Safety and Efficacy results from a Phase 1/ 2 Clinical trial of OCU400 modifier gene therapy for treatment of retinitis pigmentosa

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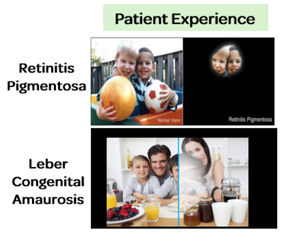
Background: RP and LCA– High Unmet Medical Need

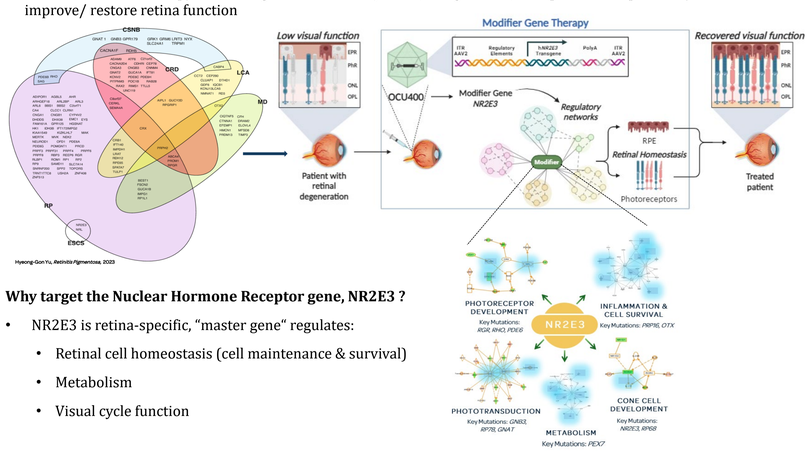
- IRDs, such as RP and LCA, are a group of heterogenous genetic disorders that affect the retina, the light-sensitive tissue at the back of the eye
- They often lead to a gradual loss of vision over time and can ultimately result in blindness
- Despite its prevalence, RP and LCA patients have limited treatment options
- More than 125 mutated genes are associated with RP and LCA, and developing a single therapy to treat each mutation is not feasible
- Approved and upcoming gene therapies focus on addressing effects of individual genes

	Global	United States	Genes
Inherited Retinal Disease	2 million	~400,000	>300 genes
Retinitis Pigmentosa	1.6 million	110,000	>100 genes
Leber Congenital Amaurosis	~158,000	15,000	>25 genes



OCU400 Targets NR2E3 to Potentially Treat Multiple IRDs

- OCU400 Modifier Gene Therapy Can Potentially Address Multiple Genetic Defects with a Single, Gene Agnostic Product
- Potential curative therapy with a single sub-retinal injection, using NR2E3, with potential to preserve/ improve/ restore retina function

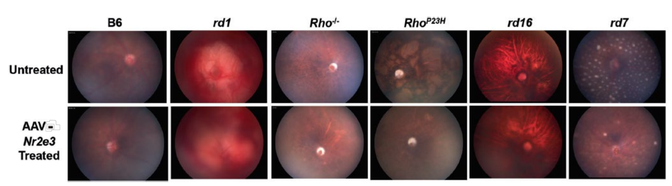


Why target the Nuclear Hormone Receptor gene, NR2E3 ?

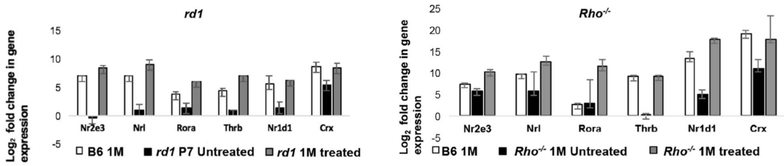
- NR2E3 is retina-specific, "master gene" regulates:
  - Retinal cell homeostasis (cell maintenance & survival)
  - Metabolism
  - Visual cycle function

Pre-clinical studies in the RP mouse models

AAV-*Nr2e3* treatment preserves retinal morphology and retinal integrity in RP models



AAV-*Nr2e3* rescues RP degeneration by regulating key transcription factors in the Retina



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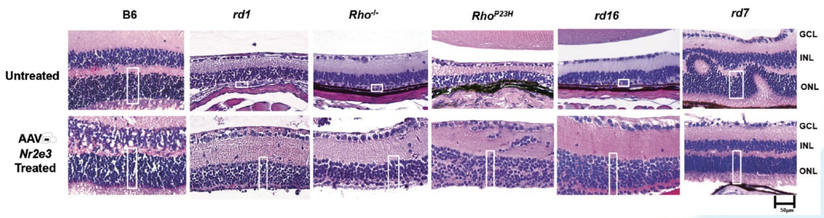


Phase 1/2 study design to assess the safety and Efficacy of OCU400 for RP and LCA

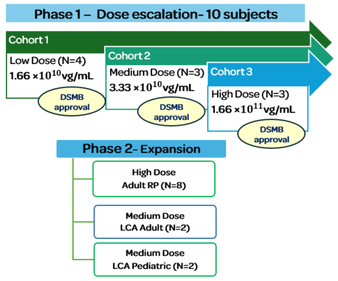
- Multi -center, open-label, 3+3 dose-escalation and dose expansion study in two subgroups of subjects with RP and LCA
- Treated subjects received a single subretinal injection of OCU400 in the study eye

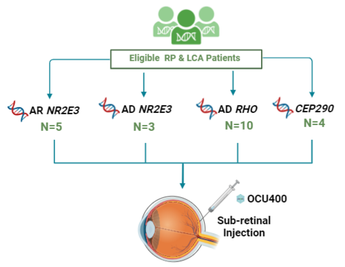
Inclusion Criteria

- Age ≥ 18 years with a confirmed genetic, clinical diagnosis of RP
- BCVA ≤ 20/160 for sentinel, & ≤20/50 in non-sentinel RP subjects
- BCVA of ≥ LogMar+0.7 but ≤ Log Mar 3.5 for LCA subjects
- Visual field <20° in any meridian
- Able to perform a Multi-Luminance Mobility Test (MLMT)
- Presence of photoreceptors in the pericentral and/or peripheral regions as determined by SD-OCT.

Exclusion Criteria

- Previous treatment with a gene or cell product
- History of corticosteroid IOP spikes, uncontrolled glaucoma and high myopia ≥10 diopters
- Lacks evidence of outer nuclear layer as determined by SD-OCT
- Active ocular/intraocular infection
- Presence of an active implantable medical device in the retina





Clinical Trials.gov Identifier: **NCT05203939**

Primary Endpoints

- Study Drug-related adverse events (SDAE)
- Treatment-Emergent adverse events (TEAEs)
- Serious adverse events (SAEs)

Secondary Endpoints

- Bioanalytical assessment of anti-AAV5 or anti-hNR2E3 antibodies
- Laboratory parameters, serum chemistry and hematology

Exploratory endpoint measures

- Best Corrected Visual Acuity (BCVA)
- Low-Luminance Visual Acuity (LLVA)
- Multi-Luminance Mobility Test (MLMT)
- Contrast sensitivity (CS)
- Changes in ellipsoid zone width/length (EZ)
- Fundus Auto Fluorescence (wf-FAF)
- Full Field Light Stimulation Threshold (FST) and Electroretinogram (ERG)
- The National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ25)

OCU400 – Overall Safety and SAE Summary

- Safety data evaluated from the Phase 1/2 clinical study show that OCU400 delivered by sub-retinal injection is generally safe and well tolerated

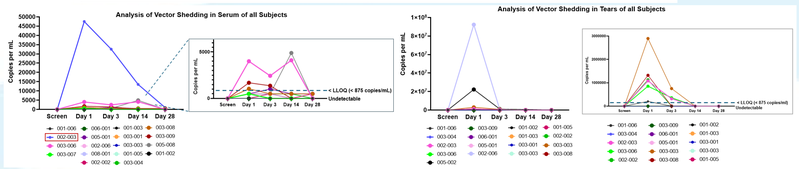
	Cohort 1 Low dose	Cohort 2 Medium Dose	Cohort 3 High Dose	Open Enrollment (Phase II) MTD
Number of Subjects	4	3	3	8
Type of AE	SAE	AESI	SAE	SAE
Subject Mutation	RHO	AR-NR2E3	AR-NR2E3	1. RHO 2. AD-NR2E3
Fovea Detached during surgery	Yes	Yes	Yes	No
AE Grade	Grade 4	Grade 4	Grade 4	1. Grade 3 2. Grade 4
SAE/AESI Term	Worsening GERD	Panuveitis	Blurred vision- decreased BCVA	1. Decreased BCVA 2. Steroid induced Psychosis
Relationship and Causality	Not Related to surgery or OCU400	Related to OCU400	Related to surgery and to OCU400	1. Decreased BCVA (Related to Surgery) 2. Steroid induced Psychosis (Not related to Surgery or OCU400)
Status Update	Resolved in a month	Resolved	Ongoing at End of Study visit	Resolved

- A total of 22 subjects (RP and LCA) received treatment of OCU400 during the ongoing Phase 1/2 clinical trial
  - ✓ OCU400 investigational product is generally safe and well tolerated
  - ✓ No serious adverse events (SAEs) deemed related to the OCU400 Investigational Product (IP) in the low or medium dose cohorts
  - ✓ SAEs were reported for four subjects
  - ✓ Adverse events (AEs) were primarily related to surgical procedure

Bioanalytical Assessment of Subjects Treated with OCU400

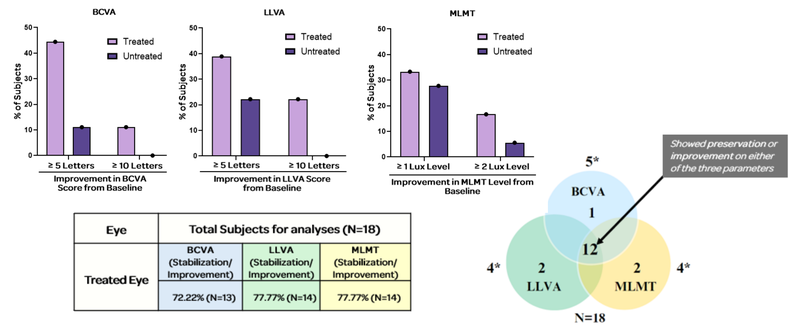
- No subjects developed Anti-Drug Antibodies (ADA) against NR2E3 protein
- ADA against AAV5 - Of the positive subjects, 80% (8/10) were pre-dosing anti-AAV5 positive. In all cases the ADA titers did not significantly increase during the study. ADA titers were low with all titers <100

Immunogenicity	All Subjects (N=18)	Low Dose (N=4)	Mid dose (N=3)	High Dose (N=11)
ADA positive patient at any timepoint	10 (55.5%)	2 (50.0%)	1 (33.3%)	7 (63.6%)
Pretreatment ADA	8 (44.4%)	2 (50.0%)	1 (33.3%)	5 (45.5%)
Treatment emergent ADA	2 (11.1%)	0	0	2 (18.2%)
Endpoint titer ≥100 at any timepoint	0	0	0	0



- In all subjects, vector shedding was undetectable in Serum and Tears at Day 28 post treatment

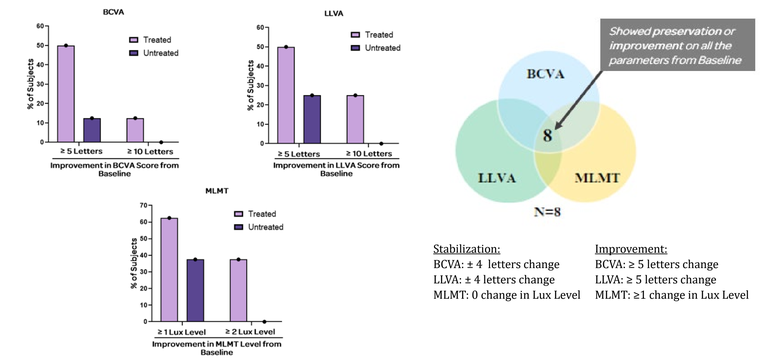
OCU400- Efficacy Summary



Eye	Total Subjects for analyses (N=18)		
	BCVA (Stabilization/ Improvement)	LLVA (Stabilization/ Improvement)	MLMT (Stabilization/ Improvement)
Treated Eye	72.22% (N=13)	77.77% (N=14)	77.77% (N=14)

Responder analysis of the subject population evaluated by stabilization or improvements across either of the three endpoints, BCVA, LLVA, and MLMT. Two subjects experienced stabilization or improvements in MLMT alone. The non-responders on the parameter are denoted by * sign next to it. Stabilization: BCVA and LLVA (± 4 letters change), MLMT: 0 change in Lux Level; Improvement: BCVA and LLVA (≥ 5 letters change); MLMT: ≥1 change in Lux Level.

OCU400- Efficacy Summary for Intent to treat Population

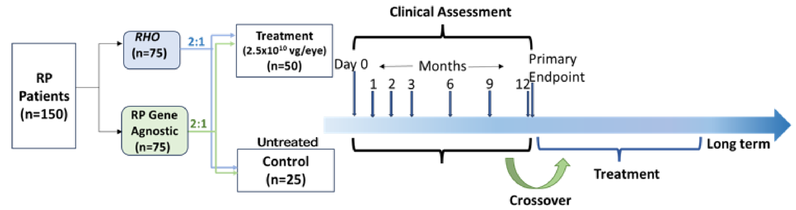


Stabilization:
BCVA: ± 4 letters change
LLVA: ± 4 letters change
MLMT: 0 change in Lux Level

Improvement:
BCVA: ≥ 5 letters change
LLVA: ≥ 5 letters change
MLMT: ≥1 change in Lux Level

Sub-set analysis of subjects with autosomal dominant *RHO* mutations, AD-RHO (N=5) and autosomal recessive *NR2E3* mutations, AR-NR2E3 (N =3) qualified as Intent to Treat (ITT) population-based on stabilization or improvement in efficacy measurements for BCVA, LLVA and MLMT

Phase 3 Study Design (US enrollment)



Study Design	
Population	• Patient with ≥8 years of age with Clinical and Molecular Diagnosis of Retinitis Pigmentosa
Key Eligibility Criteria	• BCVA ≥25 letters and worse (ETDRS Chart) • Able to perform LDNA at ≤ 500 Lux but unable to pass the LDNA at ≤ 0.35 at the Screening visit • Presence of photoreceptors
Endpoints	
Primary	• Proportion of responder (**LDNA ≥ 2 Lux Level from Baseline- Study Eyes**) in treatment vs control arm **LDNA: Luminance Dependent Navigation Assessment**
Secondary	• Proportion of responder EYES (**LDNA ≥ 2 Lux Level from Baseline**) in treatment vs control • Proportion of responder (LLVA score change of 0.3logMAR from Baseline) in treatment vs control

Conclusions and Perspectives

- OCU400 is generally safe and well-tolerated in subjects across different mutations and dose levels
- Efficacy measurements suggest ***positive trends*** in Best-Corrected Visual Acuity (BCVA) and Multi-Luminance Mobility Testing (MLMT), and Low-Luminance Visual Acuity (LLVA) among treated eyes
- 89% (16/18) of subjects demonstrated ***preservation or improvement*** in the treated eye either on ***BCVA or LLVA or MLMT*** scores from baseline
- 78% (14/18) of subjects *demonstrated* ***preservation or improvement*** in treated eyes in MLMT scores from baseline
- 80% (8/10) *of RHO* mutation subjects experienced *either preservation or improvement in MLMT scores* from baseline
- Treatment effect in *RHO* patients supports the gene-agnostic mechanism of action of OCU400

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