PYC Therapeutics

27 June 2025

PROGRESS IN PHELAN-MCDERMID SYNDROME PROGRAM TO BE PRESENTED AT PMS GLOBAL CONGRESS

- **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 has recently generated data supporting the progression of its PMS drug candidate into clinical development, including:**
    - **Efficacy data generated in brain cells derived from patients with PMS demonstrating that PYC's drug candidate:**
        - **Restores the missing gene expression that causes PMS back to the levels observed in unaffected individuals[2];**
        - **Enables these brain cells to form the missing connections that underlie the neurodevelopmental deficits that characterise the syndrome[3]; and**
        - **Enhances the levels of communication occurring between these brain cells – an indicator of brain activity[4].**
    - ***In vivo* data demonstrating that PYC's drug candidate effectively controls target gene expression in the key regions of the brain implicated in PMS**
- **The Company will present this data at the Phelan-McDermid Syndrome Global Congress to be held in Barcelona, Spain between 26-29 June 2025**
- **PYC's PMS program is expected to advance into clinical trials in ~12 months' time – marking the fourth first-in-class drug candidate with disease-modifying potential that PYC has advanced into human trials**

[1] PMS Foundation
[2] See Figure 1
[3] See Figure 2
[4] See Figure 3

PERTH, Australia and SAN FRANCISCO, California – 27 June 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.

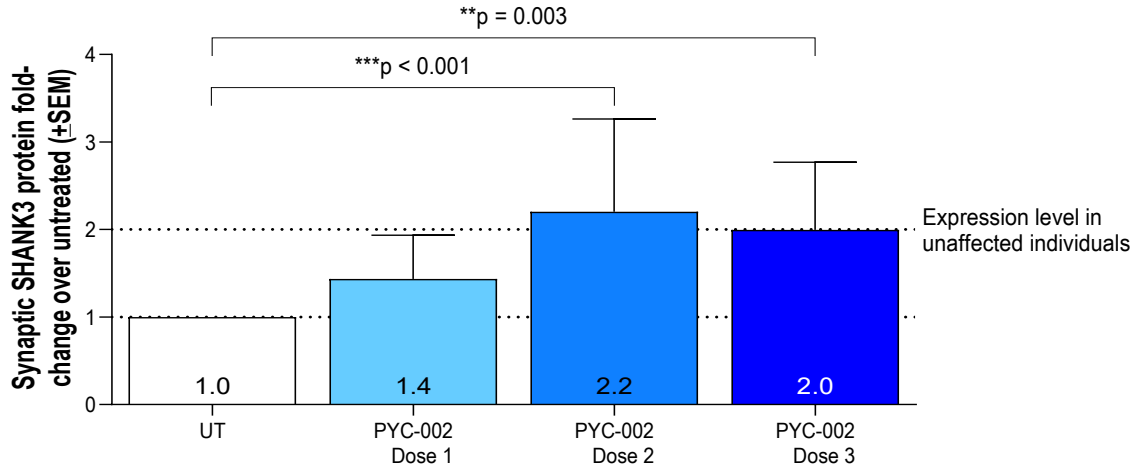
The Company currently has three clinical-stage drug development programs and a fourth pre-clinical stage program directed towards a severe neurodevelopmental disorder known as Phelan-McDermid Syndrome (PMS). PMS affects 1 in every 10,000[5] children and there are currently no treatment options available 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-002 works by increasing expression of *SHANK3* from the remaining 'good' copy of the gene to compensate for the decreased expression caused by the mutation in the affected ('bad') copy of the gene. Because PYC-002 addresses the underlying cause of PMS, it is expected that it will impact not only the quantitative dimension of *SHANK3* gene insufficiency but also the functional deficits in neurons that are caused by this missing gene expression.

PYC today announces that it is presenting data supporting the progress made in the PYC-002 program at the PMS Global Congress to be held in Barcelona, Spain between 26-29 June 2025. The data presented demonstrates that PYC-002 restores the missing gene expression that causes PMS in brain cells derived from patients and rescues the functional deficits in these neurons that underlie the neurodevelopmental delays that characterise the syndrome. In addition, PYC will also present *in vivo* data for its clinical candidate demonstrating effective control of target gene expression in the key regions of the brain implicated in PMS.

A full copy of the presentation to be made at the conference is attached to this announcement with selected data highlights included below.

Figure 1. Restoration of target gene (*SHANK3*) expression in neurons derived from patients with PMS[6]



[5] PMS Foundation

[6] High content imaging assessment of the mean fold-change of SHANK3 protein on 100 µm of neurite compared to the untreated (UT) group at day 21 following treatment with PYC-002 in 1-2 biological replicates of two PMS patient-derived iPSC-neurons (N=3). Each biological replicate represents the median of 5-12 technical replicates. Error bars represent standard error. **p<0.01 assessed using unpaired t-test of n=34 untreated technical replicates vs n=19 technical replicates treated with PYC-002

Figure 2. Increase in neuronal synapse (communication channel) density in neurons derived from patients with PMS following treatment with PYC-002[7]

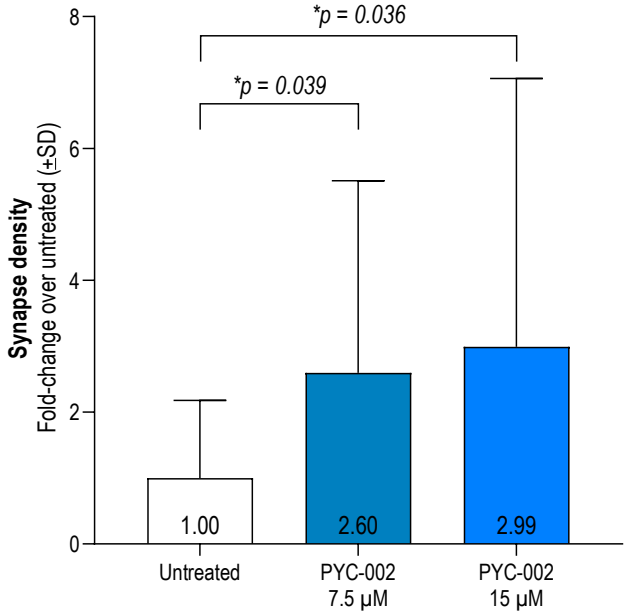
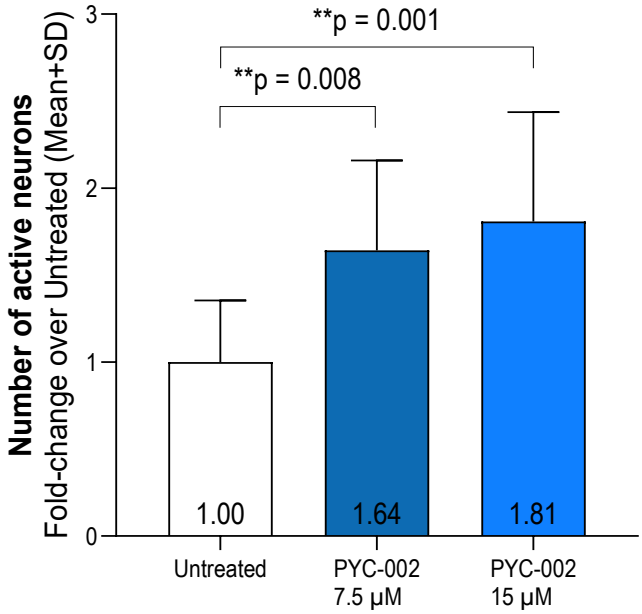


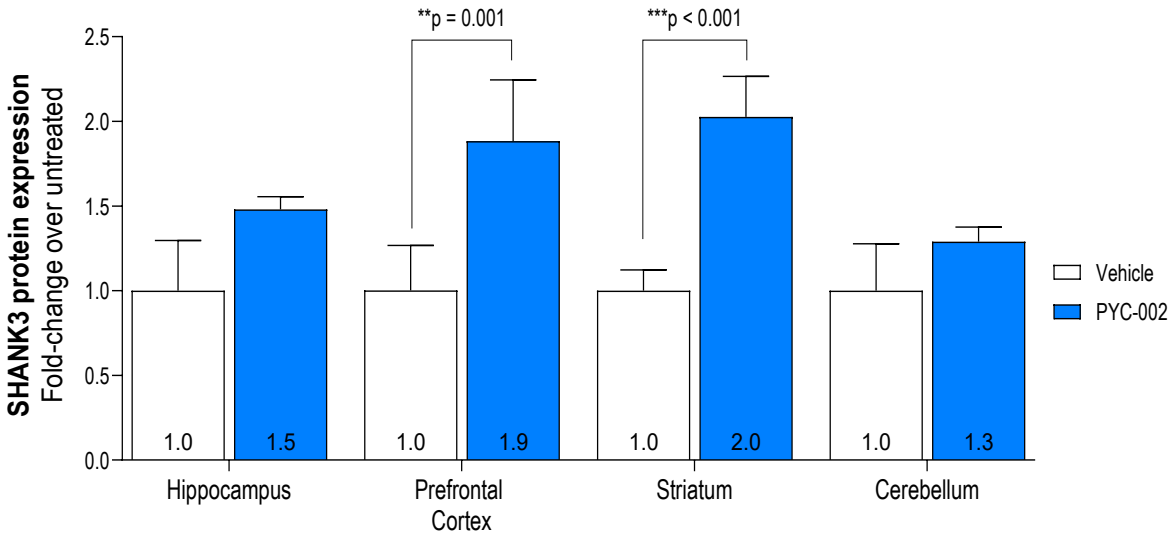
Figure 3. Increase in excitation of neurons derived from patients with PMS following treatment with PYC-002[8]



[7] Bar graphs represent the mean +Standard Deviation (SD) of the fold-change in synapse counts in two biological replicates of one PMS patient-derived iPSC-neuron after 21 days of treatment with PYC-002 compared to the untreated control. The 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 two-sided unpaired Welch's t-test comparing each treatment concentration of PYC-002 to untreated PMS-patient derived neurons (n=20 technical replicates for untreated group, n= 17 technical replicates for each PYC-002 treatment concentration)

[8] Bar graphs represent mean +SD of the fold-change of the number of neurons that are active as assessed by calcium signalling pathway activation when compared to the untreated group. Statistical significance evaluated using two-sided unpaired Welch's t-test comparing each treatment concentration of PYC-002 to untreated PMS-patient derived neurons (n=12 technical replicates per group)

Figure 4. SHANK3 expression in the key regions of the brain implicated in PMS in wild-type Sprague Dawley rats following administration of a single dose of PYC-002[9]



Next steps

PYC-002 is currently progressing through the final pharmacokinetic and dose-range finding studies required before initiating formal Investigational New Drug (IND)-enabling studies. The program is currently expected to enter human trials next year[10].

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**[11].

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

[9] SHANK3 expression in wild-type Sprague Dawley rats with and without treatment with PYC-002. Rats received a single intrathecal dose of vehicle control or PYC-002 (900 µg). Assessment of SHANK3 protein levels in key brain regions was completed 14 days post-treatment (n=3 treated with PYC-002 and n=6 vehicle). **p<0.01 determined using two-way ANOVA comparing PYC-002 treated to vehicle group in each brain region

[10] Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025

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

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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PYC Therapeutics

Life-changing science

PYC-002: Targeting *SHANK3* with an RNA Therapeutic Approach for Phelan-McDermid Syndrome

June 2025

Disclaimer

The purpose of this presentation is to provide an update of the business of PYC Therapeutics Limited (ASX:PYC) ['PYC']. These slides have been prepared as a presentation aid only and the information they contain may require further explanation and/or clarification. Accordingly, these slides and the information they contain should be read in conjunction with past and future announcements made by PYC Therapeutics and should not be relied upon as an independent source of information. Please contact PYC and/or refer to the Company's website for further information.

The views expressed in this presentation contain information derived from publicly available sources that have not been independently verified. No representation or warranty is made as to the accuracy, completeness or reliability of the information.

Any forward looking statements in this presentation 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 PYC's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this presentation include known and unknown risks. Because actual results could differ materially to assumptions made and PYC's current intentions, plans, expectations and beliefs about the future, you are urged to view all forward looking statements contained in this presentation with caution.

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

Executive Summary

PYC Therapeutics

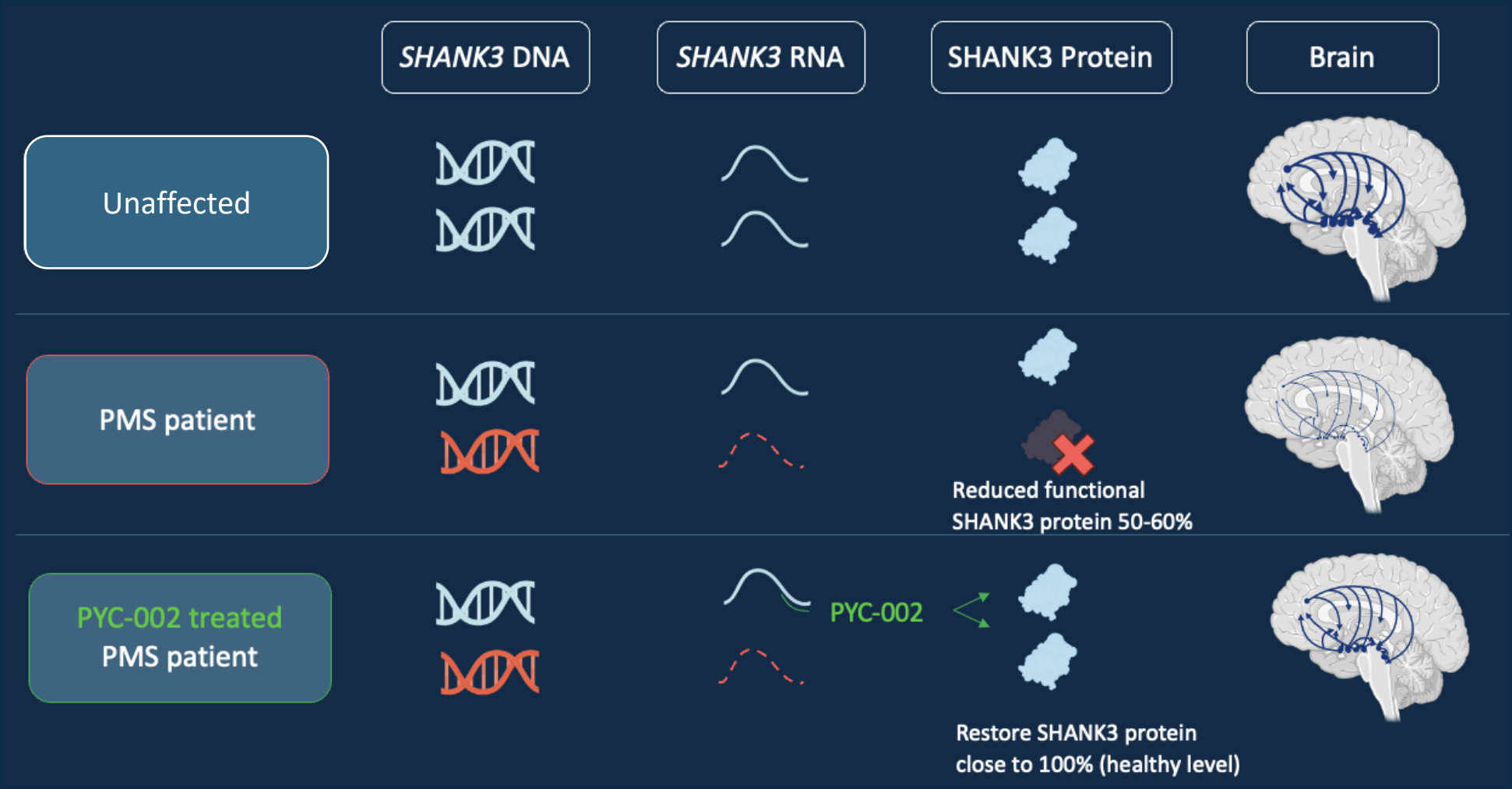
- PYC-002 is a pre-clinical stage drug candidate that addresses the underlying cause of PMS (haploinsufficiency of the SHANK3 protein in the neurons of the brain)

- PYC-002 combines human efficacy (*in-vitro*) with fully integrated safety/tolerability/PK/PD data *in vivo*:
  - *In vitro:* PYC-002 restores SHANK3 protein expression to wild-type/unaffected levels and leads to functional benefit in PMS patient-derived neurons
  - *In vivo:* PYC-002 reaches the target cell and modulates gene expression at safe and well-tolerated doses

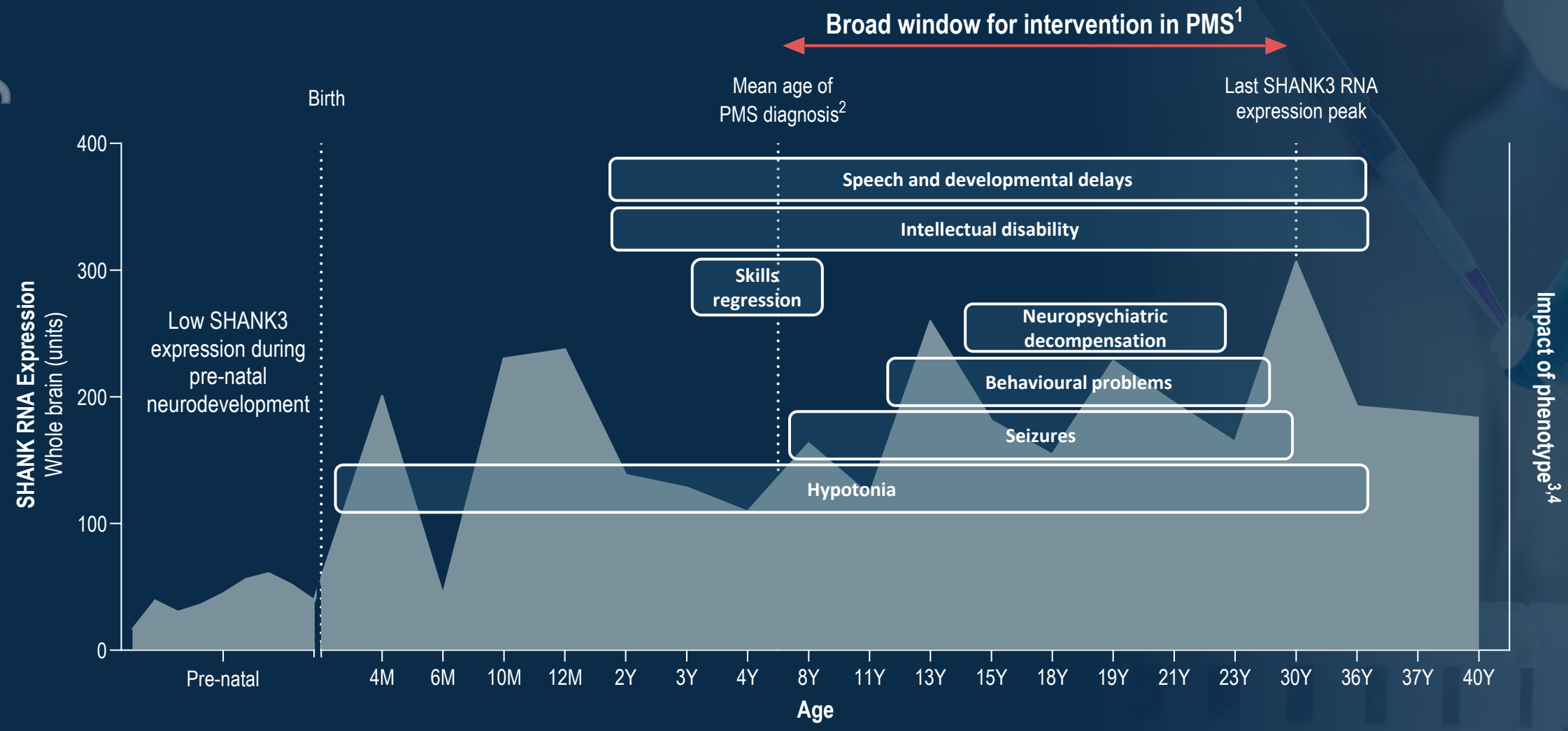
- PYC-002 will progress to human trials in 2026 – further development of this program is de-risked by the ability to leverage an established clinical development pathway
  - Delivered by lumbar puncture (intrathecal) to bypass the blood-brain barrier, minimising systemic exposure
  - Treatment frequency to be confirmed - expected to be dosed every 3–6 months

PYC-002 addresses the root cause of PMS by increasing *SHANK3* expression in the target cell within the brain

PYC Therapeutics



The neurodevelopmental expression level of *SHANK3* enables a broad opportunity for intervention in PMS



1. Kang HJ, et al. Spatio-temporal transcriptome of the human brain. Nature. 2011 Oct 26; 478(7370):483-9.
2. Nevado J, et al. Variability in Phelan-McDermid Syndrome in a Cohort of 210 Individuals. Frontiers in Genetics. 2022;13.
3. Annemiek M. Landlust, Sylvia A. Koza, Maya Carbin, Margreet Walinga, Sandra Robert, Jennifer Cooke, Klea Vyshka, Ingrid D.C. van Balkom, Conny van Ravenswaaij-Arts, Parental perspectives on Phelan-McDermid syndrome: Results of a worldwide survey, European Journal of Medical Genetics, Volume 66, Issue 7, 2023, 104771, ISSN 1769-7212, https://doi.org/10.1016/j.ejmg.2023.104771.
4. Betancur C, Buxbaum JD. SHANK3 haploinsufficiency: a "common" but underdiagnosed highly penetrant monogenic cause of autism spectrum disorders. Mol Autism. 2013 Jun 11;4(1):17. doi: 10.1186/2040-2392-4-17. PMID: 23758743; PMCID: PMC3695795.

PMS is caused by haploinsufficiency of the SHANK3 protein

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Unaffected neurons

PMS neurons

Unaffected SHANK3 protein levels

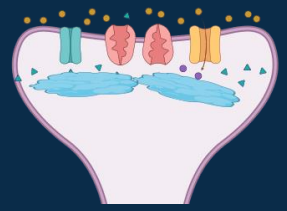
SHANK3 protein

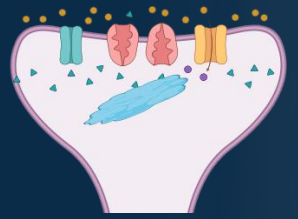
SHANK3 haploinsufficiency (50-65% of unaffected)

Proper synaptic protein interaction

Synapse protein interactome

Impaired synaptic protein interaction

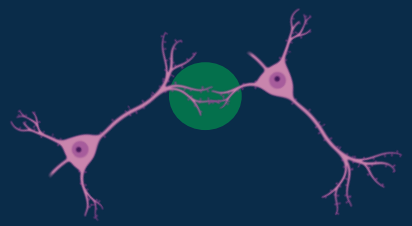


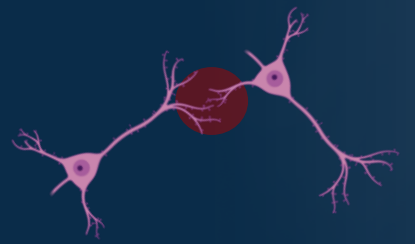


Correct synaptic function

Neuronal structure

Abnormalities in synaptic structure and function





Functional neuronal communication, synaptic signalling, and plasticity

Synaptic activity

Impaired neuronal communication, synaptic signalling, and plasticity

Phelan-McDermid Syndrome

PYC-002 restores SHANK3 protein expression back to the levels seen in unaffected individuals in patient-derived models

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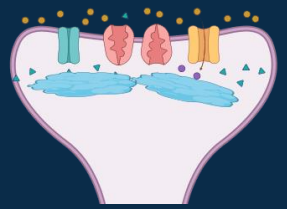
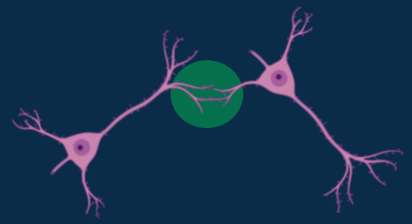
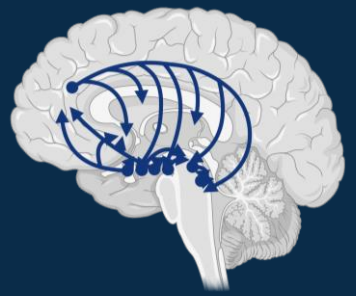
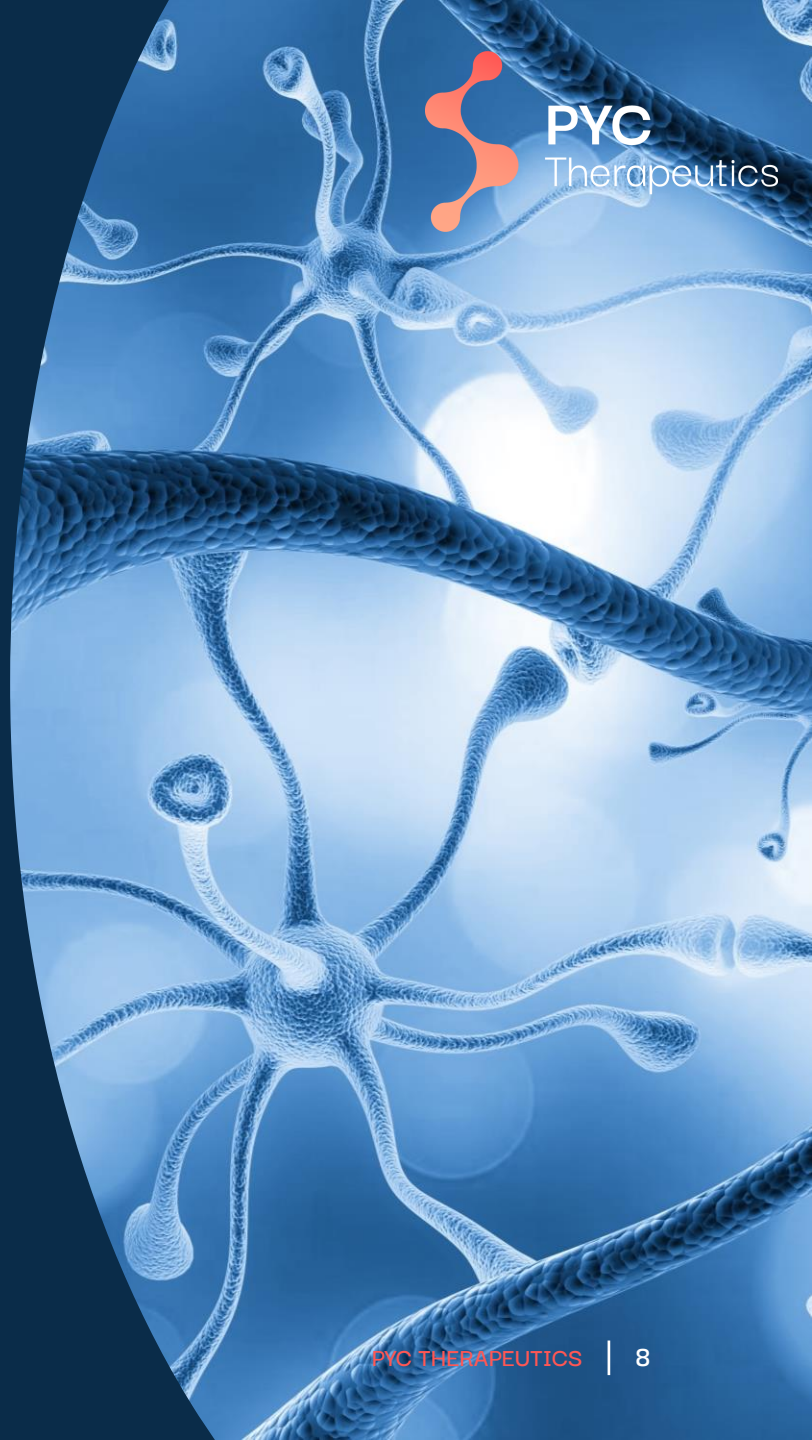
	PMS neurons + PYC-002	*Rescue in vitro assays*
SHANK3 protein	 Restored SHANK3 expression in neurons	Total SHANK3 protein ✓
Synapse protein interactome	 Improved SHANK3 at synapses and synaptic protein interaction	SHANK3 protein expression at synaptic site ✓
Neuronal structure	 Restoration of synaptic structure and function	Neuronal structure (synapse density) ✓
neuronal activity	 Improved neuronal communication, synaptic signalling, and plasticity	Neuronal signalling (active neurons count and calcium oscillation) ✓

Efficacy and Safety profile

1. PYC-002 restores *SHANK3* levels and reverses key PMS-related neuronal deficits in patient-derived neurons *in vitro*:
    a) Increases SHANK3 protein expression at the synapse
    b) Improves neuronal structure (synapse density) and restores neuronal signalling (active neuron count and calcium oscillation)

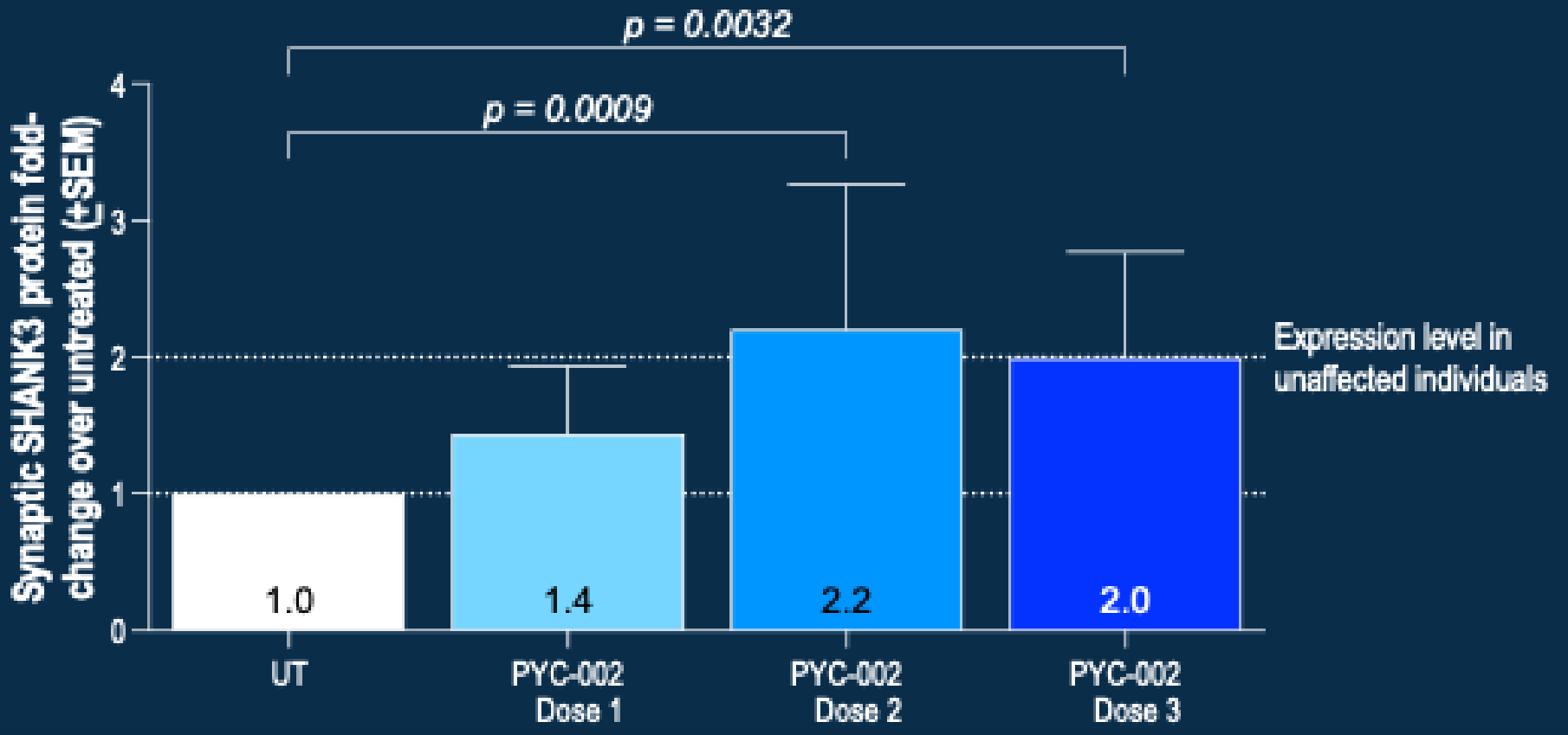
2. PYC-002 has a fully integrated safety/tolerability/PK/PD data pack *in vivo:*
    a) PYC-002 distributes to all key regions of the brain *in vivo* and can modulate gene expression at safe and well-tolerated doses



1a) PYC-002 completely rescues the deficient SHANK3 protein expression in PMS patient-derived neurons

PYC Therapeutics

Up to 2-fold increase in synaptic SHANK3 protein expression in PMS-patient derived neurons[1]



- Total SHANK3 protein
- SHANK3 protein expression at synaptic site

1. Mean fold-change of SHANK3 protein on 100 µm of neurite over untreated group after 21 days of PYC-002 gymnotic treatment of two PMS patient-derived iPSC-neurons, assessed by high content imaging (HCI). Each biological replicate represents the median of 5-24 technical replicates. Error bars represent standard error. **p<0.01 assessed using unpaired t-test of n=34 untreated technical replicates vs n=19 technical replicates treated with PYC-002.

1b) Restoring SHANK3 protein expression results in improved neuronal structure and signalling

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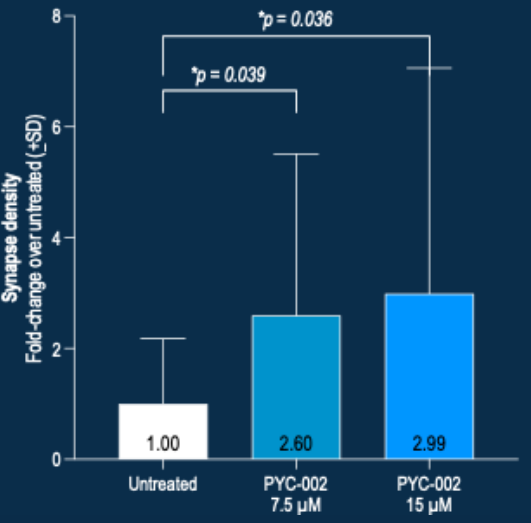
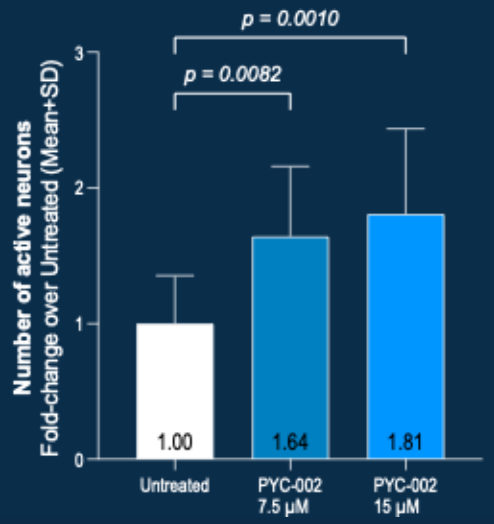
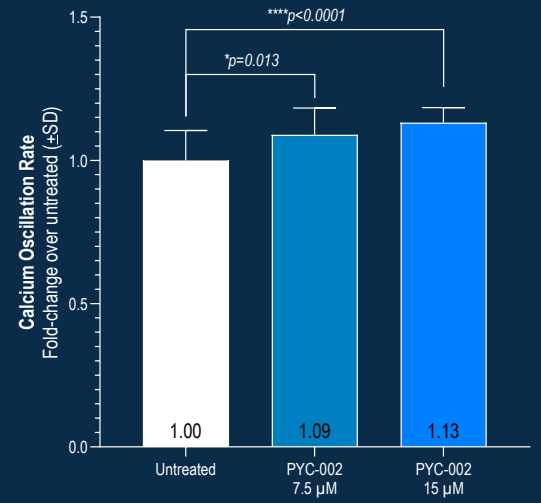
Restoration of neuronal structure and signalling in PMS-patient derived neurons

Density of synapses[1] → Number of active neurons[2] → Calcium oscillation[3]





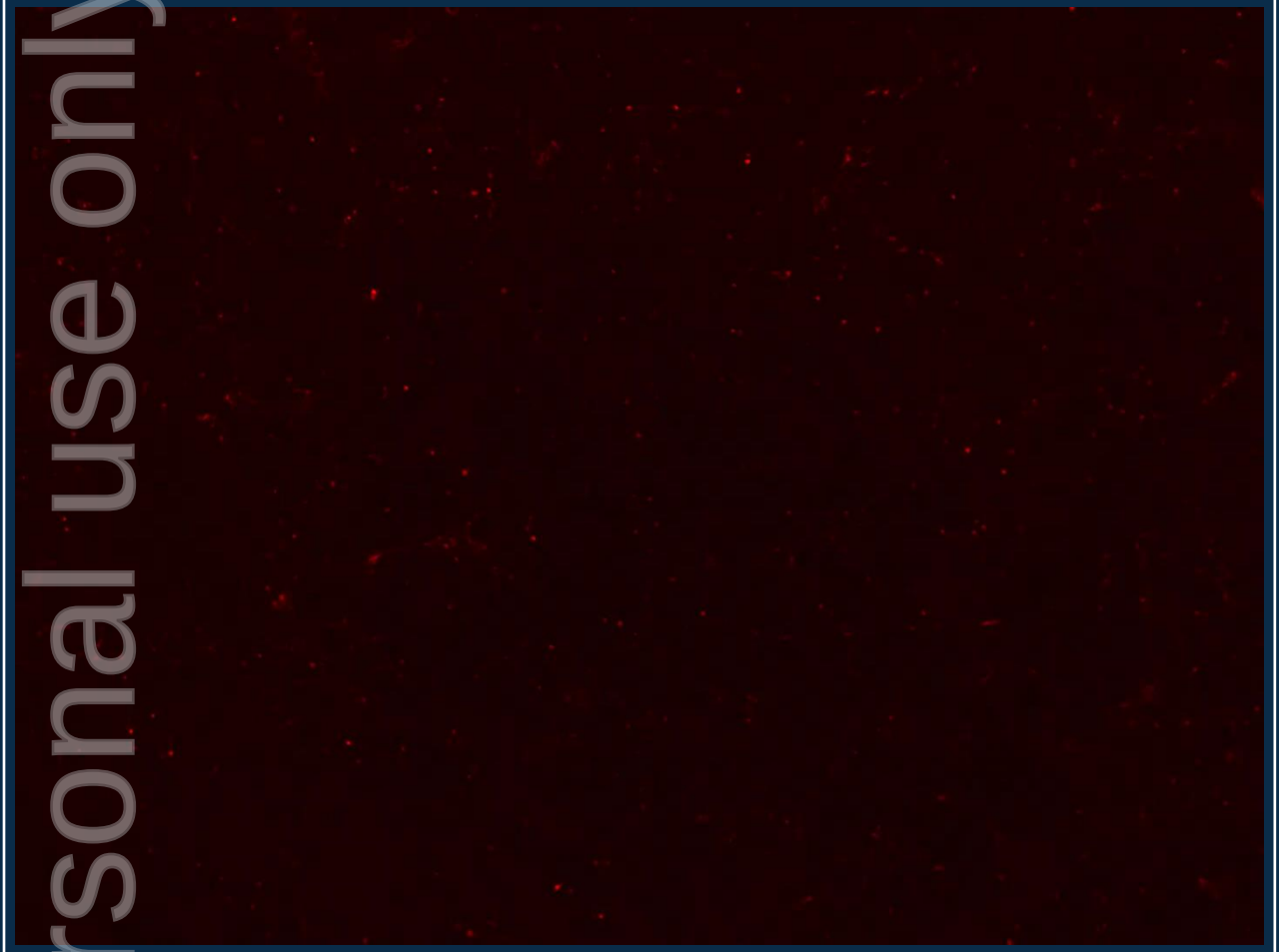


- Neuronal structure (synapse count)
- Neuronal signalling (active neurons count and calcium oscillation)

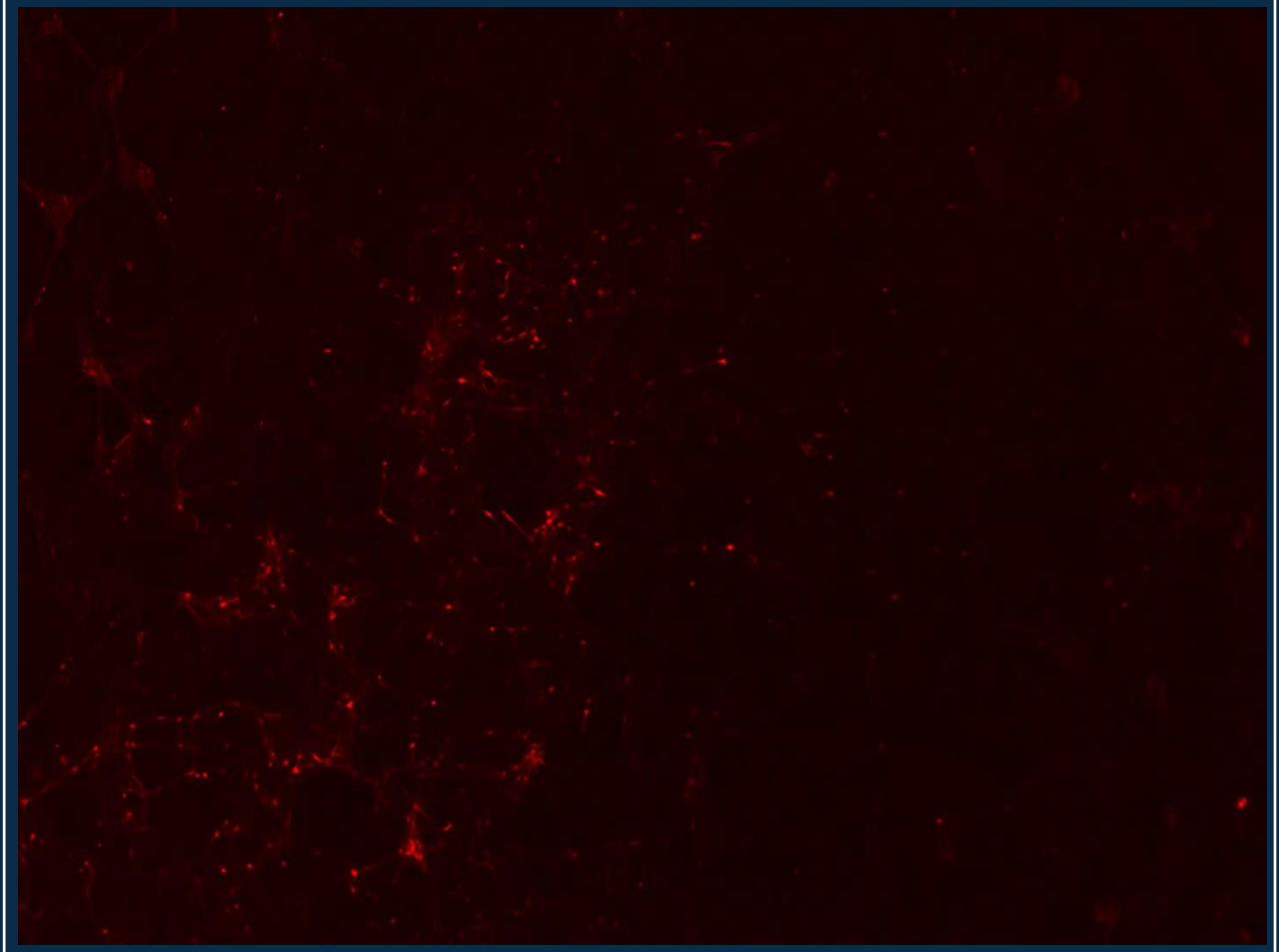
1. Bar graphs represent the mean ±SD of fold-change in synapse counts in two biological replicates of one PMS patient-derived iPSC-neurons after 21 days of PYC-002 treatment. The synapse is defined as the co-localization of SHANK3 (post-synaptic marker), SYNAPSIN (pre-synaptic marker) and Tuj-1 (neurite marker) proteins. Statistical significance evaluated using two-sided unpaired Welch's t-test comparing each treatment concentration of PYC-002 to untreated PMS-patient derived neurons (n=20 technical replicates for untreated group, n= 17 technical replicates for each PYC-002 treatment concentration)
2. Bar graphs represent mean ±SD of the fold-change of number of neurons that is active by Calcium signaling pathway over untreated. Statistical significance evaluated using two-sided unpaired Welch's t-test comparing each treatment concentration of PYC-002 to untreated PMS-patient derived neurons (n=2 biological replicates; n=6 technical replicates per biological replicate)
3. Bar graphs represent mean ± SD of the fold-change of calcium oscillation rate over untreated. Statistical significance evaluated using two-sided unpaired Welch's t-test comparing each treatment concentration of PYC-002 to untreated PMS-patient derived neurons (n=23 technical replicates for untreated group, n=17 technical replicates for each PYC-002 treatment concentration)

1b) PYC-002 rescues neuronal signalling in PMS-patient derived neurons

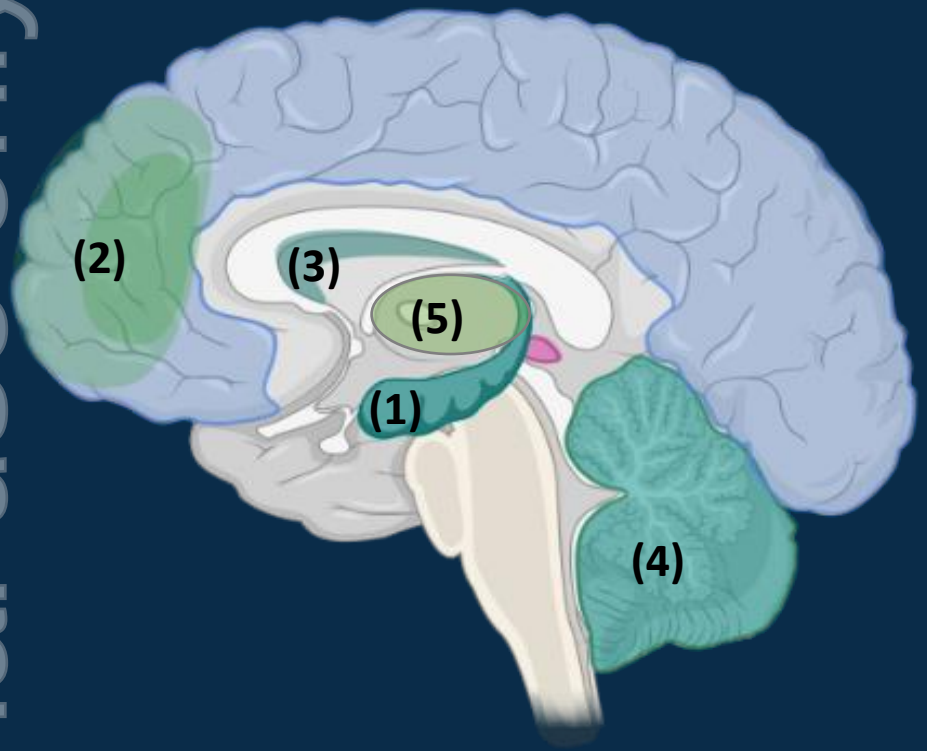
Untreated PMS-derived neurons



PYC-002 treated PMS-derived neurons (day 29)



Deficient *SHANK3* levels in multiple brain regions disrupt neuronal communication contributing to the PMS phenotype



Brain regions implicated in PMS and impact on phenotype

1. **Hippocampus:** critical for learning and memory processes
2. **Prefrontal cortex:** important for decision making, social behaviours and cognitive functions
3. **Striatum:** plays a crucial role in synaptic function and plasticity, essential for decision making, emotion and motor control
4. **Cerebellum:** functions in balance and motor/movement control
5. **Thalamus:** receiving incoming sensory and motor information

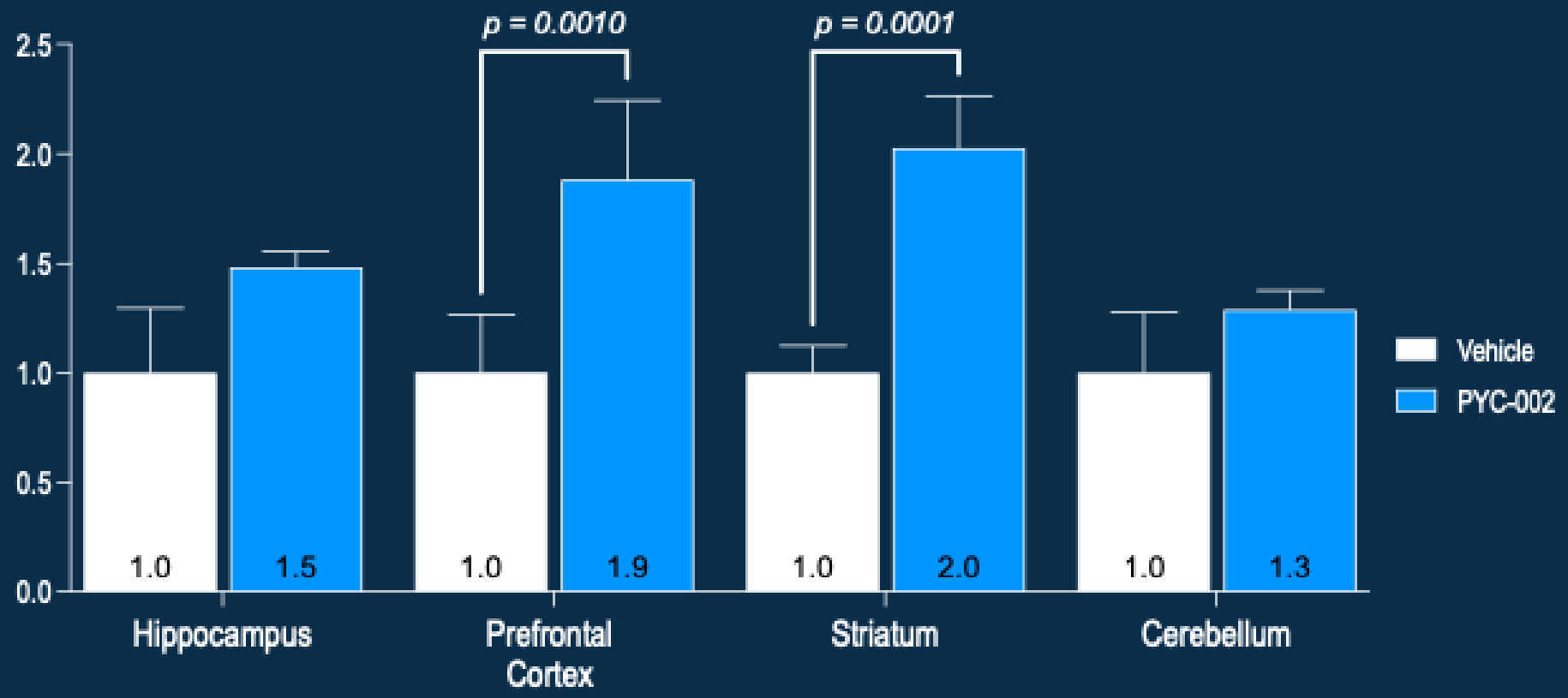
1. Kang, H. J., Y. I. et al (2011). "Spatio-temporal transcriptome of the human brain." Nature **478**(7370): 483-489.
2. Bouquier, N., et al (2022). "The Shank3(Venus/Venus) knock in mouse enables isoform-specific functional studies of Shank3a." Front Neurosci 16: 1081010.
3. Wang, X., et al (2014). "Transcriptional and functional complexity of Shank3 provides a molecular framework to understand the phenotypic heterogeneity of SHANK3 causing autism and Shank3 mutant mice." Mol Autism 5: 30.

2a) PYC-002 upregulates SHANK3 protein in key brain regions following a single safe and well-tolerated dose

Up to 2-fold increase in SHANK3 protein expression in key brain regions implicated in PMS

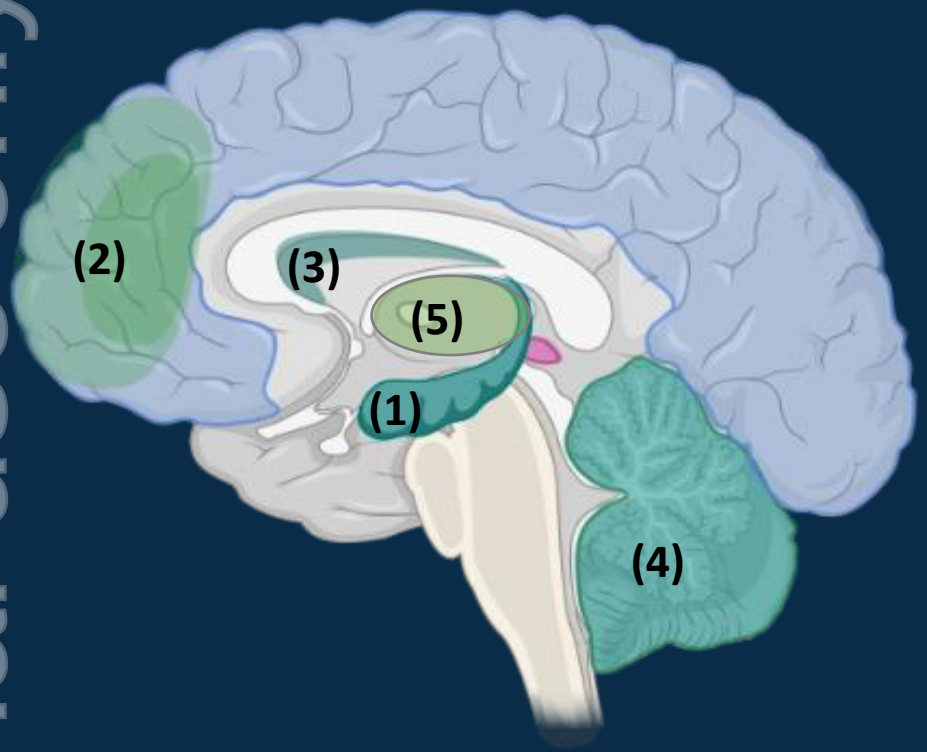
Achieved with a dose that is ~4x lower than the NOAEL

Total SHANK3 protein



1. SHANK3 expression in wild-type Sprague Dawley rats with and without treatment with PYC-002. Rats received a single intrathecal dose of vehicle control or PYC-002 (900 µg). Assessment of SHANK3 protein levels in key brain regions was completed 14 days post-treatment (n=3 treated with PYC-002 and n=6 vehicle). Samples from thalamus were not collected as part of this study. Statistical analyses using two-way ANOVA comparing PYC-002 treated to vehicle group in each brain region.

Each of the brain regions implicated in PMS has a distinct SHANK3 protein isoform expression profile

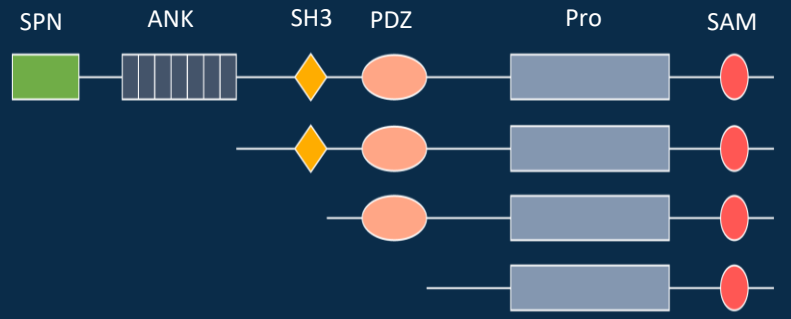


Relative expression of SHANK3 protein isoforms in the brain[1-3]

Region	Isoform A	Isoform C	Isoform D	Isoform E
1. Hippocampus	~50%	~25%	~25%	<10%
2. Prefrontal Cortex	~30%	~30%	~30%	10%
3. Striatum	~70%			30%
4. Cerebellum		~50%	~50%	
5. Thalamus	~70%		~20%	10%

Next slide

SHANK3 protein Isoform[1,2,3]



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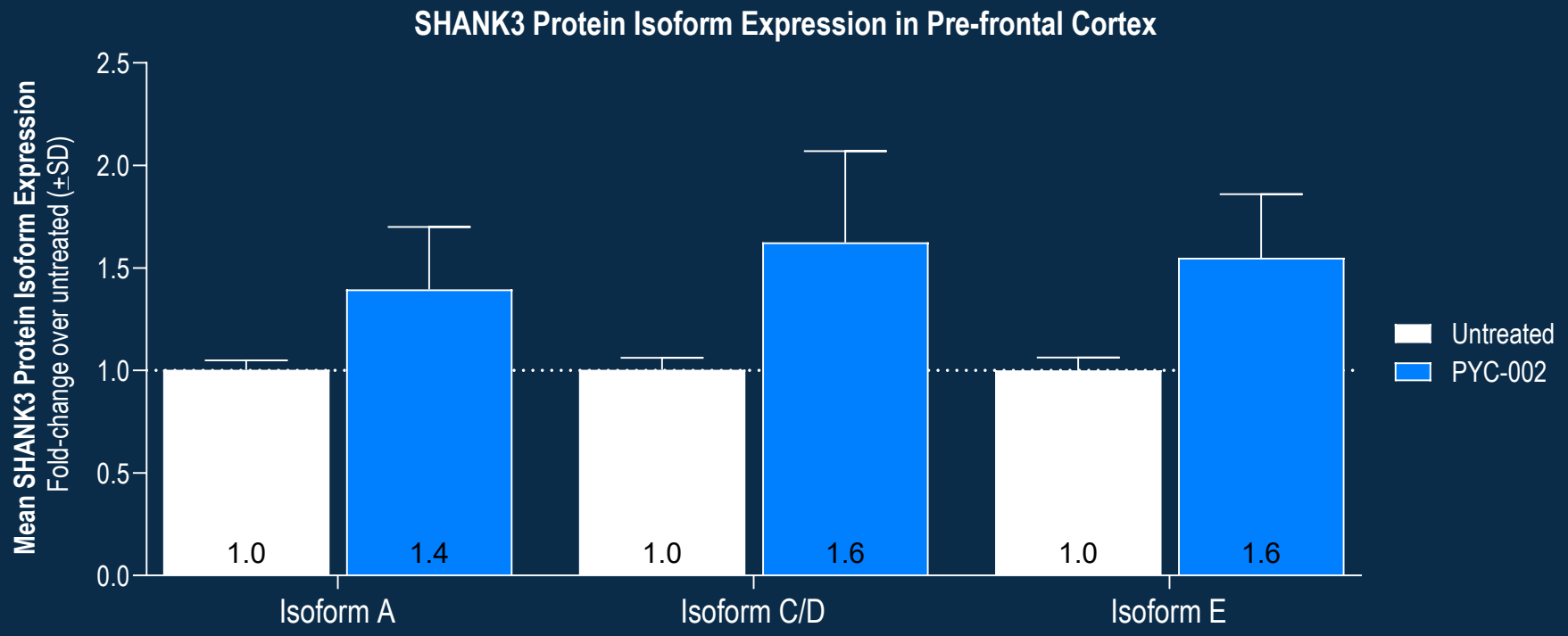
3. Wang, X., et al (2014). "Transcriptional and functional complexity of Shank3 provides a molecular framework to understand the phenotypic heterogeneity of SHANK3 causing autism and Shank3 mutant mice." Mol Autism 5: 30.

3) PYC-002 upregulates all SHANK3 protein isoforms expressed in the brain

PYC-002 increases the expression of all SHANK3 isoforms expressed in the brain[1]

An isoform agnostic mechanism of action maximizes potential for phenotypic rescue



1. SHANK3 protein isoform expression in pre-frontal cortex in rats (n=2) assessed using western blot at day 14 post-treatment. Rats received a single intrathecal dose of vehicle control or PYC-002 (900 µg).

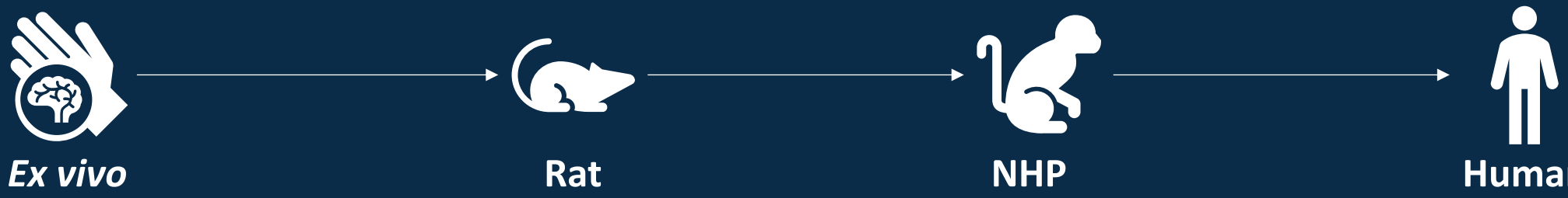
PYC-002 leverages an established clinical development path

PYC Therapeutics

For this combination of:

- Chemically modified ASO
- Administration: intrathecal
- Target cell: neurons

There is an **established path** through non-clinical species to **clinical validation**[1]



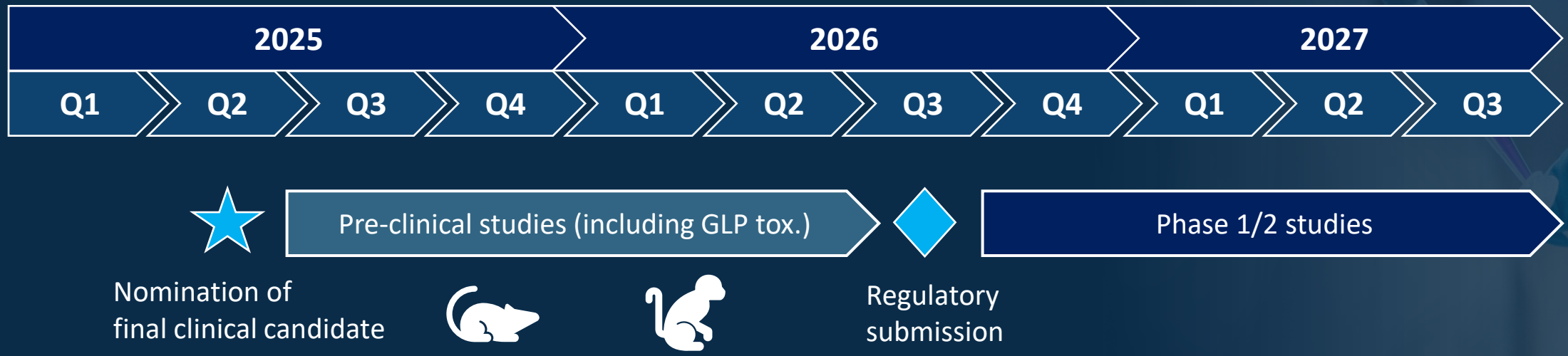
PYC-002 restores SHANK3 expression in PMS patient-derived models and has fully-integrated *in vivo* data

Established pathway

The pattern of ASO distribution and activity in the CNS of pre-clinical species translates to the human CNS[1]

1. 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.

PYC-002 will progress to human trials in 2026[1]



1. Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025