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Emixustat Hydrochloride for Geographic Atrophy Secondary to Age-Related Macular Degeneration

A Randomized Clinical Trial

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Purpose: To determine whether emixustat hydrochloride (emixustat) reduces the rate of enlargement of geographic atrophy (GA) compared with placebo in subjects with age-related macular degeneration (AMD) and to evaluate the safety and tolerability of emixustat over 24 months of treatment.

Design: Multicenter, randomized, double-masked, placebo-controlled, phase 2b/3 clinical trial.

Participants: Patients with GA secondary to AMD, a visual acuity score of at least 35 letters, and GA with a total area of 1.25 to 18 mm^2 were enrolled.

Methods: Subjects were randomized (1:1:1:1) to emixustat 2.5 mg, 5 mg, 10 mg, or placebo, administered orally once daily for 24 months. Visits included screening, baseline, and months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, and 25.

Main Outcome Measures: The primary efficacy end point was the mean annual growth rate of total GA area in the study eye, as measured by a central reading center using fundus autofluorescence (FAF) images. The change from baseline in normal luminance best-corrected visual acuity (NL-BCVA) was a secondary efficacy end point.

Results: Of 508 randomized subjects, 320 completed the study. Demographics and baseline characteristics were comparable between treatment groups. On average, GA lesions in the study eye grew at a similar rate in each group (emixustat: 1.69 to 1.84 mm^2/year; placebo: 1.69 mm^2/year; $P \geq 0.81$). Changes in NL-BCVA were also comparable between groups. Subjects with a larger low luminance deficit (LLD) at baseline (≥20 letters) demonstrated a more rapid growth of GA over 24 months. No relationship was observed between the risk-allele status of the AMD-associated single-nucleotide polymorphisms tested and the growth rate of GA. The most common adverse events in emixustat-treated subjects were delayed dark adaptation (55%), chromatopsia (18%), visual impairment (15%), and erythropsia (15%).

Conclusions: Emixustat did not reduce the growth rate of GA in AMD. The most common adverse events were ocular in nature and likely related to the drug's mechanism of action. Data gained from this study over a 2-year period add to the understanding of the natural history of GA and the baseline characteristics affecting the growth rate of GA. *Ophthalmology 2018;■:1–12 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Geographic atrophy (GA), the late form of nonexudative (dry) age-related macular degeneration (AMD), is characterized by progressive atrophy in the macula involving the retinal pigment epithelium (RPE), the overlying photoreceptors, and the underlying choriocapillaris.[1,2] Patients with GA experience difficulty with reading, recognizing faces, discriminating colors, and dark adaptation; however, their foveas, and thus their central visual acuities, are often spared until late in the disease. In 2000, approximately 1 million people in the United States had GA,[3] with this number expected to double by 2050.[4] There are currently no therapies approved for the treatment of GA.

Many risk factors have been associated with the development of AMD, including age, ethnicity, smoking history, diet, and family history.[5–7] The pathogenesis of AMD is multifactorial; factors thought to be involved include inflammation, oxidative stress, and the accumulation of lipofuscin.[2] Progressive dysfunction of the RPE is a key feature of AMD pathogenesis, and the toxicity of lipofuscin components such as bisretinoids has been implicated in this process.[8] Bisretinoids form when excess 11-*cis*- and all-*trans*-retinal accumulate in the RPE because of the inability of phagolysozomes to digest them.[9] The accumulation of

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these bisretinoids, such as A2E, is thought to result in RPE dysfunction (and eventual RPE death) because of photooxidation, photodegradation, and complement activation. The RPE apoptosis and accompanying photoreceptor loss lead to the clinical picture of GA.

Emixustat hydrochloride (emixustat, formerly ACU-4429) is an orally administered small molecule that inhibits the visual cycle isomerohydrolase, RPE65.[10] The visual cycle is a series of enzymatic steps that occur in the RPE and overlying photoreceptors, recycling vitamin A compounds to supply 11-*cis*-retinal for phototransduction.[11] Slowing the visual cycle by inhibiting the mobilization of vitamin A from retinyl ester stores by RPE65, thus decreasing the availability of 11-*cis*- and all-*trans*-retinal, has been proposed as a means to reduce the accumulation of bisretinoids, which have been implicated in the pathogenesis of AMD.

In preclinical studies, emixustat inhibited the isomerase activity of RPE65, slowed the visual cycle (as demonstrated by a prolonged recovery of rod b-wave amplitude on electroretinography after photobleaching), inhibited retinal neovascularization in the vascular endothelial growth factor-driven mouse model of oxygen-induced retinopathy, and reduced the accumulation of lipofuscin and A2E in a mouse model of Stargardt disease, a disease characterized by RPE dysfunction and death, leading to loss of photoreceptors and subsequent visual dysfunction due to an excessive buildup of toxic bisretinoid-containing lipofuscin.[10] In phase 1 and 2 clinical studies in healthy volunteers and subjects with GA secondary to AMD, the safety, tolerability, and pharmacodynamics of emixustat have been examined.[12-14] The majority of adverse events were ocular in nature and mild to moderate in severity. The most common adverse events were consistent with slowing of the visual cycle, with visual color distortions, such as chromatopsia, and delayed dark adaptation most commonly reported. The biological activity of emixustat as measured by electroretinography was confirmed in these clinical studies. In a phase 2 study of subjects with GA, suppression of rod b-wave amplitude recovery postbleach was observed in a dose-dependent manner after 2 weeks of treatment (median suppression of 42%, 78%, and 99% for emixustat 2, 5, and 10 mg, respectively) and was reversible after cessation of dosing.

The phase 2b/3, multicenter, randomized, double-masked, placebo-controlled study described in this article evaluated the efficacy and safety of emixustat compared with placebo in subjects with GA secondary to non-exudative AMD. The primary objective was to determine if emixustat reduces the rate of enlargement of GA lesions compared with placebo in subjects with AMD. Subjects in the **S**afety and **E**fficacy **A**ssessment **T**reatment **T**ria**L**s of **E**mixustat hydrochloride (SEATTLE) study were to receive treatment for 24 months, and this period of treatment allowed for the effect of emixustat on the progression of GA lesions to be assessed.

Methods

Study Design

The study was conducted according to Good Clinical Practice principles, the principles of the Declaration of Helsinki (1964), including all amendments and Notes of Clarification, and all national, state, and local laws or regulations. For each site, an Institutional Review Board or Ethics Committee prospectively approved the study. Each subject provided written informed consent before any study-specific procedures were performed. An independent, unmasked Data Monitoring Committee monitored safety aspects of the study and periodically reviewed safety summaries and listings prepared by an independent external biostatistics contract research organization.

After a 30-day screening period, subjects were randomly assigned (1:1:1:1) to 24 months of emixustat 2.5, 5, or 10 mg or placebo, self-administered orally, once daily, in the evening, with a 30-day off-drug follow-up period. The study was conducted at 49 sites in the United States and 7 sites in Germany from February 2013 to April 2016 (clinicaltrials.gov: NCT01802866). Randomization was stratified by country using an interactive web response system. To enhance tolerability, subjects assigned to emixustat 10 mg received a dose of 5 mg for the first month, stepping up to 7.5 mg after 1 month, and 10 mg after 2 months. Doses for subjects in the other treatment groups were mock-titrated after 1 and 2 months of treatment. During the month after the up-titration to emixustat 10 mg, subjects who experienced an ocular adverse event that the investigator determined was likely to lead to discontinuation of treatment could undergo a dose reduction to 5 mg. To preserve masking, subjects in other treatment groups with such an ocular event could receive a mock-reduction in dose during the third month of treatment. Eligible subjects ($\geq$55 years of age) had a clinical diagnosis of GA secondary to nonexudative AMD in 1 or both eyes. The study eye had a total GA area of 1.25 to 18 mm^2 by blue light (488 nm) fundus autofluorescence (FAF) imaging. If GA was multifocal, then $\geq$1 GA locus was $\geq$1.25 mm^2. The entire lesion could be visualized in a macula-centered image, and it was not contiguous with any peripapillary atrophy. Normal luminance (NL) best-corrected visual acuity (BCVA) scores in the study eye were $\geq$35 Early Treatment Diabetic Retinopathy Study letters ($\sim$20/200 Snellen).

Subjects did not have a history of or active choroidal neovascularization (CNV) associated with AMD in the study eye; GA not associated with AMD in either eye; an active ocular disease significantly affecting visual function; a history of macular edema, external beam radiation, macular surgery, or transpupillary thermotherapy in the study eye; a history of intraocular or ocular surface surgery in either eye during 3 months before screening; a history of myocardial infarction, stroke, unstable ischemic heart disease, uncontrolled cardiac arrhythmia, or hospitalization for congestive heart failure within 6 months of screening; cancer within 1 year of screening (except nonmetastatic in situ or well-controlled carcinoma); or unstable or poorly controlled medical conditions that would interfere with safety evaluations. Female subjects were not pregnant or lactating, and subjects with reproductive potential were to use effective contraception during and for 30 days after treatment. Strong inducers or inhibitors of the cytochrome P450 enzyme CYP3A4 and strong inducers or strong to moderate inhibitors of CYP2D6 were prohibited throughout the study, beginning 4 weeks before screening.

If both of a subject's eyes met the inclusion/exclusion criteria, the study eye had the smaller GA lesion. If GA lesion sizes were equal, the study eye had the better normal luminance best-corrected visual acuity (NL-BCVA) score. If GA lesion sizes and NL-BCVA scores were equal, the study eye was the right eye. Study eyes were determined by investigators, with GA lesion characteristics confirmed by a masked central image reading center (Duke Reading Center, Duke University, Durham, NC).

End Points

The primary efficacy end point was the mean annual growth rate (mm^2/year) in the total area of the GA lesion(s) in the study eye as