16 December 2024

# PYC NOMINATES FOURTH CLINICAL DRUG CANDIDATE IN PHELAN-MCDERMID SYNDROME PROGRAM

- **PYC is a clinical-stage biotechnology company developing a pipeline of first-in-class drug candidates for patients in areas of major unmet need**
- **One of the Company's assets is an investigational drug candidate (known as PYC-002) being developed for the ~1 in every 10,000 people affected by a severe neurodevelopmental disorder known as Phelan-McDermid Syndrome[1] (PMS) who have no treatment options available**
- **The underlying cause of PMS is insufficient expression of the *SHANK3* gene in neurons within the brain**
- **PYC today announces the nomination of its clinical drug candidate for PMS following the successful completion of pre-clinical studies demonstrating that PYC-002:**
    - **Increases *SHANK3* gene expression in the critical regions of the brain implicated in PMS in animal models; and**
    - **Restores *SHANK3* gene expression in neurons derived from PMS patients back to the levels seen in unaffected individuals.**
- **PYC will now progress PYC-002 into an Investigational New Drug (IND)-enabling pathway prior to progression into human trials that are anticipated to commence in 1H 2026[2]**

**PERTH, Australia and SAN FRANCISCO, California – 16 December 2024**

PYC Therapeutics (ASX:PYC) is a clinical-stage biotechnology company creating first in class precision therapies for patients with genetic diseases and no treatment options available. One of the Company's assets is an investigational drug candidate (known as PYC-002) that addresses the underlying cause of Phelan-McDermid Syndrome (PMS). PYC is preparing to progress PYC-002 into human trials in 1H 2026 and today announces the nomination of its clinical candidate following successful studies in both patient-derived and animal models.

PMS is caused by an inability of neurons within the brain to communicate to one another due to insufficient expression of the SHANK3 protein at the communication junction between the neurons that is known as a synapse. PMS patients have a loss of function

[1] PMS Foundation
[2] Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 14 March 2024

mutation in one of the two copies of the *SHANK3* gene causing there to be half as much SHANK3 protein as is required within the neuronal synapse (resulting in the communication deficit).

The nomination of the clinical candidate in PYC's PMS drug development program follows successful completion of pre-clinical studies demonstrating that PYC-002:

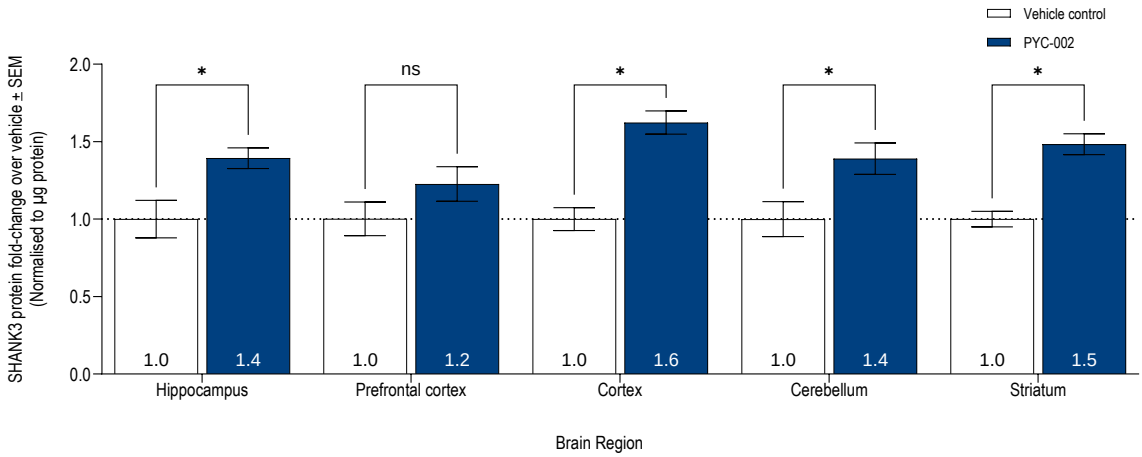
- Reaches the critical regions of the brain implicated in PMS *in vivo*; and
- Corrects the underlying cause of PMS in neurons derived from PMS patients *in vitro*.

PYC's CEO, Dr. Rohan Hockings, commented on the milestone: "*We are very pleased for the PMS community to be progressing this drug candidate into human trials. The data supporting this milestone show great potential for the first RNA therapy in this indication. The read-through benefits from other clinically-validated drug candidates within this class in different diseases occurring in the same target cell and organ provide a clear path to the patient-impact that we are striving for.*"

### *PYC-002 increases target gene expression in vivo*

PYC-002 is capable of increasing SHANK3 protein in the regions of the brain affected in PMS in an animal model predictive of the biodistribution of RNA therapies in humans[3] (*See Figure 1*).

**Figure 1.** SHANK3 expression in wild-type Sprague Dawley rats with and without treatment with PYC-002 (n=3 animals per group).



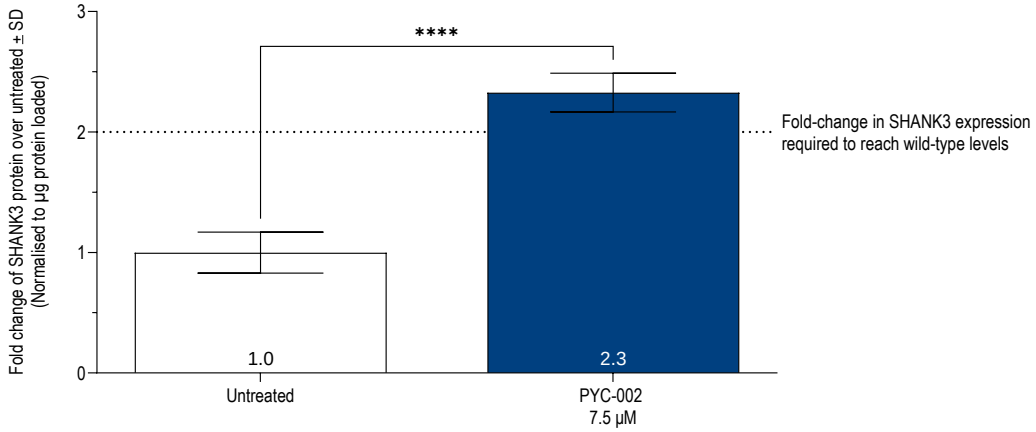

Rats received a single intrathecal dose of vehicle control or PYC-002. Assessment of SHANK3 protein levels in key brain regions was completed 14 days post-treatment. Statistical significance was determined using multiple unpaired Student's *t*-tests (*$p<0.05$).

### *PYC-002 corrects the underlying cause of PMS*

PYC-002 is capable of increasing expression of the *SHANK3* gene in neurons derived from patients with PMS back to levels seen in unaffected individuals (*See Figure 2*).

**Figure 2.** *SHANK3* gene expression in PMS patient-derived neurons with and without PYC-002 treatment. PMS patient-derived neurons treated with PYC-002 express the *SHANK3* gene at the same levels observed in neurons with two functional copies of the gene (i.e. those derived from individuals unaffected by PMS).

[3] Jafar-Nejad P, et al. The atlas of RNase H antisense oligonucleotide distribution and activity in the CNS of rodents and non-human primates following central administration. Nucleic Acids Res. 2021 Jan 25;49(2):657-673. doi: 10.1093/nar/gkaa1235.




Assessment of SHANK3 protein levels in PMS patient-derived neurons 14 days post-treatment. Statistical significance determined using unpaired student's *t*-test. *(****p<0.0001)*

Together, these results demonstrate that PYC-002 is successfully delivered inside the target cells within the critical regions of the brain affected by PMS *in vivo* and that, once there, the drug candidate can restore the missing gene expression that causes the disease.

***Next steps***

PYC will now commence the studies required to enable progression of PYC-002 into human trials. The Company expects First In Human trials of PYC-002 to commence in 1H 2026[4].

**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**[5].

**PYC's drug development programs**

**Retinitis Pigmentosa type 11**

- A blinding eye disease of childhood affecting 1 in every 100,000 people[6]
- Currently progressing through phase 1/2 clinical trials with preparation under way for a potentially registrational trial to commence in 2025[7]

**Autosomal Dominant Optic Atrophy**

- A blinding eye disease of childhood affecting 1 in every 35,000 people[8]

[4] Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 14 March 2024
[5] Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232
[6] Sullivan L, et al. Genomic rearrangements of the PRPF31 gene account for 2.5% of autosomal dominant retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2006;47(10):4579-88
[7] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024
[8] 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

- Currently progressing through clinical trials with human safety and efficacy read-outs anticipated in 2025[9]

**Autosomal Dominant Polycystic Kidney Disease**

- A chronic kidney disease affecting 1 in every 1,000 people[10] that leads to renal failure and the need for organ transplantation in the majority of patients
- Clinical trials are expected to commence in early 2025 with human safety and efficacy data anticipated in 2025 and 2026[11]

**Phelan McDermid Syndrome**

- A severe neurodevelopmental disorder affecting 1 in every 10,000 people[12]
- PYC will initiate Investigational New Drug (IND)-enabling studies in 2025 to facilitate progression into human trials

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 Board of PYC Therapeutics Limited*

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[9] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024
[10] Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. 2002 Jan 10 [Updated 2022 Sep 29]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993-2023.
[11] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024
[12] Phelan-McDermid Syndrome Foundation. https://pmsf.org/about-pms/