PROTOCOL TITLE:	A Phase 3 Multicenter, Randomized, Double-Masked Study Comparing the Efficacy and Safety of Emixustat Hydrochloride with Placebo for the Treatment of Macular Atrophy Secondary to Stargardt Disease
PROTOCOL NUMBER:	4429-301 (NCT03772665)
NAME OF TEST ARTICLE:	Emixustat hydrochloride
IND NUMBER:	IND 101,084
EUDRACT NUMBER:	2018-003498-82
INDICATION:	Stargardt Disease
DEVELOPMENT PHASE:	Phase 3
STUDY DESIGN:	Multicenter, randomized, double-masked, placebo-controlled, parallel-group
SPONSOR:	Acucela Inc. 818 Stewart St, Suite 1110 Seattle, WA 98101
DATE OF PROTOCOL:	Original: 12 September 2018 Amendment 1: 7 November 2018 Amendment 2: 10 June 2019 Amendment 3: 21 May 2020

3 Protocol Summary

Protocol Number:	4429-301
Protocol Title:	A Phase 3 Multicenter, Randomized, Double-Masked Study Comparing the Efficacy and Safety of Emixustat Hydrochloride with Placebo for the Treatment of Macular Atrophy Secondary to Stargardt Disease
Phase:	Phase 3
Study Objectives Primary:	To determine if emixustat hydrochloride (emixustat) reduces the rate of progression of macular atrophy (MA) compared to placebo in subjects with Stargardt disease (STGD)
Study Population:	Subjects who have MA secondary to STGD

Study Design:	This is a multicenter, randomized, double-masked, placebo-controlled study to evaluate the efficacy and safety of emixustat compared to placebo in subjects who have MA secondary to STGD. Subjects will be randomly assigned to one of two treatment arms in a 2:1 ratio. Treatment arms include: • Emixustat 10 mg • Placebo Subjects will take study drug once daily (QD) in the evening for 24 continuous months. Subjects randomly assigned to the emixustat arm will start taking a dose of 5 mg on Day 1 and step-up to 10 mg at the Month 1 visit, then maintain that dose for the remainder of the dosing period, unless a dose reduction is taken.
Number of Subjects:	Approximately 189 subjects across multiple clinical sites will be enrolled in order to obtain approximately 159 evaluable subjects (106 emixustat and 53 placebo).
Inclusion Criteria:	Subjects who meet all of the following criteria at Screening and Baseline (unless otherwise indicated) may be eligible for inclusion in the study: 1. Males or females, age ≥ 16 years. 2. Clinical diagnosis of MA secondary to STGD in one or both eyes as determined by the Investigator. 3. The subject must have 1 or more pathogenic mutation(s) of the ABCA4 (ATP binding cassette subfamily A member 4) gene. If only one ABCA4 pathogenic mutation is identified or if two ABCA4 pathogenic mutations that typically occur on the same allele (ie, “in cis”) are identified, the subject must have a typical STGD phenotype (at least one eye has flecks at the level of the retinal pigmented epithelium [RPE] typically seen in STGD) and

	be approved by the Sponsor. If 2 or more pathogenic mutations that do not typically occur on the same allele are identified, a typical STGD phenotype and separate Sponsor approval are not required. Segregation analysis is not required. The pathogenicity of all mutations will be determined by the Sponsor working with experts in ophthalmic genetics. 4. The study eye must meet the following criteria as determined by the central reading center's assessment of FAF imaging at Screening: a. Total area of DDAF i. If the lesion is unifocal: ≥ 3.0 – 22.0 mm^2 (~1.2 – 8.7 disc areas) in size. ii. If the lesion is multifocal: ≥ 1.0 – 22.0 mm^2 (~0.4 – 8.7 disc areas) in size. b. The entire lesion must be completely visualized on the macula-centered image (Field 2 – Macula Image). The DDAF lesion must be able to be imaged in its entirety, and all lesion borders must be ≥ 300 microns from all image edges. 5. Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA letter score of ≥ 25 letters (approximately ≥ 20/320 Snellen) in the study eye at Screening. 6. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of macular atrophy in the study eye as determined by the Investigator. 7. Able to reliably administer oral medication by self or with available assistance. 8. Able and willing to provide written informed consent/assent a. For subjects ≥ 18 years of age: able and willing to provide written informed consent before undergoing any study-related procedures. b. For subjects ≥ 16 and < 18 years of age: able and willing to provide written informed assent, and has a parent or legal guardian able and willing to provide written informed consent for the minor before the subject undergoes any study-related procedures. Where required by local regulations, both parents must consent to the subject's participation in the study, if both have legal custody.

Exclusion Criteria:	Subjects will be excluded from participation in the study if they meet any of the following criteria at Screening or Baseline (unless otherwise indicated): 1. Macular atrophy associated with a condition other than STGD in either eye. 2. DDAF with contiguous area of peripapillary atrophy in the study eye, as determined by the reading center. 3. Mutation(s) in any of the following genes – elongation of very long chain fatty acids-like 4 (ELOVL4), prominin 1 (PROM1), or peripherin 2 (PRPH2)/retinal degeneration slow (RDS) – determined by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing. 4. If tested, any mutation(s): a. In a gene(s) encoding a visual cycle protein [e.g., retinal pigment epithelium 65 (RPE65), lecithin:retinol acyltransferase (LRAT), retinol dehydrogenase 12 (RDH12), RDH5, and retinaldehyde binding protein 1 (RLBP1)], confirmed by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing. Testing for these mutations is not required. b. Associated with a non-STGD retinal dystrophy/degeneration, confirmed by the Sponsor working with experts in ophthalmic genetics to likely be disease-causing. Testing is not required. 5. Presence in either eye of an active ocular disease that in the opinion of the Investigator compromises or confounds visual function, including, but not limited to, choroidal neovascularization, diabetic retinopathy, uveitis, other macular diseases, or uncontrolled glaucoma/ocular hypertension. 6. History of any intraocular or ocular surface surgery in either eye ≤ 3 months prior to Screening. 7. Current or previous participation in an interventional study to treat STGD using gene therapy or stem cell therapy. 8. Current or previous participation in a study to treat STGD using a vitamin A derivative ≤ 6 months prior to Screening. 9. Current or previous participation in a study to treat STGD using a complement inhibitor ≤ 6 months prior to Screening.

	10. Known hypersensitivity to emixustat or any of the excipients in emixustat tablets (ie, silicified microcrystalline cellulose, pregelatinized starch, colloidal silicon dioxide, and stearic acid). 11. Prohibited medications: a. Systemic use of a strong inducer of or a strong or moderate inhibitor of cytochrome P450 2D6 (CYP2D6) beginning 4 weeks prior to Screening or between Screening and Baseline, or planned use during the study period. b. Systemic use of a Vitamin A or beta-carotene supplement beginning 4 weeks prior to Screening or between Screening and Baseline, or planned use during the study period. c. As determined by the Investigator, use of medications known to affect vision (eg, hydroxychloroquine, isotretinoin) or that might interfere with the evaluation of the efficacy or safety of emixustat, beginning 4 weeks prior to Screening or between Screening and Baseline, or planned use during the study period. 12. Any of the following laboratory abnormalities at Screening: a. Aspartate transaminase (AST) or alanine transaminase (ALT) > 3.0 × upper limit of normal (ULN) b. Total bilirubin > 1.5 × ULN c. Serum creatinine > 2.0 mg/dL d. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 e. Impaired hematologic function: hemoglobin < 11 g/dL; neutrophil count < 1.6 × 10^9/L; or platelet count < 100 × 10^9/L. Any laboratory screening test that meets the abnormality criteria stated above can be repeated once within the 45-day period from Screening to Baseline. 13. Participation in any study using an investigational drug within 30 days or 5 half-lives (of the investigational drug) of Screening. 14. Participation in any study of an interventional, investigational device within 60 days of Screening.

	15. Anticipated participation during the study period in any study using an investigational drug or an interventional, investigational device. 16. Presence of other medical or ophthalmic disease, physical examination finding, or clinical laboratory finding that in the opinion of the Investigator contraindicates the use of an investigational drug, places the subject at risk by participating in the study, might interfere with the evaluation of the efficacy or safety of emixustat, negatively impacts subject compliance with the protocol, confounds the ability to interpret data from the study, or jeopardizes the subject's ability to complete the protocol. 17. Current or history of cancer (except for adequately treated basal cell or squamous cell carcinoma of the skin) within 1 year of Screening. 18. History of myocardial infarction, stroke, unstable ischemic heart disease, uncontrolled cardiac arrhythmia, or hospitalization for congestive heart failure within 6 months of Screening. 19. Abnormal electrocardiogram (ECG) results that are considered by the Investigator to be clinically significant at Screening. 20. Female subjects who are pregnant or lactating. 21. Female subjects of childbearing potential [ie, not postmenopausal (without menses for 12 months without an alternative medical cause) and not surgically sterile via hysterectomy, bilateral salpingectomy, or bilateral oophorectomy] 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 true abstinence, estrogen+progestogen hormonal contraceptives, progestogen-only hormonal contraceptives, nonhormonal or hormonal intrauterine contraceptive device, bilateral tubal occlusion, male or female condom, contraceptive sponge with spermicide, diaphragm with spermicide, or cervical cap with spermicide. True abstinence is when abstinence from heterosexual intercourse is in line with the preferred and usual lifestyle of the subject and is not just limited to the duration of this study. 22. 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 Procedures:	The scheduled visits include Screening (within 45 days prior to Baseline), Baseline (Day 1), and Months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24. The visits conducted at Months 9, 15, and 21 will be performed on the telephone. A study exit visit will be performed 60 days after the last dose of study drug. During the COVID-19 crisis, visit windows are extended. Subjects who discontinue from the study early will undergo an Early Termination visit where safety and efficacy assessments will be performed when study drug is stopped, or as soon as possible after stopping study drug. Subjects who discontinue from treatment will remain in the study, attending all clinical site visits through Month 24.
Criteria for Evaluation Variables:	

Efficacy	Efficacy variables will include total areas of the definitely decreased and questionably decreased autofluorescence MA lesion(s), total area of EZ loss, mean ONL thickness, extent of abnormal near-infrared FAF, BCVA letter score, reading speed, contrast sensitivity, photopic microperimetry retinal sensitivity, and QOL instruments.
Safety	Safety variables will include the incidence of ocular and non-ocular AEs, and the changes from baseline in BCVA letter score, slit-lamp biomicroscopy and dilated ophthalmoscopy findings, IOP, spectral domain optical coherence tomography (SD-OCT) and scotopic microperimetry assessments, physical examination findings, vital signs, ECG parameters, and clinical laboratory tests. Pregnancy tests will be conducted in women of childbearing potential. An independent Data Monitoring Committee (DMC) will monitor the safety aspects of the study and periodically review safety summaries prepared by an external group.
Study Endpoints:	
Primary Efficacy	The primary efficacy endpoint will be the mean rate of change from baseline in the total area of the MA lesion(s) in the study eye (in mm^2 per year), defined as the area of definitely decreased autofluorescence as imaged by reduced-illuminance FAF.

Statistical Analyses:	The sample size is determined based on the primary efficacy endpoint, the mean rate of change from baseline in area of DDAF in the study eye. Approximately 189 subjects will be enrolled in order to obtain approximately 159 evaluable subjects (106 emixustat and 53 placebo). This sample size will provide approximately 90% power to detect a difference in means between treatment arms of 0.50 mm^2 per year (1.00 mm^2/year for placebo vs. 0.50 mm^2/year for emixustat), or a 50% improvement with emixustat over placebo. These estimates are based on using a Student's t-test and assuming a common standard deviation of 0.90 mm^2 per year and a 0.049 two-sided significance level. The primary efficacy analysis will be performed on the data through Month 24 in order to determine the magnitude of effect of emixustat compared to placebo. Efficacy analyses will be performed on the intent-to-treat (ITT) and efficacy evaluable (EE) sets of subjects. Safety and tolerability will be assessed on the basis of ocular and non-ocular AEs, serious adverse events, ophthalmic examination findings, vital signs, physical examination findings, ECG findings, and laboratory analyses. Safety assessments will be summarized descriptively.
Study Duration:	The protocol calls for up to 45 days between initial Screening and Baseline (Day 1), a 24-month dosing duration, and follow-up 60 days after last the study drug dose; this yields a total duration of up to 27 months. During the COVID-19 crisis, the window for screening is extended to up to 59 days, the window for the Month 24 visit is extended by 42 days, and the window for follow-up (Study Exit visit)

	is extended by 42 days to 102 days; this yields a total duration of up to approximately 31 months.