A Phase 1a Clinical Trial of PYC-003 for the Treatment of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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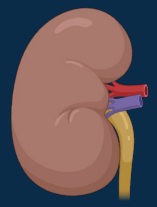
Objectives for today

- Introduce you to the clinical development pathway for PYC-003 – the first investigational drug candidate to address the root cause of Polycystic Kidney Disease (PKD)
    - PYC-003 is an RNA therapy that increases Polycystin 1 (PC1) protein expression and rescues the cystic phenotype in pre-clinical models of PKD
    - This drug candidate has now progressed into a combined Phase 1a/1b clinical trial and has:
        - A favourable emerging safety/tolerability profile in Healthy Volunteers; and
        - Is now being administered to PKD patients in a Single Ascending Dose (SAD) study
    - Disease-modifying drugs hold unique potential in PKD and the ongoing SAD and upcoming Multiple Ascending Dose (MAD) studies of PYC-003 will seek to demonstrate the impact of this approach in PKD patients for the first time

ADPKD is an area of major unmet need due to its high prevalence and devastating consequences

Polycystic Kidney Disease

Healthy adult kidney



Polycystic kidney

High prevalence

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

Life-changing

Half of all ADPKD 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**

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.

PYC-003 is the first drug candidate that directly addresses the root cause of ADPKD to have advanced into human trials

PYC-003

- PYC-003 is an antisense oligonucleotide conjugated to a delivery peptide which is administered via intravenous infusion
- The oligonucleotide stabilises *PKD1* at the mRNA level and enhances translation – increasing expression of the missing PC1 protein

Efficacy

- PYC-003 increases PC1 expression *in vitro* and rescues the cystic phenotype in a 3D cyst assay derived from patients with advanced polycystic kidney disease

Delivery

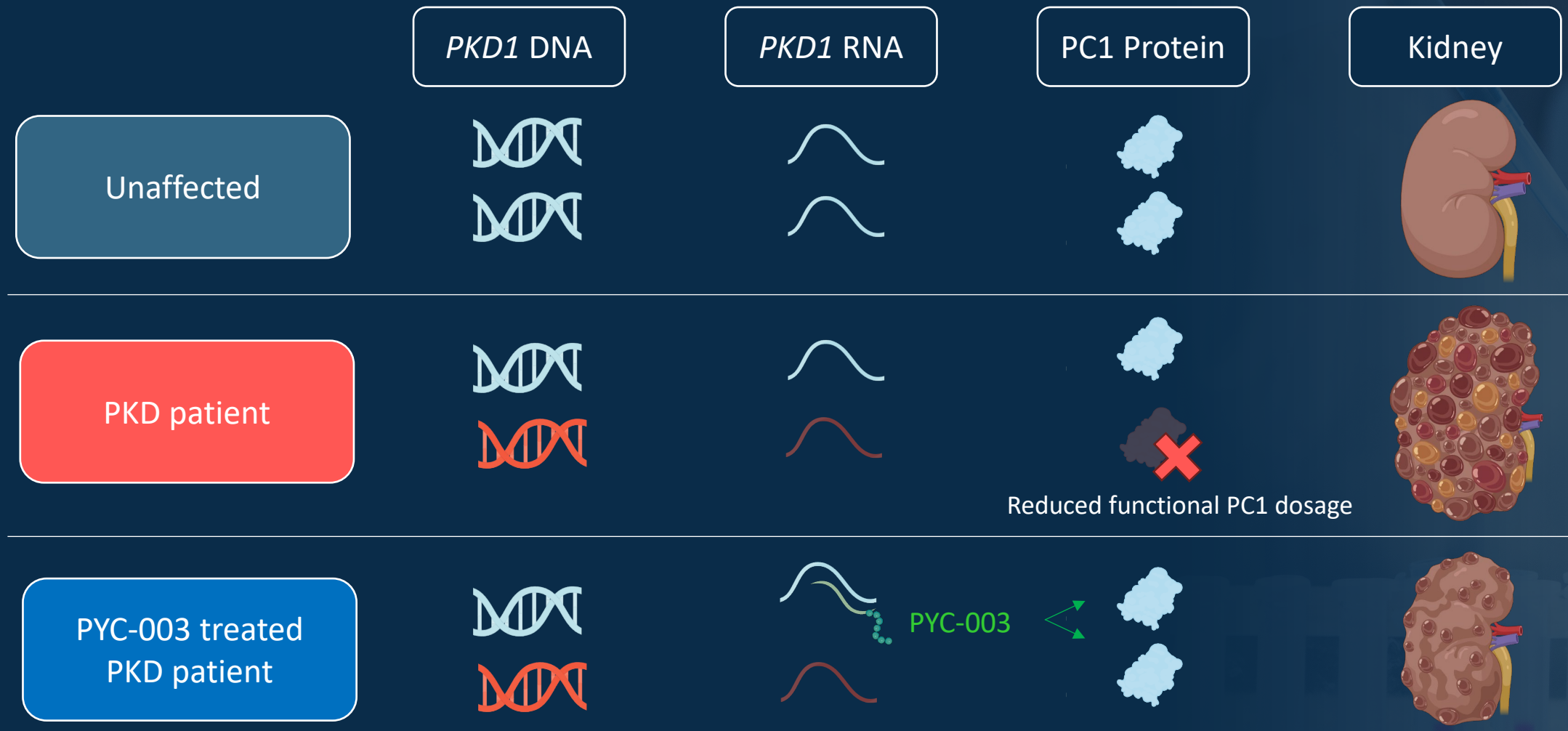
- PYC distributes primarily to the two key organs affected in PKD – the kidney and the liver
- Within the kidney, PYC-003 is taken up by Renal Tubular Epithelial Cells including the cyst-lining cells in animal models of PKD

Safety

- PYC-003 achieves target tissue concentrations at safe and well tolerated doses *in vivo* that exceed the pharmacodynamic range *in vitro* and *ex vivo*

For more details see poster #74

PYC-003 is an RNA therapy with disease-modifying potential for ADPKD patients



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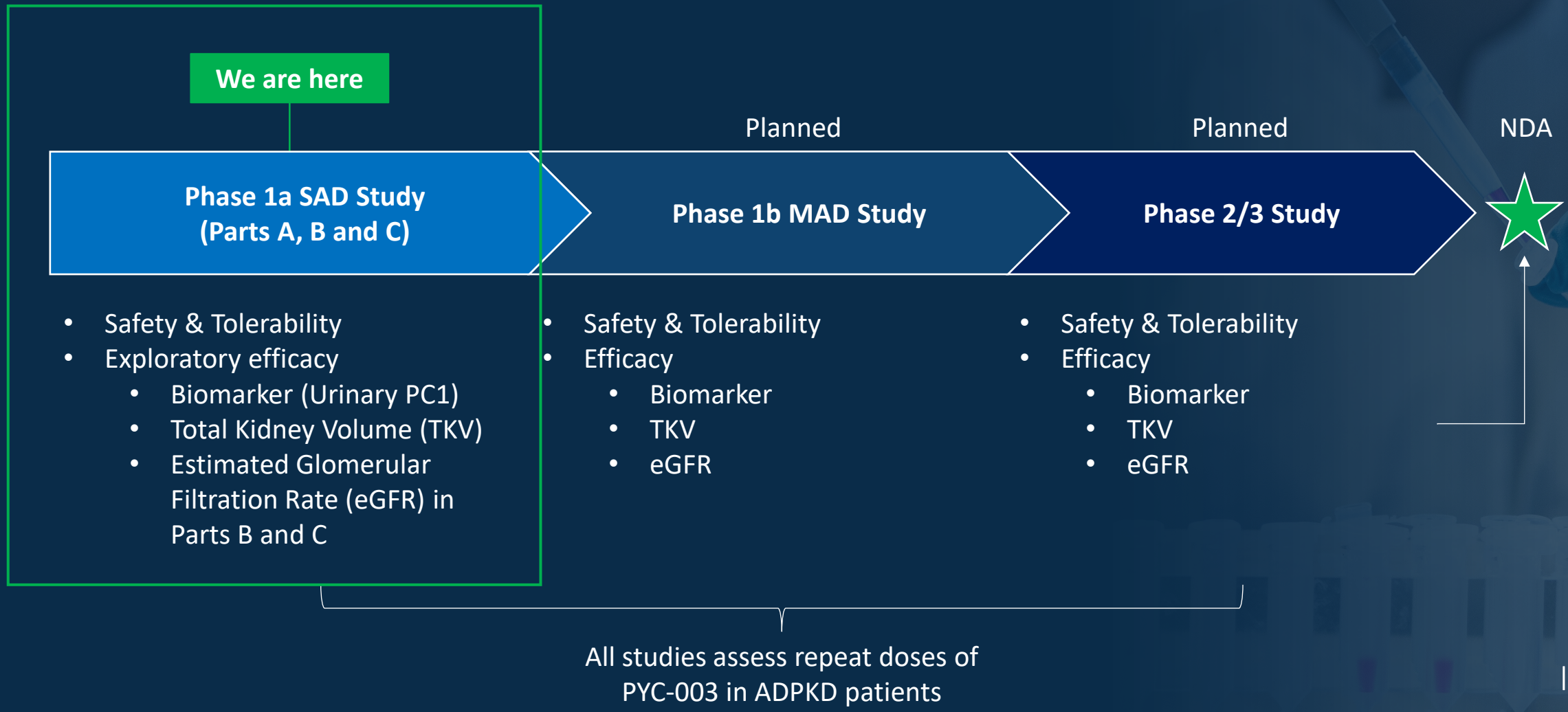
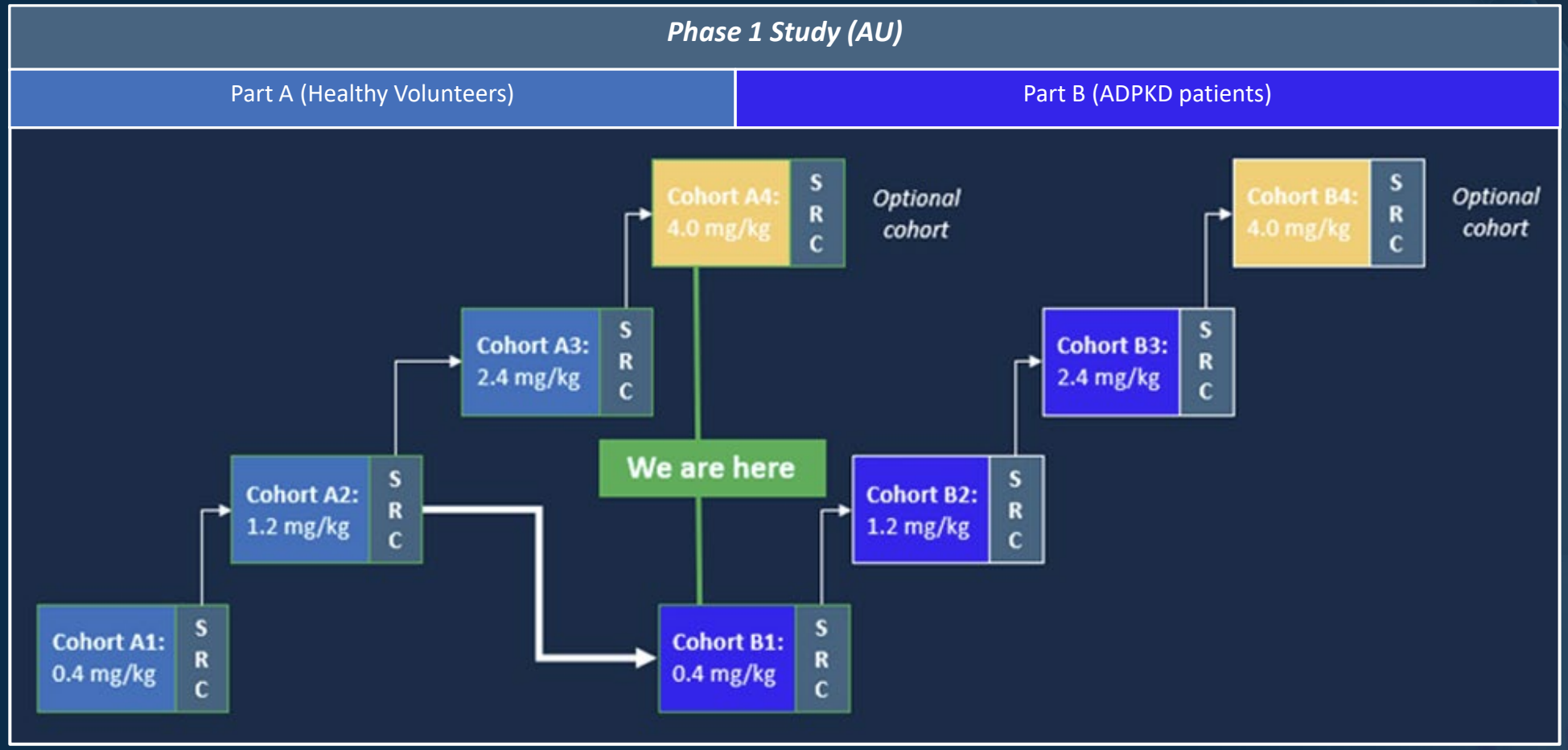
PYC-003 has a high-velocity path to a New Drug Application



PYC-003-CL-001: Phase 1 Study to Evaluate the Safety and Tolerability of Intravenously Administered PYC-003

- Phase 1 Parts A and B are ongoing and an amendment to add Part C (MAD) study is in preparation



Part B key eligibility criteria are:

Inclusion criteria

- Male or female aged 18 to 60 years (inclusive) at the time of informed consent.
- ADPKD diagnosis based on Ravine Pei diagnosis criteria (Pei et al. 2009)
- 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 (Irazabal et al. 2015)
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m2 via the CKD EPI 2021 calculation (Inker et al. 2021)
- BMI ≥ 18.0 and ≤ 32.0 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

PYC-003 was safe and well-tolerated at doses up to 2.4 mg/kg in Healthy Volunteers

- **No Treatment Emergent Serious Adverse Events**
- **No changes in serum or urinary electrolytes (creatinine, magnesium, potassium levels)**
- **No evidence of renal injury following administration of PYC-003**

Cohort 1 (0.4 mg/kg)

AE term	Comments
Headache	Not related
Viral illness	Not related
Headache	Unlikely
Headache	Unlikely

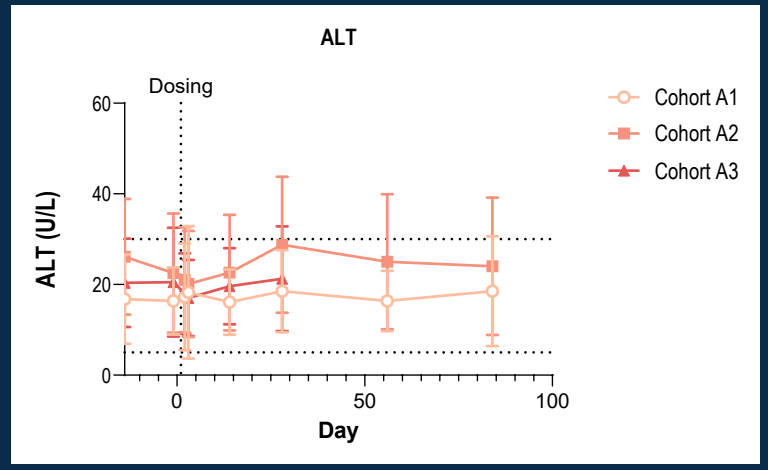
Cohort 2 (1.2 mg/kg)

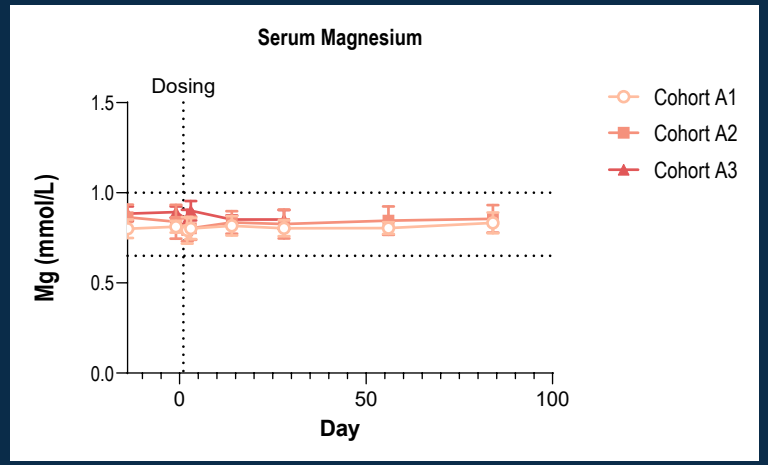
AE term	Comments
Tinnitus	Possibly related
Upper back pain-Muscle Spasm	Not related
Hyperpigmentation from IPL	Not related
Simple headache	Not related
Upper respiratory tract infection	Not related
Headache	Not related
Bruise, right big toe	Not related
Abdominal cramps	Not related
Headache	Unlikely related
Erythema -venipuncture site	Not related

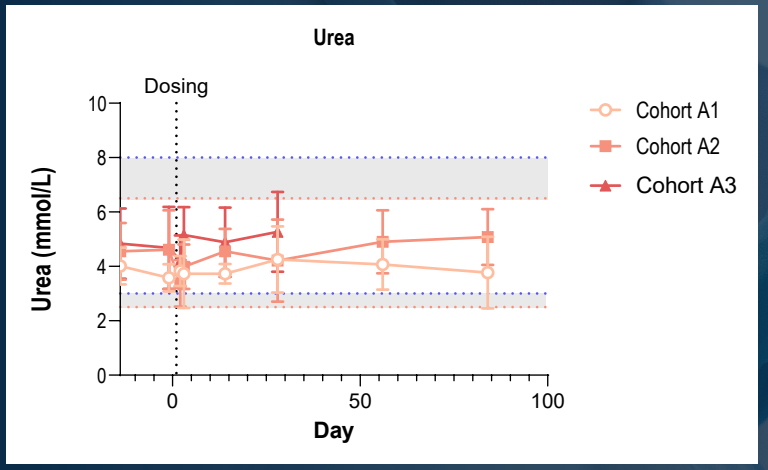
Cohort 3 (2.4 mg/kg)

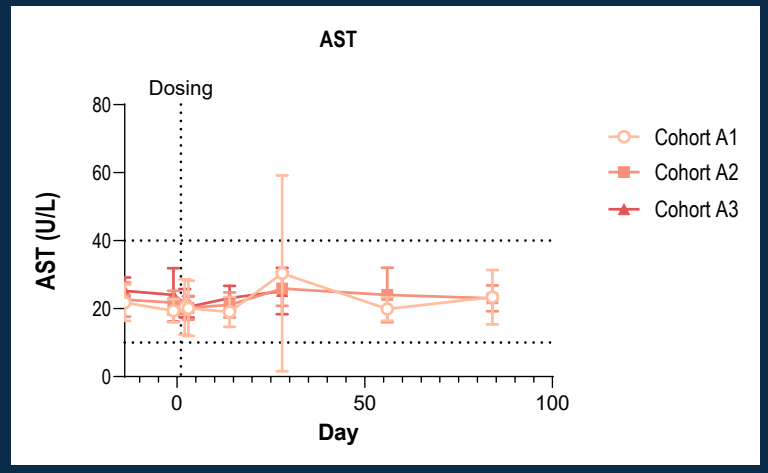
AE term	Comments
Headache	Unlikely related
Headache	Not related
Diarrhea	Unlikely related

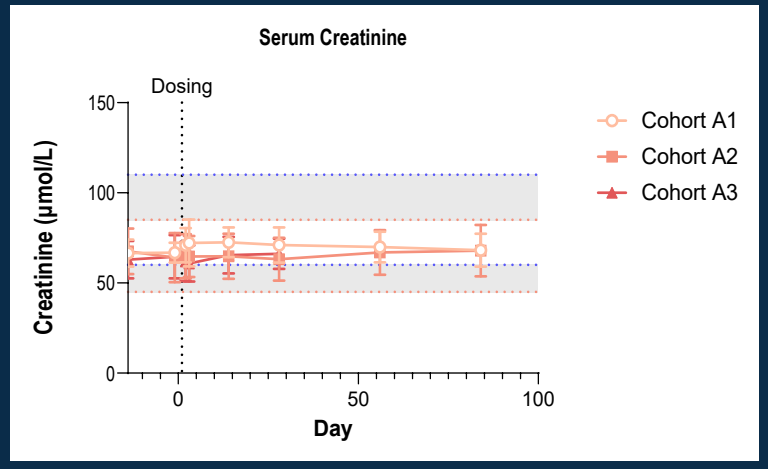
No changes in blood chemistry or increases in kidney markers were seen in HVs dosed up to 2.4 mg/kg

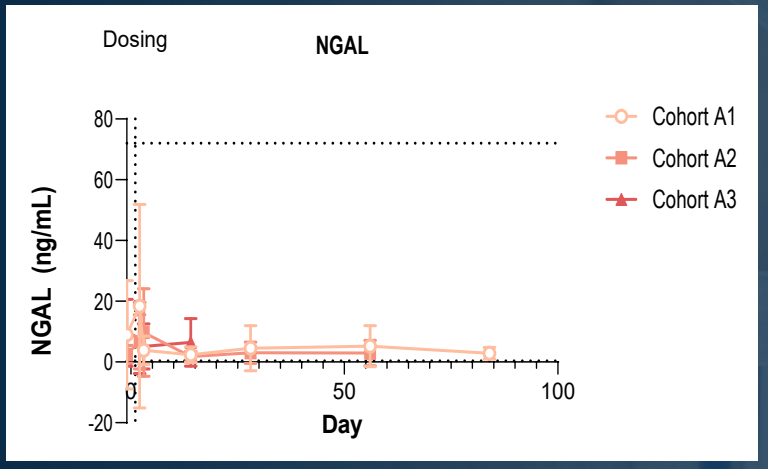












The ongoing Phase 1a/1b studies are currently active across 5 sites with 2 more pending activation

Activation pending:

- Sunshine Hospital in collaboration with Doherty Clinical Trials
- Concord Hospital

To learn more about this clinical trial visit clinicaltrials.gov, email pkd@pyctx.com or scan the QR code