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Phase II, Randomized, Placebo-controlled, 90-day Study of Emixustat HCL in Geographic Atrophy Associated with Dry Age-Related Macular Degeneration

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Abstract

Purpose—This study assessed the safety, tolerability, and pharmacodynamics of emixustat hydrochloride (ACU-4429), a novel visual cycle modulator, in subjects with geographic atrophy (GA) associated with dry age-related macular degeneration (AMD).

Methods—Subjects were randomly assigned to oral emixustat (2, 5, 7, or 10 mg once daily) or placebo (3:1 ratio) for 90 days. Recovery of rod photoreceptor sensitivity following a photobleach was measured by electroretinography. Safety evaluations included analysis of adverse events (AEs) and ophthalmic examinations.

Results—Seventy-two subjects (54 emixustat, 18 placebo) were evaluated. Emixustat suppressed rod photoreceptor sensitivity in a dose-dependent manner. Suppression plateaued by Day 14, and was reversible within 7-14 days after drug cessation. No systemic AEs of concern were noted. Dose-related ocular AEs (chromatopsia, 57% emixustat vs. 17% placebo; and delayed dark adaptation, 48% emixustat vs. 6% placebo) were mild to moderate, and the majority resolved on study or within 7-14 days after study drug cessation.

Conclusions—In this phase II study, emixustat produced a dose-dependent, reversible effect on rod function, and an ocular AE profile that is consistent with the proposed mechanism of action.

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Conflict of Interest: Authors Dugel, Csaky and Birch are paid advisory board members and consultants of Acucela Inc. Author Kubota is the Founder, President, CEO, a Board member, and an employee of Acucela Inc. He is a patent inventor on behalf of the company, has received reimbursement for travel expenses, and owns stock in the company.

These results support further testing of emixustat for the treatment of GA associated with dry AMD.

Keywords

ACU-4429; age-related macular degeneration; emixustat hydrochloride; geographic atrophy; phase II; safety; visual cycle modulator

Age-related macular degeneration (AMD) is a common, progressive retinal disease that typically causes severe and irreversible loss of vision, and is a major cause of blindness in older individuals.^{1,2} AMD affects 15 million people in the United States,³ and is reported to be the third leading cause of blindness worldwide.^{4,5} There are two types of AMD: exudative (wet) and nonexudative (dry), with dry AMD accounting for approximately 85% of all AMD cases.⁶ The progression of dry AMD leads to geographic atrophy (GA), a slowly progressive blinding disease for which there is currently no available treatment. It is estimated that up to 3 million Americans have GA.^{3,7} With an increasingly elderly population, and no available treatment options, this number is expected to nearly double by 2050.⁸

There is a diverse etiology associated with GA, and our understanding of the pathophysiology underlying the development of GA lesions continues to evolve. However, there is general agreement among researchers and clinicians that dysfunction of the retinal pigment epithelium (RPE) is an early component of GA pathogenesis^{9,10} and there is a large body of pre-clinical¹¹⁻¹⁵ and clinical¹⁶⁻²⁰ evidence that implicates vitamin A-based toxins in the development and progression of GA lesions. The most well characterized vitamin A-based toxin, *N*-retinylidene-*N*-retinylethanolamine (A2E), is known to be generated during photobleaching of rhodopsin.¹² In animal models that have been developed to study retinal pathology associated with A2E, inhibition of rhodopsin biosynthesis has been effective to halt accumulation of A2E and preserve health and integrity of the retina.²¹⁻²⁴

Emixustat hydrochloride (ACU-4429) is an orally available small molecule that has been designed to inhibit the visual cycle isomerase, retinal pigment epithelium-specific 65 kDa protein (RPE65), as a means of reducing the accumulation of toxic vitamin A-based toxins, such as A2E. Emixustat is the first representative compound in a unique therapeutic drug class designated Visual Cycle Modulators. It is theorized that modulation of visual cycle activity with emixustat may be effective to slow or even halt the progression of GA lesions.

Treatment with emixustat is expected to reduce rod photoreceptor activity as it decreases the level of available rhodopsin. This effect, which can be readily assessed by electroretinography (ERG), serves as a pharmacodynamic biomarker of emixustat activity in the eye. The rod-photoreceptor derived b-wave amplitude of the ERG has historically been regarded as the most reliable measure of signal processing in the retina,²⁵ and there is a proportional relationship between the magnitude of the rod b-wave amplitude and rhodopsin levels.²⁶ Thus, reduction of the rod b-wave amplitude indicates a reduction in rhodopsin levels.

In an early Phase I study,²⁷ 46 healthy volunteers received single oral doses of emixustat (2 mg to 75 mg; n=38 total) or placebo (n=8) in order to evaluate safety and the pharmacokinetic and pharmacodynamic properties of emixustat. A dose-dependent suppression of rod b-wave amplitudes was observed. Maximum suppression occurred at 24 hours post dose in volunteers who received 40 to 75 mg emixustat; suppression recovered completely by Day 9 post dose. Mean drug exposure and elimination data, as well as the reversible effect on rod responses, supported a daily dosing regimen for emixustat. Across all doses, the most common adverse events were primarily ocular in nature and resolved within a few days of onset.

In a subsequent multiple-dose Phase I study,²⁸ 40 healthy volunteers received a 14-day course of oral emixustat at doses ranging from 5 mg to 40 mg (n=30 total) or placebo (n=10) taken once daily. Emixustat was rapidly absorbed and readily eliminated: peak plasma levels occurred approximately 3 to 5 hours post dose and the mean elimination half-life ranged from 4.6 to 7.9 hours. Mean dose-normalized exposures were generally similar across all dose cohorts, indicating that systemic exposure to emixustat increased in a roughly dose-proportional manner. Additionally, there appeared to be no significant accumulation of emixustat during the 14 days of dosing. Systemic adverse events were minimal. Mild ocular adverse events were reported for 67% of volunteers who received emixustat. Similar to the Phase 1a single dose study, in this multi-dose study, the most common adverse events across all emixustat doses included chromatopsia (63%), blurred vision (17%), reduced visual acuity (13%), abnormal color vision tests (13%), headache (10%), and visual field defect (10%). All ocular adverse events resolved within 7 to 14 days after study completion.

The present report describes the first dose-ranging evaluation of oral emixustat in subjects with GA associated with dry AMD. The primary objectives of this study were to assess safety and tolerability, and to explore the pharmacodynamics of emixustat administered over a 90-day period in subjects with GA associated with dry AMD.

Methods

Study Design

This was a Phase IIa, multicenter, randomized, double-masked, placebo-controlled, dose-ranging study conducted from December 2009 to June 2012 at 15 study centers in the United States. The study was conducted in accordance with the Declaration of Helsinki and with Health Insurance Portability and Accountability Act regulations. The protocol and informed consent form were approved by the institutional review board for each study site, and all subjects provided written informed consent before study-specific procedures began. The study is registered with ClinicalTrials.gov as # NCT01002950.

The primary objectives were to assess safety and tolerability, and to explore the pharmacodynamics of oral emixustat administered over a 90-day period. Evaluation of pharmacokinetics was a secondary objective.

In this placebo-controlled dose-ranging study, cohort and dosing decisions were based on recommendations of an independent data monitoring committee and agreement of the

Sponsor. Dose cohorts were sequentially enrolled, and subjects were randomly assigned in a 3:1 ratio to receive emixustat or placebo orally once daily for 90 days (Figure 1). Cohorts 1 (5 mg emixustat or placebo), 2 (2 mg or placebo), 3 (10 mg or placebo), and 4 (7 mg or placebo) received study drug once every morning (qAM). The final cohort, Cohort 5 (5 mg or placebo once every evening [qPM]), was evaluated to determine if an evening dosing regimen might augment tolerability.

The study was double masked within each cohort to avoid bias, and the emixustat and placebo tablets were identical in appearance. The computer-generated randomization code was kept under lock and key, and no investigators or subjects were inadvertently unmasked.

Participants

Eligible participants were adults with a clinical diagnosis of GA, as defined by well demarcated areas of partial or complete retinal pigment epithelium depigmentation or loss and confirmed by a central reading center. Subjects had best-corrected visual acuity (BCVA) equal to or better than 20/400 in the study eye. Subjects were excluded from study participation if they had GA in either eye associated with ocular disease other than AMD; known congenital/inherited color vision abnormalities; active exudative AMD or current treatment for exudative AMD in the study eye; cataract or other intraocular surgery within 3 months or laser-assisted in situ keratomileusis surgery, glaucoma filtration surgery, or corneal transplant within 6 months of study entry in either eye; or active ocular disease or clinically significant ocular abnormalities in either eye that would interfere with study evaluations (see Appendix, Supplemental Digital Content 1, for a list of all entry criteria). Twelve subjects (10 emixustat, 2 placebo) were granted exemptions to entry criteria due primarily to changes in medication prior to study dosing that could be permitted on an individual basis per protocol; these exemptions were not anticipated to affect data interpretation.

Ophthalmic procedures performed during screening included color vision test D-28, BCVA, slit-lamp biomicroscopy, intraocular pressure (IOP), fundus autofluorescence where available, fundus photography, fluorescein angiography, optical coherence tomography (OCT), and dilated ophthalmoscopy. If only one eye of a subject qualified for the study, then that eye was designated as the study eye. If both eyes qualified for the study, then the worse eye (the eye with the largest lesion of GA) was designated as the study eye. If both eyes had the same lesion size and met all inclusion criteria, the right eye was designated as the study eye.

Assessments and Statistical Analysis

Modulation of the visual cycle by emixustat was assessed by evaluating the time course of recovery of rod sensitivity (rod b-wave amplitude) after exposure to a bleaching light. Full-field ERG procedures were performed on both eyes of each subject throughout the study according to International Society for Clinical Electrophysiology of Vision (ISCEV) methodology, and were standardized across all study centers in order to minimize variability. The ERG procedure included maximal dilation of each subject's pupils using 10% tropicamide, followed by a 30-minute period of dark adaptation. At the end of this

period, an electrode (corneal contact lens or Dawson Trick Litzkow fiber) was placed on each eye under dim red light, and a rod response was recorded. Following a 10-minute period of light adaptation, cone responses were obtained from cone amplitude measures to a single light intensity and to a 31 Hz flicker. Subjects' eyes were then photobleached for 3 minutes; rod responses were recorded immediately after and at 10, 20, and 30 minutes following the photobleach. ERG measurements were recorded at baseline; Days 14, 60, and 90; and at study exit, 7 to 14 days after discontinuation of study drug. For the 5 mg qAM group, ERG measurements also were obtained on Days 7 and 30. What time of day was the ERG collected. Was it the same for AM and PM dosing, ie. Was the testing longer after taking the drug in one case than in the other?

Safety measures included evaluation of adverse events, clinical laboratory tests, vital signs and physical examinations, and changes in ophthalmologic findings, as assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS)²⁹ BCVA, slit-lamp examination, IOP, and dilated ophthalmoscopy. In addition, as a part of the routine safety monitoring, an independent central reading center evaluated masked OCT images for changes that were not consistent with the natural disease progression.

Pharmacokinetic parameters were to be calculated from plasma emixustat concentrations in samples taken predose. However, the multiple dose Phase I study²⁸ showed that samples from healthy volunteers who received 5 mg or 10 mg emixustat daily typically had trough levels below the lower limit of quantitation for the assay. Based on those results, the protocol was amended to discontinue sample collection for pharmacokinetic analysis. Consistent with the earlier results, emixustat concentrations were below the lower limit of quantitation for approximately two-thirds of the samples collected and tested in this study.

Statistical methods were primarily descriptive in nature. Analyses were performed on all randomized subjects who received at least one dose of study drug, and were based on the intention-to-treat principle. ERG values from both eyes were averaged for all data summaries. Rod b-wave amplitude post bleach was considered a key measure of biologic activity. Rod amplitudes were expressed as a percentage of the baseline pre-bleach rod amplitude for each subject. The rate of rod recovery (slope) for each treatment group at Day 14 was compared to the corresponding rate of recovery at baseline to determine the degree of suppression. Data were analyzed by dose cohort as well as for the pooled emixustat group. Placebo subjects from all cohorts were pooled and considered as one group for data analyses.

Results

Subject Characteristics

A total of 72 subjects (54 emixustat, 18 placebo) were enrolled and received at least 1 dose of double-masked study drug: 42 subjects received emixustat qAM at doses of 2 mg (n=12), 5 mg (n=12), 7 mg (n=12), or 10 mg (n=6); 12 subjects received emixustat 5 mg qPM; and 18 subjects received placebo. For the study as a whole, 47 of 72 subjects (65%) were female, 67 (93%) were white, and the median age was 80 years (range, 55 – 95 years). The total emixustat group had a slightly lower median age (78.5 years vs. 82 years placebo) and a

larger proportion of female subjects (69% vs. 56% placebo) (Table 1). The minimum BCVA in the 7 mg and 10 mg groups was 19 letters and 18 letters, respectively, compared to a minimum of 30 letters for all other treatment groups at baseline. The median lesion size, as assessed by fluorescein angiography, was 8.98 mm² (range 0.68 to 31.01) for the pooled emixustat subjects compared with 8.23 mm² (range, 0.16 to 23.13) for placebo subjects.

Pharmacodynamics

Suppression of rod photoreceptor activity as measured by ERG served as a measure of the pharmacological activity of emixustat. At baseline, mean rod b-wave amplitudes were comparable in all groups following dark adaptation (range, 139 – 195 μ V) and a photobleach produced a similar suppression of the rod response across all groups (mean for each group <30 μ V). Rod responses recovered slowly to 76% to 86% of pre-bleach amplitude during the 30-minute period post bleach (Figure 1A).

Following 14 days of study drug administration, recovery of rod responses was suppressed in the emixustat groups compared to placebo (Figure 1B). The slope of recovery of the rod b-wave amplitude relative to baseline, an indicator of the extent of suppression, appeared to be dose dependent, with the smallest amount of suppression in the 2 mg group (26%) and the greatest amount of suppression in the 10 mg group (89%) (Table 2). Post-bleach suppression was similar for subjects who received 5 mg qAM and 5 mg qPM.

Seven to 14 days following drug cessation, the post-bleach mean rod b-wave amplitudes returned to baseline levels with the exception of the 10 mg group, which was affected by one subject with outlying values. The mean rod b-wave amplitudes in the other 4 emixustat groups ranged from 111 to 135 μ V at 30 minutes, similar to the amplitudes observed at baseline (Figure 1C).

Suppression of the b-wave also was observed in the dark adapted responses (I.e prior to bleaching (Figure 1B and data on file). A greater degree of suppression was observed in the 5 mg qPM group compared to the 5 mg qAM group (~100 μ V compared to ~150 μ V, respectively). Although the suppression was less marked than observed post-bleaching, it also appeared to be dose related.

In order to determine if there was a cumulative effect of emixustat on rod photoreceptor function during chronic dosing, rod b-wave suppression at various time points during the 90-day study was analyzed. For the 5 mg qAM treatment group, the degree of suppression relative to baseline ranged from 53.4% to 63.3%, indicating very little change in rod photoreceptor suppression beyond Day 7 (Table 3).

Cone responses were recorded prior to the bleach but at the end of a 10-minute period of light adaptation. There was no significant effect of emixustat on the cone photoreponse as measured by single flash or 31-Hz flicker ERG(data on file).

Safety

The planned duration of dosing was 90 days. However, the 7 mg and 10 mg dose cohorts were discontinued by the Sponsor prematurely due to the frequency and severity of adverse

events. Moderate and related ocular adverse events occurred in 3 of 12 subjects in the 7 mg group and 4 of 6 subjects in the 10 mg group. These adverse events tended to have an early onset, within 7 days after first dose, but resolved after study drug discontinuation. The median exposure for the 7 mg and 10 mg emixustat groups was 25 days, compared with 90 days for the other treatment groups.

A total of 8 subjects, all of whom received emixustat, discontinued study drug due to an adverse event. All adverse events leading to discontinuation of study drug were ocular in nature, including chromatopsia in 7 subjects; all were mild to moderate in severity, and resolved after emixustat discontinuation. Thirty-one (53%) emixustat subjects and 12 (63%) placebo subjects completed the study (Figure 3).

Three emixustat subjects experienced serious adverse events that subsequently resolved. One subject who received 2 mg emixustat was hospitalized for an exacerbation of chronic obstructive pulmonary disease but completed the study. Two subjects who received 5 mg emixustat (one qAM and the other qPM) experienced moderate events of chromatopsia ("dark tint to vision") that were considered serious by the Sponsor because they occurred while driving. One subject had a driver's license restriction after dark, when the SAE occurred. The other subject had no known driving restrictions and the SAE occurred during the daylight hours. Both subjects were withdrawn from the study as a precaution.

Overall, systemic (non-ocular) adverse events were reported in 57% of emixustat-treated subjects and 67% of placebo subjects. Nonserious systemic adverse events were observed in all dose cohorts; no dose-related pattern was noted. Across all dose levels, the most commonly reported systemic adverse events were headache (5 subjects, 9% emixustat vs. 1 subject, 6% placebo), urinary tract infection (4 subjects, 7% emixustat vs. 0% placebo), dizziness (3 subjects, 6% emixustat vs. 1 subject, 6% placebo), and nausea (3 subjects, 6% emixustat vs. 1 subject, 6% placebo). Most systemic adverse events were mild in severity; moderate events were typically isolated occurrences in one subject each, except for moderate urinary tract infection (3 subjects, 6% emixustat) and moderate ligament sprain (2 subjects, 4% emixustat). Most systemic adverse events were considered by the investigator to be unrelated to study drug. With the exception of nausea (3 subjects, 6% emixustat), related systemic events were also isolated occurrences in one subject each.

Fifty emixustat subjects (93%) and 5 placebo subjects (28%) experienced at least one ocular adverse event. The most commonly reported ocular adverse events across all dose levels were chromatopsia (typically described as dark or colored tint to vision; 57% emixustat vs. 17% placebo), delayed dark adaptation (48% emixustat vs. 6% placebo), visual impairment (26% emixustat vs. 6% placebo), blurred vision (15% emixustat vs. 6% placebo), visual field defect (15% emixustat vs. 0% placebo), and reduced visual acuity (11% emixustat vs. 0% placebo) (Table 4). A dose-dependent pattern was observed for both chromatopsia (33% in the 2 mg group, increasing to 83% in the 10 mg group) and delayed dark adaptation (25% in the 2 mg group, increasing to 83% in the 10 mg group).

For subjects who received 5 mg emixustat, the proportion of subjects with treatment emergent ocular adverse events was identical in the qAM and qPM groups (11 subjects,

92%), but the number of ocular adverse events was substantially reduced in the qPM group (53 events qAM vs. 30 events qPM). In particular, chromatopsia was less frequent with evening dosing (67% qAM vs. 42% qPM). For moderate ocular adverse events, both the incidence (3 subjects, 25% qAM vs. 1 subject, 8% qPM) and number (5 events qAM vs. 1 event qPM) were reduced by evening dosing.

Seven subjects who received emixustat doses ranging from 2 mg to 10 mg experienced a decrease in visual acuity during the study period, including one subject with transient bilateral vision loss. Only 2 of these subjects experienced a clinically significant decrease of 15 or more letters from baseline. BCVA for the left eye of one subject in the 7 mg dose group was 78 letters at baseline, decreased to 62 letters at Day 14, and improved to 69 letters at the last visit. BCVA for the right eye of the other subject, who received emixustat 5 mg qPM, was 53 letters at baseline, decreased to 9 letters at Day 14, and rebounded to 57 letters at the last visit.

No severe adverse events were reported in the study. Moderate ocular adverse events were reported for 14 emixustat subjects (26%) and no placebo subjects. The onset of moderate ocular adverse events for subjects at the 7 mg and 10 mg dose levels usually occurred during the first week, in contrast to observations for subjects at the 2 mg and 5 mg dose levels, where onset usually occurred within 2 to 8 weeks.

Most ocular events in both the emixustat and placebo groups were considered by the investigator to be related to study drug. Investigators considered chromatopsia events to be related in 30 of 31 emixustat subjects and 3 of 3 placebo subjects. Similarly, delayed dark adaptation was considered study drug related in 25 of 26 emixustat subjects and 0 of 1 placebo subjects.

Regardless of severity and relationship, the majority of ocular adverse events (approximately 85%) resolved on study or within 7 to 14 days after study drug discontinuation. No clinically relevant findings were observed in safety assessments of clinical laboratory tests, vital signs, physical examinations, electrocardiograms, slit-lamp biomicroscopy, IOP, and dilated ophthalmoscopy (data on file). A masked, independent central reading center assessed OCTs and no clinically relevant safety findings were detected. No correlations were observed between adverse events and GA lesion size, baseline visual acuity, or ERGs in this 90-day study.

Discussion

Improving outcomes among individuals with AMD remains a formidable challenge. Therapy with emixustat, a novel visual cycle modulator that is orally administered, is an attractive strategy.

The safety profile of emixustat in this double-masked, placebo-controlled study was consistent with observations in healthy volunteers.^{27,28} No systemic adverse events of concern were observed despite oral dosing, although the 7 mg and 10 mg doses of emixustat were less well tolerated in these small cohorts. Early discontinuation of the 7 mg and 10 mg dose cohorts was based on ocular adverse event data available at the time. Later review of

the complete dataset, however, revealed that the pattern of ocular adverse events observed at the 7 mg and 10 mg dose levels of emixustat was consistent with those in the lower dose cohorts, and there was no increase in withdrawal due to adverse event.

Approximately one-quarter of the emixustat subjects experienced a moderate ocular adverse event; all other ocular events were mild. The majority of ocular adverse events resolved on study or within 7 to 14 days after cessation of study drug. No clinically relevant findings were observed in safety assessments of clinical laboratory tests, vital signs, physical examinations, electrocardiograms, slit-lamp biomicroscopy, IOP, and dilated ophthalmoscopy. No clinically relevant safety findings were detected by OCT.

Pharmacologic modulation of the visual cycle is expected to result in certain transient and reversible changes in visual perception.²⁷ The most commonly occurring ocular adverse events, including chromatopsia and delayed dark adaptation, are consistent with the mechanism of action of emixustat as a visual cycle modulator, and reversible upon cessation of the drug.

The last cohort studied evaluated evening dosing whereas the other 4 cohorts evaluated morning dosing. This evening dosing regimen (5 mg qPM) was selected based on the temporal relationship between peak circulating plasma levels of emixustat (approximately 4 hours post-dose) and the onset of ocular events of interest observed in the 5 mg qAM cohort. The objective for this last cohort was to determine if an evening dosing regimen might augment tolerability. For subjects who received 5 mg emixustat, the number of moderate ocular adverse events and the number of ocular adverse events overall was lower with evening dosing relative to morning dosing. In particular, the incidence of chromatopsia was lower with evening dosing (67% qAM vs. 42% qPM), consistent with the pharmacology of emixustat.^{27,28} Additionally, the greater degree of suppression of the rod response observed in the 5 mg qPM group compared to the 5 mg qAM group is consistent with the pharmacokinetics of emixustat. These observations helped inform the design of an ongoing Phase IIb/III study, in which all treatment groups receive study drug in the evening.

The dose-dependent suppression of rod b-wave recovery following light exposure demonstrated in this study and in the single-dose study²⁷ also is consistent with modulation of the visual cycle by emixustat. In the 5 mg qAM cohort, suppression of rod activity plateaued by Day 7 of dosing, and was reversible 7-14 days following cessation of emixustat after up to 90 days of administration. The ability to monitor pharmacodynamic effects of emixustat by non-invasive ERG techniques represents an advantage in the development of this therapeutic approach.

Despite potential limitations of the study, which include the shorter length of exposure to study drug in the 7 mg and 10 mg cohorts and the relatively small sample size, results of this study demonstrated a dose-related and reversible suppression of rod b-wave recovery by emixustat, consistent with the earlier report.²⁷ No systemic adverse events of concern were observed following oral administration of emixustat for up to 90 days. The ocular adverse events observed in the study were of mild to moderate severity, and were generally reversible on study or within 7 to 14 days after study drug cessation. These results provide

sufficient proof of concept to support the further development of emixustat for the treatment of GA associated with AMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Study Design

Fig. 2.

Mean b-wave rod responses at (A) baseline, (B) Day 14 of dosing, and (C) 7 to 14 days following drug cessation (means for the 10 mg group were affected by one subject with outlying values). The ERG procedure included maximal dilation of each subject's pupils followed by a 30-minute period of dark adaptation, and a subsequent 10-minute period of light adaptation prior to photobleaching for 3 minutes. Rod responses were recorded immediately after the photobleach (0 minutes) and at 10, 20, and 30 minutes.

Fig. 3. Subject Disposition

Table 1

Demographics and Baseline Characteristics

Characteristic	Emixustat						Placebo (N=18)
	2 mg qAM (N=12)	5 mg qAM (N=12)	5 mg qPM (N=12)	7 mg qAM (N=12)	10 mg qAM (N=6)	Total Emixustat (N=54)	
Age in years, median (range)	78.0 (55, 88)	75.5 (60, 89)	82.0 (67, 91)	79.0 (65, 95)	77.0 (73, 85)	78.5 (55, 95)	82.0 (55, 87)
Sex, n (%)							
Male	2 (16.7)	4 (33.3)	4 (33.3)	5 (41.7)	2 (33.3)	17 (31.5)	8 (44.4)
Female	10 (83.3)	8 (66.7)	8 (66.7)	7 (58.3)	4 (67.7)	37 (68.5)	10 (55.6)
Race, n (%)							
White	11 (91.7)	10 (83.3)	11 (91.7)	12 (100)	6 (100)	50 (92.6)	17 (94.4)
Asian	1 (8.3)	1 (8.3)	0	0	0	2 (3.7)	1 (5.6)
Other	0	1 (8.3)	1 (8.3)	0	0	2 (3.7)	0
Study eye							
OD, n (%)	6 (50.0)	7 (58.3)	7 (58.3)	7 (58.3)	2 (33.3)	29 (53.7)	9 (50.0)
OS, n (%)	6 (50.0)	5 (41.7)	5 (41.7)	5 (41.7)	4 (66.7)	25 (46.3)	9 (50.0)
BCVA, median (range)	68.0 (33, 83)	74.0 (34, 85)	58.5 (30, 84)	52.5 (19, 74)	60.0 (18, 85)	63.0 (18, 85)	65.0 (40, 79)
Lesion size (mm ²), * median (range)	9.61 (0.84, 28.77)	7.38 (2.24, 14.34)	11.77 (0.68, 31.01)	9.37 (4.79, 23.42)	7.47 (5.36, 25.56)	8.98 (0.68, 31.01)	8.23 (0.16, 23.13)

BCVA = best corrected visual acuity; OD = right eye; OS = left eye.

* As assessed by fluorescein angiography.

Table 2
Slope of Rod ERG Recovery Function at Day 14 Relative to Baseline

	Emixustat					
	Placebo (N=18)	2 mg qAM (N=12)	5 mg qAM (N=11)	5 mg qPM (N=11)	7 mg qAM (N=11)	10 mg qAM (N=5)
Slope at Day 0 *	2.68	2.40	2.55	2.84	2.45	2.55
Slope at Day 14 *	2.68	1.77	0.99	0.96	0.89	0.28
Degree of suppression†	0%	26.3%	61.2%	66.2%	63.7%	89.0%

* Percent recovery per minute.

† (|slope at Day 0 – slope at Day 14|)/slope at Day 0 × 100; obtained during the 30-minute recovery period.

Table 3
Slope of Rod ERG Recovery Function in the 5 mg qAM Group at Each Visit Relative to Baseline

	Visit				
	Day 7 (N=9)	Day 14 (N=11)	Day 30 (N=8)	Day 60 (N=10)	Day 90 (N=10)
Slope at Day 0 *	2.66	2.55	2.70	2.51	2.51
Slope at Follow-up *	1.17	0.99	1.23	0.92	1.17
Degree of suppression †	56.0%	61.2%	54.4%	63.3%	53.4%

* Percent recovery per minute.

† $(\text{slope at Day 0} - \text{slope at follow-up}) / \text{slope at Day 0} \times 100$; obtained during the 30-minute recovery period.

Table 4
Ocular Adverse Events Occurring in 2 Subjects in the Total Emixustat Group

Adverse Event	Emixustat							Total Emixustat (N=54)	Placebo (N=18)
	2 mg qAM (N=12)	5 mg qAM (N=12)	5 mg qPM (N=12)	7 mg qAM* (N=12)	10 mg qAM* (N=6)				
Chromatopsia	4 (33.3)	8 (66.7)	5 (41.7)	9 (75.0)	5 (83.3)			31 (57.4)	3 (16.7)
Delayed dark adaptation	3 (25.0)	6 (50.0)	6 (50.0)	6 (50.0)	5 (83.3)			26 (48.1)	1 (5.6)
Visual impairment	1 (8.3)	5 (41.7)	4 (33.3)	2 (16.7)	2 (33.3)			14 (25.9)	1 (5.6)
Blurred vision	2 (16.7)	2 (16.7)	3 (25.0)	1 (8.3)	0			8 (14.8)	1 (5.6)
Visual field defect	1 (8.3)	4 (33.3)	0	1 (8.3)	2 (33.3)			8 (14.8)	0
Reduced visual acuity	1 (8.3)	0	2 (16.7)	2 (16.7)	1 (16.7)			6 (11.1)	0
Photopsia	1 (8.3)	1 (8.3)	1 (8.3)	1 (8.3)	1 (16.7)			5 (9.3)	1 (5.6)
Vitreous detachment	0	2 (16.7)	1 (8.3)	0	0			3 (5.6)	0
Photophobia	0	1 (8.3)	1 (8.3)	0	0			2 (3.7)	0

*The 7 mg and 10 mg cohorts were prematurely discontinued by the Sponsor.