



 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

PRESENTATION OF CLINICAL DATA AT NOSA 2025

- 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 eyes¹
- PYC is now progressing PYC-001 into a global Phase 1/2 Multiple Ascending Dose (MAD) study that is anticipated to commence in Q4 2025²

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 35,000³ 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.

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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



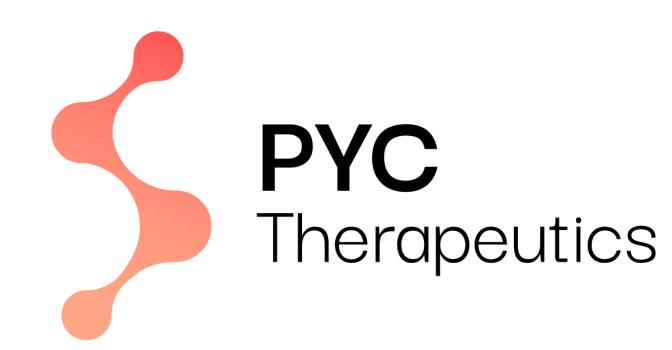


SAVE SIGHT

Sydney Hospital &

FOR EYE RESEARCH AUSTRALIA 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

Deteriorating vision of an ADOA patient



Clare Fraser¹, Doron Hickey², Aishwarya Kundu³, George Mitchell³, Timothy Masarei³, Sri Mudumba³, Paula Cunningham³, Tracy Chai³, Fern Utama³, Janya Grainok³

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

30 YEARS OLD

50 YEARS OLD



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

The deficiency of OPA1 protein in ADOA patients triggers a cascade of bioenergetic deficits

OPA1

Cristae

ultrastructure

Morphology

Bioenergetics

Cell-death

PYC-001 has demonstrated the potential to address the root cause of ADOA in a mutation independent manner

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

Bioenergetics in ADOA

ulli

Loss of vision

OPA1 haploinsufficient

Disorganized, wide cristae

Fragmented mitochondria

Lower respiratory efficiency

~50-70% expression

and cristae junctions

Higher sensitivity to

challenge

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 10¹
- There are no treatments available for patients with ADOA

Wild type OPA1 protein

Slim, and tight mitochondrial

Elongated mitochondria

Improved respiratory

More resistant to cell

expression

(validated in material derived from multiple patients)

The 5'UTR of the OPA1 mRNA contains a stem-loop that hinders protein translation

expression (100%)

ultrastructure

efficiency

death

Small ribosome subunit

- 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
- PYC is an intravitreally administered RNA-peptide drug conjugate that binds to OPA1 mRNA

that culminate in cell death and loss of vision

Unaffected bioenergetics

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-001⁵.

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 dose⁴.

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

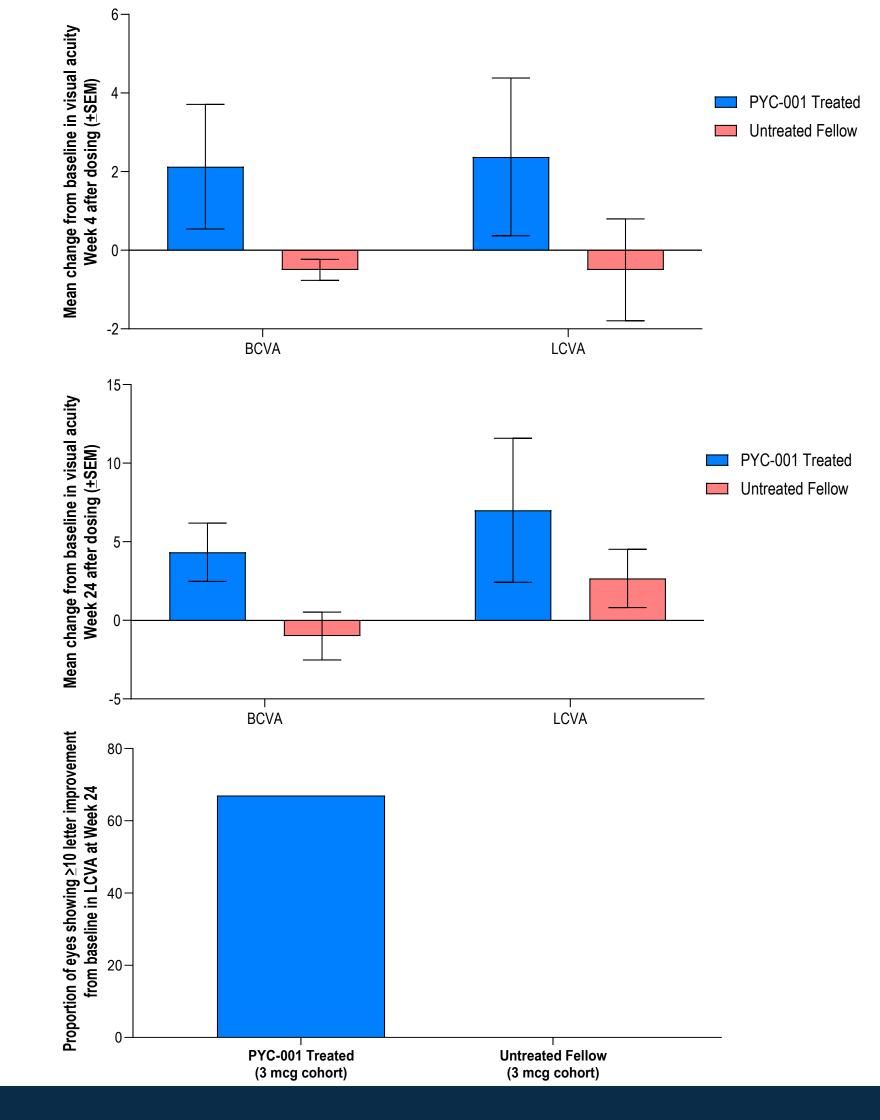
- No Treatment Emergent-Serious Adverse Events (TE-SAEs) observed in any patient dosed with PYC-001 to date
- No Treatment-Related Treatment-Emergent Adverse Events, and no intraocular inflammation were observed in any patient following injection of PYC-001
- Treatment-Emergent Adverse Events were mostly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

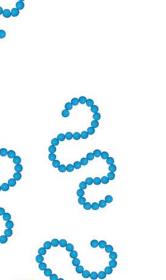
Encouraging early trend towards improvement in measures of visual acuity (relative to both control eye and baseline) have been observed in ADOA patients treated with PYC-001 in the SAD Study

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





☐ Untreated PYC-001 Patient 2 Patient 3

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

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

ADOA

PSC-RG

PYC-00

ADOA

subunit

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

Increasing OPA1 protein levels rescues the functional deficits associated with ADOA in

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

PYC-001 treatment

structural defects in

ADOA iPSC-RGCs

~1.5-fold increase

bioenergetics in

derived models

following treatment

ADOA patient

with PYC-001

mitochondrial

corrects

in cellular

Vehicle ntreated control establishes baseline expression of OPA1 protein in the NHP retina RNFL **RGC layer** Single IPL dose of **PYC-001** PYC-001 Increased expression of OPA1 protein **RGC layer**

patient-derived models

- **RGC OPA1 staining RGC + RNFL OPA1 Staining** Intensity rary Units • A single 15 μg dose of PYC-001 increases OPA1 protein
- ADOA at 29 days following treatment This result was achieved with a dose of PYC-001 that is safe and well tolerated in NHPs

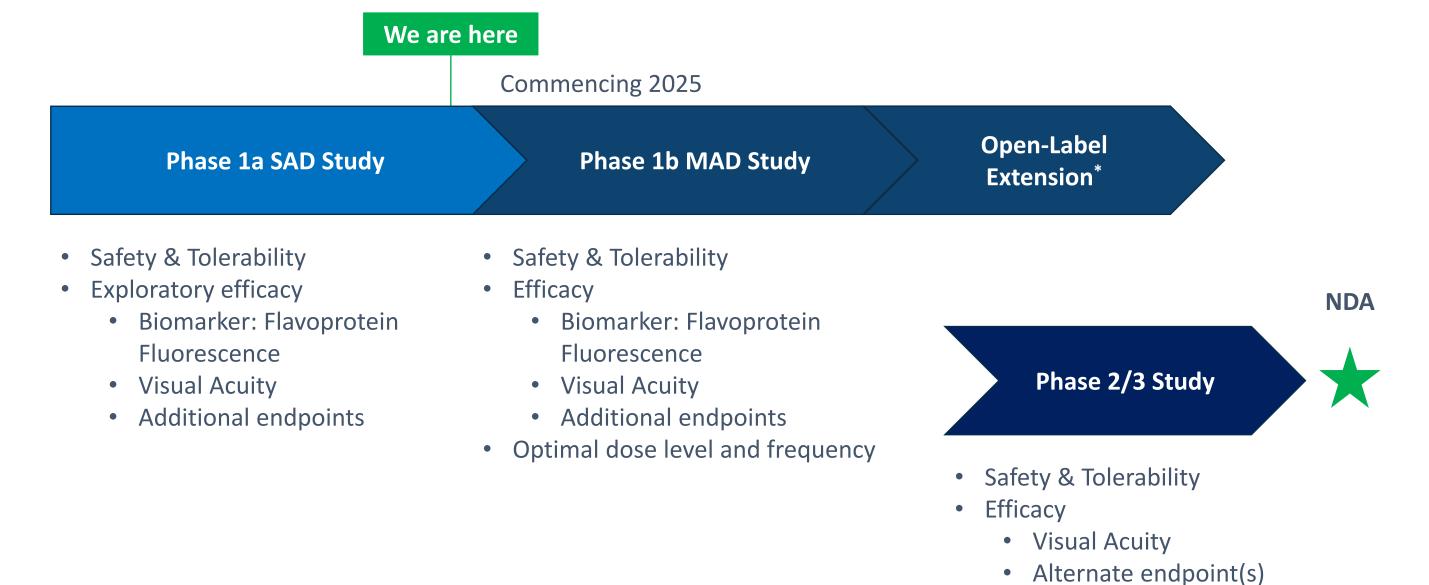
expression in NHPs in the two cellular layers affected by

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



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'

Preclinical and clinical findings support continued development of PYC-001

Conclusions

- ✓ 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

2.25 µM $2.25 \mu M$ Untreated Untreated PYC-001 PYC-001

Maximal Respiration Patient 2

PSC-RGC 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 Disclosure Block: Clare Fraser; (Consultant/Contractor) Sydney Hospital & Sydney Eye Hospital, (Consultant/Contractor) The Royal Victorian Eye and Ear Hospital, (Visiting Researcher) Centre for Eye Research Australia, (Consultant/Contractor) PYC Therapeutics, Doron Hickey; (Consultant/Contractor) PYC Therapeu Therapeutics, Aishwarya Kundu; (Employment) PYC Therapeutics, Janya Grainok; (Employment) PYC Therapeutics, Fern Utama; (Employment) PYC Therapeutics, Fern Utama; (Employment) PYC Therapeutics, Paula Cunningham;

Maximal Respiration Patient 1

(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 peptideconjugated 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 Diagrams created with Biorender.com