PYC Therapeutics

13 October 2025

PHELAN-MCDERMID SYNDROME – PRE-CLINICAL DATA SUPPORT PROGRESSION TO HUMAN TRIALS

- **PYC is developing a drug candidate that addresses the underlying cause of a severe neurodevelopmental disorder known as Phelan-McDermid Syndrome (PMS)**
- **PMS affects 1 in every 10,000 children[1] and there are no approved treatment options available for PMS patients**
- **PYC today announces the results of successful Non-Human Primate (NHP) studies[2] that complement earlier data generated in PMS patient-derived brain cells[3] and support progression of this drug development program into human trials[4]**
- **PYC expects to progress its investigational drug candidate for PMS into clinical trials in 2026[5]**
- **PYC will present the latest data for PYC-002 in PMS at the Oligonucleotide Therapeutic Society conference in Budapest, Hungary on 19 October 2025 in a poster presentation that has been attached to this announcement**

PERTH, Australia and SAN FRANCISCO, California – 13 October 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 and a fourth pre-clinical stage program directed towards a severe neurodevelopmental disorder known as Phelan-McDermid Syndrome (PMS). PMS affects 1 in every 10,000[6] children and there are currently no treatment options available for PMS patients.

PYC is developing a drug candidate (known as PYC-002) that addresses the underlying cause of PMS – insufficient expression of the *SHANK3* gene in neurons (brain cells). PYC-

[1] PMS Foundation
[2] Non-Good Laboratory Practice (Non-GLP) studies
[3] See ASX announcements of 27 June 2025 and 16 December 2024
[4] Subject to successful completion of Good Laboratory Practice toxicology studies, necessary regulatory approvals and other risks and uncertainties set out in the Company's ASX disclosures of 17 February 2025
[5] The Company anticipates submission of an Investigational New Drug filing with the US Food and Drug Administration following successful completion of GLP toxicology studies in 2H CY26 subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025
[6] PMS Foundation

002 works by increasing expression of *SHANK3* from the remaining 'good' copy of the gene in PMS patients to compensate for the decreased expression caused by the mutation in the affected ('bad') copy of the gene.

PYC today announces that PYC-002 has generated data in Non-Human Primate (NHP) studies that support progression of this drug candidate into human trials. Specifically, data from the Non-Good Laboratory Practice (Non-GLP) studies in NHPs demonstrate that:

- **Safety/Tolerability**: PYC-002 is safe and well-tolerated at doses that are predicted to be pharmacologically active at the equivalent human dose (see Figure 1)[7];
- **Biodistribution**: PYC-002 effectively distributes to the key regions of the brain affected in PMS following administration of doses of the drug candidate that are safe and well-tolerated (See Figure 2); and
- **Comparative data**: The pre-clinical data generated in support of PYC-002 (across safety/tolerability, biodistribution and efficacy dimensions) compares favourably with another RNA therapy targeting a different neurodevelopmental disorder[8] that has shown promising results in human trials on the cognitive and behavioural dimensions that are critical to PMS patients and their families[9] (See Figures 4 and 5).

Importantly, the concentration of drug achieved in the NHP brain at safe and well-tolerated doses *in vivo* is higher than what was required to restore *SHANK3* gene expression and achieve functional rescue in the neurons (brain cells) derived from PMS patients *in vitro*[10]. This creates a fully integrated safety/tolerability, pharmacokinetic and pharmacodynamic pre-clinical data pack in support of the utility of PYC-002 in addressing the underlying cause of PMS.

In addition, PYC-002 has demonstrated the ability to control target gene expression in both rats and NHPs. This has enabled PYC to assess the impact of treatment with PYC-002 on target gene expression *in vivo*. Early data from important regions of the rat and NHP brain implicated in PMS demonstrate increased target gene expression following treatment with PYC-002 (see Figures 3 and 4) adding further conviction to the pre-clinical data pack generated in support of PYC-002's disease-modifying potential in PMS.

[7] Based on cerebrospinal fluid (CSF) volume cross-species scaling from NHPs to humans

[8] Benchmarking to comparator antisense oligonucleotide (ASO), Zorevunersen (STK-001), that has the same chemistry and route of administration as PYC-002, and targets neurons. Zorevunersen has demonstrated clinically meaningful patient impact in a neurodevelopmental disorder and progressed to Phase 3 study.

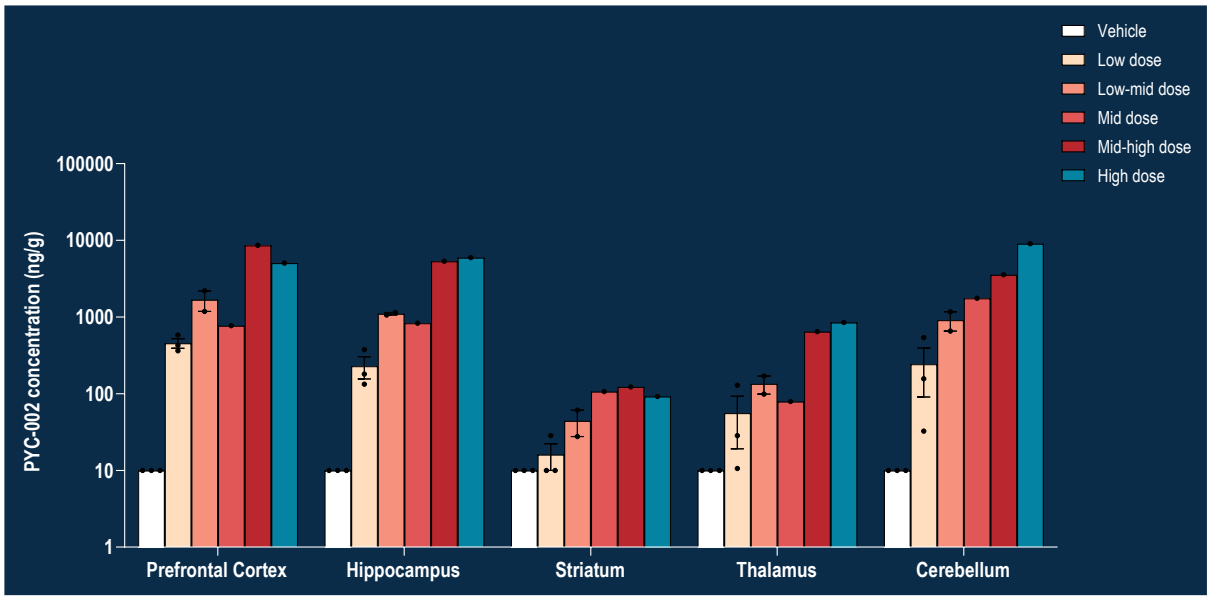
[9] See Stoke Therapeutics Corporate Presentation September 2025

[10] See ASX announcements of 27 June 2025 and 16 December 2024

Figure 1. Safety/Tolerability profile of PYC-002 in Non-GLP safety studies in NHPs[11]

Dose of PYC-002	Number of NHPs assessed	No findings of adverse tolerability at week 4 (conclusion of study) # of NHPs (% of population)	Findings of adverse tolerability at week 4 (conclusion of study) # of NHPs (% of population)
Control	3	3 (100%)	0 (0%)
Low	3	3 (100%)	0 (0%)
Low-mid	3	3 (100%)	0 (0%)
Mid	1	1 (100%)	0 (0%)
Mid-high	1	1 (100%)	0 (0%)
High	1	1 (100%)	0 (0%)

Figure 2. Biodistribution in Non-Human Primate (NHP) brain following a single dose of PYC-002[12]



PYC-002 demonstrates broad distribution to regions of the NHP brain that are implicated in PMS. The prefrontal cortex and hippocampus in particular are responsible for many of the key functions that form part of the PMS phenotype.

[11] Safety/tolerability was evaluated following a single intrathecal injection of vehicle or test article, PYC-002, at increasing dose levels to Cynomolgus monkeys (NHPs) and confirmed following observations that there was no decrease in platelet counts, no change in hepatic or renal function, no clinical signs or symptoms over 28 day period after administration and normal histopathology in brain, liver and kidney following dosing for all dose cohorts.

[12] Concentration of PYC-002 (ng drug per g tissue, mean + SEM) in brain tissue samples from Cynomolgus monkeys (Macaca fascicularis) 28 days after treatment with a single intrathecal injection, assessed by hy-ELISA.

Figure 3. Target gene expression *in vivo* in NHP prefrontal cortex following a single dose of PYC-002[13]

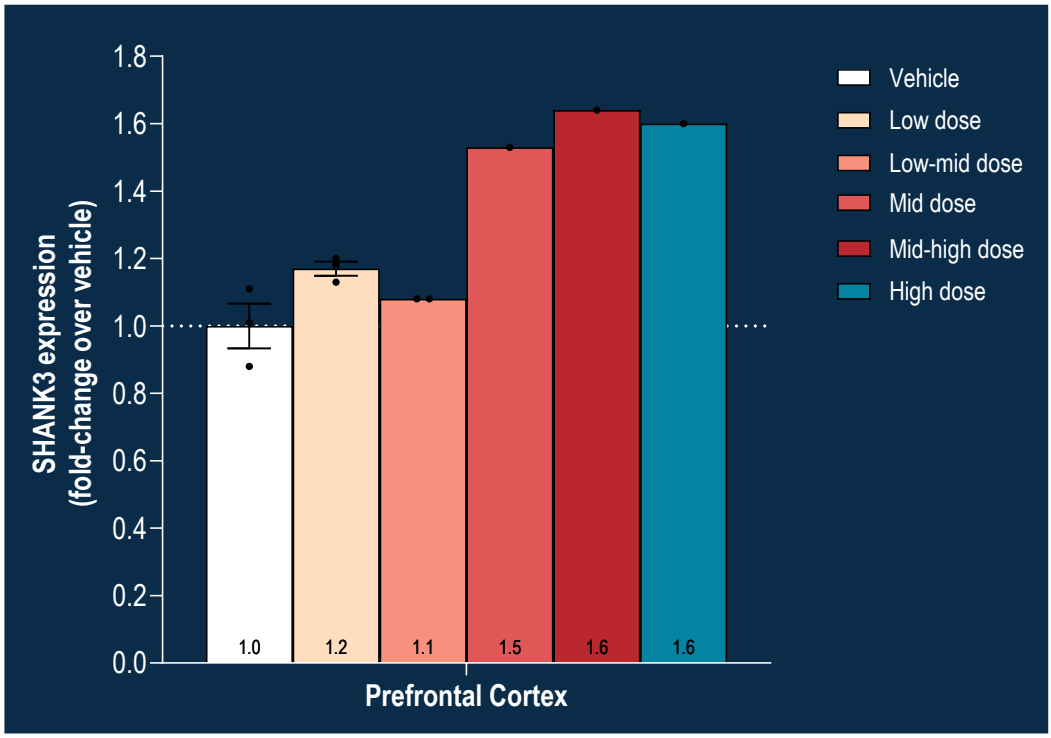
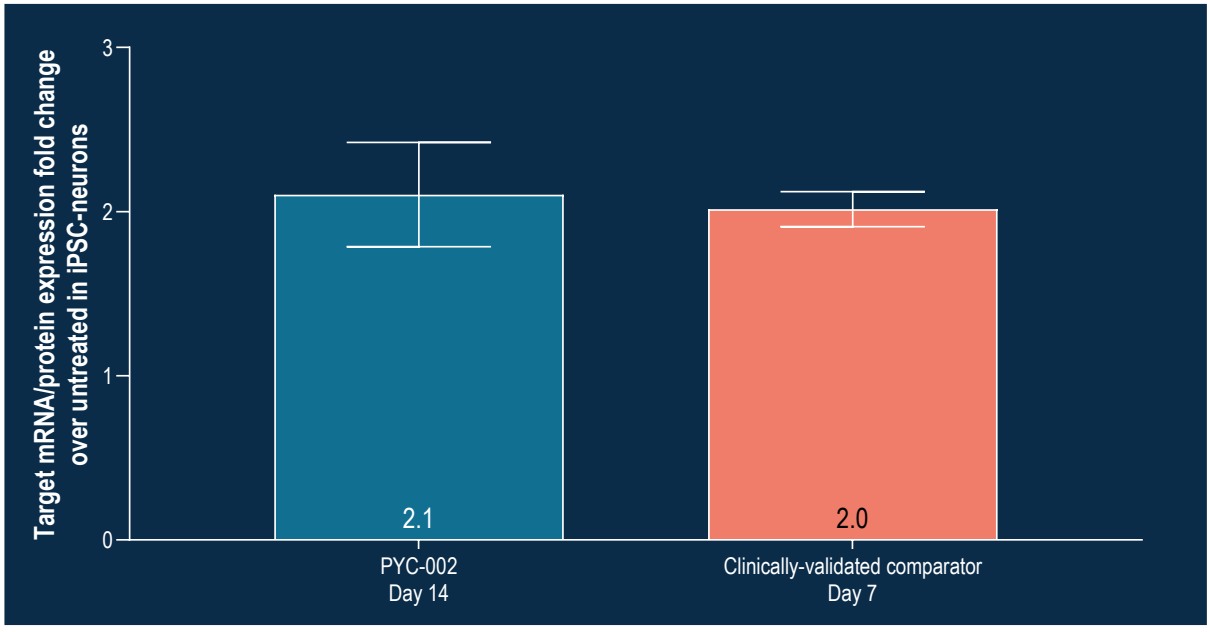


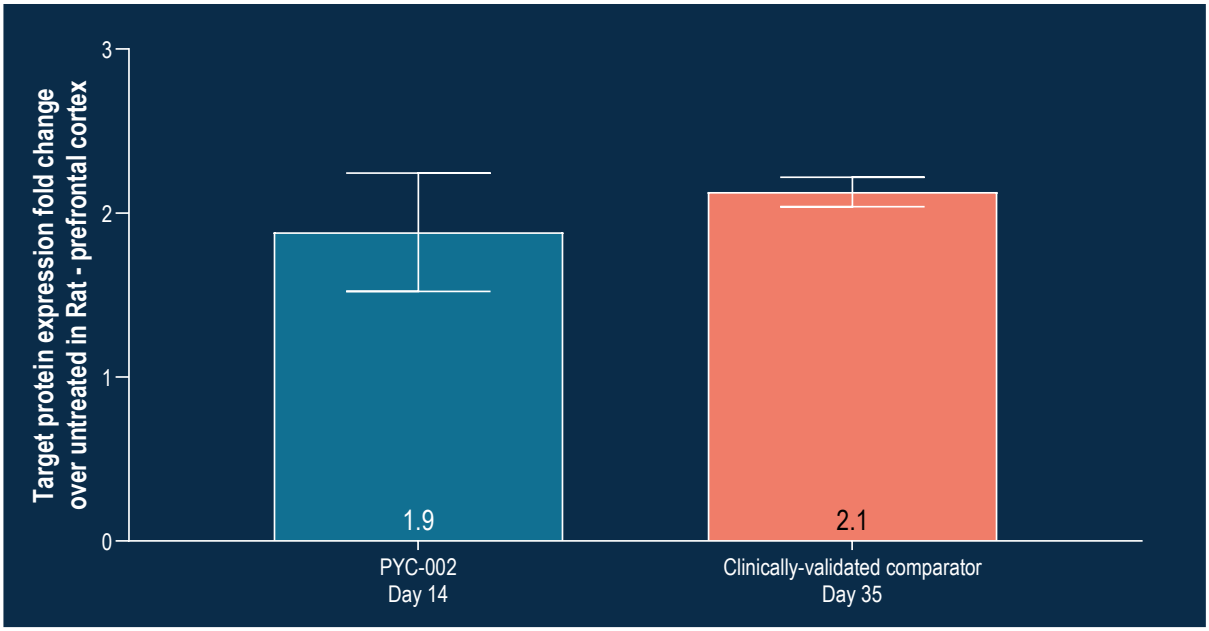
Figure 4. Potency of PYC-002 *in vitro* (iPSC-derived neurons) benchmarked to a clinically-validated RNA therapy for a neurodevelopmental disorder[14]



[13] SHANK3 protein expression in the prefrontal cortex of cynomolgus monkeys 28 days after intrathecal injection of PYC-002, expressed as fold-change vs the vehicle-treated group. SHANK3 protein was assessed by ELISA. Error bars represent standard error. Data from one mis-injected animal in the low-mid dose group was excluded from analysis.

[14] Blue bar graph represents the mean ± SEM of fold-change of SHANK3 protein upregulation following PYC-002 treatment in PMS patient-derived iPSC-neurons at day-21 (one biological replicate; 9 technical replicates). Red bar graph represents the mean ± SEM of mRNA upregulation following benchmark ASO treatment in healthy control iPSCs-neurons at day-7 (one biological replicate; 3 technical replicates). The same dose of PYC-002 and benchmark ASO was administered.

Figure 5. Potency of PYC-002 *in vivo* (Rat – prefrontal cortex) benchmarked to a clinically-validated RNA therapy for a neurodevelopmental disorder [15]



Next steps

PYC-002 is now progressing into formal Investigational New Drug (IND)-enabling studies. The program is expected to enter human trials in 2026[16].

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**[17].

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

[15] Blue bar graph represents the mean ± SEM of fold-change of SHANK3 protein upregulation following PYC-002 intrathecal injection in wild-type Sprague Dawley rats at day-14 (n=3). Red bar graph represents the mean ± SEM of target protein upregulation following benchmark ASO intrathecal injection in wild-type Sprague Dawley rats at day-35 (n=5). The same dose of PYC-002 and benchmark ASO was administered.
[16] Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025
[17] Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232

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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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PYC-002: Targeting SHANK3 with an RNA therapeutic approach for the treatment of Phelan-McDermid syndrome

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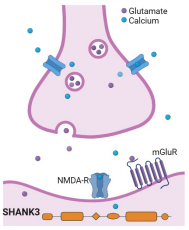
PYC Therapeutics

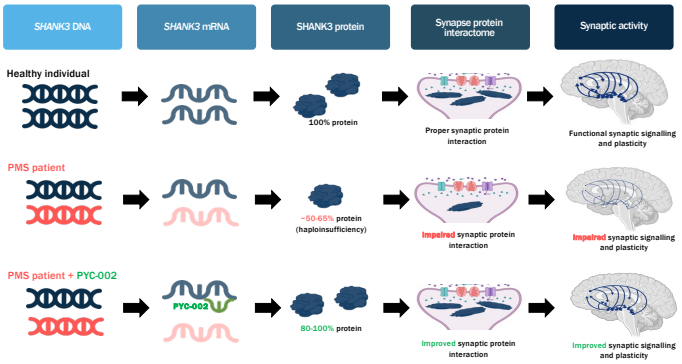
1. Phelan-McDermid syndrome is a severe neurodevelopmental disorder affecting children with no available disease-modifying treatments

- Phelan-McDermid syndrome (PMS) is associated with a variety of symptoms including intellectual disability, developmental and speech delays, autism-spectrum features, seizures, and hypotonia[1,2]
- PMS is caused by a mutation in, or deletion of, one copy of the ***SHANK3*** gene and requires a genetic diagnosis[3]
- Haploinsufficiency of SHANK3 protein, which plays a critical scaffolding role in postsynaptic neurons, results in impaired synaptic signalling and plasticity[2,3]
- PMS affects ~1 in 10,000 people with an estimated ~34,000* addressable patients[3,4]
- There is a major unmet patient need with no disease-modifying therapies currently available
- PYC-002 is a drug candidate that seeks to **precisely address the underlying cause of PMS** using antisense oligonucleotides to restore SHANK3 protein expression

* Patient estimates are based on prevalence multiplied by population in Western World (Australia, Europe, and USA) aged under 30 years.



2. PYC-002 addresses the root cause of PMS – SHANK3 haploinsufficiency



3. PYC-002 increases expression of SHANK3 protein, improves synaptic density and restores calcium-mediated synaptic signalling in PMS neurons

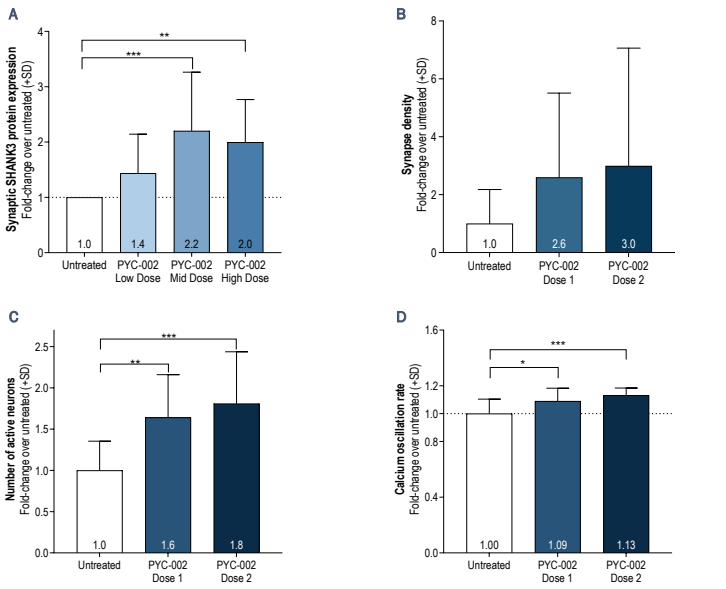


Figure 1. A) PYC-002 increases synaptic SHANK3 expression. Mean fold-change (+SD) of SHANK3 protein expression on 100 µm of neurite over untreated group after 21 days of PYC-002 gymnotic treatment of PMS patient-derived iPSC-neurons (n=2 biological replicates, each with 5 – 24 technical replicates), assessed by high content imaging. Statistical significance assessed using 2-way ANOVA. **B) PYC-002 improves synapse structure.** Mean fold-change (+SD) in synapse density in PMS patient-derived iPSC-neurons (n=2 biological replicates, each with 8 – 15 technical replicates) after 21 days of gymnotic treatment with PYC-002 compared to the untreated control. A synapse is defined as the co-localization of SHANK3 (post-synaptic marker), SYNAPSIN (pre-synaptic marker) and Tuj-1 (neurite marker) proteins. Statistical significance evaluated using 2-way ANOVA. **C) PYC-002 increases neuronal activity.** Mean fold-change (+SD) of the number of PMS patient-derived iPSC-neurons that are active by Calcium signalling pathway after 21 days of PYC-002 gymnotic treatment compared to the untreated control (n=2 biological replicates, n=6 technical replicates per group). Statistical significance evaluated using 2-way ANOVA. **D) PYC-002 increases calcium signalling.** Mean fold-change (+SD) of calcium oscillation rate in PMS patient-derived iPSC-neurons (n=3 biological replicates), after 21 days of PYC-002 gymnotic treatment compared to the untreated control. Each biological replicate contained n=13 technical replicates per PYC-002 treatment group and n=23 untreated replicates. Statistical significance evaluated using 2-way ANOVA.
*p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001

4. PYC-002 has desirable safety and tolerability profile in two pre-clinical species

Sprague-Dawley Rat (*Rattus norvegicus*), specific pathogen-free grade

Dose	Number of animals	Safety/Toxicology
Vehicle control	9	Well-tolerated
Low	9	Well-tolerated
Low-mid	3	Well-tolerated
Mid	11	Well-tolerated
High	6	Well-tolerated

Cynomolgus Monkey (*Macaca fascicularis*), conventional grade

Dose	Number of animals	Safety/Toxicology
Vehicle control	3	Well-tolerated
Low	3	Well-tolerated
Low-mid	3	Well-tolerated
Mid	1	Well-tolerated
Mid-high	1	Well-tolerated
High	1	Well-tolerated

5. PYC-002 shows broad distribution to disease-relevant brain regions following intrathecal administration

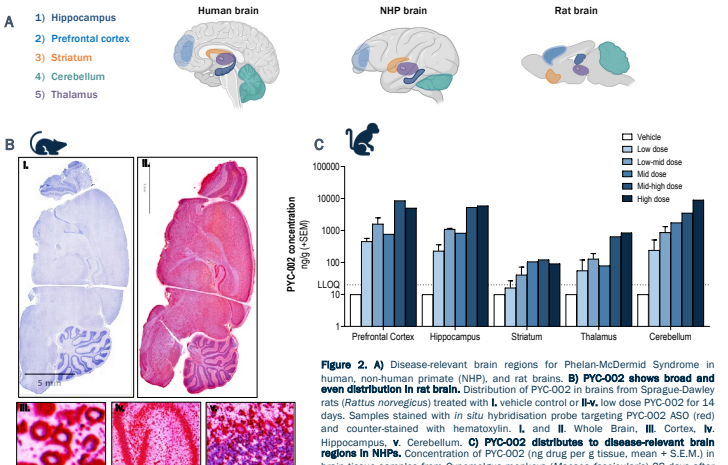


Figure 2. A) Disease-relevant brain regions for Phelan-McDermid Syndrome in human, non-human primate (NHP), and rat brains. **B) PYC-002 shows broad and even distribution in rat brain.** Distribution of PYC-002 in brains from Sprague-Dawley rats (*Rattus norvegicus*) treated with **I.** vehicle control or **II-v.** low dose PYC-002 for 14 days. Samples stained with *in situ* hybridisation probe targeting PYC-002 ASO (red) and counter-stained with hematoxylin. **I.** and **II.** Whole Brain, **III.** Cortex, **IV.** Hippocampus, **V.** Cerebellum. **C) PYC-002 distributes to disease-relevant brain regions in NHPs.** Concentration of PYC-002 (ng drug per g tissue, mean + S.E.M.) in brain tissue samples from Cynomolgus monkeys (*Macaca fascicularis*) 28 days after treatment, assessed by hy-ELISA.

6. A single dose of PYC-002 causes upregulation of multiple SHANK3 isoforms and dose-dependent upregulation in the prefrontal cortex

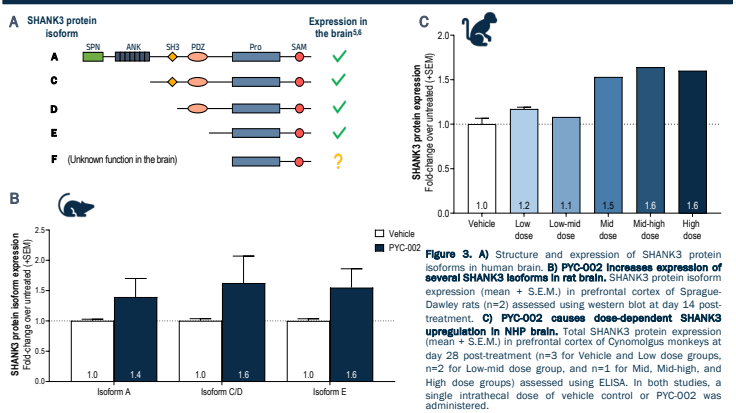


Figure 3. A) Structure and expression of SHANK3 protein isoforms in human brain. **B) PYC-002 increases expression of several SHANK3 isoforms in rat brain.** SHANK3 protein isoform expression (mean + S.E.M.) in prefrontal cortex of Sprague-Dawley rats (n=2) assessed using western blot at day 14 post-treatment. **C) PYC-002 causes dose-dependent SHANK3 upregulation in NHP brain.** Total SHANK3 protein expression (mean + S.E.M.) in prefrontal cortex of Cynomolgus monkeys at day 28 post-treatment (n=3 for Vehicle and Low dose groups, n=2 for Low-mid dose group, and n=1 for Mid, Mid-high, and High dose groups) assessed using ELISA. In both studies, a single intrathecal dose of vehicle control or PYC-002 was administered.

7. Conclusion: Preclinical findings support the development of PYC-002 as a treatment for PMS

- PYC's mutation agnostic PYC-002 drug candidate increased synaptic SHANK3 protein and improved synaptic structure and function in human iPSC-derived PMS neurons
- PYC-002 has a favourable safety profile in rats and non-human primates (NHPs) following intrathecal administration
- PYC-002 shows broad distribution throughout the brain including in disease-relevant regions in rats and NHPs
- A single, safe dose of PYC-002 upregulated multiple endogenous isoforms of SHANK3 critical for neuronal function in rats and PYC-002 caused dose-dependent upregulation in the prefrontal cortex of NHPs
- PYC is progressing through preclinical testing and is anticipated to enter human clinical trials in H2 2026.

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