PYC Therapeutics

Life-changing science

PYC-002, a disease modifying RNA therapeutic approach to treat Phelan-McDermid syndrome

2026 PMSF Family Conference

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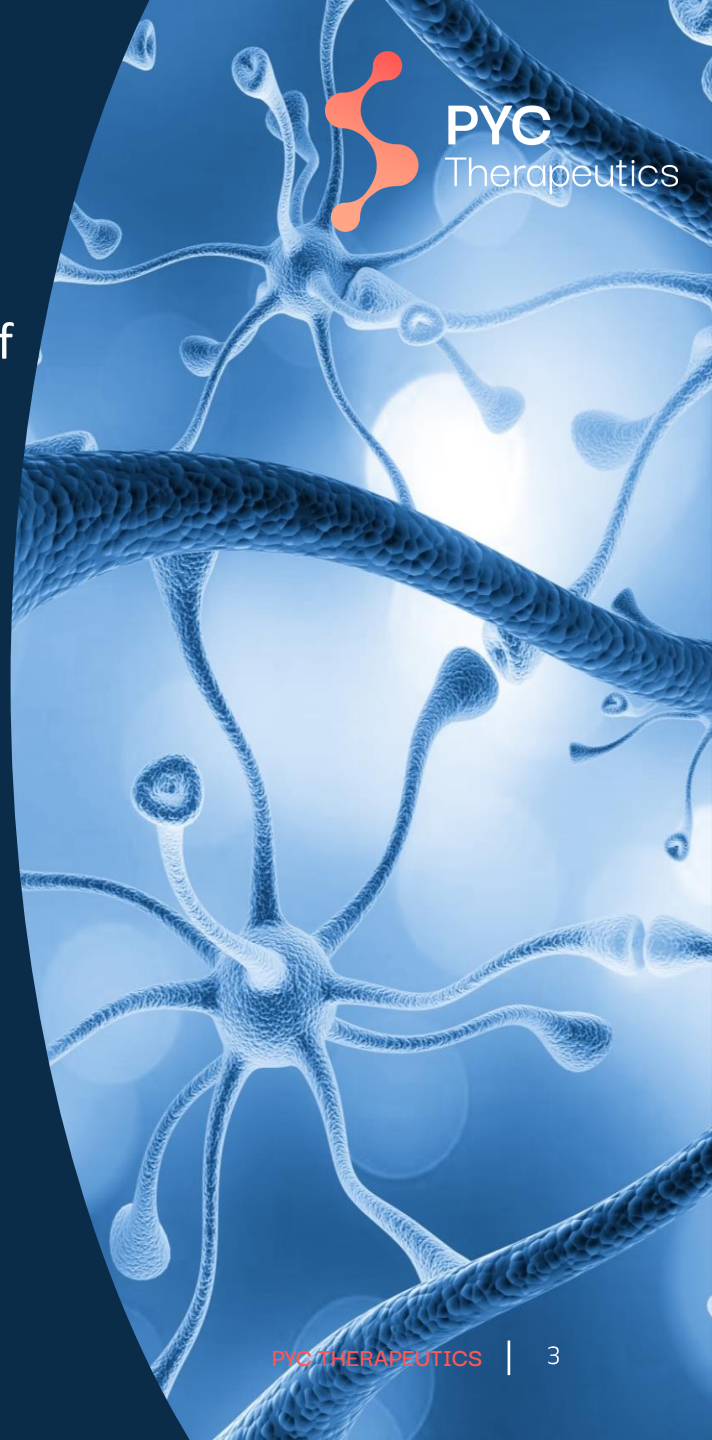
PYC-002 is a disease modifying approach that targets SHANK3 upregulation to treat Phelan-McDermid syndrome

- PYC is developing PYC-002, an antisense oligonucleotide for the treatment of Phelan-McDermid syndrome (PMS).
- PYC-002 is designed to target the underlying cause of PMS by increasing SHANK3 expression towards healthy levels.
- By restoring SHANK3, our goal is to help rebuild neuronal connections and improve communication between brain cells.
- The drug is administered via a lower back (IT) injection to deliver the medicine to the brain.
- PYC-002 is currently in the IND-enabling stage, with a natural history study launching in Q4 2026 and first clinical trials planned to begin in 2027.#



 # Timelines are estimated and may change as studies progress

PYC-002 targeting the root cause of PMS to restore neuronal structure and improve connection between brain cells

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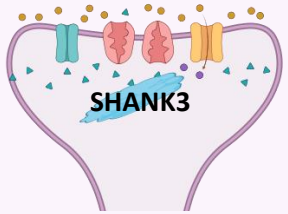
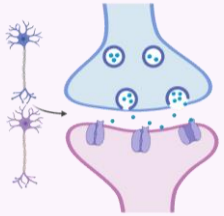
PMS BIOLOGY: WHAT HAPPENS

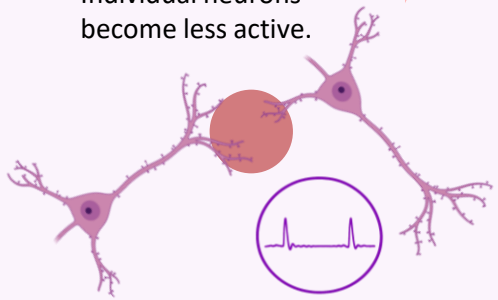
1 Reduced SHANK3
SHANK3 helps brain cells build and maintain healthy connections.



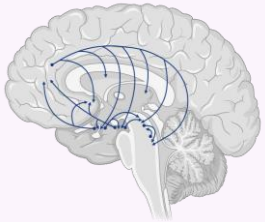
2 Fewer healthy connections
Brain cells are less well connected.



3 Reduced brain cell activity
Individual neurons become less active.



4 Less effective communication
Neural networks communicate less effectivity.



5 Challenges in daily life
Impaired learning, communication and behavioral challenges.

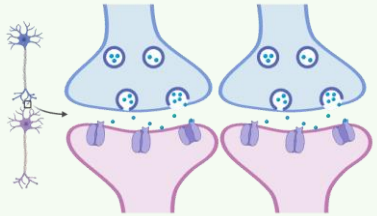
Learning Communication Behavior

HOW PYC-002 IS DESIGNED TO HELP

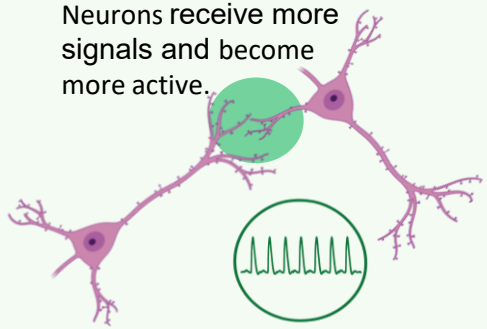
PYC-002 is designed to restore SHANK3 – the underlying biology of PMS.

1 Increase SHANK3
PYC-002 is designed to increase the cell's own SHANK3 protein.

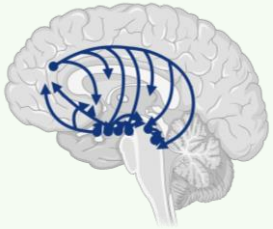
2 Restore brain cell connections
More SHNAK3 helps rebuild and strength connection.



3 Restore brain cell activity
Neurons receive more signals and become more active.



4 Improve communication between brain cells
Neural networks communicate more effectively.



Potential to improve the symptoms of PMS

By targeting the root cause of PMS, PYC-002 has the potential to be a disease-modifying therapy.

PYC-002 is a precision ASO designed to restore SHANK3

What is an ASO?

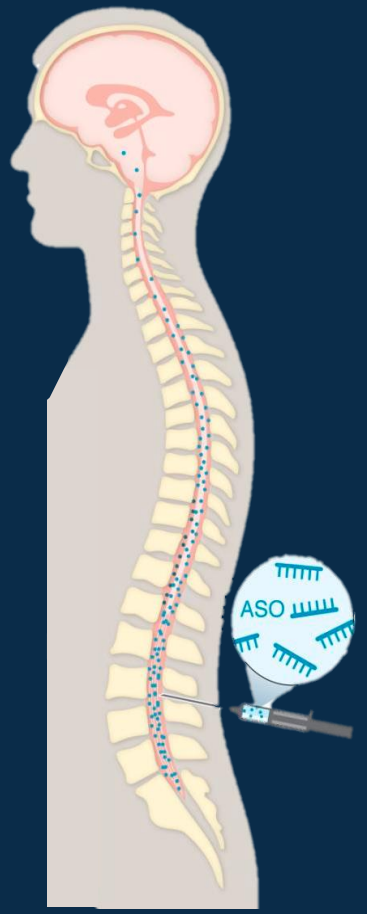
An ASO is synthetic, short strings of RNA/DNA designed to target the disease at the RNA level—the direct middle step between our DNA blueprint and the protein itself.

- Designed to be highly specific to target
- Optimized for stability to support durable benefits
- Several ASO drugs are already approved and have been used in the clinic

Why this approach?

- **Specifically target SHANK3 – the root cause of PMS**
- **Uses the cell's good copy of the SHANK3 gene to make more SHANK3 protein**
- **Maintains the cell's natural control and balance**
- **Designed to increase SHANK3 where it is needed**
- **Built on a clinically validated ASO technology**

PYC-002 is delivered by intrathecal (IT) injection, allowing it to reach target brain regions to restore SHANK3 towards healthy levels



What is an IT injection?

A small amount of drug is gently injected into the cerebrospinal fluid through the lower back.

Why IT injection

Allows the transport and delivery of the drug to the brain for an efficient targeting of SHANK3 in neurons.

Our goal

To deliver the right amount of drug to the right place, to help make the biggest possible difference.

Safety is our priority

IT injection are commonly used in patients for several approved ASOs (>10 years) and late-stage clinical studies; and are generally considered safe.

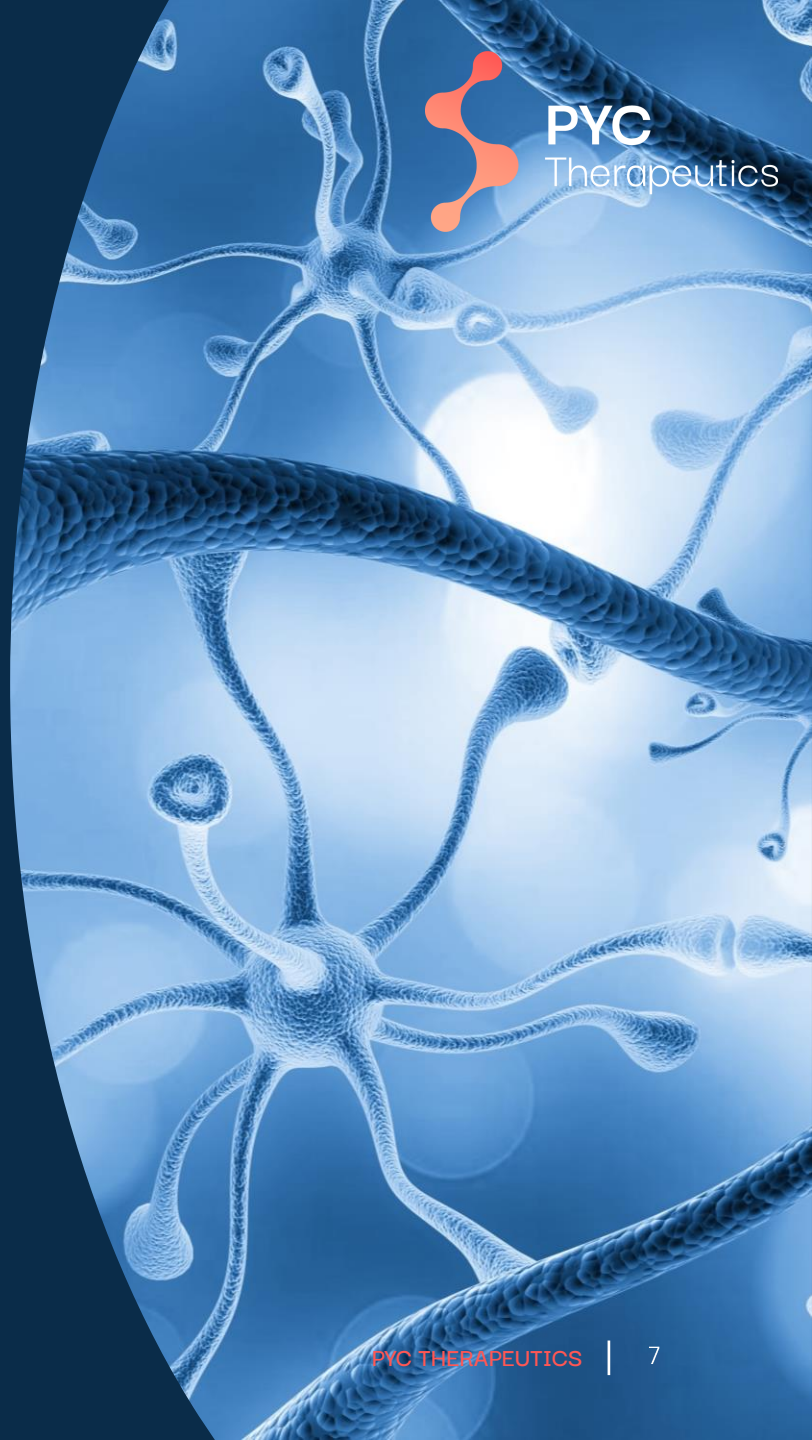
How often will the drug be given?

Intrathecal delivery of ASOs has supported durable brain drug exposure. Dosing is given a few times per year (as determined by the study).

Image adapted from Summer, CJ., et al (2024). “The expanding application of antisense oligonucleotides to neurodegenerative diseases” **J Clin Invest**

Encouraging evidence in pre-clinical studies supports PYC-002 moving towards clinical studies

- In studies using PMS patient-derived cells, PYC-002 restored SHANK3 protein expression toward healthy levels; and
- Restoring SHANK3 protein helps brain cells form healthier connections and communicate more effectively; and
- In animal studies, PYC-002 reached the target brain cells and increased SHANK3 protein at well-tolerated doses.



Preclinical studies support the potential of PYC-002 to address the underlying cause of PMS

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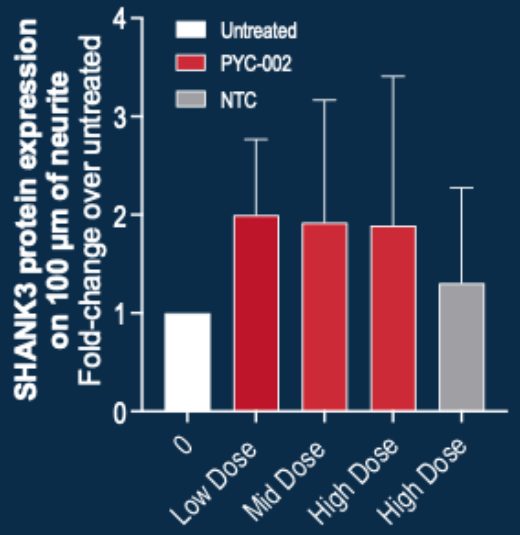
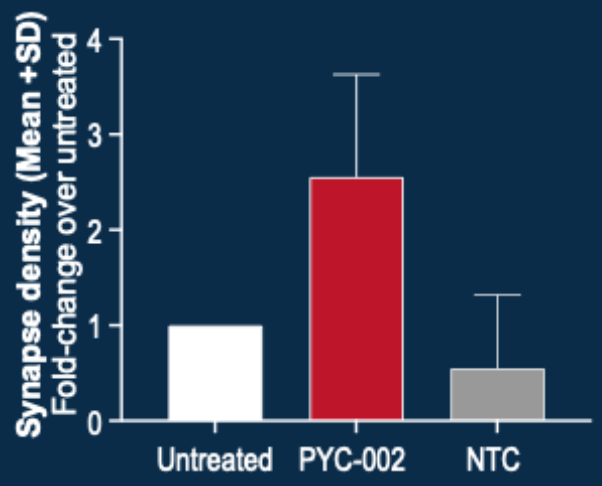
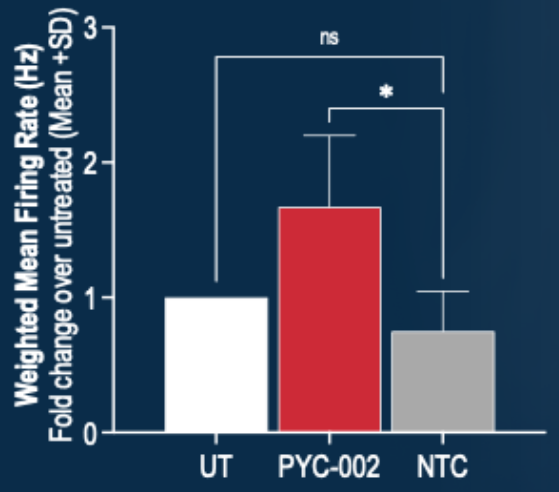
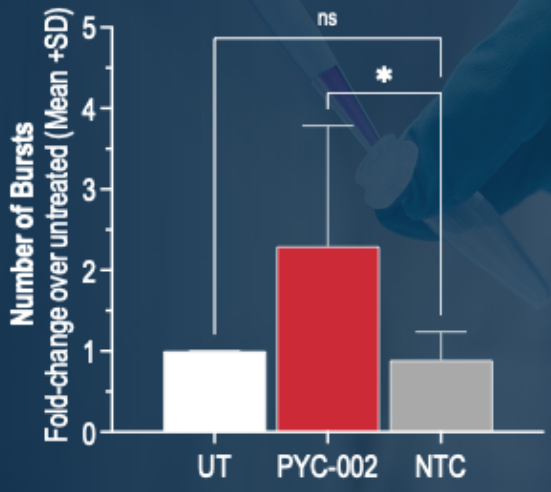
1. SHANK3 protein
2. Neuronal connections
3. Neuronal activity
4. Neuronal communication









- SHANK3 protein increase
- Rebuilds connections between brain cells
- More brain cells are active
- Stronger communication between neurons

Each plot represents the effect in one or more PMS patient-derived induced pluripotent cells (iPSCs) glutamatergic neurons on the parameter measured treated gymnotically with vehicle (untreated, white bars), PYC-002 (red bars) or with a non-targeting control ASO (NTC gray bars) for 21 days for protein and synapse density and for 28 days for Weighted Mean Firing rate and number of bursts. Dose # are indicated when different doses were tested and matched in the NTC group. Each bar represents the mean + standard deviation (SD) of 2, 2, 3 and 3 biological replicates (N), respectively in plots from left to right. Each N is the representative of the mean of 5-12, 3-15, 4 and 4 technical replicates, respectively in plots from left to right. SHANK3 on neurite and synapse density were assessed by high content imaging (HCI), Weighted Mean Firing Rate and number of burst by multi-electrode array (MEA) assay. Significance against the NTC group was calculated using Kruskal-Wallis and Dunnet test. ns = non-significance; *p<0.05.

More details at poster #21

Restoring SHANK3 protein helps patient-derived brain cells communicate more effectively

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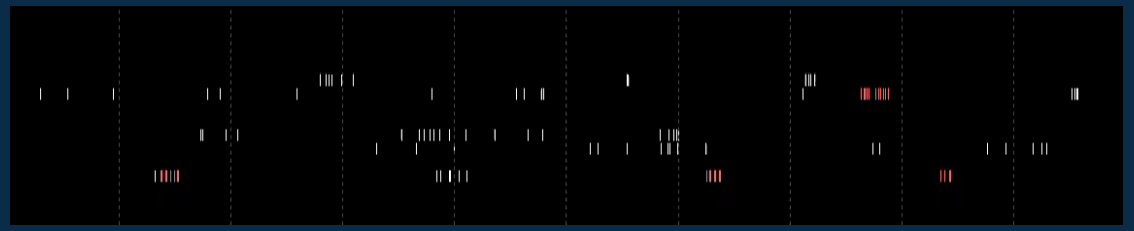
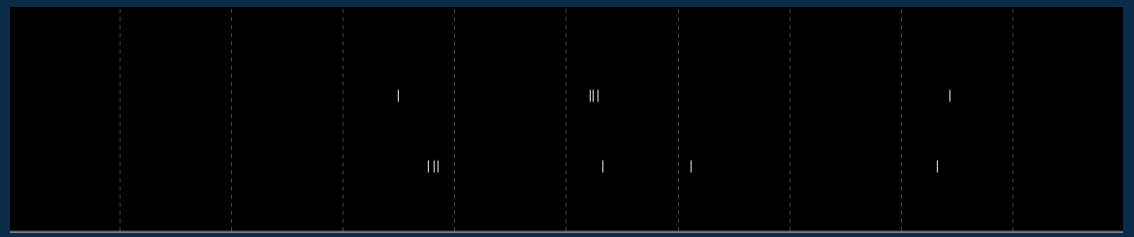
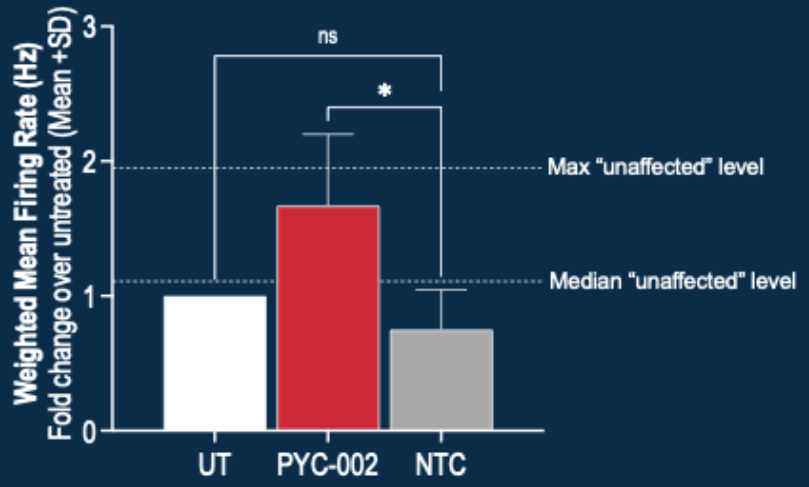
Untreated Healthy control-derived neurons

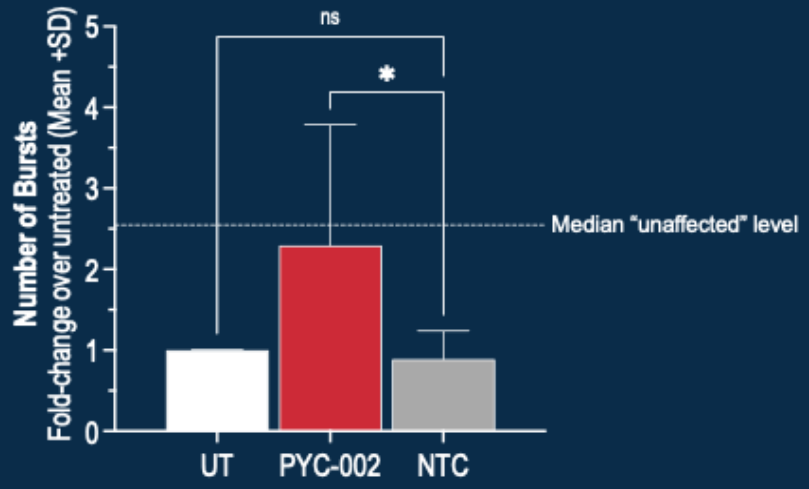


Untreated PMS patient-derived neurons



PYC-002 + PMS patient-derived neurons

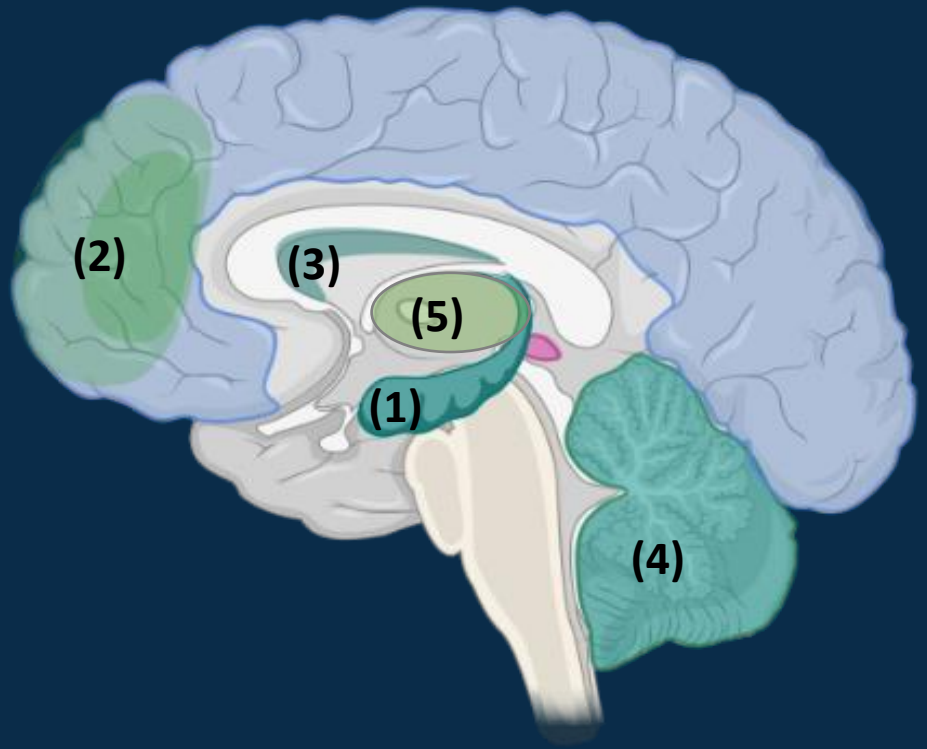




The upper plot shows the mean+SD of weighted mean firing rate (Hz), expressed as fold-change relative to untreated samples (white bar) measured by Multiple-Electrode Array (MEA) assay after 28 days post-gymnotic-treatment with PYC-002 (red bar) or non-targeting control (NTC, grey bar). Bars represent three biological replicates of iPSC-derived glutamatergic neurons from three different patients with PMS.
The lower plot shows the mean+SD of Number of Bursts fold-change over untreated samples (white bar) measured by MEA assay after 28 days post-gymnotic-treatment with PYC-002 (red bar) or NTC (grey bar). Bars represent three biological replicates of iPSC-derived glutamatergic neurons from three different patients with PMS. The median and maximum (Max) of unaffected levels were calculated using iPSCs glutamatergic neurons derived from eight unaffected lines. These values were compared as fold-change with untreated PMS measurements (white bar). Significance against the NTC group was calculated using Kruskal-Wallis and Dunnet test. ns = non-significance; *p<0.05.

More details at poster #21

Deficient SHANK3 levels in multiple brain regions disrupts neuronal communication contributing to the PMS phenotype[1-3]



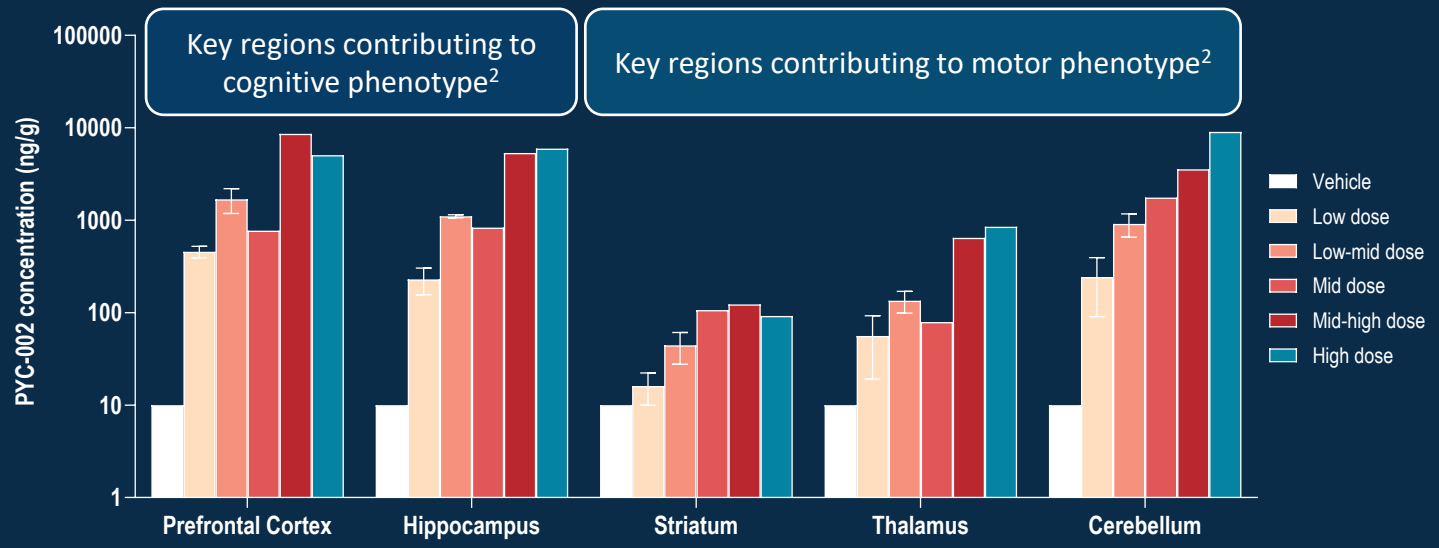
Brain regions implicated in PMS and impact on phenotype

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

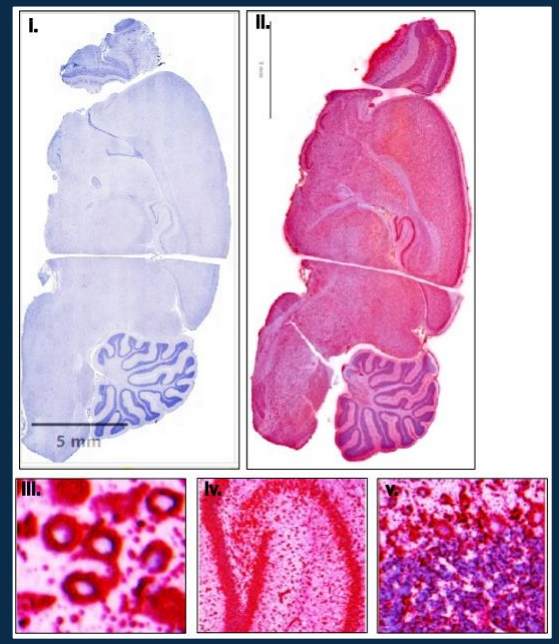
1. Kang, H. J., Y. I. et al (2011). "Spatio-temporal transcriptome of the human brain." Nature **478**(7370): 483-489.
2. Bouquier, N., et al (2022). "The Shank3(Venus/Venus) knock in mouse enables isoform-specific functional studies of Shank3a." Front Neurosci 16: 1081010.
3. Wang, X., et al (2014). "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.

PYC-002 distributes to all key brain regions implicated in PMS at safe and well-tolerated doses[1]

Concentration of PYC-002 in the NHP brain after single dose[2]



Distribution of PYC-002 in the rat brain after single dose[3]



- PYC-002 demonstrates broad distribution to regions of the NHP and rat 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

1. Refer ASX Announcement 13 October 2025
2. 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. (n=3 for vehicle, low dose, low-mid dose, n=1 for mid dose, mid-high dose and high dose).
3. 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

PYC-002 increases SHANK3 protein at safe and well-tolerated doses

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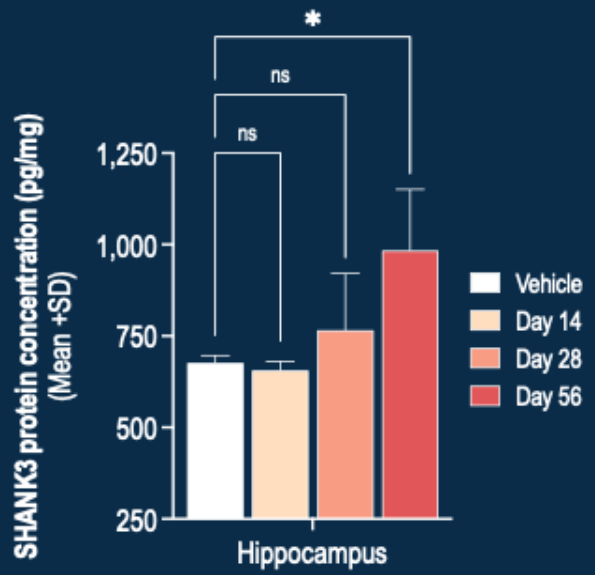
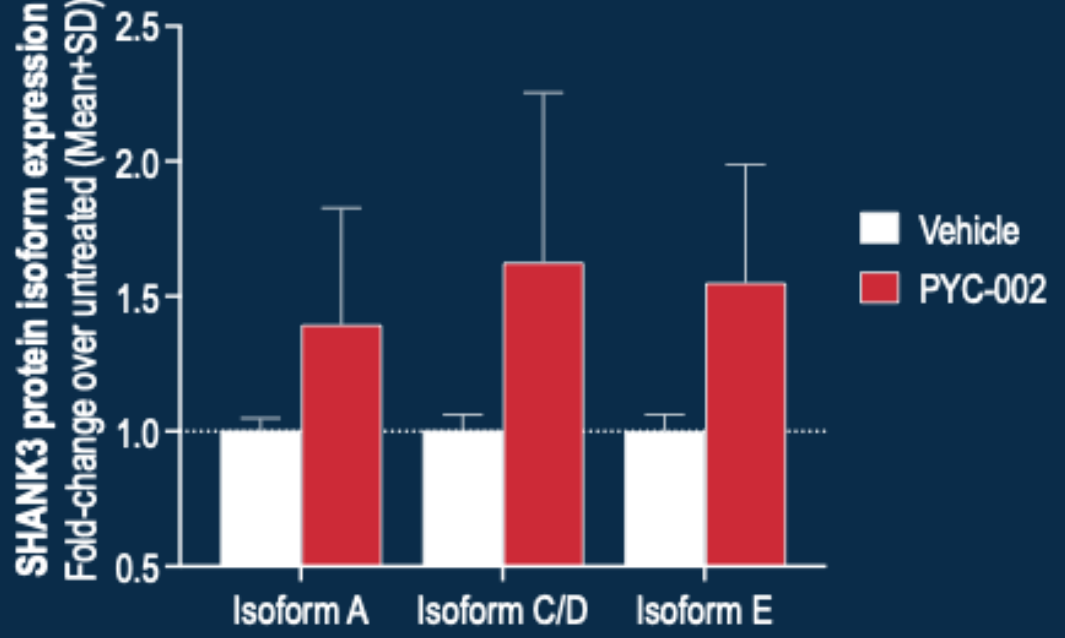
SHANK3 protein increased up to 1.5-fold in monkey brain following a single IT injection[1]



A single dose of PYC-002 increases SHANK3 protein up to 2-fold in rat brains[2]



1. Concentration of SAHNK3 protein (pg protein per mg tissue, mean ± SD) in brain tissue samples from Cynomolgus monkeys (Macaca fascicularis) 15, 28, 56 days after treatment with a single intrathecal injection, assessed by ELISA. (n=3 for vehicle, n=2 for day 14, n=4 for day 28 and n=4 for day 56). Significance tested with one-way ANOVA and Dunnet's, ns= non-significant, *= $p< 0.05$
2. 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.

Where we are today – and what's next

PYC Therapeutics

IND-enabling study
In progress

Start NHS enrollment
~Q4 2026

Start MAD treatment
~Q4 2027

Start OLE/LTE
~2H 2028

IND-ENABLING STUDIES

Completing key safety studies and preparing the information needed to apply to start human trials

NHS (OBSERVATIONAL PERIOD)

- *Natural history study to better understand PMS over time*
- *Establish each participant's own baseline before treatment*
- *Help us better measure treatment benefits*

INTERVENTIONAL (MAD)

Multiple ascending dose study to evaluate safety, PK, and how the treatment is working

OLE/LTE (LONG TERM EXTENSION)

Open-label extension for ongoing treatment and long-term safety and efficacy monitory

WHEN WILL EFFICACY BE MEASURED	6-MONTH EFFICACY	LONG-TERM EFFICACY
	Primary evaluation of how the treatment is working	*Assessment of duration of benefits and long-term outcomes*
	~6-months after first-dose	*>12 months after first dose*

Criteria: *PMS diagnosis with SHANK3 variant, Class I or Class II deletion, age 2-16 years old*

Timelines are estimated and may change as studies progress. We will share updates along the way

HIPPOCAMPUS An Observational Study

History of **P**rogression in **P**helan-McDermid: **O**bservational **C**haracterization and **A**ssessment of **M**apped **P**henotypes **U**nderlying **S**HANK3 Deficiency

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Understanding PMS today to inform future clinical studies

Natural History Study

Follow-up every 6 months

Baseline

6 months

12 months

Potential follow-up for up to 24 months

Future PYC-002 clinical studies

Eligibility

- Age 2-16 years
- Confirmed PMS
- English questionnaires (completed by participant or care givers)

Key Endpoint Analysis

- Cognition
- Language and Communication
- Behavior
- Biomarkers

Study sites

Study sites are in the US.
To be announced.

Study initiation

Q4 2026

More information will be shared as the study opens and updates will be provided.

PYC-002: an RNA drug candidate for the treatment of Phelan-McDermid syndrome

Dulce B. Vargas-Landin, Abbie Francis, Sasiwimon "Fern" Utama, Donna Bezner, Wontaek Oh, Priyanka Sain, Rungtiwa Nutalai, Tracy Chai, Tanisha Verma, Dean De Alvis, Linda de Castro, Laura Florez, Philipp Bayer, Alexander de Bont, Jeremy Ash, George Mitchell, Adam D. Martin, Maria Kerfoot, Janya Grainok

All authors from PYC Therapeutics, Harry Perkins Institute of Medical Research, Nedlands, Western Australia, Australia

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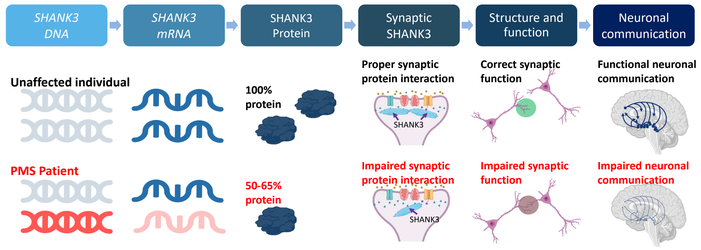
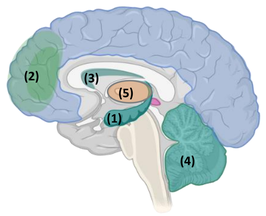
pmsf Family CONFERENCE

Understanding the disease

Phelan-McDermid syndrome (PMS) is a severe neurodevelopmental disorder caused by the deletion of, or a pathogenic sequence variant in, one copy of the *SHANK3* gene leading to an insufficiency of the SHANK3 protein[1]. SHANK3 is a scaffolding protein critical for the structure, integrity and function of neuronal communication across the brain.



SHANK3 protein is expressed in brain regions essential for memory and cognition, such as the hippocampus and prefrontal cortex, where alternative SHANK3 protein forms, called isoforms, are present[2].

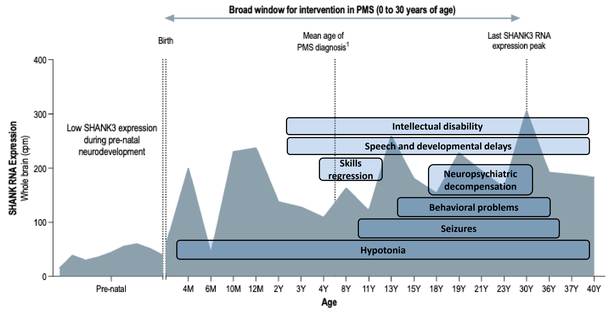


Relative expression of SHANK3 protein isoforms in the brain[2,3]

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%

SHANK3 protein Isoform[2,3]

SHANK3 postnatal and lifelong expression[3] provides a broad window for therapeutic intervention, from early childhood to adulthood.

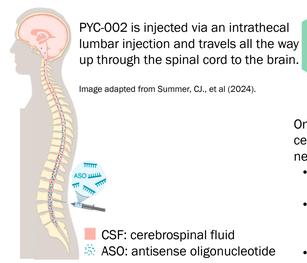


The plot shows in a gray shade the *SHANK3* RNA expression levels in the brain[3] throughout the life of a person, highlighting its postnatal expression and changes through development. Key symptoms in PMS[4] are overlaid with their approximate time of onset.

PYC-002, an RNA drug candidate for PMS

How does PYC-002 work?

PYC-002 Delivery → *SHANK3* mRNA → SHANK3 Protein → Synaptic SHANK3 → Synaptic function → Neuronal communication



Once in the brain, PYC-002 enters cells called neurons. Inside the neurons, PYC-002:

- does NOT modify the DNA of the patient
- binds to the present *SHANK3* RNA to increase its protein production
- its effect is NOT permanent

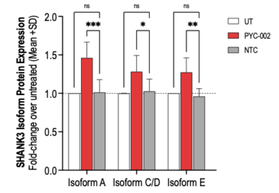
What is an ASO?

An ASO is a synthetic, short string of genetic material (DNA/RNA) designed to target and modify specific messages in our cells (RNA). Because they work on temporary cellular messages, their effects are not permanent. ASOs can act like a dimmer switch, either turning up or turning down their target protein products.[4] Thanks to their safety and effectiveness, many ASO drug candidates are in development to treat rare pediatric neurodevelopmental disorders, such as Dravet syndrome.[4]

Does PYC-002 work?

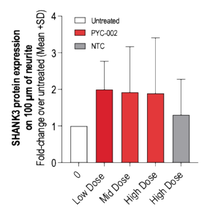
Increased protein towards healthy levels keeping isoform protein balance

Patient A	Untreated	PYC-002	NT Control
Isoform A	~34%	~38%	~34%
Isoform C/D	~41%	~41%	~41%
Isoform E	~25%	~20%	~25%



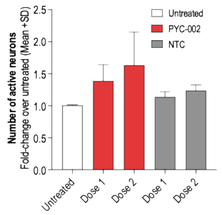
PYC-002 increases SHANK3 protein and its brain isoforms, maintaining their natural expression ratio.

Increased SHANK3 protein localized at synapses



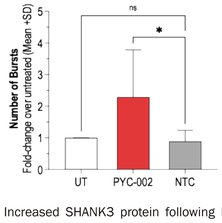
The SHANK3 proteins produced by PYC-002 localize to the part of the synapse where neurons receive signals, called the post-synaptic site.

Improved synaptic function



PYC-002's SHANK3 protein increase is reflected in a higher numbers of actively signaling neurons.

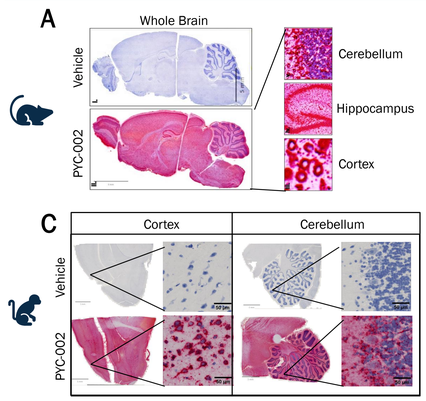
Improved neuronal communication



Increased SHANK3 protein following PYC-002 treatment enhances electrical activity across neurons thereby improved neuronal communications.

Each plot represents the effect in PMS patient-derived induced pluripotent cells (iPSCs) glutamatergic neurons on the parameter measured treated gymnotically with vehicle (untreated, white bars), PYC-002 (red bars) or with a non-targeting control ASO (NTC gray bars) for 21 days for protein assays and for 23-29 days for functional assays. Dose # are indicated when different doses were tested and matched in the NTC group. Each bar represents the mean + standard deviation (SD) of 3, 2, 4 and 3 biological replicates (N), respectively in plots from left to right. Each N is the representative of the mean of 4, 5-12, 5-6 and 4 technical replicates, respectively in plots from left to right. Protein isoform was evaluated by Western Blot and significance against the NTC group was calculated using two-way ANOVA. ns= non-significance; *p<0.05, **p<0.01, ***p<0.001. SHANK3 on neurite was evaluated by high content imaging (HCI) and Number of active neurons by Ca+ Oscillation assay. Number of Bursts was evaluated by multi-electrode array (MEA) assay and significance against the NTC group was calculated using Kruskal-Wallis and Dunnet test. ns = non-significance; *p<0.05. .

Where does PYC-002 go in the brain?

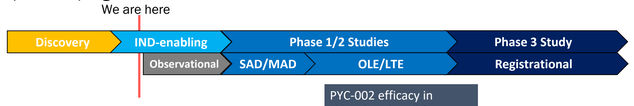


- ✓ PYC-002 shows broad and even distribution in rat and monkey brains (A and C).
- ✓ A single intrathecal injection of PYC-002 increases expression of several SHANK3 isoforms in rat brain after 14 days post-treatment (B).
- ✓ A single intrathecal injection of PYC-002 significantly increases the expression of SHANK3 in the hippocampus of monkeys at Day 56 (D), which is enabled by an effective and sustained ASO concentration (E).

Panels A and C show the distribution of PYC-002 in brains from adult Sprague-Dawley rats (*Rattus norvegicus*) and cynomolgus monkeys (*Macaca fascicularis*) treated with vehicle control or low dose PYC-002 for 14 days in rats, or high dose in monkeys for 28 days. Samples are stained with in situ hybridization probe targeting PYC-002 ASO (red) and counter-stained with hematoxylin (blue). Panel B shows SHANK3 protein isoform expression (mean + SD) in prefrontal cortex of rats (n=2 per group) assessed using western blot at day 14 post-treatment. Panel D shows SHANK3 protein increase (mean +SD) in hippocampus of cynomolgus monkeys (n=3-4 per timepoint/treatment group) assessed by ELISA at day 14, 28 or 56 post-treatment. Significance of the effect of treatment against vehicle was tested with one-way ANOVA with Dunnett's. (* *p-value* < 0.05; ns non-significant) Panel E shows the concentration of PYC-002 (ng drug per g tissue, mean + SD) in hippocampus tissue samples (n=4) from cynomolgus monkeys 56 days after treatment, assessed by hy-ELISA.

What is next for PYC-002?

PYC-002 plans to progress to human trials in 2027#



PYC-002 efficacy in clinical trials will focus on:

- Cognition
- Language
- Behavior

PYC is starting an observational study to characterize the PMS disease phenotype

For more information scan the QR code!

#Subject to regulatory feedback and/or change.
SAD= Single Ascending Dose
MAD= Multiple Ascending Dose
OLE= Open label extension
LTE= Long-term extension

Is PYC-002 safe?

PYC-002 uses a drug class chemistry and route of administration that have been used in the clinic for >10 years in another pediatric disorder, proving their safety and efficacy. To evaluate the safety profile of PYC-002, exploratory (non-GLP) studies in juvenile rats and monkeys have been performed and resulted in no adverse findings related to the PYC-002 treatment at the end of the study. More safety studies are currently ongoing to support our clinical trial design.

Juvenile Sprague-Dawley Rat (*Rattus norvegicus*), 56 days after first injection

Dose Regimen	Dose	Number of animals
Single	Low	6
Single	Mid-high	6
Single	High	4
Single	Very High	2
Double	Low	6
Double	Mid-high	6
Double	High	6

Juvenile Cynomolgus Monkey (*Macaca fascicularis*), 85 days after first injection

Dose Regimen	Dose	Number of animals
Single	Mid	3
Single	Very High	1
Double	Mid-High	3
Double	High	2

All animals were dosed via intrathecal lumbar injection.

Conclusion

- PYC-002 drug candidate targets the root cause of Phelan-McDermid syndrome, the insufficiency of SHANK3 protein.
- PYC's mutation agnostic PYC-002 drug candidate:
  - increases SHANK3 protein expression level and maintains the balance of SHANK3 protein isoforms
  - increases the synaptic SHANK3 protein, needed for neuronal communication
  - improves synaptic structure and function in human iPSC-derived PMS neurons
  - improves neuronal communication in human iPSC-derived PMS neurons
- PYC-002 shows a broad distribution throughout the brain including in disease-relevant regions in rats and monkeys after single intrathecal injection.
- PYC-002 has a favorable safety profile in rats and monkeys following single and repeat intrathecal administration.
- A single, safe dose of PYC-002 upregulated multiple natural isoforms of SHANK3 critical for neuronal function in rats and PYC-002 caused upregulation in the hippocampus of monkeys.
- PYC is progressing through preclinical testing and is anticipated to enter human clinical trials in 2027#.

References

1. Yin, Rui et al. "Phenome-wide profiling identifies genotype-phenotype associations in Phelan-McDermid syndrome using family-sourced data from an international registry." *Molecular autism* vol. 15,1 40. 30 Sep. 2024, doi:10.1186/s13229-024-00619z
2. Bouquier, Nathalie et al. "The Shank3$^{Venus/Venus}$knock in mouse enables isoform-specific functional studies of Shank3a." *Frontiers in neuroscience* vol. 16 1081010. 8 Dec. 2022, doi:10.3389/fnins.2022.1081010
3. Kang, Hyo Jung et al. "Spatio-temporal transcriptome of the human brain." *Nature* vol. 478,7370 483-9. 26 Oct. 2011, doi:10.1038/nature10523
4. Landlust, Annemiek M et al. "Parental perspectives on Phelan-McDermid syndrome: Results of a worldwide survey." *European journal of medical genetics* vol. 66,7 (2023): 104771. doi:10.1016/j.ejmg.2023.104771
5. Hill, Sophie F, and Miriam H Meisler. "Antisense Oligonucleotide Therapy for Neurodevelopmental Disorders." *Developmental neuroscience* vol. 43,3-4 (2021): 247-252. doi:10.1159/000517686

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