PYC Therapeutics

27 November 2024

PYC TO PROGRESS POLYCYSTIC KIDNEY DISEASE DRUG CANDIDATE INTO HUMAN TRIALS

- **PYC is a clinical-stage biotechnology company developing an investigational drug candidate (known as PYC-003) for the ~1 in every 1,000 people affected by Autosomal Dominant Polycystic Kidney Disease (PKD) who have no effective treatment options available**
- **In preparation for the commencement of First In Human (FIH) trials of PYC-003 in early 2025[1], PYC has successfully completed pre-clinical studies of this drug candidate demonstrating that it is both safe and effective in animal and patient-derived models**
- **Highlights of the pre-clinical studies for PYC-003 include:**
    - **Effective control of gene expression *in vitro* and *in vivo* (in both mouse[2] and Non-Human Primates (NHPs)) at safe and well-tolerated doses**
    - **Efficacy in the 'killer experiment' – human 3D kidney cyst models derived from patients with end-stage renal failure due to PKD[3]**
    - **An established safety/tolerability profile in Good Laboratory Practice (GLP) toxicology studies in Non-Human Primates (NHPs) with a No Observable Adverse Effect Level (NOAEL) of 12 mg/kg**
    - **High target tissue concentrations at low doses (3 mg/kg) in NHPs informing an anticipated human therapeutic dose of between 0.8 and 3 mg/kg**
    - **Drug distribution to cyst-forming cells in animal models of PKD**
- **PYC-003 is now set to enter FIH studies in early 2025 with a compelling pre-clinical data pack in an area of major unmet patient need[4]**

[1] Subject to the risks and uncertainties set out in the Company's ASX disclosures of 14 March 2024
[2] See ASX announcement 17 November 2023
[3] See ASX announcement 13 November 2023
[4] Subject to the risks and uncertainties set out in the Company's ASX disclosures of 14 March 2024

- **The Company will host an investor webinar at 9am AWST (12pm AEDST) on Thursday 28 November 2024 to present these results. Shareholders who would like to attend the meeting can register for the webinar at the following link:**

  https://us02web.zoom.us/webinar/register/WN_wPzDQSOnTwW8NwE_VW0cJw

PERTH, Australia and SAN FRANCISCO, California – 27 November 2024

PYC Therapeutics (ASX:PYC) is a clinical-stage biotechnology company creating first in class precision therapies for patients with genetic diseases and no treatment options available. One of the Company's assets is an investigational drug candidate (known as PYC-003) that addresses the underlying cause of Autosomal Dominant Polycystic Kidney Disease (PKD). PYC is preparing to progress PYC-003 into human trials in early 2025 and today announces the completion of pre-clinical studies in this drug development program.

PYC's CEO, Dr Rohan Hockings, commented on the completion of the pre-clinical data pack:

"*We are excited to progress this drug candidate into the clinic for the polycystic kidney disease patient community on the back of the strength of this pre-clinical data. The potential of a disease-modifying drug in this indication is profound and we look forward to assessing the impact of this drug candidate in patients alongside our two other clinical stage programs*."

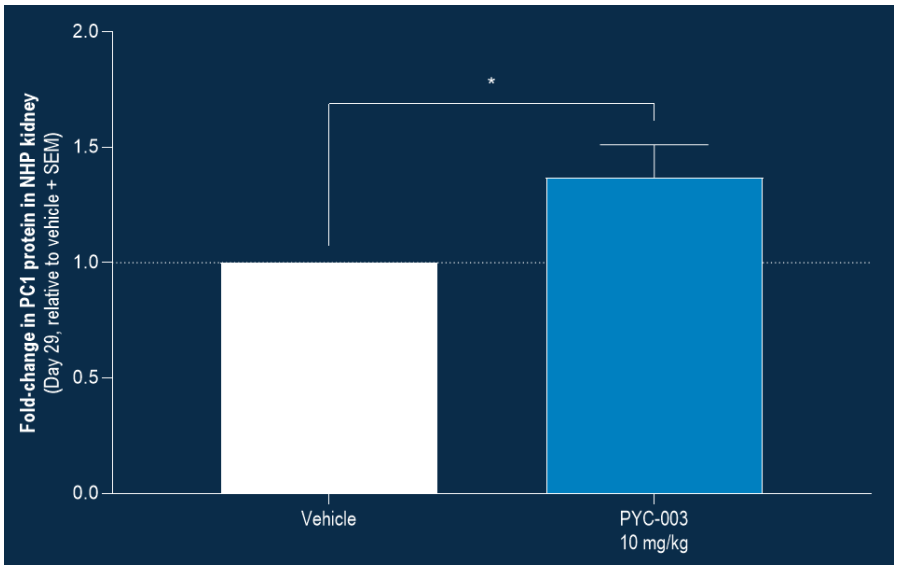
A detailed overview of the current data pack in its entirety is attached to this presentation. A description of the new data included in the updated data pack is provided below.

Integrated safety/tolerability and efficacy in Non-Human Primates (NHPs) *in vivo*

New data released today demonstrates the ability of PYC-003 to increase PC1 protein in the kidneys of Non-Human Primates (NHPs) (See Figure 1). Deficient PC1 protein is the underlying cause of PKD and restoring its expression has been shown to reverse the disease process in animal models of PKD[5].

[5] Dong K, Zhang C, Tian X, Coman D, Hyder F, Ma M, Somlo S. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet. 2021 Dec;53(12):1649-1663. doi: 10.1038/s41588-021-00946-4. Epub 2021 Oct 11. PMID: 34635846; PMCID: PMC9278957.

Figure 1. *PC1 protein quantification in vehicle and PYC-003 treated NHPs demonstrating an increase in protein expression in the PYC-003 treated NHPs (*p<0.05 calculated using one-way ANOVA). Data presented as the mean + standard error of the mean.*



PYC-003 treated NHPs received a single dose of 10 mg/kg in a non-Good Laboratory Practice (Non-GLP) Dose-Range Finding (DRF) study in which protein expression was assessed by Western Blot 28-days after dosing in two biological replicates with two technical replicates per biological replicate. PYC-003 was determined to be safe and well-tolerated in the DRF at this dose providing an integrated PD/safety-tolerability read-out.

Good Laboratory Practice (GLP) Toxicology studies[6]

GLP toxicology studies in NHPs have been completed and demonstrate that PYC-003 is safe and well-tolerated in NHPs with a No Observable Adverse Effect Level (NOAEL) of 12 mg/kg (See Figure 2).

Figure 2. *Outcomes of Good Laboratory Practice (GLP) toxicology studies of PYC-003 in NHPs demonstrating a NOAEL of 12 mg/kg and highlighting that there are no changes in serum creatinine or magnesium at doses up to and including the NOAEL[7].*

Cohort	Number of subjects	Treatment group	Treatment Related Adverse Events (occurrence / number of animals)	Outcome	Change in serum magnesium outside normal range[7]	Change in creatinine outside normal range[7]
1	8	Vehicle control	0/8	Tolerated	No	No
2	8	4.8 mg/kg	0/8	Tolerated	No	No
3	8	12 mg/kg	0/8	Tolerated	No	No
4	8	30 mg/kg	8/8	Not tolerated	Yes	Yes

A non-tolerated dose of PYC-003 was also established at 30 mg/kg in these studies with adverse effects (regenerative changes observed upon histopathological evaluation with

[6] Subjects were monitored for 28 days following a single intravenous administration of PYC-003 at the relevant dose. Potential adverse events were monitored for via in-life observations and biochemical markers through regular blood testing. All major organs were analysed for histopathological changes upon completion of the in-life study period.
[7] Mean change in blood biochemical markers

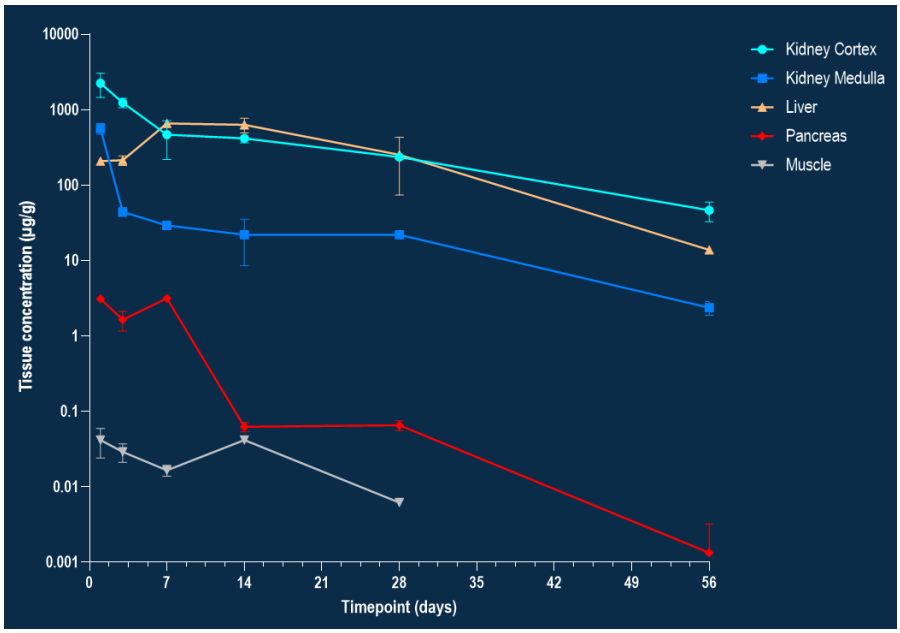
associated clinical pathology findings) limited to the target organ (kidney) and likely reflecting the concentration of drug in the target organ at these doses (>3,000,000 ng/g of PYC-003 in kidney at Day 1 following a single dose).

Pharmacokinetic studies[8]

Non-GLP Pharmacokinetic (PK) studies were conducted in NHPs to evaluate the biodistribution and half-life of PYC-003 *in vivo*. These studies confirmed that PYC-003:

- Preferentially distributes to the target organs in PKD (see Figure 3);
- Achieves high concentrations of drug in target tissue ((>500,000 ng/g) following a single 3 mg/kg dose; and
- Has a half-life of approximately 14 days in the kidney - affording an expected dosing interval of approximately 2 months in humans.

Figure 3. *PK studies in NHPs demonstrating concentration of PYC-003 in major organs following a single 10 mg/kg intravenous infusion. The data is presented as the mean tissue concentration in each organ +/- standard deviation.*

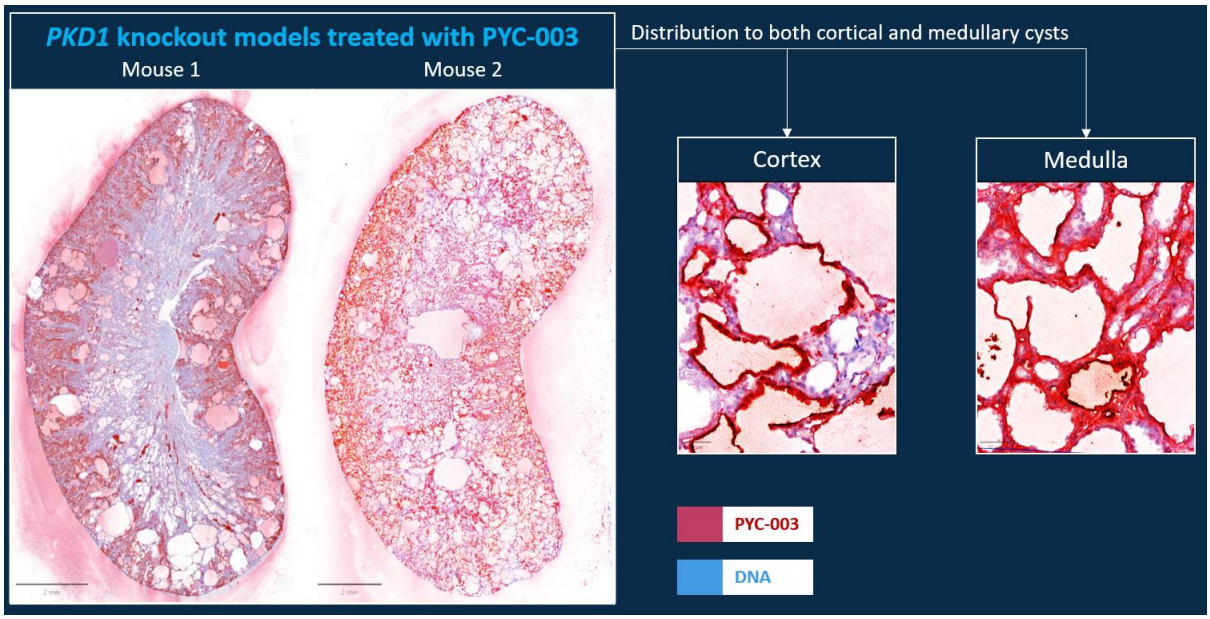


Animal models of PKD - biodistribution to cyst-forming cells

A biodistribution study in a mouse model of PKD (known as a *PKD1* knockout model) was conducted to evaluate the ability of PYC-003 to reach the cyst-forming cells *in vivo*. Results of the study confirm the ability of PYC's drug candidate to reach the cells that are driving the disease process *in vivo*.

[8] Non-GLP PK studies conducted in NHPs with 6 cohorts of 2 subjects each receiving a single 10 mg/kg dose of PYC-003 informing assessment of tissue concentration in all major organs across multiple time-points through to 56 days of follow up.

Figure 4. *Biodistribution of PYC-003 to cyst-forming cells in an animal model of PKD.*



Images captured using miRNAscope at day 3 following a single 10 mg/kg dose of PYC-003 demonstrating that the drug candidate reaches the cyst-forming cells in both the cortex and medulla of the polycystic kidney. PYC-003 drug presence is denoted by pink dots in this study with the red stain indicating high levels of drug in the cyst-forming cells in the images above (particularly the higher resolution images on the right-hand side).

Next steps

Following successful completion of these pre-clinical studies, PYC is now in a position to lodge the regulatory submission required to enable progression into human studies. A response from the relevant regulatory authorities is expected in Q1 2025.

About PYC-003 – a first-in-class drug candidate with disease-modifying potential in PKD

PKD affects ~1 in every 1,000 people. The disease is characterised by large numbers of cysts forming in patient kidneys. These cysts increase in size over time and ultimately destroy the kidney tissue resulting in renal failure with the majority of PKD patients requiring a kidney transplant[9].

Approximately 95% of patients with PKD have no treatment options available to them today[10]. As a result of this major unmet need, the US Food and Drug Administration has outlined a pathway for a New Drug Application to be submitted in PKD following a Phase 2 clinical trial based on a surrogate endpoint[11].

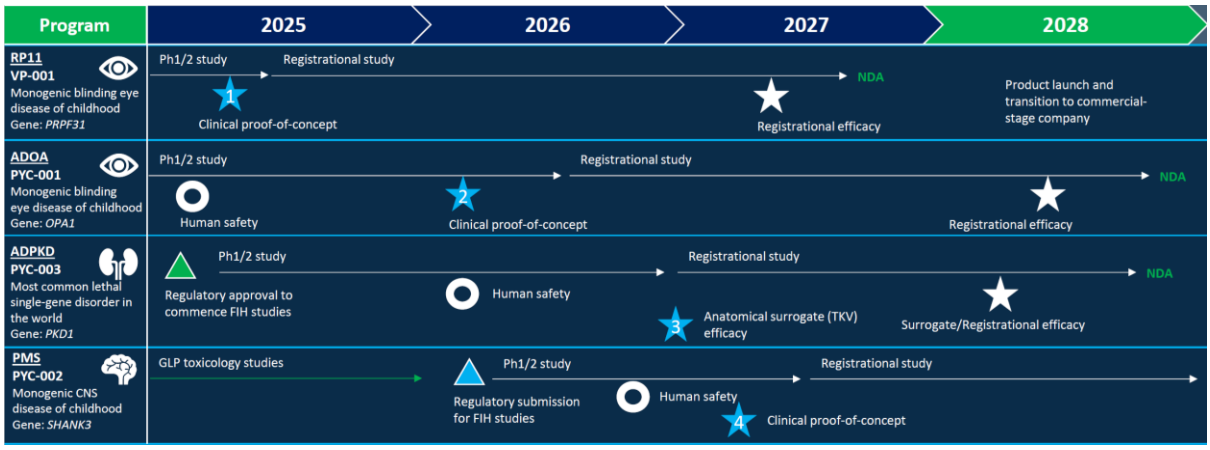
PKD represents an estimated >US$10 billion p.a. market[12]. PYC-003 holds potential for both first-in-class and best-in-class status in this indication[13] due to its highly specific mechanism of action that targets the underlying cause of the disease.

[9] Cloutier M, et al. The societal economic burden of autosomal dominant polycystic kidney disease in the United States. BMC Health Serv Res. 2020;20(1):126.
[10] See footnote 5
[11] See footnote 3
[12] Based on prevalence of the indication of 1 in 1,000 as per the PKD Foundation and median orphan drug pricing of US$160k p.a. as per EvaluatePharma
[13] Refer ASX Announcement 17 November 2023

PYC's pipeline

PYC remains on track to deliver its operational roadmap for its pipeline of first-in-class drug candidates including generating human safety and efficacy data in 2025 for three drug programs intended to create a treatment option for the 1 in every 1,000 people who have one of these life-changing conditions who do not have one today[14] (see Figure 5).

Figure 5. *PYC's operational roadmap*



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**[15].

PYC's drug development programs

Retinitis Pigmentosa type 11

- A blinding eye disease of childhood affecting 1 in every 100,000 people[16]
- Currently progressing through phase 1/2 clinical trials with preparation under way for a potentially registrational trial to commence in 2025[17]

Autosomal Dominant Optic Atrophy

- A blinding eye disease of childhood affecting 1 in every 35,000 people[18]
- Currently progressing through clinical trials with human safety and efficacy read-outs anticipated in 2024 and 2025[19]

[14] Subject to the risks and uncertainties outlined in the Company's ASX filings of 14 March 2024
[15] Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232
[16] Sullivan L, et al. Genomic rearrangements of the PRPF31 gene account for 2.5% of autosomal dominant retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2006;47(10):4579-88
[17] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024
[18] Yu-Wai-Man, P. et al. The Prevalence and Natural History of Dominant Optic Atrophy Due to OPA1 Mutations Ophthalmology. 2010;117(8):1538-46 doi: 10.1016/j.ophtha.2009.12.038
[19] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024

Autosomal Dominant Polycystic Kidney Disease

- A chronic kidney disease affecting 1 in every 1,000 people[20] that leads to renal failure and the need for organ transplantation in the majority of patients
- Clinical trials are expected to commence in early 2025 with human safety and efficacy data anticipated in 2025 and 2026[21]

Phelan McDermid Syndrome

- A severe neurodevelopmental disorder affecting 1 in every 10,000 people[22]
- PYC will initiate Investigational New Drug (IND)-enabling studies in 2025 to facilitate progression into human trials

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 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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[20] 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.
[21] Subject to the risks outlined in the Company's ASX announcement of 14 March 2024
[22] Phelan-McDermid Syndrome Foundation. https://pmsf.org/about-pms/

PYC Therapeutics

Life-changing science

Polycystic Kidney Disease Program

Pre-clinical data pack

November 2024

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.

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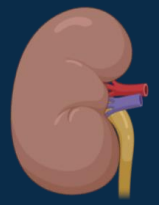
Autosomal Dominant Polycystic Kidney Disease (PKD) is an area of major unmet need due to its high prevalence and devastating consequences

PYC Therapeutics

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.

Executive Summary

- Autosomal Dominant Polycystic Kidney Disease (PKD) is the most prevalent single-gene disease in humans
  - **Cause:** In ~75% of cases, it is caused by a mutation in one copy of the *PKD1* gene leading to insufficient PC1 protein in the kidneys
  - **Patient journey:** Patients experience high morbidity and a progressive decline in kidney function to end-stage renal failure
  - **Creating a therapy:** Addressing the underlying cause of PKD (insufficient PC1 protein in the kidney) holds unique potential as a therapeutic approach and the possibility of reversing this currently untreatable condition[1,2]

- PYC-003 is a first-in-class drug candidate that addresses the underlying cause of PKD – this data pack highlights its:
  - **Mechanism of action**
  - **Efficacy profile**
    - *In vitro*
    - *In vivo*
    - *Ex vivo*
  - **Delivery profile**
    - Target organ delivery/distribution profile
    - Cellular level distribution within the target organ
    - Drug distribution within a polycystic kidney
    - Half-life profile (dosing interval)
  - **Safety/tolerability profile**
    - No Observable Adverse Effect Level in Non-Human Primates
    - Important safety outcomes: Magnesium and Creatinine levels in Good Laboratory Practice (GLP) toxicology studies
    - Anticipated human therapeutic doses

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

An introduction to Polycystic Kidney Disease (PKD)

1. The pathogenesis of PKD
2. The patient journey in PKD
3. Why disease-modification is so important in PKD
4. The promise of disease reversibility when the underlying cause of PKD is addressed

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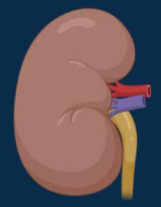
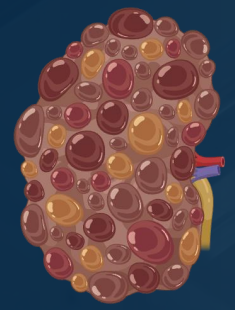
PKD is caused by reduced levels of PC1 protein in the kidney

PYC Therapeutics

Unaffected		ADPKD patient
	PKD1 DNA	~75% of PKD patients have a mutation in one copy of *PKD1* DNA[1]
	PKD1 mRNA	
Wild type PC1 protein expression (100%)	PC1 protein	**Haploinsufficient PC1 protein (~50% of wild-type levels)[2]**
Balanced	Ca^{2+} signalling	**Balance lost**
Normal	Renal tubule architecture	**Abnormal**
	Kidney	





PC1 protein is the rate-limiting modulator of cystic disease[2]

It has a critical role regulating Ca^{2+} signalling and maintaining the normal structure of renal tubules[2]

PKD is characterized by cyst formation and enlargement in kidney due to deficient PC1 protein[2]

1. Cordido et al. The Genetic and Cellular Basis of Autosomal Dominant Polycystic Kidney Disease-A Primer for Clinicians. Front Pediatr. 2017;5:279.
2. Lee SH, Somlo S. Cyst growth, polycystins, and primary cilia in autosomal dominant polycystic kidney disease. Kidney Res Clin Pract. 2014;33(2):73-8.
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The patient journey in PKD – high morbidity and accelerated mortality

PYC Therapeutics

~50% of patients develop end-stage renal failure (ESRF) by the age of 60[1]

- The current treatment framework is outlined below[2]

1. Symptoms of PKD	2. Dialysis	3. Kidney transplant	4. Immunosuppression
1. PKD is characterised by the growth of fluid-filled cysts that impair the function of the kidney[3] **Symptoms include:** • High blood pressure • Abdominal/flank pain • Hepatic cysts • Brain aneurysms • Heart valve and colon conditions	2. Dialysis artificially filters the blood to remove waste and water when the kidneys are not working It only provides 15% of normal kidney function Once started, it must be continued life-long, unless a kidney transplant is performed	3. Kidney transplantation involves removing a kidney from a donor and transferring it to a PKD patient with ESRF Criteria for suitability, lack of donors and long waiting times (up to several years) make this procedure unviable for many patients	4. Patients are treated with life-long immunosuppression after a transplant **Complications of immunosuppression:** • Vulnerability to infections and cancer • High blood pressure • Kidney problems • Osteopenia (weakening of the bones)

1. Cornec-Le Gall E, et al. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 24: 1006–1013, 2013
2. ADPKD Patient Route Map – PKD Foundation
3. Harris PC, Torres VE. Polycystic Kidney Disease, Autosomal Dominant. 2002 Jan 10

Why disease-modification is so important in PKD

DISEASE MODELS

Reversing polycystic kidney disease

A new study shows that re-expressing *PKD* genes early in the course of the disease can fully reverse polycystic kidney disease in mice. These results reveal an unexpected ability of the kidney to regenerate following genetic rescue of polycystin function.

Alessandra Boletta

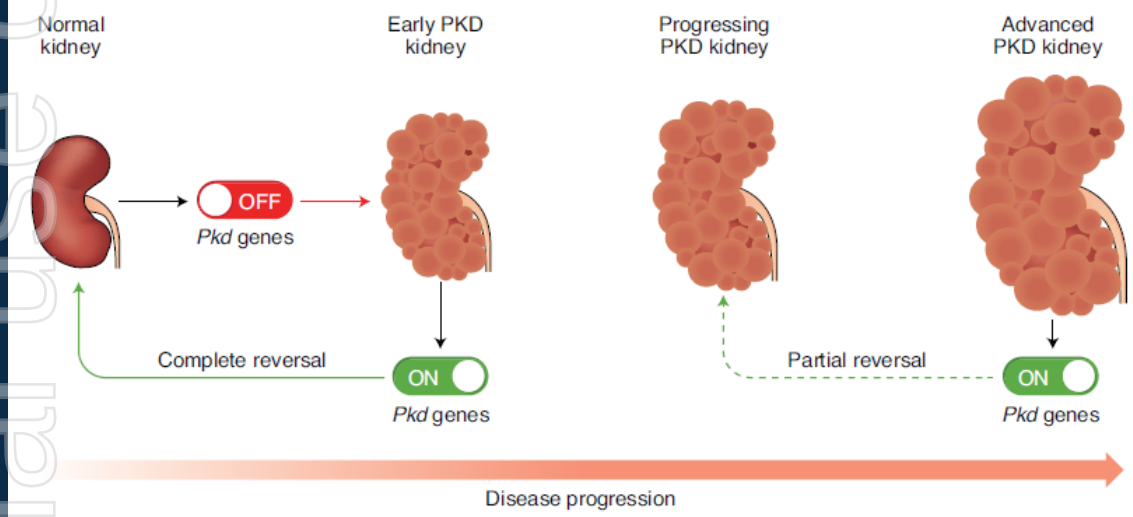


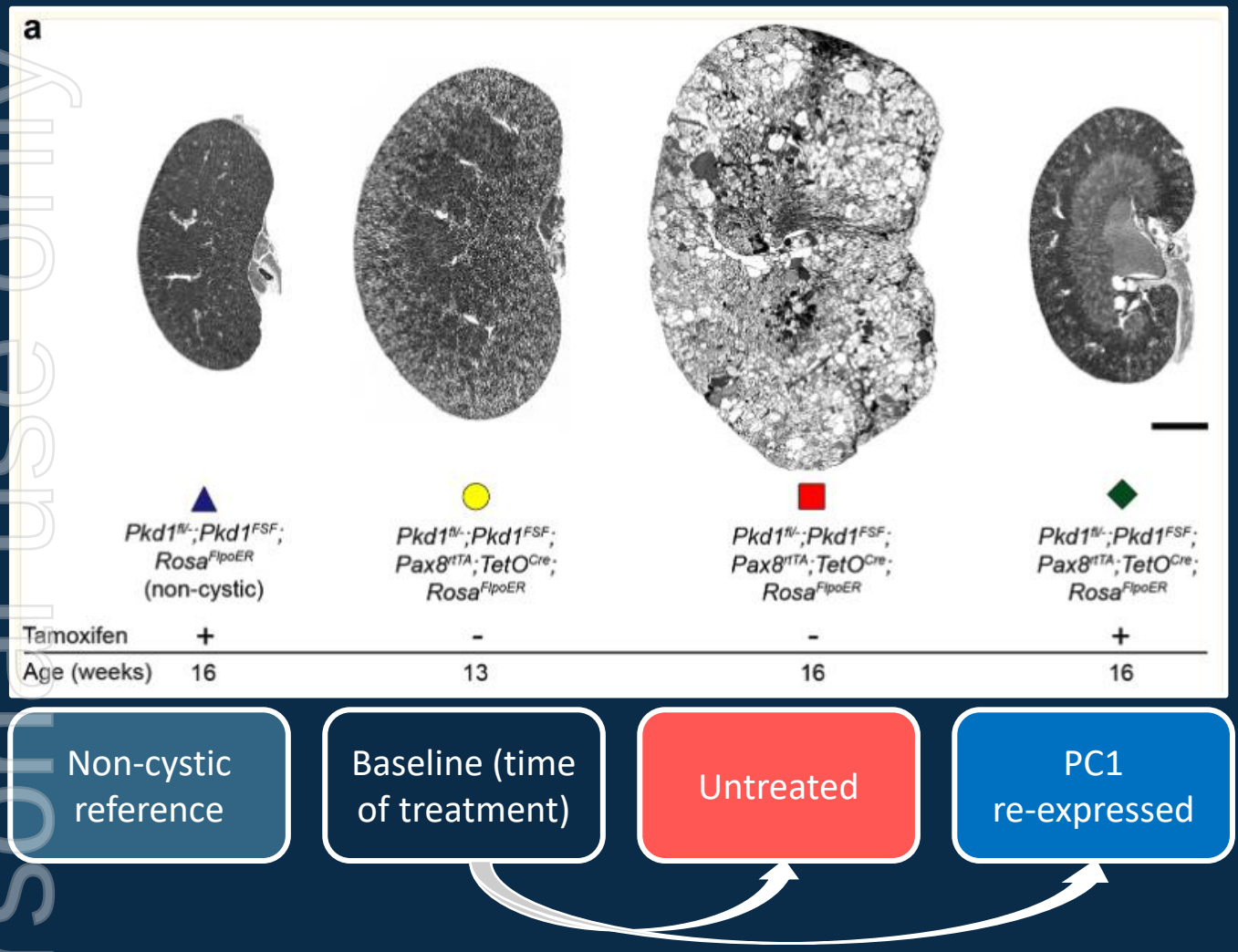
Fig. 1 | Progression and reversal of PKD. Inactivation of *Pkd* genes in normal kidneys leads to development of PKD, the manifestations of which worsen with time. Dong et al. show that re-expressing *Pkd* genes early in the disease process completely reverses PKD in mice. Re-expression at later stages causes partial but not complete reversal.

"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 promise of disease reversibility when the underlying cause of PKD is addressed[1]



"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]

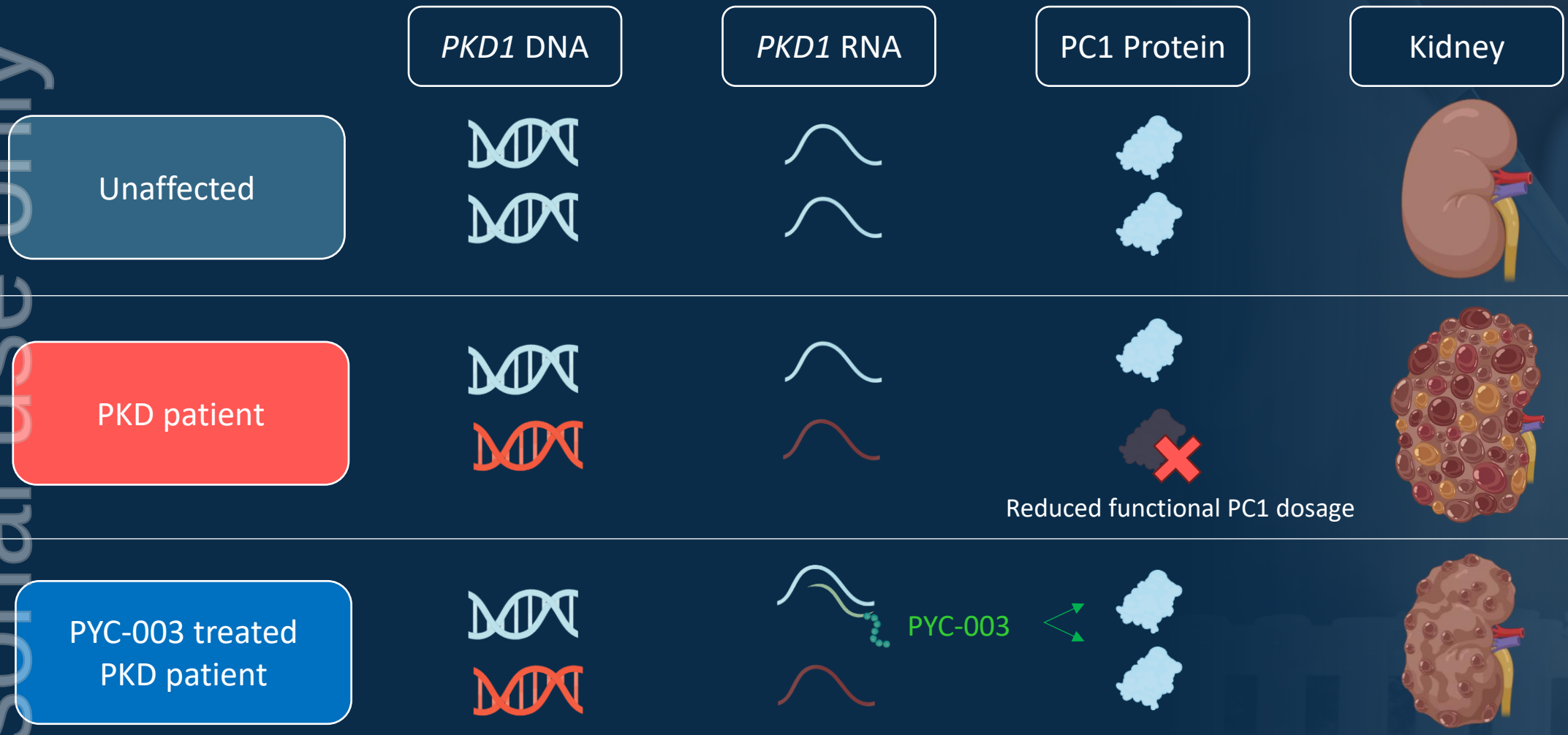
1. Dong, K., Zhang, C., Tian, X. et al. Renal plasticity revealed through reversal of polycystic kidney disease in mice. Nat Genet 53, 1649–1663 (2021). https://doi.org/10.1038/s41588-021-00946-4
2. Boletta, A. Reversing polycystic kidney disease. Nat Genet 53, 1623–1624 (2021). https://doi.org/10.1038/s41588-021-00963-3

PYC-003's mechanism of action

PYC-003 addresses the root cause of PKD by increasing PC1 protein expression in the target cell within the kidney

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

PYC Therapeutics



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Efficacy profile

PYC-003 addresses the root cause of PKD by increasing Polycystin-1 (PC1) protein levels in the target cell within the kidney (Renal Tubular Epithelial Cells or RTECs)

PYC-003 is effective:

a) *In vitro* – in cells derived from human kidneys

b) *In vivo* – in both mice and Non-Human Primates (NHPs)

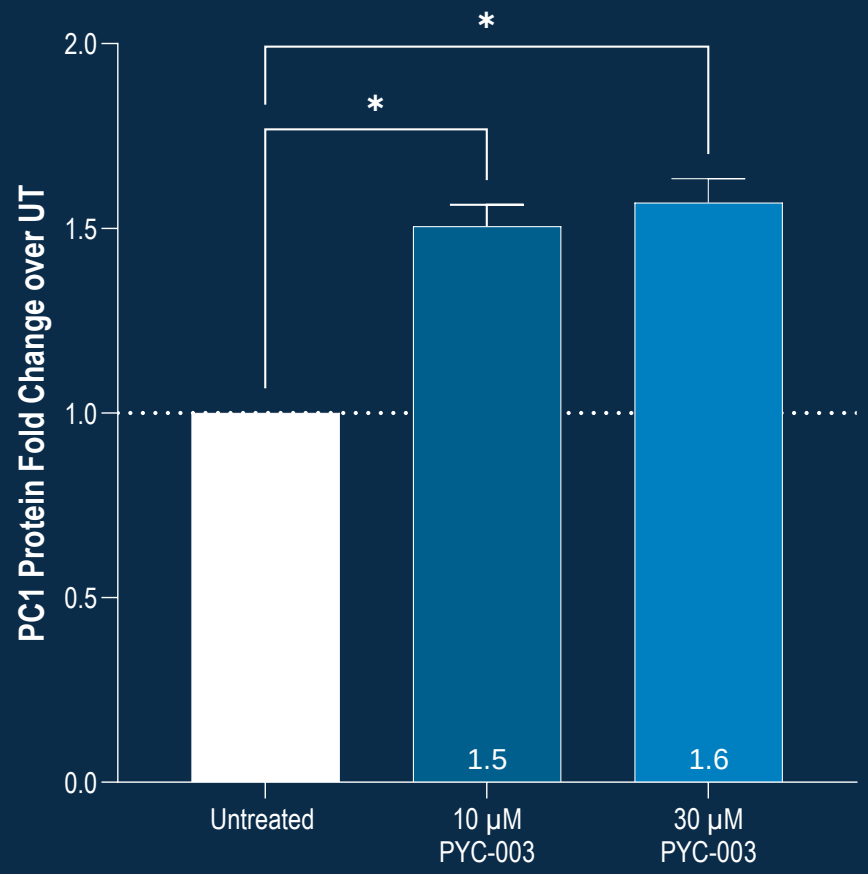
c) *Ex vivo* – in 3D models created from human kidneys removed from PKD patients due to end-stage renal failure

PYC-003 increases PC1 protein levels *in vitro* in human kidney cells[1]

PYC Therapeutics

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



- Efficacy
- Delivery
- Safety

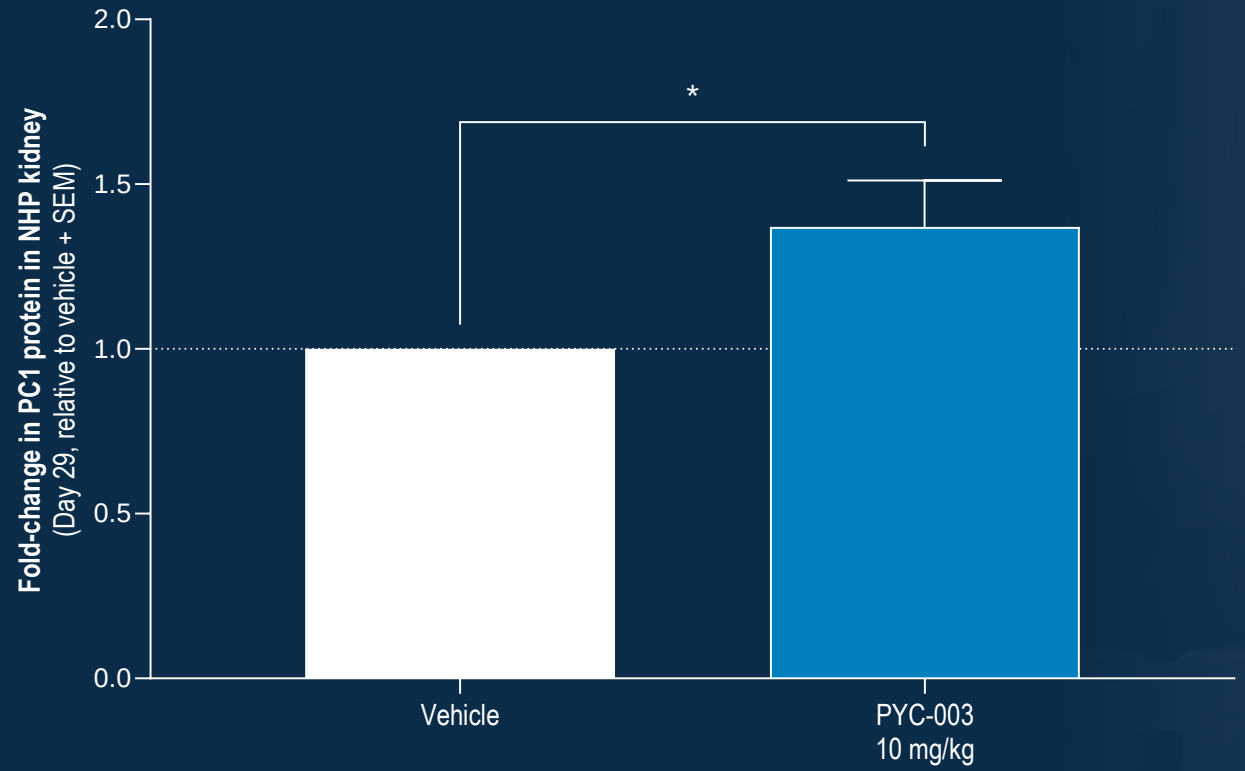
1. Refer ASX Announcement 17 November 2023
2. PC1 full length protein fold-change over untreated (normalised to total protein) assessed at day 3 following treatment with either 10 µM or 30 µM PYC-003. Data presented mean+S.D (n=2 for protein). The data show a statistically significant (Dunnett's post-hoc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

PYC-003 increases PC1 protein levels *in vivo* in both mice[1] and NHPs

PYC Therapeutics

PYC-003 has a fully integrated PK/PD/tolerability profile *in vivo*

PYC-003 increases levels of PC1 protein (the missing protein that causes PKD) in Non-Human Primate (NHP) kidneys 28 days after a single safe and well-tolerated dose[2]



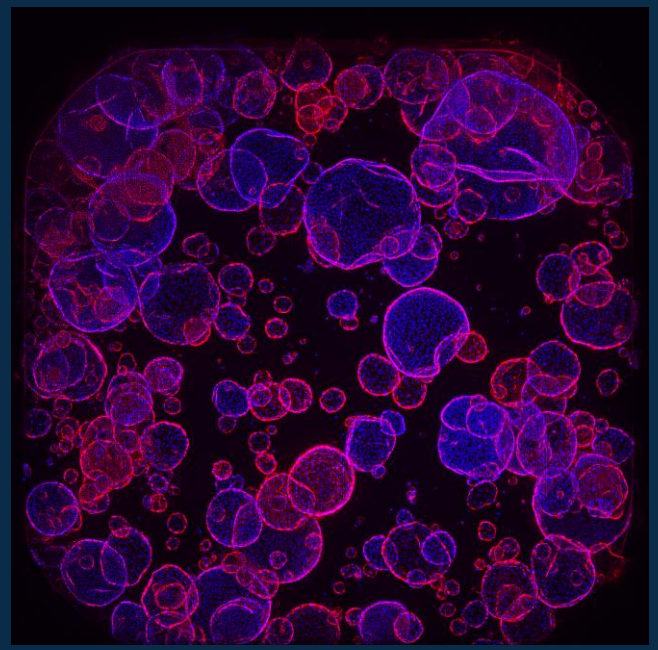
- Efficacy
- Delivery
- Safety

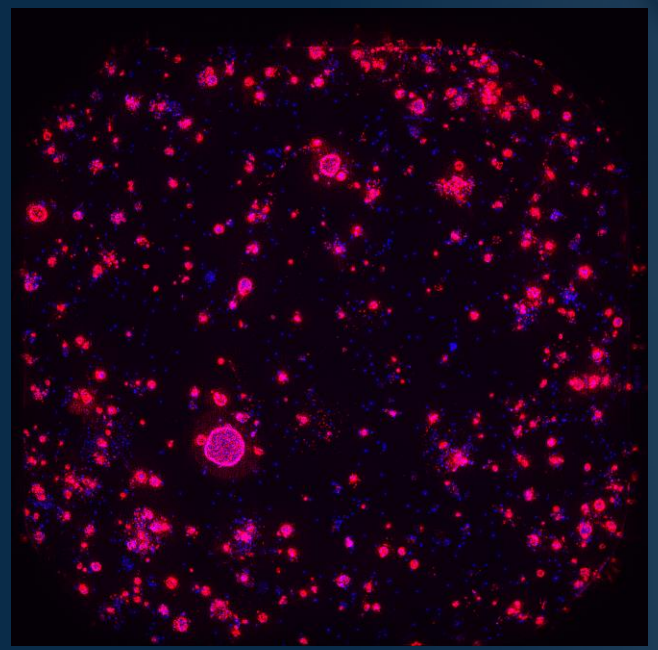
1. Refer ASX Announcement 17 November 2023
2. PC1 protein following either vehicle control or a single 10 mg/kg dose of PYC-003 normalised to total protein. Data shown as mean + SEM of n=2 WB experiments (n=2, 2 biological and 2 technical replicates). One-way ANOVA *p<0.05

PYC-003 rescues the disease phenotype in *ex vivo* models of PKD derived from patients with end-stage renal failure

PYC Therapeutics

Untreated → **PYC-003 Treated**





- Efficacy
- Delivery
- Safety

3D polycystic kidney disease model derived from an end-stage renal failure patient

Patient organoids/3D kidney models are the 'most informative model for therapeutic testing in PKD'[2]

1. Refer ASX Announcement 13 November 2023
2. Sieben CJ, Harris PC. Experimental Models of Polycystic Kidney Disease: Applications and Therapeutic Testing. Kidney360. 2023;4(8):1155-73.

Delivery profile

1. PYC-003 preferentially distributes to the target organs in PKD – the kidney and, to a lesser extent, the liver

2. Within the kidney, PYC-003 is present in the cells that drive the disease – the Renal Tubular Epithelial Cells

3. PYC-003 distributes to the cyst-forming cells in animal models of PKD

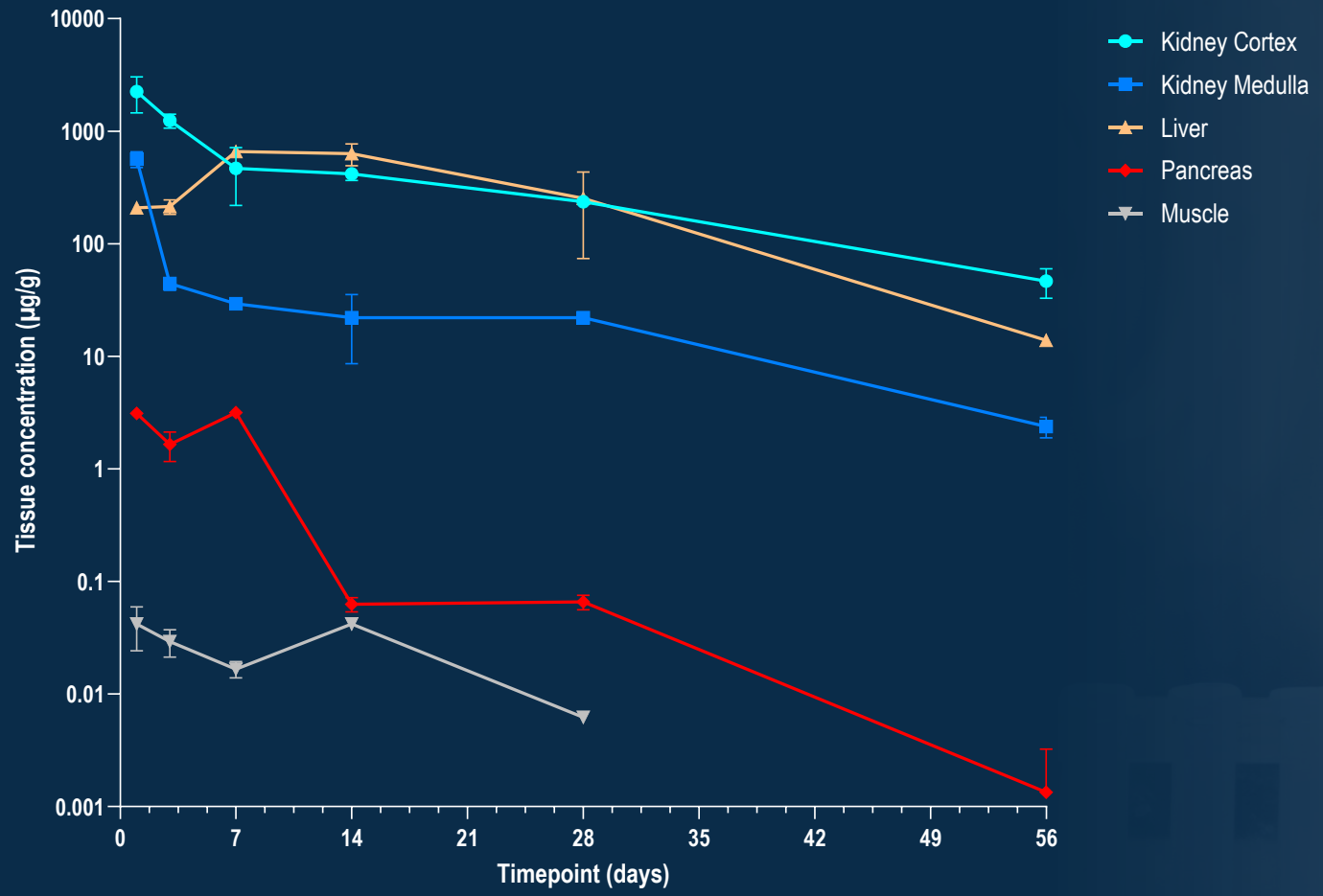
4. PYC-003 has a sustained half-life in the target organ – affording a patient-preferred dosing interval of approximately one intravenous infusion every 2 months

PYC Therapeutics

The delivery peptide selected for PYC-003 has been specifically chosen for its preferential distribution profile to the affected organs

PYC Therapeutics

Distribution of PYC-003 in NHPs is strongly biased towards target organs (kidney and liver)



- Efficacy
- Delivery
- Safety

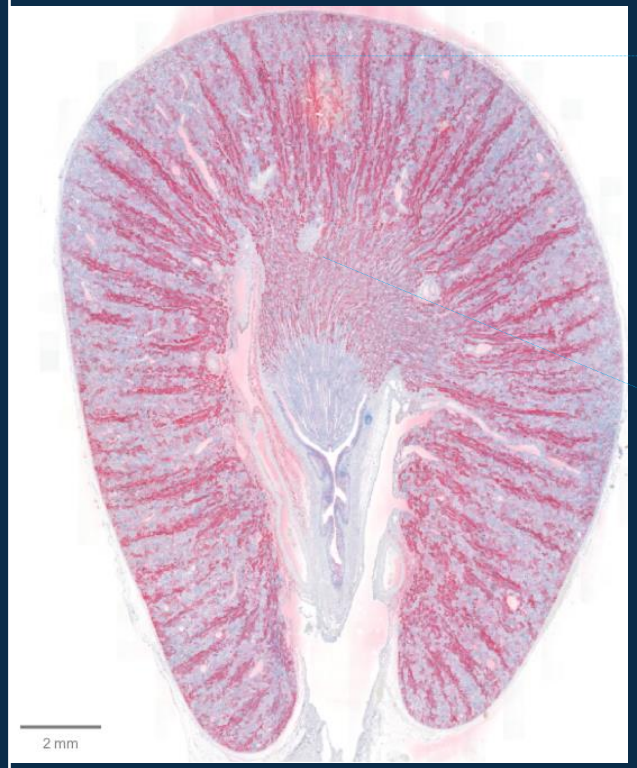
Non-GLP PK studies conducted in NHPs with 6 cohorts of 2 subjects each receiving a single 10 mg/kg dose of PYC-003 informing assessment of tissue concentration in all major organs across multiple time-points through to 56 days of follow up.

PYC-003 distributes to the Renal Tubular Epithelial Cells (RTECs) that drive PKD

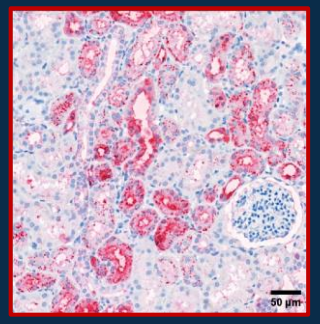
PYC Therapeutics

Effective delivery to the RTECs in NHP kidney

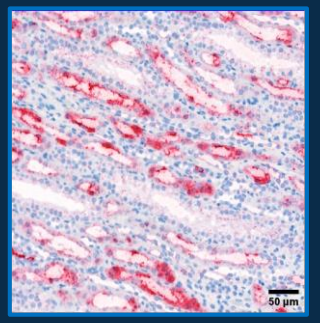
Distribution in NHP kidney[1]
PYC-003 treated



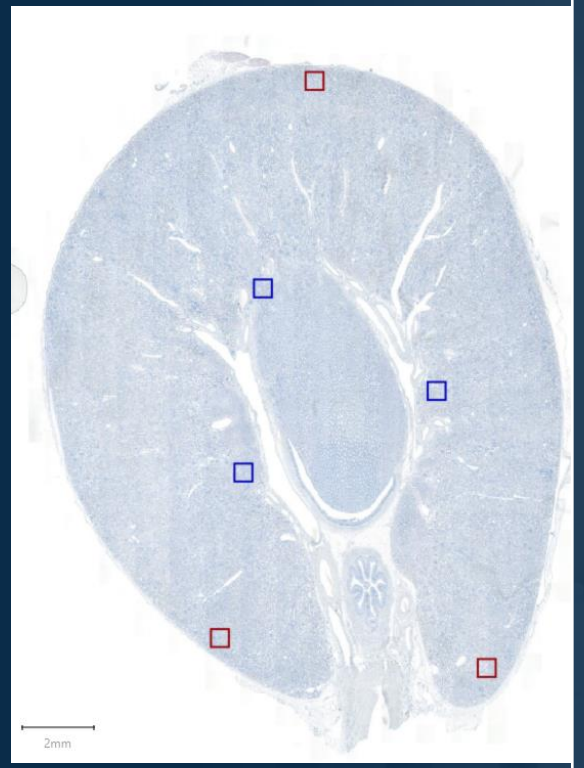
✓ Cortex



✓ Medulla



Distribution in NHP kidney
PBS Control



miRNAscope image of an NHP kidney with PYC-003 (represented by pink dots) at 59 µM concentration[1]

- Efficacy
- Delivery
- Safety

PYC-003

DNA

1. Distribution of PYC-003 to wild-type NHP kidney at a concentration of 59 µM – the expected Cmax following a single 3 mg/kg dose

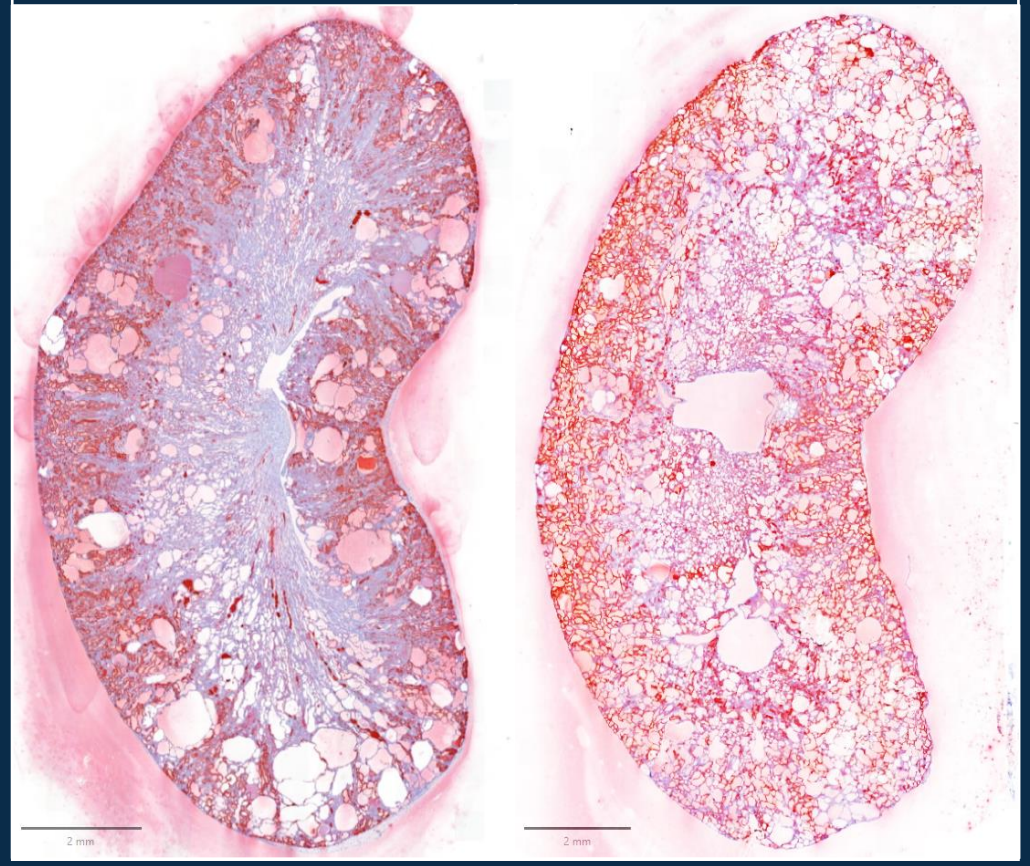
PYC-003 distributes to cyst-forming cells in animal models of PKD

PYC Therapeutics

Distribution of PYC-003 to the cyst-forming cells in mouse models of PKD[1]

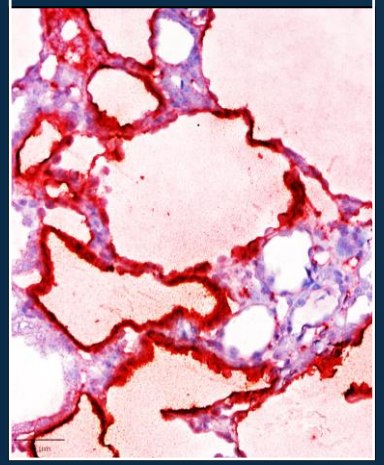
***PKD1* knockout models treated with PYC-003**

Mouse 1 | Mouse 2

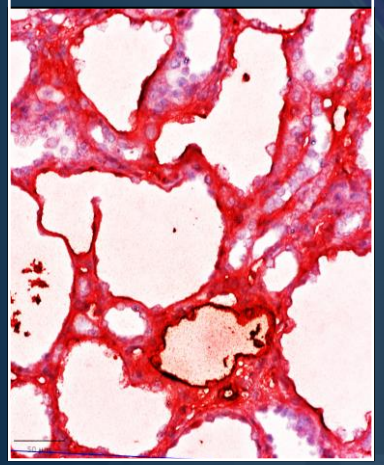


Distribution to both cortical and medullary cysts

Cortex



Medulla



- Efficacy
- Delivery
- Safety

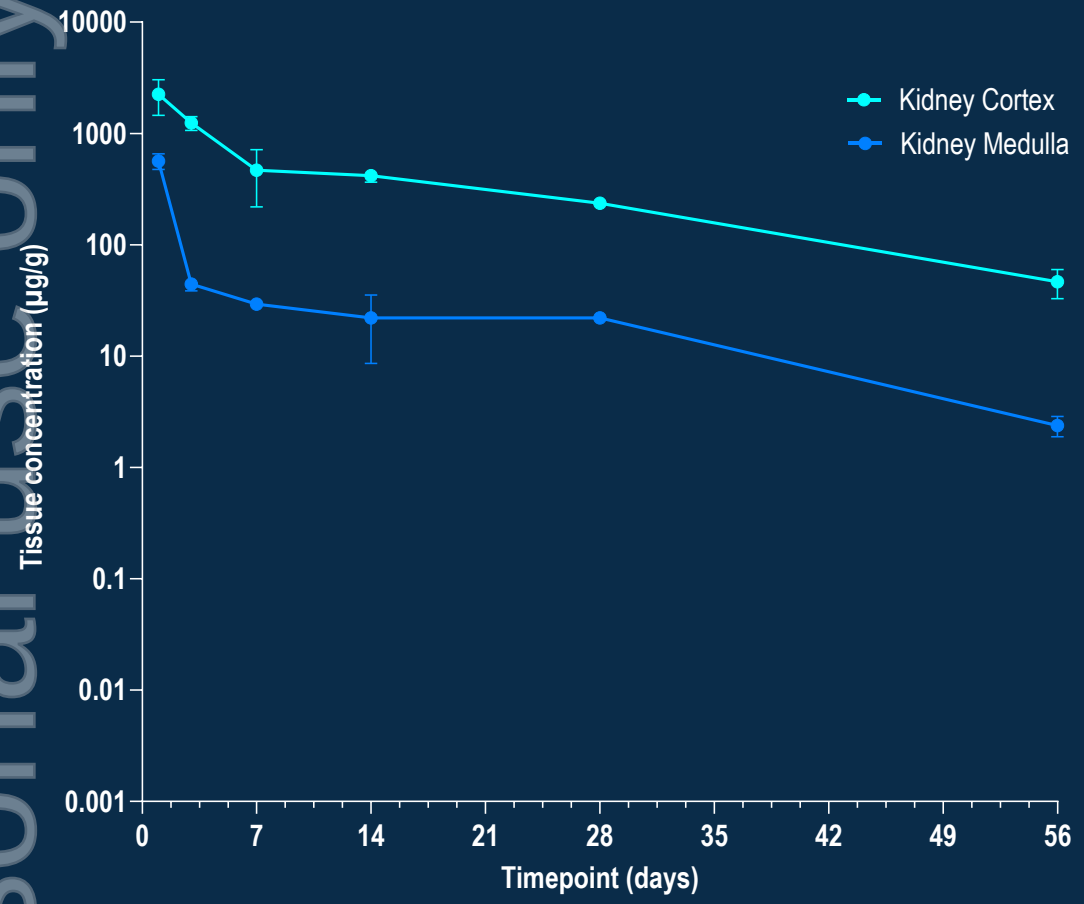
PYC-003

DNA

1. Distribution of PYC-003 to cystic kidney in PKD1 knockout (KO) model of PKD. Images captured Day 3 post-dose single 10 mg/kg dose of the drug candidate and measured by miRNAscope

PYC-003 has a long half-life in kidney – affording a patient-preferred dosing interval of one intravenous infusion up to every 2 months[1]

PYC Therapeutics



Half-life of 14 days[2] in the kidney affords a human dosing interval of approximately 2 months[1]

- Efficacy
- Delivery
- Safety

1. The expected human dosing interval for PYC-003 is approximately once every two months. Non-GLP PK studies conducted in NHPs with 6 cohorts of 2 subjects each receiving a single 10 mg/kg dose of PYC-003 informing assessment of tissue concentration in all major organs across multiple time-points through to 56 days of follow up.
2. Calculated after Day 7

Safety-tolerability profile

1. PYC-003 has a No Observable Adverse Effect Level (NOAEL) of 12 mg/kg in NHPs

2. There is no evidence of impaired renal function in NHPs following dosing with PYC-003[1]

3. PYC-003 has an anticipated human therapeutic range of 0.8 to 3 mg/kg[2]

PYC Therapeutics

1. At doses up to 12 mg/kg (the NOAEL as assessed in GLP toxicology studies)
2. Based on allometric scaling from mouse and NHP PK results and effective concentrations *in vitro* and *ex vivo*

PYC-003 has a No Observable Adverse Effect Level (NOAEL) of 12 mg/kg in NHPs

PYC Therapeutics

12 mg/kg is the NOAEL in NHPs in GLP toxicology studies

Cohort	Number of animals	Treatment Group	Treatment Related Adverse Events (occurrence/number of animals)	Outcome (Tolerated/ not Tolerated)
1	8	Vehicle control	0/8	Tolerated
2	8	4.8 mg/kg PYC-003	0/8	Tolerated
3	8	12 mg/kg PYC-003	0/8	Tolerated
4	8	30 mg/kg PYC-003	8/8	Not tolerated[1]

NOAEL

Efficacy

Delivery

Safety

- Study animals were monitored for 28 days following a single intravenous administration of PYC-003 or vehicle control at the relevant dose
- Potential adverse events were monitored for via in-life observations and biochemical markers through regular blood testing
- All major organs were analysed for histopathological changes upon completion of the in-life study period
- No Treatment Related Adverse Effects were reported in any of the study animals at any of the doses of PYC-003 administered up to and including the NOAEL

1. A non-tolerated dose of PYC-003 at 30 mg/kg was also established in these studies with adverse effects (regenerative changes observed upon histopathological evaluation with associated clinical pathology findings) limited to the target organ (kidney) and likely reflecting the concentration of drug in kidney at these doses (>3,000,000 ng/g of PYC-003 in kidney at Day 1 following a single dose).

There is no evidence of impaired renal function in NHPs treated with PYC-003 doses up to and including the NOAEL

PYC Therapeutics

Good Laboratory Practice (GLP) toxicology study electrolyte results

Cohort	Number of animals	Treatment Group	Change in serum Magnesium outside normal range[1]	Change in Creatinine outside normal range[1]
1	8	Vehicle control	No	No
2	8	4.8 mg/kg PYC-003	No	No
3	8	12 mg/kg PYC-003	No	No
4	8	30 mg/kg PYC-003	Yes	Yes

NOAEL

Efficacy

Delivery

Safety

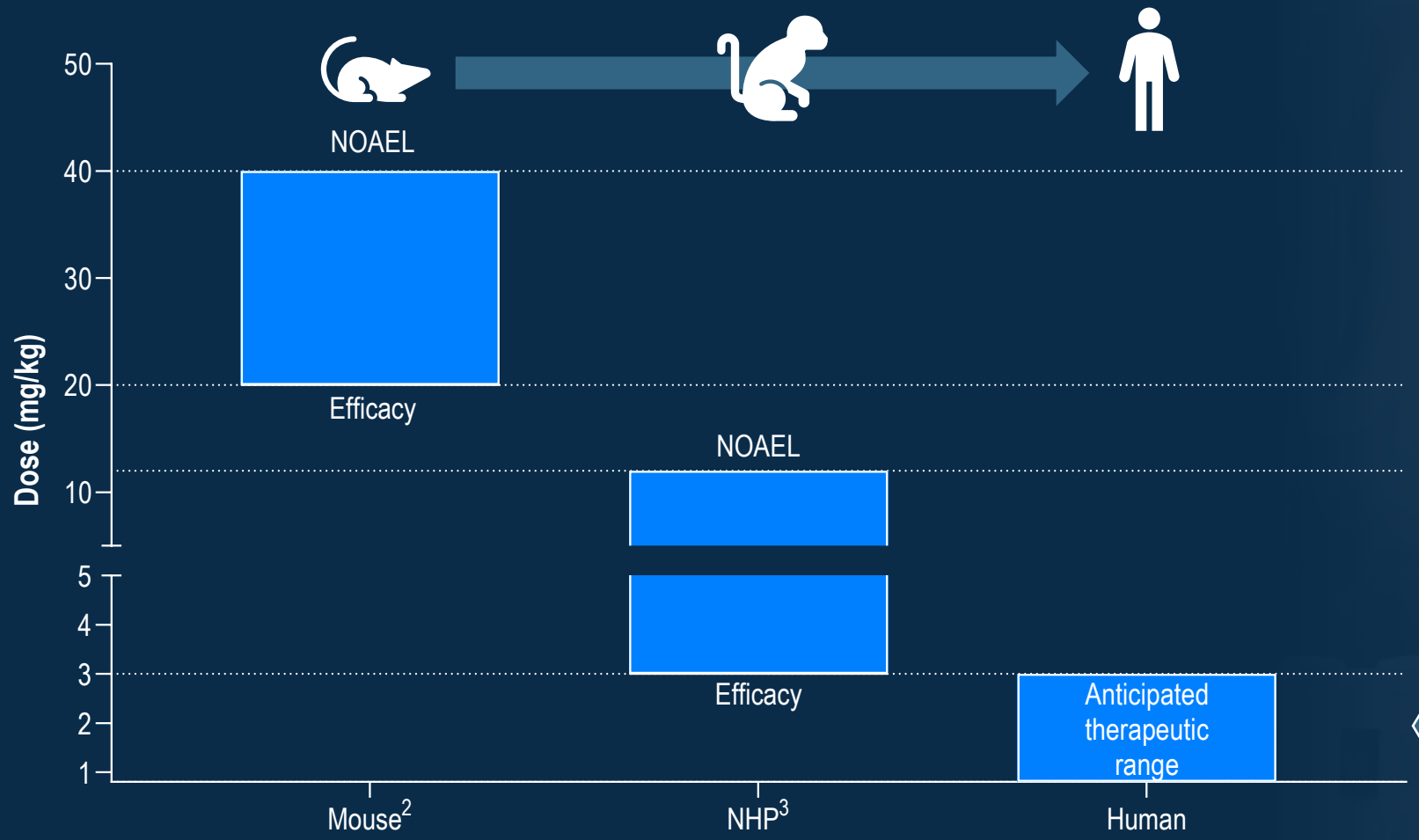
- Study animals were monitored for 28 days following a single intravenous administration of PYC-003 or vehicle control at the relevant dose
- Potential adverse events were monitored for via in-life observations and biochemical markers through regular blood testing
- All major organs were analysed for histopathological changes upon completion of the in-life study period
- No Treatment Related Adverse Effects were reported in any of the study animals at any of the doses of PYC-003 administered up to and including the NOAEL

1. Mean change in blood biochemical markers

PYC-003 dosing of 0.8 to 3 mg/kg is expected to reach therapeutic levels in humans[1]

PYC Therapeutics

PYC-003 has an anticipated human therapeutic dose range of 0.8 – 3 mg/kg based on allometric scaling[1]



Efficacy

Delivery

Safety

PYC-003 prevents cyst growth in PKD patient-derived kidneys at concentrations expected to be achieved in the human kidney at doses between 0.8 and 3 mg/kg[1]

1. Management estimates as at 27 November 2024. PYC-003 is effective at reducing cyst area and frequency in PKD-patient derived 3D cyst model at treatment concentrations as low as 30 uM, without transfection.
2. PYC-003 NOAEL determined as 40 mg/kg in GLP mouse toxicology study. 1.4-fold upregulation of *PKD1* mRNA achieved with mouse surrogate (used for PD study due to differences in target region of transcript) Day 3 after single 20 mg/kg dose.
3. PYC-003 NOAEL determined as 12 mg/kg in GLP NHP DRF study. A 1.4-fold and statistically significant increase in PC1 protein was observed in wild-type monkeys 28 days after a single 10 mg/kg dose of PYC-003.

Clinical pathway for PYC-003

1. PYC-003 will progress to human trials in 2025 with potential for a rapid path through the clinic[1]

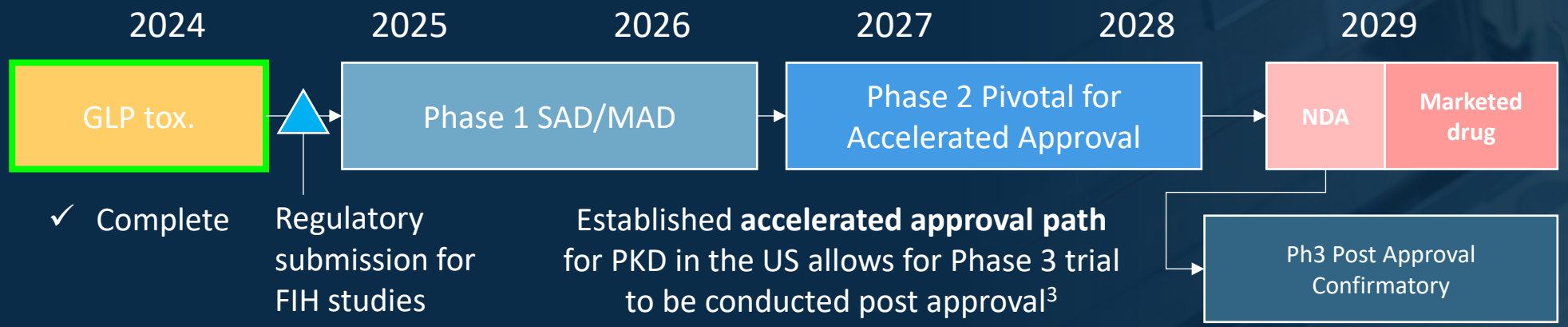
2. Initial safety and efficacy insights for PYC-003 are expected to be available in 2025/2026[1]

1. Clinical trial plan is subject to confirmation and depends on multiple factors, including the duration of action of the therapeutic candidate and regulatory discussions. Management forecast as of 27 November 2024.

PYC-003 will progress to human trials in 2025 with potential for a rapid path through the clinic[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[3]

FDA special designations

Potentially accelerating path to market:

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

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

Initial insights on safety and efficacy are expected to be available through the 1a/1b studies[1]

2025/2026

Phase 1 SAD/MAD

Phase 1a SAD | Phase 1b MAD

Phase 1a Part A | Phase 1a Part B | Phase 1b MAD

Phase 1a Part A

Randomized double-blinded placebo-controlled study in **healthy volunteers**

- 3 dose cohorts (low, mid, high dose of PYC-003)
- 6 healthy volunteers receive PYC-003 per cohort
- 2 healthy volunteers receive placebo per cohort
- Ages included: 18–60 years
- Total healthy volunteers: 24

Phase 1a Part B

Open-label study in ***PKD1*-ADPKD patients**

- 3 dose cohorts (low, mid, high dose of PYC-003)
- 6 *PKD1*-ADPKD patients receive PYC-003 per cohort
- Ages included: 18–60 years
- Total *PKD1*-ADPKD patients: 18

Phase 1b MAD

Randomized double-blinded placebo-controlled study in ***PKD1*-ADPKD patients**

- 2-3 PYC-003 dose cohorts
- 9 *PKD1*-ADPKD patients receive PYC-003 per cohort
- 3 *PKD1*-ADPKD patients receive placebo per cohort
- Dose frequency: 6-8 weekly
- Ages included: 18–60 years
- Total *PKD1* patients: 24–36

★ *Safety insights*

★ *Efficacy insights*

Endpoints

Primary:
Safety and tolerability of PYC-003

Secondary:
Characterise the pharmacokinetics (PK) of PYC-003

Exploratory:
Assess potential treatment benefit using:

1) Exploratory biomarkers
2) Advanced imaging techniques
3) Surrogate/registrational endpoints (htTKV, eGFR)

Assessed at Month 1, 3, and 6

1. Clinical trial plan is subject to confirmation and depends on multiple factors, including the duration of action of the therapeutic candidate and regulatory discussions. Management forecast as of 27 November 2024.