PYC Therapeutics

Life-changing science

Polycystic Kidney Disease program

November 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.

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.

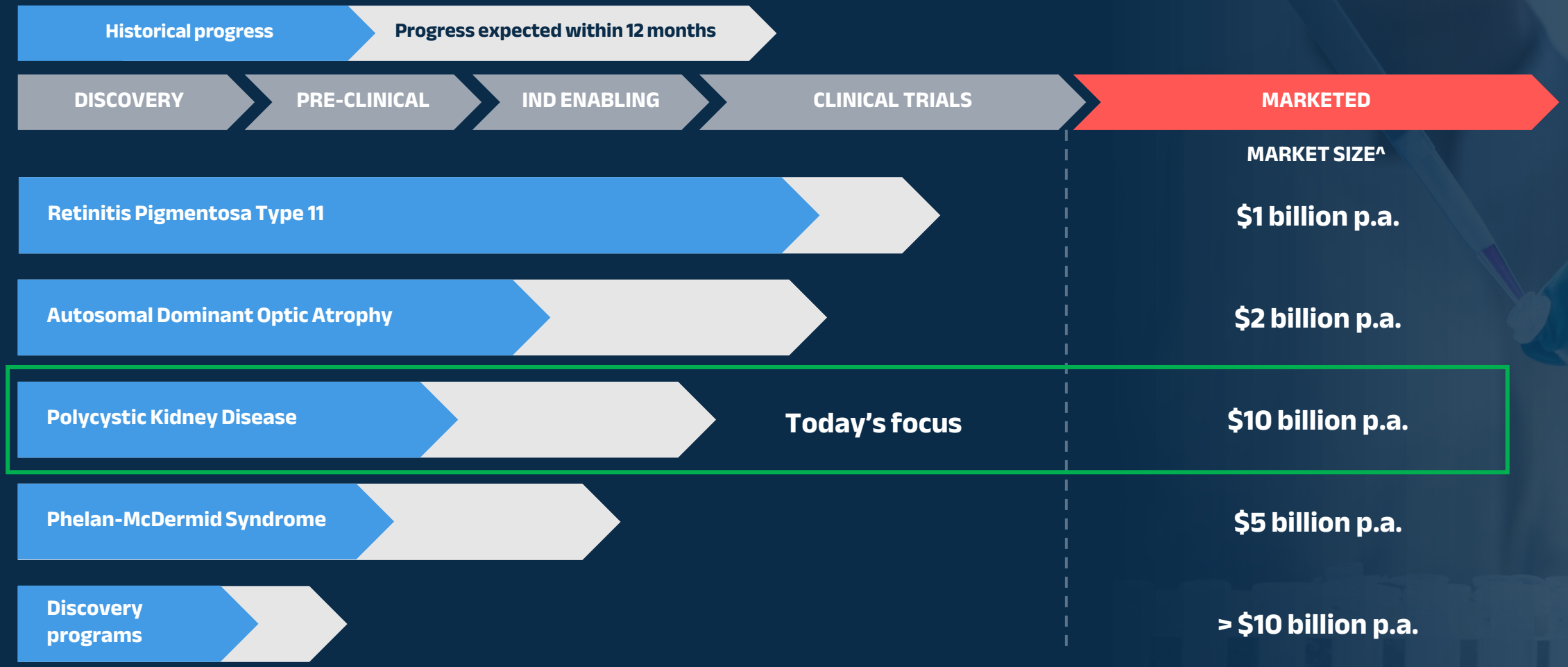
This presentation should not be relied on as a recommendation or forecast by PYC. Nothing in this presentation should be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.

PYC Therapeutics

- Is a **clinical-stage** drug discovery & development company
- Creates **first-in-class** RNA drugs for patients with genetic diseases and inadequate treatment options
- Develops drugs with the **highest likelihood of success in human studies** (5x higher than the industry average)[1]

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

PYC has added a first-in-class drug candidate to its pipeline for the >5 million people worldwide with Polycystic Kidney Disease



PYC Therapeutics

* PYC 96.2% ownership of VP-001 (3.8% ownership by Lions Eye Institute, Australia) and 100% ownership of all other pipeline programs
^ Market size is projected by multiplying patient prevalence per indication by the median orphan drug price of $150k p.a. EvaluatePharma. Orphan Drug Report. 2019.

PYC's drug candidate for Polycystic Kidney Disease has 6 defining features

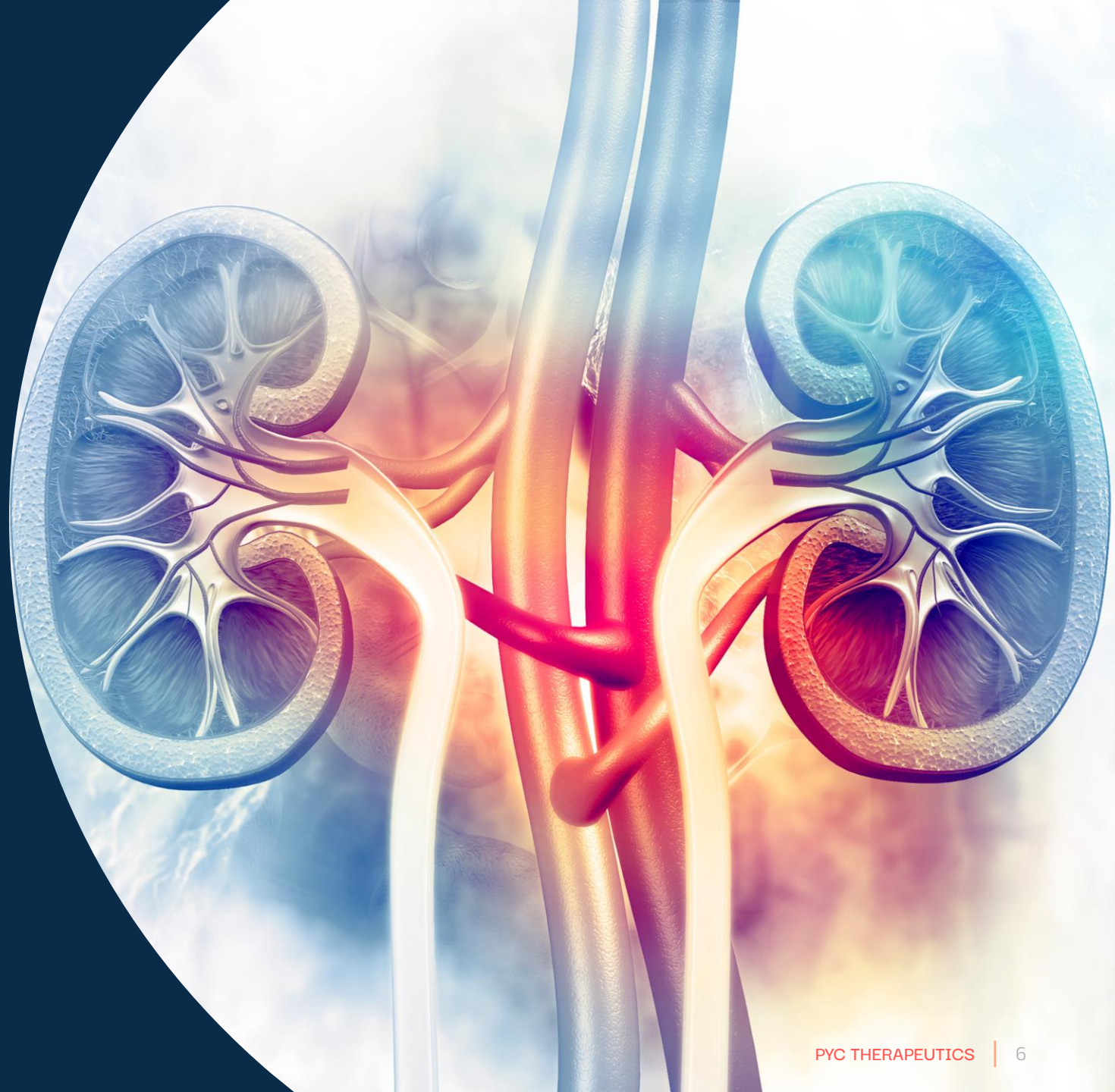
1. Addresses a major unmet patient need[1]
2. Overcomes the delivery challenge[2]
3. Has already demonstrated efficacy[2]
4. Will progress to human trials in 2024[5]
5. Has a high-velocity path to a >$10 billion p.a. market – currently anticipated in 2027[1-5]
6. Benefits from >5x the likelihood of success in human trials[6] as a monogenic disorder

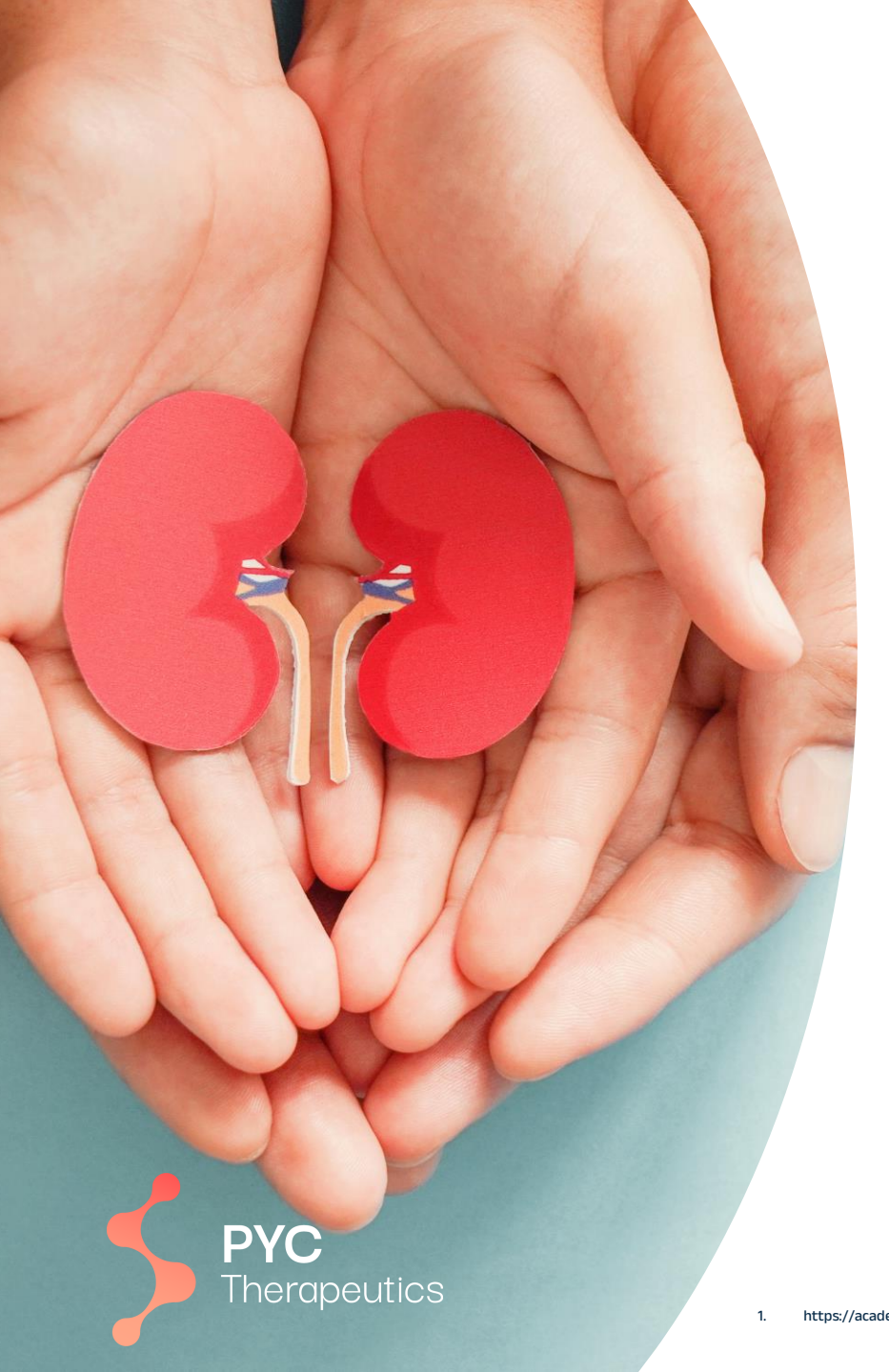
PYC Therapeutics

1. 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.
2. Refer ASX Announcement: 13 November 2023
3. FDA. Development and Approval Process | Drugs. 2022. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
4. Market size is projected by multiplying patient prevalence per indication by the median orphan drug price of $150k p.a. EvaluatePharma. Orphan Drug Report. 2019.
5. Subject to regulatory approvals. Management forecast as of November 2023.
6. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232

PYC-003

A first-in-class drug candidate for the treatment of Autosomal Dominant Polycystic Kidney Disease (PKD)





PKD patient experience

For patients with PKD, the erratic onset of pain contributes to the unpredictability of daily living, dictates career and family planning, is socially limiting, and renders those affected unable to establish and pursue their long-term life goals[1]

PYC Therapeutics

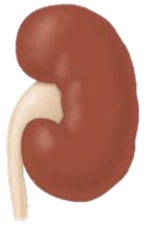
1. https://academic.oup.com/ndt/article/30/5/790/2332864

1. Polycystic Kidney Disease is an area of major unmet patient need

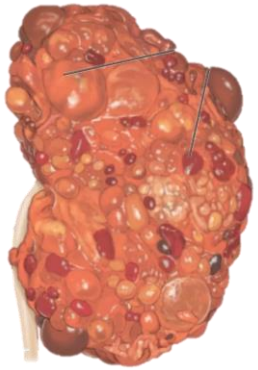
There is an urgent need for treatments with disease-modifying potential in Polycystic Kidney Disease

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]

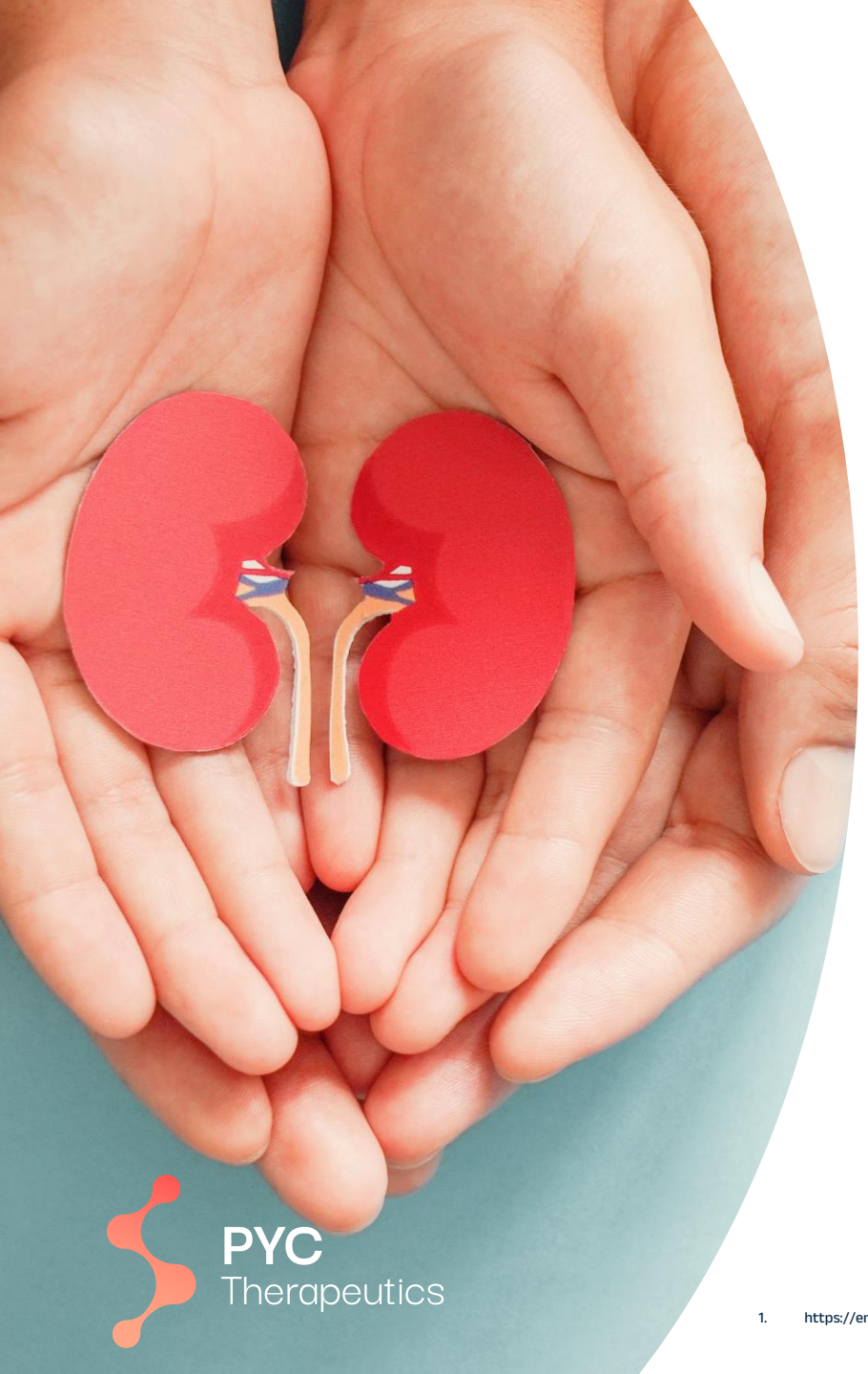
Life-changing

Half of all PKD patients will require a **kidney transplant** by the age of 60 due to **end-stage renal failure**[2]

Limited treatment options

There are **no drugs available** that address the underlying cause of the disease

1. 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.
2. 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.



The delivery challenge

‘While everybody else was so hyped and giving Nobel Prizes for CRISPR and all that, we realized those weren’t really the limitations”

‘The limitations were really delivery’[1]

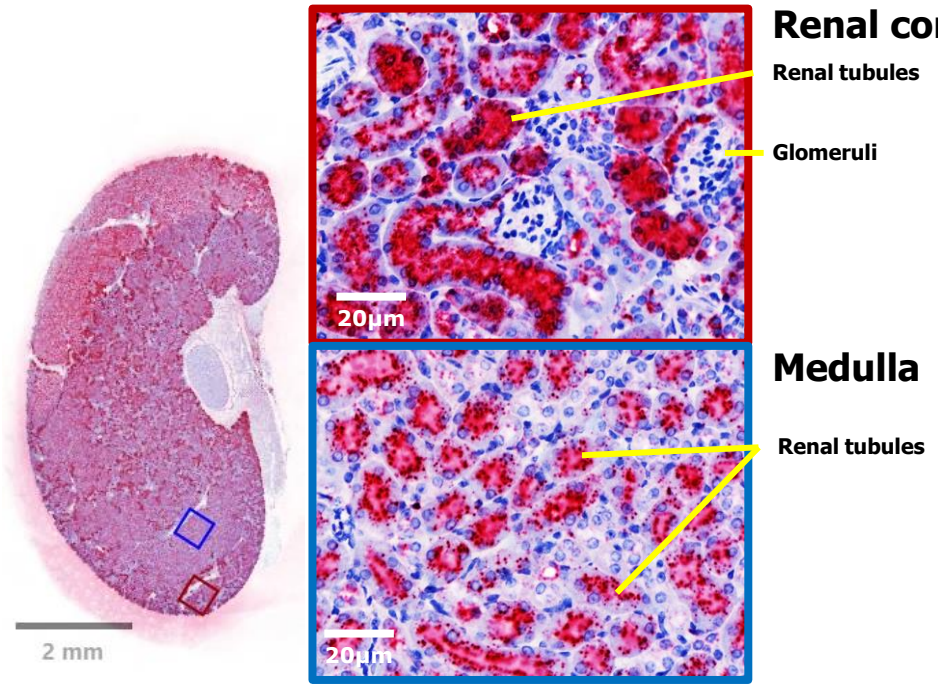
- George Yancopoulos
President and CSO, Regeneron

PYC Therapeutics

1. https://endpts.com/regeneron-brings-its-antibody-chops-to-gene-editings-biggest-problem/

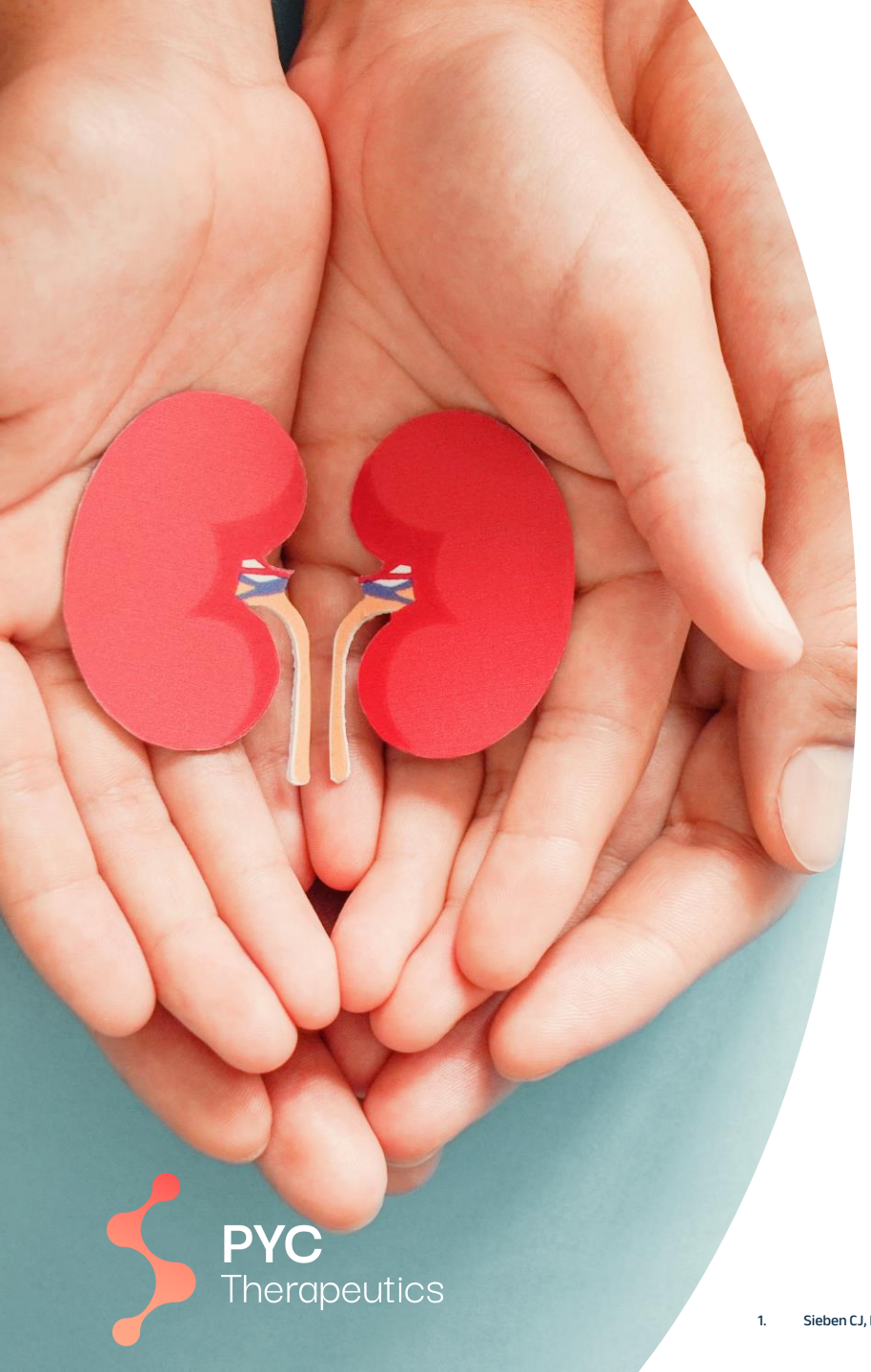
2. PYC's proprietary delivery technology overcomes the major challenge for precision medicine in the kidney

PYC's drug candidate for PKD can reach all of the cells affected by the disease - PYC-003* achieves a broad, even and deep distribution throughout the kidney following a single 10mg/kg dose *in vivo*



Drug distribution in C57BL/6 mouse kidney 3 days after a single intravenous 10 mg/kg dose of the mouse equivalent of PYC-003 as measured by miRNAscope (pink dots represent drug presence)

PYC-003 mouse surrogate used due to difference in PKD1 sequence between humans and mice.



The ‘killer experiment’

Patient organoids/3D kidney models are the ‘most informative model for therapeutic testing in PKD”[1]

- Peter C. Harris

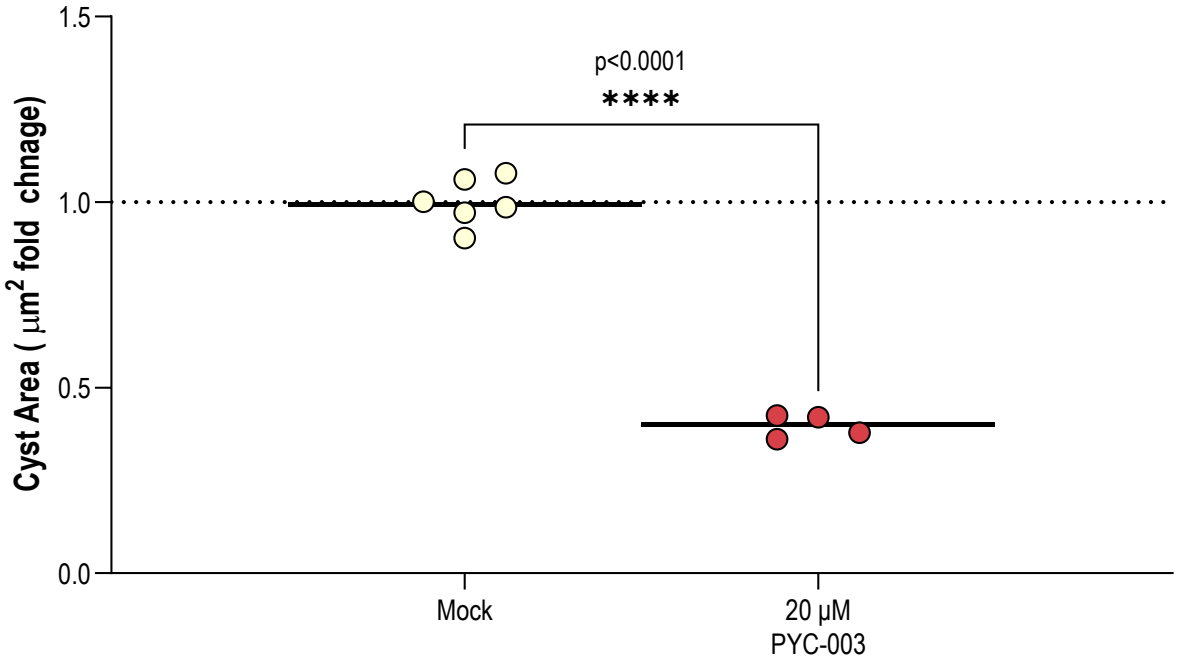
Leading PKD Genetic Researcher, Mayo Clinic

PYC Therapeutics

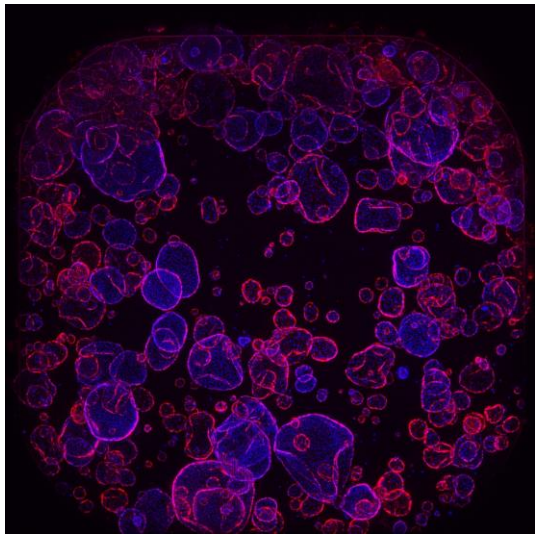
1. Sieben CJ, Harris PC. Experimental Models of Polycystic Kidney Disease: Applications and Therapeutic Testing. Kidney360. 2023;4(8):1155-73.

3. PYC's PKD drug candidate has already demonstrated efficacy in 3D kidney models from patients with the disease

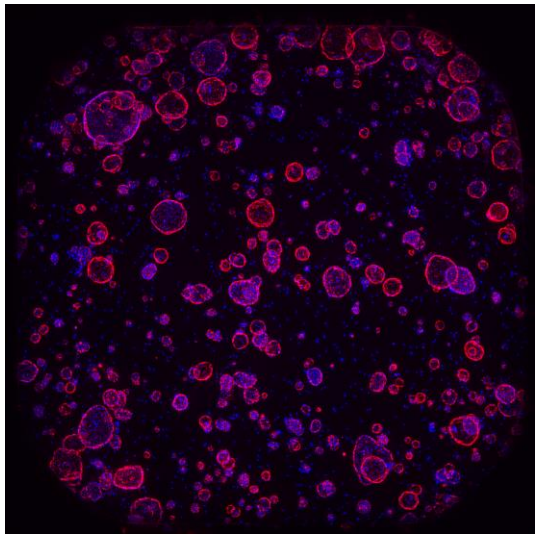
PYC's drug candidate for PKD is effective in 'the killer experiment' - Treatment with PYC-003 results in decreased frequency and area of cysts in a 3D model of PKD derived from patients with late-stage disease



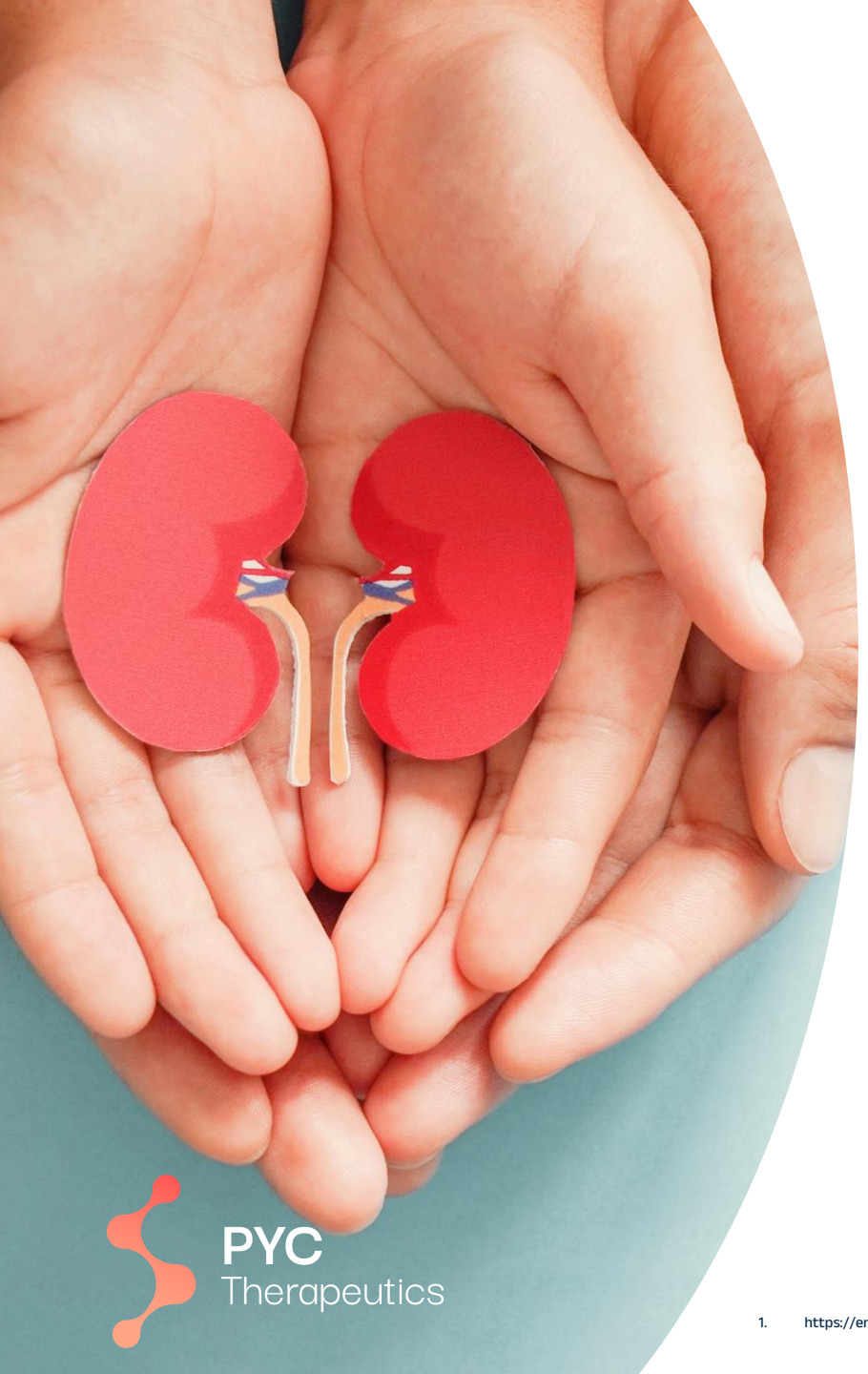
Untreated 3D cyst model



PYC-003 treated 3D cyst model



Treatment with PYC-003 results in decreased frequency and area of cysts in a 3D model of PKD derived from patients with late-stage disease. Images captured 7 days after treatment. Mock control samples treated with 5% H20. Data are presented as mean+S.D (N=1 biological replicate with 4-6 technical replicates). Statistical significance was analyzed using Student's t-test. *p=0.05, **p=0.01, ***p=0.005, ****p<0.0001. See https://www.crownbio.com/hubfs/WRCrownbio2021%20Assets/Resources/FactSheet/Crown-Bioscience-Factsheet-Cyst-Swelling-Assay-for-ADPKD.pdf for details of model and ASX release of 13 November 2023



High-velocity path to market

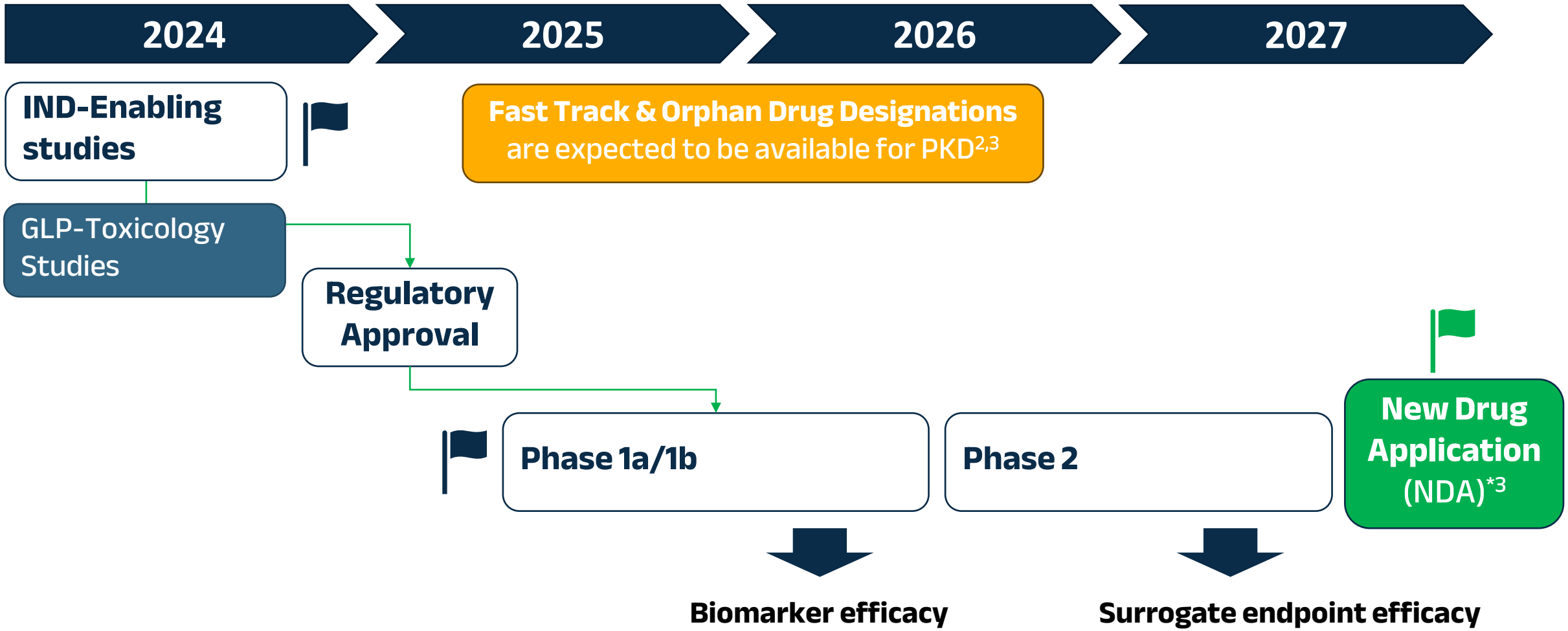
‘[Accelerated approval is] a way of getting there that will benefit individuals in medical need, at the earliest possible timepoint while ultimately giving us the opportunity to get the data we need for turning those to traditional approvals’[1]

- Peter Marks
Director Center for Biologics Evaluation and Research, FDA

PYC Therapeutics

1. https://endpts.com/qa-fdas-peter-marks-ready-to-encourage-more-accelerated-approvals-for-rare-diseases/

4. PYC-003 will progress to human trials in 2024[1]

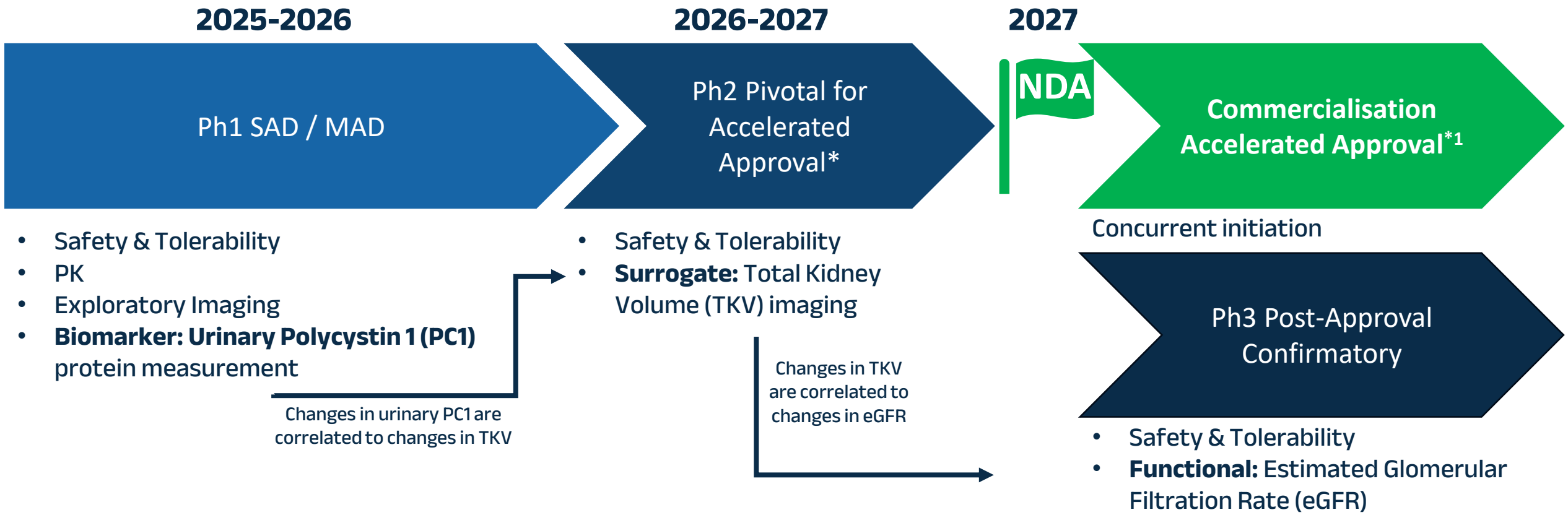


1. Clinical trial plan is subject to confirmation and depends on multiple factors, including the duration of action of the therapeutic candidate and regulatory discussions. Management forecast as of November 2023.
2. Waxman H.A. H.R.5238-97th Congress (1981-1982): Orphan Drug Act. 1983
3. FDA. Development and Approval Process | Drugs. 2022. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program

*Accelerated approval allows for the earlier approval of drugs that treat serious conditions, and fill an unmet medical need based on a surrogate endpoint. There is an established accelerated approval path in PKD, which allows for Phase 3 trial to be conducted post approval. FDA has designated TKV as a reasonably likely surrogate endpoint (U.S. Food and Drug Administration, 2020) https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

5. PYC-003 has a high-velocity path to market with the potential for approval after a Phase 2 clinical trial

PYC-003 Clinical Development Plan with Accelerated Approval*[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 November 2023. Potential for approval after a Phase 2 clinical trial with concurrent commercialisation and Phase 3 studies. Based on single pivotal trial demonstrating statistically significant reduction in TKV compared to placebo

*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. Development and Approval Process | Drugs. 2022. https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program. There is an established accelerated approval path in PKD, which allows for Phase 3 trial to be conducted post approval. FDA has designated TKV as a reasonably likely surrogate endpoint (U.S. Food and Drug Administration, 2020) https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

6. Drugs targeting single gene diseases are 5 to 8 times more likely to succeed in human trials

PYC Therapeutics

PYC focuses on severe diseases caused by a single gene

These have the highest likelihood of success in the clinic[1-3]

How likely is a drug targeting a monogenic disease to succeed in the clinic?	Source
6x more likely than the industry average (of ~10%) with a 64% likelihood of successful marketing approval on commencement of Phase 1 studies	Alnylam – pipeline retrospective[1]
Up to 8x more likely	Atlas Ventures[2]
5x more likely	UK Biobank[3]

Why?

Increased probability of efficacy

Address the root cause of disease, potential to address all symptoms important to patients

+

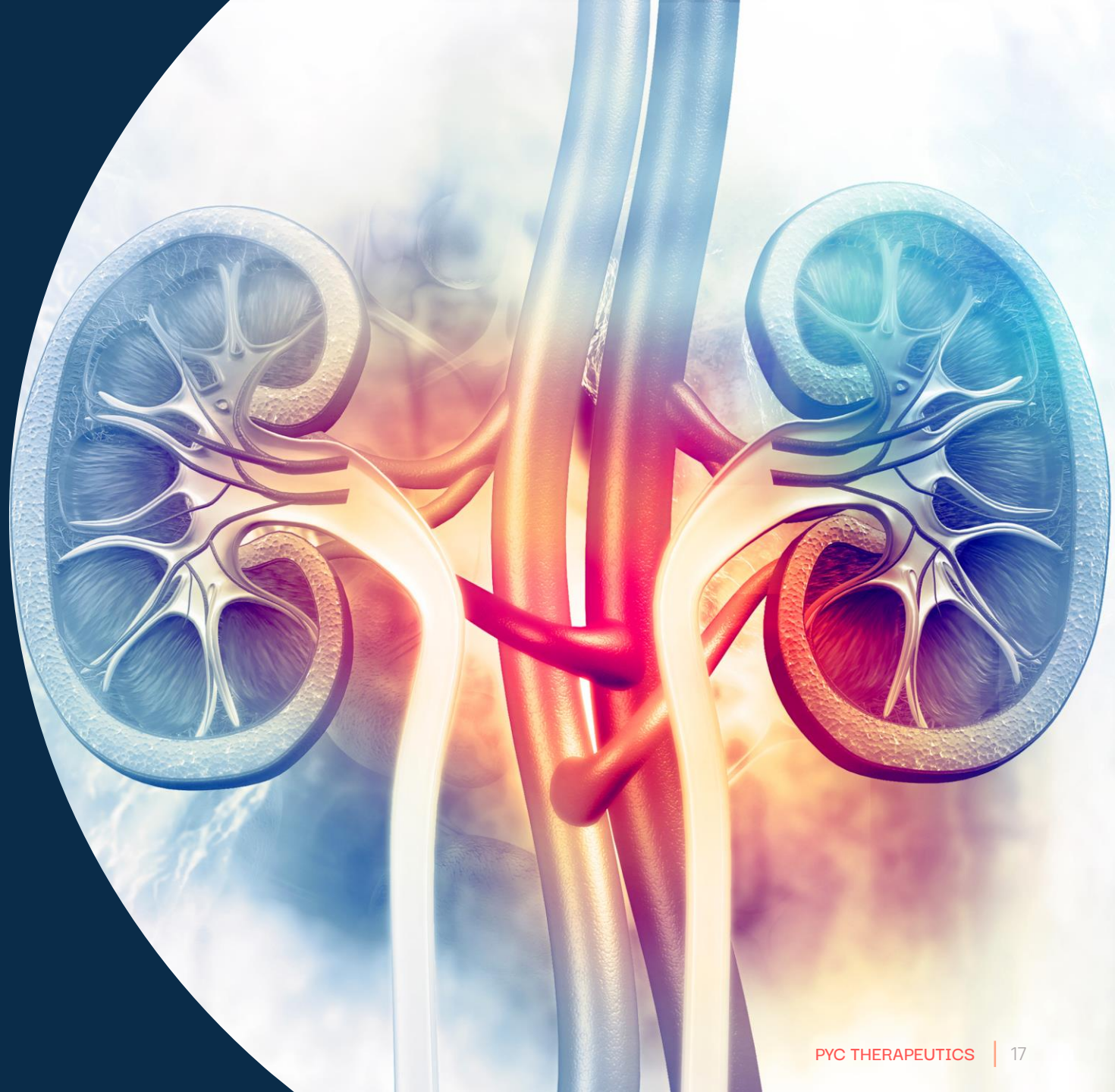
Increased probability of safety

Decreased probability of off-target safety issues due to specificity of effect

1. https://news.alnylam.com/rnai/articles/harnessing-human-genetics-power-next-wave-rnai-therapeutics
2. https://www.youtube.com/watch?v=L0NM9ekseJ4
3. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: https://doi.org/10.1101/2020.11.02.20222232

PYC-003

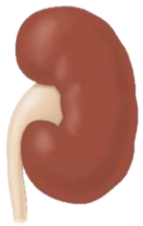
Addresses the root cause of the disease with potential to regenerate damaged kidneys and restore function

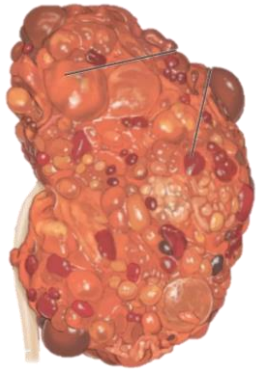


PKD is caused by a mutation in one copy of a single gene

PYC Therapeutics

	Unaffected		PKD Patient
		PKD1 DNA	
		PKD1 mRNA	
Wild type PC1 protein expression (100%)		PC1 protein	
	Balanced	Ca^{2+} signalling	**Balance lost**
	Normal	Renal tubule architecture	**Abnormal**
		Kidney	





80% of PKD patients have a mutation in one copy of *PKD1* DNA[1]

Haploinsufficient PC1 protein (~50% of wild-type levels)[2]

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

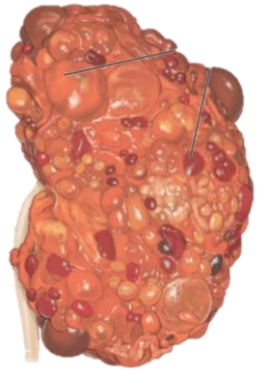
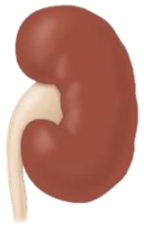
It has a critical role regulating Ca^{2+} signalling and maintaining the normal structure of renal tubules[2]

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.

PYC-003 addresses this genetic mutation at its root cause

PYC Therapeutics

	PKD Patient		PKD Patient + PYC-003
80% of PKD patients have a mutation in one copy of *PKD1* DNA[1]		*PKD1* DNA	
		PKD1 mRNA	PYC-003
Haploinsufficient PC1 protein (~50% of wild-type levels)		PC1 protein	
	Balance lost	Ca^{2+} signalling	**Balance restored**
	Abnormal	Renal tubule architecture	**Restored**
PKD is characterized by cyst formation and enlargement in kidney due to deficient PC1 protein[2]		Kidney	

PYC-003 effectively

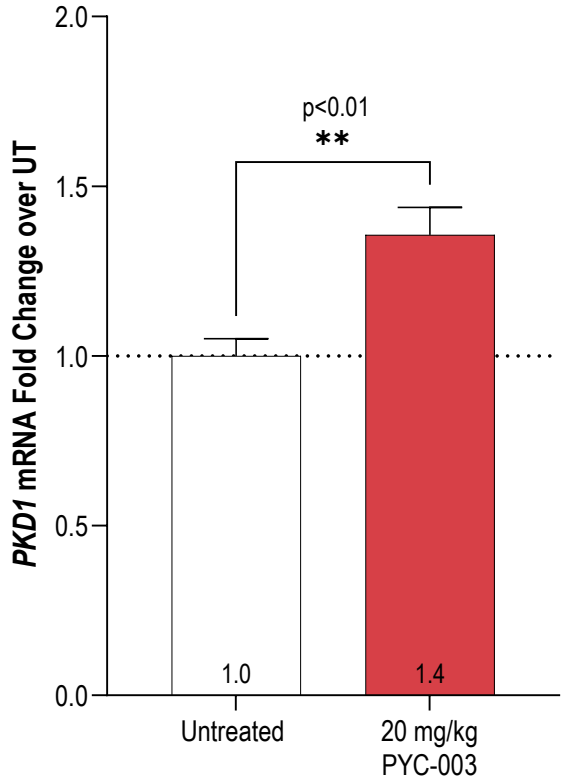
- ✓ Increases *PKD1* mRNA
- ✓ Increases PC1 protein
- ✓ Prevents progression in cyst model from kidneys of PKD patients

1. See Previous Slide
2. See Previous Slide

PYC-003 addresses the root cause of PKD in animals and human kidney cells

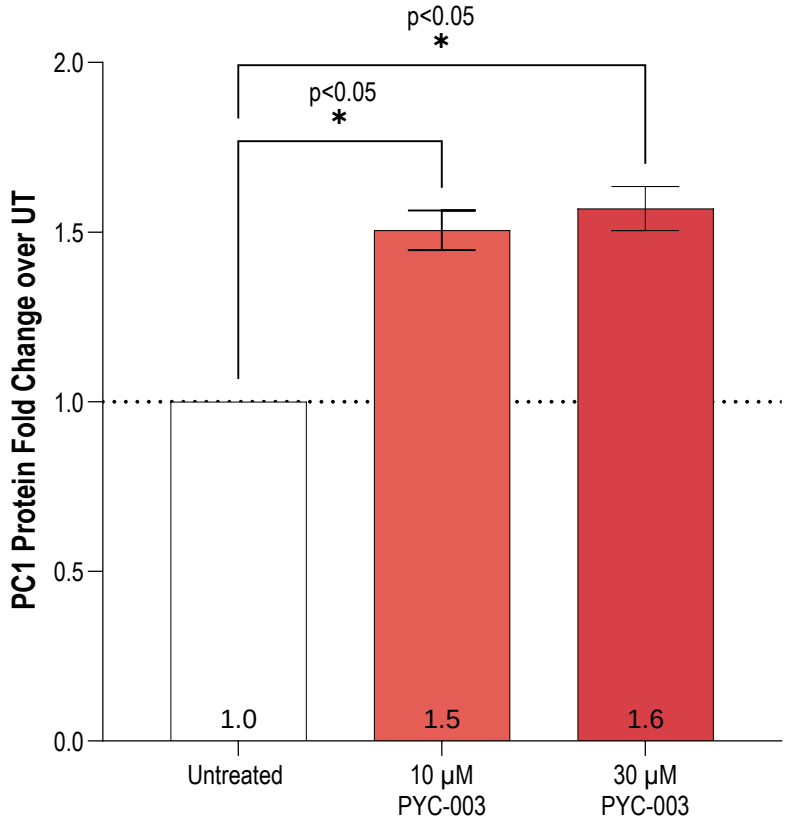
In Animals[1]

Safe & effective upregulation of *PKD1* mRNA
in mouse kidney 3 days after a single 20 mg/kg dose



In Human Kidney Cells[2]

Upregulation of PC1 protein in human kidney cell line
PC1 is the rate-limiting modulator of cystic disease[2]



1. PYC-003* mouse surrogate used due to difference in PKD1 sequence between humans and mice. PKD1 mRNA levels assessed at Day 3 post treatment. Data presented mean+S.E.M (n=6). The data show a statistically significant (student's t test ** = <0.01) difference between treatment groups. *PKD1* expression fold-change over 0 dose sample, which used PBS as 'untreated' vehicle control. Highest tolerated dose in mice was 20 mg/kg and showed no signs of clinical toxicity.
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 *** = <0.001, * <0.05) difference between treatment groups. Assessed in HEK293 cells.

PYC's new drug candidate for Polycystic Kidney Disease

- Has the potential to change the lives of > 5 million patients worldwide with this condition[1,3]
- Is >5x more likely to succeed in human trials[2]
- Addresses a target market worth greater than US $10 billion per annum[4]
- Is expected to reach market in 2027[5]

1. Refer ASX Announcement: 13 November 2023
2. Monogenic disease compared to drug targets lacking genetic evidence. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank https://doi.org/10.1101/2020.11.02.20222232
3. 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.
4. Market size is projected by multiplying patient prevalence per indication by the median orphan drug price of $150k p.a. EvaluatePharma. Orphan Drug Report. 2019.
5. Subject to regulatory approvals. Management forecast as of November 2023.