PYC Therapeutics

5 SEPTEMBER 2025

SECOND BLINDING EYE DISEASE PROGRAM – PRESENTATION OF CLINICAL DATA AT NOSA 2025

- **PYC is progressing a drug candidate (known as PYC-001) that addresses the underlying cause of a blinding eye disease called Autosomal Dominant Optic Atrophy (ADOA) through clinical trials**
- **The Company today announces that it:**
  - **Has completed dosing of all ADOA patients in the Phase 1 Single Ascending Dose (SAD) study of PYC-001**
  - **Will present safety and early efficacy data from this SAD study at the Neuro-Ophthalmology Society of Australia (NOSA) conference in Auckland, NZ between 11-13 September 2025 highlighting:**
    - **Safety - No treatment-emergent serious adverse events in any patient dosed with PYC-001 to date; and**
    - **Efficacy – encouraging early trend towards improvement in measures of visual acuity in the PYC-001 treated eyes[1]**
- **PYC is now progressing PYC-001 into a global Phase 1/2 Multiple Ascending Dose (MAD) study that is anticipated to commence in Q4 2025[2]**

PERTH, Australia and SAN FRANCISCO, California – 5 September 2025

PYC Therapeutics Limited (ASX:PYC) (PYC or the Company) is a precision medicine Company dedicated to changing the lives of patients with genetic diseases who have no treatment options available.

The Company currently has three clinical-stage drug development programs including a drug candidate (known as PYC-001) that addresses the underlying cause of a blinding eye disease called Autosomal Dominant Optic Atrophy (ADOA). ADOA affects 1 in every 35,000[3] people and there are currently no approved treatment options available for patients.

PYC today announces that it will be presenting data from the ongoing Phase 1 Single Ascending Dose (SAD) study in ADOA patients at the Neuro-Ophthalmology Society of Australia (NOSA) conference in Auckland, New Zealand between 11 and 13 September 2025.

[1] See details below
[2] Subject to the risks and uncertainties outlined in the Company's ASX filings of 17 February 2025
[3] Yu-Wai-Man, P. et al. The Prevalence and Natural History of Dominant Optic Atrophy Due to OPA1 Mutations Ophthalmology. 2010;117(8):1538-46 doi: 10.1016/j.ophtha.2009.12.038

The presentation will highlight the safety/tolerability profile of PYC-001 in the SAD study and the absence of any treatment-emergent serious adverse events in any patient dosed with the drug candidate to date. In addition, an encouraging early trend of improvement in measures of visual acuity in the treated-eye of patients enrolled in the SAD will also be presented.

A copy of the NOSA poster presentation is attached to this announcement.

Next Steps

PYC is now preparing to progress into a global Multiple Ascending Dose (MAD) study of PYC-001 in patients with ADOA with an objective of establishing clinical proof-of-concept prior to progression into a global registrational trial directed towards supporting a New Drug Application for PYC-001 in ADOA. The global Phase 1/2 MAD study is expected to commence in Q4 of 2025.

About PYC Therapeutics

PYC Therapeutics (ASX: PYC) is a clinical-stage biotechnology company creating a new generation of RNA therapies to change the lives of patients with genetic diseases. The Company utilises its proprietary drug delivery platform to enhance the potency of precision medicines within the rapidly growing and commercially proven RNA therapeutic class. PYC's drug development programs target monogenic diseases – the indications with the highest likelihood of success in clinical development [4].

For more information, visit pyctx.com, or follow us on LinkedIn and X.

Forward looking statements

Any forward-looking statements in this ASX announcement have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations, and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside the Company's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this ASX announcement include known and unknown risks. Because actual results could differ materially to assumptions made and the Company's current intentions, plans, expectations, and beliefs about the future, you are urged to view all forward-looking statements contained in this ASX announcement with caution. The Company undertakes no obligation to publicly update any forward-looking statement whether as a result of new information, future events or otherwise.

This ASX announcement should not be relied on as a recommendation or forecast by the Company. Nothing in this ASX announcement should be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.

This ASX announcement was approved and authorised for release by the Board of PYC Therapeutics Limited

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[4] Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232

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

Clare Fraser[1], Doron Hickey[2], Aishwarya Kundu[3], George Mitchell[3], Timothy Masarei[3], Sri Mudumba[3], Paula Cunningham[3], Tracy Chai[3], Fern Utama[3], Janya Grainok[3]

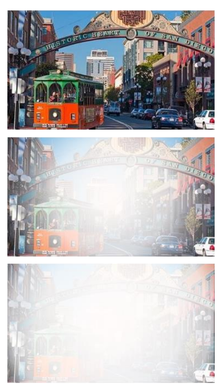
[1]Sydney Eye Hospital, New South Wales, [2]The Royal Victorian Eye and Ear Hospital, Victoria, [3]PYC Therapeutics, Harry Perkins Institute of Medical Research, Western Australia

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

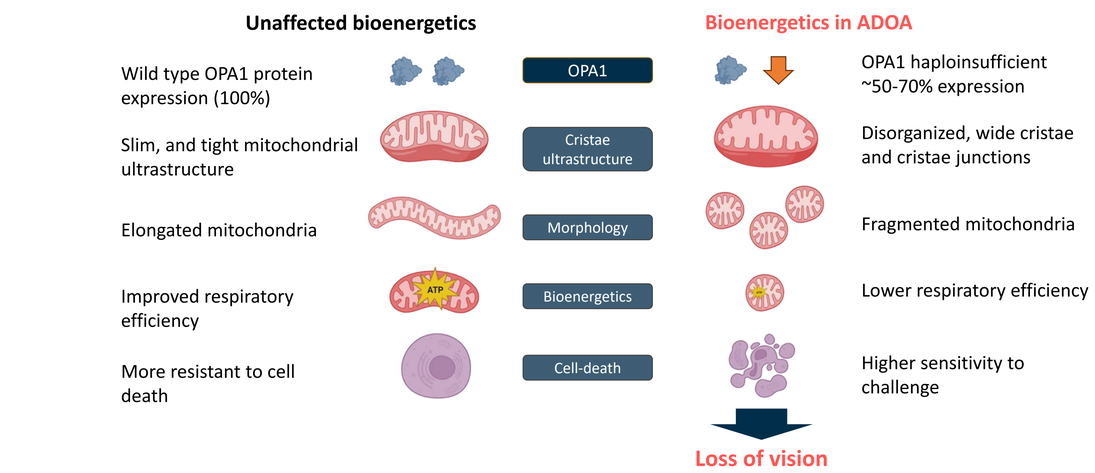
Autosomal Dominant Optic Atrophy (ADOA) & PYC-001

- A progressive and irreversible blinding eye disease
- It is the most common inherited optic neuropathy with **9,000 – 16,000** addressable patients 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** in Retinal Ganglion Cells (RGCs) that form the optic nerve of the eye
- **PYC-001 increases OPA1 protein levels** to enhance **mitochondrial structure** 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

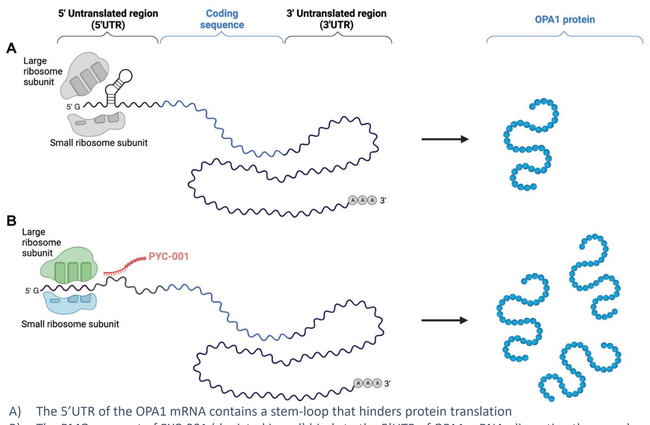


The deficiency of OPA1 protein in ADOA patients triggers a cascade of bioenergetic deficits that culminate in cell death and loss of vision

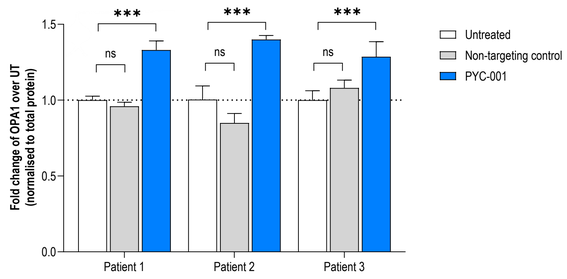


PYC-001 specifically addresses the underlying cause of ADOA by increasing OPA1 protein expression

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 patients

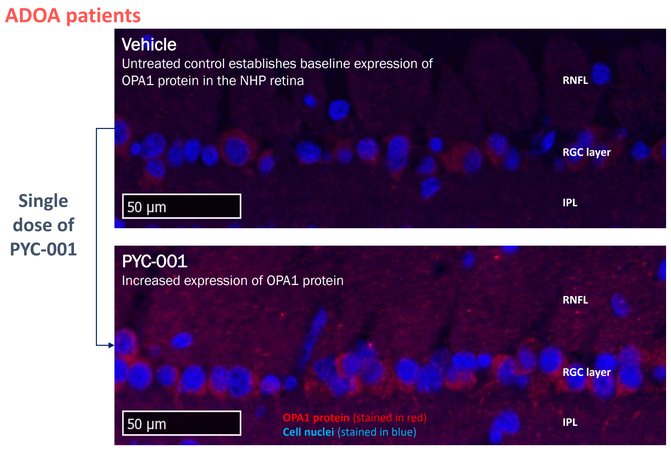


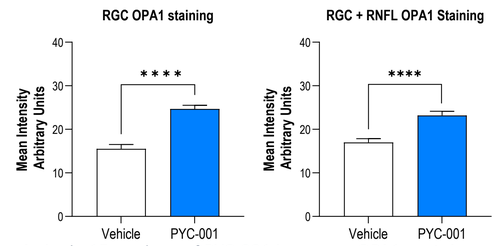
Bar graph represents mean+SD @ day 5 following PYC-001 incubation in iPSC-RGCs. Patient 1, *OPA1* c.985-1G>C.; Patient 2, *OPA1* c.2608delA; Patient 3, OPA1 c.2708-2711delTTAG. n=1 biological replicate, 3 technical replicates. One-way ANOVA ***p<0.005

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

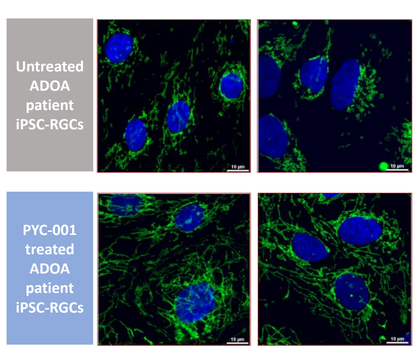




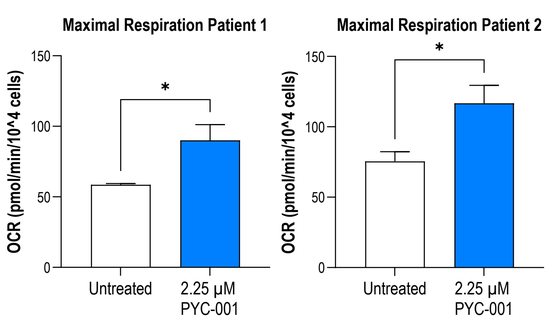
- A single 15 µg dose of PYC-001 increases OPA1 protein expression in NHPs in the two cellular layers affected by ADOA at 29 days following treatment
- This result was achieved with a dose of PYC-001 that is safe and well tolerated in NHPs
- The 1.6-fold increase in OPA1 protein expression seen *in vivo* 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 µg/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 µg). Each participants received a unilateral intravitreal injection of PYC-001 in the worst affected eye and are followed for adverse events. Dose escalation was determined 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.

SUNDEW, a Phase 1 Single Ascending Dose study shows encouraging safety and exploratory efficacy data in ADOA

Safety/Tolerability Profile of PYC-001 in the Phase 1 Single Ascending Dose (SAD) Study

- No Treatment Emergent-Serious Adverse Events (TE-SAEs) observed in any patient dosed with PYC-001 to date
- No Treatment-Related Treatment-Emergent Adverse Events, and no intraocular inflammation were observed in any patient following injection of PYC-001
- Treatment-Emergent Adverse Events were mostly mild, and procedure related with no ongoing adverse events

Encouraging early trend towards 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 SAD Study

Figure 1. Mean change from baseline in Best-Corrected Visual Acuity (BCVA) and Low-Contrast Visual Acuity (LCVA) at Week 4 in ADOA patients treated with PYC-001 (all patients with data available: n=3 patients from 3 µg cohort, n=3 patients from 10 µg cohort, n=2 patients from 30 µg cohort)

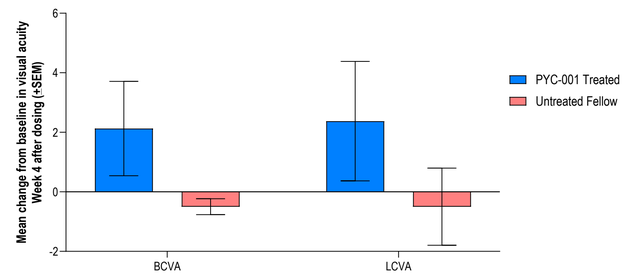


Figure 2. Mean change from baseline in Best-Corrected Visual Acuity (BCVA) and Low-Contrast Visual Acuity (LCVA) at Week 24 in ADOA patients treated with PYC-001 (all patients with data available: n=3 patients from 3 µg cohort)

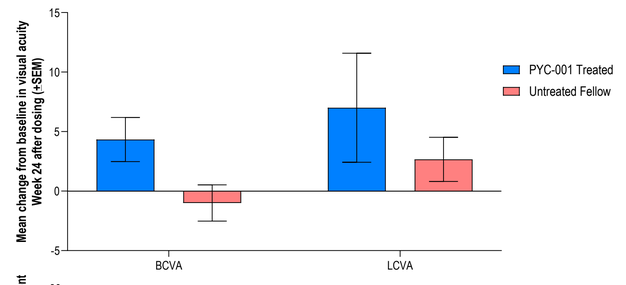
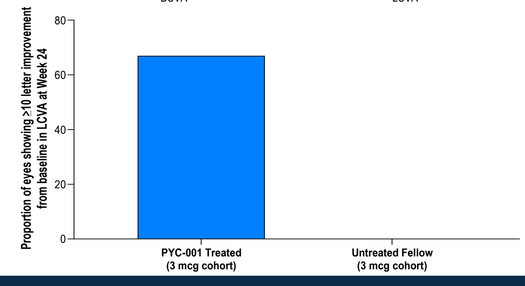
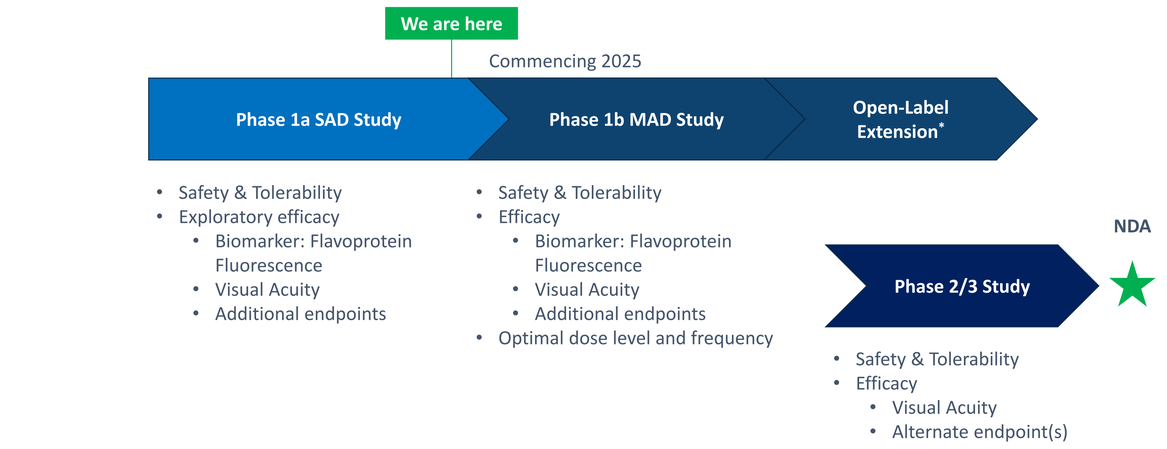


Figure 3. Proportion of eyes showing ≥10 letter improvement from baseline in Low-Contrast Visual Acuity (LCVA) at Week 24 in ADOA patients treated with PYC-001 (all patients with data available: n=3 patients from 3 µg cohort)



Clinical Path – PYC-001 is a drug candidate with 'best-in-indication' potential



*PYC may engage the regulator to discuss the potential for an open-label extension of the 'Phase 1b MAD study'

Conclusions

Preclinical and clinical findings support continued development of PYC-001

- ✓ Dosing of PYC-001 has been completed in the *SUNDEW* Phase 1a SAD study and is the first precision therapy to be dosed in patients with ADOA
- ✓ The results from *SUNDEW* SAD demonstrates that a single intravitreal injection of PYC-001 is safe and well tolerated at 3, 10 and 30 µg doses
- ✓ No Treatment-Emergent Serious Adverse Events (TE-SAEs) were observed in any patient who have received a single dose of PYC-001 in the SAD study
- ✓ Encouraging early improvements in visual acuity have been observed in ADOA patients that have received a single dose of PYC-001
- ✓ PYC-001 is expected to progress into a Phase 1b Multiple Ascending Dose (MAD) study in 2025 to evaluate the safety and efficacy profile and determine the optimum dose regimen of repeat doses in ADOA patients

Disclosure Block: 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, 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

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