A Phase 1 Study of PYC-003, a Peptide-Oligonucleotide Conjugate Designed to Increase PC1 Expression in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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ADPKD is an area of major unmet patient need

ADPKD is a highly prevalent, potentially lethal single-gene disorder

- Autosomal Dominant Polycystic Kidney Disease (ADPKD) affects ~1 in every 1,000 people, indicating over 12.5 million people are affected worldwide [1]
- Approximately 95% of patients with ADPKD have no treatment options available,[2] and there are no drugs that address the underlying cause of the disease
- ~80% of ADPKD patients have a mutation in one copy of *PKD1* DNA leading to insufficient Polycystin-1 (PC1) protein [3]
- One non-functional *PKD1* allele leaves ~50% of wild-type PC1, and that shortfall drives loss of Ca^{2+} signaling, abnormal tubule architecture and patients develop fluid filled cysts in the kidneys [4,5]
- These cysts grow over time, destroying the architecture and ultimately the function of the kidney, with half of the patients progressing to end-stage renal failure by the age of 60 [6]

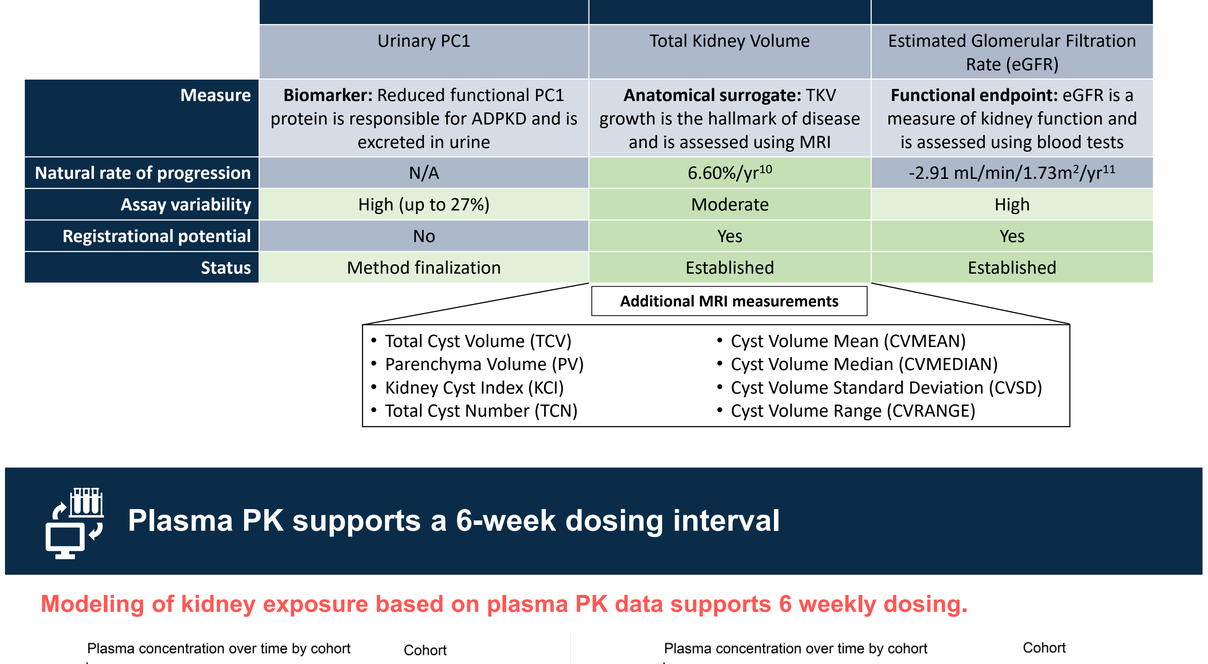
PYC-003 is designed to address the root cause of ADPKD

- PYC-003 is designed to address the underlying cause of PKD by increasing PC1 expression.
- PYC-003 increases PC1 protein levels and in a cyst model derived from ADPKD patient kidneys it prevents cyst progression
- PYC-003 has progressed from the Single Ascending Dose (SAD) protocol into the Multiple Ascending Dose (MAD) study
- PYC-003 demonstrates a favorable safety profile observed across all dose levels

Normal kidney[7] → **Polycystic kidney**

Clinical development overview for PYC-003

PYC-003 is currently progressing through a combined Phase 1a/1b clinical study in patients



Study objectives and endpoints

- **Primary:** Safety and tolerability
- **Secondary:** Plasma pharmacokinetics (PK)
- **Exploratory:** Pharmacodynamic biomarkers (uPC1), disease progression markers (TKV, eGFR), urinary PK, metabolites, and immunogenicity

Disease progression

	Urinary PC1	Total Kidney Volume	Estimated Glomerular Filtration Rate (eGFR)
Measure	**Biomarker:** Reduced functional PC1 protein is responsible for ADPKD and is excreted in urine	**Anatomical surrogate:** TKV growth is the hallmark of disease and is assessed using MRI	**Functional endpoint:** eGFR is a measure of kidney function and is assessed using blood tests
Natural rate of progression	N/A	6.60%/yr[10]	-2.91 mL/min/1.73m^2/yr[11]
Assay variability	High (up to 27%)	Moderate	High
Registrational potential	No	Yes	Yes
Status	Method finalization	Established	Established

Additional MRI measurements

- Total Cyst Volume (TCV)
- Parenchyma Volume (PV)
- Kidney Cyst Index (KCI)
- Total Cyst Number (TCN)
- Cyst Volume Mean (CVMEAN)
- Cyst Volume Median (CVMEDIAN)
- Cyst Volume Standard Deviation (CVSD)
- Cyst Volume Range (CVRANGE)

Overview of Inclusion/Exclusion Criteria Part B/C

Inclusion criteria

- Male or female aged **18 to 65 years** (inclusive at the time of informed consent
- ADPKD diagnosis as confirmed by the presence of genetic mutations associated with ADPKD, including, but not limited to, the **presence of *PKD1* mutation**
- **Class 1C, 1D or 1E per Mayo Imaging Classification** System for Predicting Kidney Outcomes in ADPKD[8]
- (Estimated glomerular filtration rates **(eGFR) ≥ 30 mL/min/1.73m^2** via the CKD EP1 2021 calculation[9]
- 18 ≤ BMI ≤ 35 kg/m2 and weight ≥ 50 kg

Exclusion criteria

- **Presence of potentially confounding genetic mutations** including, but not limited to, the presence of *PKD2*, *HNF1B*, *GANAB*, *IFT140* and/or *DNAJB 11* mutations
- **Use of (or anticipated use of) Tolvaptan and/or metformin administration within 30 days** prior to the first administration of IP until study completion
- Has only 1 kidney or has a kidney transplant
- Abnormal ECG findings at Screening, Day -1 or pre-dose that are considered by the PI or designee to be clinically significant
- **History of borderline to low blood magnesium and potassium levels** and/or Screening or Day -1 blood magnesium level < 0.7 mmol/L and potassium levels < 3.5 mmol/L

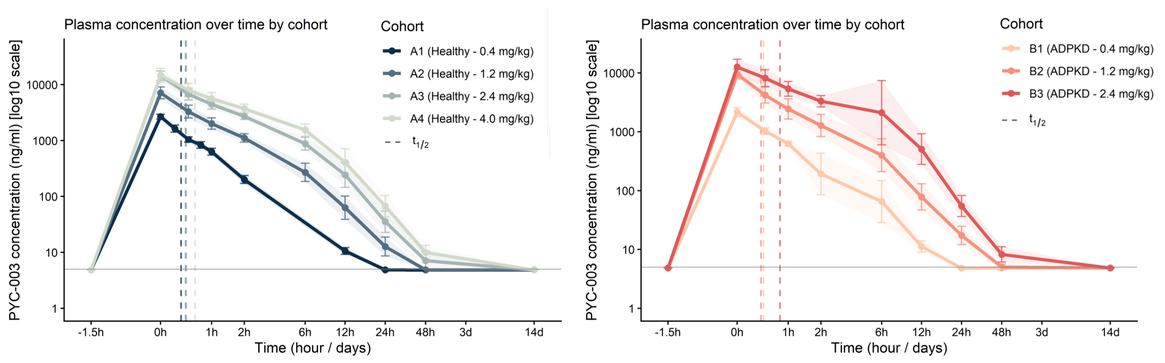
No treatment-related serious adverse events across all completed cohorts

Single doses of PYC-003 were safe and well-tolerated in Healthy volunteers and PKD patients

	Healthy volunteers				ADPKD patients		
	A1 (0.4 mg/kg) N = 8	A2 (1.2 mg/kg) N = 8	A3 (2.4 mg/kg) N = 8	A4 (4.0 mg/kg) N = 8	B1 (0.4 mg/kg) N = 6	B2 (1.2 mg/kg) N = 6	B3 (2.4 mg/kg) N = 6
Number of any Treatment Emergent Adverse Events (TEAEs)	4	11	5	13	9	8	12
Participants with at least one treatment related TEAEs*	0	1	0	2	0	1	1
Number of any Treatment Emergent Serious Adverse Events (TESAEs)	0	0	0	0	1	0	0
Number of any Treatment Related TESAEs	0	0	0	0	0	0	0
Any TEAEs leading to discontinuation	0	0	0	0	0	0	0

Plasma PK supports a 6-week dosing interval

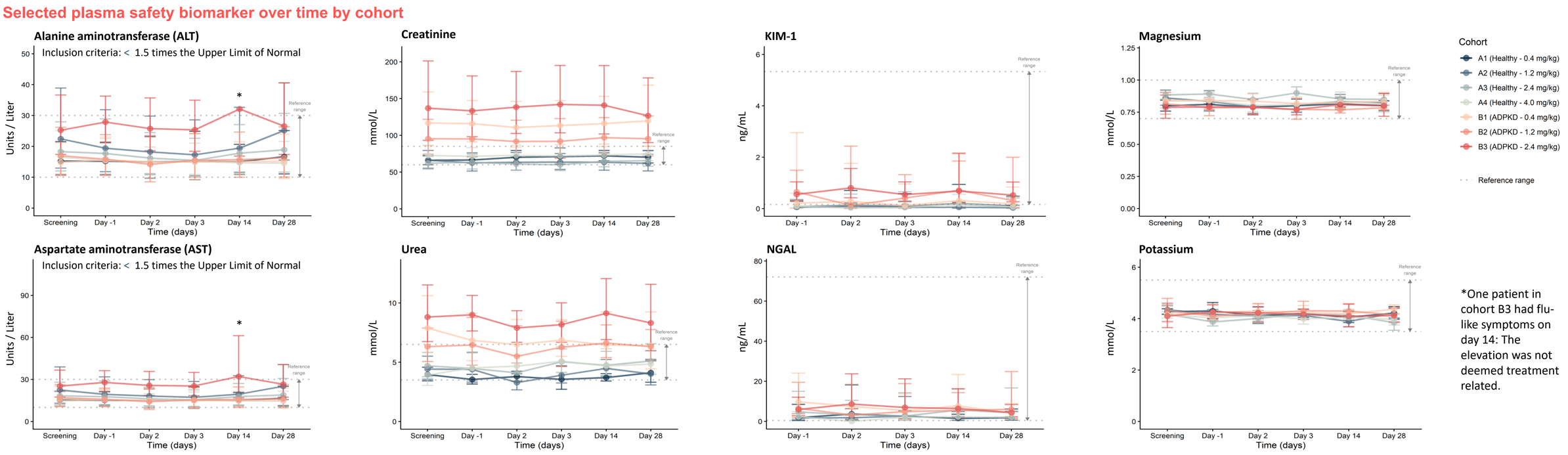
Modeling of kidney exposure based on plasma PK data supports 6 weekly dosing.



Data was generated from n=6 participants for cohort A and n=4-6 participants for cohort B. Points represent the geometric mean with error bars extending the 95% CI

No PYC-003-related effects were observed across key safety biomarkers.

Selected plasma safety biomarker over time by cohort



*One patient in cohort B3 had flu-like symptoms on day 14: The elevation was not deemed treatment related.

Data was generated from n=8 for cohort A and n = 6 for cohort B, with exceptions on Day 2 (AST n=5 for B1; KIM, NGAL n=7 for A3, n=5 for B2), Day 3 (KIM, NGAL n=5 for B2), Day 14 (KIM, NGAL n=5 for B3) and Day 28 (n=7 for A3 and n=5 for B3). Points represent the geometric mean with error bars extending the 95% CI

References

1. Willey, C. J., et al. (2019). Kidney Diseases, 5(2), 107–117.
2. Gansevoort, R. T., et al. (2016). Nephrology Dialysis Transplantation, 31(3), 337–348.
3. Cordido, A., et al. (2017). Frontiers in Pediatrics, 5, 279.
4. Ferreira, F. M., Watanabe, E. H., & Onuchic, L. F. (2015). In X. Li (Ed.), Polycystic kidney disease (Chap. 7). Codon Publications.
5. Lee, S. H., & Somlo, S. (2014). Kidney Research and Clinical Practice, 33(2), 73–78.
6. Cloutier, M., et al. (2020). BMC Health Services Research, 20(1), 126.
7. Adapted from MacAskill CJ et al. (2026). Pediatr Radiol, PMID: 42517885, CC BY 4.0. Cropped and intensity-matched. Different subject, age and acquisition to the ADPKD image; illustrative only.
8. Irazabal, M. V., et al. (2015). Journal of the American Society of Nephrology, 26(1), 160-172.
9. Inker LA, et al. (2021). N Engl J Med. 2021;385:1737-1749.
10. Average TKV growth rate of 6.60%/yr for Mayo Classification C, D and E - from STAGED-PKD trial
11. Average eGFR rate of decline of -2.91 mL/min/1.73m2/yr for Mayo Classification C, D and E - from STAGED-PKD trial

Clinical development plan is subject to confirmation with relevant regulatory authorities and may change. Subject to the risks and uncertainties outlined in PYC Therapeutics ASX disclosures of 2 February 2026.

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