10/10/2021 2:40PM

Optogenetics in the Clinic: Safety and Efficacy Updates on the Phase I/II Clinical Trial PIONEER

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OBJECTIVE Evaluate GS030, an optogenetic treatment combining a gene therapy and a medical device, in subjects with end-stage non-syndromic retinitis pigmentosa.

PURPOSE Retinitis pigmentosa (RP) is a progressive inherited blinding disease caused by mutations in many different genes. Optogenetic is a gene agnostic approach for restoring visual function at late stages of RP. The phase I/II study PIONEER evaluates GS030 combined optogenetic therapy for patients with advanced non-syndromic RP.

METHODS PIONEER is an open-label dose-escalation clinical study of GS030 combined therapy. The GS030 viral vector encoding ChrimsonR targets retinal ganglion cells upon intravitreal injection. The GS030 light-stimulating goggles encode the visual scene and project corresponding light pulses in real-time to stimulate the optogenetically transduced retinal ganglion cells at a specifically tailored wavelength and intensity.

RESULTS Nine RP patients with a maximal visual acuity of Light Perception were included in three dose-escalation cohorts (5E10, 1.5E11, and 5E11 vg/ eye) and received a single injection of viral vector in their worse-seeing eye. Light stimulation with the goggles started 4 months after injection and was well tolerated. The main ocular adverse event related to

gene therapy was mild to moderate intraocular inflammation responsive to corticosteroid treatment. Following systematic visual training with the goggles, a patient was able to perceive, locate, touch, and count objects on a table using the treated eye alone and only whilst wearing the goggles. Electroencephalography recordings showed vision.related cortical activity during the visual perception tasks. More study patients are now able to be assessed, as the COVID pandemic is better controlled.

CONCLUSION GS030 demonstrates a good safety profile up to 2 years after vector administration, and preliminary efficacy assessment shows partial functional recovery in a patient.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

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Intravitreal AAV2 Optogenetic Vision Restoration in retinal degenerative patients with ABCA4 mutation

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OBJECTIVE The objective of this study is to evaluate efficacy of intravitreal Optogenetic therapy targeting ON-bipolar cells in Retinitis Pigmentosa (RP)patients with ABCA4 mutation.

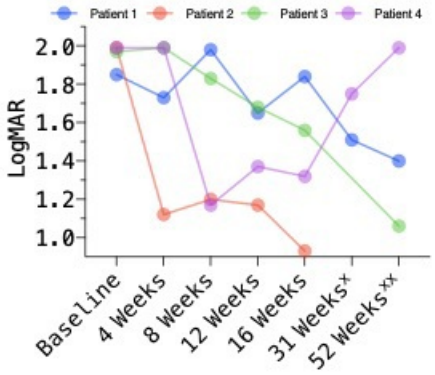
PURPOSE Optogenetics offers the potential for vision restoration in RP by photosensitizing higher order bipolar neurons. It is “gene-agnostic”, focusing on disease phenotype in a mutation independent manner, and applicable to a wide population of patients with retinal degenerations. This therapy diffesrs by not require an external device for stimulation.

METHODS Methods: Multi-Characteristic Opsin (MCO) is an engineered broadband opsin sensitive to ambient light avoiding the need for an external amplifying device and associated phototoxicity. Upon Intravitreal delivery of MCO encoding genes by AAV2 vector, ON-bipolar neurons are reprogrammed to be activated at ambient light. Reengineering the degenerated retina with MCO-transduced abundant ON-bipolar cells acting as new photoreceptors has potential for greater spatial resolution. Four subjects with severe (RP) caused by ABCA4 mutation received a single intravitreal injection of AAV2-MCO (vMCO). Safety and exploratory efficacy of intravitreal vMCO injection was evaluated for 52 weeks.

RESULTS Results: Overall improvement in visual function, as measured by Freiburg visual acuity (Mean at Baseline: 1.95 logMAR vs. 1.46 logMAR @ 52 weeks), mobility score, shape discrimination accuracy, and Visual field was achieved with a single intravitreal dose of 3.5x1011 vg/eye. The improved vision correlated with patient reported outcome, as assessed by Visual Function Questionnaire. The therapy was well-tolerated with no reported serious adverse events. Mild-Moderate transit IOP increase that was resolved with topical IOP lowering meds w/o sequalae. Mild self-limited ocular inflammation was observed, which was controlled with topical steroid. No patient required topical or oral medication at the end of the study.

CONCLUSION Safety profile of vMCO was well-tolerated with no serious adverse events. vMCO showed a positive trend in visual functions improvement in patients with RP independent of underlying gene mutations. This proof-of-concept study demonstrates promise in restoring vision for ABCA4 mutation RP patients, and has potential in other inherited retinal degenerations

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.



Phase 1/2 Clinical Trial of Intravitreal 4D-125 AAV Gene Therapy in Patients with Advanced XLRP: Interim Safety & Preliminary Activity

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OBJECTIVE To assess safety, tolerability, and activity of 4D-125 AAV gene therapy administered intravitreally in males with advanced XLRP due to mutations in the RPGR gene.

PURPOSE Intravitreal (IVT) delivery of AAV gene therapy is desirable but inefficient with conventional AAV. Directed evolution was used to develop the R100 AAV capsid for IVT retinal gene therapy. 4D-125 comprises the R100 capsid carrying the RPGR transgene. Here we report initial clinical findings from the dose-escalation phase of an ongoing Phase 1/2 study of IVT 4D-125 treatment of XLRP.

METHODS A Phase 1/2 dose-escalation and expansion trial is being conducted to evaluate a single IVT administration of 4D-125 in males with advanced XLRP at two dose levels (3×1011 and 1×1012 vector genomes (vg)/eye). A standard 3+3 dose-escalation design was used, followed by dose expansion. Patients received a brief tapering corticosteroid regimen after dosing. Safety and tolerability were assessed. Preliminary biological activity was assessed using microperimetry (MP) to measure retinal sensitivity and SD-OCT to measure ellipsoid zone area (EZA). The dose-expansion portion of the study is ongoing.

RESULTS Seven subjects (median age 42.0 years; range 27-56 years) received 4D-125 at the time of abstract submission: 3×1011vg/eye (n=3) and 1×1012 vg/eye (n=4) with follow-up of 4.2-12.5 mos. 4D-125 was well-tolerated, with no dose-limiting or serious adverse events observed. Intraocular inflammation (4/7 subjects) was mild or moderate, transient (duration 0.9-1.6 mos), and steroid-responsive. Most of the subjects had advanced disease, with only 2 having both measurable EZA and mean MP retinal sensitivity (mMPRS)

at baseline (BL) in both eyes and follow-up of at least 4 mos. Both subjects had a greater increase from BL in mMPRS in the treated vs. untreated eye (+1.65 dB vs. +0.25 dB at 9 mos and +0.50 dB vs. +0.10 dB at 4 mos; BL values 1.5-3.2 dB) and number of loci gaining ≥7 dB sensitivity (6 vs. 1 at 9 mos and 3 vs. 0 at 4 mos.). Relative decreases from BL EZA were less in the treated vs. untreated eye for both subjects (-12.4% vs. -16.2% at 9 mos and -20.2% vs. -28.7% at 6 mos).

CONCLUSION IVT 4D-125 was well-tolerated with mild or moderate, transient, and steroid-responsive intraocular inflammation. Possible signs of biologic activity were observed in 2 evaluable dose escalation subjects based on microperimetry and SD-OCT. These findings support dose expansion with the 1×1012 vg/eye dose in XLRP subjects with less advanced disease in the ongoing Phase 1/2 study.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.