APL-2, a complement C3 inhibitor, slows the growth of geographic atrophy secondary to AMD: 18-month results of a phase 2 trial (FILLY).

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BACKGROUND

- Geographic Atrophy (GA) is an advanced stage of age-related macular degeneration (AMD) and a major cause of legal blindness. Vision loss associated with GA significantly affects quality of life.1
- GA is characterized by a loss of RPE, photoreceptors, and atrophy of the choriocapillaris.2
- GA affects almost 1 million people in the United States alone. Additionally, about 50% of patients develop bilateral GA within 7 years of diagnosis of GA in the first eye. GA also frequently develops within 5 years of starting treatment with VEGF inhibitors in patients with neovascular AMD.3
- To date there is no treatment available to prevent GA or slow GA progression.
- Dysregulation of the complement system is a major contributor to the pathogenesis of AMD. Complement genetic variants and oxidative stress may activate the three complement activation pathways.4
- Due to the key position of C3 in the complement cascade, APL-2, a PEGylated cyclic peptide inhibitor of C3, may block all complement activation pathways and effectors of the complement cascade and is being investigated as a therapeutic to slow GA progression.

PURPOSE

The Filly phase 2 trial was designed to evaluate the safety and efficacy of APL-2 (pegcetacoplan, 15mg) administered intravitreally for 12 months, followed by an additional 6 months without treatment, in subjects with GA secondary to AMD.

MAJOR ENTRY CRITERIA

- At least 50 years old
- With reference to study eye:
  - Best-corrected visual acuity (BCVA) of 24 letters or better (20/30Snellen equivalent).
  - GA secondary to AMD, with a GA area size of ≥2.5 x 2.5 mm² and ≤7.5 x 7.5 mm², and at least one focal lesion ≥1.25 mm² if GA was multifocal.
- Major exclusion criteria: GA due to causes other than AMD, history or current evidence of exudative AMD, retinal disease other than AMD.
- GA or exudative AMD was permitted in the fellow eye.

STUDY DESIGN

Figure 1: Clinical trial flowchart. Eligible subjects were randomized to receive intravitreal injection of sham or APL-2 monthly, or every other month (EOM), for 12 months. Patients return at months 15 and 18 for safety and efficacy follow-up. "Modified intent-to-treat (mITT)" population was used for the analysis and is defined as all patients who received at least one injection and had at least one visit at month 3 or later at which primary efficacy data was collected.

BASELINE CHARACTERISTICS

Table 1: Baseline characteristics in ITT population.

RESULTS: PRIMARY EFFICACY ENDPOINTS – GA LESION GROWTH

Figure 2: Change from baseline in GA area. Panel A. Least-squares (LS) means and their standard errors (SE) were estimated from a mixed effect model that included treatment and visit as factors, and baseline GA as a covariate, as well as the interaction term of treatment × visit × baseline. The p-values versus Sham-Pooled for APL-2 Monthly and Every-Other-Month (EOM), respectively, were 0.010 and 0.001 at Month 12, and 0.044 and 0.007 at Month 18. Panel B. LS means and SEs were estimated from a mixed effect model that included treatment and visit×baseline as factors, and baseline GA as a covariate, as well as the interaction term of treatment × visit × visit × baseline. The p-values versus Sham-Pooled for APL-2 and Sham-Pooled for EOM were nonsignificant. C. Post hoc exploratory analysis: Growth in GA lesion size (mm²) per 6-month period.

RESULTS: VISUAL ACUITY

Figure 3: Change from baseline in visual acuity. BCVA is best-corrected visual acuity assessed with the ETDRS chart. LL = low luminance; LL-VA deficit = low-luminance visual acuity deficit which is derived by subtracting LL-BCVA from BCVA. Least-squares (LS) means and standard errors (SE) were estimated from a mixed effect model that included treatment and visit as factors, and baseline value of the endpoint as a covariate, as well as the interaction term of treatment × visit × baseline.

RESULTS: SAFETY DATA

Table 2: Major safety data in ITT population. “Two cultures positive for coagulas-negative Staphylococcus. One culture negative in the monthly group. ** Coded as visual impairment in the Month-12 analysis.

CONCLUSIONS

• The Filly Phase 2 trial met its primary endpoint. APL-2 demonstrated pronounced and statistically significant reductions in GA growth over 18 months as compared to sham groups despite no treatments for 6 months.
• No differences in visual acuity were observed between the groups.
• Incidence of exudative AMD, reported by the Investigators, seems to be more frequent in the APL-2 treated subjects.
• The risk/benefit profile at 18 months supports the decision to move to Phase 3 trial.

REFERENCES