PYC Therapeutics

6 June 2023

PHELAN-MCDERMID SYNDROME PRESENTATION MATERIALS FOR BIO CONFERENCE

- **PYC is currently attending BIO 2023 – one of the industry's primary business development events - in Boston**
- **The Company's presentation materials for the Central Nervous System platform and Phelan-McDermid Syndrome program are attached**
- **The Company previously released presentation materials for the conference covering PYC's ophthalmology platform and programs on 18 April 2023**

PERTH, Australia and SAN FRANCISCO, California – 6 June 2023

PYC today announced presentation materials providing an overview and highlighting pre-clinical data supporting the Company's Central Nervous System platform and Phelan-McDermid Syndrome program to be provided for partnering discussions at BIO 2023 held in Boston, 5-8 June. BIO 2023 is one of the industry's primary business development events.

A delegation of PYC's senior management will be attending the conference to discuss potential partnering and investment opportunities with industry participants.

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**[1].

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.

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

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 Chief Executive Officer of PYC Therapeutics Limited

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PYC Therapeutics

Life-changing science

Phelan-McDermid Syndrome program

June 2023

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.

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Executive Summary

- Phelan-McDermid Syndrome (PMS) is a **severe neurodevelopmental disorder** affecting 1 in every 10,000 children[1] that can cause a wide range of medical, intellectual and behavioural challenges

- PMS is caused by **haploinsufficiency of the *SHANK3*** gene

- There are **no available therapies** for patients with PMS today

- The optimal therapy for PMS will:
  - target the underlying *SHANK3* deficiency
  - have a broad, even and deep distribution to the affected neurons in the brain
  - maintain the physiological expression profile of *SHANK3* within these cells
  - leave control over total SHANK3 protein expression regulated by the cell (overexpression also induces a phenotype)

- PYC has designed an RNA therapeutic that meets this profile in PMS – the candidate is:
  - capable of restoring *SHANK3* gene expression to wild-type levels[2]
  - able to reach the cells affected with clinical and commercial 'proof of concept' established for this modality/route of administration/target cell combination
  - set to enter clinical development in ~18 months time

1. PMS Foundation https://pmsf.org/about-pms/
2. >2-fold increase in SHANK3 protein levels in SH-SY5Y cells following treatment with RNA candidate

There is a pressing need for a disease-modifying approach in Phelan-McDermid Syndrome

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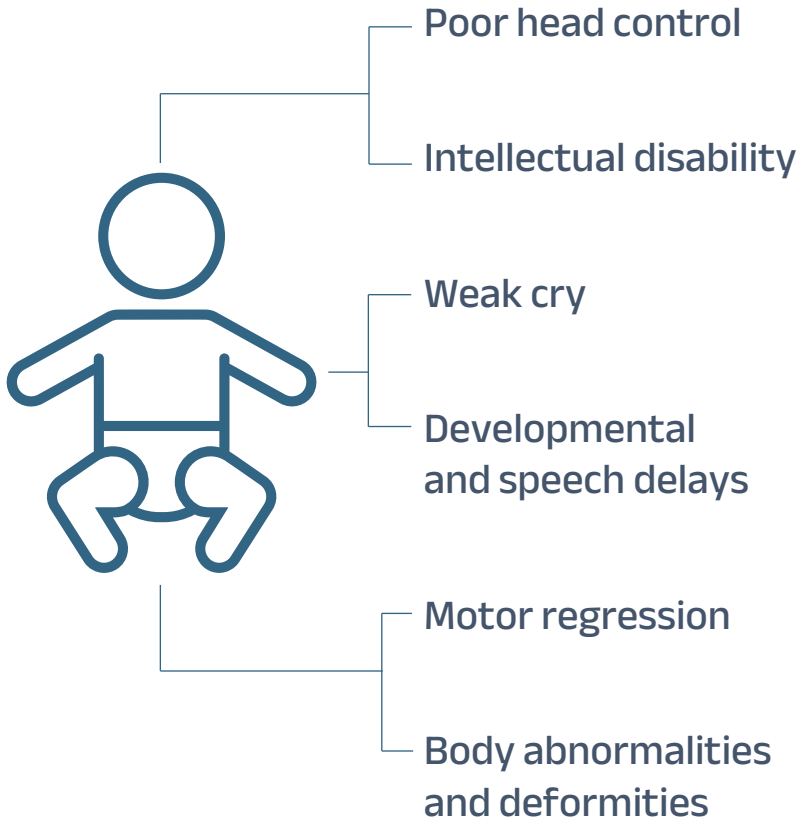
Phelan-McDermid Syndrome (PMS):

- Is a rare and severe neurodevelopmental disorder causing life-long disability
- ~28,000 addressable patients in the Western World[1-3]
- Is caused by a mutation in (or deletion of) one copy of the *SHANK3* gene
- Represents a major unmet patient need with no disease-modifying therapies available for patients

Signs and symptoms of PMS



1. Cochoy DM, et al. Phenotypic and functional analysis of SHANK3 stop mutations identified in individuals with ASD and/or ID. Mol. Autism. 2015;6(23) doi: 10.1186/s13229-015-0020-5
2. Zeidan J, et al. Global prevalence of autism: A systematic review update. Autism Research. 2022;1–13. doi: 10.1002/aur.2696
3. https://pmsf.org/about-pms/

PYC has designed an RNA therapy that addresses the underlying cause of PMS

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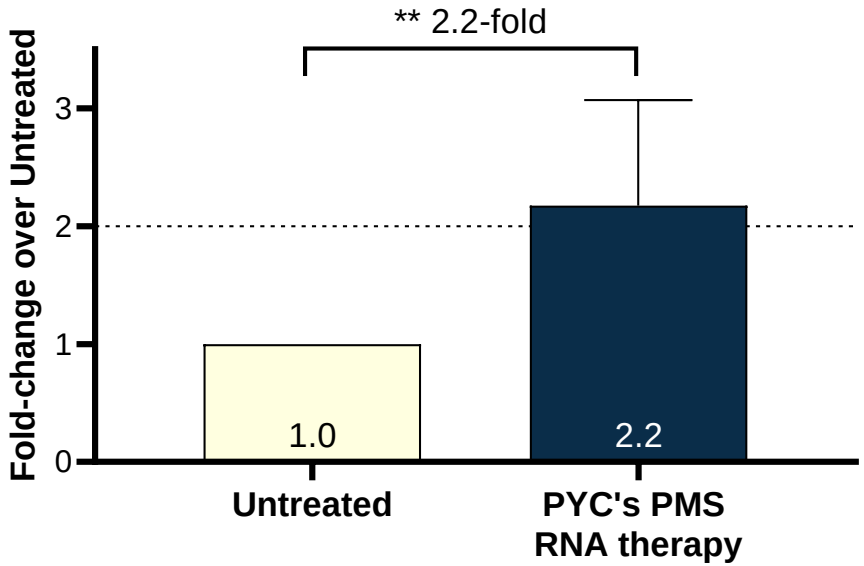
Phelan McDermid Syndrome (PMS) is caused by insufficient (~50%) expression of SHANK3 protein in neurons

PYC has designed an RNA drug candidate capable of increasing SHANK3 protein expression >2-fold in a neuronal cell line[1]



Theoretical increase required to restore gene expression in a haploinsufficiency to wild-type (physiological) levels[2]

*Normalised fold-change in expression of SHANK3 protein assessed by western blotting in an SH-SY5Y cell line. SHANK3 protein expression is shown relative to the level in transfection control cells (a transfection control without an RNA therapeutic). Data are presented as mean +/- Standard Deviation (n = 3). ** = statistical significance of p≤0.01 calculated as two-way unpaired t-test between treatment and transfection control.*

Restoring *SHANK3* expression to physiological levels holds the promise of disease-modifying impact in PMS patients

1. Refer ASX announcement 27 September 2022
2. Assumes a 50% reduction in gene expression in a haploinsufficiency

The RNA therapy rescues the underlying gene expression that causes PMS by increasing translation from the healthy allele

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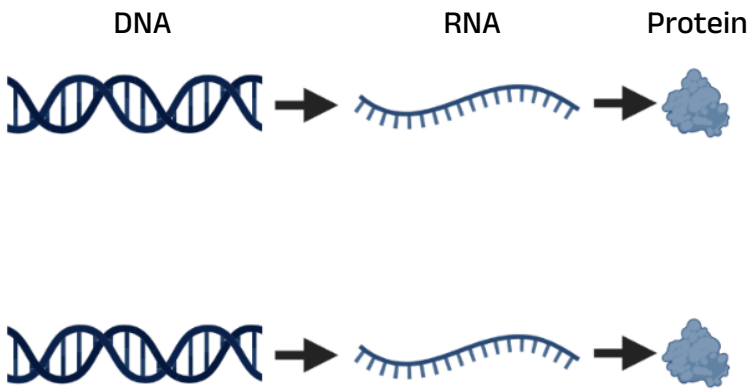
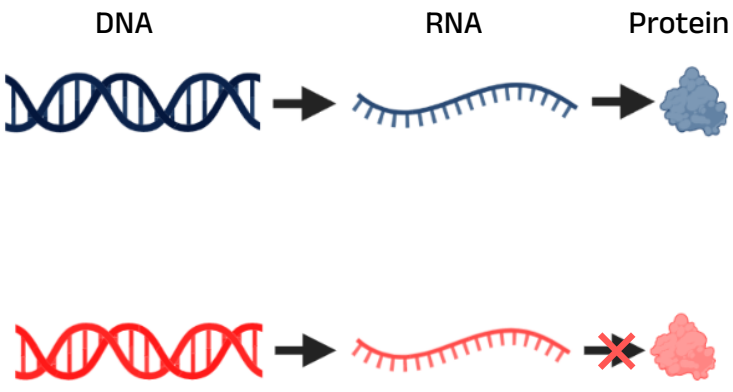
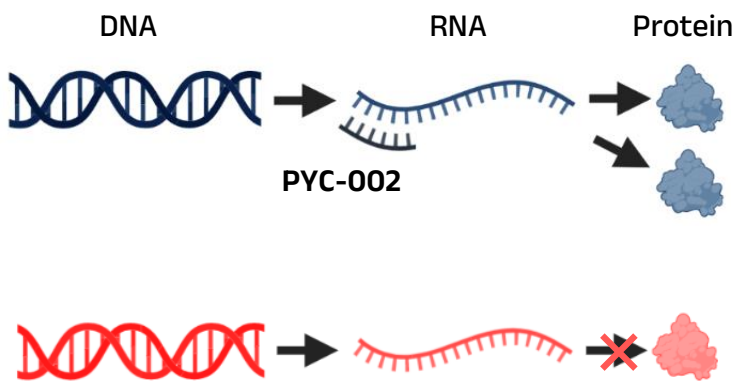
PYC's RNA therapy for PMS (known as 'PYC-002') restores SHANK3 protein expression from the remaining healthy allele

Unaffected individual	PMS patient[1]	PMS patient treated with PYC-002[2]
		
Functional *SHANK3* expression = 100% 2 'healthy' copies of *SHANK3* results in sufficient SHANK3 protein expression	**Functional *SHANK3* expression = ~50-70%** Insufficient functional SHANK3 protein expression (i.e. due to loss of function mutation or deletion in one copy of the *SHANK3* gene)	**Restoration of *SHANK3* expression towards 100%** PYC-002 increases expression of the remaining 'healthy' copy of *SHANK3* to compensate for the protein insufficiency (loss of expression from the mutated allele)

1. De Rubeis S, et al. Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations. Mol Autism. 2018;9:31
2. PYC has not yet confirmed its lead candidate PYC-002

PYC has optimised two different chemistries/mechanisms of action in parallel - creating optionality in the development path

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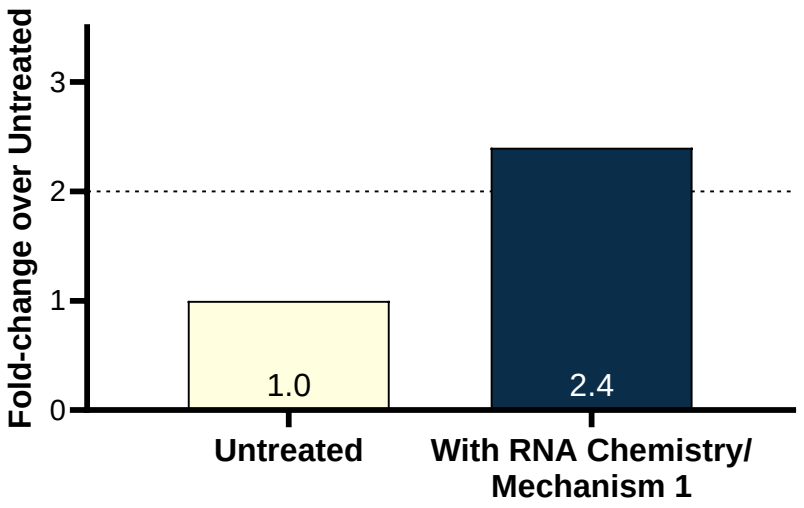
2'MOE

RNA Chemistry/Mechanism 1

Clinically validated RNA chemistry
Naked RNA drug

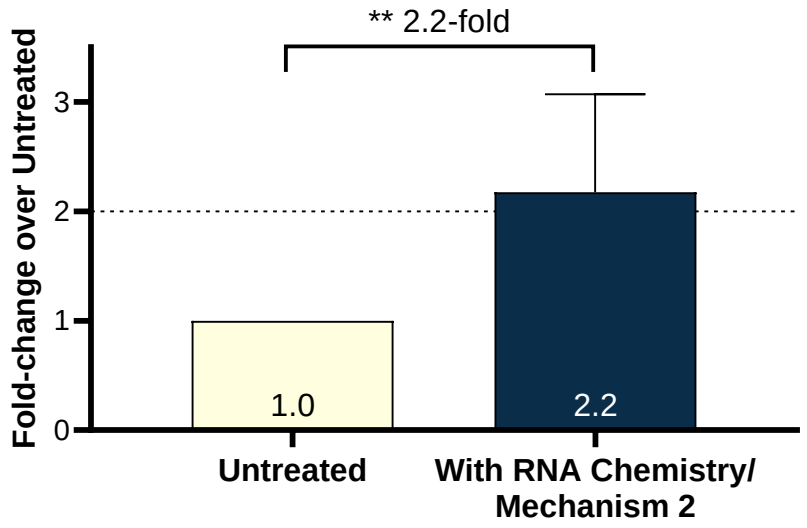


Normalised fold-change in expression of SHANK3 protein assessed by western blotting in an SH-SY5Y cell line. SHANK3 protein expression is shown relative to the level in transfection control cells (a transfection control without an RNA therapeutic). Data are presented as mean (n=1), preliminary study.

PPMO

RNA Chemistry/Mechanism 2

Next generation RNA drug conjugate
Delivery peptide improves potency



Normalised fold-change in expression of SHANK3 protein assessed by western blotting in an SH-SY5Y cell line. SHANK3 protein expression is shown relative to the level in transfection control cells (a transfection control without an RNA therapeutic). Data are presented as mean +/- Standard Deviation (n = 3).
*** = statistical significance of p≤0.01 calculated as two-way unpaired t-test between treatment and transfection control.*

>2-fold upregulation of SHANK3 protein can be achieved with either chemistry/mechanism

1. Refer ASX announcement 27 September 2022

PYC's 2′MOE RNA drug (chemistry/mechanism 1) has an established path through clinical development

For this combination of:

- Chemistry: 2′MOE PS
- Administration: intrathecal
- Target cell: neurons

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

PYC has generated PK/PD/safety data in rats → Established pathway

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

1. Jafar-Nejad P, Powers B, Soriano A, Zhao H, Norris DA, Matson J, DeBrosse-Serra B, Watson J, Narayanan P, Chun SJ, Mazur C, Kordasiewicz H, Swayze EE, Rigo F. 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. PMID: 33367834; PMCID: PMC7826274.

The *in vivo* data pack for this RNA candidate links in to this pathway and sets the program up for success in the clinic

For this combination of:

- Chemistry: 2'MOE PS
- Administration: intrathecal
- Target cell: neurons

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

PD
>2-fold upregulation of *SHANK3*

PK/PD/safety at 600 µg dose of 2'MOE oligo[2] delivered IT:
- Safe and well tolerated
- Yields a target tissue concentration of ~10,000ng/g at D7 (average across cerebellum and cortex)
- Results in target engagement of 5-30% (varies by brain region – see next page for detail)

PK/PD/safety able to be inferred from rat data[1]

PYC is currently progressing this program to first in human studies with remaining non-clinical data to be generated in 23/24 prior to IND submission

1. Jafar-Nejad P, Powers B, Soriano A, Zhao H, Norris DA, Matson J, DeBrosse-Serra B, Watson J, Narayanan P, Chun SJ, Mazur C, Kordasiewicz H, Swayze EE, Rigo F. 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. PMID: 33367834; PMCID: PMC7826274.
2. MOE oligo is a reporter designed to provide a PD read-out in rats and not the therapeutic candidate for PMS

PYC's PPMO RNA drug (chemistry/mechanism 2) has an improved *in vivo* PK/PD profile relative to the 2′MOE candidate

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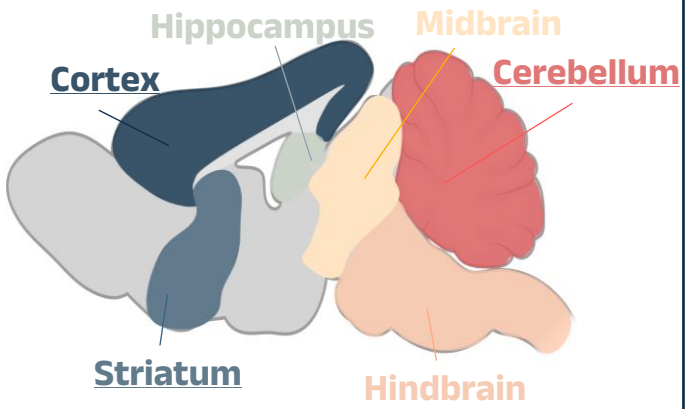
Brain regions implicated in PMS



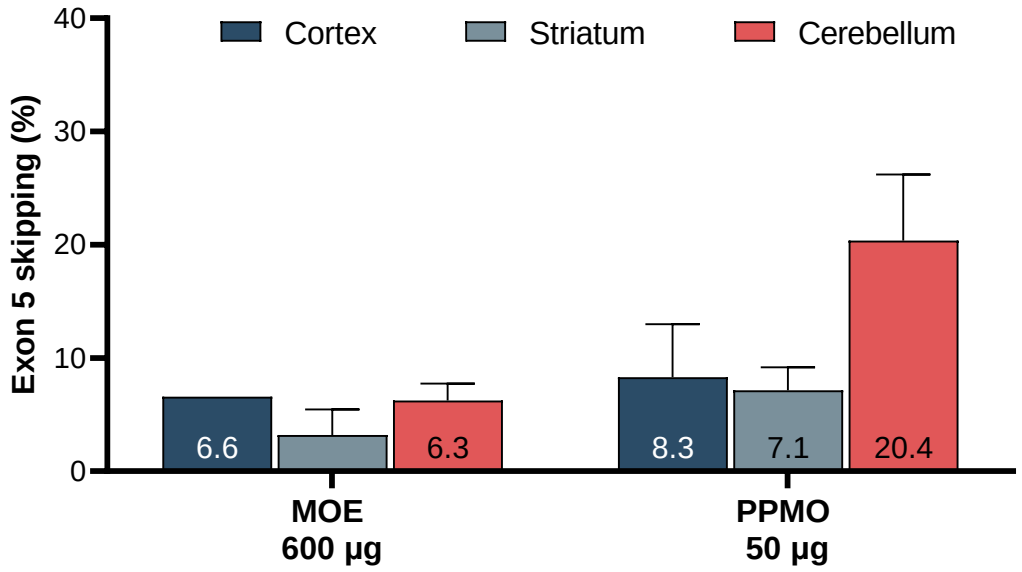
Cortex
- Speech/language
- Social interaction

Cerebellum
- Hypotonia

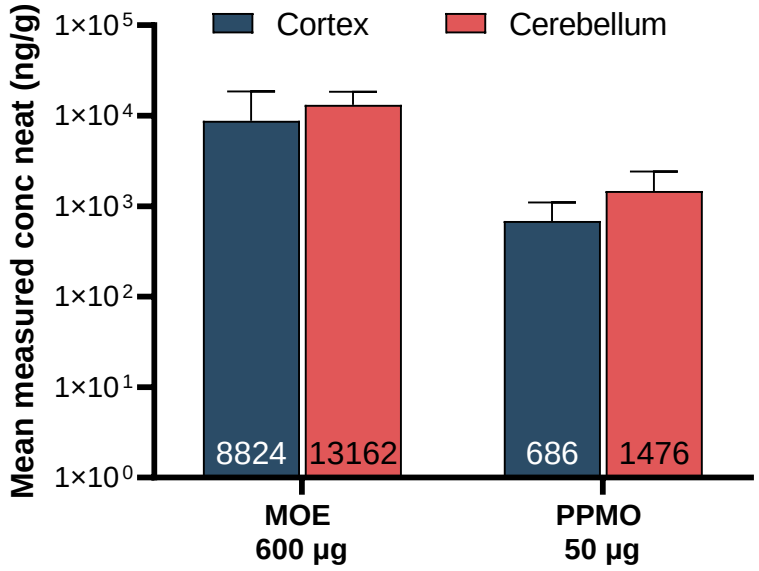
Striatum
- Motivation
- Sensory control
- Repetitive behaviours

PPMO shows enhanced target engagement profile (at lower tissue concentration) in the brain via a clinically relevant route of administration (intrathecal) in rats[1]

PD - Exon skipping at D7



PK - DELFIA drug recovery assay at D7



PYC is progressing both modalities through non-clinical read-outs to determine the best candidate for patients

1. Biodistribution assessed by DELFIA & target engagement (Smn exon 5 skipping) assessed by RT-PCR in brain regions at D7 following intrathecal injection (with flush) of 50µg PPMO or 600µg MOE into 8-12wk old rats (n=1-3). Oligos are reporter designed to provide a PK/PD read-out in rats and not the therapeutic candidate for PMS.
2. Additional studies without flush showed similar results (not presented) and follow on exploratory studies are underway.

PYC's preferred candidate is expected to have a differentiated clinical profile due to its disease-modifying potential

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1 → 2 → 3 → 4

1 Symptoms that are important to patients

'Untreatable'

- Developmental and speech delays
- Repetitive behaviours

'Poorly managed'

- Intellectual disability
- Seizures
- Hypotonia
- Neuropsychiatric illnesses
- Sleep issues
- Skills regression
- Overheating risks

2 Clinical endpoints tailored to the symptoms

- **Aberrant behaviour checklist – social withdrawal**
- **Repetitive behavioural scale**
- **CGI-I (PMS-specific skills assessment)**
- **MB-CDI (early language development assessment)**
- **Additional endpoints**

3 Non-clinical models linked to clinical endpoints

- **Patient derived neurons**

(Protein upregulation, mechanism of action, functional readout - dendritic growth, calcium influx, restoration of normal neuronal firing)

- ***SHANK3* mouse models**

(Protein upregulation, mechanism of action, functional readout - dendritic growth, improved social behavior)

- **Large animal models**

(PK – brain tissue concentration, particularly cerebellum, cortex, striatum, key areas linked to phenotype = dose scaling + PK/PD predictive capacity)

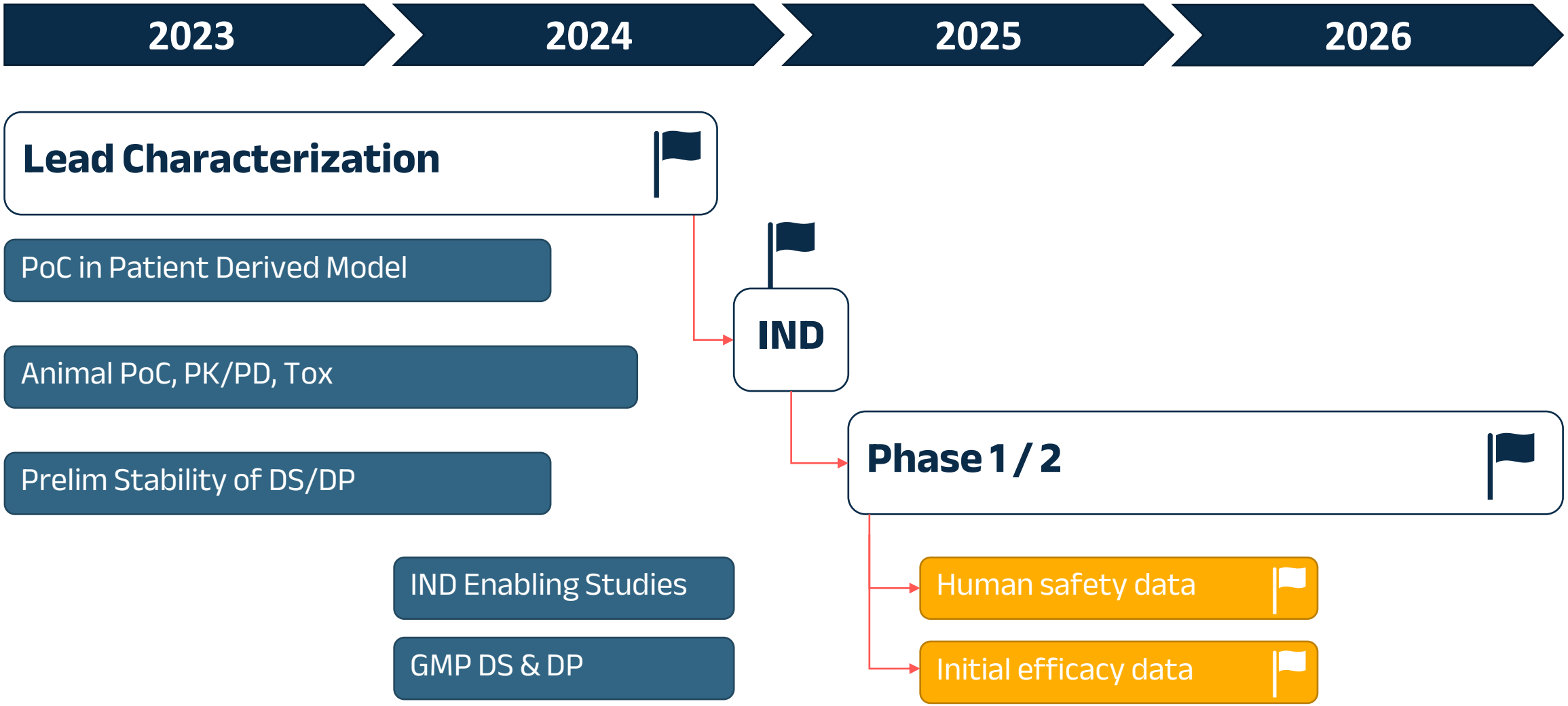
(PD – target engagement in critical brain regions, associated functional outcomes)

4 Conviction in a potentially differentiated therapeutic for PMS

- ✓ **Target root cause of disease** with specific upregulation of SHANK3 expression
- ✓ **Potential to treat 'untreatable' symptoms** via effective delivery to PMS implicated brain regions
- ✓ **Non-viral, reversible,** nonimmunogenic, no compromise on gene size
- ✓ **Physiological isoform balance** can be maintained/restored
- ✓ CNS ASOs have low systemic exposure and long half-lives[1]

1. O. Khorkova, C. Wahlestedt, Oligonucleotide therapies for disorders of the nervous system. Nat. Biotechnol. 35, 249–263 (2017).

Human safety and initial efficacy data are expected in 2025



1. Clinical trial plan depends on multiple factors, including the duration of action of the therapeutic candidate.

FDA special designations assist in efficiently creating the first treatment option for patients with PMS

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Potential eligibility for 3 FDA special designations

Orphan Drug Designation (ODD)[1]

Orphan drugs address patient populations of fewer than 200,000 people in the US[1]*

✓ **PMS** (~28k in WW)

Orphan drugs benefit from attractive pricing and market exclusivity, the median annual cost of orphan drugs for genetic disorders[2] is:

US $275,000

Rare Pediatric Disease Designation[3]

Rare diseases with serious or life-threatening manifestations primarily affecting patients from birth to 18 years[3]

✓ **PMS** (congenital disorder)[4]

Therapeutics that receive RPD designation may qualify for a Priority Review Voucher, which can be sold for an estimated price of[5]:

US $100,000,000

Accelerated Approval[3]

Allows for the earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint[3]

✓ **PMS** (unmet need)

RNA therapeutics for genetic diseases, such as those for DMD, have received accelerated approval based on **modulation of gene expression as a surrogate endpoint**

3 FDA special designations could enhance the velocity and attraction of PYC-002 as it progress through human studies

1. Waxman H.A. H.R.5238-97th Congress (1981-1982): Orphan Drug Act. 1983
2. Althobaiti H, et al. Disentangling the Cost of Orphan Drugs Marketed in the United States. Healthcare (Basel). 2023;11(4):558.
3. FDA. Development and Approval Process | Drugs. 2022. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
4. Nevado J, et al. Variability in Phelan-McDermid Syndrome in a Cohort of 210 Individuals. Frontiers in Genetics. 2022;13.
5. https://www.businesswire.com/news/home/20230106005087/en/bluebird-bio-Sells-Second-Priority-Review-Voucher-for-95-Million