL]-6, IL-8, interferon-gamma inducible protein [IP]-10, platelet-derived growth factor [PDGF]-AA, transforming growth factor [TGF]β-1, monocyte chemo-attractant protein [MCP]-1, IL-1β, and vascular endothelial growth factor [VEGF]) associated with proliferative diabetic retinopathy (PDR) from baseline to Day 85
Secondary:	To evaluate the effects of oral emixustat on: 1. Change in area of retinal neovascularization (NV) from baseline to Day 85 2. Change in degree of vitreous hemorrhage from baseline to Day 85 3. Change in degree of preretinal hemorrhage from baseline to Day 85 4. Change in normal luminance best-corrected visual acuity (NL-BCVA) from baseline to Day 85 5. Change in central subfield thickness (CST) as assessed from spectral domain optical coherence tomography (SD-OCT) from baseline to Day 85 in subjects with diabetic macular edema (DME) 6. Change in retinal vessel oxygen saturation as measured by retinal oximetry imaging from baseline to Day 85 7. Safety and tolerability compared to placebo when administered orally for 84 days

Exploratory:	n/a
Study Population:	Subjects newly or recently diagnosed with PDR, with or without DME
Study Design:	This is a multicenter, randomized, double-masked, placebo-controlled study to evaluate the effects of emixustat in subjects with PDR. Subjects will be randomly assigned to one the following treatment arms in a 1:1 ratio: • Emixustat, up to 40 mg (step-up titration) • Placebo Subjects will be treated once daily (QD), in the evening, for a total of 84 days. Subjects assigned to the emixustat arm will receive 5 mg QD oral emixustat for the first week, then the dose will be doubled on a weekly basis to 10 mg QD (week 2), 20 mg QD (week 3), and 40 mg QD (week 4). Subjects who do not tolerate dose escalations will be returned to and held stable at the last tolerated dose; after week 4, all subjects will be held at a stable dose for the remainder of the study. Dose reduction may be undertaken only once and is only available at Visit 4, Visit 5, or Visit 6. Subjects in the placebo group will be mock-titrated on the same schedule as those in the step-up titration arm.
Number of Subjects:	Approximately 20 subjects from up to 7 clinical sites in the United States will be enrolled.
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. Able and willing to provide a written informed consent before undergoing any study-related procedures. 2. In the opinion of the investigator, the ability and willingness to return for all scheduled visits and perform all assessments. 3. Males or females, ≥ 18 and ≤ 85 years of age at the Screening Visit.

	4. A documented diagnosis of type 1 or type 2 diabetes mellitus. Any one of the following will be sufficient evidence that diabetes is present: a. Current regular use of insulin for the treatment of diabetes b. Current regular use of an oral anti-hyperglycemia agent for the treatment of diabetes c. Documented diabetes by American Diabetes Association (ADA) and/or World Health Organization (WHO) criteria (see Appendix C for definitions) 5. The following ocular criteria for the study eye: a. Presence of PDR with or without DME for which, in the Investigator's judgment, interventional treatment can be safely deferred for at least 4 weeks after the Day 1 visit. b. No prior pan-retinal photocoagulation (PRP); defined as ≥ 500 burns placed previously outside the posterior pole. c. No intravitreal injection of an anti-VEGF agent in the 3 months prior to randomization (Day 1). d. No intravitreal or peri-bulbar injection of a corticosteroid in the 4 months prior to randomization (Day 1). e. Early Treatment Diabetic Retinopathy Study (ETDRS) NL-BCVA letter score of ≥ 24 (approximate Snellen equivalent 20/320) on the day of randomization (Day 1). f. Media clarity, pupillary dilation, and subject cooperation sufficient to obtain adequate fundus photographs and SD-OCT.

Exclusion Criteria:	Subjects will be excluded from participation in the study if they meet any of the following criteria at screening and baseline (unless otherwise indicated): 1. Any condition that, in the opinion of the investigator, would preclude participation in the study (eg, unstable medical status including blood pressure, cardiovascular disease, or glycemic control). 2. Subjects with poor glycemic control, including those who initiated intensive insulin treatment (a pump or multiple daily injections) in the 4 months prior to Screening, or plan to do so in the next 4 months. 3. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant. 4. Elevated blood pressure (defined as > 180/110; systolic above 180 or diastolic above 110). Subjects with elevated blood pressure, when attributable to specific circumstances (eg, missed medication, stress etc.), may be retested on the same or later date, as appropriate (within the period between Screening and randomization (Day 1). 5. History of myocardial infarction or other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 60 days prior to randomization. 6. Previous participation (ie, randomization) in a study of emixustat. 7. Participation (ie, randomization) in another investigational trial within 30 days of the Screening Visit that involved treatment with any drug that has not received regulatory approval for the indication being studied. 8. Known allergies to fluorescein sodium for injection in angiography, to emixustat, or to any excipients in the emixustat tablets (ie, silicified microcrystalline cellulose, pre-gelatinized starch, colloidal silicon dioxide, or stearic acid).

	9. Prohibited medications: a. Systemic use of a strong inducer of or a strong or moderate inhibitor of cytochrome P450 2D6 (CYP2D6;as listed in Appendix B) beginning 4 weeks prior to screening and throughout the duration of the study period. b. Anti-coagulant therapy (eg, heparins, warfarin, other oral anti-coagulants) beginning 14 days prior to screening and throughout the duration of the study. Anti-platelet therapy (eg, aspirin, clopidogrel) is allowed. 10. History of systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization or plan for such treatment during the course of the study. 11. Any of the following laboratory abnormalities at screening: a. Aspartate transaminase (AST)/alanine transaminase (ALT) >3.0 x upper limit of normal (ULN) b. Total bilirubin >1.5 x ULN c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 d. Impaired coagulation: International Normalized Ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) >1.25 x ULN e. Impaired hematologic function: hemoglobin <9.0 g/dL; neutrophil count <1.6 x 10^9/L; or platelet count <100 x 10^9/L f. Any laboratory screening test that meets the abnormality criteria stated above can be repeated once within the period from screening to baseline. 12. Any of the following ocular characteristics in the study eye: a. Tractional retinal detachment involving the macula. A tractional retinal detachment is not an exclusion if it is

	outside the posterior pole (not threatening the macula) and, in the Investigator's opinion, is not considered a contraindication to deferring PRP, anti-VEGF therapy, or surgical intervention. b. Exam evidence of NV of the angle (NV of the iris alone is not an exclusion if it does not preclude deferring PRP or anti-VEGF therapy) c. A decrease in BCVA due to causes other than diabetic retinopathy (eg, foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, previous vitreoretinal surgery, non-retinal condition, substantial cataract, or macular ischemia) in the Investigator's opinion. d. An ocular condition (other than diabetic retinopathy) that, in the opinion of the Investigator, might alter visual acuity during the course of the study (eg, retinal vein or artery occlusion, uveitis or other ocular inflammatory disease, neo-vascular glaucoma, etc.). A vitreous or preretinal hemorrhage is not an exclusion if it is out of the visual axis and, in the Investigator's judgement, is not having any effect on visual acuity. e. History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within 3 months prior to the Screening Visit or anticipated to occur during the course of the study. f. History of YAG posterior capsulotomy performed within 2 months prior to randomization (Day 1) or anticipated during the course of the study. g. Aphakia h. Uncontrolled glaucoma (in the Investigator's judgement).

	i. Exam evidence of periocular or ocular infection (eg, blepharitis, chalazion, or conjunctivitis). j. Implantation of any of the following intraocular corticosteroid implants in the timeframe indicated: i. Fluocinolone acetonide (Iluvien®), in the 30 months prior to randomization (Day 1) ii. Dexamethasone (Ozurdex®), in the 4 months prior to randomization iii. Any other corticosteroid implant, in the 4 months prior to randomization k. Macular edema due to anything other than DME (eg, post ocular surgery, age-related macular degeneration, uveitis, retinal vein occlusion, or drug toxicity) 13. Change in a systemic prescription medication or a systemic medication newly prescribed within 30 days prior to screening and between screening and baseline or anticipated during the course of the study. 14. Presence of other disease, physical examination finding, or clinical laboratory finding that, in the opinion of the Investigator, gives reasonable suspicion of a disease or condition which contraindicates the use of an investigational drug, places the subject at risk by participating in the study, or confounds the ability to interpret data from the study. 15. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year prior to screening. 16. Electrocardiogram (ECG) 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. 17. Female subjects who are pregnant or lactating.

	18. 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 following the completion of the study. Medically accepted methods of birth control include abstinence, hormonal contraceptives, non-hormonal intrauterine contraceptive device with spermicide, condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide. 19. 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 completion of the study.
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 investigator should select the study eye as the eye with the least potential to require PRP, anti-VEGF therapy, or local corticosteroids during the study, in his/her opinion.
Test Product, Dose, and Mode of Administration:	Emixustat (2.5, 5, or 10 mg) tablets or placebo will be packaged in identical, tamper-proof, blister packaging to maintain masking. Study drug will be taken orally, QD, in the evening for 84 days. During Week 1, subjects randomized to emixustat will receive 4 tablets (two placebo, two 2.5 mg) per day for a 5 mg dose. During Week 2, subjects will receive 4 tablets (two placebo, two 5 mg) per day for a 10 mg dose. During Week 3, subjects will receive 4 tablets (two placebo, two 10 mg) per day for a 20 mg dose. During Weeks 4 through 12, subjects will receive four 10 mg tablets per day for a 40 mg dose. Subjects who do not tolerate dose escalations will be returned to and held at the last tolerated dose; after Week 4, all subjects will be held at a stable dose for the remainder of the study.

	Dose reduction may be undertaken only once and is only available at Visit 4, Visit 5, or Visit 6.
Reference Product, Dose, and Mode of Administration:	Placebo tablets will be packaged in identical appearing, tamper-proof, blister packaging to maintain masking. The placebo arm will include identical tablets with only inactive ingredients (0 mg emixustat). Subjects will receive 4 placebo tablets per day.
Study Procedures:	The scheduled visits include Screening (within 30 days prior to baseline), baseline (Day 1), and days 8, 15, 22, and 29 (±1 day) and days 57 and 85 (±5 days). The Day 85 visit will be one day after the last drug/placebo treatment. A Study Exit visit will be performed 30 days (±5 days) after the last dose of study drug. **Screening:** The screening visit (Visit 1) will occur within 30 days prior to baseline. Subjects who consent to participate will have a screening visit at which eligibility criteria will be reviewed, demographic data, previous/concomitant medications and medical/surgical/ocular history will be collected; abbreviated physical exam, vital signs, and 12-lead ECG will be performed; samples will be obtained for safety laboratory tests (blood chemistry, hematology, coagulation, urinalysis), including glycosylated hemoglobin A1c (HbA1c) and a serum pregnancy test for women of childbearing potential; NL-BCVA, ophthalmic exams (slit lamp, dilated ophthalmoscopy, intraocular pressure [IOP], gonioscopy), and SD-OCT will be performed. **Masked Dose Escalation Phase:** At Visit 2 (Baseline, Day 1), eligibility criteria will be reviewed again, and qualifying subjects will be randomized to 1 of the 2 treatment arms. Previous/concomitant medications and medical/surgical/ocular history will be reviewed, vital signs will be assessed, and samples for safety laboratory tests will be obtained (if Day 1 is >14 days after the screening visit); a urine pregnancy test will be performed in women of childbearing potential; NL-BCVA and LL-BCVA will be done, and ophthalmic examinations (slit lamp, dilated ophthalmoscopy, IOP, gonioscopy), fluorescein angiography (FA), color fundus photographs, SD-OCT, and retinal oximetry imaging (selected sites) will be performed. A 50

	µl sample of aqueous humor will be collected from the study eye by paracentesis and shipped the same day on dry ice. A one week supply of study drug (5 mg emixustat or placebo) will be dispensed, and subjects will self-administer drug (4 tablets) orally, QD, in the evening for 7 (± 1) days. Adverse events (AEs) will be assessed. At Visit 3 (Day 8 ± 1), subjects return for study drug, review of concomitant medications, and assessment of AEs; each subject will receive a 1 week supply of double the dose received at Visit 2 (10 mg emixustat or placebo), to be dispensed for self-administration, orally, QD (4 tablets) in the evening for 7 days (± 1 day). At Visit 4 (Day 15 ± 1), subjects return for study drug, a review of concomitant medications, and assessment of AEs; each subject will receive a 1 week supply of double the dose received at Visit 3 (20 mg emixustat or placebo), to be dispensed for self-administration, orally, QD, in the evening, for 7 days (± 1 day). At Visit 5 (Day 22 ± 1), subjects return for study drug, a review of concomitant medications, and assessment of AEs; each subject will receive a 1 week supply of double the dose received at Visit 4 (40 mg emixustat or placebo), to be dispensed for self-administration, orally, QD (4 tablets) in the evening for 7 days (± 1 day). Subjects who do not tolerate dose escalations due to AEs that, in the opinion of the investigator would otherwise lead to discontinuation of study drug will be returned to and held stable at the last tolerated dose (ie, dose reduction). Dose reduction may only be undertaken once and is only available at Visit 4 (Day 15), Visit 5 (Day 22), or Visit 6 (Day 29). **Masked, Fixed Dose Phase:** At Visit 6 (Day 29 ± 1), subjects return for study drug; a review of concomitant medications, urine pregnancy test (for women of childbearing potential), NL-BCVA, ophthalmic exams (slit lamp biomicroscopy, IOP, dilated ophthalmoscopy), SD-OCT, and retinal oximetry imaging (selected sites) will be performed. Each subject will receive a 4-week supply of study drug (40 mg emixustat or the last tolerated emixustat dose; or placebo), to be

	dispensed for self-administration, orally, QD (4 tablets) in the evening for 28 days. At Visit 7 (Day 57 ± 5), subjects return for study drug; a review of concomitant medications, urine pregnancy test (for women of childbearing potential), NL-BCVA, ophthalmic exams (slit lamp biomicroscopy, IOP, dilated ophthalmoscopy), SD-OCT, and retinal oximetry imaging (selected sites) will be performed. Each subject will receive a 4-week supply of study drug (40 mg emixustat or the last tolerated emixustat dose; or placebo), to be dispensed for self-administration, orally, QD (4 tablets), in the evening for 28 days. One day after the last dose of study drug, subjects return on Visit 8 (Day 85 ± 5 days) for a review of concomitant medications, and a urine pregnancy test (for women of childbearing potential) and vital signs recheck; samples for safety laboratory tests (including HbA1c) will be collected, and an abbreviated physical exam and 12-lead ECG will be performed; NL-BCVA and LL-BCVA will be measured, and ophthalmic examinations (slit lamp biomicroscopy, IOP, dilated ophthalmoscopy, gonioscopy), FA, color fundus photography, SD-OCT, and retinal oximetry imaging (selected sites) will be conducted. A 50 µl sample of aqueous humor will be collected from the study eye by paracentesis and shipped the same day on dry ice. **Study Exit:** A Study Exit visit will be performed 30 days (± 5 days) after the last dose of study drug. Concomitant medications will be reviewed and a urine pregnancy test (for women of childbearing potential), NL-BCVA, SD-OCT, and ophthalmic examinations (slit lamp biomicroscopy, IOP, dilated ophthalmoscopy) will be performed. **Rescue Treatment Criteria for PDR:** All subjects will be eligible for PRP or anti-VEGF therapy for PDR in the study eye as of Day 29 (Visit 6) of the study if the following criterion is met: • There is new NV or growth of NV of the retina, disc, angle, OR iris such that the NV is greater in extent than at Day 1 (Visit 2/Baseline). **Rescue Treatment Criteria for DME:**

	All subjects will be eligible for therapy for DME in the study eye as of Day 29 (Visit 6) of the study if either of the following criteria are met: a. Development or worsening of DME as illustrated by an increase in central retinal thickness of ≥100 microns from any previous visit (as measured by the Investigator). b. A BCVA decrease of ≥10 letters from any previous visit that is deemed secondary to DME. Subjects for whom it is determined that treatment with PRP, anti-VEGF therapy, or local corticosteroids in the study eye is necessary will discontinue study drug, be discontinued from the study, and undergo Early Termination assessments prior to any of these therapies. PRP, anti-VEGF agent therapy, focal laser therapy, or local corticosteroid therapy in the non-study eye is allowed at any time, at the Investigator's discretion. **Early Termination from Study:** Subjects who discontinue from the study early will undergo an Early Termination visit where all Day 85 visit assessments will be performed 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. Subjects who have received study drug for less than 21 days will not undergo collection of an aqueous humor sample at the Early Termination visit. If the Early Termination visit occurs ≥25 days after last study drug dose, the Early Termination and Study Exit visits may be combined.
Criteria for Evaluation Variables: Efficacy	Efficacy variables will include: 1. Aqueous humor concentration of the following biomarkers: IL-6, IL-8, IP-10, PDGF-AA, TGFβ-1, MCP-1, IL-1β, and VEGF 2. Area of retinal NV 3. Degree of vitreous hemorrhage 4. Degree of preretinal hemorrhage

	5. NL-BCVA 6. CST as assessed by SD-OCT in subjects with DME 7. Retinal vessel oxygen saturation
Pharmacodynamic:	Cytokine assessments constitute the pharmacodynamic efficacy variables.
Safety:	Safety variables will include AEs, NL-BCVA, LL-BCVA, slit-lamp biomicroscopy, SD-OCT, IOP, gonioscopy, dilated ophthalmoscopy, physical examination findings, vital signs, ECGs, and clinical laboratory tests. Pregnancy tests will be conducted in women of childbearing potential.
Study Endpoints Primary Efficacy:	The primary study endpoints are the change in aqueous humor concentration of eight biomarkers (IL-6, IL-8, IP-10, PDGF-AA, TGFβ-1, MCP-1 and IL-1β, and VEGF) from baseline (Day 1) to Day 85, the conclusion of a 84-day course of study drug. Analysis will include both absolute change and percent change from Baseline (Visit 2/Day 1) to Day 85 (Visit 8/Study Exit).
Secondary Efficacy:	The secondary efficacy endpoints will include the change in the following between the Baseline Visit and Day 85 (Visit 8): 1. Area of retinal NV 2. Degree of vitreous hemorrhage 3. Degree of preretinal hemorrhage 4. NL-BCVA 5. CST as assessed by SD-OCT in subjects with DME. 6. Retinal vessel oxygen saturation
Statistical Analyses:	Eight subjects per arm yields 80% power to detect a difference between emixustat and placebo in each aqueous humor biomarker, assuming an effect size of 1.31, using a two-sample t-test and a two-sided alpha level of 0.10. To account for potential early termination subjects, two additional subjects per treatment arm, for a total of 10 subjects per arm, will be enrolled. Primary and secondary endpoints will be summarized using standard quantitative (sample size, mean, SD, median, minimum, maximum, and 90% and 95% t-distribution confidence intervals [CI] around the mean) and qualitative (frequency counts, percentages, and exact 90%

	and 95% CIs around the percentages) summary statistics and assessed using two-sided 90% and 95% t-distribution CIs and two-sided, two-sample t-tests around the differences between treatment groups for quantitative measures. For the assessment of changes from baseline in aqueous humor concentration of the 8 biomarkers, both absolute and percent changes will be analyzed. Additionally for quantitative measures, 1-sample t-tests will be completed on the change from baseline values within a treatment group. Qualitative measures will be analyzed by exact McNemar's test for changes within a treatment group and Fisher's Exact Test for differences between treatment groups. Differences in proportions and 90% and 95% CIs will also be presented for comparisons between treatment groups for qualitative variables.
Study Duration:	The protocol calls for up to 30 days between initial screening and baseline (Day 1), an 84-day dosing duration and follow-up 30 days after last study drug dose; this yields a total duration of ~ 20 weeks, or 5 months.

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5 Glossary of Abbreviations and Definition of Terms

ABBREVIATION	DEFINITION
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
βHCG	ß-human chorionic gonadotropin
CFR	Code of Federal Regulations
CI	confidence interval
CRA	clinical research associate
CST	central subfield thickness
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450 (eg, CYP2D6)
DME	diabetic macular edema
ECG	electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FDA	Food and Drug Administration
HbA1c	glycosylated hemoglobin A1c
ICF	informed consent form
ICH	International Conference for Harmonisation
IL	interleukin (eg, IL-1, IL-2)
IND	Investigational New Drug (Application)
INR	international normalized ratio
IOP	intraocular pressure
IP-10	Interferon-gamma inducible protein 10
IRB	Institutional Review Board
LL-BCVA	low luminance best corrected visual acuity
MCP-1	monocyte chemotactic protein-1
msec	milliseconds
NL-BCVA	normal luminance best corrected visual acuity
NV	neovascularization
PDGF	platelet-derived growth factor

ABBREVIATION	DEFINITION
PDR	proliferative diabetic retinopathy
Pmin	minimum oxygen pressure
PO_2	partial oxygen pressure
PRP	panretinal photocoagulation
PT	prothrombin time
QD	once daily
SAE	serious adverse event
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
T4	thyroxine
TGFβ-1	transforming growth factor beta 1
ULN	upper limit of the normal range
VEGF	vascular endothelial growth factor
WHO	World Health Organization

6 Introduction

6.1 Background

Diabetes mellitus is one of the most common endocrine disorders in the world; it affected roughly 6% of the global population in the year 2000, and it is estimated that it will affect 300 million people by 2025(1). Diabetic retinopathy affects 28.5% of patients in the US adult diabetic population (2) and is the main cause of permanent vision loss in the US working population (3).

Early stages of diabetic retinal pathology involve microaneurysms, hemorrhages and other disruptions in retinal circulation. This early, non-proliferative stage may be followed by proliferative diabetic retinopathy (PDR), characterized by the pathological formation of new retinal blood vessels. Despite progress in diagnostics and therapies, PDR, if untreated, may lead to a terminal stage of neovascularization (NV) that is characterized by the development of secondary neovascular glaucoma in a number of cases. There is convincing scientific and clinical evidence that hypoxia is the driving force that mediates the development of retinal neovascularization (NV) in patients with diabetic retinopathy and other ischemic retinopathies (4-7).

6.2 Rationale for the Study

Emixustat directly modulates the visual cycle, the biochemical pathway that restores the chromophore (11-*cis* retinal) needed for phototransduction. It targets the RPE65 protein, which functions as a retinol isomerase. RPE65 converts all-*trans* retinyl esters to 11-*cis* retinol which, in turn, is converted to 11-*cis* retinal; 11-*cis* retinal is then again available for interaction with opsin and detection of light (Figure 1). In dark conditions (eg, while sleeping), phototransduction is inactive and photoreceptors consume large amounts of ATP and oxygen to fuel an ion pumping activity that is necessary to maintain electrochemical gradients across the outer segment membrane (4). This ion pumping activity is referred to as the dark current. The dark current is reversed during light adaptation when light causes the conversion of the chromophore 11-*cis* retinal to all-*trans* retinal. The chromophore dissociates from the opsin protein, producing apo-opsin – which activates the phototransduction machinery causing closure of ion channels and a decrease in retinal ATP and oxygen consumption by 40%–60%, relative to the dark adapted state (8).

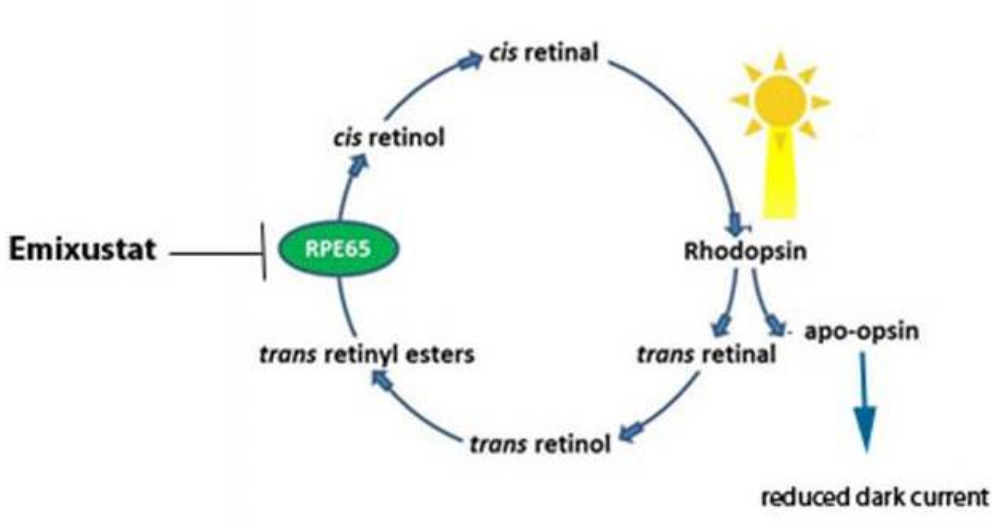

Figure 1 Emixustat inhibits the RPE65 isomerase in the visual cycle

Emixustat decreases levels of visual chromophore in photoreceptors, which is expected to result in increased levels of free opsin (ie, apo-opsin). Increased levels of apo-opsin have been shown to prevent complete dark adaptation through constitutive activation of rod phototransduction; this has been theorized to prevent hypoxia and preserve vasculature of the inner retina. [redacted]

[redacted]

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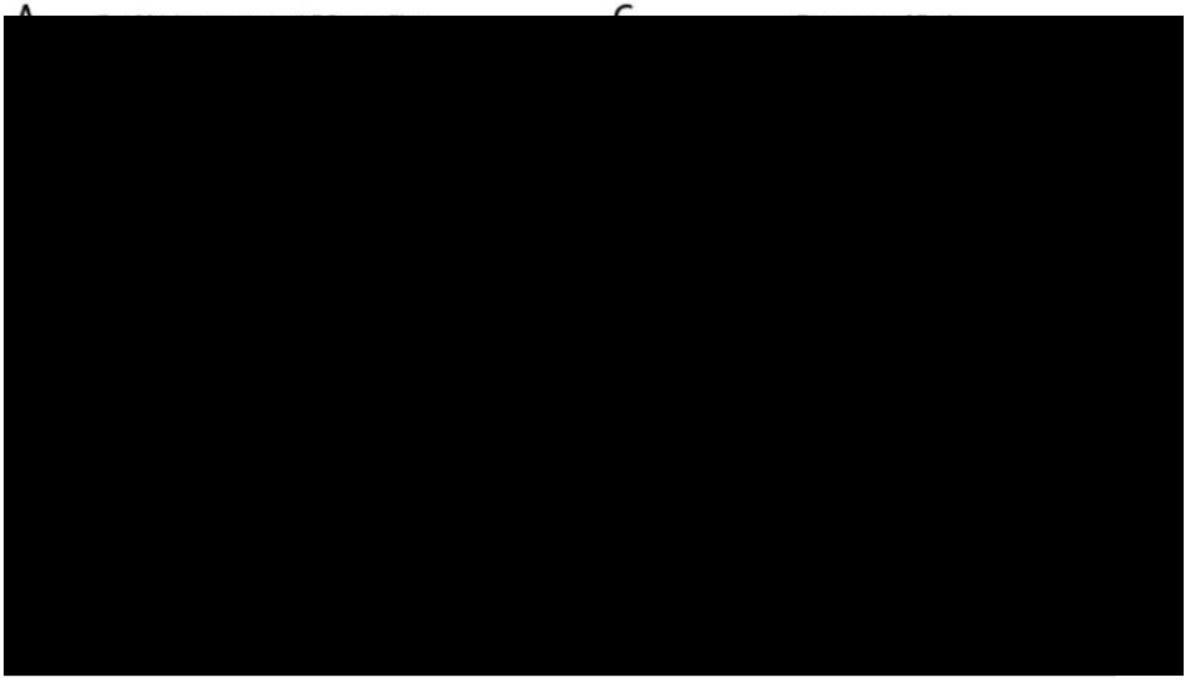

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Levels of biomarkers including interleukin 6 (IL-6), interleukin 8 (IL-8), monocyte chemo-attractant protein-1(MCP-1), interferon gamma-inducible protein 10 (IP-10), transforming growth factor beta 1 (TGFβ-1), vascular endothelial growth factor (VEGF), platelet-derived growth factor AA (PDGF-AA), and interleukin-1β have been shown to be elevated in the intraocular fluid of subjects with PDR (13-19). The association of visual cycle modulation to the levels of biomarkers in the aqueous humor of subjects with PDR is not known. The Sponsor is proceeding with a Phase 2 study which will evaluate the effect of emixustat on this panel of biomarkers in aqueous humor.

[redacted]

[redacted]

6.3 Rationale for Dose Selection

To evaluate the effect of visual cycle modulation on aqueous humor biomarkers in subjects with PDR, doses within the range previously assessed for safety 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 (20). 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 across the 10 mg to 40 mg cohorts, indicating no accumulation following QD dosing with emixustat for 14 days. A step-wise dose escalation regimen will be used to evaluate the safety of, and tolerability to, dosing durations longer than 2 weeks. Subjects will be treated for a total of 84 days. Subjects assigned to the emixustat arm will receive 5 mg daily oral emixustat for the first week, then the dose will be doubled on a weekly basis to 10 mg (week 2), 20 mg (week 3), and 40 mg (week 4). Subjects who do not tolerate dose escalations

will be returned to and held stable at the last tolerated dose; after week 4, all subjects will be held at a stable dose for the remainder of the study.

7 Study Objectives

7.1 Primary Objective

The primary objective of this study is to evaluate the effects of oral emixustat on aqueous humor biomarkers (interleukin [IL]-6, IL-8, interferon-gamma inducible protein [IP]-10, platelet-derived growth factor [PDGF]-AA, transforming growth factor [TGF]β-1, monocyte chemo-attractant protein [MCP]-1, IL-1β, and vascular endothelial growth factor [VEGF]) in subjects with PDR with or without diabetic macular edema (DME), from baseline to Day 85.

7.2 Secondary Objectives

The secondary objectives of this study are to evaluate the effects of oral emixustat on:

1. Change in area of retinal NV from baseline to Day 85
2. Change in degree of vitreous hemorrhage from baseline to Day 85
3. Change in degree of preretinal hemorrhage from baseline to Day 85
4. Change in normal luminance best-corrected visual acuity (NL-BCVA) from baseline to Day 85
5. Change in central subfield thickness (CST) as assessed by spectral domain optical coherence tomography (SD-OCT) from baseline to Day 85 in subjects with DME
6. Change in retinal vessel oxygen saturation as measured by retinal oximetry imaging from baseline to Day 85
7. Safety and tolerability compared to placebo when administered orally for 84 days

7.3 Exploratory Objectives

Not applicable

8 Investigational Plan

8.1 Overall Study Design and Plan

This is a multicenter, randomized, double-masked, placebo-controlled study to evaluate the effects of emixustat in subjects with PDR. Subjects will be randomly assigned to one the following treatment arms in a 1:1 ratio:

- Emixustat, up to 40 mg (step-up titration)
- Placebo

Subjects will take 4 tablets of study drug (emixustat or placebo) orally, QD, in the evening, for 84 days.

Emixustat (2.5, 5, or 10 mg) tablets or its placebo will be packaged in identical, tamper proof, blister packaging to maintain masking.

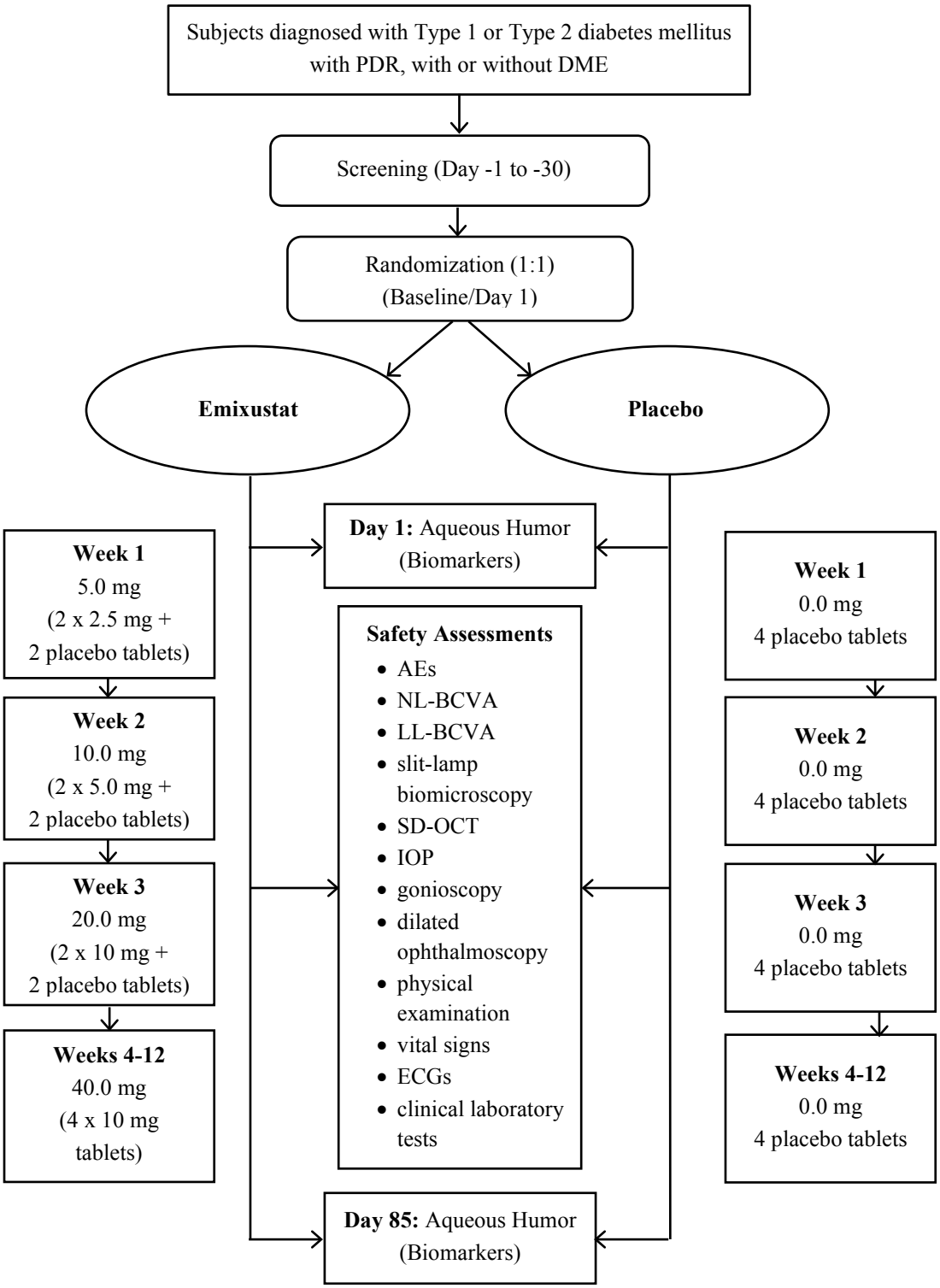
During Week 1, subjects randomized to emixustat will receive 4 tablets (two placebo, two 2.5 mg) per day for a 5 mg dose. During Week 2, subjects will receive 4 tablets (two placebo, two 5 mg) per day for a 10 mg dose. During Week 3, subjects will receive 4 tablets (two placebo, two 10 mg) per day for a 20 mg dose. During Weeks 4 through 12, subjects will receive four 10 mg tablets per day for a 40 mg dose. Subjects who do not tolerate dose escalations will be returned to and held stable at the last tolerated dose; after week 4, all subjects will be held at a stable dose for the remainder of the study.

Subjects in the placebo group will undergo the same dosing regimen of 4 tablets, QD, with the placebo therapy.

Aqueous humor collection for biomarkers will be conducted on Day 1 (Visit 2) and Day 85 (Visit 8). Safety assessments throughout the study will include adverse events (AEs), NL-BCVA, LL-BCVA, slit-lamp biomicroscopy, SD-OCT, intraocular pressure (IOP), dilated ophthalmoscopy, gonioscopy, physical examination findings, vital signs, electrocardiograms (ECGs), and clinical laboratory tests (blood chemistry, hematology, coagulation, urinalysis).

The study design is presented schematically in Figure 6.

Figure 6 Study Design Schema



8.2 Number of Subjects

Approximately 20 subjects will be enrolled in the study.

8.3 Study Sites

This study will be conducted at up to 7 clinical sites in the United States.

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

Randomization and double-masking will be used to minimize bias in subject selection and the evaluation of subjects during the study. A placebo control is included to provide an objective comparison for the safety and efficacy of emixustat.

Doses within the range previously assessed for safety have been selected, and a QD dosing regimen is based on the pharmacokinetic profile characterized in the Phase 1 program (Kubota 2014). The step-wise dose escalation regimen and option to return to and hold subjects at a stable dose will allow for the evaluation of safety and tolerability of dosing durations longer than 2 weeks.

The 84-day dosing period is expected to provide the opportunity to evaluate the effects of emixustat on PDR-associated aqueous humor biomarkers.

8.5 Efficacy Variables

Efficacy variables will include:

1. Aqueous humor concentration of the following biomarkers: IL-6, IL-8, interferon-gamma inducible protein (IP)-10, PDGF-AA, TGFβ-1, MCP-1, IL-1β, and VEGF
2. Area of retinal NV
3. Degree of vitreous hemorrhage
4. Degree of preretinal hemorrhage
5. NL-BCVA
6. CST as assessed by SD-OCT in subjects with DME
7. Retinal vessel oxygen saturation

8.6 Pharmacodynamic Variables

Cytokine assessments constitute the pharmacodynamic efficacy variables.

8.7 Safety Variables

Safety variables will include AEs, NL-BCVA, LL-BCVA, slit-lamp biomicroscopy, SD-OCT, IOP, gonioscopy, dilated ophthalmoscopy, physical examination findings, vital signs, 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 between the ages of 18 and 85 years diagnosed with PDR, with or without DME.

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. Able and willing to provide a written informed consent before undergoing any study-related procedures.
2. In the opinion of the investigator, the ability and willingness to return for all scheduled visits and perform all assessments.
3. Males or females, ≥ 18 and ≤ 85 years of age at the Screening Visit.
4. A documented diagnosis of type 1 or type 2 diabetes mellitus. Any one of the following will be sufficient evidence that diabetes is present:
    a. Current regular use of insulin for the treatment of diabetes
    b. Current regular use of an oral anti-hyperglycemia agent for the treatment of diabetes
    c. Documented diabetes by American Diabetes Association and/or World Health Organization (WHO) criteria (see Appendix C for definitions)
5. The following ocular criteria for the study eye:
    a. Presence of PDR with or without DME for which, in the Investigator's judgment, interventional treatment can be safely deferred for at least 4 weeks after the Day 1 visit.
    b. No prior pan-retinal photocoagulation (PRP); defined as ≥ 500 burns placed previously outside the posterior pole.
    c. No intravitreal injection of an anti-VEGF agent in the 3 months prior to randomization (Day 1).
    d. No intravitreal or peri-bulbar injection of a corticosteroid in the 4 months prior to randomization (Day 1).

e. Early Treatment Diabetic Retinopathy Study (ETDRS) NL-BCVA letter score of ≥ 24 (approximate Snellen equivalent 20/320) on the day of randomization (Day 1).

f. Media clarity, pupillary dilation, and subject cooperation sufficient to obtain adequate fundus photographs and SD-OCT.

9.3 Exclusion Criteria

Subjects will be excluded from participation in the study if they meet any of the following criteria at screening and baseline (unless otherwise indicated):

1. Any condition that, in the opinion of the investigator, would preclude participation in the study (eg, unstable medical status including blood pressure, cardiovascular disease, or glycemic control).
2. Subjects with poor glycemic control, including those who initiated intensive insulin treatment (a pump or multiple daily injections) in the 4 months prior to Screening, or plan to do so in the next 4 months.
3. Significant renal disease, defined as a history of chronic renal failure requiring dialysis or kidney transplant.
4. Elevated blood pressure (defined as > 180/110; systolic above 180 or diastolic above 110). Subjects with elevated blood pressure values, when attributable to specific circumstances (eg, missed medication, stress, etc.), may be retested on the same or later date, as appropriate (within the period between Screening and randomization (Day 1).
5. History of myocardial infarction or other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 60 days prior to randomization.
6. Previous participation (ie, randomization) in a study with emixustat.
7. Participation (ie, randomization) in an investigational study of emixustat, or in another investigational trial within 30 days of the Screening Visit that involved treatment with any drug that has not received regulatory approval for the indication being studied.
8. Known allergies to fluorescein sodium for injection in angiography, to emixustat, or to any excipients in the emixustat tablets (ie, silicified microcrystalline cellulose, pre-gelatinized starch, colloidal silicon dioxide, or stearic acid).
9. Prohibited medications:

a. Systemic use of a strong inducer of or a strong or moderate inhibitor of cytochrome P450 2D6 (CYP2D6; as listed in Appendix B) beginning 4 weeks prior to screening and throughout the duration of the study period.

b. Anti-coagulant therapy (eg, heparins, warfarin, other oral anti-coagulants) beginning 14 days prior to screening and throughout the duration of the study. Anti-platelet therapy (eg, aspirin, clopidogrel) is allowed.

10. History of systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization or plan for such treatment during the course of the study.

11. Any of the following laboratory abnormalities at screening:

a. Aspartate transaminase (AST)/alanine transaminase (ALT) >3.0 x upper limit of normal (ULN)

b. Total bilirubin >1.5 x ULN

c. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2

d. Impaired coagulation: International Normalized Ratio (INR), prothrombin time (PT), or activated partial thromboplastin time (aPTT) >1.25 x ULN.

e. Impaired hematologic function: hemoglobin <9.0 g/dL; neutrophil count <1.6 x 10^9/L; or platelet count <100 x 10^9/L

f. Any laboratory screening test that meets the abnormality criteria stated above can be repeated once within the period from screening to baseline.

12. Any of the following ocular characteristics in the study eye:

a. Tractional retinal detachment involving the macula. A tractional retinal detachment is not an exclusion if it is outside the posterior pole (not threatening the macula) and, in the Investigator's opinion, is not considered a contraindication to deferring PRP, anti-VEGF therapy, or surgical intervention.

b. Exam evidence of NV of the angle (NV of the iris alone is not an exclusion if it does not preclude deferring PRP or anti-VEGF therapy)

c. A decrease in BCVA due to causes other than diabetic retinopathy (eg, foveal atrophy, pigment abnormalities, dense sub-foveal hard exudates, previous vitreoretinal surgery, non-retinal condition, substantial cataract, or macular ischemia) in the Investigator's opinion.

d. An ocular condition (other than diabetic retinopathy) that, in the opinion of the Investigator, might alter visual acuity during the course of the study (eg, retinal vein or artery occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.). A vitreous or preretinal hemorrhage is not an exclusion if it is out of the visual axis and, in the Investigator's judgement, is not having any effect on visual acuity.

e. History of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, any intraocular surgery, etc.) within 3 months prior to the Screening Visit or anticipated to occur within during the course of the study.

f. History of YAG capsulotomy performed within 2 months prior to randomization (Day 1) or anticipated during the course of the study.

g. Aphakia

h. Uncontrolled glaucoma (in the Investigator's judgement).

i. Exam evidence of periocular or ocular infection (eg, blepharitis, chalazion, or conjunctivitis).

a. Implantation of any of the following intraocular corticosteroid implants in the timeframe indicated:

i. Fuocinolone acetonide (Iluvien®), in the 30 months prior to randomization (Day 1)

ii. Dexamethasone (Ozurdex®), in the 4 months prior to randomization

iii. Any other corticosteroid implant, in the 4 months prior to randomization

j. Macular edema due to anything other than DME (eg, post ocular surgery, age-related macular degeneration, uveitis, retinal vein occlusion, or drug toxicity)

13. Change in a systemic prescription medication or a systemic medication newly prescribed within 30 days prior to screening and between screening and baseline or anticipated during the course of the study.

14. Presence of other disease, physical examination finding, or clinical laboratory finding that, in the opinion of the Investigator, gives reasonable suspicion of a disease or condition which contraindicates the use of an investigational drug, places the subject at risk by participating in the study, or confounds the ability to interpret data from the study.

15. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year of screening.
16. ECG 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.
17. Female subjects who are pregnant or lactating.
18. 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 following the completion of the study. Medically accepted methods of birth control include abstinence, hormonal contraceptives, non-hormonal intrauterine contraceptive device with spermicide, condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide.
19. 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 completion of the study.

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 investigator should select the study eye as the eye with the least potential to require PRP, anti-VEGF therapy, or local corticosteroids during the study, in his/her opinion.

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 consist of 5 digits: a 2-digit site number and a consecutive 3-digit subject screening number. 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 Visits 1 and 2, they will be enrolled and randomly assigned to study treatment through the use of an interactive web response system (IWRS).

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:

- AEs
- 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 reason(s) 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). Whenever possible, all subjects who withdraw from the study prematurely will undergo assessments listed for the Early Termination visit.

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

At Baseline (Day 1), eligible subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- Emixustat, up to 40 mg (step-up titration)
- Placebo

Randomization will be stratified by DME status (DME vs. no DME) and will occur in a masked fashion according to a randomization scheme generated by an interactive web response system (IWRS). A randomization number will be assigned to each subject at this time. The screening number which was assigned when the subject enrolled will be the subject ID number for the remainder of the study

10.2 Masking

Study subjects, Investigators and their staff, and Sponsor personnel involved with the conduct and monitoring of the study will be masked to the identity of treatment until after the final database is locked. Emixustat and placebo will be identical appearing tablets, and each treatment will be packaged in identical, tamper-proof, blister packaging to maintain masking.

All subjects will receive masked replacement (resupply) kits provided through the IWRS. In order to maintain masking, subjects randomized to the placebo arm will be mock-titrated on the same schedule as those in the step-up titration arm.

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 a serious adverse event (SAE) is assessed as unexpected and related to study drug, and meets the requirement for expedited regulatory submission, the Sponsor's Drug Safety department will unmask the treatment assignment for the individual subject, if warranted. Expedited

reports will be submitted to regulatory authorities in accordance with applicable regulations. Expedited reports will also be distributed to Investigators without revealing the treatment assignment and will be submitted to IRB in accordance with institutional guidelines.

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

11.1.1 Emixustat Hydrochloride

Study drug will be taken orally, QD, in the evening for 84 days. Subjects will receive 4 tablets per day as follows:

- Week 1 = 5 mg emixustat/day – two 2.5 mg tablets plus two placebo tablets
- Week 2 = 10 mg emixustat/day – two 5 mg tablets plus two placebo tablets
- Week 3 = 20 mg emixustat/day – two 10 mg tablets plus two placebo tablets
- Week 4 through Week 12 = 40 mg emixustat/day = four 10 mg tablets

11.1.2 Comparative Treatment (Placebo)

Subjects in the placebo group will undergo the same dosing regimen as the active treatment group with subjects taking 4 placebo tablets orally, QD, in the evening for 84 days. The placebo tablets will be identical in appearance to the emixustat tablets but with only inactive ingredients.

11.1.3 Dose Reduction

Subjects who do not tolerate dose escalations will be returned to and held stable at the last tolerated dose; after week 4, all subjects will be held at a stable dose for the remainder of the study. Dose reduction is available for subjects who do not tolerate dose escalations due to AEs that in the opinion of the investigator would otherwise lead to discontinuation of study drug. Dose reduction may be undertaken only once and is only available at Visit 4, Visit 5, or Visit 6.

11.1.4 Rescue Therapy

Rescue Treatment Criteria for PDR

All subjects will be eligible for PRP or anti-VEGF therapy for PDR in the study eye as of Day 29 (Visit 6) of the study if the following criterion is met:

- There is new NV or growth of NV of the retina, disc, angle, OR iris such that the NV is greater in extent than at Day 1 (Visit 2/Baseline).

Rescue Treatment Criteria for DME

All subjects will be eligible for therapy for DME in the study eye as of Day 29 (Visit 6) of the study if either of the following criteria are met:

a. Development or worsening of DME as illustrated by an increase in central retinal thickness of ≥100 microns from any previous visit (as measured by the Investigator)

b. A BCVA decrease of ≥10 letters from any previous visit that is deemed secondary to DME.

Subjects for whom it is determined that treatment with PRP, anti-VEGF therapy, or local corticosteroids in the study eye is necessary will discontinue study drug, be discontinued from the study, and undergo Early Termination assessments prior to any of these therapies.

PRP, anti-VEGF agent therapy, focal laser therapy, or local corticosteroid therapy in the non-study eye is allowed at any time, at the Investigator's discretion.

11.2 Supply, Packaging, Labeling, and Storage

Emixustat (2.5, 5, or 10 mg) tablets and placebo tablets will be packaged in identical, tamper-proof, blister packaging to maintain masking.

11.3 Measurement of Study Drug Adherence

Study drug will be taken orally, QD, in the evening, for 84 days. At each study visit, the subject will be queried regarding compliance with the treatment regimen.

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 can be returned to the Sponsor or designee according to applicable state and federal regulations.

If study drug is returned by the site, it must be accompanied by the 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.

If study drug is authorized by the Sponsor to be destroyed at the site, it is the Investigator's responsibility to ensure that arrangements have been made for the appropriate disposal. Written authorization should be issued by the Sponsor; procedures for proper disposal should be established according to applicable regulations, guidelines and procedures. Appropriate records of the disposal should be maintained.

11.5 Prior and Concomitant Therapy

In addition to the exclusion criteria, the following are excluded during the course of the study:

- Systemic use of a strong inducer of or a strong or moderate inhibitor of CYP2D6 (as listed in Appendix B)
- Anti-coagulant therapy (eg, heparins, warfarin, other oral anti-coagulants). Anti-platelet therapy (eg, aspirin, clopidogrel) is allowed.
- Systemic anti-VEGF or pro-VEGF treatment

If elective, urgent, or emergency surgery is required at any time between randomization and Day 85, 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 Appendix B) 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 Appendix A. A detailed accounting of assessments performed at each study visit is presented below.

The scheduled visits include Screening (within 30 days prior to baseline), Baseline (Day 1), and days 8, 15, 22, and 29 (each ±1 day) and days 57 and 85 (each ±5 days). The Day 85 visit will be one day after the last drug/placebo treatment. The Study Exit visit will be performed 30 days (±5 days) after the last dose of study drug.

12.1 Visit 1: Screening (≤30 days prior to Baseline [Day 1]):

The following procedures will be performed at Visit 1, Screening (≤30 days prior to Baseline [Day 1]):

- Explain the purpose and conduct of the study visits to the subjects, answer the subject's questions, and obtain written informed consent
- Review inclusion/exclusion criteria
- Obtain demographic data
- Obtain medical, surgical, and ocular history
- Review previous and concomitant medications
- Perform abbreviated physical exam including height and weight
- Obtain 12-lead ECG
- Obtain vital signs
- Blood sample for serum pregnancy test for women of childbearing potential
    - Blood samples for clinical chemistry, hematology (including glycosylated hemoglobin A1c [HbA1c]), and coagulation. (Note: Any laboratory screening test that meets the abnormality criteria stated in Exclusion Criterion No. 10 [Section 9.3, Exclusion Criteria] can be repeated once within the 30 day period from screening to baseline.)
- Urinalysis
- The following ophthalmic procedures will be performed:
    - NL-BCVA
    - Slit-lamp biomicroscopy

- IOP
- Gonioscopy
- Dilated ophthalmoscopy
- SD-OCT

- AEs
- Schedule subject to return for Baseline Visit (Day 1) within the specified window of time.

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.

12.2 Masked Dose Escalation Phase

12.2.1 Visit 2: Baseline (Day 1)

The following procedures will be performed at Visit 2, Baseline (Day 1):

- Review inclusion/exclusion criteria
- Review and update medical, surgical, and ocular history
- Review concomitant medications
- Randomization
- Obtain vital signs
- Urine pregnancy test (for women of childbearing potential)
- Blood sample for clinical chemistry, hematology, and coagulation. If screening laboratories were performed ≤14 days prior to Baseline (Day 1), these tests do not have to be repeated.
- Urinalysis. If screening laboratories were performed ≤14 days prior to Baseline (Day 1), this test does not have to be repeated.
- The following ophthalmic procedures will be performed:
  - NL-BCVA
  - LL-BCVA
  - Slit-lamp bio-microscopy

  - IOP
  - Gonioscopy
  - Dilated ophthalmoscopy
  - FA
  - Color fundus photographs
  - SD-OCT
  - Retinal oximetry imaging (may be performed at selected sites)
- Aqueous humor collection (50 µl) from the study eye by paracentesis and shipped the same day on dry ice.
- AEs
- Dispense 1 week supply of masked study drug (5 mg emixustat or placebo) for subjects to self-administer 4 tablets (orally, QD, in the evening) for 7 days.
- Schedule subject to return for Visit 3 (Day 8 ± 1 day).

12.2.2 Visit 3 (Day 8 ± 1 day)

- AEs
- Review concomitant medications
- Collect blister pack of study drug and review compliance
- Dispense a 1 week supply of double the dose received at the Day 1 visit (10 mg emixustat or placebo) for self-administration of 4 tablets (orally, QD, in the evening) for 7 days.

12.2.3 Visit 4 (Day 15 ± 1 day)

- AEs
- Review concomitant medications
- Collect blister pack of study drug and review compliance
- Dispense a 1 week supply of double the dose received at the Day 8 visit (20 mg emixustat or placebo) for self-administration of 4 tablets (orally, QD, in the evening) for 7 days.

Note: Dose reduction is available for subjects who do not tolerate dose escalations due to AEs that in the opinion of the investigator would otherwise lead to discontinuation of study drug. The subject will be returned to and held stable at the last tolerated dose.

12.2.4 Visit 5 (Day 22 ± 1 day)

- AEs
- Review concomitant medications
- Collect blister pack of study drug and review compliance
- Dispense a 1 week supply of double the dose received at the Day 15 visit (40 mg emixustat or placebo) for self-administration of 4 tablets (orally, QD, in the evening) for 7 days.

Note: Dose reduction is available for subjects who do not tolerate dose escalations due to AEs that in the opinion of the investigator would otherwise lead to discontinuation of study drug. The subject will be returned to and held stable at the last tolerated dose.

12.3 Masked, Fixed Dose Phase

12.3.1 Visit 6 (Day 29 ± 1 day)

- Urine pregnancy test (for women of childbearing potential)
- Review concomitant medications
- The following ophthalmic procedures will be performed:
  - NL-BCVA
  - Slit-lamp biomicroscopy
  - IOP
  - Dilated ophthalmoscopy
  - SD-OCT
  - Retinal oximetry imaging (may be performed at selected sites)
- AEs
- Collect blister pack of study drug and review compliance

- Dispense a 4 week supply of drug (40 mg emixustat or the last tolerated emixustat dose; or placebo), to be dispensed by self-administration of 4 tablets (orally, QD, in the evening) for 28 days.

Note: Dose reduction is available for subjects who do not tolerate dose escalations due to AEs that in the opinion of the investigator would otherwise lead to discontinuation of study drug. The subject will be returned to and held stable at the last tolerated dose.

12.3.2 Visit 7 (Day 57 ± 5 days)

- Urine pregnancy test (for women of childbearing potential)
- Review concomitant medications
- The following ophthalmic procedures will be performed:
  - NL-BCVA
  - Slit-lamp biomicroscopy
  - IOP
  - Dilated ophthalmoscopy
  - SD-OCT
  - Retinal oximetry imaging (may be performed at selected sites)
- AEs
- Collect blister packs of study drug and review compliance
- Dispense a 4 week supply of drug (40 mg emixustat or the last tolerated emixustat dose; or placebo), to be dispensed by self-administration of 4 tablets (orally, QD, in the evening) for 28 days.

12.3.3 Visit 8 (Day 85 ± 5 days)

- Review concomitant medications
- Collect blister packs of study drug and review compliance
- Urine pregnancy test (for women of childbearing potential)
- Physical exam including weight
- Vital signs
- Blood samples for clinical chemistry, hematology (including HbA1c), and coagulation

- Urinalysis
- 12-lead ECG
- The following ophthalmic procedures will be performed:
  - NL-BCVA
  - LL-BCVA
  - Slit-lamp biomicroscopy
  - IOP
  - Gonioscopy
  - Dilated ophthalmoscopy
  - FA
  - Color fundus photography
  - SD-OCT
  - Retinal oximetry imaging (may be performed at selected sites)
- Aqueous humor collection (50 µl) from the study eye by paracentesis and shipped the same day on dry ice.
- AEs

12.4 Study Exit

A Study Exit visit will be performed 30 days (± 5 days) after the last dose of study drug.

- Review concomitant medications
- Urine pregnancy test (for women of childbearing potential)
- The following ophthalmic procedures will be performed:
  - NL-BCVA
  - Slit-lamp biomicroscopy
  - IOP
  - Dilated ophthalmoscopy
  - SD-OCT

12.5 Early Termination

Subjects who discontinue from the study early will undergo an Early Termination visit where all Day 85 visit assessments will be performed 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. Subjects who have received study drug <21 days will not undergo collection of an aqueous humor sample at the Early Termination visit. If the Early Termination visit occurs ≥25 days after last study drug dose, the Early Termination and Study Exit visits may be combined.

12.6 Unscheduled Visits

Unscheduled visits may be necessary due to AEs or 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 (Appendix A). For full details on each study assessment, refer to the Study Manual.

13.1 Informed Consent

At Visit 1 (Screening, within 30 days prior to Baseline [Day 1]), 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 Visit 1 (Screening [Day -30 to Day -1], within 30 days prior to Baseline [Day 1]), each inclusion and exclusion criterion must be checked for each subject, as well as restricted and prohibited prior and concomitant therapy. At Baseline (Visit 2/Day 1), eligibility requirements must be reviewed to determine if the subject is still eligible to continue in the study.

13.3 Demographic Data

Demographic data, including age, gender, 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 (Day -30 to Day -1) and updated at Baseline (Day 1), 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 (see Section 11.5) will be assessed at Baseline (Visit 2/Day 1). Concomitant therapies will be collected and recorded throughout the study.

13.6 Pregnancy Testing

A serum pregnancy test will be conducted at the Screening visit (Day -30 to Day -1) and a urine pregnancy test will be conducted at Baseline (Visit 2/Day 1), Visit 6/Day 29 (± 1 day), Visit 7/Day 57 (± 5 days), and Visit 8/Day 85 (± 5 days; Study Exit) for women of childbearing potential.

13.7 Abbreviated Physical Examinations

Abbreviated physical examination, including a review of body systems and height and weight, will be performed by qualified study personnel. Height will only be recorded at the Screening Visit. Abnormal findings will be recorded.

13.8 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 position for at least 5 minutes.

13.9 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. ECGs will be read by the Investigator or other qualified designee.

13.10 Clinical Laboratory Evaluations

The laboratory assessments listed in (Table 1) are to be performed according to the Schedule of Events (Appendix A).

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study on the AE CRF. All laboratory results must be reviewed prior to the next study visit to evaluate the subject's safety for continued treatment. With the exception of the urine pregnancy test and urinalysis, all laboratory assessments will be performed by a central laboratory.

Table 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 estimated glomerular filtration rate (eGFR, by the Modification of Diet in Renal Disease Study equation)
Hematology	Hematocrit, hemoglobin, red blood cell count, platelet count, white blood cell count with automated differential (% and absolute count), and HbA1c
Urinalysis	Routine urinalysis (ie, dipstick) without microscopic examination
Coagulation	Prothrombin time (PT), international normalized ratio (INR), fibrinogen, and activated partial thromboplastin time (aPTT)
Pregnancy [a] (serum at Screening, urine at each monthly visit[b])	ß-human chorionic gonadotropin

[a] Women of childbearing potential only
[b] Urine pregnancy testing will be conducted at Visit 2, Visit 6, Visit 7, Visit 8, and Visit 9 (Study Exit).

13.11 Aqueous Humor Collection for Biomarkers

A 50 µl sample of aqueous humor will be collected from the study eye by paracentesis and shipped the same day on dry ice.

13.12 Visual Acuity

Best-corrected visual acuity (BCVA) will be measured using the ETDRS retro-illuminated chart, the ETDRS electronic visual acuity (ETDRS-EVA) system, or the standard ETDRS wall chart in normal luminance lighting (NL-BCVA). NL-BCVA will be recorded as total letter score in each eye.

Low luminance BCVA (LL-BCVA) will be measured after BCVA is measured in normal luminance. A 2.0 log unit neutral density filter (ie, a filter that lowers luminance by 100 times, such as a Kodak Wratten filter, Rochester, NY), provided by the Sponsor, will be placed over the best correction for each eye in order to perform LL-BCVA.

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.

Detailed instructions for obtaining BCVA will be provided in a study-specific BCVA protocol.

13.13 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed 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 described.

13.14 Intraocular Pressure

IOP 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.

13.15 Gonioscopy

The anterior chamber angle will be assessed for degree of openness and NV with gonioscopy at Visits 1, 2, and 8. Gonioscopy may be performed at any other visit, based on the Investigator's clinical judgement.

13.16 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 described.

13.17 Color Fundus Photography

Color fundus photographs (both eyes, 9 fields) will be performed to assess lesion characteristics of each eye for all subjects. Photographs will be transmitted to and evaluated by the central reading center.

Color fundus photographs will be obtained using a fundus camera which has been certified by the central reading center. The study personnel who perform fundus photography will be trained and certified by the central reading center prior to enrollment of subjects.

Detailed instructions for imaging and image transfer will be provided in the study-specific Image Acquisition and Submission Protocol.

13.18 Spectral Domain Optical Coherence Tomography

SD-OCT will be performed to assess lesion characteristics and retinal structure of each eye for all subjects. For SD-OCT, Heidelberg Spectralis models must be used. Images will be evaluated by the Investigator. The images will also be transmitted to and evaluated by the central reading center.

The study personnel who perform SD-OCT will be trained and certified by the central reading center prior to enrollment of subjects.

Detailed instructions for imaging and image transfer will be provided in the study-specific Image Acquisition and Submission Protocol

13.19 Fluorescein Angiography

Fluorescein angiography (FA; both eyes, 9 fields) will be performed to examine the circulation of the retina on each eye for all subjects. Images will be evaluated by the Investigator. Images will also be transmitted to the central reading center.

The study personnel who perform FA will be trained and certified by the central reading center prior to enrollment of subjects.

Detailed instructions for imaging and image transfer will be provided in the study-specific Image Acquisition and Submission Protocol

13.20 Retinal Oximetry Imaging

Non-invasive retinal oximetry imaging may be performed at selected sites. If obtained, images will be transmitted to and evaluated by the central reading center.

The study personnel who perform retinal oximetry imaging will be trained and certified by the central reading center prior to enrollment of subjects.

13.21 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.

13.21.1 Definitions

An **adverse event** 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 an 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 13.21.4.

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 Adverse Event** 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. Hospitalization for surgery planned before study entry is not considered an SAE.
- 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; related to other etiologies such as concomitant medications or conditions.

13.21.2 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.

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.

13.21.3 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 and will be submitted to the IRB in accordance with institutional guidelines and local regulation.

13.21.4 Pregnancy

Pregnancy itself is not an AE. However, any report of pregnancy that occurs in a female subject or the female partner of a male subject during study participation or within 90 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.

All abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will be recorded on the AE eCRF and SAE form. The associated SAE form will be sent to and followed up by the Sponsor according to the procedure described in Section 13.21.2.

An AE eCRF and/or SAE form, as appropriate, will be completed for subjects who are maternal to the child or fetus and if the subject sustains an AE. The SAE form will be sent to the Sponsor in accordance with Section 13.21.2.

13.21.5 Overdose

Overdose is defined as any dose higher than the defined or prescribed dose of study drug. Occurrences of overdose leading to AEs 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 13.21.2.

13.21.6 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 $\leq$ 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.

13.21.7 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

No involvement of an Independent Data Monitoring Committee is planned. A Safety Review Team consisting of Sponsor staff and/or consultants will periodically review masked safety data.

15 Study Endpoints

15.1 Primary Efficacy Endpoint

The primary study endpoints are the change in aqueous humor concentration of eight biomarkers (IL-6, IL-8, IP-10, PDGF-AA, TGFβ-1, MCP-1 and IL-1β, and VEGF) from baseline (Day 1) to Day 85, the conclusion of an 84-day course of study drug. Analysis will include both absolute change and percent change from Baseline (Visit 2/Day 1) to Day 85 (Visit 8/Study Exit).

15.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will include:

1. Change in area of retinal NV from baseline to Day 85, as assessed by the central reading center from color fundus photographs
2. Change in degree of vitreous hemorrhage from baseline to Day 85, as assessed by the central reading center from color fundus photographs
3. Change in degree of preretinal hemorrhage from baseline to Day 85, as assessed by the central reading center from color fundus photographs
4. Change in NL-BCVA from baseline to Day 85
5. Change in CST from baseline to Day 85, as assessed by the central reading center from SD-OCT, in subjects with DME
6. Change in retinal vessel oxygen saturation from baseline to Day 85, as assessed by the central reading center from retinal oximetry imaging

16 Statistical Analysis and Study Variables

Eight subjects per arm yields 80% power to detect a difference between emixustat and placebo in each aqueous humor biomarker, assuming an effect size of 1.31, using a two-sample t-test and a two-sided alpha level of 0.10. To account for potential early termination subjects, 2 additional subjects per treatment arm, for a total of 10 subjects per arm, will be enrolled.

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 (SD), median, minimum and maximum), and categorical variables will be summarized using the count and percentage of subjects in each category.

Primary and secondary endpoints will be summarized using standard quantitative (sample size, mean, SD, median, minimum, maximum, and 90% and 95% t-distribution confidence intervals [CI] around the mean) and qualitative (frequency counts, percentages, and exact 90% and 95% CIs around the percentages) summary statistics and assessed using two-sided 90% and 95% t-distribution CIs and two-sided, two-sample t-tests around the differences between treatment groups for quantitative measures. For the assessment of changes from baseline in aqueous humor concentration of the 8 biomarkers, both absolute and percent changes will be analyzed. Additionally for quantitative measures, 1-sample t-tests will be completed on the change from baseline values within a treatment group. Qualitative measures will be analyzed by exact McNemar's test for changes within a treatment group and Fisher's Exact Test for differences between treatment groups. Differences in proportions and 90% and 95% CIs will also be presented for comparisons between treatment groups for qualitative variables.

The assessment of safety will be based on the summaries of ocular and non-ocular AEs, NL-BCVA, LL-BCVA, ophthalmic examination findings (slit lamp biomicroscopy, dilated ophthalmoscopy, IOP, gonioscopy), SD-OCT, vital signs, physical examination findings, ECGs, and clinical laboratory values. Subjects will be summarized in the group according to the treatment received, and all subjects receiving emixustat will be combined into one group.

AEs 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 two 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.

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.

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 Conference for Harmonisation (ICH) guideline E6 (R1): Good Clinical Practice: 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 Good Clinical Practice 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 and/or his/her legal guardian will be given a full explanation of the nature of the study and the action of the study drug. The subject/legal guardian will be informed that participation is voluntary and that they can withdraw from the study at any time. The subject/legal guardian will be allowed to read the approved ICF. Once the Investigator is assured that the subject/legal guardian agrees to participate in the study, the subject/legal guardian 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 and/or legal guardian. The original shall be maintained in the subject's medical records at the site.

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 or the subject's legal guardian. 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
- ICF 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 (or the subject's guardian), 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 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 significant protocol requirements. All important 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 an excluded 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. 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 time line 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 or legal guardians
- IRB approval of the Investigator, protocol, and 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 Multicenter, Randomized, Double-Masked, Placebo-Controlled, Pilot Study to Evaluate Effects of Emixustat Hydrochloride on Aqueous Humor Biomarkers Associated with Proliferative Diabetic Retinopathy", and in accordance with generally accepted standards of Good Clinical Practice, 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 section on study ethical considerations (Section 18) and administrative considerations (Section 19).

_____
Principal Investigator's Name

_____ _____
Principal Investigator's Signature Date

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22 Appendices

22.1 Appendix A: Schedule of Events

	Screening	Treatment						Study Exit	
Visit:	**1**	**2** (Baseline)	**3**	**4**	**5**	**6**	**7**	**8** (and Early Termination[a])	**9**
Day:		**1**	**8**	**15**	**22**	**29**	**57**	**85**	**30 ± 5 days after last dose**
Window: / **Assessment:**	**≤30 days prior to Baseline**	--	**± 1 day**				**± 5 days**		
Informed consent	X								
Review inclusion/ exclusion criteria	X	X							
Demographic data	X								
Medical, surgical, ocular history	X	X							
Previous and concomitant medication	X	X	X	X	X	X	X	X	X
Randomization		X							
Abbreviated Physical exam[b]	X							X	
12 Lead ECG[c]	X							X	
Vital signs[d]	X	X						X	
Pregnancy test[e]	X	X				X	X	X	X
Blood chemistry, hematology, coagulation,urinalysis	X[f]	X[g]						X	
HbA1c	X							X	
NL-BCVA (ETDRS)	X	X				X	X	X	X
LL-BCVA (ETDRS)		X						X	
Slit lamp biomicroscopy	X	X				X	X	X	X
IOP	X	X				X	X	X	X
Gonioscopy	X	X						X	
Dilated ophthalmoscopy	X	X				X	X	X	X
Color fundus photo-graphy, both eyes[h]		X						X	
FA, both eyes[h]		X						X	
SD-OCT, both eyes	X	X				X	X	X	X
Retinal oximetry imaging, both eyes		X				X	X	X	

	Screening	Treatment							Study Exit
Visit:	**1**	**2** (Baseline)	**3**	**4**	**5**	**6**	**7**	**8** (and Early Termination[a])	**9**
Day:	**≤30 days prior to Baseline**	**1**	**8**	**15**	**22**	**29**	**57**	**85** (one day after the last study drug dose)	**30** (± 5 days after last dose)
Window: / **Assessment:**		--	± 1 day				± 5 days		
Aqueous humor collection for biomarkers (50ul) [a, i]		X						X	
Dispense oral study medication[j]		X	X	X	X	X	X		
Collect oral study medication			X	X	X	X	X	X	
AE Assessment	X	X	X	X	X	X	X	X	

Abbreviations: AE= adverse event; ECG= electrocardiogram; ETDRS= Early Treatment Diabetic Retinopathy Study; FA= fundus angiography; HbA1c= glycosylated hemoglobin; IOP= intraocular pressure; LL-BCVA= low luminance best-corrected visual acuity; NL-BCVA= normal luminance best-corrected visual acuity; SD-OCT= spectral domain optical coherence tomography

[a] Subjects who discontinue the study early will undergo an Early Termination visit where all Day 85 visit assessments will be performed when study drug is stopped, or as soon as possible after stopping study drug; they will then undergo study exit visit evaluations 30 days later. Subjects who have received study drug less than 21 days will not undergo collection of an aqueous humor sample at the Early Termination visit. If the Early Termination visit occurs ≥25 days after last study drug dose, the Early Termination and Study Exit visits may be combined.

[b] Including weight (assessed at all visits) and height (collected only at Screening).

[c] 12-lead ECG should be taken prior to vital sign assessments and blood draws.

[d] Vital sign assessments (blood pressure, pulse rate, and respiratory rate), are conducted after ECGs and prior to blood draws when possible

[e] In women of childbearing potential, a serum pregnancy test will be taken at Screening; a urine pregnancy test will be taken at Baseline (Day 1, Visit 6 (Day 29 ± 1 day), Visit 7 (Day 57 ± 5 days), Visit 8 (Day 85 ± 5 days), and Study Exit (30 days ± 5 days after the last dose of study drug).

[f] Any laboratory screening test that meets the abnormality criteria stated in Exclusion 10 (see **Section 9.3**) can be repeated once within the period from screening to baseline.

[g] If screening laboratories performed ≤14 days prior to Baseline (Day 1), these tests do not have to be repeated.

[h] Color fundus photography to be performed prior to FA.

[i] Study eye only.

[j] Dose reduction can only occur at Visit 4, 5, or 6 and the dose can only be reduced once.

22.2 Appendix B: Prohibited CYP2D6 Inhibitors and Inducers

The medications listed in the table below are the systemic CYP2D6 inhibitors and inducers prohibited during the study or within **4 weeks** prior to screening.

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

22.3 Appendix C: ADA and WHO Diabetes Criteria[c]

ADA Criteria for Diabetes Diagnosis
A1C ≥6.5%[a, b] Perform in lab using NGSP-certified method and standardized to DCCT assay Or **FPG ≥126 mg/dL** (7.0 mmol/L)[b] Fasting defined as no caloric intake for ≥8 hrs Or **2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)**[b] Performed as described by the WHO, using glucose load containing the equlivalent of 75g anhydrous glucose dissolved in water Or **Random PG ≥200 mg/dL (11.1 mmol/L)** In persons with symptoms of hyperglycemia or hyperglycemic crisis [a] Test should be performed in a lab using a NGSP-certified method and standardized to the Diabetes Control and Complications Trial (DCCT) assay [b] In the absence of unequivocal hyperglycemia results should be confirmed using repeat testing [c] Source: http://www.ndei.org/dsl/newslide.aspx?Slideid=3024

WHO Criteria for Diabetes Diagnosis[a]
FPG ≥ 7.0mmol/l (126mg/dl) Or **2-hr PG ≥11.1mmol/l (200mg/dl)**

[a]http://apps.who.int/iris/bitstream/10665/85975/1/WHO_NMH_MND_13.2_eng.pdf