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RGLS8429 Cohort 1 Results in Patients with ADPKD

September 2023

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Executive Summary

- Study execution on track
- RGLS8429 at 1mg/kg dosed every 2 weeks over 12 weeks was well tolerated with no safety concerns
- Clear evidence of polycystin (PC) increase at 1mg/kg dose level
  - Statistically significant increases in PC1; numerical increases in PC2
  - PC pattern consistent with tissue PK profile in non-clinical studies
  - Emerging dose response in polycystin with antisense oligonucleotide targeting miR-17 when combined with all clinical dosing across both RGLS4326 and RGLS8429
  - Data consistent with PK/PD modeling and indicates opportunity to demonstrate greater PC responses in Cohorts 2 & 3
- As anticipated, no evidence of impactful changes to renal function or MRI measures of kidney volume or cystic architecture
  - In setting of short treatment duration, small patient numbers, and measurement variability

Cohort 1 meets expectations and continues to establish polycystin as a valid pharmacodynamic marker for dose-ranging prior to a pivotal Phase 2 trial

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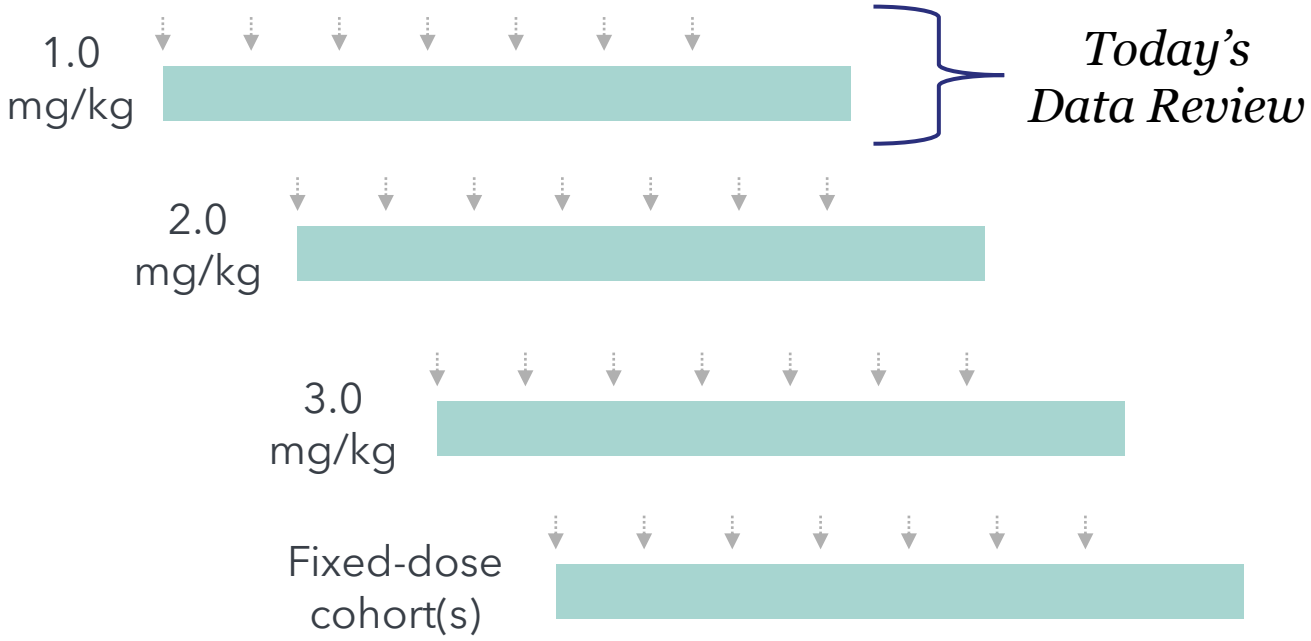
Multiple Ascending Dose in Patients with ADPKD to Evaluate Safety, PK, PD (Biomarkers), eGFR, and TKV



STUDY DESIGN

- ADPKD Patients
- 12 subjects per cohort
- Randomized 3:1 (RGLS8429:Placebo)
- 3-month dosing (Q2W x 7)
- Safety, PK, PD/biomarkers, eGFR, TKV, and novel cyst imaging analysis (TCN, TCV and CPSA)
- PC measured at days 29, 57, 85/86, and 92, 99, 113

Cohort 2 Data on track for Q1 2024

Cohort 3 screening starting October 2023

EXPECTATIONS

- Clear increase in PC1 & PC2 with dose response
- Experience with using novel imaging markers ahead of Ph2

TCN = total cyst number ; TCV = total cyst volume ; CPSA = cyst-parenchyma surface area

Cohort 1: Baseline Characteristics are Balanced Across Groups

Baseline Characteristics	RGLS8429 N=9	Placebo N=3
Age (years) mean (SD)	52 (12)	42 (13)
Female n (%)	5 (56%)	2 (67%)
White n (%)	9 (100%)	3 (100%)
BMI mean (SD)	30 (5)	30 (4)
Prior tolvaptan use in prior 3 months n (%)	2 (22%)	0
eGFR (mL/min/1.73m$^{2)}$) mean (SD)	47 (20)	42 (9)
htTKV (mL/m) mean (SD)	1698 (737)	2091 (502)
Mayo Class n (%)		
1C/1D/1E	5 (56%) / 3 (33%)/ 1 (11%)	0 / 2 (67%)/ 1 (33%)
Genetic Mutation		
PKD1/PKD2/Other/Negative#	5 (56%) / 3 (33%) / 0/1 (11%)	2* (67%) / 0 /1* (33%)/1 (33%)

*One subject positive for PKD1 and other

#Among all 18 genes within the PKDNext-expanded panel:COL4A1, GANAB, HNF1B, PKD1, PKD2, PKHD1, PRKCSH, TSC2, NOTCH2, OFD1, SEC61A1, VHL, DNAJB11, IFT140, SEC63, LRP5, ALG8, SEC61B

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Safety and PK Results

- Well tolerated
- Majority of TEAEs were Grade 1 or 2
- One SAE of appendicitis not related to study drug
- No clinically significant changes in laboratory values, vitals, and ECGs
- No AE's leading to early withdrawal

- PK results similar to results seen for RGLS4326
- No accumulation observed in plasma or urine with repeat dosing.
- AUC plasma exposure in patients nearly twice that of healthy volunteers and consistent with ~ 35% reduction in renal excretion.
- Plasma to tissue modelling suggests 1mg/kg is less than half of dose response curve

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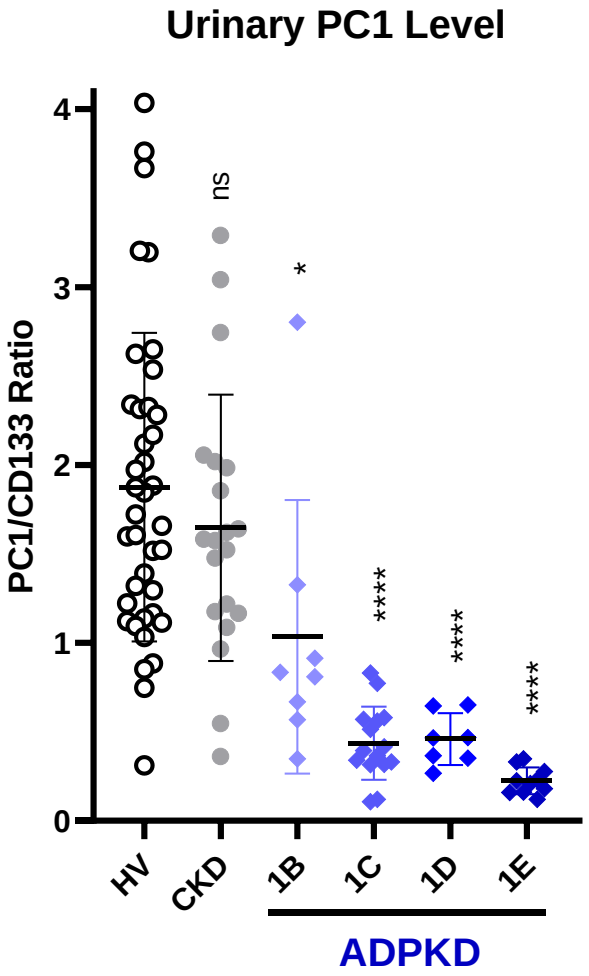
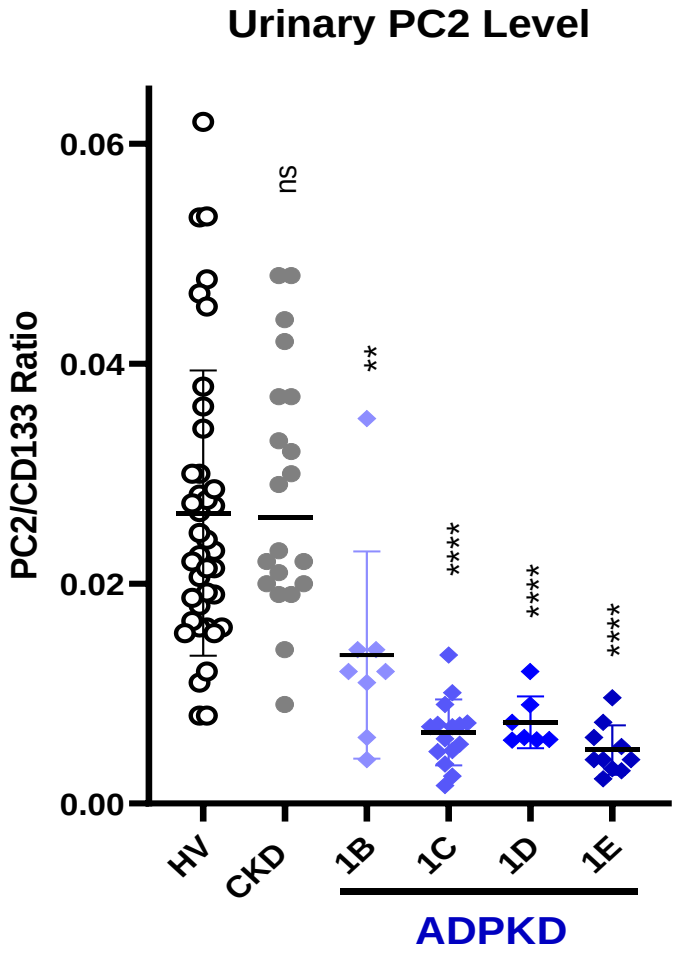
Polycystin Results

Urinary Biomarker Assay Can Detect PC1 & PC2 in Humans.

PROTEIN LEVELS INVERSELY CORRELATED WITH DISEASE SEVERITY SPECIFICALLY FOR ADPKD





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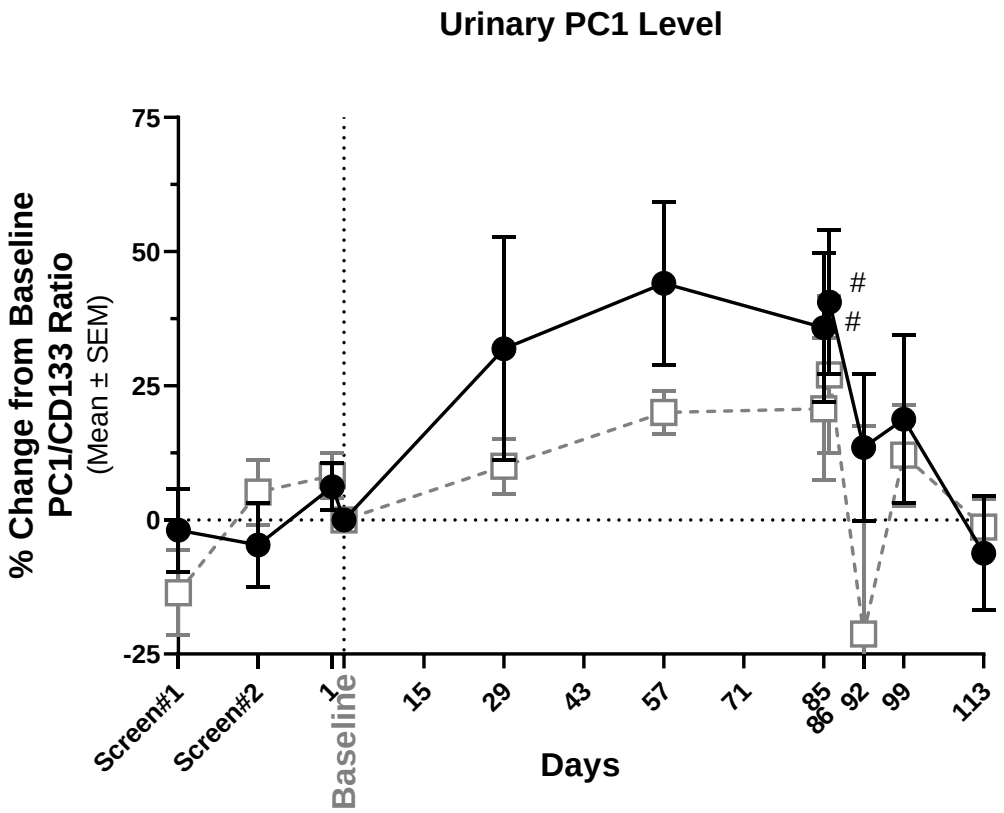
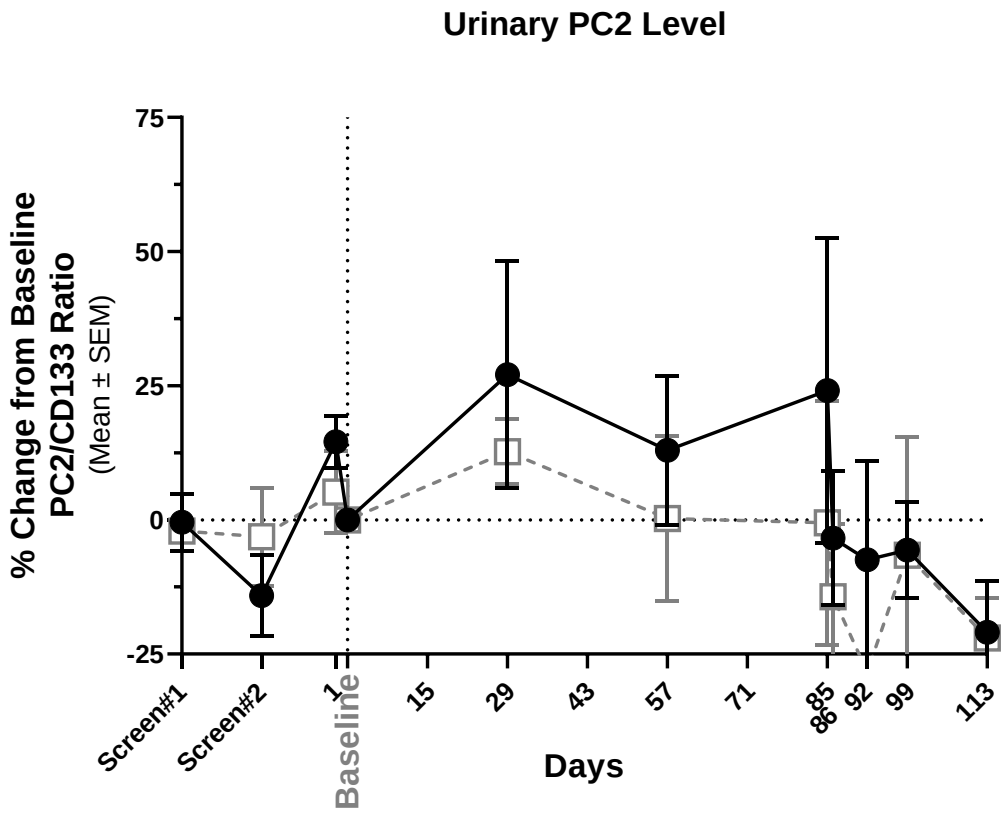
Updated from: Lee (2022) FASEB-PKD Conference Presentation
Manuscript in preparation

HV, Healthy volunteers; CKD, Chronic Kidney Disease (non-ADPKD);
ADPKD, Autosomal Dominant Polycystic Kidney Disease;
*p-values, One-way ANOVA compared to HV with Dunnett's correction

Polycystin Levels Increased During Treatment with RGLS8429



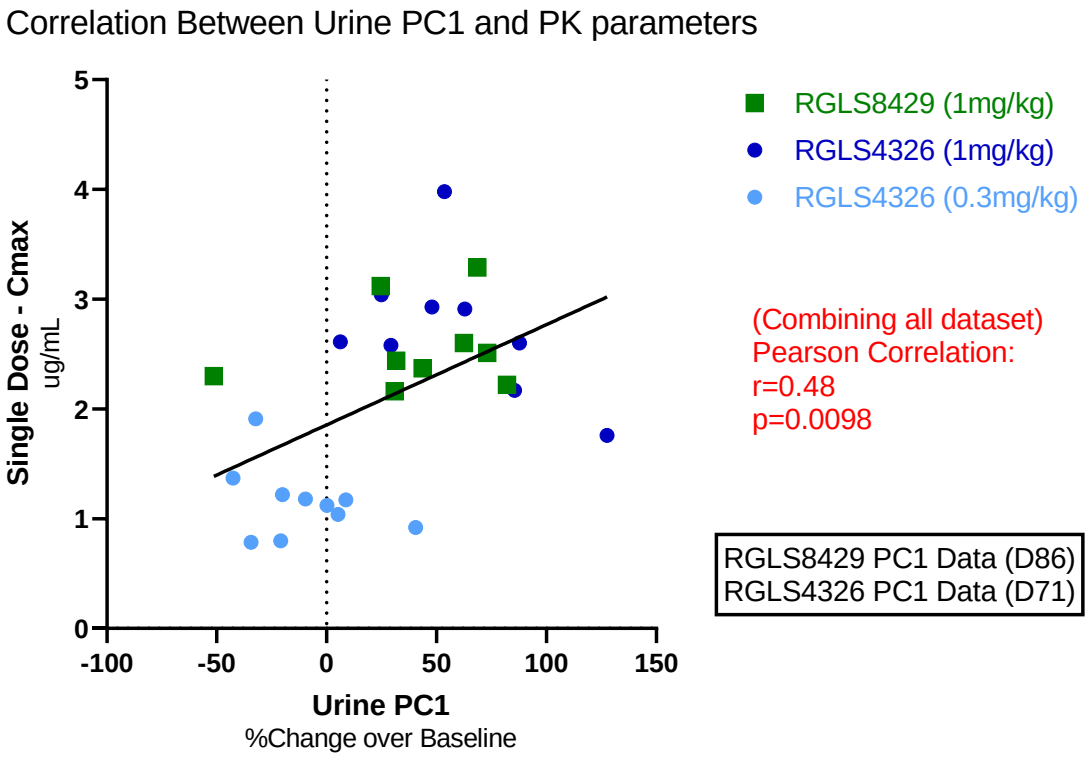


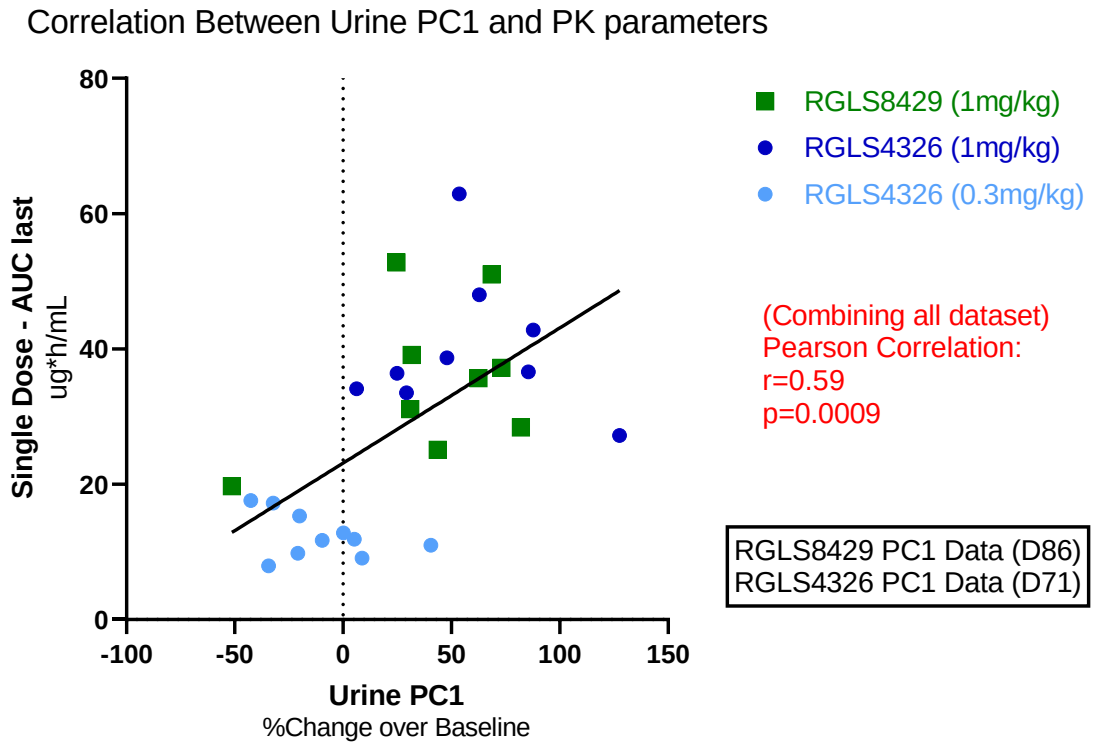
■ RGLS8429 (1 mg/kg Q2W x7) (Total N=9 subjects, with Mayo Class 1C/1D/1E=5/3/1)
□ Placebo (Q2W x4) (Total N=3 subjects, with Mayo Class 1C/1D/1E=0/2/1)

#, Change from Baseline for RGLS8429; Statistical Significance by Wilcoxon Sign-Ranked Test (alpha=0.05) at Day 85 and Day 86

Plasma Exposure Correlation Suggests Dose Response for Polycystin

- Positive correlation between PC1 and both C_{max} and AUC_{last} when combining 4326 & 8429 datasets
- Similar PD response between both 4326 and 8429 at 1mg/kg dose level





Renal Function and Imaging Analyses

- Baseline measurements consistent with stage of ADPKD Mayo Classification
- No notable changes in renal function measures seen over 12 weeks
  - eGFR, UACR, SCr, BUN, U-NGAL, U-KIM-1
- No notable changes in MRI measures seen over 12 weeks
  - TKV, CPSA, TCN, TCV, PV, LV
- Additional exploratory analyses will be conducted with future cohorts and the final combined dataset

Renal function and imaging results are as expected based on short-term treatment and small number of subjects

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TKV = total kidney volume; CPSA = cyst-parenchyma surface area
TCN = total cyst number; TCV = total cyst volume;
PV = parenchyma volume; LV = liver volume

RGLS8429 Phase 1b Cohort 1 Summary

- RGLS8429 dosed at 1mg/kg once-every-two-weeks over 12 weeks was well tolerated with no safety findings
- Statistically significant increases from baseline in PC1 noted at 12 weeks of dosing (36-41% on days 85 and 86)
- Increases from baseline were also observed in urinary PC2 at 12 weeks; however, the changes did not reach statistical significance
- As expected, renal function parameters and renal MRI measures did not demonstrate meaningful changes over short-term, 12-week dosing
- Urinary polycystin exhibits appropriate PK/PD correlation to serve as a key pharmacodynamic biomarker in ADPKD
  - Emerging dose response is observed when examining 0.3mg/kg and 1mg/kg RGLS4326 along with 1mg/kg RGLS8429
  - Correlation between PK and urinary PC1 response at 1mg/kg is comparable between RGLS4326 and RGLS8429
- Data suggest the opportunity to demonstrate greater urinary polycystin response at the higher doses planned in subsequent cohorts in Phase 1b
- Cohort 1 meets expectations and continues to establish polycystin as a valid pharmacodynamic marker for dose-ranging prior to a pivotal Phase 2 trial
  - Cohort 2 (2mg/kg) enrolled; Cohort 3 (3mg/kg) to initiate next month

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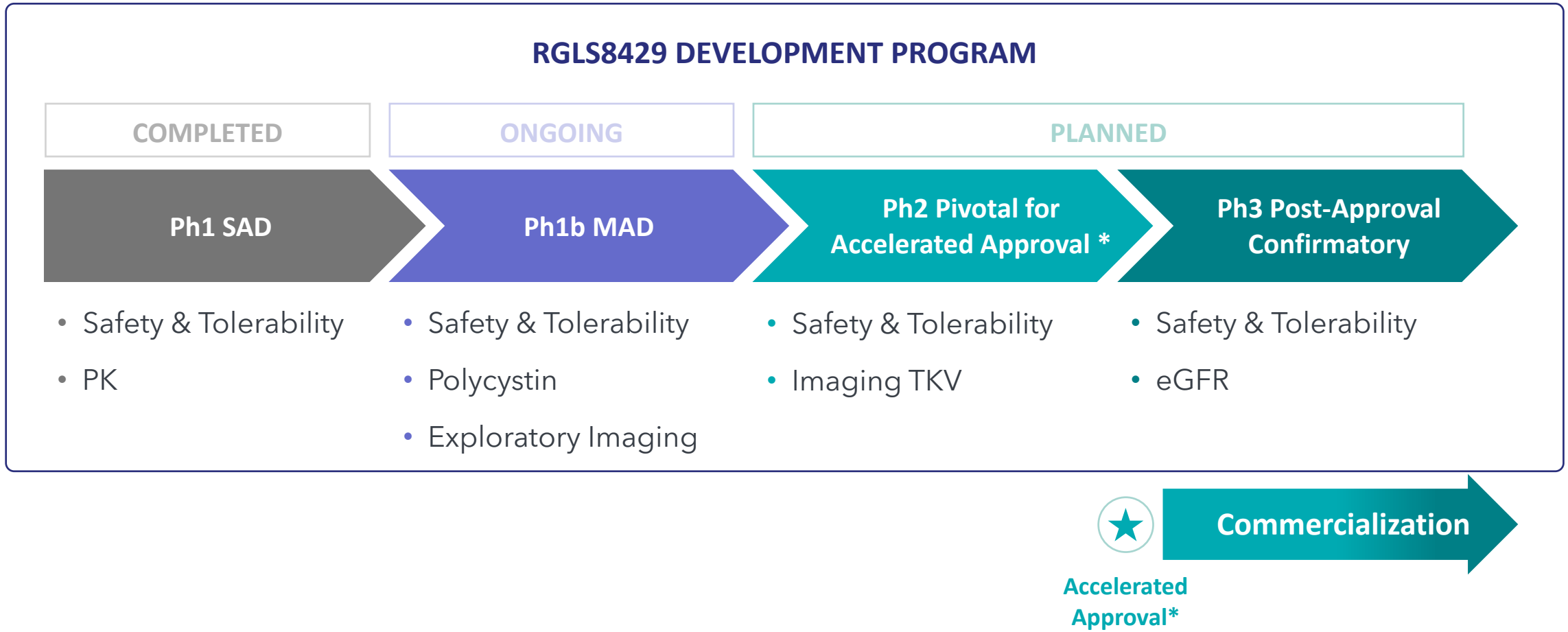
Q&A

Streamlined RGLS8429 Clinical Development Based on Accelerated Approval



TKV = total kidney volume; eGFR = estimated glomerular filtration rate

*Subject to confirmation with FDA