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TITLE

Oral Synthetic *cis*-Retinoid Therapy to Rescue Vision in Subjects with Leber Congenital Amaurosis (LCA) due to Lecithin:Retinol Acyltransferase (*LRAT*) or Retinal Pigment Epithelial 65 Protein (*RPE65*) mutations: Preliminary Results of a Phase Ib Trial

AUTHORS

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PURPOSE

LCA is characterized by severe vision loss at birth, sensory nystagmus, poor pupillary responses due to progressive retinal degeneration and an absent or severely diminished electroretinogram (ERG). This study assessed visual function changes and safety parameters in subjects with LCA after the oral administration of QLT091001, a synthetic retinoid therapy. There are no proven therapies for this disease. QLT091001 has been shown to restore vision in mouse and dog models with LCA.

SETTING

Ongoing single-centre trial of subjects treated at Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada.

METHODS

This is an IRB approved, Phase Ib open-label, proof-of-concept clinical trial to evaluate the safety and efficacy of QLT091001 in subjects with LCA due to *RPE65* or *LRAT* gene mutations. Subjects are treated with oral QLT091001 daily for 7 days. Visual function testing (Early Treatment of Diabetic Retinopathy Study [ETDRS] visual acuity, Goldmann visual fields

[GVFs], Full-field stimulus threshold testing, Electroretinograms, Ishihara Color Testing, Optical Computed Tomography, and SKILL low contrast vision acuity testing) complete ophthalmic and physical examinations, electrocardiograms and laboratory blood work are completed before and after treatment at predetermined time points. We identified homozygous frameshift and missense mutations in *LRAT* and *RPE65* by SNP genotyping, followed by Sanger sequencing, confirmed by a CLIA certified lab.

RESULTS

Nine of 12 planned subjects with LCA due to *LRAT* or *RPE65* mutations have been enrolled to date. Preliminary results show improvements in best-corrected visual acuity (BCVA) and Goldmann visual fields (GVF). In some cases, BCVA and GVF improvements have persisted for up to 11 months beyond the end of treatment. Many subjects reported meaningful improvements in their activities of daily living (ADLs). There were no serious adverse events. Transient headache and photophobia were reported and reversible elevations in triglyceride levels and reduction in HDL were recorded. LFT, ECG, vitals, physical exams, and kidney function tests were all within normal limits.

CONCLUSIONS

In this study, seven days of oral QLT091001 was generally well-tolerated and led to rapid and sustained vision improvements, as well as subjective improvements in ADLs. Adverse events were transient and/or reversible. These results suggest the existence of a population of dormant photoreceptors with the ability to respond to external manipulation. We are currently enrolling the remainder of the LCA subjects and expect to report on the full study results upon study completion.

FINANCIAL DISCLOSURE

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