SUNDEW: A Phase 1A Single Ascending Dose Study of PYC-001; a peptide conjugated oligonucleotide designed to treat OPA1 mutation-associated Autosomal Dominant Optic Atrophy

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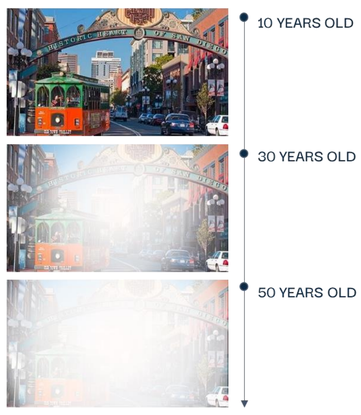
ADOA is a progressive and blinding eye disease of childhood for which there are no available treatment options

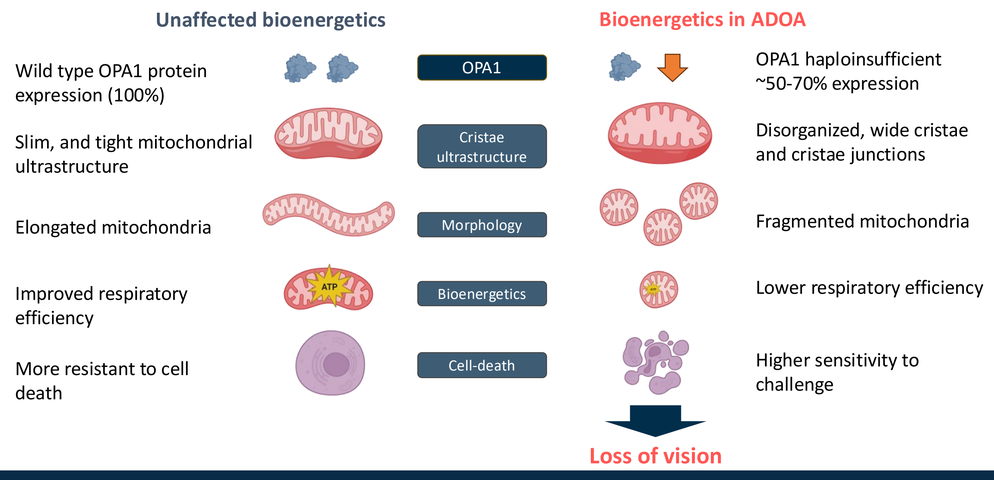
Autosomal Dominant Optic Atrophy (ADOA) & PYC-001

- A progressive and irreversible blinding eye disease
- It is the most common inherited optic neuropathy with **9,000 – 16,000** affected individuals in the western world[1,2]
- Median age of onset at 7 years of age, with 80% of patients symptomatic before age 10[1]
- **There are no treatments available** for patients with ADOA
- Caused by **haploinsufficiency of the *OPA1* gene,** resulting in the loss of Retinal Ganglion Cells (RGCs) whose axons form the optic nerve
- **PYC-001 increases OPA1 protein levels** to restore the **mitochondrial network** and improve **cellular bioenergetics** in models derived from patients with ADOA in a mutation independent manner
- **PYC is an intravitreally administered RNA-peptide drug conjugate that binds to *OPA1* mRNA**

Deteriorating vision of an ADOA patient

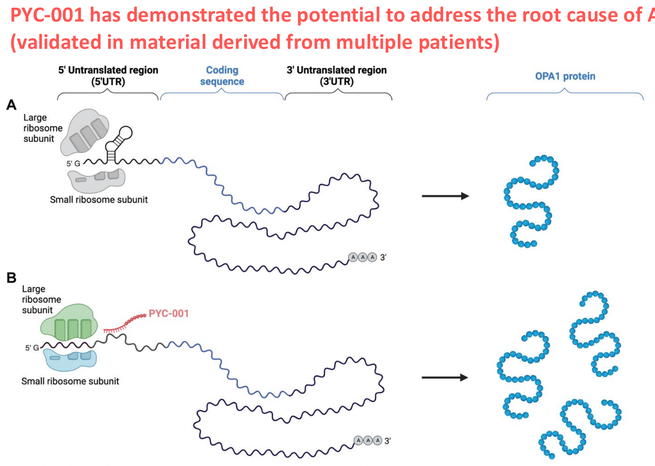


The deficiency of OPA1 protein in ADOA patients triggers a cascade of bioenergetic deficits that culminate in RGC cell death and loss of vision

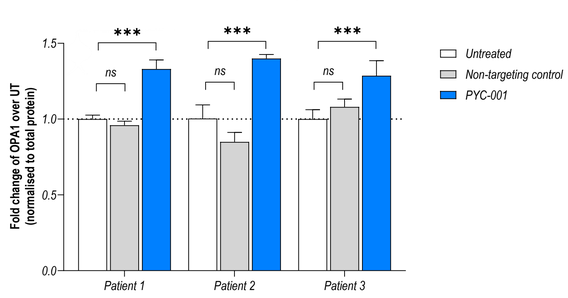


PYC-001 specifically addresses the underlying cause of ADOA by increasing OPA1 protein expression

PYC-001 has demonstrated the potential to address the root cause of ADOA in a mutation independent manner (validated in material derived from multiple patients)



OPA1 protein upregulation in iPSC-RGCs derived from ADOA patients

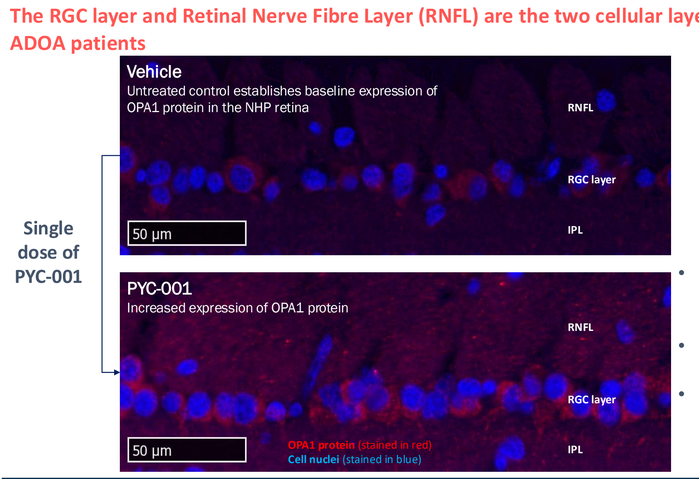


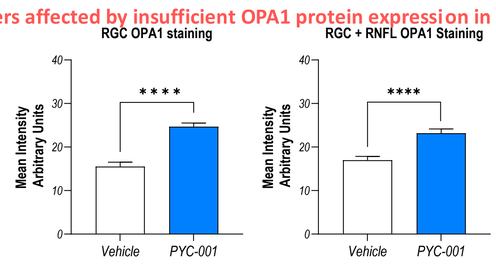
Bar graph represents mean+SD @ day 5 following PYC-001 incubation in iPSC-RGCs. Patient 1, *OPA1* c.985-1G>C.; Patient 2, *OPA1* c.2608delA; Patient 3, OPA1 c.2708-2711delTTAG. n=1 biological replicate, 3 technical replicates. One-way ANOVA ***p<0.005

A) The 5'UTR of the OPA1 mRNA contains a stem-loop that hinders protein translation
B) The PMO segment of PYC-001 (depicted in red) binds to the 5'UTR of OPA1 mRNA, disrupting the complex secondary structure, particularly a stem-loop associated with negative protein translation regulation. Consequently, it induces a modification in the secondary structure and mediates upregulation of OPA1 protein translation

PYC-001 increases OPA1 protein levels in the retina at safe and well-tolerated doses in Non-Human Primates

The RGC layer and Retinal Nerve Fibre Layer (RNFL) are the two cellular layers affected by insufficient OPA1 protein expression in ADOA patients

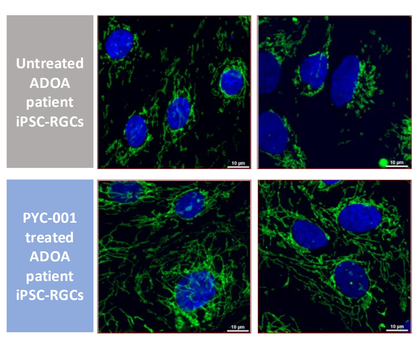




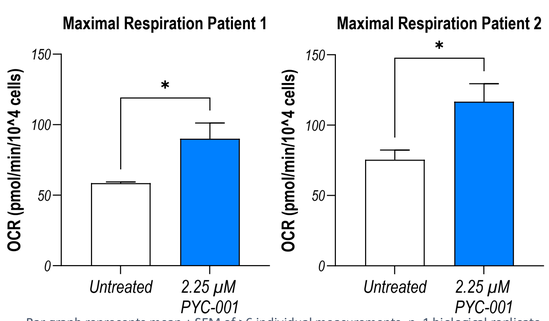
- A single 15 mcg dose of PYC-001 increases OPA1 protein expression in NHPs in the two cellular layers affected by ADOA at 29 days following treatment
- This result was achieved with a dose of PYC-001 that is safe and well tolerated in NHPs
- The 1.6-fold increase in OPA1 protein expression seen *in vivo* in NHPs is associated with rescue of the functional deficits seen in ADOA patient-derived models *in-vitro*

Increasing OPA1 protein levels rescues the functional deficits associated with ADOA in patient-derived models

PYC-001 treatment restores mitochondrial impairments and cellular bioenergetics in iPSC-RGCs derived from ADOA patients[3,4]



- PYC-001 treatment corrects mitochondrial structural defects in ADOA iPSC-RGCs
- ~1.5-fold increase in cellular bioenergetics in ADOA patient derived models following treatment with PYC-001



Bar graph represents mean + SEM of >6 individual measurements. n=1 biological replicate. Statistical difference was analyzed using One-way analysis of variance (ANOVA). *p=0.05

Methods

Design of PYC-001

A translational enhancing oligonucleotide conjugated to a cell-penetrating peptide (PYC-001) was developed, designed to increase expression of the OPA1 protein from the remaining wild-type allele in patients affected by Autosomal Dominant Optic Atrophy (ADOA)[4].

In vitro preclinical efficacy data

Generated in iPSC-derived Retinal Ganglion Cells (RGCs) from multiple ADOA patients, confirmed mutation-agnostic intended mechanism of action in target cells, following treatment with PYC-001[5].

In vivo preclinical efficacy data

Cynomolgus monkeys were dosed bilaterally with PYC-001 by IVT injections of 15 mcg/eye. Immunohistochemistry of the RGC and confirmed modulation of target gene expression in the affected cell type/layer in the retina with a single, safe and well tolerated dose[4].

SUNDEW, a Phase 1 Single Ascending Dose (SAD) First-in-Human (FIH) study

Nine participants with genetically confirmed OPA1 mutation-associated ADOA were recruited at 2 sites in Australia in 3 cohorts (3, 10 and 30 mcg). Each participants received a unilateral intravitreal injection of PYC-001 in the worst affected eye and were followed for adverse events. Dose escalation was approved by a Safety Review Committee (SRC). Safety and tolerability are assessed based on both ocular and non-ocular adverse events reporting in conjunction with clinical chemistry parameters, measures of visual function, functional vision and imaging. Exploratory efficacy was assessed using Visual Acuity.

MYRTLE, a Phase 1b Multiple Ascending Dose (MAD) study

Up to 18 participants with genetically confirmed OPA1 mutation-associated ADOA were recruited at sites across APAC, into 5 cohorts (10 mcg Q8W, Q12W, 30 mcg Q8W, Q12W and a 60 mcg single dose cohort followed by repeat doses Q12W). Participants receive unilateral injections of PYC-001 and are followed for adverse events. Safety and tolerability are assessed based on both ocular and non-ocular adverse events reporting in conjunction with clinical chemistry parameters, measures of visual function, functional vision and imaging. Exploratory efficacy was assessed using visual acuity and Flavoprotein Fluorescence. Participants will receive at least 3 doses of PYC-001.

Clinical Data Generated in SUNDEW and MYRTLE

Safety/Tolerability Profile of Single Doses of PYC-001

- No Treatment Related-Serious Adverse Events (TR-SAEs) observed in any patient following injection of PYC-001 to date (3 mcg, 10 mcg, 30 mcg and 60 mcg)[6]
- Treatment-Emergent Adverse Events were mostly mild, and procedure related with no ongoing adverse events

Encouraging improvement in measures of visual acuity (relative to both control eye and baseline) have been observed in ADOA patients treated with PYC-001 in the SUNDEW and MYRTLE studies

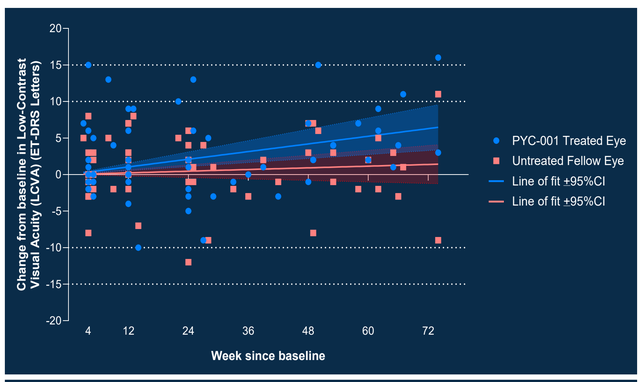


Figure 1. Change from baseline in Low-Contrast Visual Acuity (LCVA) in *OPA1* ADOA patients treated with PYC-001^

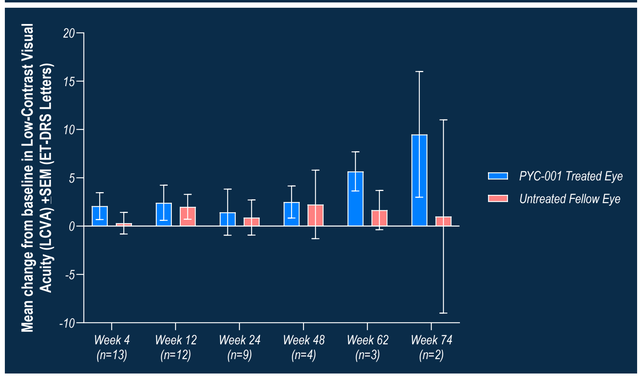
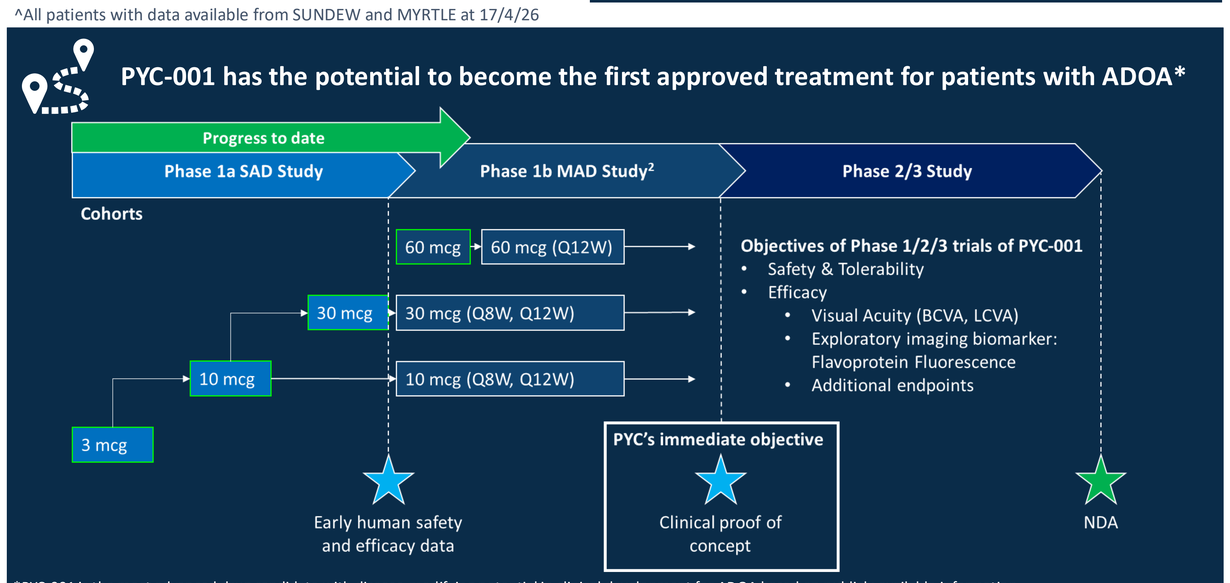


Figure 2. Mean change from baseline in Low-Contrast Visual Acuity (LCVA) (±SEM) in *OPA1* ADOA patients treated with PYC-001^

Select timepoints where n≥2

^All patients with data available from SUNDEW and MYRTLE at 17/4/26

PYC-001 has the potential to become the first approved treatment for patients with ADOA*



*PYC-001 is the most advanced drug candidate with disease-modifying potential in clinical development for ADOA based on publicly available information. Future development is subject to risks and uncertainties outlined in the Company's ASX filings of 2 February 2026.

Conclusions

Clinical and pre-clinical data support continued development of PYC-001

- ✓ **PYC-001 is the first precision therapy** to be dosed in patients with *OPA1* ADOA with disease-modifying observed potential in clinical development for ADOA
- ✓ **No Treatment-Related Serious Adverse Events (TR-SAEs)** were observed in any patient who received a single dose of PYC-001 to date (doses of 3, 10, 30 and 60 mcg)
- ✓ **Preliminary data indicate improvements in visual acuity** for patients with *OPA1* ADOA who have received PYC-001
- ✓ **Pre-clinical data:** PYC-001 restored mitochondrial function in patient-derived models of *OPA1* ADOA and the doses were found to be safe and effective in NHPs
- ✓ **Next steps:** PYC is progressing PYC-001 through a repeat dose study (MYRTLE – Phase 1b) in patients with *OPA1* ADOA to demonstrate clinical proof of concept

Disclosure Block: Patrick Yu-Wai-Man; (Consultant) PYC Therapeutics, (Consultant) Chiesi, (Consultant), (Consultant) GenSight Biologics, (Consultant) Stoke Therapeutics, Clare Fraser; (Consultant/Contractor) Sydney Hospital & Sydney Eye Hospital, (Consultant/Contractor) Save Sight Institute, University of Sydney, (Consultant/Contractor) PYC Therapeutics, Doron Hickey; (Consultant/Contractor) The Royal Victorian Eye and Ear Hospital, (Visiting Researcher) Centre for Eye Research Australia, (Consultant/Contractor) PYC Therapeutics, Andrea Vincent (Consultant/Contractor) University of Auckland, New Zealand, (Consultant/Contractor) Retina Specialists, New Zealand; Aishwarya Kundu; (Employment) PYC Therapeutics, Janya Grainok; (Employment) PYC Therapeutics, George Mitchell; (Employment) PYC Therapeutics, Timothy Masarei; (Employment) PYC Therapeutics, Sri Mudumba; (Employment) PYC Therapeutics, Tracy Chai; (Employment) PYC Therapeutics, Fern Utama; (Employment) PYC Therapeutics, Paula Cunningham; (Employment) PYC Therapeutics, Jessica Stevenson; (Employment) PYC Therapeutics, Katherine Lee; (Employment) PYC Therapeutics

References: **1.** Yu-Wai-Man, P., *et al.*, *Pattern of retinal ganglion cell loss in dominant optic atrophy due to OPA1 mutations.* Eye, 2011. **25**(5): p. 596-602. **2.** Amati-Bonneau, P. et al. OPA1-associated disorders: phenotypes and pathophysiology. The international journal of biochemistry & cell biology, 2009;41(10), 1855–1865 **3.** See PYC Company Poster titled PYC-001, a peptide-conjugated phosphorodiamidate morpholino oligomer for the treatment of autosomal dominant optic atrophy **4.** See ASX Announcement 4 October 2023 **5.** See ASX Announcement 3 April 2023. **6.** See ASX Announcement 15 April 2026

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