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

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 after a photobleach was measured by electroretinography. Safety evaluations included analysis of adverse events and ophthalmic examinations.

Results: Seventy-two subjects (54 emixustat and 18 placebo) were evaluated. Emixustat suppressed rod photoreceptor sensitivity in a dose-dependent manner. Suppression plateaued by Day 14 and was reversible within 7 days to 14 days after drug cessation. Most systemic adverse events were not considered treatment related. Dose-related ocular adverse events (chromatopsia, 57% emixustat vs. 17% placebo and delayed dark adaptation, 48% emixustat vs. 6% placebo) were mild to moderate in severity, and the majority resolved on study or within 7 days to 14 days after study drug cessation. Reversibility of these adverse events with long-term administration, however, is undetermined.

Conclusion: In this Phase II study, emixustat produced a dose-dependent reversible effect on rod function that is consistent with the proposed mechanism of action. These results support further testing of emixustat for the treatment of geographic atrophy associated with dry age-related macular degeneration.

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 Age-related macular degeneration is estimated to affect 6.5% of the population of age 40 years and older3 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 1 million Americans have GA.3,7 With an increasing 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 pathogenesis9,10 and there is a large body of preclinical11-15 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 and regeneration of rhodopsin. 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.

Emixustat hydrochloride (ACU-4429) is an orally available small molecule that has been designed to inhibit the visual cycle isomerase (RPE-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. In in vivo studies, treatment with emixustat decreases the level of available rhodopsin and is, therefore, expected to reduce rod photoreceptor activity. This effect, which can be readily measured by electroretinography (ERG), serves as a pharmacodynamic biomarker of emixustat activity in the eye. The rod photoreceptor–derived b-wave amplitude of the ERG is routinely utilized to assess retinal function, and there is a proportional relationship between the magnitude of the rod b-wave amplitude and rhodopsin levels. Thus, reduction of the rod b-wave amplitude indicates a reduction in rhodopsin levels, which in turn indicates a reduction in the substrates used for biosynthesis of vitamin A-based toxins. It is theorized that reduction of rhodopsin levels with emixustat may be effective to slow or even halt the progression of GA lesions.

In an early Phase I study, 46 healthy volunteers received single oral doses of emixustat (2–75 mg; n = 38 total) or placebo (n = 8) to evaluate the safety and pharmacokinetic and pharmacodynamic properties of emixustat. A dose-dependent suppression of rod b-wave amplitudes was observed. Maximum suppression occurred at 24 hours after dose in volunteers who received 40 mg to 75 mg of emixustat; mean rod b-wave amplitudes recovered completely by Day 7 after 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, 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 hours to 5 hours after dose and the mean elimination half-life ranged from 4.6 hours to 7.9 hours. Mean dose-normalized exposures were generally similar across all emixustat 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 Phase I 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 days 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 90-day study were to assess the safety and tolerability of emixustat and to examine its pharmacodynamic effects on retinal function. Lesion growth data were also collected to evaluate potential relationships between lesion size and pharmacodynamic effects of emixustat.

Methods

Study Design

This was a Phase II-a, multicenter, randomized, double-masked, placebo-controlled, dose-ranging study conducted from December 2009 to June 2012 at 12 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 the safety and tolerability and to explore the pharmacodynamics of oral emixustat administered over a 90-day period.

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. Treatment compliance was assessed at each study visit by pill counts and review of diary cards.

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 RPE depigmentation or loss that was confirmed by a central reading center. Subjects had best-corrected visual acuity 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/hereditary 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, http://links.lww.com/IAE/A344, for a list of all entry criteria). Twelve subjects (10 emixustat and 2 placebo) were granted exemptions to entry criteria due primarily to changes in medication before 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, best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure, fundus autofluorescence where available, color fundus photography, fluorescein angiography (FA), optical coherence tomography, and dilated ophthalmoscopy. If only one eye of a subject qualified for the study,
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\textsuperscript{20}) methodology and were standardized across all study centers to minimize variability. Full-field ERGs were recorded after dilation of each subject’s pupils using 1% 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. Responses were obtained from both eyes simultaneously and included ISCEV standard rod response (0.03 cd/m\(^2\) per second) and combined response (1.5 cd/m\(^2\) per second) in the dark and the 31-Hz flicker response (2.25 cd/m\(^2\) per second) and 1-Hz cone response (2.25 cd/m\(^2\) per second) in the presence of a background illumination (34 cd/m\(^2\)). After a 3-minute exposure to a full-field bleaching light (approximately 500 cd/m\(^2\)), recovery of the ERG was measured for 30 minutes at 10-minute intervals. Electroretinographic measurements were recorded at baseline, Days 14, 60, and 90, and at study exit (7–14 days after discontinuation of study drug) for all patients; measurements were also recorded at Days 7 and 30 for the 5-mg QAM treatment group. Because the dark-adapted rod b-wave amplitudes varied significantly between subjects, recovery values were normalized to a common scale by transforming each postbleach b-wave amplitude to the percentage of the prebleach amplitude at baseline. The rate of rod recovery after bleach (over a 30-minute period) was then calculated from the transformed rod b-wave amplitude data, and a mean slope value (\%/minute ± SD) for each cohort was obtained.

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 Diabetic Retinopathy Study\textsuperscript{30} best-corrected visual acuity, slit-lamp examination, intraocular pressure, and dilated ophthalmoscopy. In addition, as a part of the routine safety monitoring, an independent central reading center evaluated masked optical coherence tomography images for changes that were not consistent with natural disease progression.

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. Electroretinogram values from both eyes were averaged for all data summaries. Rod b-wave amplitude after bleach was considered a key measure of biologic activity. The rate of rod b-wave recovery after bleach (slope in percent recovery per minute over a 30-minute period) for each subject was calculated using the b-wave amplitude data. Mean slope values (±SD) for each treatment group were analyzed to assess drug effect on rod photoreceptor function. Cone response data were analyzed as peak-to-peak amplitudes (30-Hz flicker) and final amplitude (single flash) in microvolts. Each of the 5 emixustat dose groups was compared with the placebo group using analysis of variance on the rod and cone responses at Day 14 and at study exit. To adjust for multiple treatment group comparisons, the mean values were compared using Dunnett’s test.

Results

Disposition

A total of 72 subjects (54 emixustat and 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 (Figure 2; placebo-treated subjects from all cohorts were pooled and considered as 1 group for data analyses). Eight subjects, all of whom received emixustat, discontinued study drug; all discontinuations were due to adverse event(s). The planned duration of dosing was 90 days. However, the 7-mg and 10-mg dose cohorts were discontinued by the sponsor early because of initial estimates of the frequency and severity of adverse events, which led to the discontinuation of an additional 15 emixustat subjects (28%) and 6 placebo subjects (33%). Thus, 31 emixustat subjects (57%) and 12 placebo subjects (67%) completed the study. All treated subjects completed a study exit visit 5 days or more after receiving their last dose of emixustat or placebo. Because 2 cohorts were discontinued before the completion of planned dosing, the median exposures for the 7-mg and 10-mg emixustat groups were each 25 days, compared with 90 days for the
other treatment cohorts. Compliance (percentage of expected doses received for time on study) was >90% for all but 6 subjects, which included 4 subjects with low calculated compliance because of missing data.

**Subject Characteristics**

For the study as a whole, 47 of the 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 vs. 82 years placebo) and a larger proportion of female subjects (69 vs. 56% placebo) (Table 1). The minimum best-corrected visual acuity in the 7-mg and 10-mg groups was 19 letters and 18 letters, respectively, compared with 30 letters for all other treatment groups at baseline. The median lesion size, as assessed by FA, was 8.98 mm² (range, 0.68–31.01 mm²) for the pooled emixustat subjects compared with 8.23 mm² (range, 0.16–23.13 mm²) for placebo subjects.

**Safety**

Overall, systemic (nonocular) 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, and most were considered by the investigator to be unrelated to study drug. Across all dose levels, the most commonly reported systemic adverse events were headache (emixustat: 5 subjects, 9% vs. placebo: 1 subject, 6%), urinary tract infection (emixustat: 4 subjects, 7% vs. placebo: 0%), dizziness (emixustat: 3 subjects, 6% vs. placebo: 1 subject, 6%), and nausea (emixustat: 3 subjects, 6% vs. placebo: 1 subject, 6%). Most systemic adverse events were mild in severity; moderate-severity events were typically isolated occurrences in 1 subject each, except for moderate-severity urinary tract infection (emixustat: 3 subjects, 6%) and moderate-severity ligament sprain (emixustat: 2 subjects, 4%). With the exception of nausea (emixustat: 3 subjects, 6%), treatment-related systemic events were also isolated occurrences in 1 subject each.

Fifty emixustat subjects (93%) and 5 placebo subjects (28%) experienced at least 1 ocular adverse event. The most commonly reported ocular adverse events across all dose levels were chromatopsia (57% emixustat vs. 17% placebo; typically described as dark or colored tint to vision), 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 2). A dose-dependent pattern was observed for both chromatopsia (33% in the 2-mg emixustat 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 commonly reported with evening dosing (67% qAM subjects vs. 42% qPM). For moderate-severity 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.

All adverse events leading to discontinuation of study drug were ocular in nature; a total of 13 events were reported for 8 emixustat-treated subjects (5 mg qAM: n = 2; 5 mg qPM: n = 3; 7 mg qAM: n = 2; and 10 mg qAM: n = 1), most commonly chromatopsia (n = 7) and delayed dark adaptation (n = 3). All events leading to discontinuation were mild or moderate in severity and resolved after discontinuation of emixustat.

Overall, in the cohorts that were discontinued early, a total of 13 ocular adverse events that were of moderate severity and were considered by the investigators to be related to study treatment were reported for 3 of the 12 subjects in the 7-mg emixustat group and 4 of the 6 subjects in the 10-mg group. The events resolved during (5 events) or after (8 events) discontinuation of emixustat.

Three emixustat subjects experienced serious adverse events, all of which 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 (1 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 serious adverse event occurred. The other subject had no known driving restrictions, and the event occurred during the daylight hours. Both subjects were withdrawn from the study as a precaution.

Seven subjects who received emixustat doses ranging from 2 mg to 10 mg experienced a decrease
in visual acuity during the study period, including 1 subject with transient bilateral vision loss. Only 2 of these subjects experienced a decrease of ≥15 letters from baseline. Best-corrected visual acuity for the left eye of 1 subject in the 7-mg dose group was 78 letters (Snellen equivalent ~20/25) at baseline, decreased to 62 letters (~20/63) at Day 14, and rebounded to 69 letters (~20/60) at the posttreatment visit. Best-corrected visual acuity for the right eye of this subject was 51 letters (~20/100) at baseline and 55 to 56 letters (~20/80) at subsequent visits. Best-corrected visual acuity for the right eye of the second subject, who received emixustat 5 mg qPM, was 53 letters (~20/80) at baseline, decreased to 9 letters (~20/640) at Day 14, and rebounded to 57 letters (~20/80) at the posttreatment visit (Day 60). Best-corrected visual acuity in the left eye of this second subject was 66 letters (~20/50) at baseline, 64 letters (~20/50) at the posttreatment visit, and remained at 61 letters (~20/63) or above at visits during the treatment period. No anatomical changes were observed to explain the vision loss in either subject. The investigator considered the vision loss to be possibly related to study drug and mild in severity in each of these two cases.

No severe adverse events were reported in the study. Moderate-severity ocular adverse events were reported for 14 emixustat subjects (26%) and no placebo subjects, with 25 of the events considered related to treatment. Time of onset was available for 24 of these moderate-severity treatment-related adverse events. Onset for subjects at the 7 mg and 10 mg dose levels usually occurred during the first week of treatment (11 of the 13 events reported for 7 subjects), in contrast to observations for subjects at the 2 mg and 5 mg dose levels, where onset usually occurred within 2 weeks to 8 weeks of beginning treatment (9 of the 11 events reported for 7 subjects).

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 treatment related in 30 of the 31 emixustat subjects and 3 of the 3 placebo subjects. Similarly, delayed dark adaptation was considered treatment related in 25 of the 26 emixustat subjects and 0 of the 1 placebo subject.

Regardless of severity and relationship, the majority of ocular adverse events (approximately 85%) resolved on study or within 7 days to 14 days after study drug discontinuation. A total of 56 events of chromatopsia were reported for 34 subjects (emixustat: 31 and placebo: 3). The date of resolution was available for 53 events, with 29 events (54.7%) resolving before the end of dosing and 24 events (45.3%) resolving at or after the end of dosing. A total of 30 events of delayed dark adaptation were reported for 27 subjects (emixustat: 26 and placebo: 1). The date of resolution was available for 26 events, with 6 events (23.1%) resolving before the end of dosing and 20 events (76.9%) resolving at or after the end of dosing.

A total of 31 events of visual impairment were reported for 15 subjects (emixustat: 14 and placebo: 1), with 24 events (77.4%) resolving before the end of dosing and 7 events (22.6%) resolving at or after the end of dosing. It is important to note that some of the events that resolved at or after the end of dosing were ongoing in subjects who were discontinued because of adverse events or because of sponsor closure of the 7-mg and 10-mg cohorts; thus, these events would not have been able to be resolved during the treatment period.
No clinically relevant findings were observed in safety assessments of clinical laboratory tests, vital signs, physical examinations, electrocardiograms, slit-lamp biomicroscopy, intraocular pressure, and dilated ophthalmoscopy (data on file). A masked independent central reading center assessed optical coherence tomography, 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.

**Pharmacodynamics**

Suppression of rod photoreceptor activity as measured by ERG served as a measure of the pharmacological activity of emixustat. To determine if there was a cumulative effect of emixustat on rod photoreceptor function during chronic dosing, rod b-wave suppression was analyzed at various time points during the 90-day study. Data from subjects in the 5 mg qAM treatment group were used as a representative example for drug effect in this analysis. In this group of subjects, the degree of suppression relative to baseline ranged from 56.0% on Day 7 to 53.4% on Day 90. Although rod photoreceptor suppression on Days 14 and 60 was slightly higher (61.2 and 63.3%, respectively), data over the entire 90-day dosing period indicated very little change beyond Day 7 (Table 3).

An analysis of the effects of emixustat on both rod and cone photoreceptor function was conducted to examine dose–response relationships and reversibility after drug cessation. In this analysis, mean rod recovery rates (% recovery of the b-wave amplitude over time) after photobleaching and cone responses (30-Hz flicker and single-flash amplitudes) were analyzed at baseline (Day 0), Day 14, and at study exit (7–20 days after treatment ended). At baseline, mean rod b-wave recovery rates and cone amplitudes were comparable across all treatment groups. On Day 14, a dose-dependent suppression of rod b-wave recovery rates was observed (Figure 3A). The level of suppression (relative to placebo) ranged from 34% in the 2-mg treatment group to 90% in the 10-mg treatment group. Seven to 14 days after drug cessation, mean rod b-wave slopes returned to baseline levels in all emixustat treatment groups. There was no detectable effect on cone photoreceptor function as measured by 30-Hz flicker (Figure 3B) or single-flash ERG (Figure 3C) in any treatment group at any time point.

**Lesion Size Analysis**

Geographic atrophy lesions were measured using three different imaging modalities: color fundus photography, fundus autofluorescence photography, and FA. These data were collected to compare lesion size data across the three measurement methods and to examine potential relationships between lesion size and the pharmacodynamic effect of emixustat on rod photoreceptor function. Given the short duration of the study, no effect of emixustat on lesion growth was anticipated.

Analysis of lesion size change from baseline to Day 90 showed a general agreement among the 3 methods. Lesion size change in the placebo group at Day 90 was ~0.4 mm² on color fundus photography and FA imaging and ~0.2 mm² on fundus autofluorescence (Table 4). Assuming a linear lesion size growth over time, the annualized growth rate for the placebo group would be ~1.6 mm² per year, which is consistent with reported natural history of lesion size growth in GA subjects (i.e., 1.8–2.0 mm² per year). Although somewhat lower growth values were observed in the emixustat treatment arms, the differences relative to placebo were not statistically significant.

Regarding the potential effect of lesion size on the pharmacodynamic effect, it is noteworthy that although there was a difference in median lesion sizes of 4.39 mm² between the 5-mg qAM and 5-mg qPM groups at baseline (7.38 vs. 11.77 mm², respectively; Table 1) and a slightly lower change in lesion growth at Day 90 for the 5-mg qPM group compared with the 5-mg qAM group (Table 4), there was no difference in the extent of rod b-wave suppression between these 2 groups (Figure 3A). Thus, it appears that lesion size, within the ranges examined in this study, does not influence the effect of emixustat on rod photoreceptor function.

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope at Day 0*</td>
<td>2.66</td>
<td>2.55</td>
<td>2.70</td>
<td>2.51</td>
<td>2.51</td>
</tr>
<tr>
<td>Slope at follow-up*</td>
<td>1.17</td>
<td>0.99</td>
<td>1.23</td>
<td>0.92</td>
<td>1.17</td>
</tr>
<tr>
<td>Degree of suppression, † %</td>
<td>56.0</td>
<td>61.2</td>
<td>54.4</td>
<td>63.3</td>
<td>53.4</td>
</tr>
</tbody>
</table>

*Percent recovery per minute.
†(Slope at Day 0 – slope at follow-up)/(slope at Day 0 × 100); obtained during the 30-minute recovery period.
Discussion

Improving outcomes among individuals with AMD remains a formidable challenge. Although effective therapies are available for the treatment of wet AMD, treatments for GA associated with dry AMD have not yet been developed. The aberrant accumulation of lipofuscin in the RPE is an important pathologic characteristic of GA, and the retinoid-based cytotoxin, A2E, is a major molecular component of lipofuscin. Emixustat, an orally administered nonretinoid compound, has been shown in preclinical models to reduce the production of A2E by slowing visual cycle activity. It is theorized that this mechanism of emixustat action may be effective to reduce the progression of GA lesions. As a prelude toward evaluation of this hypothesis, we have conducted a 90-day study to assess the safety and tolerability of emixustat in GA subjects and to examine its pharmacodynamic effects on retinal function.

The safety profile of emixustat in this double-masked placebo-controlled study was consistent with observations in healthy volunteers. No clinically relevant findings were observed in safety assessments of clinical laboratory tests, vital signs, physical examinations, electrocardiograms, slit-lamp biomicroscopy, intraocular pressure, and dilated ophthalmoscopy. No clinically relevant safety findings were detected by optical coherence tomography.

Pharmacologic modulation of the visual cycle is expected to result in certain transient and reversible changes in visual perception. The most commonly occurring ocular adverse events, including chromatopsia and delayed dark adaptation, could be explained by the mechanism of action of emixustat as a visual cycle modulator and were reversible on cessation of the drug. 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 days to 14 days after cessation of study drug. Resolution of some ocular events during the treatment period indicated that some patients may accommodate to some of the effects. 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 data set, however, revealed that the pattern of ocular adverse events observed with regard to duration and resolution at the 7 mg and 10 mg dose levels of emixustat appeared consistent with those in the lower dose cohorts (i.e., 2 mg qAM and 5 mg qAM). A Phase II-b/III 2-year study (clinicaltrials.gov: NCT01802866) is ongoing and will provide data over a longer period to assess the onset and resolution of ocular adverse events in a larger patient population.

The last cohort of the study (5 mg qPM) evaluated evening dosing, whereas the other 4 cohorts evaluated morning dosing. This evening dosing regimen was selected based on the temporal relationship between peak circulating plasma levels of emixustat (approximately 4 hours after dose) and the earlier onset of ocular adverse 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-severity ocular adverse events and the number of ocular adverse events overall were lower with evening dosing relative to morning dosing.
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.\textsuperscript{27,28}

The dose-dependent suppression of rod b-wave recovery after light exposure demonstrated in this study and in the single-dose study\textsuperscript{27} is consistent with the modulation of the visual cycle by emixustat. In the 5-mg qAM cohort, suppression of rod photoreceptor activity plateaued by Day 7 of dosing, indicating that a steady-state level of suppression had been achieved. Mean suppression of rod photoreceptor activity was reversible in all cohorts after 7 days to 14 days of drug cessation, and there was no detectable effect of emixustat on cone photoreceptor function. Furthermore, ERG findings suggest that emixustat is reaching the targeted tissue within the eye.

Geographic atrophy lesions were measured using color fundus photography, fundus autofluorescence, and FA, and general agreement was observed across the methods. Differences in lesion size between the emixustat treatment arms and the placebo arm after 90 days of study drug administration were not statistically significant; this outcome was expected in this short-term study. There appeared to be no effect of GA lesion size on the pharmacodynamic effect of emixustat within the range of lesion sizes examined in this study.

Limitations of the study include its small sample size and the proportion of subjects who did not complete the entire 90-day dosing period. Furthermore, the shorter length of exposure to study drug in the 7-mg and 10-mg cohorts did not allow us to evaluate the safety and tolerability at those dose levels for the same duration as the 2-mg and 5-mg cohorts. Although the majority of ocular adverse events resolved on study or within 7 days to 14 days after drug cessation, the reversibility of these adverse effects in the context of long-term administration of this investigational drug is undetermined. Concerning the 2 subjects who experienced a vision decrease of \(\geq 15\) letters from baseline, it is interesting to note that although emixustat is administered orally, this level of vision decrease was observed in only 1 eye for each subject. Nonetheless, there is a possibility that the vision loss is due to a study drug mechanism that remains to be clarified. Another limitation of the study is that it was neither designed nor powered to examine the efficacy of emixustat in slowing GA progression.

No systemic adverse events of concern were observed after oral administration of emixustat for up to 90 days. The ocular adverse events observed in the study were of mild to moderate severity and could be explained by the mechanism of emixustat action. These results provide sufficient proof-of-concept to support the further development of emixustat for the treatment of GA associated with dry AMD.

Key words: ACU-4429, age-related macular degeneration, emixustat hydrochloride, geographic atrophy, Phase II, safety, visual cycle modulator.

Acknowledgments

Medical writing assistance in the form of a manuscript draft was provided by Jennifer Kissner, Nathan Mata, and Roberta Connelly, and statistical guidance was provided by John Koester, all under the sponsorship of Acucela, Inc.

References