7/14/2022 09:00 am

Dry AMD 1 Symposium

ReCLAIM-2: Phase 2 Trial of Subcutaneous Elamipretide in Patients with Noncentral Geographic Atrophy

- Jeffrey Heier, MD

Objective:
To assess the effect of elamipretide therapy in dry age-related macular degeneration (AMD) patients with noncentral geographic atrophy (NCGA) lesions.

Purpose:
Evidence suggests a key role for retinal mitochondrial dysfunction in the pathogenesis of AMD. Elamipretide restores cellular ATP production and reduces mitochondria-derived reactive oxygen species (ROS) in affected cells by stabilizing the structure and function of the mitochondrial electron transport chain. In the Phase 1 trial RECLAIM-1, elamipretide showed an acceptable safety profile and promising clinical activity to potentially slow the progression of AMD. The ReCLAIM-2 trial is a Phase 2, randomized, double-masked, placebo-controlled study investigating SC elamipretide in NCGA.

Methods:
RECLAIM-2 included participants with lesion sizes between ≥ 0.05 mm^2 and ≤ 10.16 mm^2 and located ≥150 μm from the foveal center. Other inclusion criteria were age ≥ 55 years, BCVA ≥55 letters, LLVA ≥10 letters and low-luminance deficit >5 letters. Subjects were randomized 2:1 to receive SC elamipretide 40mg or placebo for 48 weeks. Primary endpoints were changes to LLVA and GA area measured by spectral-domain optical coherence tomography (SDOCT). Secondary endpoints were changes in BCVA, Low-Luminance Reading Acuity (LLRA), and GA area measured by fundus autofluorescence (FAF).

Results:
In ReCLAIM-2, 176 subjects were enrolled. Mean Baseline (BL) age for subjects is 76.1 (SD = 8.5) years, and 60.8% (n = 107) are female. Mean BL BCVA and LLVA are 76.5 (8.6) letters and 55.32 (14.6) letters, respectively. Mean BL NCGA area was 2.59 (2.36) mm^2 on FAF and 2.57 (2.33) mm^2 on SDOCT. For comparison, the BL GA area for other clinical trials included in our review ranged from 7.33 (3.79) to 9.0 (4.47) mm^2. As a planned post-hoc analysis, incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) and complete RORA (cRORA) evaluations were conducted. At baseline, all study eyes had evidence of (iRORA) in at least one zone, while only four eyes did not present with cRORA. In the central 1mm zone, 44% of eyes had cRORA, 25% had iRORA, 3% had both, and 28% had none.

Conclusion:
RECLAIM-2 was designed to assess the impact of elamipretide therapy in an NCGA population, inclusive of participants with smaller lesions at baseline. Topline safety and efficacy results from the Phase 2 trial will be available and presented in greater detail at the meeting. The potential for patient self-administration of SC injections of elamipretide would provide ophthalmologists therapeutic options to treat appropriate patients.

IRB APPROVAL Yes

7/14/2022 09:06 am

Dry AMD 1 Symposium
Assessment of Geographic Atrophy Lesion Progression in the Phase 3 OAKS and DERBY Trials

- Roger Goldberg, MD, MBA
- Michael Singer, MD
- Eleonora Lad, MD, PhD
- Renaud Desgraz, PhD
- Emma Foos
- Ramiro Ribeiro, PhD
- Jean-Francois Korobelnik, MD
- David Boyer, MD

Objective:
To assess progression of geographic atrophy (GA) by categories of change in GA lesion size in eyes treated with pegcetacoplan or sham using observed OAKS and DERBY 12-month data.

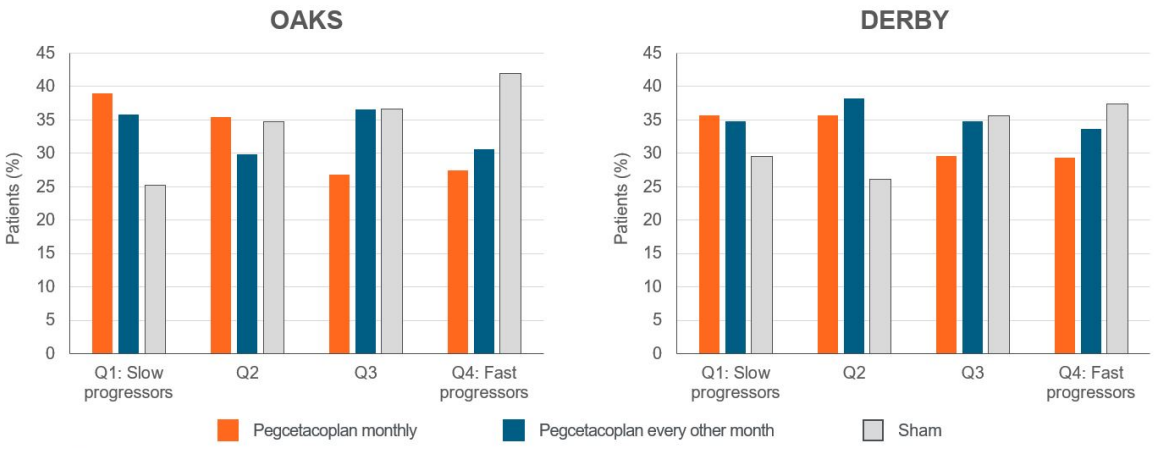
Purpose:
OAKS and DERBY are phase 3 trials assessing the efficacy and safety of investigational intravitreal pegcetacoplan for the treatment of GA secondary to age-related macular degeneration; detailed analyses of changes in lesion size are reported here.

Methods:
OAKS (NCT03525613) and DERBY (NCT03525600) are phase 3, randomized, double-masked, sham-controlled trials. The primary endpoint for both studies was change in GA lesion size via fundus autofluorescence imaging from baseline to month 12. Patients were pooled across study arms and assigned to quartiles defined by the amount of lesion growth (mm^2) over 12 months: Quartile (Q)1 (slow progressors; OAKS: <0.93, DERBY: <1.025); Q2 (OAKS: ≥0.93–<1.48, DERBY: ≥1.025–<1.62); Q3 (OAKS: ≥1.48–<2.27, DERBY: ≥1.62–<2.45); Q4 (OAKS: ≥2.27; DERBY: ≥2.45). Patients needed to have a Month 12 lesion growth measurement to be included in the analysis.

Results:
OAKS and DERBY had 494 and 461 patients, respectively, who were included in the analysis. In both OAKS and DERBY, evidence of a treatment effect of pegcetacoplan was apparent in the distribution of patients across quartiles (Figure 1). The slowest progressing quartile (Q1) had a higher proportion of patients treated with pegcetacoplan monthly (39% and 36%) or every other month (36% and 35%) than those in the sham arm (25% and 30%). Conversely, there were relatively more sham patients (42% and 37%) in the fastest growing quartile (Q4) than patients treated with pegcetacoplan monthly (27% and 29%) or every other month (31% and 34%), in OAKS and DERBY respectively. Distribution of select baseline characteristics are presented in Table 1. In the fast progressor group, baseline study eye lesion size was larger than in the slow progressor group (OAKS: 9.5 mm^2 vs 7.1 mm^2; DERBY: 9.5 mm^2 vs 6.5 mm^2, respectively). The fast progressor group also had a higher proportion of patients with extrafoveal study eye (SE) lesion location, multifocal SE GA, bilateral GA, double-layer sign present in SE and pseudodrusen present in SE. Finally, the fast progressor group had a lower proportion of patients with >20 SE intermediate or large drusen or choroidal neovascularization in the fellow eye.

Conclusion:
Pegcetacoplan shifts the distribution of patients across quartiles defined by lesion growth, supporting the treatment effect observed in the primary analysis. This analysis provides additional data on factors that may impact lesion growth; with further research, these findings may aid in identifying populations that may have a greater response to pegcetacoplan.

IRB APPROVAL Yes



Q=quartile.

Distribution of patients across quartiles in OAKS and DERBY

	OAKS		DERBY	
	Slowest progressors (Q1)	**Fastest progressors (Q4)**	**Slowest progressors (Q1)**	**Fastest progressors (Q4)**
Study eye GA lesion size (mean, mm²)	7.1	9.5	6.5	9.5
Foveal study eye lesion (%)	76	48	78	48
Unifocal study eye lesion (%)	41	16	38	20
Bilateral GA (%)	76	86	74	85
Any CNV in fellow eye (%)	29	17	20	14
Study eye pseudodrusen present (%)	78	86	78	93
Study eye DLS present (%)	15	25	16	22
Study eye intermediate or large drusen number (% with >20)	64	38	56	32

CNV=choroidal neovascularization; DLS=double-layer sign; GA=geographic atrophy; Q=quartile.

Distribution of select baseline characteristics

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Dry AMD 1 Symposium

Association Between Dysfunctional Complement Factor I: Rare Variant Status and Progression to Advanced AMD Outcomes

- Johanna Seddon, MD, ScM

Objective:
Are rare dysfunctional *CFI* genetic variants related to progression to advanced AMD?

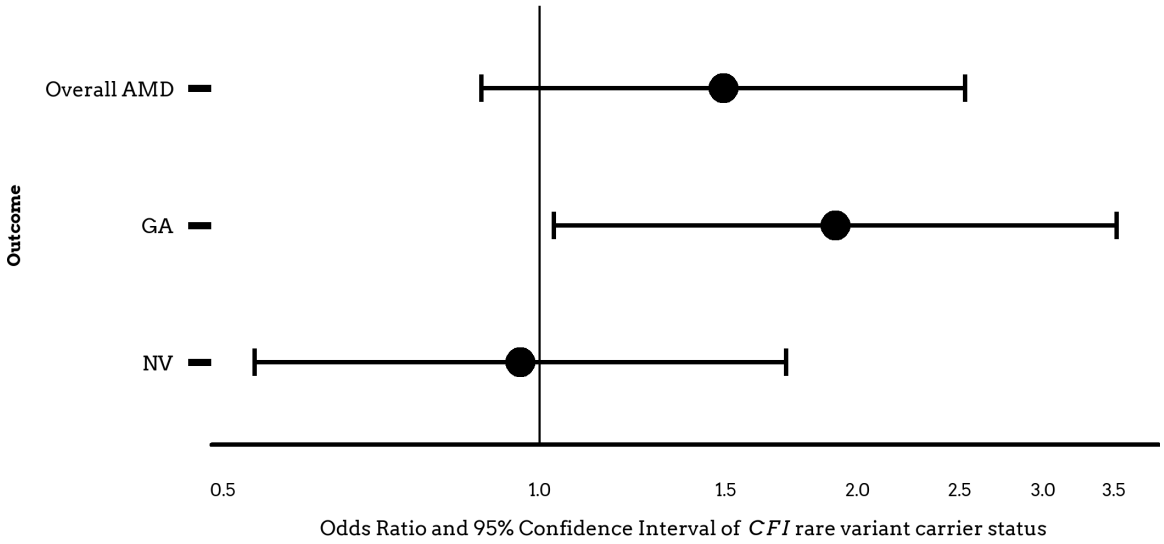
Purpose:
To evaluate the associations between dysfunctional *CFI* rare variant carrier status and progression to advanced age-related macular degeneration (AMD), geographic atrophy (GA) and neovascular disease (NV).

Methods:
Analyses were performed using the Seddon Longitudinal Cohort Study (SLCS) of AMD (N= 2116 eligible subjects, 3901 eyes, mean follow-up 8.3 years, 22% progression rate to advanced AMD, PMID 30389371) and the Age-Related Eye Disease Study (N=2837 eligible subjects, 5200 eyes, mean follow-up 9.2 years, 18% progression rate to advanced AMD). *CFI* rare variants with low serum factor I levels and decreased function in a serum based assay (PMID's 24036952 and 32908800), and other common and rare genetic variants related to AMD, demographic and behavioral factors, and baseline and follow-up macular status were evaluated. To estimate the effect of rare dysfunctional *CFI* variant status on AMD progression, independent of other variants related to progression, odds ratios (OR) were calculated based on Generalized Estimating Equations. Interactions between *CFI* carrier status and individual variants were determined.

Results:
Among the 4953 subjects (9101 eyes) in the combined population, 1% were rare *CFI* variant carriers and 44% of the carriers progressed to overall AMD compared with 20% of non-carriers ($P < .0001$). For the advanced AMD subtypes, 30% of carriers versus 10% of non-carriers progressed to GA ($P < .0001$), and 18% of carriers and 11% of non-carriers progressed to NV ($P=.049$) over a 12-year follow-up period. *CFI* carriers were more likely to have a family history of AMD (*CFI* variant: 36% with 1 family member affected and 14% with 2+ family members affected; no *CFI* variant: 19% with 1 family member affected and 8% with 2+ family members affected; P for trend =.035). *CFI* variant carrier status was associated with progression to GA (OR 1.91, 1.03-3.52) but not with NV (OR 0.96, 0.54-1.71), after adjustment for demographic and ocular factors and other genetic variants (Figure). *CFI* rare variant carrier status was associated with the common *CFI* (PMID 18685559) and hepatic lipase C (*LIPC*, PMID 20385826) genetic variants, but no significant interactions between *CFI* carrier status and other genetic variants were noted for progression to advanced AMD, GA or NV.

Conclusion:
These new findings suggest that carriers of dysfunctional *CFI* rare variants are at higher risk for progression to GA.

IRB APPROVAL Yes


Outcome
Overall AMD
GA
NV
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Odds Ratio and 95% Confidence Interval of *CFI* rare variant carrier status

7/14/2022 09:16 am

Dry AMD 1 Symposium

Safety of Intravitreal Pegcetacoplan for Geographic Atrophy: 12-Month Results of the OAKS and DERBY Trials

- Caroline Baumal, MD
- Allen Ho, MD FASRS
- Jordi Mones, MD PhD
- Preeti Joshi
- Caleb Bliss, PhD
- Ravi Metlapally
- Jeffrey Heier, MD

Objective:
To report additional details of safety outcomes observed in the OAKS and DERBY trials evaluating investigational monthly (PM) or every-other-month (PEOM) intravitreal pegcetacoplan in eyes with GA secondary to age-related macular degeneration (AMD).

Purpose:
The phase 3 OAKS and DERBY trials evaluated efficacy and safety of pegcetacoplan treatment for GA, a leading cause of irreversible vision loss worldwide. Detailed safety data not previously presented are reported.

Methods:
OAKS (NCT03525613) and DERBY (NCT03525600) are randomized, double-masked, sham-controlled trials. Enrolled patients were ≥60 years old with best-corrected visual acuity ≥24 letters and GA area 2.5–17.5 mm^2. The primary endpoint was change from baseline to Month 12 in GA lesion size measured via fundus autofluorescence. For safety, the incidence of ocular and systemic treatment-emergent adverse events (AEs) was evaluated.

Results:
At 12 months, a total of 6322 pegcetacoplan injections had been given across both trials (safety set: OAKS, N=636; DERBY, N=620). Most AEs were considered mild or moderate. In OAKS, 14 (6.6%), 16 (7.5%), and 8 (3.8%) patients in the PM, PEOM, and sham groups and in DERBY, 19 (9.2%), 13 (6.3%), and 6 (2.9%) patients in the PM, PEOM, and sham groups, respectively, had AEs in the study eye considered related to treatment. Serious ocular AEs in the study eye were reported for 3 (1.4%), 4 (1.9%), and 0 patients in OAKS; and 1 (0.5%), 0, and 2 (1.0%) patients in DERBY in the PM, PEOM, and sham arms, respectively. A total of 4 patients discontinued treatment due to ocular AEs in the study eye in OAKS (PM: n=1, PEOM: n=2, sham: n=1), and 3 patients discontinued treatment due to ocular AEs in the study eye (PM: n=0, PEOM: n=1, sham, n=2) in DERBY. In OAKS and DERBY combined, investigator-reported events of new onset exudative AMD (eAMD) in the study eye were reported in 25 (6.0%), 17 (4.1%), and 10 (2.4%) patients in the PM, PEOM, and sham arms, respectively. Study eyes that developed eAMD continued treatment with pegcetacoplan and received anti-VEGF therapy. A total of 13 study eyes across both studies receiving pegcetacoplan experienced intraocular inflammation (IOI); majority of cases were mild and 10/13 patients resumed pegcetacoplan without IOI recurrence. The rate of IOI per injection was 0.22%. There were no cases of vasculitis or occlusive vasculitis. AEs related to intraocular pressure in the study eye were reported in 8 (3.8%), 10 (4.7%), and 1 (0.5%) patients in OAKS and 7 (3.4%), 7 (3.4%), and 0 patients in DERBY, in the PM, PEOM, and sham arms, respectively.

Conclusion:
At 12 months, intravitreal pegcetacoplan administered monthly or every other month was well tolerated in patients with GA.

IRB APPROVAL Yes