Genetic Risk Factors Are Not Associated with Wet Age-Related Macular Degeneration Treatment Response to Ranibizumab

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Dear Editor,

We previously reported an association between *CFH* haplotypes and ranibizumab treatment response [1] wherein *CFH* reduced-risk haplotypes were associated with a ≥ 15 Early Treatment of Diabetic Retinopathy Study letter gain at a 6-month endpoint in a cohort of 70 treatment-naïve wet age-related macular degeneration (AMD) patients. Following the primary study outcome, we extended the trial an additional 6 months to evaluate the robustness of the findings. Herein, we report on the 12-month findings.

At baseline, treatment-naïve patients with choroidal neovascularization secondary to AMD were genotyped for *CFH* haplotypes, SNP *rs2230199* (C3), SNP *rs10490824* (ARMS2), and the mtDNA A4917G marker. The primary study outcome was a gain of ≥ 15 letters in patients with risk alleles or haplotypes for AMD. Secondary outcome measures sought to identify associations between genetic dispositions and change in visual acuity (VA) or central macular thickness. Intravitreal ranibizumab at a concentration of 0.5 mg/0.05 mL was used to treat patients. All patients received 3 monthly injections followed by a flexible pro re nata regimen. Of the 70 patients included in the 6-month analysis, 60 participated in the extended study. The 10

patients who withdrew differed from the 12-month cohort in having a worse VA by an average of 12 letters ($p = 0.0012$).

Univariate analysis suggested no association between any genotyped markers with respect to VA or central macular thickness. Consistent with the 6-month findings, 66.7% of patients expressing reduced-risk *CFH* haplotypes gained ≥ 15 letters after 1 year. 46.9% of increased-risk and greatly increased-risk haplotype-expressing patients had gained ≥ 15 letters at 1 year compared to 27.6% of patients at 6-months.

The 12-month study extension findings suffer from a number of limitations. Namely, the study was underpowered to detect the differences observed in the proportion of patients gaining ≥ 15 letters by haplotype. In addition, participants who withdrew following the 6-month endpoint had poorer VA outcomes compared to the remaining study population. 90% of dropouts expressed *CFH* risk haplotypes.

Pharmacogenetic response to ranibizumab treatment in the *CFH* reduced-risk haplotype cohort remained stable from 6 months to 12 months. Two-thirds of patients in this cohort experienced vision gains of ≥ 15 letters. Despite this, the statistically significant association between *CFH* reduced-risk haplotype-expressing patients having proportionally more individuals

achieve a ≥ 15 -letter improvement at 6 months was not replicated at 12 months. The proportion of increased-risk and greatly increased-risk *CFH* cohort patients experiencing a ≥ 15 -letter improvement at 12 months was artificially inflated by dropouts. *CFH* haplotypes may be a more stable predictor of VA changes associated with treatment than SNPs at the *rs1061170* site alone.

Disclosure Statement

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Reference

- 1 Chaudhary V, Brent M, Lam WC, Devenyi R, Teichman J, Mak M, Barbosa K, Kaur H, Carter R, Farrokhyar F: Genetic risk evaluation in wet age-related macular degeneration treatment response. *Ophthalmologica* 2016;236:88–94.