rAAV2/2-ND4 for the Treatment of LHON: 72-week Data from the REVERSE Phase III Clinical Trial

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Objective:
To assess the efficacy of a single intravitreal injection of rAAV2/2-*ND4* (GS010), an investigational gene therapy for vision loss due to *ND4*-LHON.
Background:
LHON is a mitochondrial inherited disease that causes bilateral central vision loss. A point mutation in the mitochondrial *ND4* gene accounts for 75% of all LHON cases. rAAV2/2-*ND4* is a gene therapy enabling allotopic expression and delivery of the wildtype ND4 protein to mitochondria of retinal ganglion cells.
Design/Methods:
REVERSE (NCT02652780) is a Phase III, randomized, multicenter, double-masked, sham-controlled trial of 37 LHON subjects with the G11778A-*ND4* mutation. All received a single unilateral intravitreal injection of rAAV2/2-*ND4*. Visual functions and measurements of relevant retinal anatomy were monitored for 72 weeks following treatment.
Results:
At Week 72 an improvement of +15 ETDRS letters was seen in rAAV2/2-*ND4* treated eyes. Sham-treated eyes also showed improvement in acuity (+12 ETDRS letters). Contrast sensitivity also improved: - GS010-treated and sham-treated eyes gained respectively on average +0.21 LogCS and +0.15 LogCS, compared to baseline. The proportion of GS010-treated eyes that achieved a clinically meaningful improvement of at least 0.3 LogCS (45.9%) was statistically significantly higher than that of sham-treated eyes (24.9%; p=0.0047). Ganglion cell layer (GCL) volume, papillo-macular bundle thickness and total macular ETDRS thickness were significantly preserved in treated vs. sham eyes; all 3 differences reaching statistical significance.
Conclusions:
Seventy-two weeks after rAAV2/2-*ND4* administration, a clinically meaningful improvement in visual functions and sustained preservation of LHON-relevant retinal anatomy were seen in drug-treated eyes, suggesting that the biological targets of this gene therapy were successfully engaged.