For personal use only

PYC Therapeutics

Life-changing science

Polycystic Kidney Disease Program

Investor webinar

November 2024

Disclaimer

ersonal use only

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

- On 27 November 2024, PYC released its pre-clinical data pack in support of PYC-003 – a first-in-class RNA conjugate for the treatment of Autosomal Dominant Polycystic Kidney Disease (PKD) due to mutations in the *PKD1* gene[1]

- In December 2024, PYC will make the regulatory submission required to progress PYC-003 into First In Human (FIH) studies[2]

- Today's objectives are to progress the discussion to an evaluation of:
  - Why PYC-003's disease-modifying mechanism of action is uniquely suited to addressing PKD; and
  - The extent of *PKD1* gene upregulation required to have a meaningful impact on disease progression in PKD patients

Personal use only

1. See ASX announcement of 27 November 2024
2. Management forecast accurate as at 28 November 2024 and subject to the risks and uncertainties set out in the Company's ASX disclosures of 14 March 2024

There is an urgent need to create treatment options for the PKD patient community

PYC Therapeutics

Personal use only

Polycystic Kidney Disease

Healthy adult kidney

Polycystic kidney

High prevalence

PKD affects **1 in every 1,000** people meaning **>5 million people worldwide** have the disease[1,2]

Life-changing

Half of all PKD patients will **require a kidney transplant** by the age of 60 due to **end-stage renal failure**[3]

Limited treatment options

There are **no drugs available** that address the underlying cause of the disease and there is an **urgent need for treatments with disease-modifying potential** in PKD

1. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. 2002 Jan 10 [Updated 2022 Sep 29]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993-2023.
2. Willey et al. Analysis of Nationwide Data to Determine the Incidence and Diagnosed Prevalence of Autosomal Dominant Polycystic Kidney Disease in the USA: 2013-2015. Kidney Dis (Basel). 2019;5(2):107-17.
3. Cloutier et al. The societal economic burden of autosomal dominant polycystic kidney disease in the United States. BMC Health Serv Res. 2020;20(1):126.

Targeting the root cause of PKD (insufficient PC1 protein expression) may be the only therapeutic option in this disease

PYC Therapeutics

ersonal use only

"It remains possible that multiple pathways that are directly regulated by the polycystins concur in the prevention of cyst formation and may need to be concomitantly targeted.

Thus, **re-expressing the polycystins might ultimately remain the best — or possibly the only** — way to revert the disorder"[1]

1. Boletta, A. Reversing polycystic kidney disease. Nat Genet 53, 1623–1624 (2021). https://doi.org/10.1038/s41588-021-00963-3

The *PKD1* gene in isolation drives polycystic kidney disease[1]

PYC Therapeutics

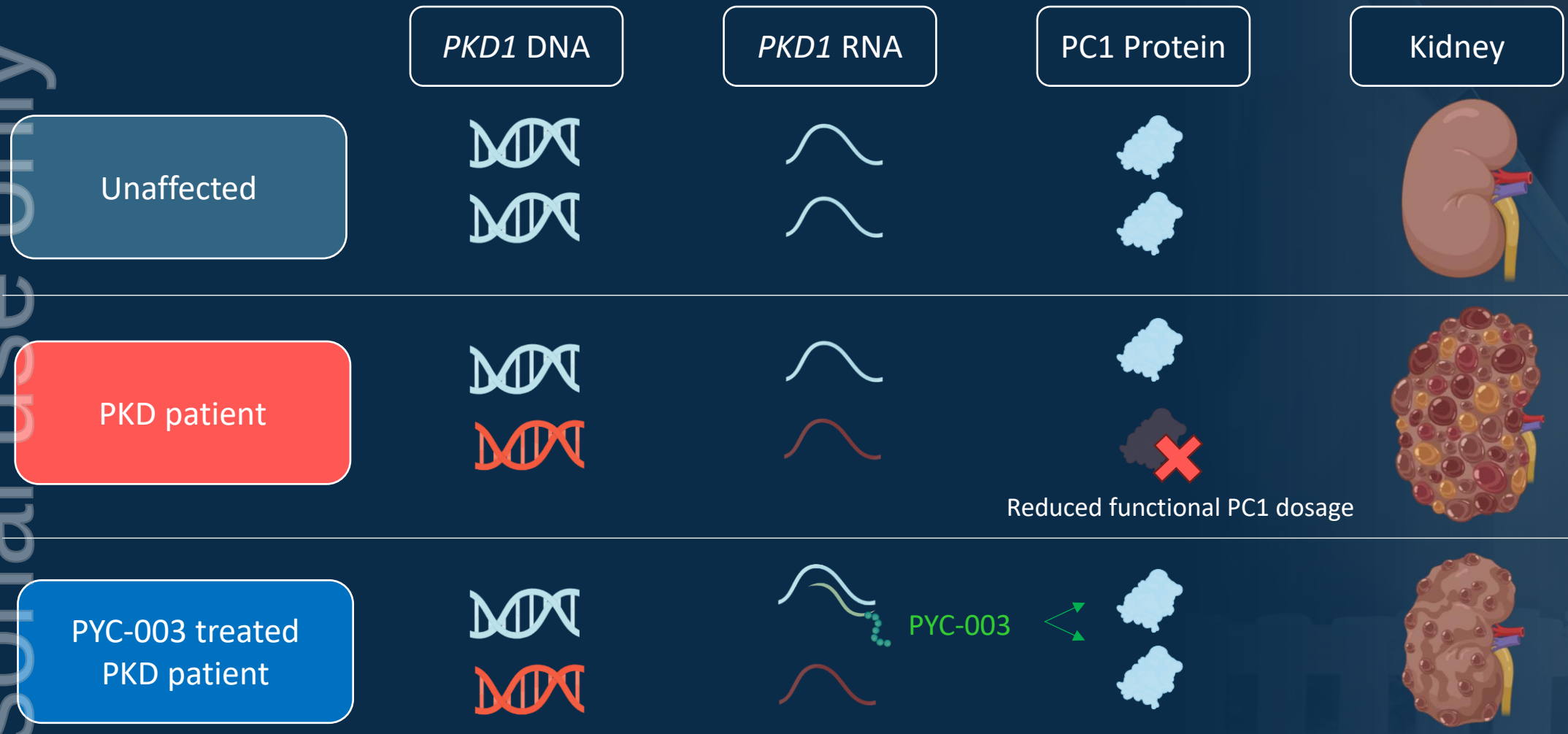
"These observations collectively point to PKD1 as the primary, if not the sole, factor governing cyst onset and growth"[1]

ersonal use only

1. In the ~75% of PKD patients with a *PKD1* mutation
2. Lakhia, R., Ramalingam, H., Chang, CM. et al. PKD1 and PKD2 mRNA cis-inhibition drives polycystic kidney disease progression. Nat Commun 13, 4765 (2022). https://doi.org/10.1038/s41467-022-32543-2

PYC-003 acts directly on the functional *PKD1* transcript to upregulate PC1 protein expression

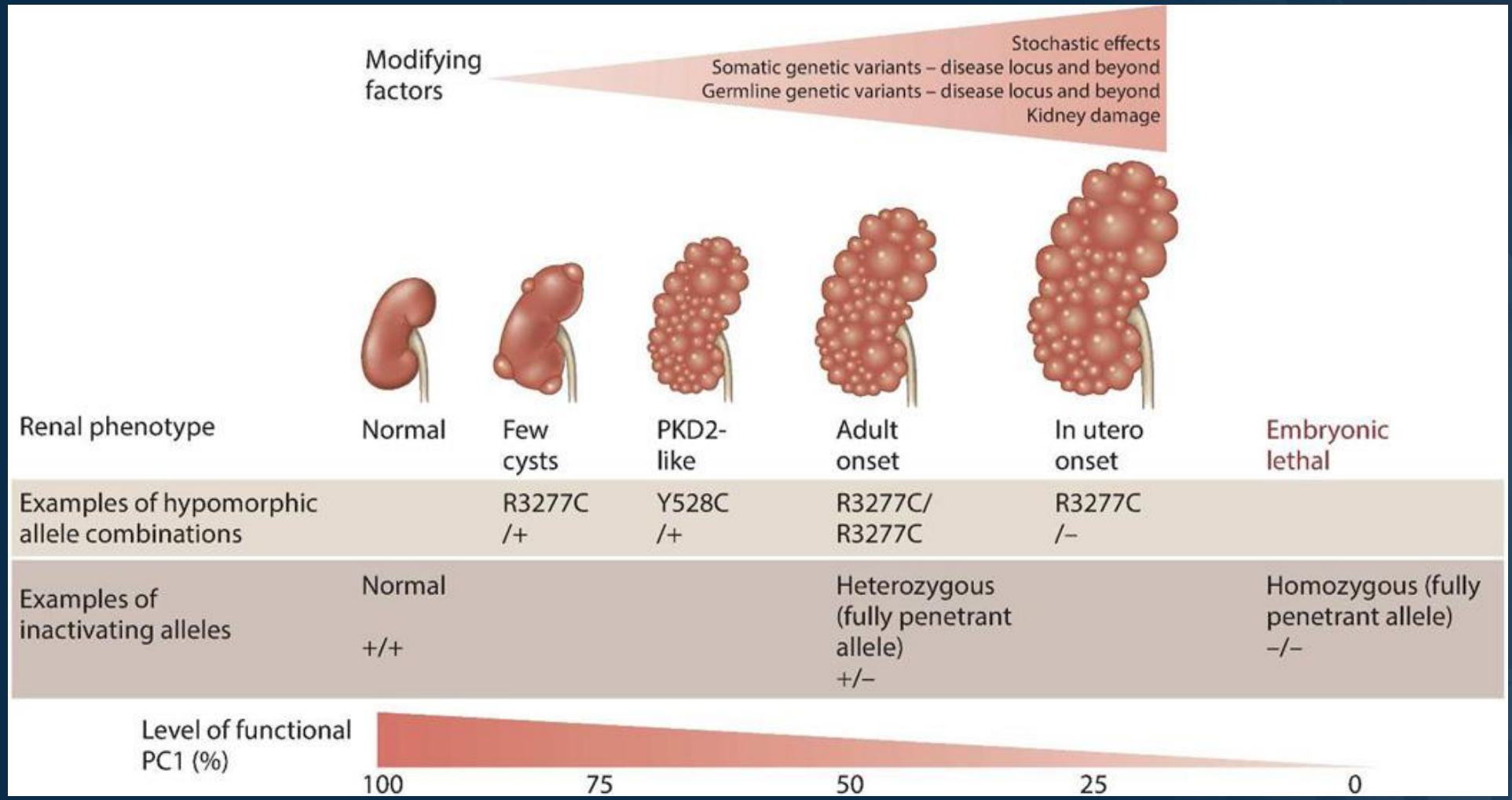
PYC Therapeutics



Personal use only

Created using BioRender

How much PC1 protein will be sufficient to make a meaningful impact on disease progression?



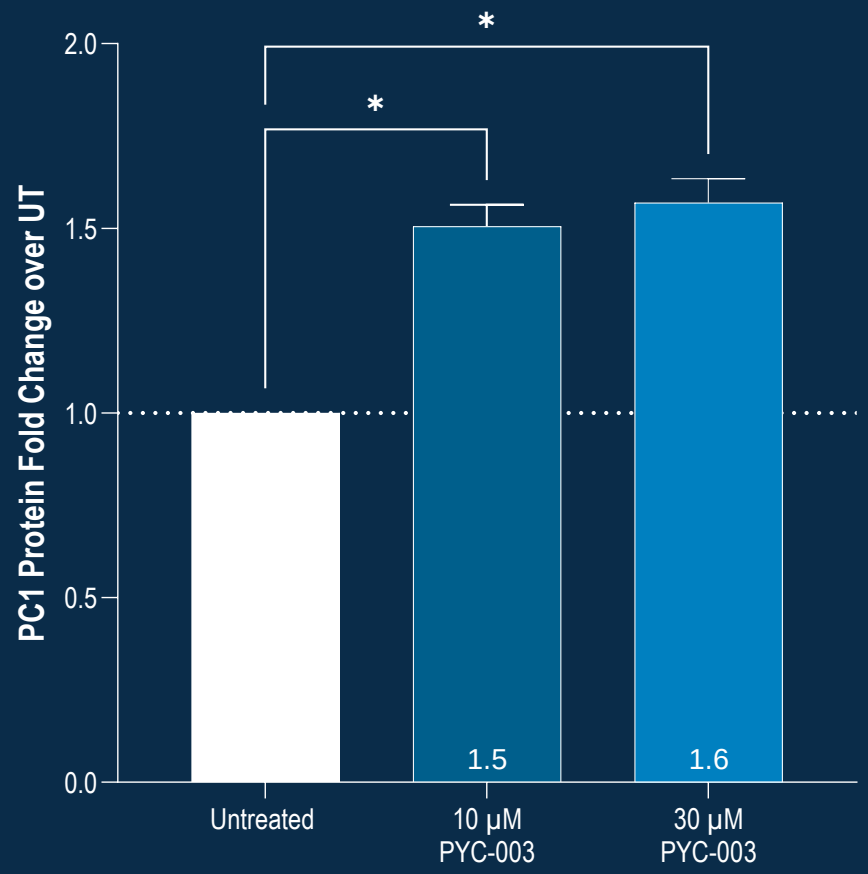
Personal use only

1. Ong AC, Harris PC. A polycystin-centric view of cyst formation and disease: the polycystins revisited. Kidney Int. 2015 Oct;88(4):699-710. doi: 10.1038/ki.2015.207. Epub 2015 Jul 22. PMID: 26200945; PMCID: PMC4589452.

PYC-003 increases PC1 protein levels by >1.5-fold[1]

PYC-003 addresses the root cause of PKD in human kidney cells[2]

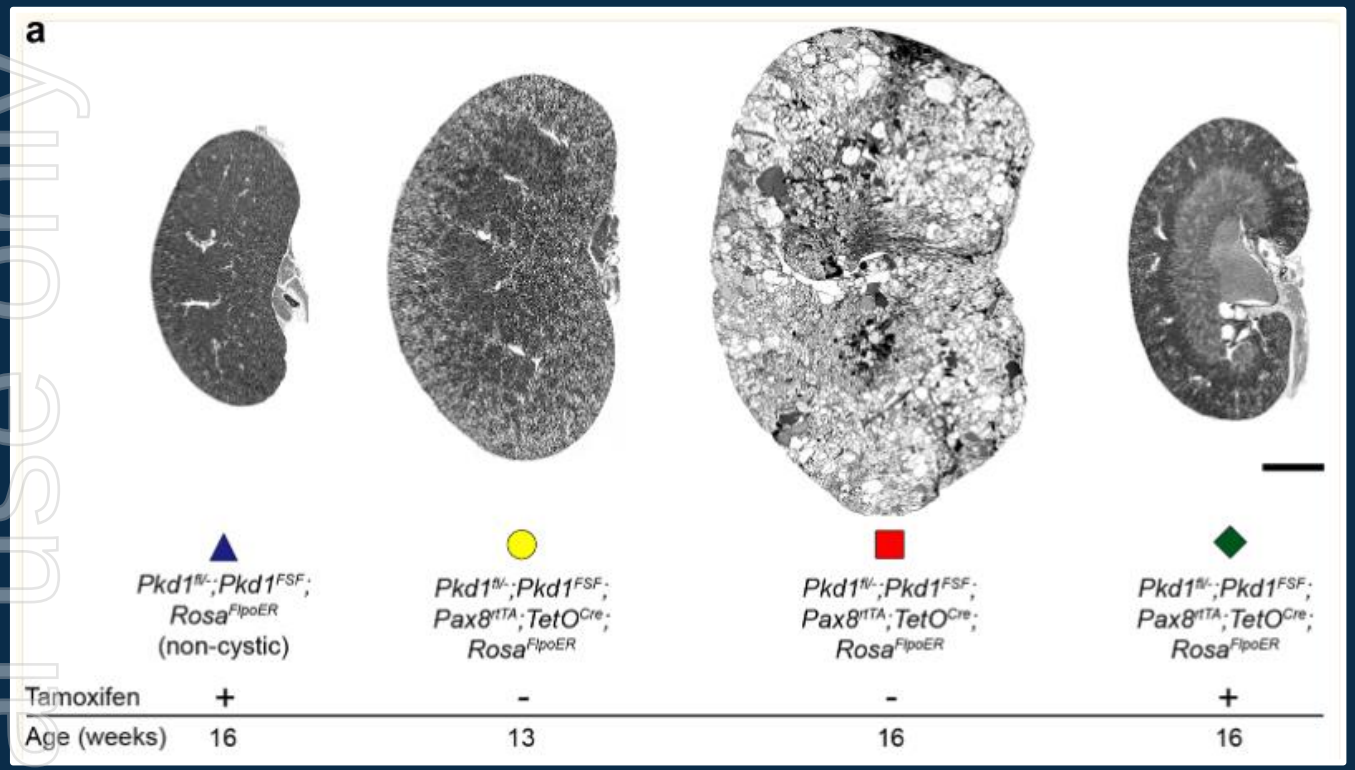
PYC-003 increases levels of PC1 protein (the missing protein that causes PKD) in a human kidney cell line



1. Refer ASX Announcement 17 November 2023
2. PC1 full length protein fold-change over untreated (normalised to total protein) assessed at day 3 following treatment with either 10 µM or 30 µM PYC-003. Data presented mean+S.D (n=2 for protein). The data show a statistically significant (Dunnett's post-hoc test, *p<0.05) difference between treatment groups. Assessed in HEK293 cells.

For personal use only

The potential of disease-modifying approaches in PKD are foreshadowed by the results of animal models



Non-cystic reference

Baseline (time of treatment)

Untreated

PC1 re-expressed

"Even if one could have hypothesized that re-expressing PKD genes would slow disease progression, **the rapidity and completeness of the reversal are astonishing** and are likely indicative of a unique and previously **unappreciated regenerative potential of the kidney**"[2]

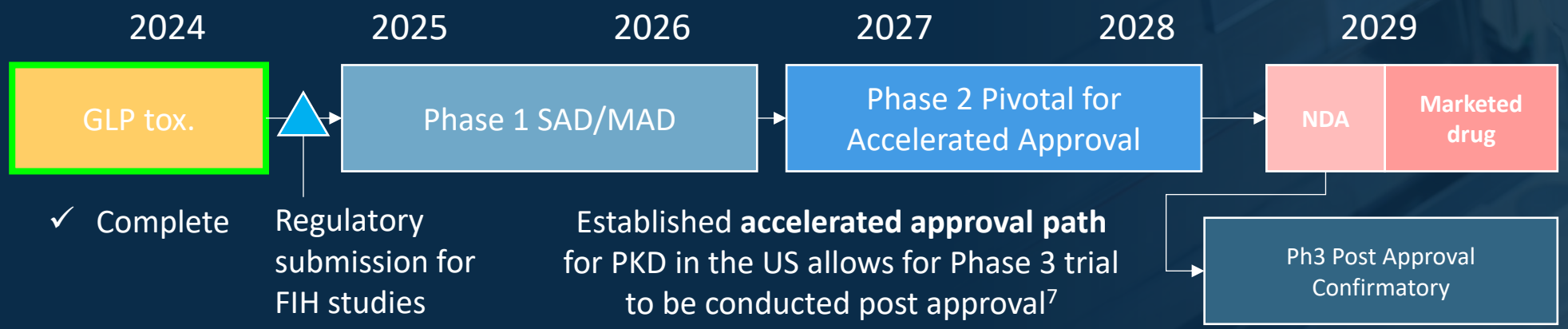
Personal use only

1. Dong, K., Zhang, C., Tian, X. et al. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet 53, 1649–1663 (2021). https://doi.org/10.1038/s41588-021-00946-4
2. Boletta, A. Reversing polycystic kidney disease. Nat Genet 53, 1623–1624 (2021). https://doi.org/10.1038/s41588-021-00963-3

PYC-003 will progress to human trials in 2025[1]

PYC Therapeutics

Clinical pathway[1-3]



✓ Complete

Regulatory submission for FIH studies

Established **accelerated approval path** for PKD in the US allows for Phase 3 trial to be conducted post approval[7]

FDA special designations

Potentially accelerating path to market:

1. **Fast Track -** Potential
2. **Orphan Drug Designation –** Potential

personal use only

1. Clinical trial plan is subject to confirmation and depends on multiple factors, including the duration of action of the therapeutic candidate and regulatory approval. Management forecast as of 27 November 2024.
2. Refer ASX announcement 13 November 2023 and 17 November 2023
3. Accelerated approval allows for the earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint. FDA has designated TKV as a reasonably likely surrogate endpoint. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

PYC-003 for Polycystic Kidney Disease (PKD)

ersonal use only

Q&A