PYC Therapeutics

4 October 2023

SECOND DRUG PROGRAM EFFECTIVE IN BOTH NON-HUMAN PRIMATES AND PATIENT-DERIVED MODELS

- PYC designs and develops precision medicines for patients who have severe diseases and no treatment options available
- The Company's second drug candidate is a first-in-class RNA drug that addresses the underlying cause of a progressive blinding eye disease of childhood called Autosomal Dominant Optic Atrophy (ADOA)
- There are currently no treatment options available for patients with ADOA – an indication that affects 1 in every 35,000 people[1] and has an addressable market size of ~A$2 billion per annum[2]
- PYC has now **successfully demonstrated that its RNA therapy for ADOA is both safe and effective in Non-Human Primates** following a single dose of the investigational drug in each study animal[3]
- **Both animal and patient-derived models[4] now highlight the potential of PYC's drug candidate to arrest progression of this disease**
- These results have a **material positive impact** on the likelihood of success for PYC's ADOA candidate in human trials
- The Company is currently preparing an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) for approval of the commencement of human trials for this drug candidate in 2024
- PYC will host an investor webinar to discuss these results in detail at 8am AWST (11am AEST) on Thursday 5 October 2023 – registration details for this webinar can be found at the bottom of this announcement

[1] 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

[2] Based on median price of orphan drugs of US$150,000 p.a. from EvaluatePharma. Orphan Drug Report. 2019.

[3] Non-Human Primates receiving 15 micrograms of PYC-001 demonstrated both no evidence of adverse tolerability and a statistically significant increase in expression of the target OPA1 protein (see Figures 1, 2 and 3 below)

[4] Patient-derived models are created from skin samples that are obtained from ADOA patients before being turned in to induced pluripotent stem cells and subsequently retinal ganglion cells to provide a precise genetic model of ADOA in the target cell affected by the disease

PERTH, Australia and SAN FRANCISCO, California – 4 October 2023

PYC Therapeutics today announces the results of successful safety and efficacy studies conducted in Non-Human Primates (NHPs) in its second drug development program. This program aims to be the first treatment available for a progressive and irreversible blinding eye disease of childhood called Autosomal Dominant Optic Atrophy (ADOA).

ADOA affects 1 in every 35,000 people[5] and represents an estimated $2 billion per annum market opportunity[6]. ADOA is caused by insufficient levels of a specific protein (called OPA1) in the retina of patients with the condition[7].

The objective of this NHP study was to show that PYC's drug candidate (known as PYC-001) was able to increase the amount of OPA1 protein in the retina of NHPs at a safe and well-tolerated dose. The results demonstrated that PYC-001 can successfully achieve this objective. Critically, these results enable the Company to link the efficacy profile of the drug *in vivo* (from these NHP studies) to the ability of the drug to rescue the functional deficits observed in the patient-derived models created from patients with ADOA (previously announced to the ASX on 3 April 2023). Together, the NHP and patient-derived results provide a comprehensive pre-clinical data pack in support of the clinical (human) translational potential of the drug candidate in ADOA[8].

"*These results are very promising for patients with ADOA*" commented PYC's CEO, Dr. Rohan Hockings. "*Drugs targeting monogenic diseases already have the highest likelihood of success in human trials. Now we can link this data from NHPs with the results that we have generated in the 'retina in a dish' models from patients with ADOA to demonstrate a fully integrated data pack suggesting that we can stop ADOA in its tracks.*"

[5] 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

[6] Based on median price of orphan drugs of US$150,000 p.a. from EvaluatePharma. Orphan Drug Report. 2019.

[7] 'Loss of Function' mutations affect ~85% of ADOA patients leading to haploinsufficiency, based on information from Amati-Bonneau, P. et al. OPA1-associated disorders: phenotypes and pathophysiology. The international journal of biochemistry & cell biology, 2009;41(10), 1855–1865. doi: 10.1016/j.biocel.2009.04.012 and Lenaers G, et al. Dominant Optic Atrophy. Orphanet J Rare Dis. 2012;7(46)

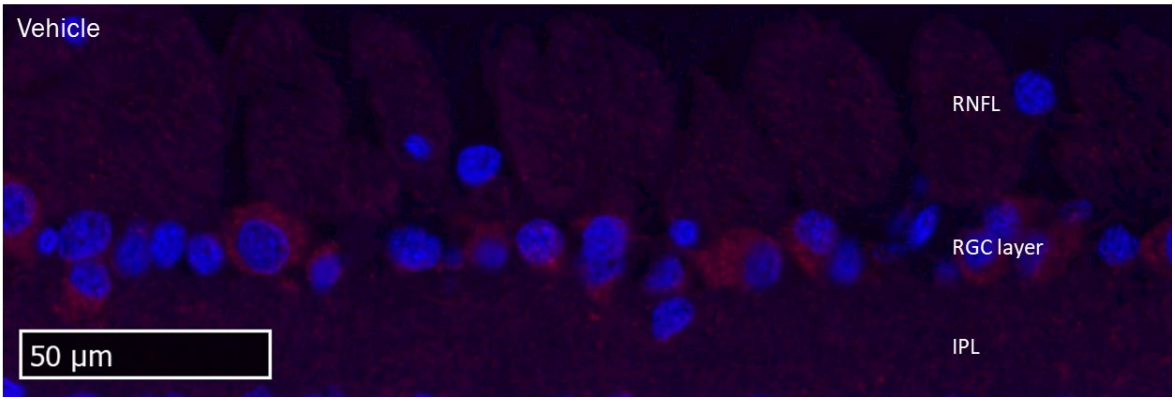
[8] PYC is currently progressing a final (elective) piece of data demonstrating that PYC-001 is capable of protecting patient-derived cells from programmed cell death ('apoptosis') – the ultimate step in the bioenergetic cascade that causes the death of Retinal Ganglion Cells in ADOA patient retinas and leads to blindness

Detailed results

1. Efficacy

Figure 1. PYC-001 demonstrating an increase in OPA1 protein (stained in red) in the Retinal Ganglion Cell (RGC) layer in the retina of a Non-Human Primate (NHP) when compared to the untreated (vehicle) control. Cell nuclei are stained in blue. The RGC layer and Retinal Nerve Fibre Layer (RNFL) are the two cellular layers affected by insufficient OPA1 protein expression in patients with ADOA.

Untreated ('vehicle') control animals – establishing baseline expression of OPA1 protein (stained in red) in the NHP retina



Animals treated with 15 micrograms of PYC-001 (a safe and well-tolerated dose - see Figure 3 below) demonstrating increased expression of OPA1 protein (stained in red) in the NHP retina when compared to the untreated controls

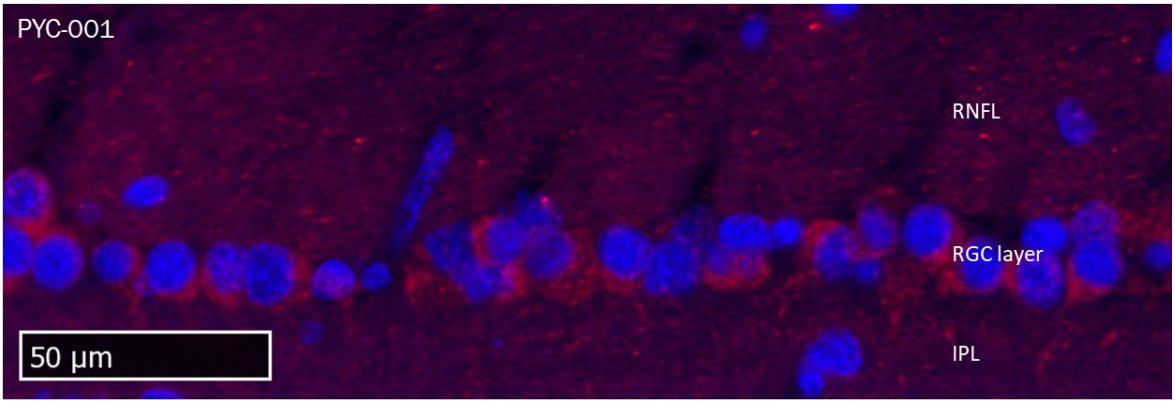
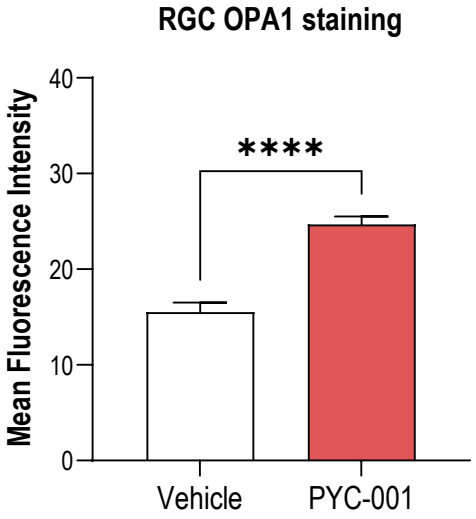


Figure 2. Quantification of OPA1 protein expression by immunofluorescence in the Retinal Ganglion Cell (RGC) layer in NHPs with and without treatment with PYC-001. The results show a statistically significant increase ($p<0.0001$ by unpaired t test) in intensity of OPA1 signal in the PYC-001 treated group following administration of a single safe and well-tolerated dose (15 micrograms) of the investigational drug candidate at 29 days following treatment.



2. Safety/Tolerability

A dose range-finding study was conducted to identify the optimal range of doses to be evaluated in the upcoming Good Laboratory Practice (GLP) toxicology studies. The results from the GLP toxicology studies will be used in support of the Investigational New Drug (IND) filing next year. The results described above (in section 1. Efficacy) were obtained from NHPs receiving 15 micrograms of PYC-001. There was no evidence of adverse tolerability in any of the NHPs who received the 15 microgram dose of PYC-001.

Figure 3. Results of clinical and histopathologic evaluation of safety and tolerability of PYC-001 in NHPs for 29 days following a single dose of the drug candidate. The conclusion of the study was that PYC-001 was safe and well tolerated at a dose of 15 micrograms per eye.

Dose of PYC-001	# eyes dosed	No findings of adverse tolerability at Day 29 (completion of study) # of eyes (% of population)	Findings of adverse tolerability at Day 29 (completion of study) # of eyes (% of population)
Control	4	4 (100%)	0 (0%)
15 µg	4	4 (100%)	0 (0%)

3. Durability/PK

The Contract Research Organisation conducting the drug recovery assays to measure the concentration of PYC-001 in NHP retina have confirmed that the amount of drug in the retina is above the upper limit of quantitation within the dynamic range of the assay - qualitatively indicating good drug distribution in the target tissue. The samples will need to be re-run following dilution with quantitative results expected in the near future.

4. Next Steps

PYC is progressing PYC-001 through to human trials in 2024. The Company has a pre-IND meeting scheduled with the US FDA in October 2023 and is expecting to submit an Investigational New Drug application in Q2 2024.

Figure 4. Non-clinical data collection checklist demonstrating progress of PYC-001 towards an Investigational New Drug (IND) filing with the US Food and Drug Administration. Good Laboratory Practice (GLP) toxicology studies are scheduled to begin in Q4 2023 to add the final body of data to the IND submission package with filing anticipated in Q2 2024.

PYC-001 non-clinical progress checklist

Dimension	Supporting Data Available	ASX announcement
Biodistribution	✓	4 October 2023
Safety/Tolerability (non-GLP)	✓	4 October 2023
Durability *in vivo*	✓	4 October 2023
Efficacy *in vivo*	✓	4 October 2023
Functional rescue of disease (Patient-derived model)	✓	3 April 2023
Safety/Tolerability (GLP)	Due to commence 4Q23	n/a

Investor Webinar

PYC's CEO, Dr. Rohan Hockings, will host an investor webinar to discuss these results in further detail at 8am AWST (11am AEST) on Thursday 5 October 2023.

Please register at the following link to receive the login details for the webinar:

https://us02web.zoom.us/webinar/register/WN_xpKphrt2RTWwbOCW816ZTw

After registering, you will receive a confirmation email containing information about joining the webinar.

About ADOA

Autosomal Dominant Optic Atrophy (ADOA) is a progressive and irreversible blinding eye disease. ADOA has an estimated addressable market size of approximately 9,000 to 16,000 patients in the western world representing a market size of ~$2 billion per annum[9].

[9] Based on median price of orphan drugs of US$150,000 p.a. from EvaluatePharma. Orphan Drug Report. 2019.

ADOA is caused by a mutation in one copy of the *OPA1* gene and in ~85% of patients, this mutation leads to insufficient levels of *OPA1* gene expression to support normal cellular function in the retinal ganglion cells of the eye. The abnormal function of the affected cells due to the *OPA1* deficiency causes cell stress and ultimately cell death. Loss of retinal ganglion cells due to cell death interrupts the normal processing of the visual signal from the retina to the brain leading to the loss of vision in ADOA patients.

PYC-001 is a precision therapy that aims to restore the expression of the OPA1 gene back to levels required for the normal function of the retina. PYC-001 utilises PYC's proprietary drug delivery technology to overcome the major challenges for RNA drugs by ensuring that sufficient drug reaches its target inside the cells affected by ADOA.

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**[10].

The Company was the first to progress a drug candidate for a blinding eye disease of childhood into human trials and is now progressing multiple 'fast-follower' programs into the clinic. For more information, visit pyctx.com, or follow us on LinkedIn and Twitter.

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 CEO of PYC Therapeutics Limited

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