10/11/2021 10:00AM

Machine Learning Enabled Outer Retinal OCT Biomarker Extraction for Identification of High-Risk AMD Eyes for Subfoveal Geographic Atrophy Progression

- Kubra Sarici, MD
- Joseph Abraham
- Duriye Damla Sevgi, MD
- Sunil Srivastava, MD
- Jon Whitney
- Annapurna Hanumanthu
- Leina Lunasco
- Jamie Reese, RN
- Justis P. Ehlers, MD

OBJECTIVE A predictive model based on specific imaging biomarkers for the development of subfoveal GA (sfGA) would be an important advancement for the development pipeline and clinical prognostication of AMD.

PURPOSE The aim of this study was to evaluate the utility of quantitative SD-OCT feature extraction of outer retinal characteristics (i.e., ellipsoid zone integrity), the sub-retinal pigment epithelium (RPE) compartment, qualitative SD-OCT biomarkers, and traditional clinical demographics to predict the development of sfGA.

METHODS This retrospective cohort study includes subjects with non-neovascular age-related macular degeneration (NNVAMD) without sfGA with 5 years of follow-up and SD-OCT imaging. Multiple SD-OCT higher-order quantitative metrics were generated including EZ-RPE thickness metrics (i.e., a surrogate for photoreceptor outer segment volume and EZ integrity) and panmacular RPE-BM thickness (i.e., a surrogate for drusen burden). Qualitative SD-OCT biomarkers were also assessed (e.g., hyperreflective foci). Univariate and multivariate assessments were calculated for comparison of non-converters and sfGA converters. The feature complexities were compared using machine learning-based random forest modeling.

RESULTS A total of 137 eyes were evaluated in this analysis. Multiple quantitative OCT parameters were significantly different between sfGA progressor and non-progressor at

baseline in both 2-year and 5-year sfGA risk assessment including, reduced mean EZ-RPE CST and increased sub-RPE compartment thickness in eyes developing sfGA ($p<0.01$). Assessment of the longitudinal change in OCT parameters during the follow-up demonstrated a significantly higher degradation of EZ integrity parameters in eyes that subsequently developed sfGA (Figure 1). Utilizing a random forest classification model, the predictive performance for classification of eyes based on five year risk conversion to sfGA demonstrated AUC of 0.92 and for two year risk demonstated an AUC of 0.96 utilizing baseline data (Figure 2). EZ integrity metrics were the identified as the features of greatest importance in prediction.

CONCLUSION Quantitative outer retinal and subRPE feature assessment utilizing a machine-learning enabled multi-layer retinal segmentation platform provides multiple parameters that are associated with long term and short term progression to sfGA. Future efforts will include additional validation in larger datasets.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

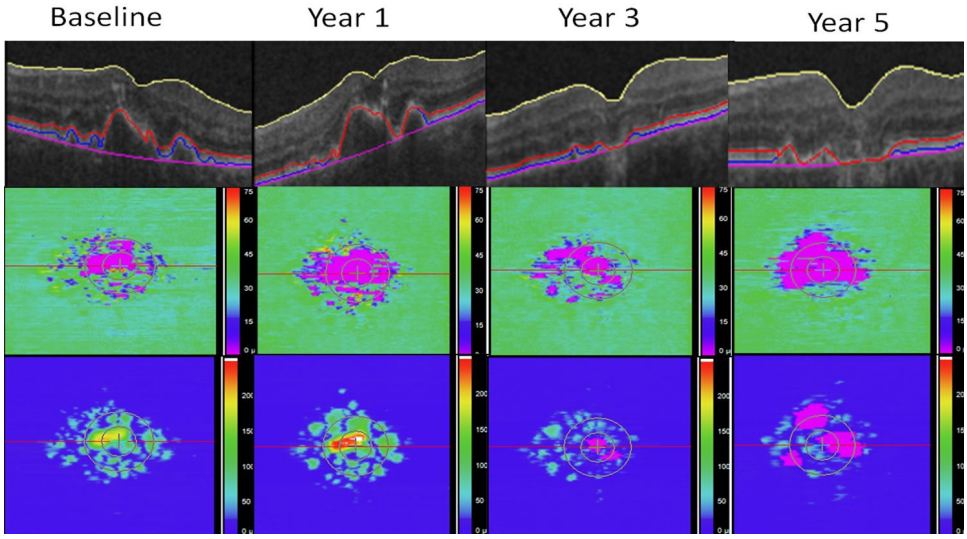
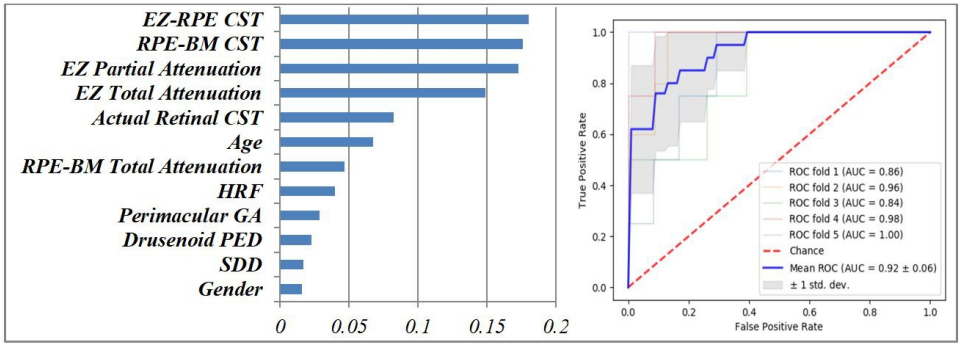


Figure 1: An example of horizontal OCT B-scan image and longitudinal change in en face retinal thickness maps. First row: Semi automatically segmented retinal layer boundaries. On the B-scan, the internal limiting membrane is segmented in yellow, EZ (Ellipsoid zone) in red, retinal pigment epithelium (RPE) in blue and Bruch membrane (BM) in the pink. Second row: En face EZ mapping-thickness between EZ and RPE. Third row: En face RPE-BM mapping-thickness between RPE and BM.

A)



B)

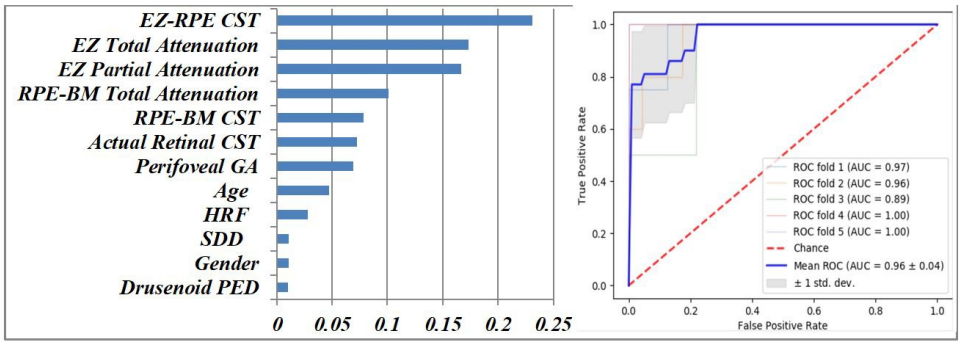


Figure 2: Bar graphs with AUC graphs showing estimated feature importance of predictive models for subfoveal geographic atrohy (sfGA) development based on baseline qualitative and quantitative SD-OCT biomarkers with clinical demographics. A) Feature importance rank of five year sfGA risk B) Feature importance rank of two year sfGA risk. Abbrevations: CST, central subfield thickness; HRF, hyperreflective foci; SDD, subretinal drusenoid deposits; PED, pigment epithelial detachment; EZ, ellipsoid zone; BM, Bruch's membrane; RPE, retinal pigment epithelium

10/11/2021 10:06AM

Clinical and Demographic Factors Associated With Loss to Follow-up in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration

- Durga Borkar, MD
- Ehsan Rahimy, MD
- M. Ali Khan, MD
- Allen C Ho, MD
- Nancy M. Holekamp, MD
- Mark Gallivan, MPH
- Alex McKeown, PhD
- Ramiro Ribeiro, PhD
- Theodore Leng, MD, MS

OBJECTIVE This IRIS® Registry study sought to compare the demographic and clinical characteristics of GA patients with <2 years and 2+ years of follow-up.

PURPOSE Systematic analyses describing clinical care and monitoring of patients with geographic atrophy (GA) are lacking. A prior IRIS Registry® study investigating clinical characteristics and outcomes of a GA cohort found that a substantial proportion of patients may be lost to follow up (LTFU). This study identifies demographic and clinical characteristics that increase risk of LTFU in this subgroup.

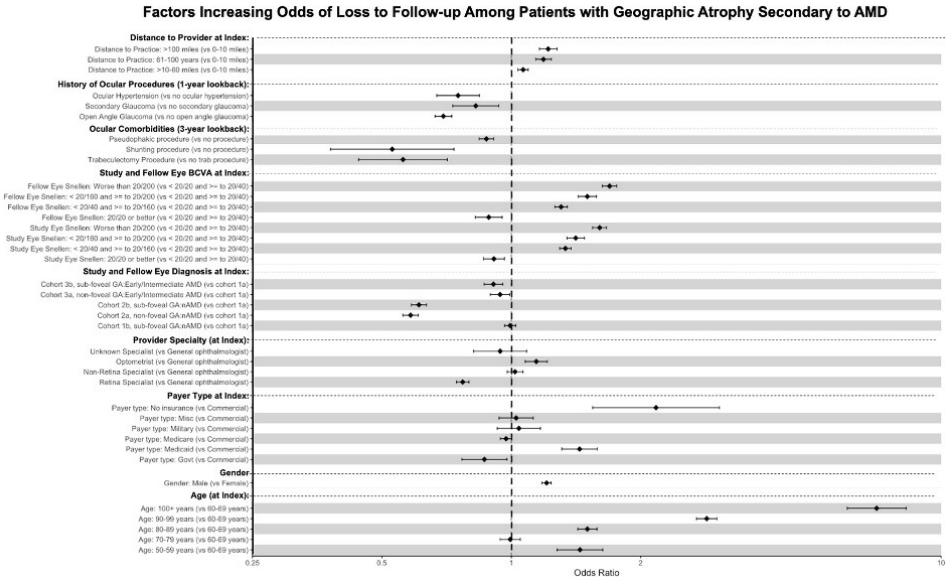
METHODS This observational study used AAO's IRIS® Registry to identify patients with a diagnosis of GA between 1/1/16 and 12/31/17. The start date was chosen based on availability of an ICD-10 code for GA and specified laterality, allowing for stratification of patients by disease stage. The study included a bivariate analysis <2 years and 2+ years of follow-up cohorts. Variables included patient demographics and clinical characteristics. Covariates strongly associated with LTFU were included in a backwards stepwise multivariate logistic regression model to estimate the odds of <2 years of follow up. An exploratory analysis included the relationship between <2 years of follow-up and provider

type.

RESULTS 230,174 patients with GA in at least 1 eye were identified, and 142,474 GA patients met the inclusion criteria. Of these, 40.6% (n=57,788) had <2 years of follow-up. The multivariate model identified several factors that increased the odds of LTFU, such as: older age (80+ years old), Medicaid or no insurance, management by an optometrist at index, VA worse than 20/40 in the study or fellow eye, and increased distance to provider. Factors contributing to lower risk of LTFU included: younger age (60-80 years old), management by a retinal specialist at index, fellow eye nAMD diagnosis, and glaucoma/cataract diagnosis/procedure. In our exploratory analysis of visit frequency, we found that patients with 2+ years of follow-up were seen more frequently in the first year, with a mean of 4.09 visits (SD 3.26) vs. LTFU patients (mean 2.91 visits; SD 2.59). This trend held in the second year, as non-LTFU patients were seen at 4.08 visits (SD 3.18) vs. 2.16 visits (SD 1.83) in LTFU patients.

CONCLUSION This observational analysis of 2,558 practices in the US indicates a significant number of GA patients are LTFU in a real-world setting. The multivariate analysis revealed patient factors that can inform decision making of both individual providers and the broader healthcare system. It will be crucial to understand this patient population as therapeutic options become available for GA.

IRB APPROVAL No — I **did not receive IRB approval** or a determination that the study/activity was exempt or that it did not require IRB approval. **Complete a Human Subject Research application** for review by the ASRS Human Research Committee. **Your abstract will not be considered without a completed application.** The ASRS HRC will review the information provided to determine whether the study qualifies as exempt or otherwise not requiring IRB approval. The ASRS HRC is not constituted as an IRB and thus cannot provide IRB approval for activities that require such.



10/11/2021 10:18AM

Avacincaptad Pegol, A Novel C5 Inhibitor, Demonstrates Continued Reduction in Geographic Atrophy Growth: 18-Month Results From GATHER1 Clinical Trial

- Jason Hsu, MD

OBJECTIVE The 18-month results of the GATHER1 trial evaluating avacincaptad pegol for the treatment of geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) are presented here.

PURPOSE To report the 18-month outcomes of monthly intravitreal injections of avacincaptad pegol, a polyethylene glycol-conjugated oligonucleotide that is a potent C5 inhibitor, on eyes with GA secondary to dry AMD.

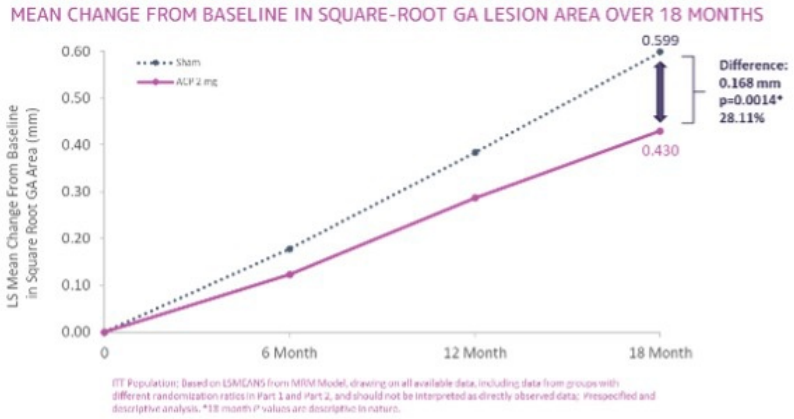
METHODS GATHER1 was a prospective, randomized, double-masked, multi-national, sham-controlled clinical trial evaluating avacincaptad pegol for the treatment of GA due to dry AMD. In part 1, subjects were randomized to receive either 1 mg or 2 mg avacincaptad pegol or sham intravitreal (IVT) injections. In part 2, subjects received either 2 mg or 4 mg avacincaptad pegol or sham IVT injections. GA progression was evaluated as the change in lesion area as measured by fundus autofluorescence. Square-root transformation was applied to mitigate the impact of baseline factors on GA growth. Other assessments included visual function (best corrected visual acuity and low-luminance visual acuity) and safety.

RESULTS A total of 286 subjects were included in this study. The least-squares mean change from baseline to month 18 in square-root GA lesion area was 0.599 mm in sham-treated subjects vs 0.430 mm in avacincaptad pegol 2 mg-treated subjects (28% reduction; $P < 0.0014$). The least-squares mean change from baseline to month 18 in square-root GA lesion area was 0.559 mm in sham-treated subjects vs 0.391 mm in avacincaptad pegol 4

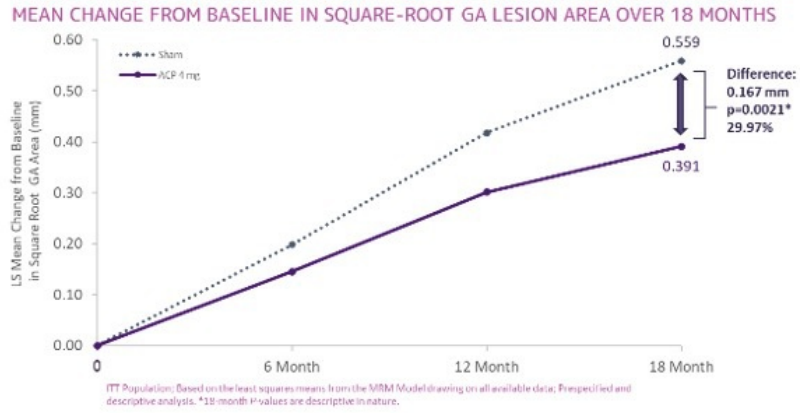
mg-treated subjects (30% reduction; P < 0.0021). There were no significant differences in best corrected visual acuity or low-luminance visual acuity between avacincaptad pegol and sham-treated subjects. Avacincaptad pegol was generally well tolerated after 18 months of administration, with no drug-related adverse events or trial discontinuations.

CONCLUSION Intravitreal avacincaptad pegol resulted in a statistically significant decrease in the rate of GA lesion growth over 18 months of treatment versus sham injection. GATHER2, a second pivotal clinical trial comparing avacincaptad 2 mg versus sham, has been initiated and is currently enrolling subjects.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.



Mean change from baseline in square-root GA lesion area at over 18 months, measured by FAF with avacincaptad pegol 2 mg vs. its corresponding sham. Least-squares means are based on estimates from a mixed model for repeated measures on the available intention-to-treat population.



Mean change from baseline in square-root GA lesion area at over 18 months, measured by FAF with avacincaptad pegol 4 mg vs. its corresponding sham. Least-squares means are based on estimates from a mixed model for repeated measures on the available intention-to-treat population.

10/11/2021 10:24AM

Avacincaptad Pegol, A Novel C5 Inhibitor, and GATHER1 Study: Results From a Post-Hoc Analysis of Nascent Geographic Atrophy

- Peter K. Kaiser, MD FASRS
- Srinivas Reddy Sadda, MD

OBJECTIVE Post-hoc analysis of the GATHER1 trial evaluating avacincaptad pegol to treat geographic atrophy (GA) secondary to dry age-related macular degeneration on nascent geographic atrophy progression.

PURPOSE To report the 12-month outcomes and investigate the progression of nascent geographic atrophy (GA) outside the GA area in patients that completed 12 months in the GATHER1 trial

METHODS GATHER1 was a prospective, randomized, double-masked, sham-controlled phase 2b/3 clinical trial evaluating avacincaptad pegol for the treatment of GA due to dry AMD. GA progression was evaluated as change in lesion area measured by fundus autofluorescence. Square-root transformation was applied to mitigate the impact of baseline factors on GA growth. Other assessments included visual function (best corrected visual acuity and low-luminance visual acuity) and safety. In this analysis, patients who completed the Month 12 visit were analyzed for the progression of nascent GA outside of the GA growth area.

RESULTS A total of 286 subjects were included in this study. The least-squares mean change from baseline to month 12 in square-root GA lesion area was 0.402 mm in sham-treated subjects vs 0.292 mm in avacincaptad pegol 2 mg-treated subjects (27.4% reduction; P = 0.0072). The least-squares mean change from baseline to month 12 in square-root GA lesion area was 0.444 mm in sham-treated subjects vs 0.321 mm in avacincaptad pegol 4 mg-treated subjects (27.8% reduction; P = 0.0051). (Fig 1) Avacincaptad pegol was generally well tolerated after 12 months of administration, with no investigator-reported drug-related adverse events or trial discontinuations. Herein, we present the post-hoc analysis of nascent GA with assessment of the rate of progression in the avacincaptad pegol-treated subjects compared to sham-treated subjects.

CONCLUSION Intravitreal avacincaptad pegol 2mg and 4mg resulted in a statistically significant decrease in rate of GA lesion growth over 12 months of treatment versus sham. Analysis of the nascent GA provides further insight into the activity of this therapy. A second pivotal clinical trial, GATHER2, has been initiated to confirm the efficacy and safety of avacincaptad 2 mg in slowing GA lesion growth.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

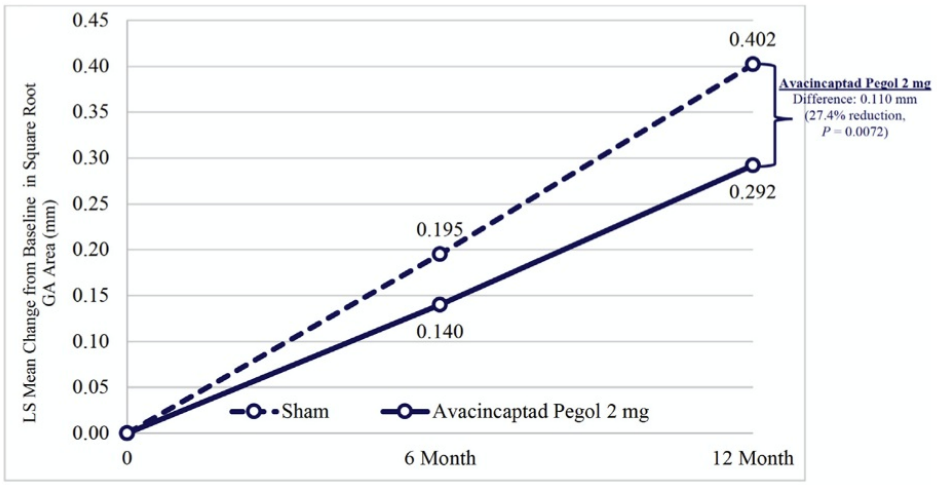
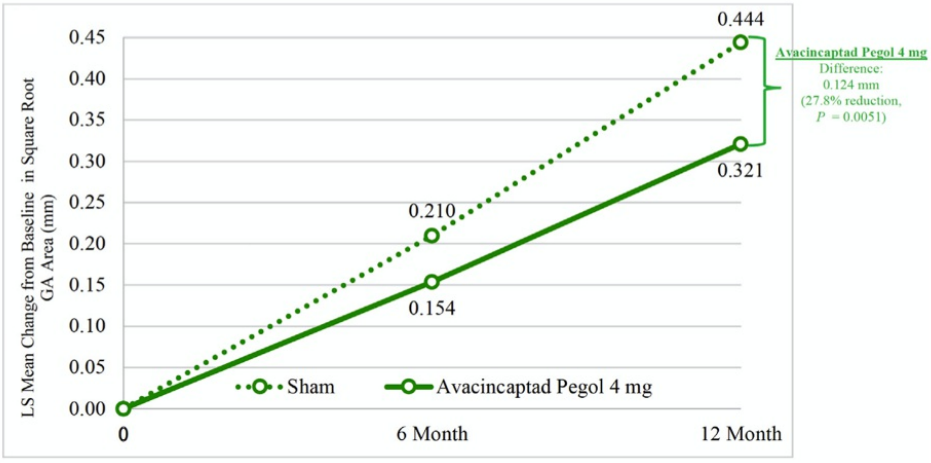


Figure 1: Mean change from baseline in square-root GA lesion area at over 12 months, measured by FAF. (A) Avacincaptad pegol 2 mg vs. its corresponding sham. (B) Avacincaptad pegol 4 mg vs. its corresponding sham. Least-squares means are based on estimates from a mixed model for repeated measures on the available intention-to-treat population.



10/11/2021 10:27AM

Safety and Efficacy of SC Elamipretide to Treat Noncentral Geographic Atrophy: ReCLAIM-1 Results and Phase II ReCLAIM-2 Baseline Characteristics

- David R Lally, MD

OBJECTIVE The ReCLAIM-1 trial evaluated the safety and efficacy of elamipretide SC to treat noncentral geographic atrophy secondary to AMD; present the baseline characteristics of the phase II ReCLAIM-2 trial

PURPOSE AMD is characterized by progressive mitochondrial dysfunction in RPE cells resulting in higher reactive oxygen species leading to cell death. Elamipretide binds to cardiolipin to stabilize mitochondrial structure and reduce ROS emission, thereby potentially slowing and reversing oxidative stress. Animal models show mitochondrial stability following elamipretide, so human studies were undertaken.

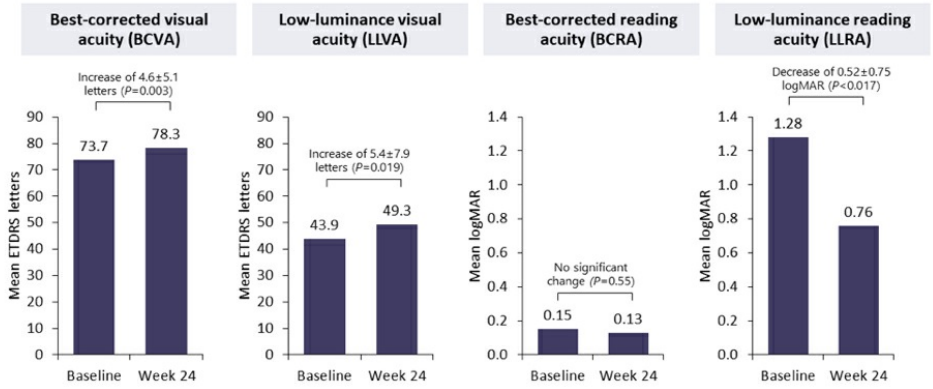
METHODS The ReCLAIM-1 trial was an open-label, Phase I study in subjects with dry AMD with non-central geographic atrophy (NCGA) or high-risk drusen treated with 40 mg SQ elamipretide daily for 24 weeks. Safety and visual function were assessed. The NCGA results are presented here. Best corrected visual acuity (BCVA) and low-luminance visual acuity (LLVA) were measured at distance and near. Area of NCGA was measured by fundus autofluorescence (FAF) and spectral-domain optical coherence tomography (SD-OCT). The ReCLAIM-2 trial is an ongoing, Phase II, randomized, double-masked, placebo-controlled study investigating SQ elamipretide in NCGA. The baseline characteristics of ReCLAIM-2 are presented.

RESULTS In ReCLAIM-1, SQ elamipretide was generally well tolerated without serious ocular/nonocular events. Injection site reactions were common. Mean BCVA and LLVA in NCGA (n = 19) improved at week 24 compared to baseline (4.6 ± 5.1,5.4 ± 7.9 letters, respectively;P < 0.05). LLVA improved > 5 letters in 53.3%, > 10 letters in 33.3%, and > 15 letters in 6.7%. (Fig 1) Mean (SD) baseline (BL) NCGA area was 3.739 mm2(3.3952) by FAF. At Week 24, this increased from BL (0.264 [0.1641] mm2;P < 0.05). When using square root area of NCGA, mean BL was 1.690 mm2(0.9773) by FAF, increasing by 0.136 mm2 (0.0831) at Week 24(P < 0.05). These results led to ReCLAIM-2 in which 165 subjects

were randomized 2:1 to receive SQ elamipretide or placebo. Primary endpoint is mean change in LLVA at Week 48. Mean BL age for subjects is 77.0 (8.5) years, and 61.2% (n = 101) are female. Mean BL BCVA and LLVA are 76.0 (8.7) letters and 55.0 (14.6) letters, respectively. Mean BL NCGA area by FAF is 2.7 (2.5) mm2. (Fig 2)

CONCLUSION Subcutaneous elamipretide appeared safe in the ReCLAIM-1 trial. BCVA and LLVA in NCGA subjects improved significantly at 24 weeks. Mean NCGA growth at 24 weeks appeared reduced compared to natural history studies, and further investigation is ongoing in the ReCLAIM-2 study.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.



Efficacy outcomes in the NCGA subgroup in ReCLAIM-1. Statistically significant improvements were seen in BCVA, LLVA, and LLRA. The difference in BCRA was not statistically significant.

	All subjects	N
Age, years • Mean (SD) • Median • Min, max	77.0 (8.5) 76.5 56, 99	165
Sex, n (%) • Male • Female	64 (38.8%) 101 (61.2%)	165
Best-corrected visual acuity (letters), mean (SD)	76.0 (8.7)	165
Low-luminance visual acuity (letters), mean (SD)	55.0 (14.6)	165
Low-luminance deficit (letters), mean (SD)	-21.0 (11.1)	165
Best-corrected reading acuity (logMAR), mean (SD)	0.30 (0.33)	165
Low-luminance reading acuity (logMAR), mean (SD)	0.90 (0.42)	165
Geographic atrophy area on FAF (mm^2), mean (SD)	2.7 (2.5)	152
Geographic atrophy distance to fovea on FAF (mm), mean (SD)	0.49 (0.36)	151
Geographic atrophy area on OCT (mm^2), mean (SD)	2.6 (2.4)	146
Geographic atrophy distance to fovea on OCT (mm), mean (SD)	0.50 (0.63)	153

Interim baseline characteristics of the ReCLAIM-2 patient population.

10/11/2021 10:33AM

Evaluating ANX007, a Novel C1q Inhibitor, in the Treatment of Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration: The ARCHER Study

- Nancy M. Holekamp, MD
- Yang Sun, MDPHD
- David Wirta, MD
- Jeffery Goldberg, MD
- Vidhu Mathur, PhD
- Anita Grover, PhD
- Lori Taylor, PhD
- Ted Yednock, PhD
- Sanjay Keswani, MBBS BSc FRCP (UK)

OBJECTIVE To assess the role of intravitreal ANX007, a novel antibody fragment targeting C1q, in the treatment of geographic atrophy (GA) secondary to age-related macular degeneration

PURPOSE C1q and the classical complement pathway, regulators of synaptic pruning in neuronal development, are aberrantly activated in neurodegenerative diseases such as GA. ANX007 is an antigen-binding fragment that binds to C1q and inhibits activation of all components of the classical pathway, including C3 and C5, but allows normal immune function of C3 and C5 as part of other complement pathways.

METHODS Studies in cynomolgus monkeys evaluated single and repeat intravitreal (IVT) doses (0, 1, 2.5 or 5 mg). Free ANX007 and C1q were measured using ELISA-based assays in aqueous, vitreous, ocular tissues, and serum. Subsequently, a Phase 1a single dose-escalation study (1.0 mg [n = 3], 2.5 mg [n = 3], or 5.0 mg [n = 3]) and a Phase 1b double-masked, randomized study (sham [n = 6], 2.5 mg [n = 6], or 5.0 mg [n = 5]) evaluated safety and tolerability of IVT ANX007 injections in patients with primary open angle glaucoma. In the Phase 1b study, injections were given at Days 1 and 29, and aqueous humor samples were collected pre-dose on both dosing occasions.

RESULTS In animal studies, all doses were well-tolerated, and vitreous ANX007 levels were measurable up to 30 days following single or repeat doses at all dose levels, the last timepoint assessed. Following two monthly 5 mg doses, ANX007 levels were measurable and C1q was engaged at 30 days post-last dose in the retina and choroid, relevant sites for GA. In Phase 1a and 1b studies, IVT ANX007 injections were well-tolerated. The PK and PD analyses conducted in the Phase 1b study demonstrated full C1q engagement in the aqueous humor at both the 2.5 and 5.0 mg doses 28 days after the first IVT ANX007 injection. Based on projections derived from animal vitreous samples and aqueous humor samples in Phase 1b, 5 mg of ANX007 is being explored to maintain C1q inhibition in the vitreous for up to 2 months in patients.

CONCLUSION This data supports clinical evaluation of ANX007 for the treatment of ophthalmic neurodegenerative diseases such as GA. A global, randomized, multi-center, double-masked Phase 2 trial designed to evaluate the efficacy and safety of IVT ANX007 in reducing the area of GA as evaluated by fundus autofluorescence is underway. Monthly and every other month dosing regimens are being evaluated.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 10:48AM

Efficacy of Intravitreal Pegcetacoplan in Geographic Atrophy: Results from the Phase 3 DERBY and OAKS Trials

- Nathan C. Steinle, MD
- David S. Boyer, MD
- Charles C Wykoff, MD, PhD, FASRS
- Jeffrey S. Heier, MD
- Rishi P. Singh, MD
- Jordi M. Mones, MD PhD
- Giovanni Staurenghi, MD
- Frank Holz, MD, FEBO
- Caleb Bliss, PhD
- Pascal Deschatelets, PhD
- Federico Grossi, MD, PhD
- Cedric Francois, MD, PhD
- Ramiro Ribeiro, PhD

OBJECTIVE To investigate the efficacy of intravitreal pegcetacoplan administered monthly or every-other-month in patients with geographic atrophy (GA) secondary to age-related macular degeneration.

PURPOSE DERBY and OAKS are two 24-month, phase 3, randomized, double-masked, sham-controlled clinical trials comparing the efficacy and safety of monthly or every-other-month intravitreal pegcetacoplan to sham in patients with GA secondary to age-related macular degeneration.

METHODS Included patients (DERBY N=621; OAKS N=638) are ≥60 years old, have best-corrected visual acuity ≥24 letters, and GA area between 2.5 and 17.5 mm2 or one focal lesion ≥1.25 mm2 if multifocal GA at baseline. Enrollment was completed in June 2020 (DERBY) and July 2020 (OAKS). The primary endpoint for both studies is change in GA lesion size via fundus autofluorescence from baseline to month 12; secondary endpoints include change from baseline in visual function. Safety measures include incidences of ocular and systemic adverse events.

RESULTS Twelve-month efficacy data will be presented.

CONCLUSION Pegcetacoplan is the only targeted C3 inhibitor being evaluated in phase 3 trials in patients to control lesion growth in GA.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 10:54AM

Safety of Intravitreal Pegcetacoplan in Geographic Atrophy: Results from the Phase 3 DERBY and OAKS Trials

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RESULTS Twelve-month safety data will be presented.

CONCLUSION Pegcetacoplan is the only targeted C3 inhibitor being evaluated in phase 3 trials in patients to control lesion growth in GA.

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