



# Corporate Presentation.

April 2024



# Safe Harbor Statement.

- Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements associated with the Company's RGLS8429 program, the future utility of biomarker assays, potentially achieving therapeutic efficacy and clinical translation for ADPKD patients, the expected timing for initiating clinical studies, the expected timing for reporting topline data, the timing and future occurrence of other preclinical and clinical activities. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "intends," "will," "goal," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Regulus' current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, the approach we are taking to discover and develop drugs is novel and may never lead to marketable products, preliminary or initial results may not be indicative of future results, preclinical and clinical studies may not be successful, risks related to regulatory review and approval, risks related to our reliance on third-party collaborators and other third parties, risks related to intellectual property, risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and in the endeavor of building a business around such drugs, and the risk additional toxicology data may be negative and our need for additional capital. These and other risks are described in additional detail in Regulus' filings with the Securities and Exchange Commission, including under the "Risk Factors" heading of Regulus' most recently filed annual report on Form 10-K. All forward-looking statements contained in this presentation speak only as of the date on which they were made. Regulus undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

# First-in-Class Antisense Therapeutics for Genetic Disease.

Leading antisense oligonucleotide company, co-founded by Ionis and Alnylam, to address genetic disease driven by dysregulated microRNA biology (anti-miRNA)

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Executing in the clinic with anti-miR-17 oligonucleotide RGLS8429, the first potential disease-modifying approach for the treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Broad platform includes oligos optimized to deliver preferentially to the kidney

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Early development programs targeting additional kidney and CNS diseases

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Seasoned leadership team experienced in nephrology drug development

# Regulus Investment Highlights.

- **RGLS8429: Phase 1b MAD study ongoing**

- Presented topline data in September 2023 from the first cohort of patients in the Phase 1b MAD study indicating increases in both PC1 and PC2 urine biomarkers after treatment
- In March 2024, presented topline data from the second cohort:
  - Greater biological activity of RGLS8429 was observed at 2 mg/kg based on urinary polycystin levels compared to 1 mg/kg and placebo
  - The largest reductions in htTKV were seen in patients with the highest increase in PC1 and PC2
- Completed enrollment in the third cohort and top-line data anticipated mid 2024
- Protocol amended to include a fourth cohort of patients who will receive open label fixed dose of RGLS8429, initiation planned in Q2 2024

- **Phase 2 enabling safety tox study and CMC activities underway**

- Chronic mouse tox completed (most sensitive species); NOAEL 300mg/kg (top dose)

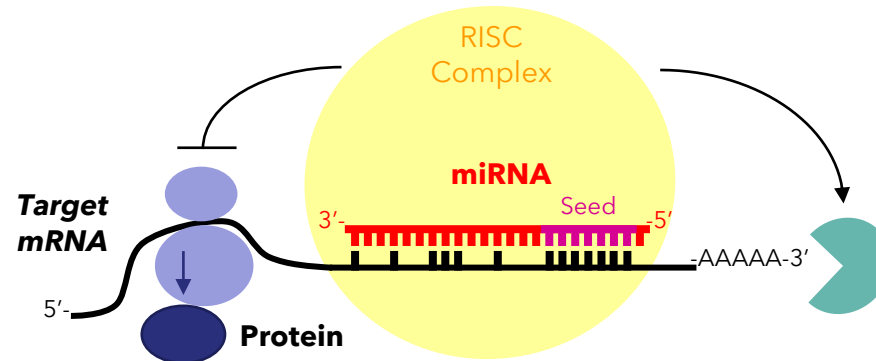
- **Completed \$100M oversubscribed private placement March 2024**

- \$23.8 in cash on balance sheet as of December 31, 2023
- Recent financing extends runway into 1H 2026

# What are MicroRNAs?

## *Post-Translational Inhibitors of Gene Expression*

- MicroRNAs (miRNAs) are short (~20nt) non-coding RNAs that bind to complementary sequences located in the 3' untranslated region (3'UTR) of target mRNA, controlling translation and eventual degradation of the target mRNA transcripts



- Aberrant expression of miRNAs has been shown to promote the progression of many human diseases, including proliferative, cardiovascular, metabolic, fibrotic, and neurodegenerative diseases
- Inhibition of specific pathogenic miRNA (by anti-miRs) have been shown to attenuate disease progression in both preclinical and clinical settings

# Innovative Pipeline: Primary Focus on Kidney Diseases.

INDICATION (TARGET)		TARGET VALIDATION	LEAD OPTIMIZATION	IND ENABLING	PHASE 1	PHASE 2	PHASE 3
NEPHROLOGY	ADPKD* RGLS8429	[Teal bar spanning Target Validation, Lead Optimization, and Ind Enabling]					
	Research Programs	[Teal bar spanning Target Validation and Lead Optimization]					
CNS	Research Programs	[Teal bar spanning Target Validation and Lead Optimization]					

\*Autosomal Dominant Polycystic Kidney Disease

# Autosomal Dominant Polycystic Kidney Disease (ADPKD).

*Orphan Disease and High Unmet Medical Need*

## The Unmet Medical Need

- 50% of patients develop ESRD by age 60 and require dialysis or transplantation
- Kidney failure average age:
  - 55 years for *PKD1* patients
  - 74 years for *PKD2* patients
- Only FDA approved therapy (tolvaptan) has boxed warning for potentially fatal liver toxicity and significant tolerability concerns related to free water excretion
  - Despite limitations, 2023 global sales were \$1.3B (represents 32% increase YoY)

## PATIENT POPULATION.

~80%

patients with  
**PKD1** mutation

160K

diagnosed  
individuals in U.S.

## HEALTH BURDEN.

50%

patients develop  
ESRD by age 60

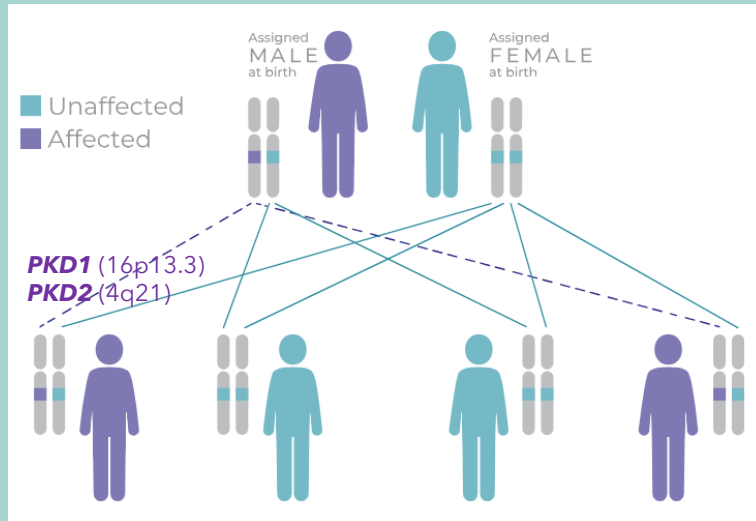
\$8B+

estimated annual  
direct & indirect cost  
in U.S.<sup>1</sup>

# ADPKD Genetic Mutation Drives Clinical Pathology.

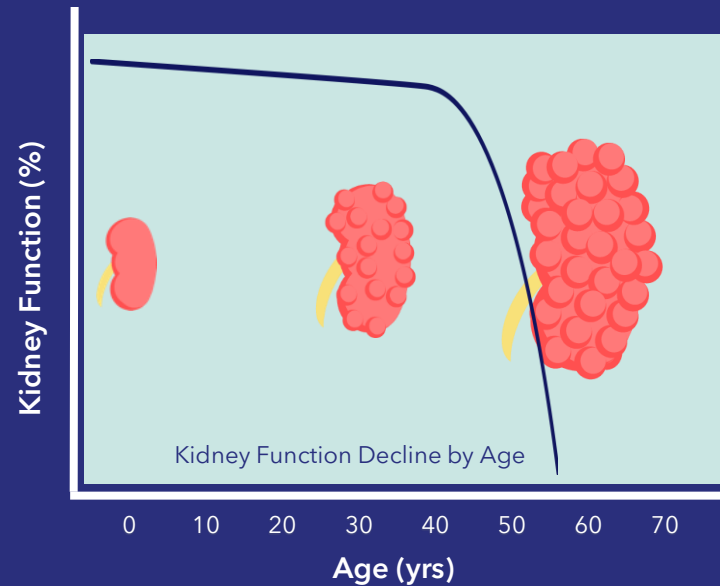
*Proliferative, Cystic Disease Leads to Enlarged Kidneys with Progressive Failure*

- Mutation of either **PKD1** or **PKD2** genes, which reduce levels of their encoded proteins polycystin-1 (PC1) or polycystin-2 (PC2), causes formation and proliferation of multiple fluid-filled cysts in the kidneys leading to loss of kidney function over time



Adapted from PKD Foundation website

- Cystic expansion drives kidney growth throughout life, while decline in kidney function generally occurs late in adulthood.



- Polycystic kidneys taken from an ADPKD patient during nephrectomy:



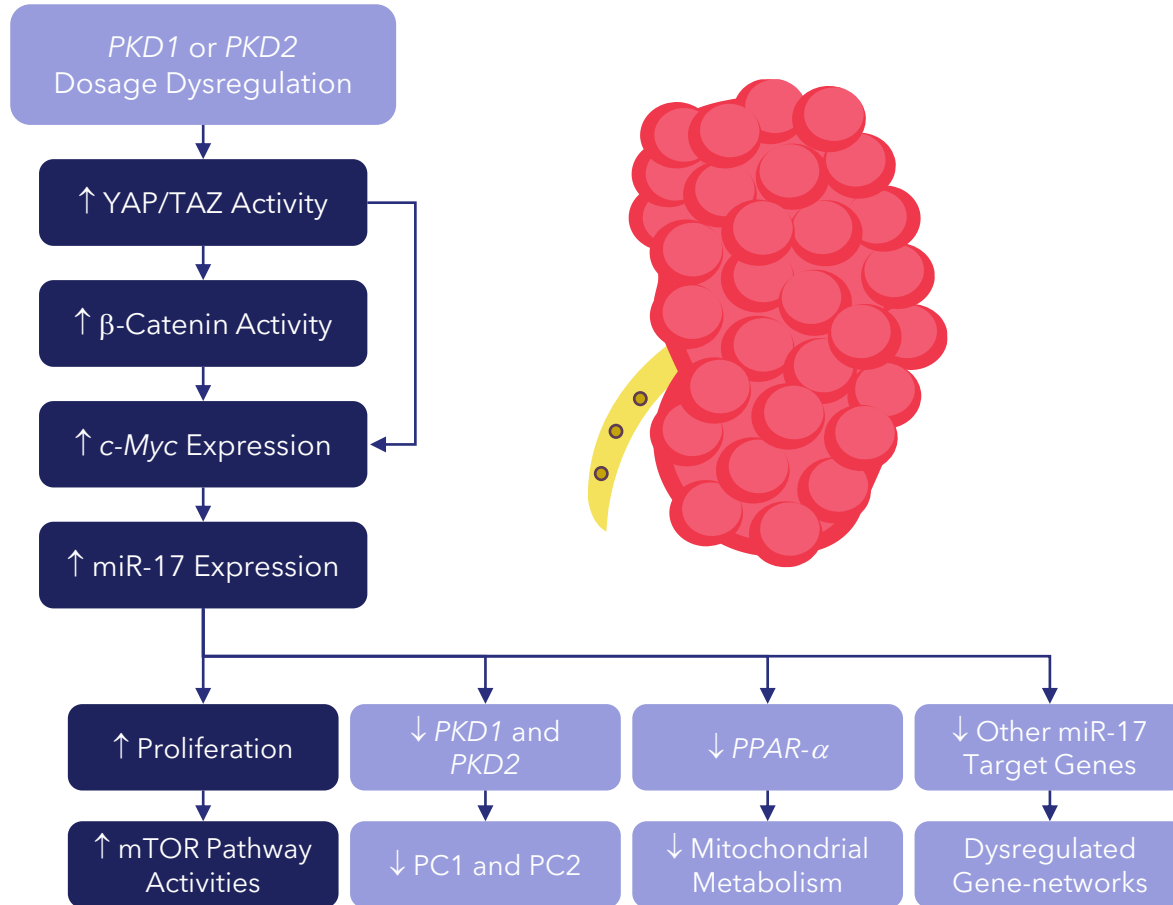
Photo courtesy of Dr. Vishal Patel



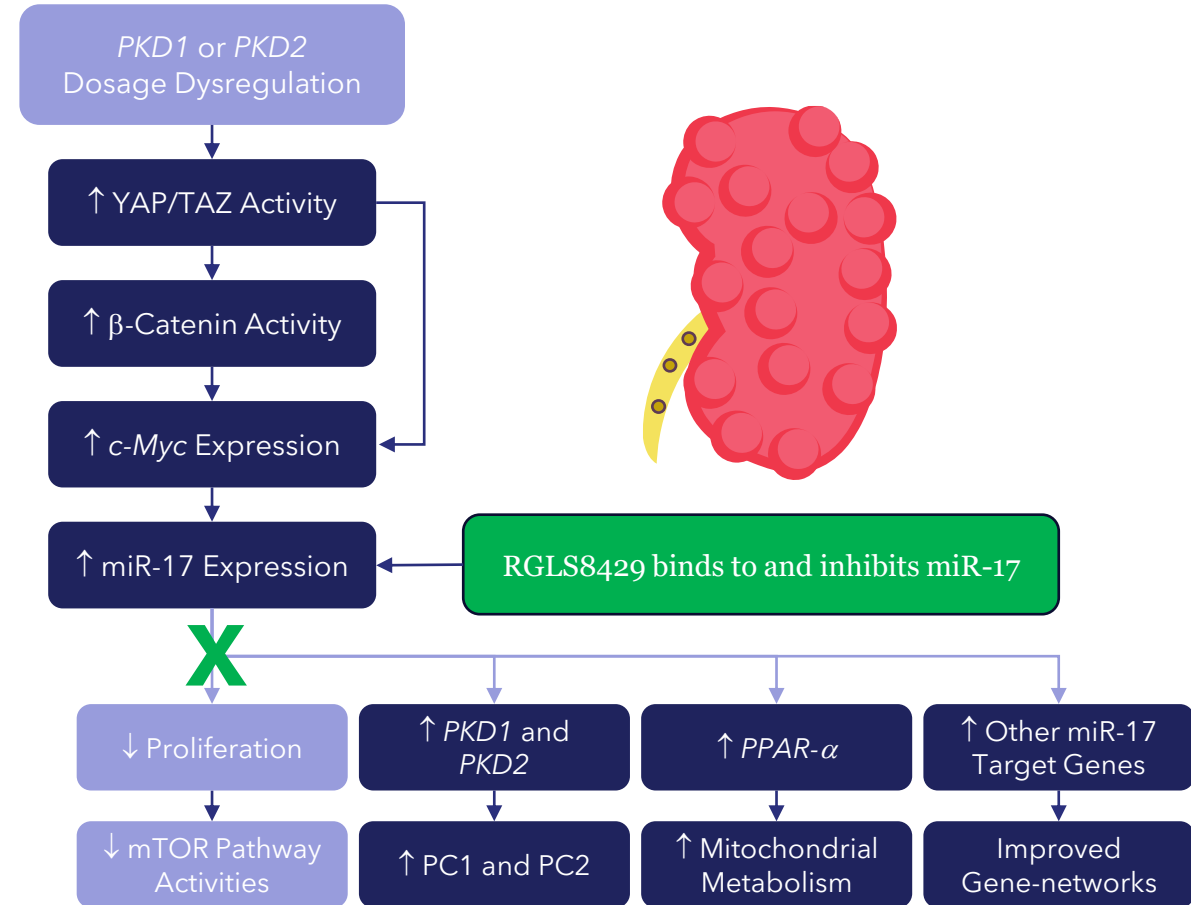
# Increased miR-17 Expression Drives Cystic Proliferation in ADPKD.

Blocking miR-17 Activity Reduces Key Proliferative Signal Pathways

## Disease State Untreated



## After Treatment with Anti-miR-17





# Anti-miR-17 as a Therapeutic Strategy in ADPKD.

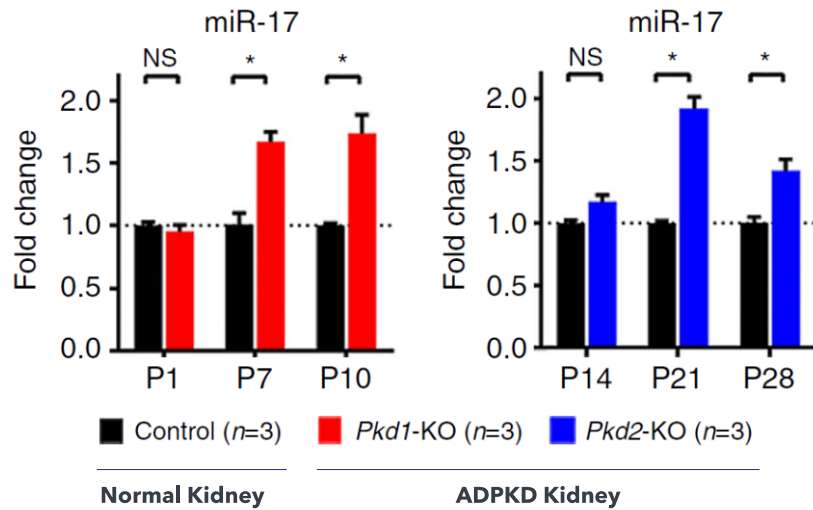
# miR-17 Is Upregulated in ADPKD.

## Overexpression of miR-17 Promotes Disease Progression

- miR-17 is upregulated in mouse kidney cysts and human ADPKD cyst cells<sup>1,2</sup>
- Overexpression of miR-17 in renal tubules in normal mice promoted kidney cyst growth<sup>1</sup>

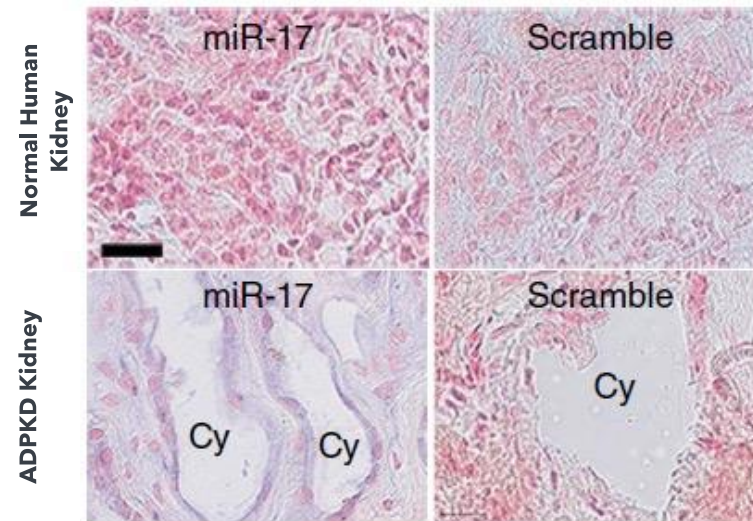
### Mouse Kidney Samples

qPCR analysis

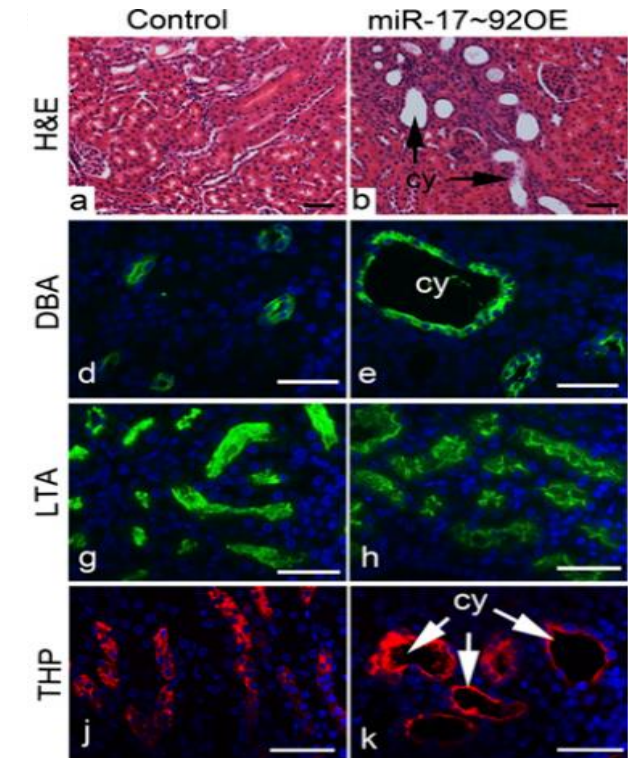


### Human Kidney Samples

*In-situ* hybridization



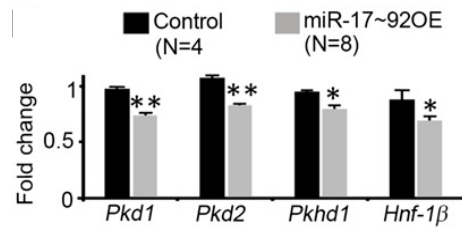
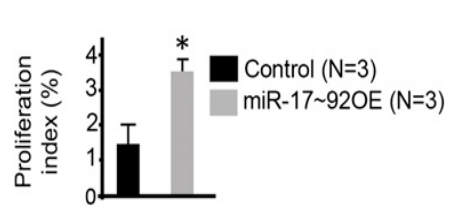
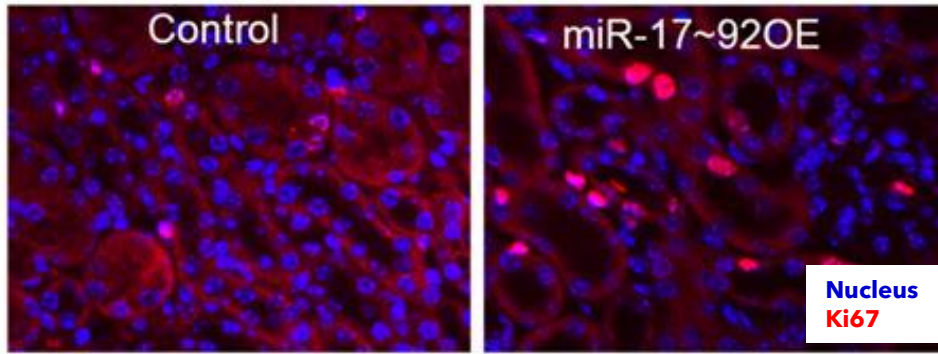
### Mouse Kidney



# MiR-17 Promotes Proliferation and Represses Many Pathogenic Genes of PKD.

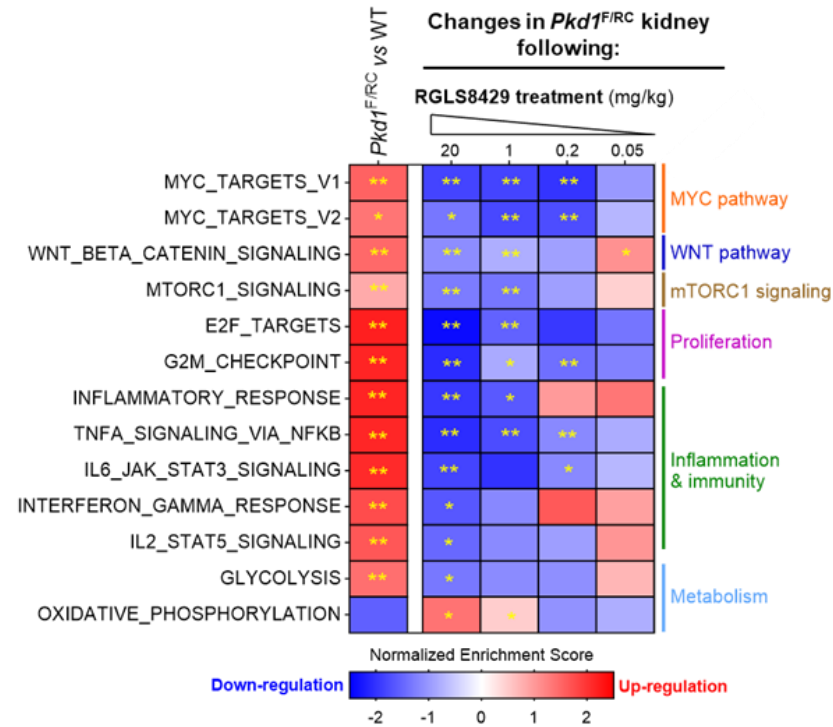
## Knockdown of miR-17 Improves Many *Pkd* Pathogenic Gene-Networks

- Overexpression of miR-17 in renal tubules promotes kidney cyst growth and proliferation, and repressed PKD-pathogenic genes, including *Pkd1* and *Pkd2*

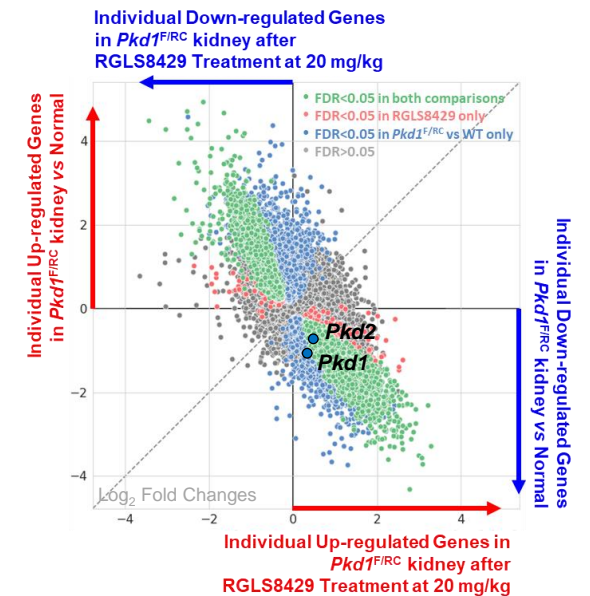


Patel 2013, PNAS.

- Genetic-knockdown or pharmacologic inhibition of miR-17 improves many PKD-pathogenic pathways, including those associated with proliferation (e.g. Myc, WNT, mTORC1, etc)



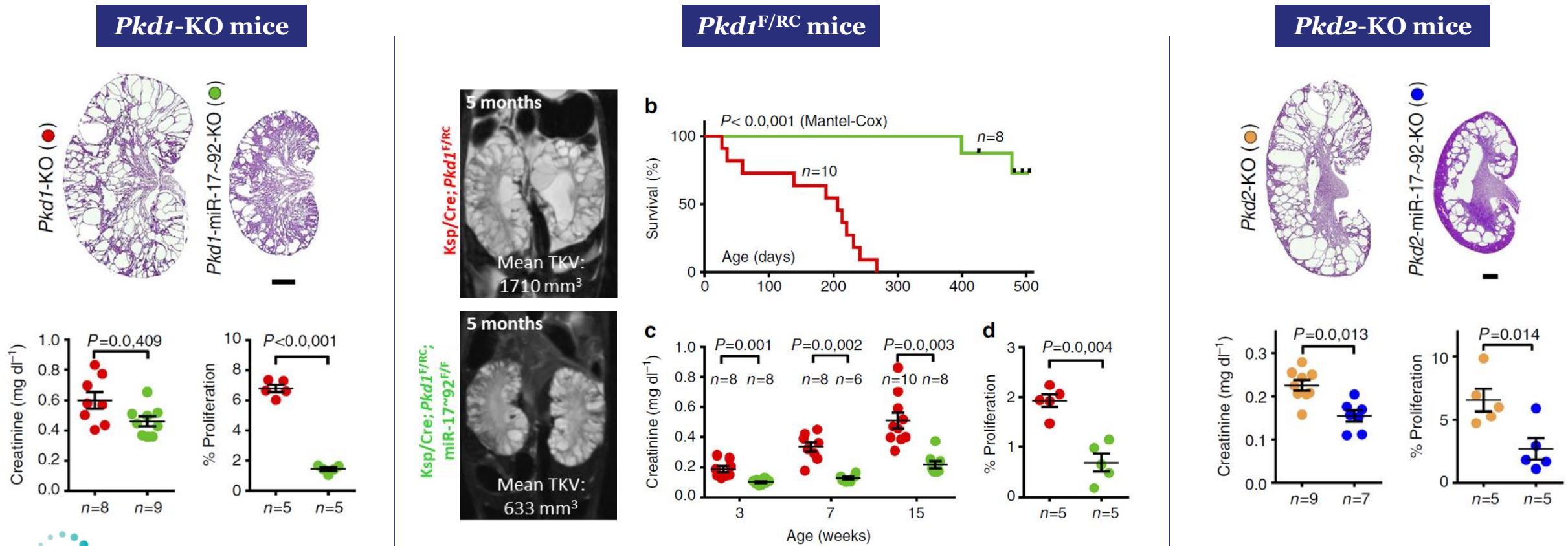
### Comparative differential gene analysis



Gene Set Enrichment Analysis (GSEA) identified PKD-pathogenic pathways that are dysregulated in *Pkd1<sup>F/RC</sup>* mouse kidney compared to normal wildtype (WT) kidney, which are in turn reverted in *Pkd1<sup>F/RC</sup>* following RGLS8429 treatment. \*FDR  $q < 0.25$ , \*\*FDR  $q < 0.05$

# Knockdown of miR-17 Attenuates Disease Progression.

- Kidney-specific knockdown of miR-17 attenuated kidney cyst growth in multiple ADPKD mouse models, including *Pkd1*<sup>null</sup>, *Pkd1*<sup>hypomorphic</sup>, and *Pkd2*<sup>null</sup> mice<sup>1-4</sup>



# Anti-miR-17 Treatment Reduces Kidney Cyst Growth in Multiple Disease Models.

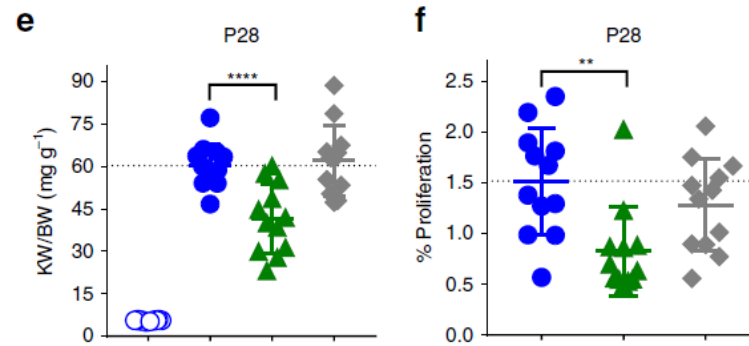
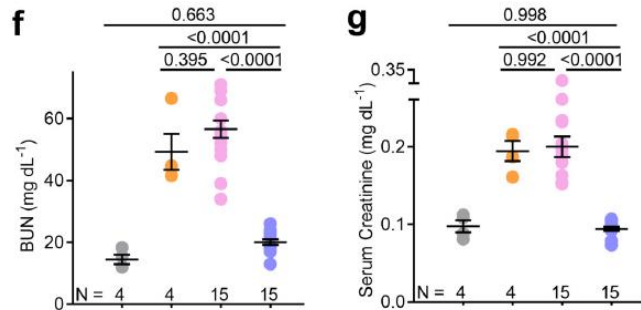
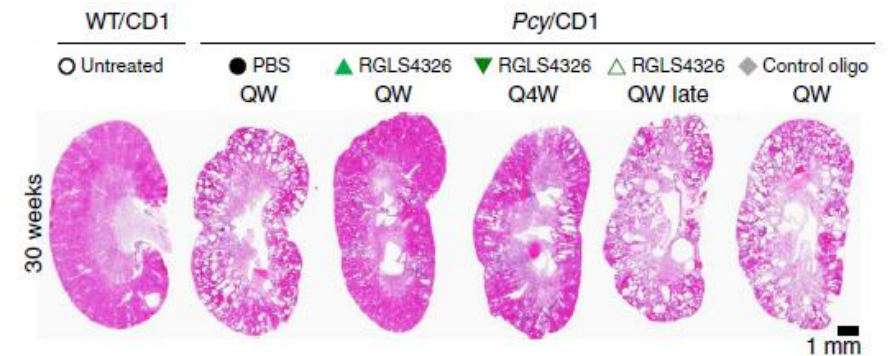
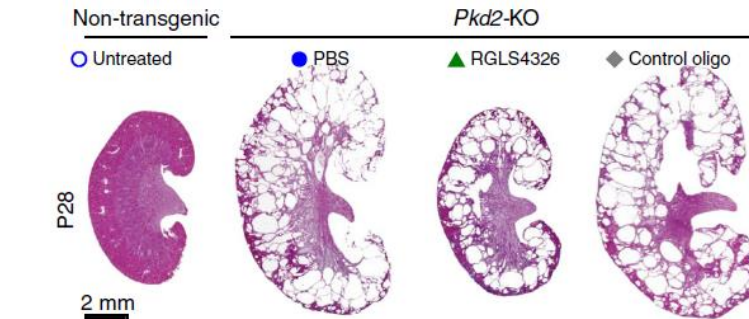
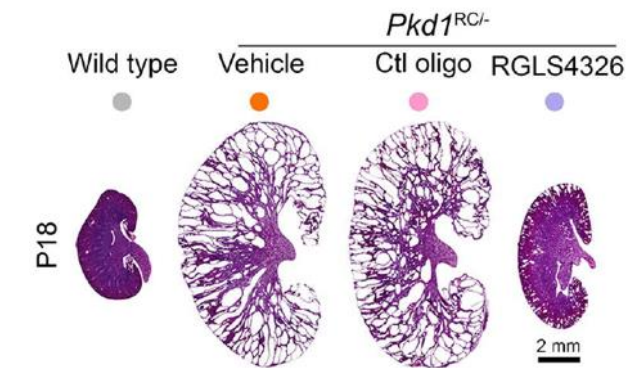
## *Pkd1/2* genes models

## Non-*Pkd* gene models

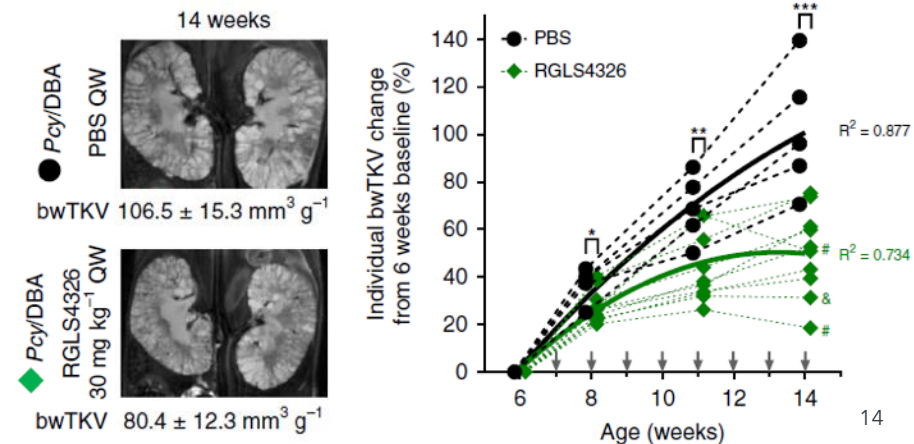
### *Pkd1*<sup>F/RC</sup> mice

### *Pkd2*-KO mice

### *Pcy*/CD1 mice

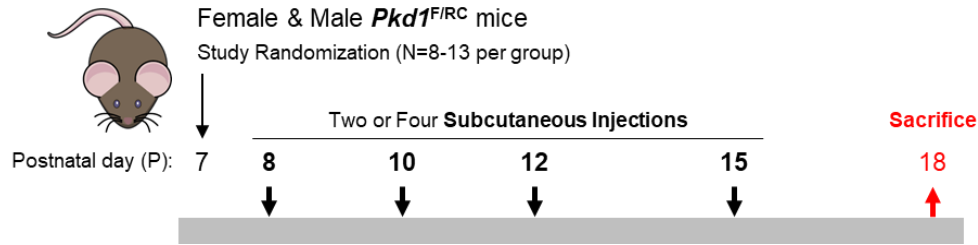


### *Pcy*/DBA mice

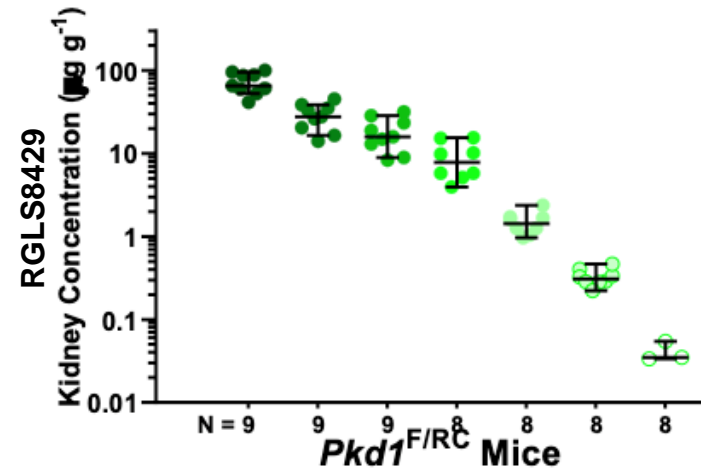


# Anti-miR-17 Treatment Exhibits a Clear Dose Response.

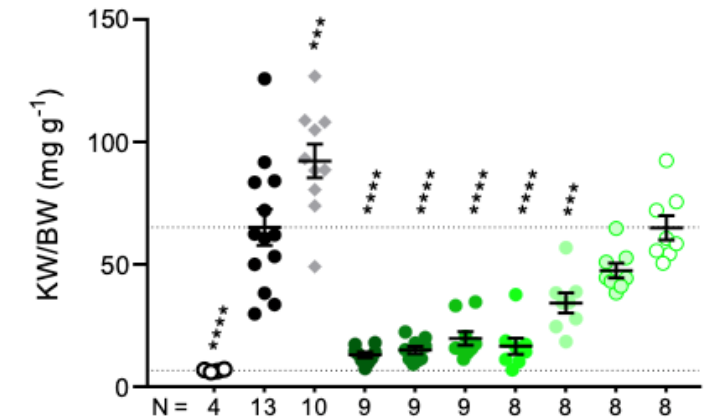
## Efficacy in $Pkd1^{F/RC}$ mice Study Design



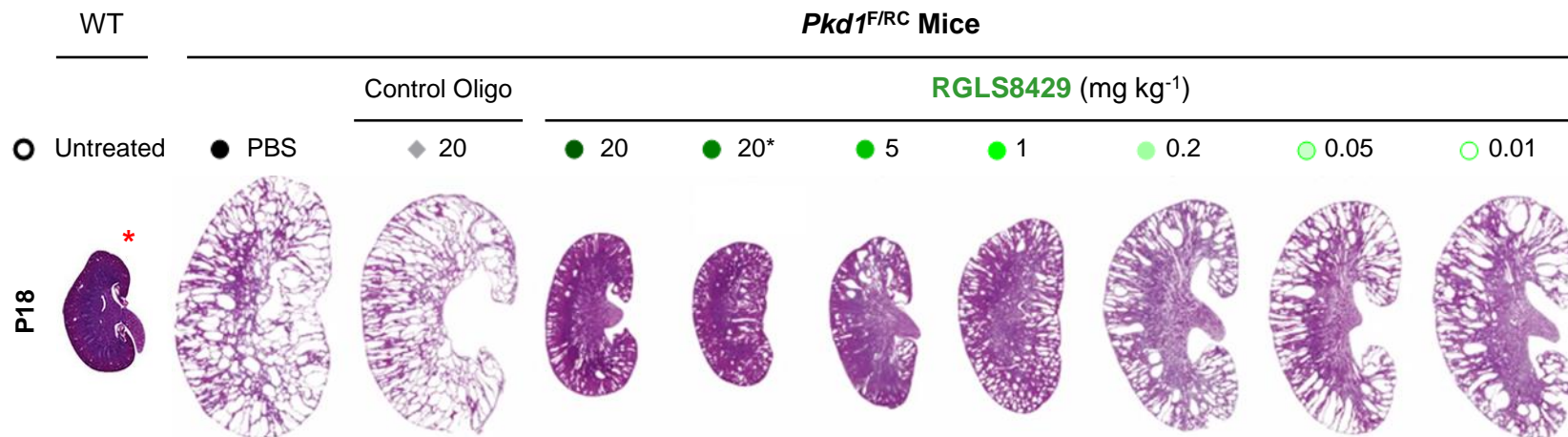
## End of study Kidney Concentration



## End of study KW/BW ratio



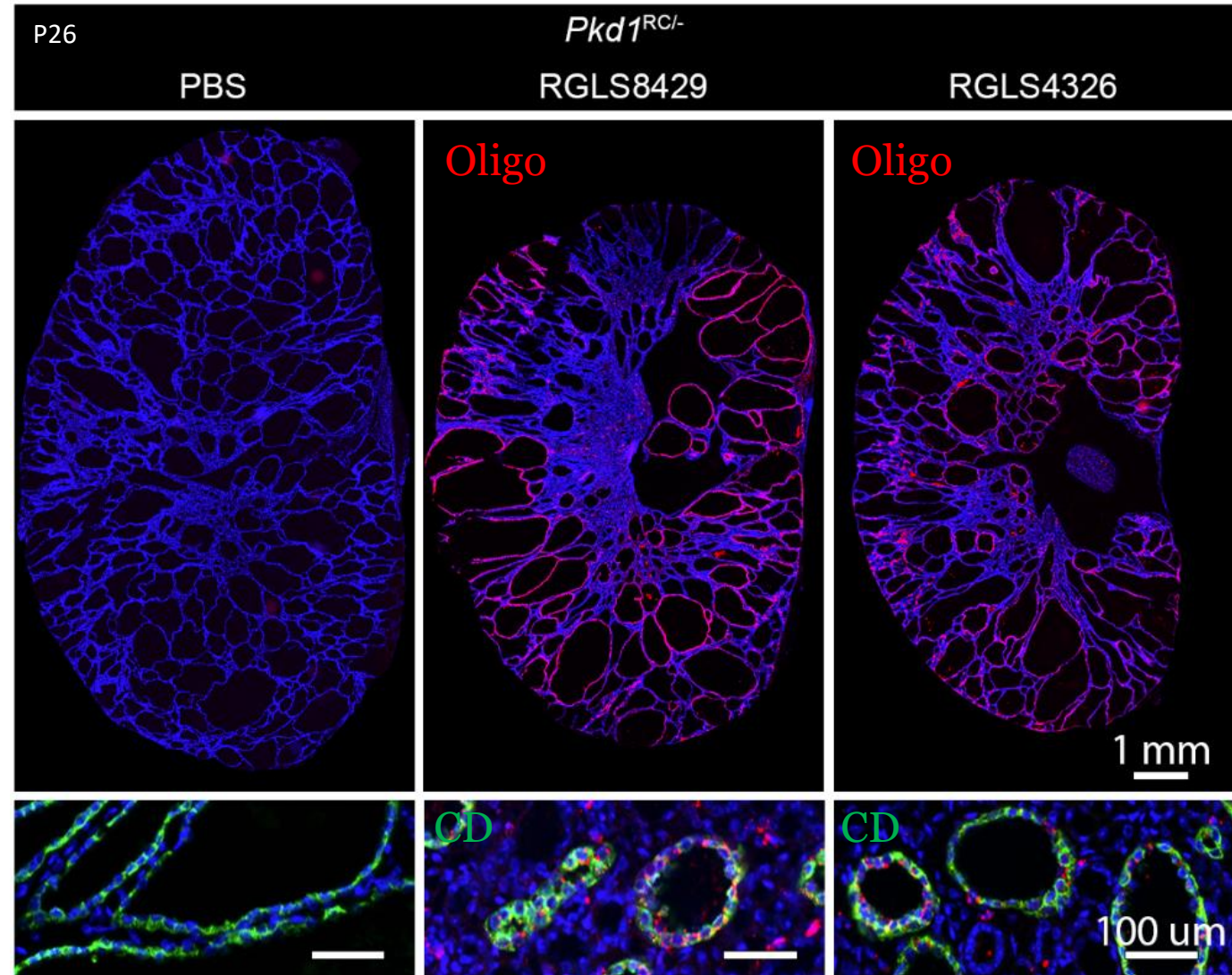
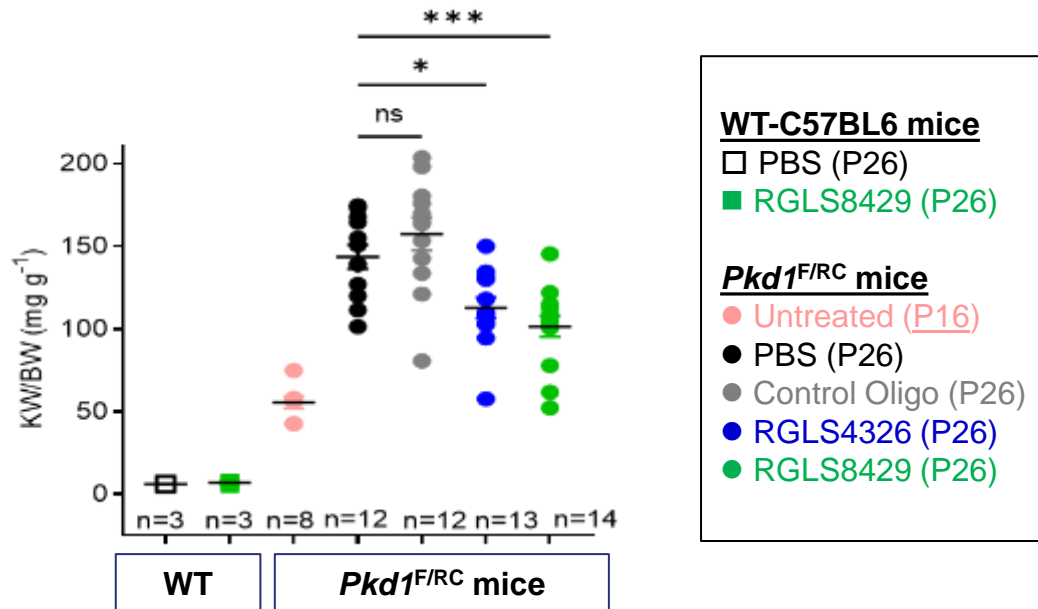
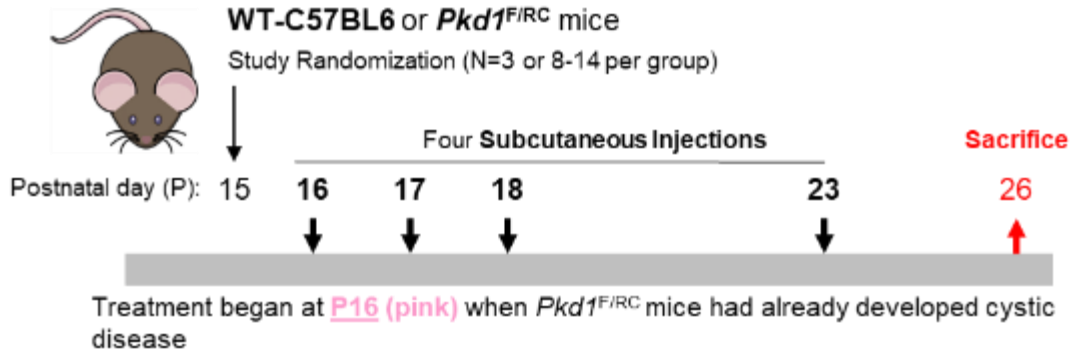
## Representative Histology



\*P8 & P12 Injections only; All others P8, P10, P12 & P15 Injections

\*Historical Data

# Anti-miR-17 Oligo Localizes to Kidney Cyst Epithelium and Confers Efficacy in *Pkd1*<sup>F/RC</sup> ADPKD Mice.

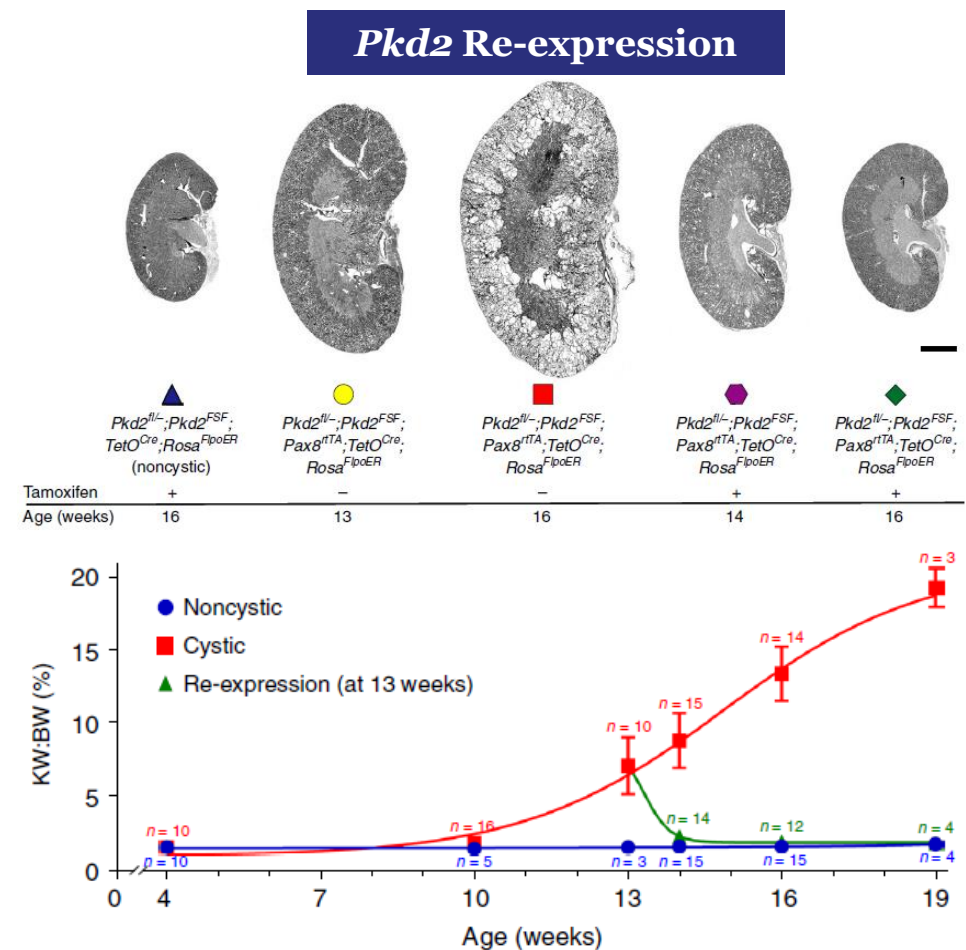
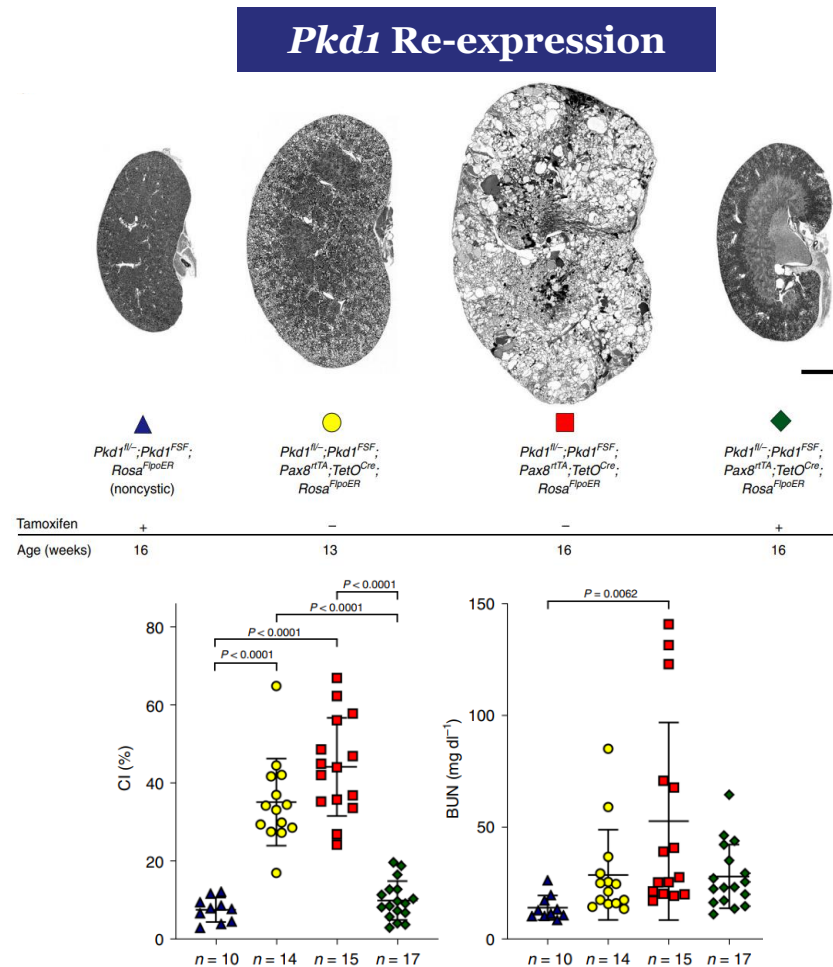


Immunofluorescence (IF) Imaging:  
RGLS: Anti-Oligo Antibody  
DBA: Collecting Duct (CD) Marker



# Re-activation of *Pkd1* or *Pkd2* Rapidly Reverse Disease in ADPKD Mice.

- Restoration of *Pkd1* or *Pkd2* gene expression, and thereby increase of PC1 or PC2 protein levels, have shown efficacy in different ADPKD mouse models by independent labs<sup>1-4</sup>.





# RGLS8429 Development.



# RGLS8429: Engineered to Block the Action of miR-17 in ADPKD.

## Oligonucleotide built with specificity against miR-17

- Directly binds to key seed region on miR-17
- Prevents miR-17 engagement with target mRNA
- Strong evidence of efficacy in vitro and in vivo

## Preferential delivery to organ of choice and favorable kinetics for Q2W delivery

- Short, naked oligo confers preferential delivery to kidney compared to liver, plasma and other compartments
- $T_{1/2}$  ~10 days in tissue enabling every-other week subcutaneous injection

## Favorable safety & tolerability profile

- Low potential for off-target effects via aptamer or nucleotide binding
- Chronic tox in mouse complete (*NOAEL* = *top dose*)
- Ph1 SAD in healthy subjects was safe and well-tolerated

## Early evidence of benefit using key pharmacodynamic and disease marker (*polycystin*) in ongoing Ph1b

- 1 and 2 mg/kg dose demonstrates increases in PC1 & PC2
- Additional 3 mg/kg cohort underway

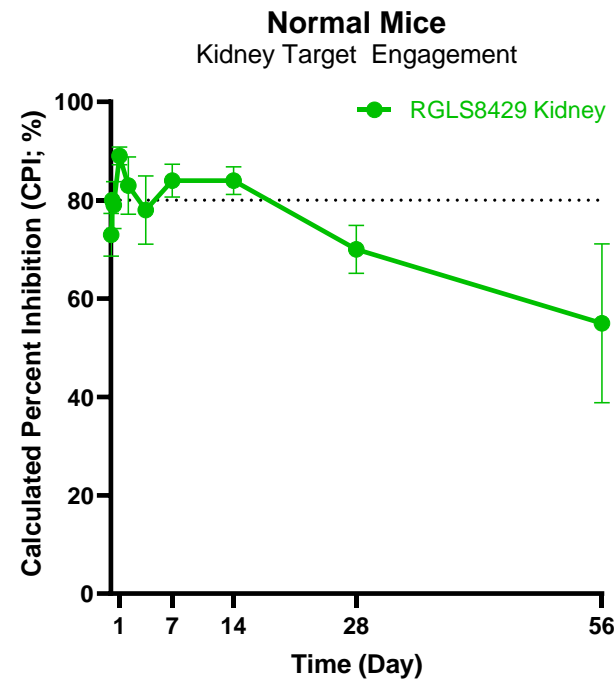
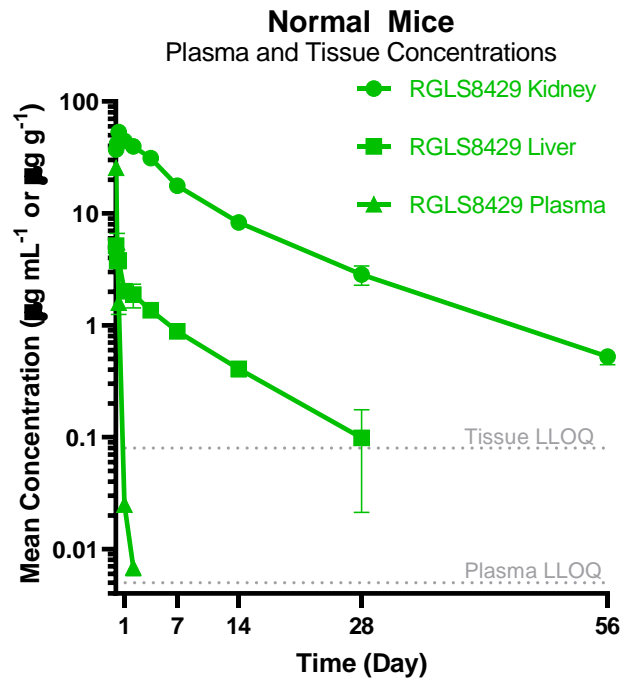


**Orphan Drug Designation:** Granted by FDA Q2 2022



**Accelerated Approval Possible with Successful Ph2 Trial:** Total Kidney Volume is accepted as a surrogate endpoint supporting accelerated approval pathway

# RGLS8429 Preferentially Distributes to Kidney and Demonstrates Strong Target Engagement.



WT-C57BL6 mice received a single subcutaneous injection of RGLS8429 at 30 mg/kg

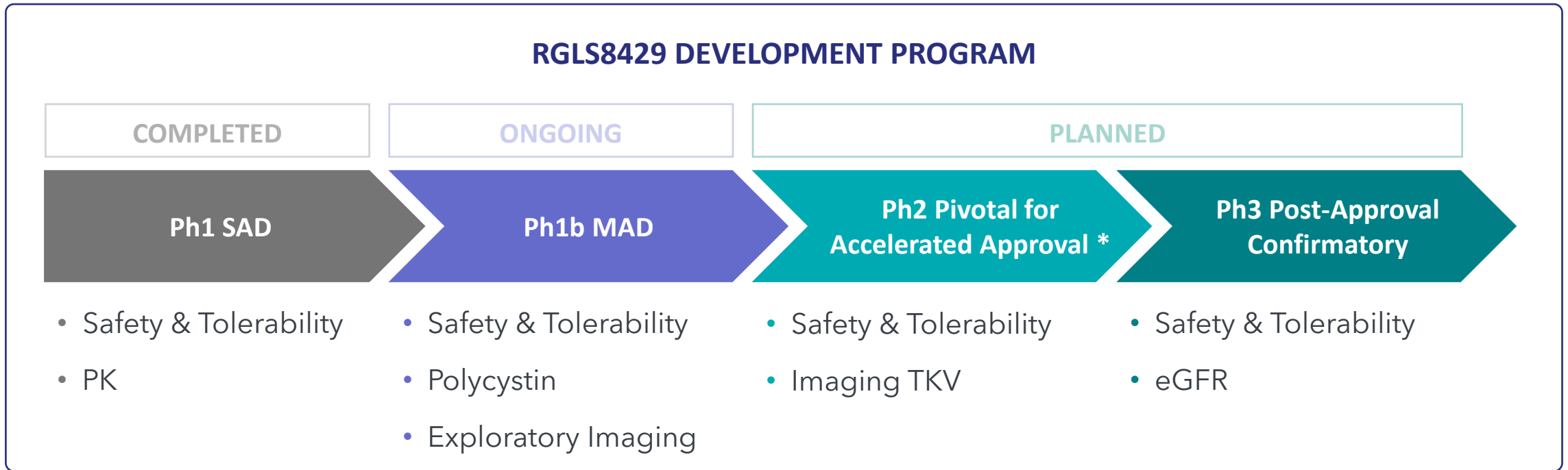
## Clinical PK mirrors nonclinical models and supports every-other week dosing

- Plasma concentrations show rapid absorption followed by rapid clearance
- RGLS8429 is metabolically stable; primary route of excretion via kidney
- Anticipated kidney tissue  $T_{1/2}$  ~10 days based on nonclinical sampling
- Extrapolation from mouse and monkey models supports optimal (~80%) miR-17 inhibition in humans at > 2.4 mg/kg

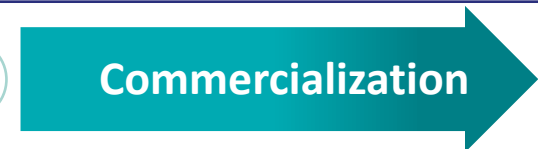
# RGLS8429 Has Favorable Safety Profile in Preclinical Toxicity Studies.

- **SC administration** in the clinical formulation, 150 mg/mL in 0.3% saline, is supported by nonclinical local tolerability study conducted in rabbits
- **Well tolerated in mice in chronic mouse toxicity study**, with no-observed-adverse-effect-level (NOAEL) of 300 mg/kg dosed subcutaneously (SC) once-every-two-weeks (Q2W)
- **Well tolerated in non-human-primates (NHP) in a 3-month toxicity study**, with NOAEL of 150 mg/kg dosed SC once-weekly (QW). Chronic toxicity study (9-months) in NHP initiated Q4 2023
- **Low potential for off-target effects** via receptor inhibition
- Has shown **no potential for genotoxicity** and **no evidence of mitochondrial toxicity**
- Has **minimal potential** for adverse effects on platelets and **low risk** for pro-inflammatory activity

# Planned RGLS8429 Clinical Development Based on Accelerated Approval.



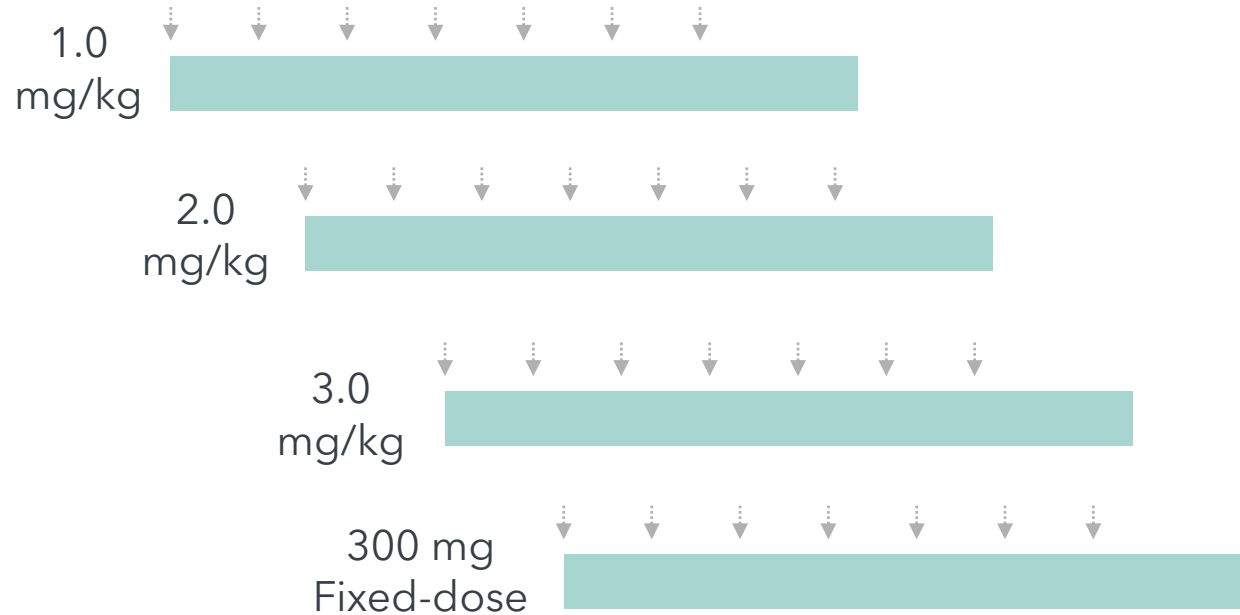
**Accelerated Approval\***





# Phase 1b Study Design, Baseline Characteristics, Safety and PK.

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



## STUDY DESIGN

### • Cohorts 1-3

- ADPKD Patients
  - Mayo Imaging Class 1C, 1D or 1E
  - eGFR 30-90 mL/min
- 12 subjects per cohort
- Randomized 3:1 (RGLS8429:Placebo)
- 3-month dosing (Q2W x 7)
- Safety, PK, PD/biomarkers, eGFR, HtTKV, and novel cyst imaging analysis (TKCN, TKCV and CPSA)

### • Cohort 4

- Up to 30 subjects
- Open label, single arm fixed dose (with similar comparisons as cohorts 1-3)

## EXPECTATIONS



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



Cohort 3 topline data anticipated mid-2024

Cohort 4 initiation planned for Q2 2024



## Cohort 1 and 2 Baseline Characteristics Representative of Target Patient Population.

Baseline Characteristics	Placebo (Cohort 1 & 2) N=6	RGLS8429 (1 mg/kg) N=9	RGLS8429 (2 mg/kg) N=11
Age (years) mean (SD)	45 (12)	52 (12)	46 (12)
Female n (%)	3 (50%)	5 (56%)	5 (46%)
White n (%)	4 (67%)	9 (100%)	10 (91%)
BMI mean (SD)	28 (5)	30 (5)	26 (3)
Tolvaptan use in prior 3 months n (%)	1 (17%)	2 (22%)	1 (10%)
eGFR (mL/min/1.73m <sup>2</sup> ) mean (SD)	52 (18)	47 (20)	68 (19)
htTKV (mL/m) mean (SD)	1684 (575)	1698 (737)	1264 (567)
Mayo Class 1C/1D/1E (%)	17%/67%/17%	56%/33%/11%	46%/36%/18%
Genetic Mutation <i>PKD1</i> / <i>PKD2</i> (%)	67%/0%	56%/33%	82%/18%

*Cohort 2 exhibits slightly milder disease evidenced by htTKV and eGFR*

Enrolled population represents significant disease burden by kidney size and reduced eGFR  
Similar enrollment criteria planned for pivotal Ph2 trial

# Cohort 1 and 2: Safety and PK Demonstrate No Significant Findings.

	Placebo (Cohort 1 & 2) N=6	RGLS8429 (1 mg/kg) N=9	RGLS8429 (2 mg/kg) N=11
Any Treatment Emergent Adverse Events (TEAEs)	3 (50%)	7 (78%)	7 (64%)
Any Treatment Related TEAEs	0	1 (11%)	5 (46%)
Any Treatment Emergent Serious Adverse Events (TESAEs)	0	1 (11%)*	0
Any Treatment Related TESAEs	0	0	0
Any TEAEs leading to early withdrawal**	0	0	1 (9%)**
Any TEAEs leading to death	0	0	0

\*Appendicitis

\*\* Grade 1 injection site reaction

## Pharmacokinetics Summary

No accumulation observed in plasma or urine with repeat every other week dosing  
AUC plasma exposure increased at 2 mg/kg as expected relative to 1 mg/kg

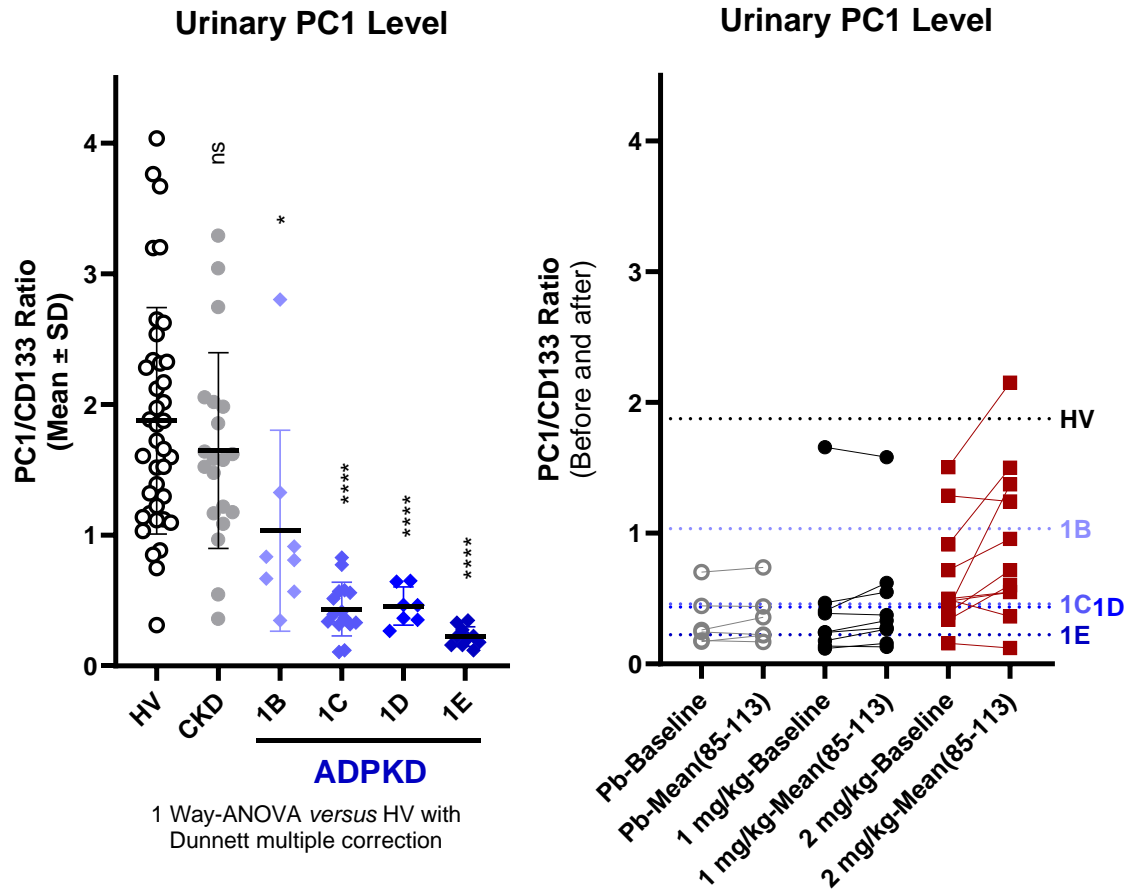


# Change in Urinary PC1 and PC2 from Baseline.

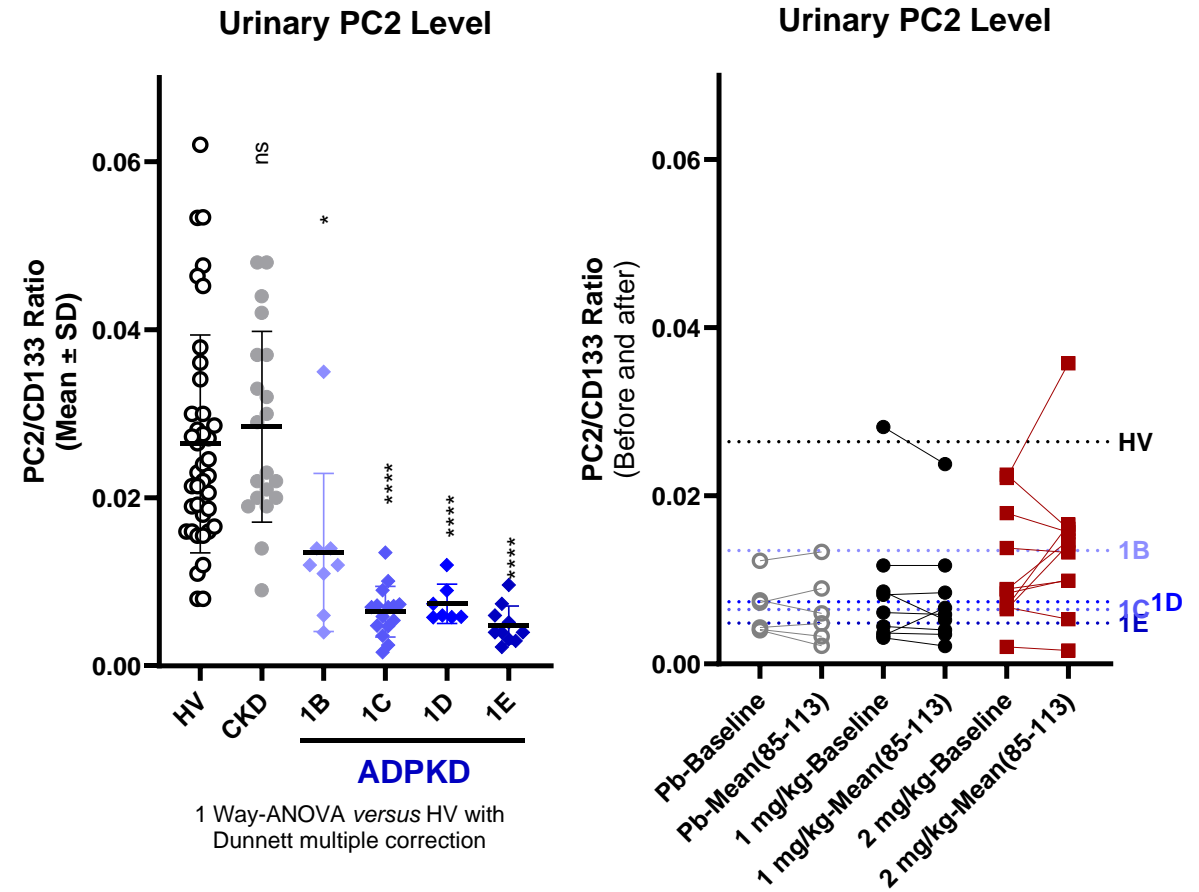
# Subject Plots of Baseline to EOS Changes in Absolute Polycystin Levels.

Greater Increases Seen with 2 mg/kg Compared to 1 mg/kg and Placebo

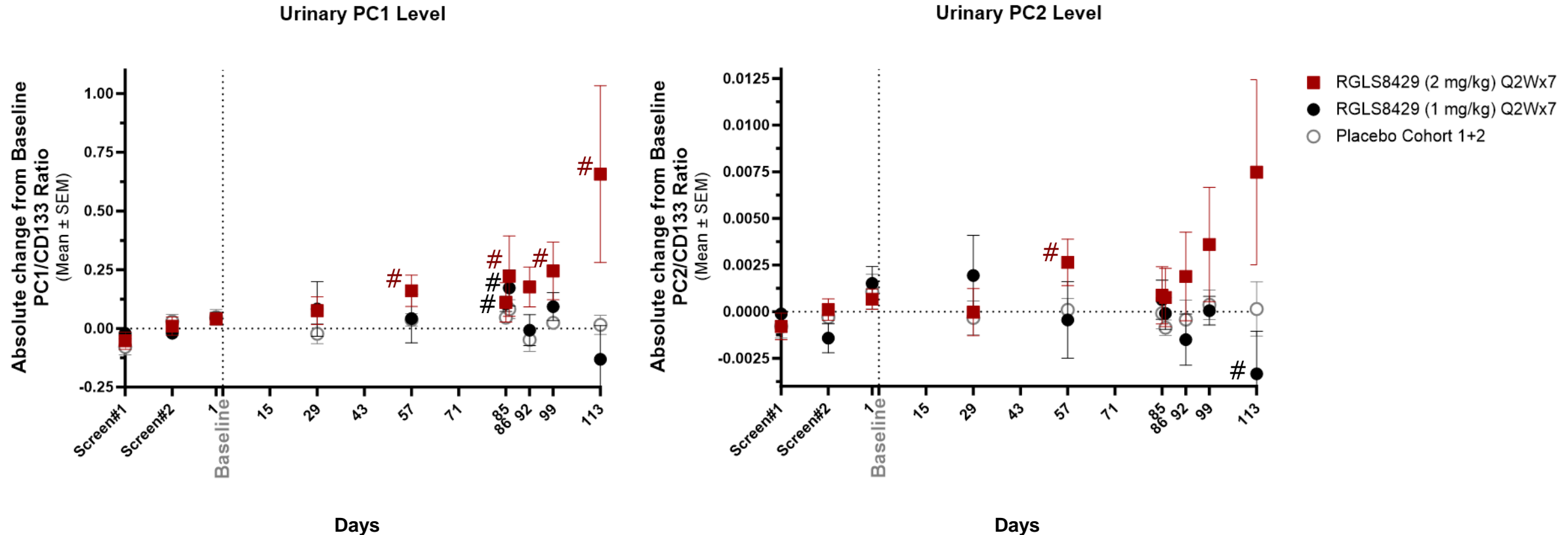
## PC1



## PC2



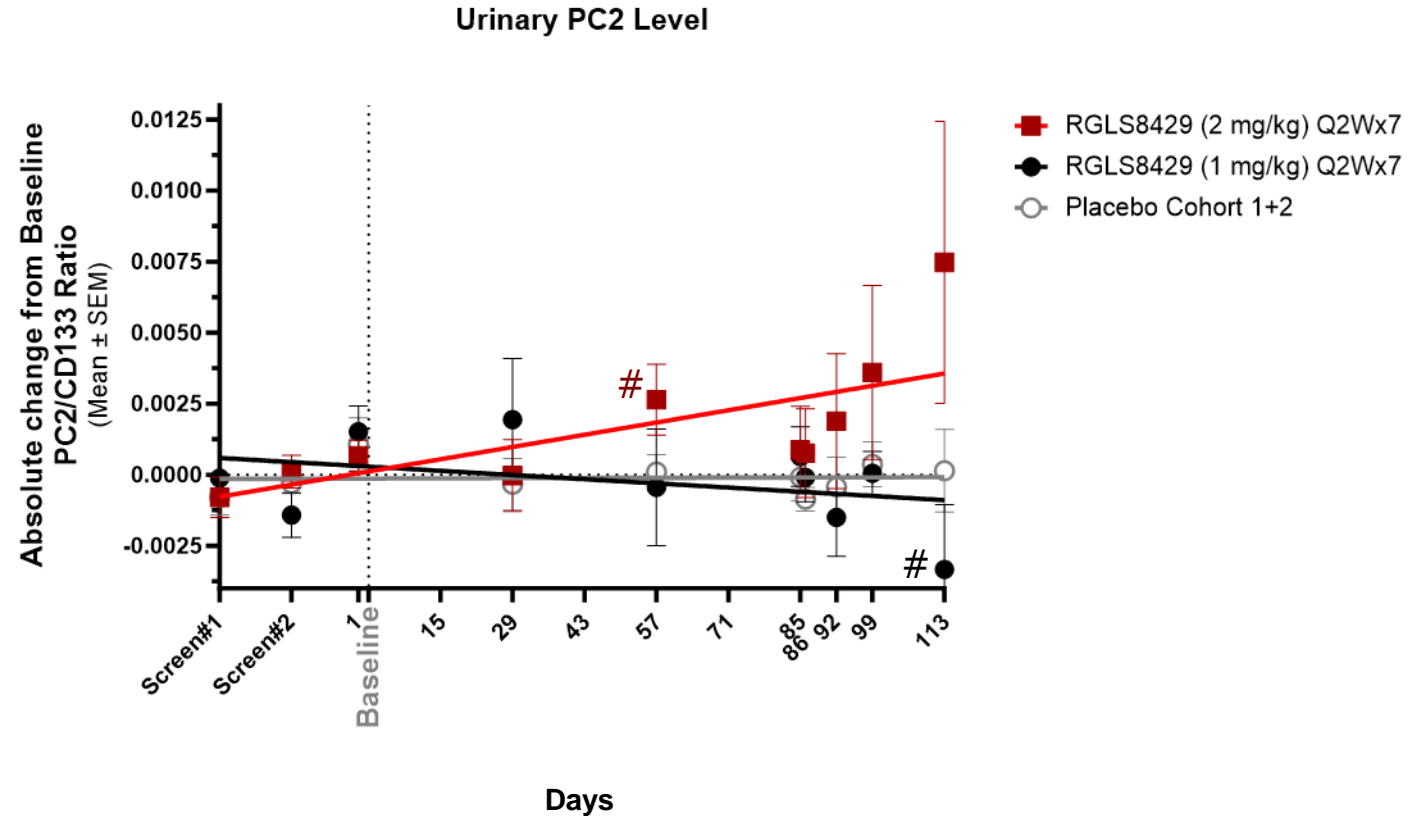
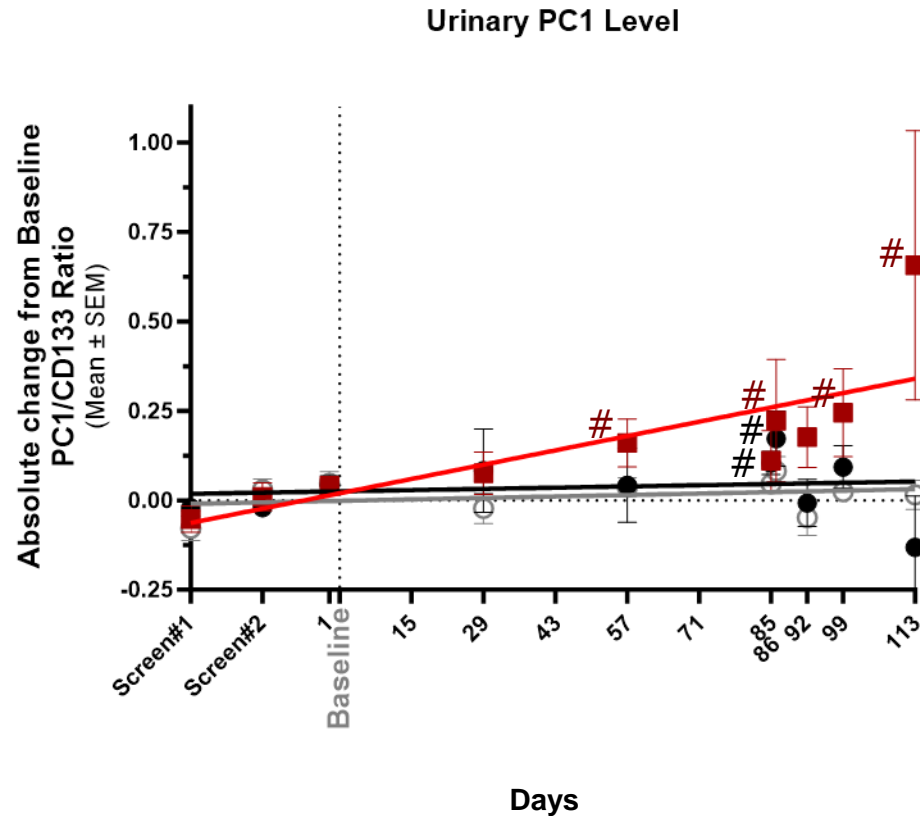
# Absolute Changes in Urinary PC1 and PC2 Ratios over Time.



#, Statistical significance by Wilcoxon matched-pairs signed (one-tailed) rank test compared to baseline values (RGLS8429: Black # for 1 mg/kg and Red # for 2 mg/kg)

Note: Exploratory regression analysis by simple linear regression

# Absolute Changes in Urinary PC1 and PC2 Ratios over Time.



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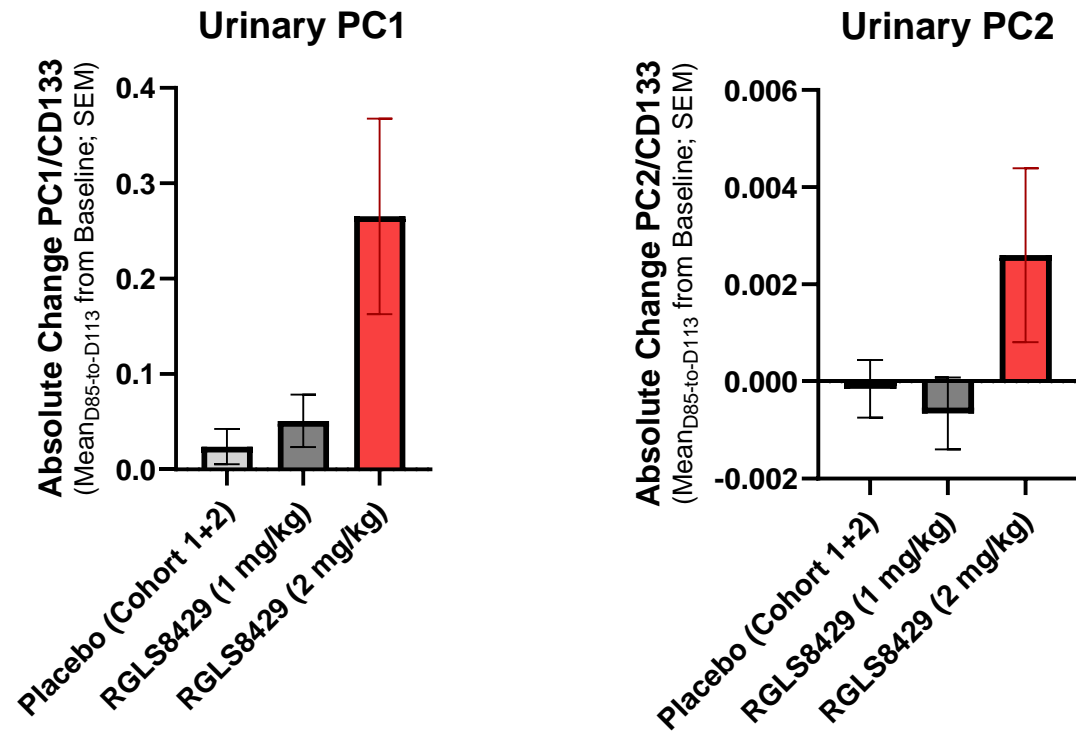
Note: Exploratory regression analysis by simple linear regression

# Mean Change from Baseline in Polycystin Levels.

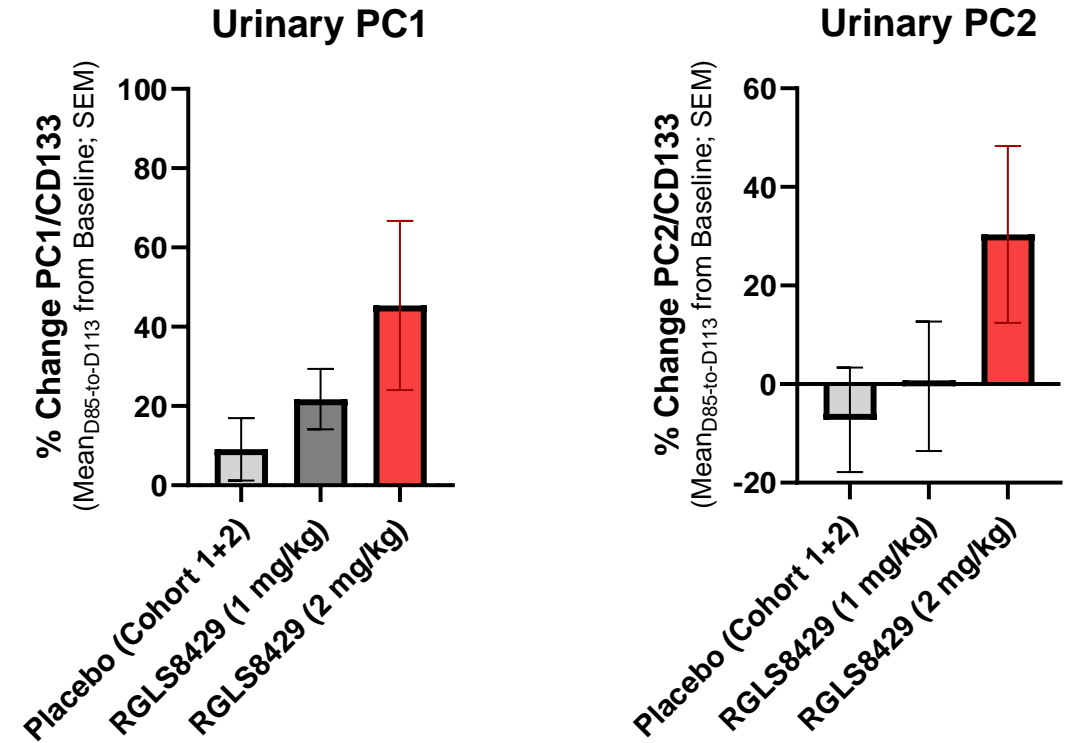
Greater Increases Seen with 2 mg/kg than with 1 mg/kg and Placebo

- RGLS8429 (2 mg/kg) Q2Wx7
- RGLS8429 (1 mg/kg) Q2Wx7
- Placebo Cohort 1+2

**Absolute Change of**  
Urinary PC1/CD133 or PC2/CD133 Ratios



**% Change of**  
Urinary PC1/CD133 or PC2/CD133 Ratios



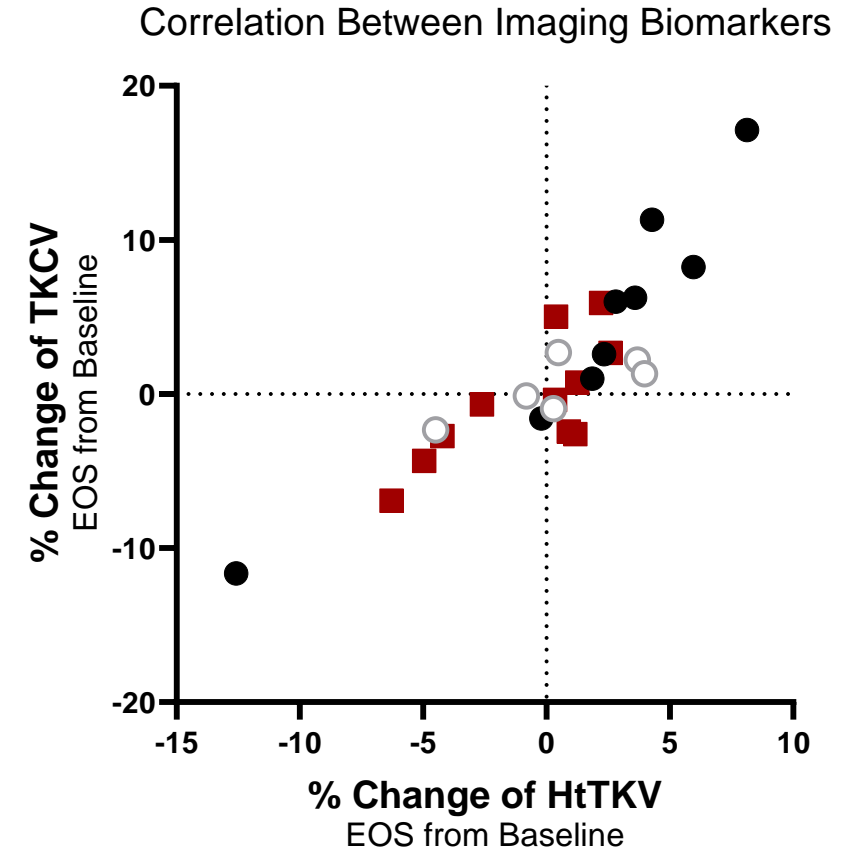
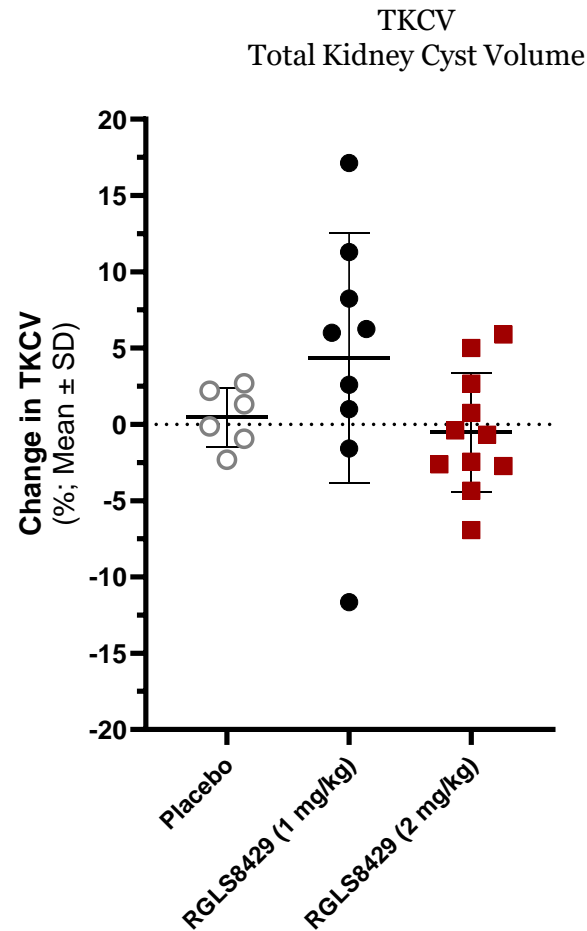
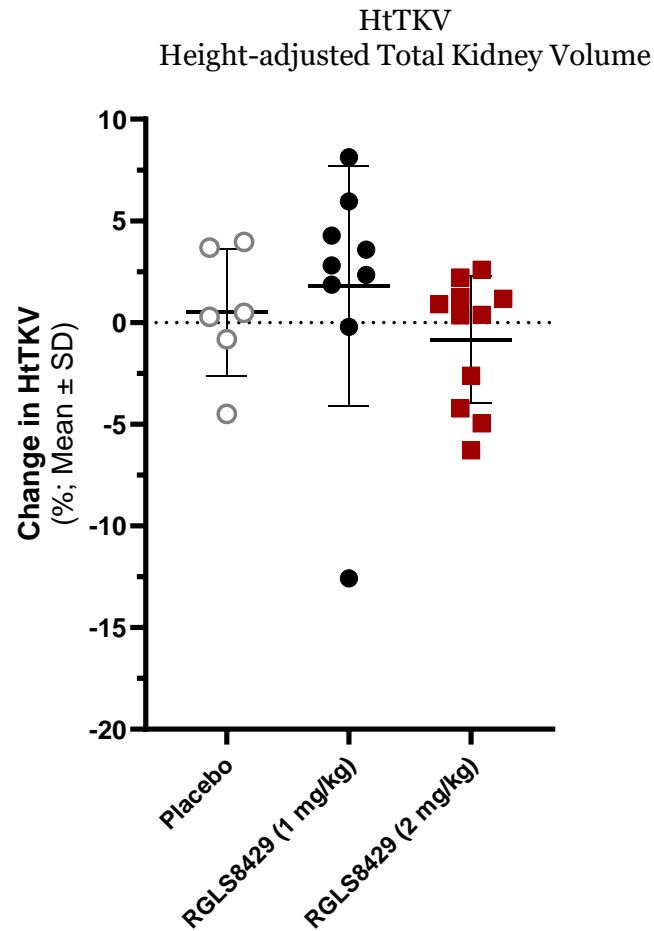


# Kidney Imaging Results.



# Changes in Height-Adjusted Total Kidney Volume and Total Kidney Cyst Volume.

*Tight Correlation between HtTKV and TKCV and a Suggestion of Notable HtTKV Reduction at 2 mg/kg*



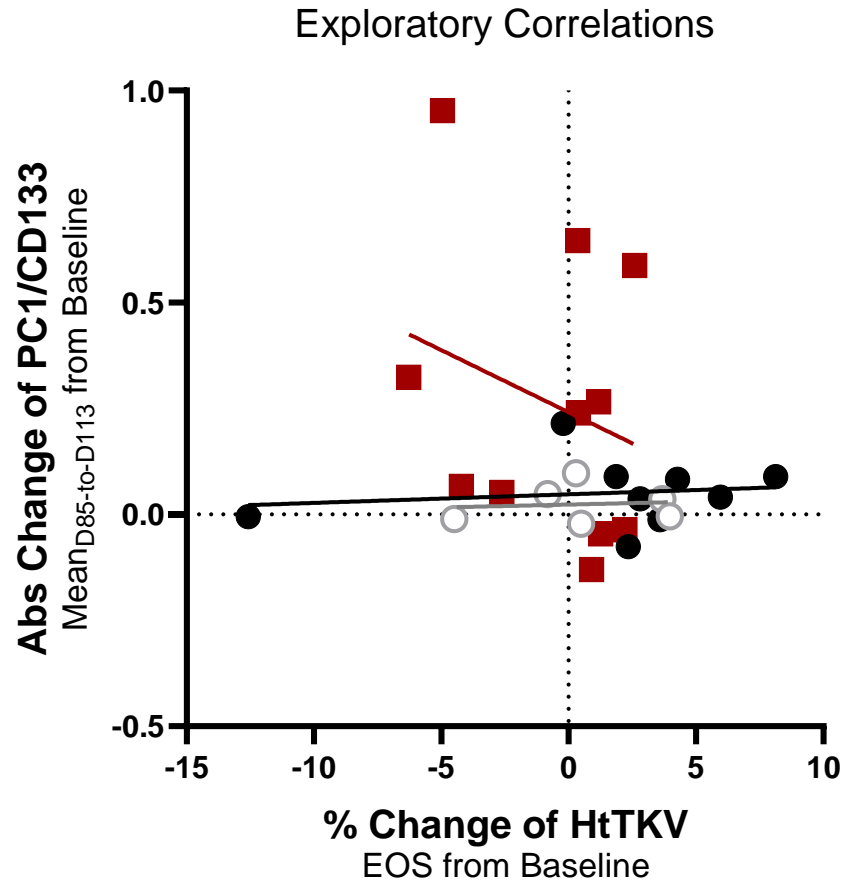
%HtTKV	Pb-All	1 mg/kg	2 mg/kg
<b>Mean</b>	+0.52	+1.79	<b>-0.84</b>
SD	3.13	5.9	3.11

% TKCV	Pb-All	1 mg/kg	2 mg/kg
<b>Mean</b>	+0.47	+4.36	<b>-0.53</b>
SD	1.94	8.21	3.9

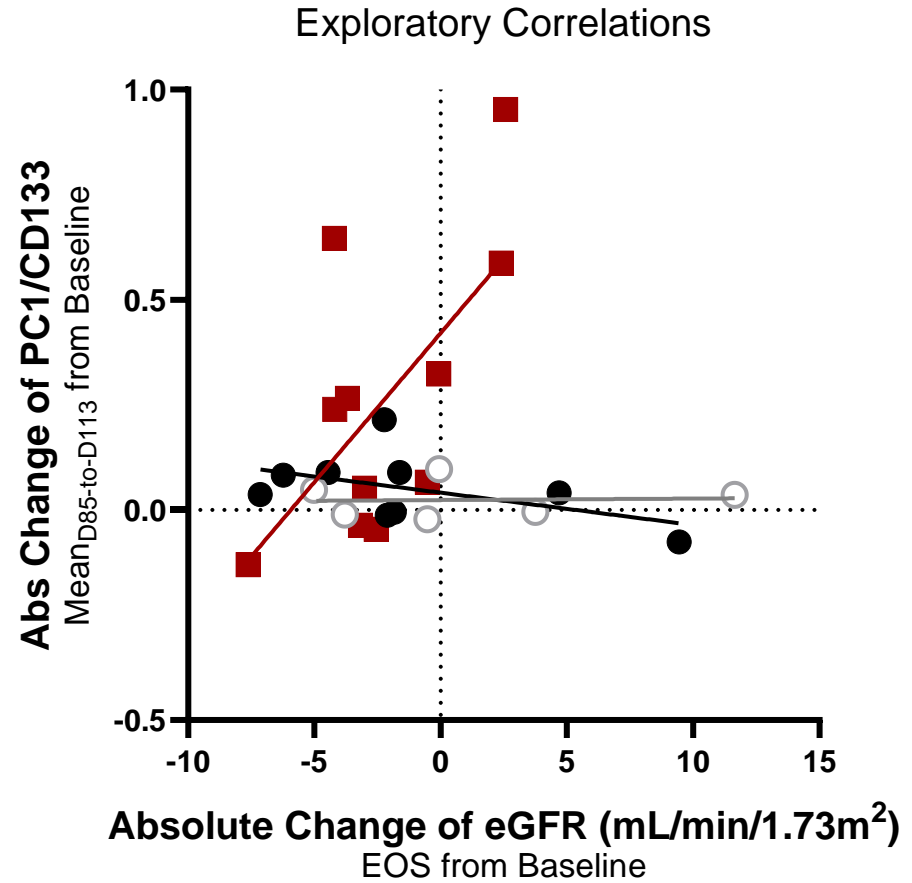
# Cohort 2 Case Highlights.

- **Among the 4 active subjects in cohort 2 with reductions in htTKV >2%, all 4 had increases in both PC1\* & PC2\***
- **The greatest increases in PC1 and PC2 were seen in subjects with the largest reductions in both htTKV and TKCV**
  - **Subject 1: highest increase in PC1 & PC2**
    - 47 y/o male diagnosed in 2006 (*PKD1*<sup>Truncation</sup>; 1C)
    - Baseline eGFR 66 mL/min and htTKV 941 mL/m
    - D113 MRI: htTKV reduced by 4.96%; TKCV reduced by 4.34%
  - **Subject 2: 2<sup>nd</sup> highest increase in PC1**
    - 44 y/o female diagnosed in 2019 (*PKD1*<sup>Non-truncating</sup>; 1D)
    - Baseline eGFR 65 mL/min and htTKV 1253 mL/m
    - D113 MRI: htTKV reduced by 6.28%; TKCV reduced by 6.93%
  - **Subject 3: 2<sup>nd</sup> highest increase in PC2**
    - 29 y/o male diagnosed in 2020 (*PKD1*<sup>Truncation</sup>; 1E)
    - Baseline eGFR 88 mL/min and htTKV 1162 mL/m
    - D113 MRI: htTKV reduced by 4.22%; TKCV reduced by 2.73%

# Exploratory Correlation: Change in PC1 Compared to Change in HtTKV and eGFR.

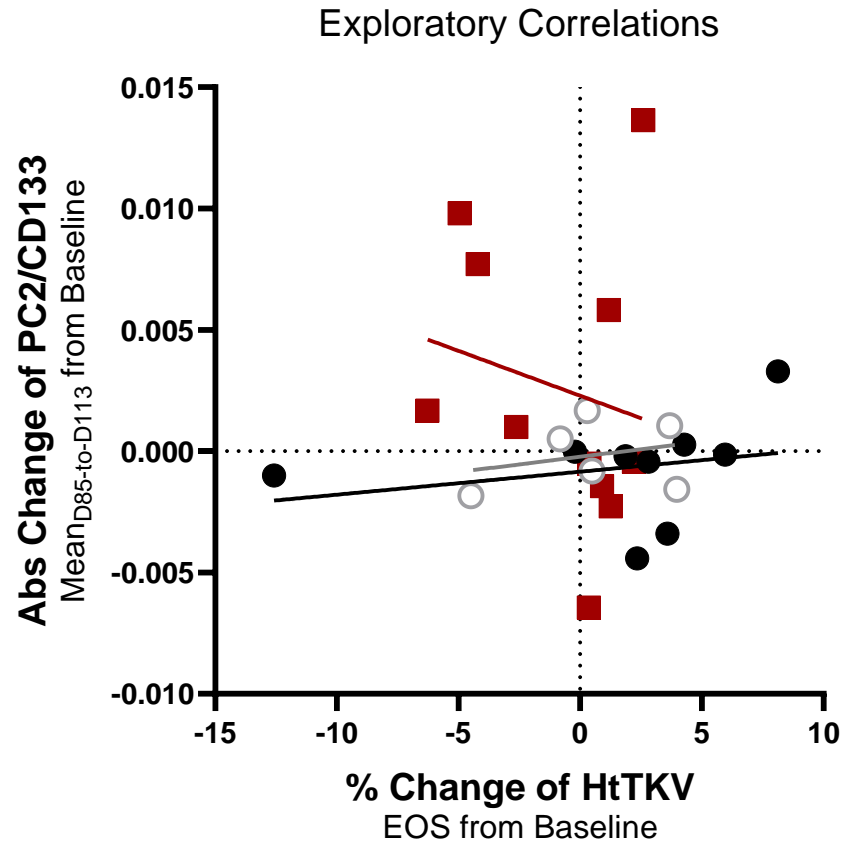


Simple Linear Regression	R <sup>2</sup>	P-value
Placebo	0.01	0.86
RGLS8429 (1 mg/kg)	0.02	0.71
RGLS8429 (2 mg/kg)	0.07	0.43

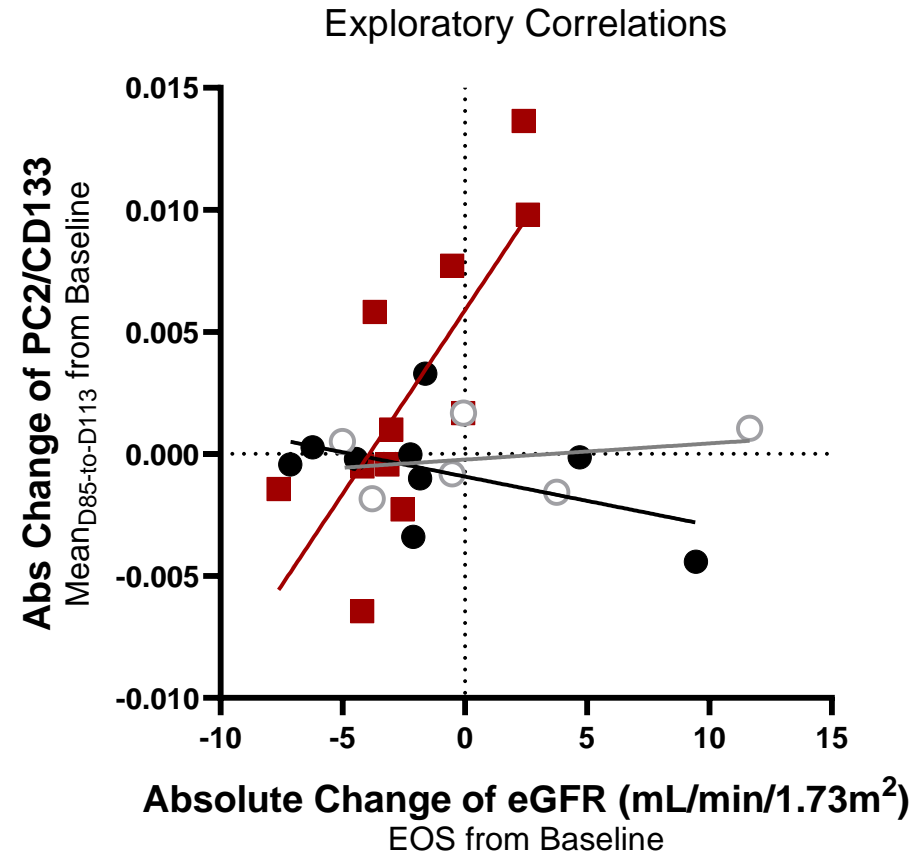


Simple Linear Regression	R <sup>2</sup>	P-value
Placebo	0.00	0.93
RGLS8429 (1 mg/kg)	0.24	0.18
RGLS8429 (2 mg/kg)	0.40	0.04

# Exploratory Correlation: Change in PC2 Compared to Change in HtTKV and eGFR.



Simple Linear Regression	R <sup>2</sup>	P-value
Placebo	0.07	0.60
RGLS8429 (1 mg/kg)	0.06	0.57
RGLS8429 (2 mg/kg)	0.04	0.51



Simple Linear Regression	R <sup>2</sup>	P-value
Placebo	0.08	0.60
RGLS8429 (1 mg/kg)	0.59	0.20
RGLS8429 (2 mg/kg)	0.22	0.01

# Summary of Phase 1b Findings through Cohort 2.

- RGLS8429 at 2 mg/kg dosed every 2 weeks over 12 weeks was well tolerated with no safety concerns to date
- Clear evidence of mechanistic dose response at 2 mg/kg dose level based on urinary polycystin (PC) analyses
  - Based on non-clinical analysis and PK/PD modeling, optimal kidney exposure and miR-17 target engagement is anticipated at >2.4 mg/kg in a human
- Exploratory results of MRI image analysis are encouraging
  - 4/11 subjects receiving 2 mg/kg demonstrated reductions in htTKV >2% along with reductions in TKCV
  - Among the 2 mg/kg cohort, the greatest reductions in htTKV were seen in patients with the highest increase in PC1 and PC2
  - Exploratory analyses suggest that across the 2 mg/kg cohort, increases in PC1 and PC2 may be associated with improvements in htTKV and eGFR

Cohort 2 meets expectations with encouraging imaging results suggesting potential impact on htTKV and cyst volume which will be explored further at higher doses in cohorts 3 & 4

# Planning for Phase 2 and Phase 3.

## *Regulatory Precedent for Accelerated Approval Based on Surrogate Endpoint*

### **FDA has adopted an accelerated approval pathway in ADPKD**

- Accelerated approval based on single pivotal trial demonstrating statistically significant reduction in TKV growth compared to placebo
- Requires confirmatory trial demonstrating statistically significant improvement in eGFR compared to placebo, which is completed in the post-approval setting
- Regulus has confirmed this accelerated approval pathway with FDA

### **Single Phase 2/3 Clinical Trial:**

- Phase 2 - Change in htTKV at 12 months as the primary endpoint
  - Patients continue blinded therapy for an additional 12 months (24 months total) and will contribute to the Phase 3 primary endpoint of eGFR
- Phase 3 - change in eGFR at 24 months as the primary endpoint

# Regulus Summary.

Anti-miR-17 approach designed to address the key control mechanism of cystogenesis and proliferation in ADPKD

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Phase 1b underway with cohort 1 and 2 data showing anticipated PD response (PC1 & PC2) and generally safe and well tolerated

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Cohort 3 topline data readout expected mid-year 2024; initiation of cohort 4 planned in Q2 2024

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Streamlined path to approval with single Phase 2 trial

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Significant market opportunity fueled by clear unmet need, targeted population, and orphan drug status

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Additional research programs in kidney and CNS where microRNA play pivotal roles in disease pathogenesis



# Corporate Presentation.

April 2024