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Five-year update for the phase 3 voretigene neparvovec-rzyl study in biallelic RPE65 mutation-associated inherited retinal disease

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Purpose:
To determine whether ambulatory navigation, light sensitivity, and visual field (VF) improvements 1 year after voretigene neparvovec-rzyl (VN) administration in subjects with biallelic RPE65 mutation-associated inherited retinal disease (IRD) are maintained at 4-5 years, and to review safety outcomes over the entire period.

Methods:
 Patients were randomized to either original intervention (OI: bilateral subretinal VN at baseline; n=20) or delayed intervention (DI: VN after 1 year; n=9). Primary endpoint was bilateral performance on the Multi-Luminance Mobility Test (MLMT) at 7 standard light levels as measured by a change score. Additional endpoints were full-field light sensitivity threshold (FST) testing, visual acuity (VA), and Goldmann kinetic VF (GVF), each averaged over both eyes. Safety outcomes included adverse event reporting, laboratory testing, and changes in pre-specified examinations.

Results:
For OI patients at Year 5 (n=18) and DI patients at Year 4 (n=8), the MLMT mean (SD) bilateral light level change score was 1.6 levels (1.1) and 2.4 levels (1.5), respectively compared to baseline. Subsequent to the 1-year outcomes, an improvement of 1 light level occurred in 6 patients, no change in the remaining 20 (N=26). Mean change in white light FST in log_{10} (cd.s/m²) was −2.02 (1.45) log_{10} at Year 5 for OI patients (n=17) and −2.58 (1.04) log_{10} at Year 4 for DI patients (n=8). Mean change in VA (Holladay Scale, logMAR) was -0.00 (0.64) at Year 5 for OI subjects (n=18) and -0.06 (0.26) at Year 4 for DI subjects (n=8). Mean change in GVF III4e sum total degrees was 166.6 (208.7) at Year 5 for OI subjects (n=15) and 178.8 (241.9) at Year 4 for DI subjects (n=8). Safety profile (N=29) remains consistent with vitrectomy and the subretinal injection procedure with 2 new reports of cataract, 1 of ptosis, and 1 of retinal detachment since the last update. No deleterious immune responses were reported.

Conclusions:
Improvements in ambulatory navigation, light sensitivity, and VF are maintained for at least 5 years after VN administration in most OI subjects. Improvements in DI subjects were consistent with those observed in OI subjects. The safety profile of VN is consistent with the administration procedure.