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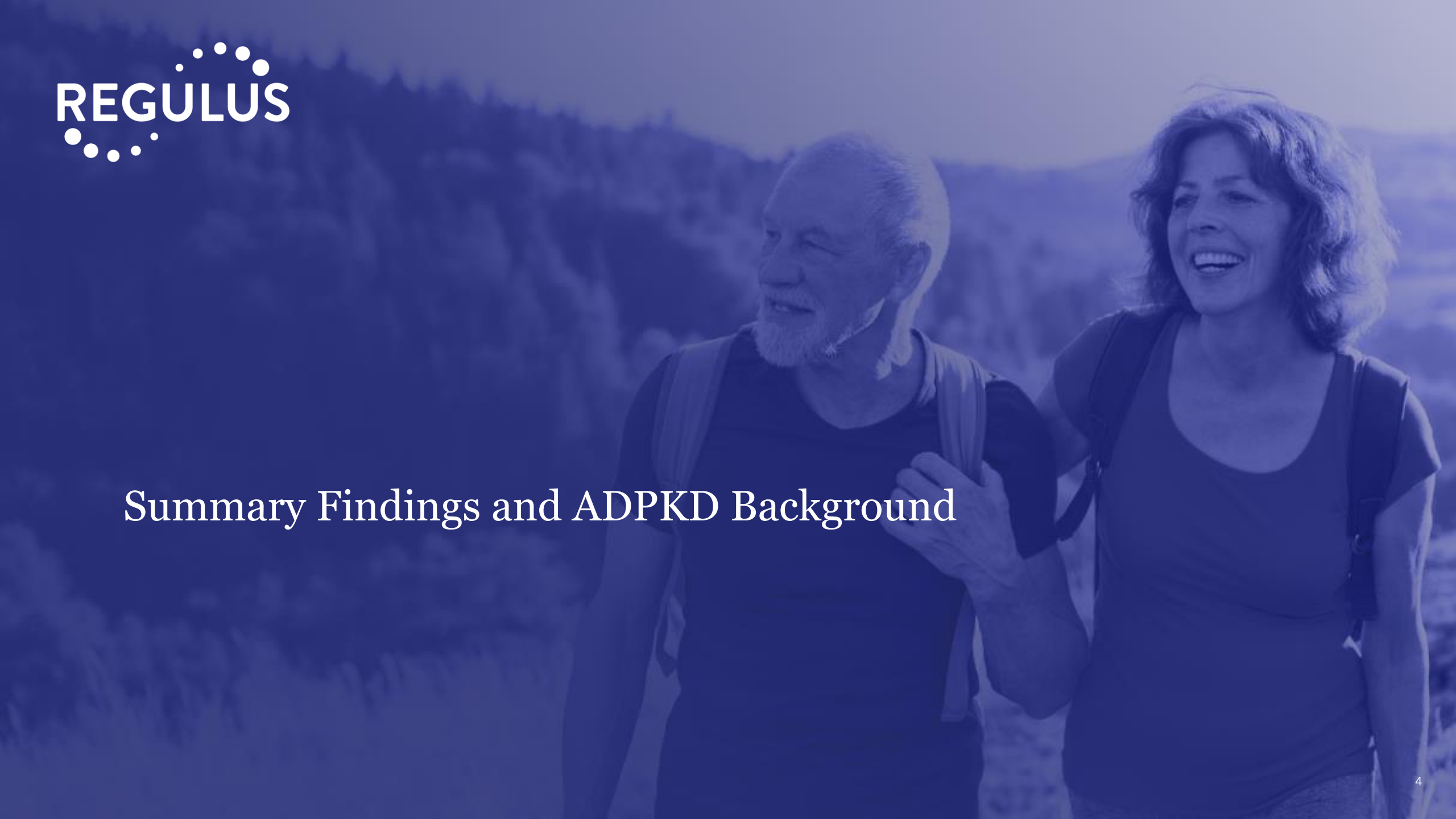
RGLS8429 Multiple Ascending Dose Cohort 2 Results

March 2024

Forward Looking Statements

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 expected timing for initiating clinical studies, potentially achieving therapeutic efficacy and the potential to address the underlying genetic causes of ADPKD, the expected timing for reporting data, the timing and future occurrence of other preclinical and clinical activities, the potential accelerated approval pathway, and other statements relating to future events or conditions. 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, 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' quarterly report on Form 10-Q for the quarter ended September 30, 2023. All forward-looking statements contained in this press release 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.

Introduction



Summary Findings and ADPKD Background

Summary of Findings from Cohort 2

- RGLS8429 at 2mg/kg dosed every 2 weeks over 12 weeks was well tolerated with no safety concerns to date
- Clear evidence of mechanistic dose response at 2mg/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

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htTKV= height-adjusted total kidney volume
TKCV= total kidney cyst volume

Autosomal Dominant Polycystic Kidney Disease (ADPKD).

ORPHAN DISEASE & 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, 2022 sales were $1.12B in US

PATIENT POPULATION.

~80%
patients with ***PKD1*** mutation

160K
diagnosed individuals in U.S.

HEALTH BURDEN.

50%
patients develop ESRD by age 60

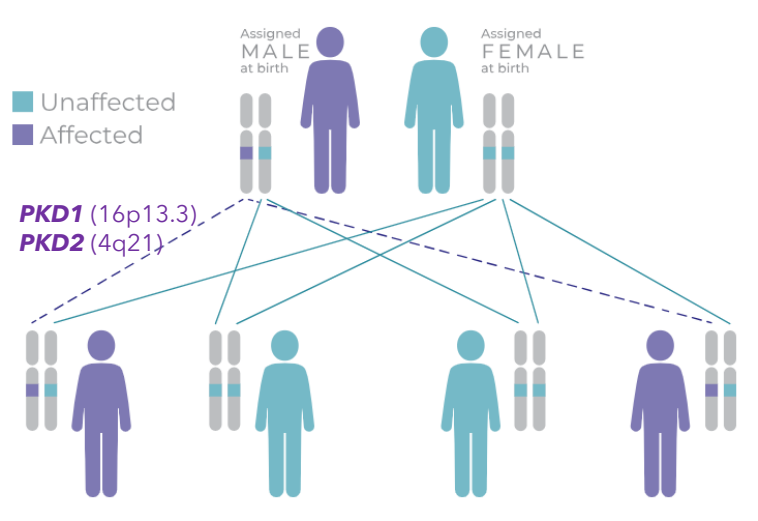
$3.8B+
estimated annual cost of renal replacement therapy in U.S.[1]

1. Cloutier et al. (2020) BMC Health Serv. Res. 20:126

ADPKD Genetic Mutation Drives Clinical Pathology.

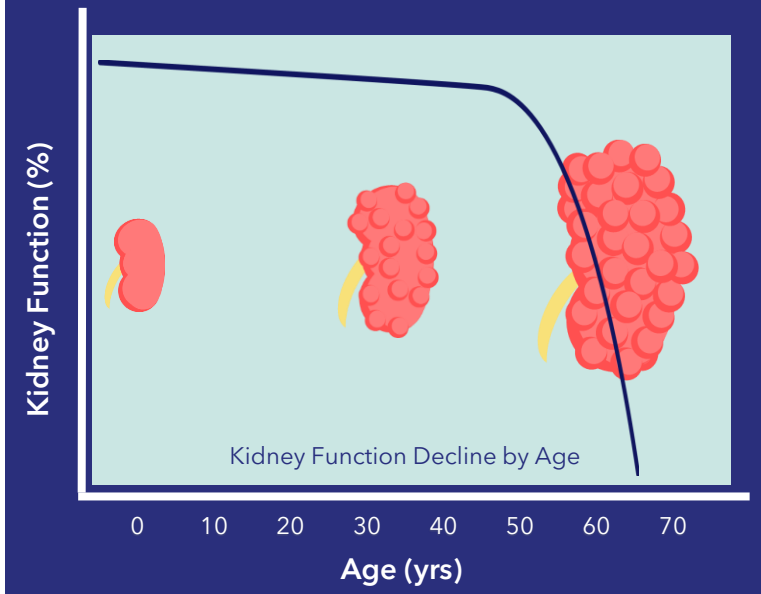
PROLIFERATIVE, CYSTIC DISEASE LEADS TO ENLARGED KIDNEYS WITH PROGRESSIVE FAILURE

- Mutation of either ***PKD1*** or ***PKD2*** genes triggers an increase in the oncogene c-Myc, which generates a broad proliferation response in the kidney due to numerous altered gene networks, including PKD, PPAR-α, PPAR-g, and MTOR. This proliferative response causes formation and growth 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:

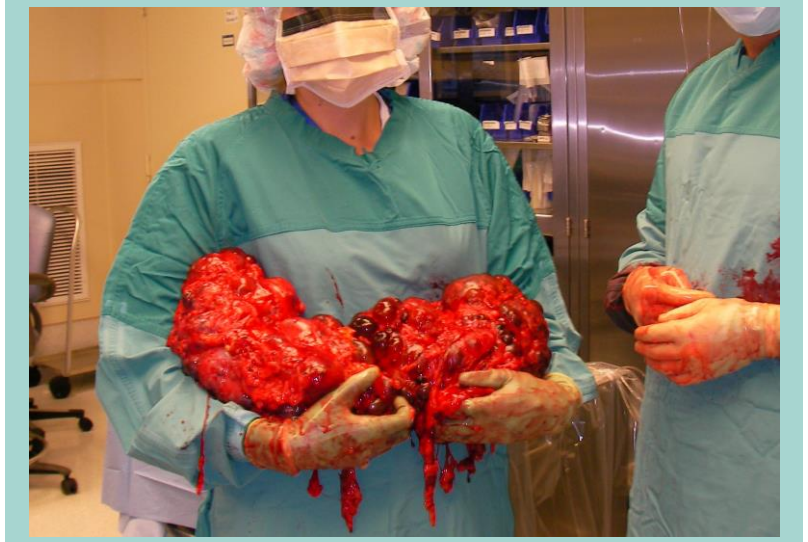


Photo courtesy of Dr. Vishal Patel

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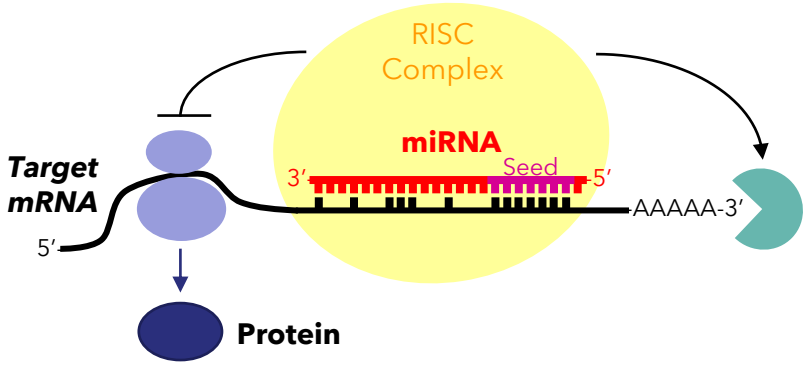
microRNA is an Important Regulator of Gene Expression

- MicroRNAs (miRNAs) are short (~20nt) non-coding RNAs that bind to complementary sequences located in 3′ untranslated region (3′UTR) of target mRNA
- Binding to mRNA results in translational repression, reduced level of the encoded proteins, and eventual degradation of the targeted mRNA transcripts.



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

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Increased miR-17 Expression Drives Cystic Proliferation In ADPKD.

BLOCKING miR-17 ACTIVITY REDUCES KEY PROLIFERATIVE SIGNAL PATHWAYS

Mutations in *PKD1* or *PKD2* genes

Increased *c-Myc* expression

Increased miR-17 expression

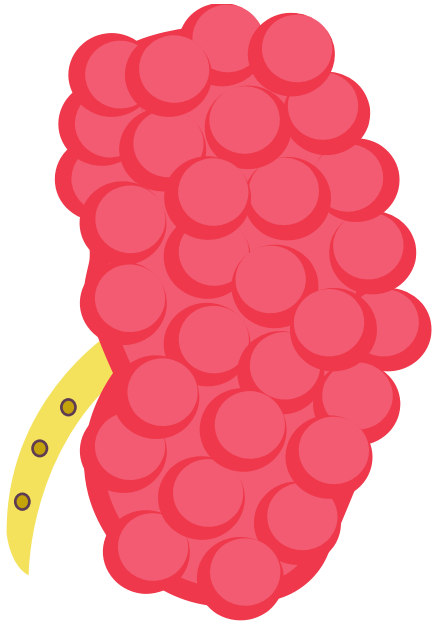
Represses miR-17 targets

Other miR-17 target genes

PKD1 PKD2

Dysregulated gene networks

Low PC1 and PC2



Mutations in *PKD1* or *PKD2* genes

Increased *c-Myc* expression

Increased miR-17 expression

Treatment with Anti-miR-17

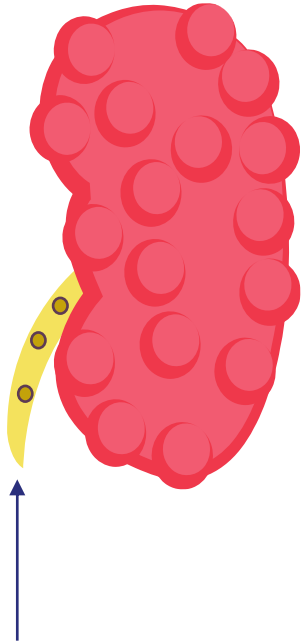
De-represses miR-17 targets

Other miR-17 target genes

PKD1 PKD2

Improved gene networks

Increase PC1 and PC2



Increase in PC1 and PC2 measured in urinary exosome

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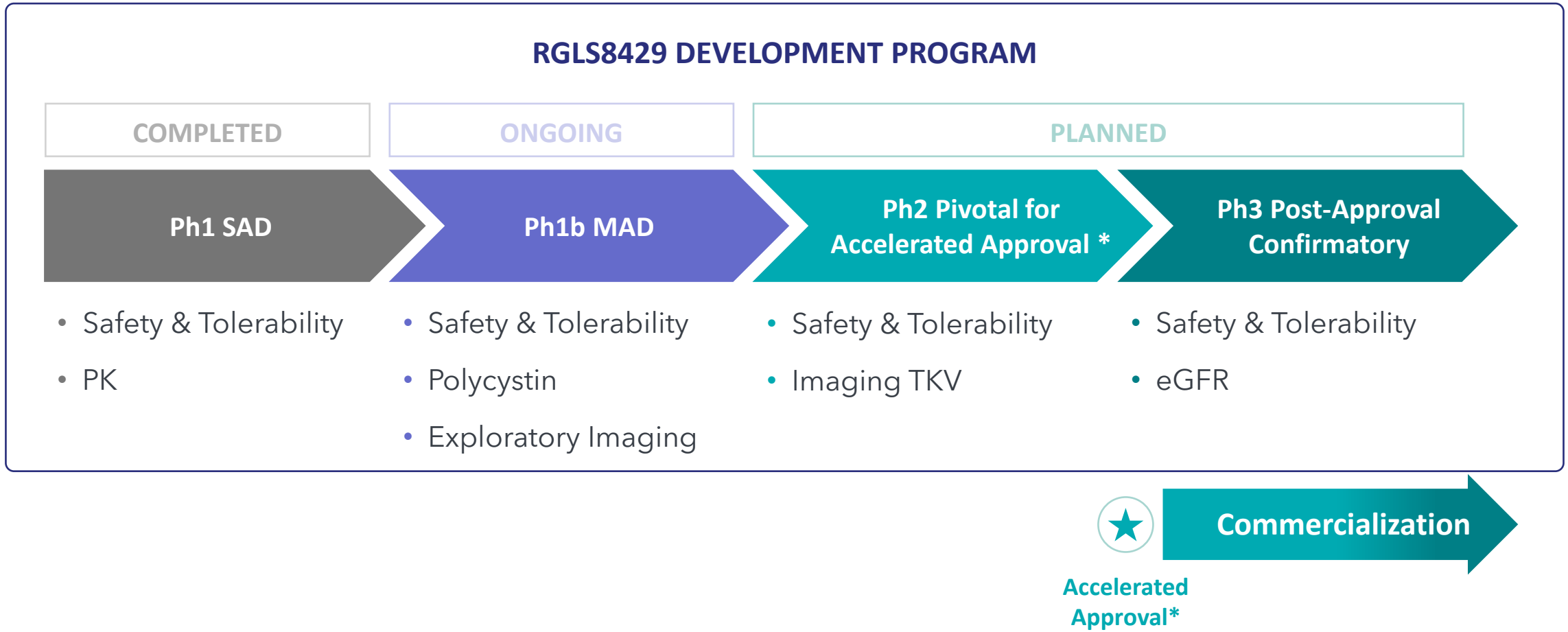
Lee (2019) Nat Commun

Study Design, Baseline Characteristics, Safety and PK

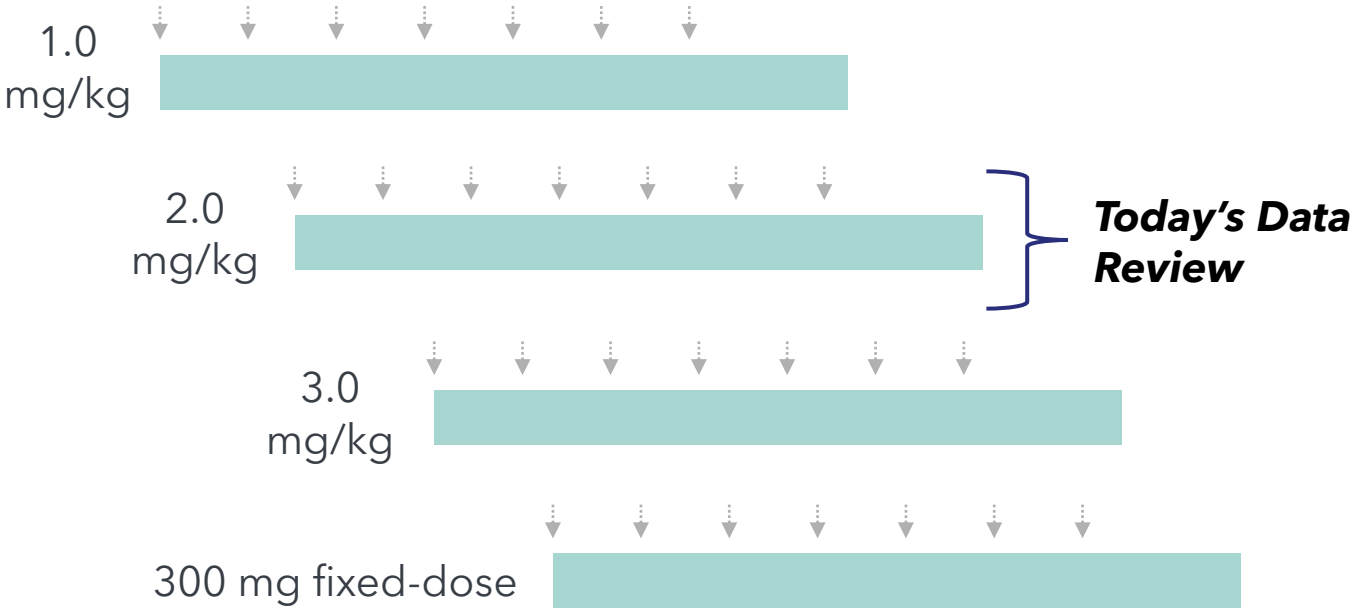
RGLS8429 Clinical Development is Streamlined Based on Accelerated Approval.



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

*Subject to confirmation with FDA

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



STUDY DESIGN

- ADPKD Patients (MIC 1C, 1D or 1E; eGFR 90-30 mL/min)
- 12-16 subjects per cohort
- Randomized 3:1 (RGLS8429:Placebo) Cohorts 1-3
- Cohort 4 300 mg fixed-dose (open label)
- 3-month SC dosing (Q2W x 7)
- Safety, PK, PD/biomarkers, eGFR, TKV, and novel cyst imaging analysis (TKCN, TKCV and CPSA)
- PC1/2 measured at baseline, days 29, 57, 85, 86, 92, 99, and 113

Cohort 3 Data on track for mid 2024

Cohort 4 screening starting Q2 2024

EXPECTATIONS

- Dose-responsive increase in PC1 & PC2
- Experience with using novel imaging markers ahead of Ph2

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TKCN = total kidney cyst number ; TKCV = total kidney cyst volume ; CPSA = cyst-parenchyma surface area

Cohort 1 and 2 Baseline Characteristics Representative of Target Patient Population

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

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

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

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

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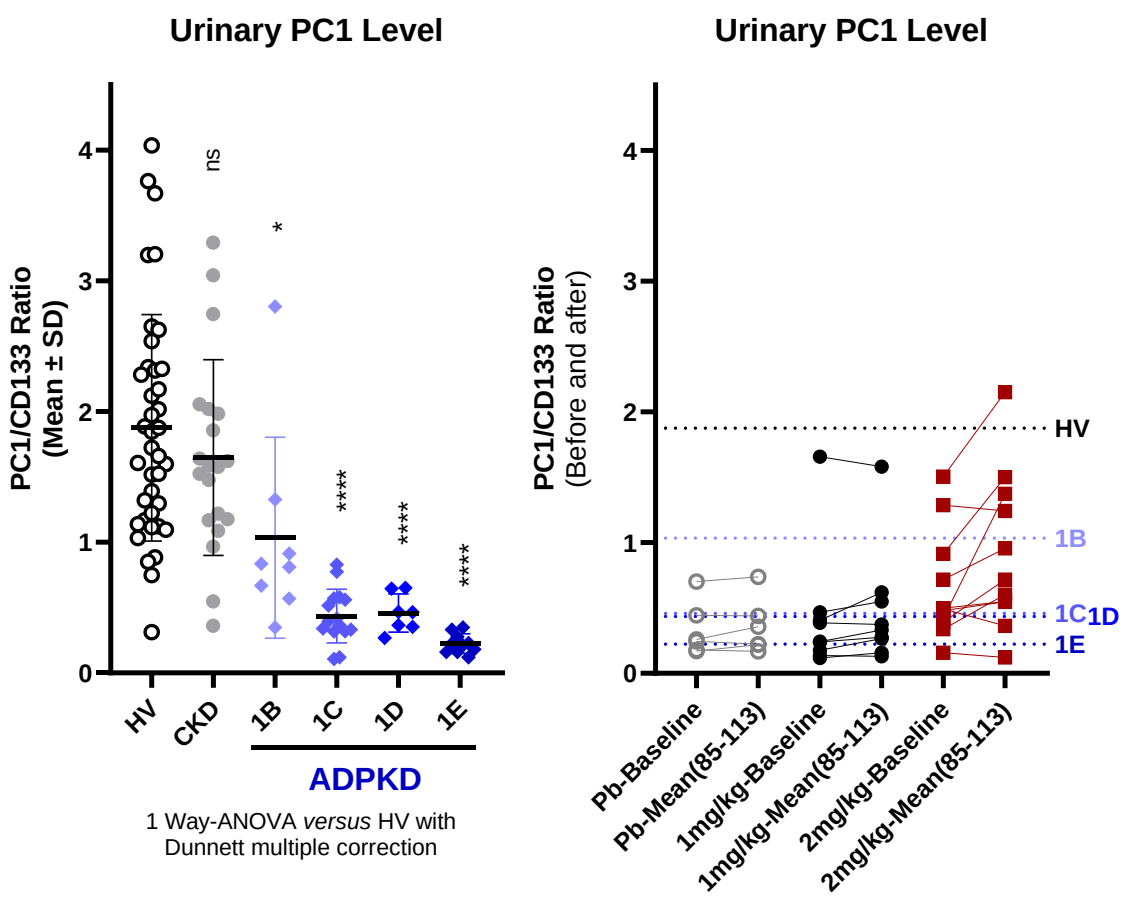
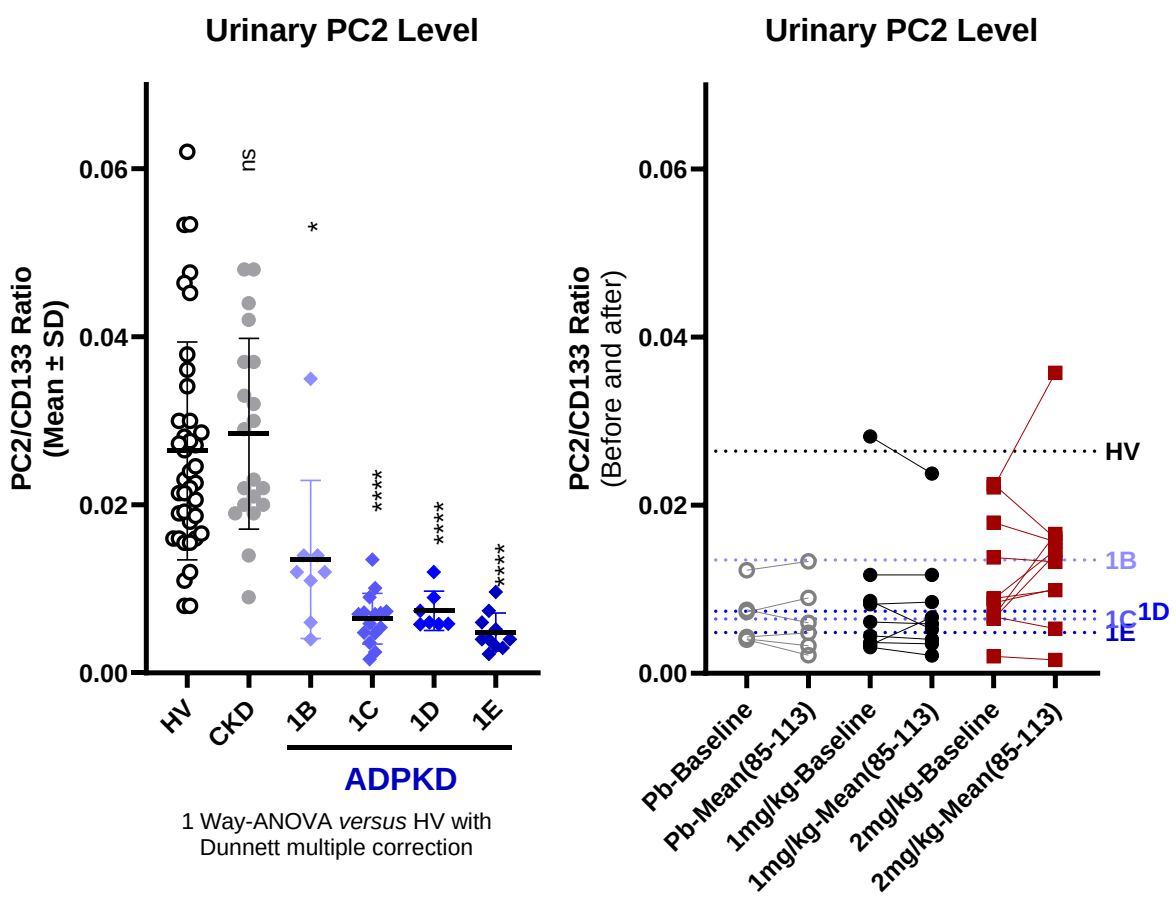
Change in Urinary PC1 and PC2 From Baseline

Individual Plots of Absolute PC1/CD133 and PC2/CD133 Ratios (Baseline to Mean of D85-D113)

PC1



PC2



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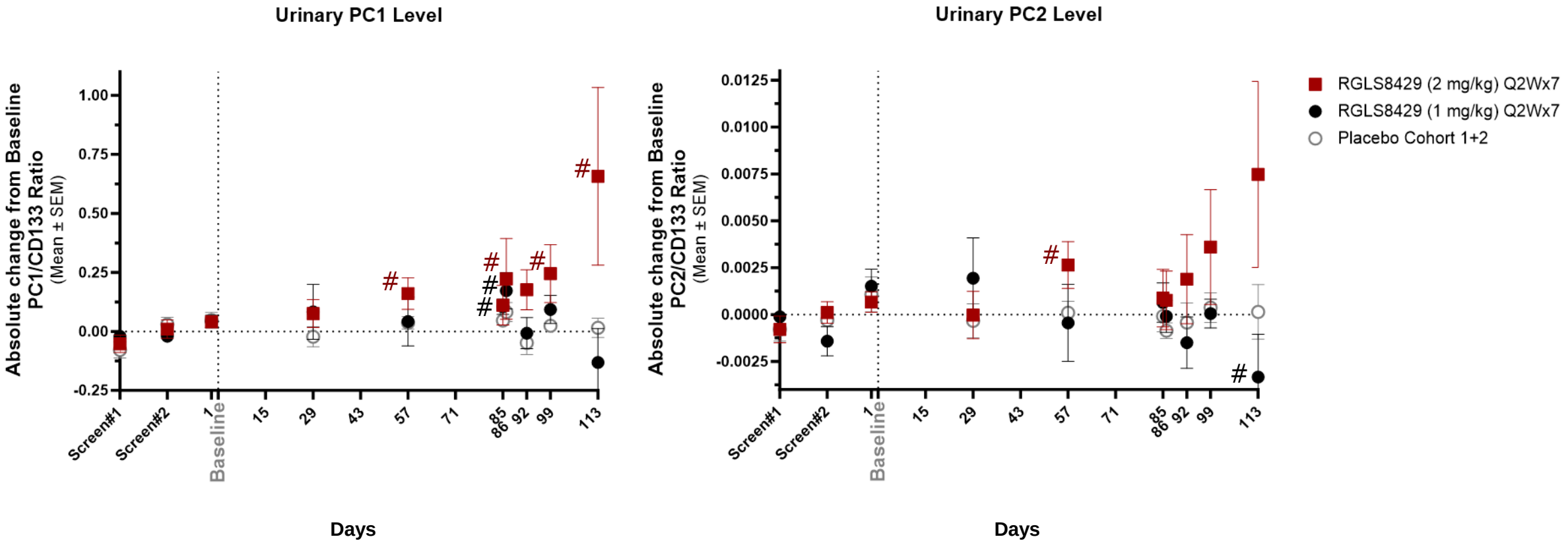
Absolute changes in urinary PC1 and PC2 ratios over time



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

Note: Exploratory regression analysis by simple linear regression

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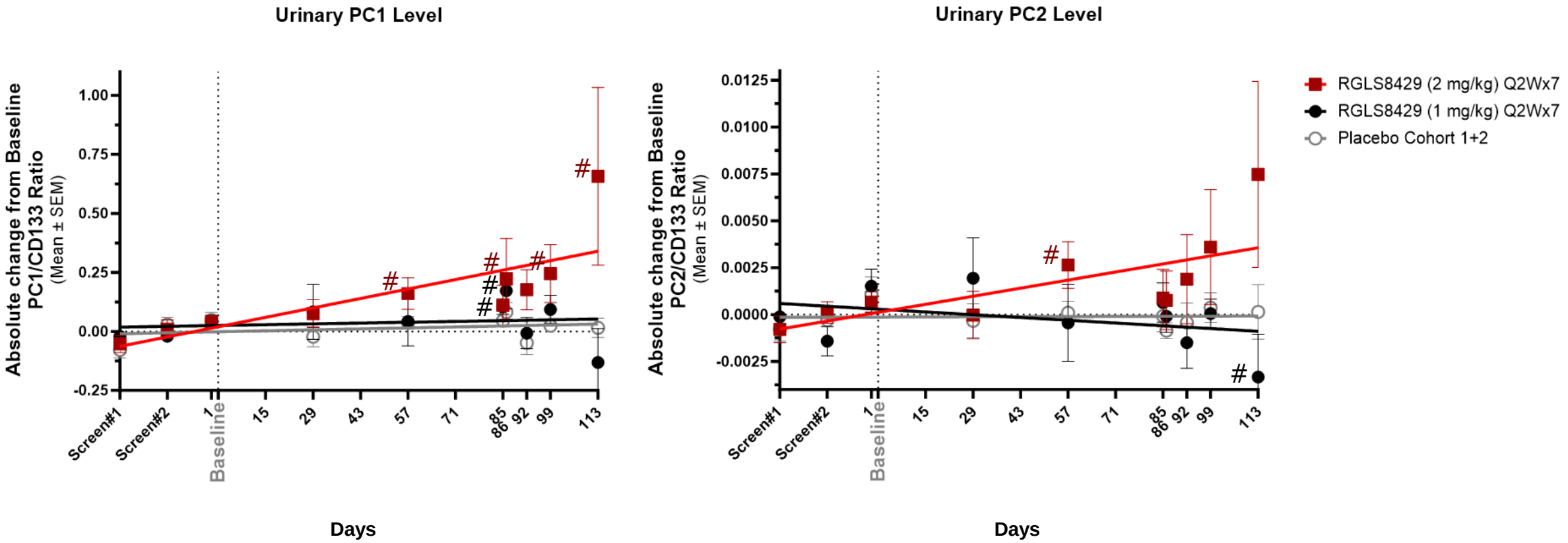
Absolute changes in urinary PC1 and PC2 ratios over time



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Note: Exploratory regression analysis by simple linear regression

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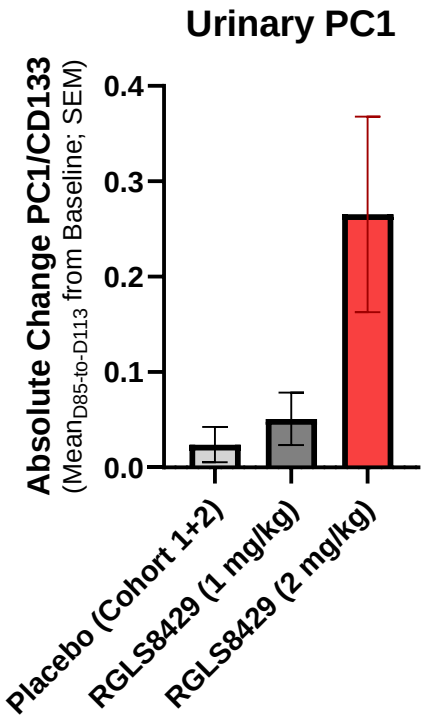
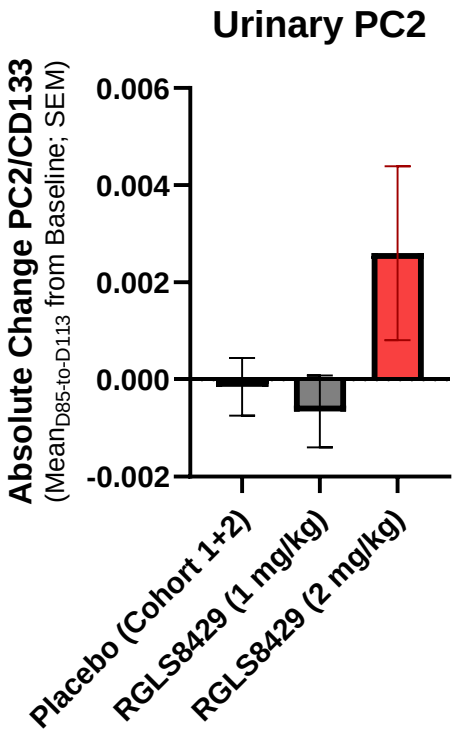
Mean Polycystin Levels after 3 Months of Dosing (Q2W)

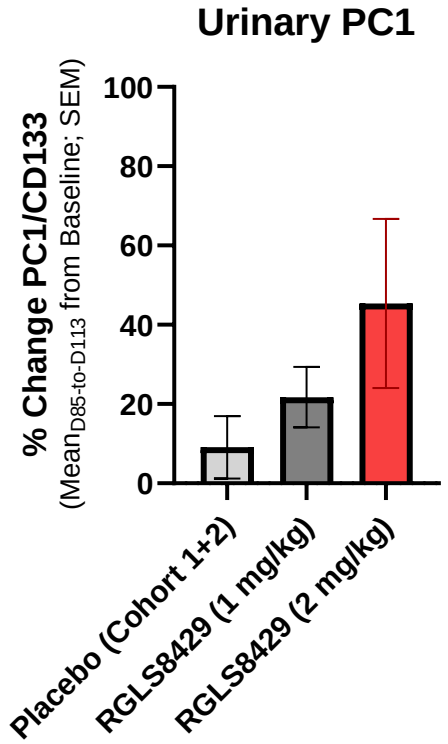
RGLS8429 (2 mg/kg) Q2Wx7
RGLS8429 (1 mg/kg) Q2Wx7
Placebo Cohort 1+2

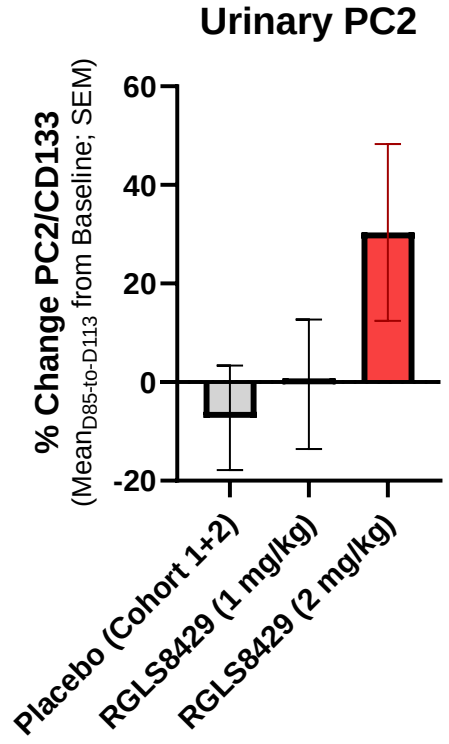
Absolute Change of
Urinary PC1/CD133 or PC2/CD133 Ratios





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





Summary of Urinary Polycystin Measures

- Urinary measurement of PC1 and PC2 demonstrates greater mechanistic activity of RGLS8429 at 2 mg/kg compared to 1 mg/kg and placebo

- Because optimal miR-17 target engagement is anticipated to be achieved at >2.4 mg/kg in a human, additional impact on urinary PC1 and PC2 is anticipated
  - The ongoing Phase 1b study is evaluating RGLS8429 dosing at 3 mg/kg in cohort 3
  - A 300 mg fixed dose will be explored in cohort 4 that will provide higher exposure (expected median dose of 3.5 mg/kg)

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Kidney Imaging Results

Renal MRI Background

- Patients with ADPKD experience ~5-6% growth in their kidneys annually based on published longitudinal studies[1-2]
  - In a Phase 3 trial, Tolvaptan demonstrated ~50% reduction in the growth of kidney volume over 1 year (2.8% vs 5.5%)
- MRI measurement of htTKV will be utilized in a registrational study to measure changes in total kidney volume over time
- Correlating measures of cystic architecture with htTKV in a therapeutic intervention trial has not been previously reported
- Previous independent published literature indicates re-expression of polycystin can arrest and reverse cystic expansion in animal models of disease[3]

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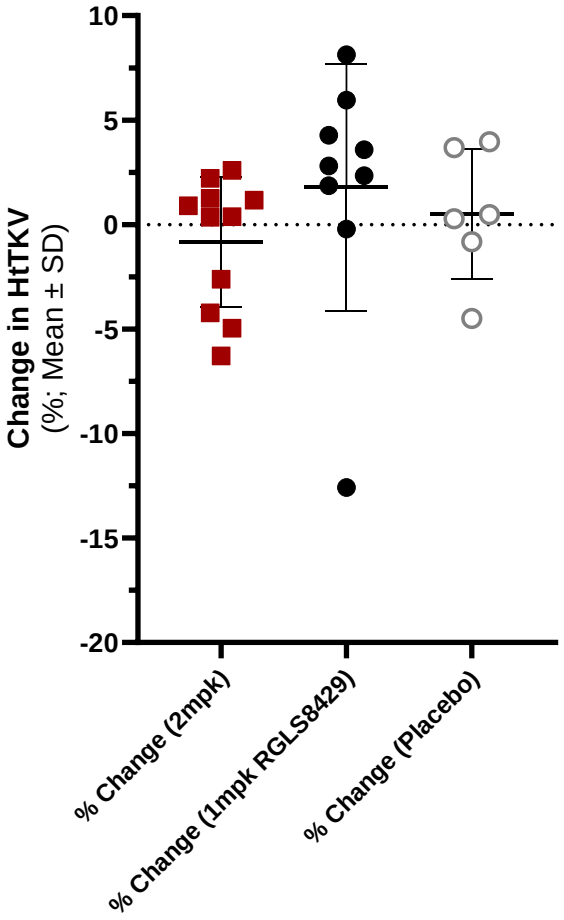
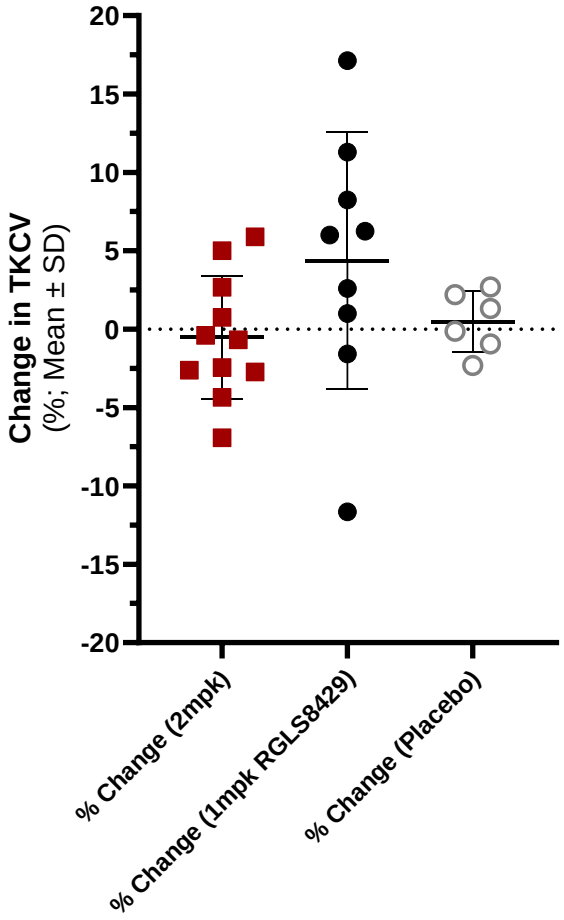
1, Torres (2013) N Engl J Med; 2, Perrone (2022) Kidney Med; 3, Dong (2021) Nat Genet;

Changes in Height-adjusted Total Kidney Volume and Total Kidney Cyst Volume

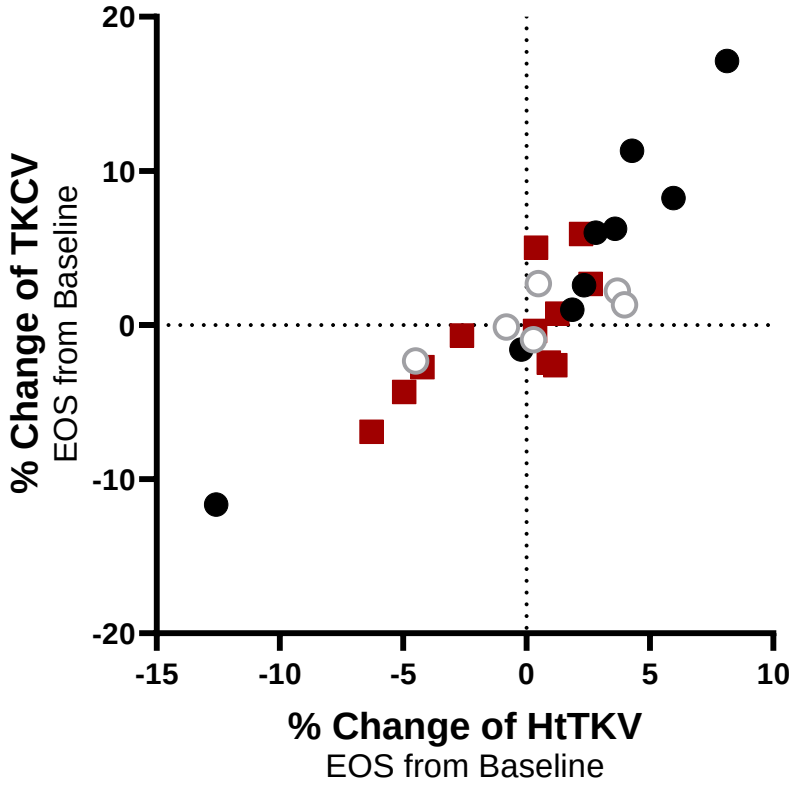
HtTKV
Height-adjusted Total Kidney Volume



TKCV
Total Kidney Cyst Volume



Correlation Between Imaging Biomarkers



%HtTKV	2mpk	1mpk	Pb-All
Mean	**-0.84**	**+1.79**	**+0.52**
SD	3.11	5.90	3.13

% TKCV	2mpk	1mpk	Pb-All
Mean	**-0.53**	**+4.36**	**+0.47**
SD	3.90	8.21	1.94

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
    - Baseline eGFR 66 mL/min and htTKV 941 mL/m
    - D113 MRI: htTKV reduced by 4.96%; TKCV reduced by 4.34%
  - **Subject 2: 2nd highest increase in PC1**
    - 44 y/o female diagnosed in 2019
    - Baseline eGFR 65 mL/min and htTKV 1253 mL/m
    - D113 MRI: htTKV reduced by 6.28%; TKCV reduced by 6.93%
  - **Subject 3: 2nd highest increase in PC2**
    - 29 y/o male diagnosed in 2020
    - Baseline eGFR 88 mL/min and htTKV 1162 mL/m
    - D113 MRI: htTKV reduced by 4.22%; TKCV reduced by 2.73%

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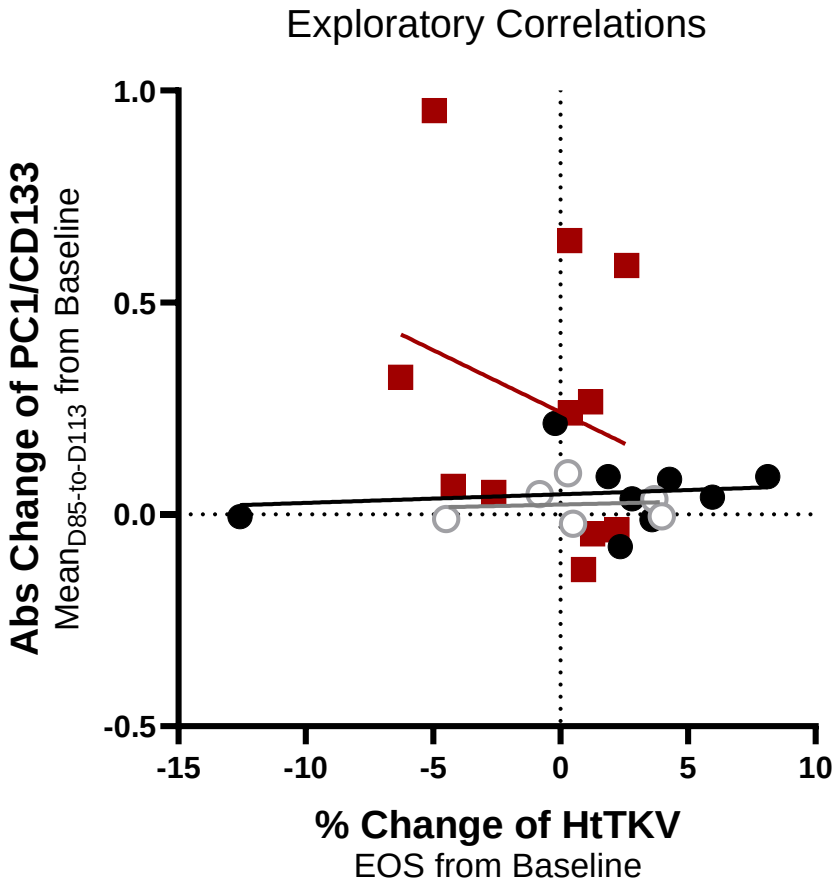
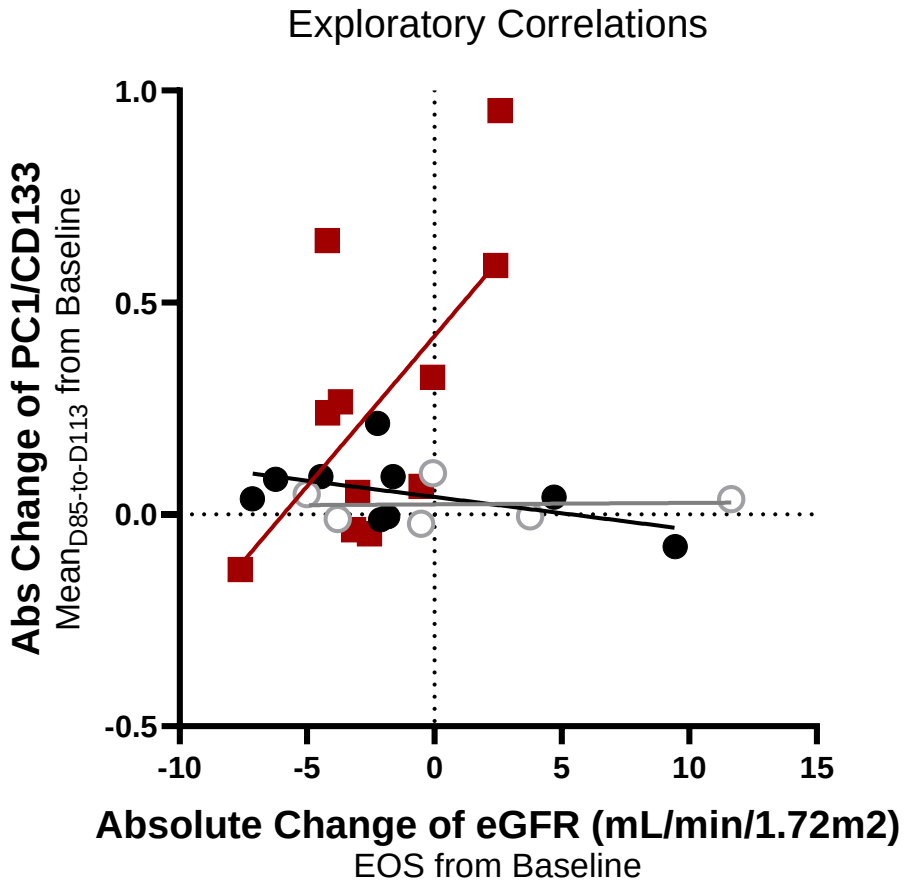
*Mean of % change D85-D113 PC

Exploratory Correlation: Change in PC1 compared to Change in HtTKV and eGFR





Simple Linear Regression	R^2	P-value
Placebo	0.0092	0.857
RGLS8429 (1mg/kg)	0.0211	0.709
RGLS8429 (2 mg/kg)	0.0719	0.425

Simple Linear Regression	R^2	P-value
Placebo	0.0021	0.930
RGLS8429 (1mg/kg)	0.2418	0.179
RGLS8429 (2 mg/kg)	0.4027	0.036

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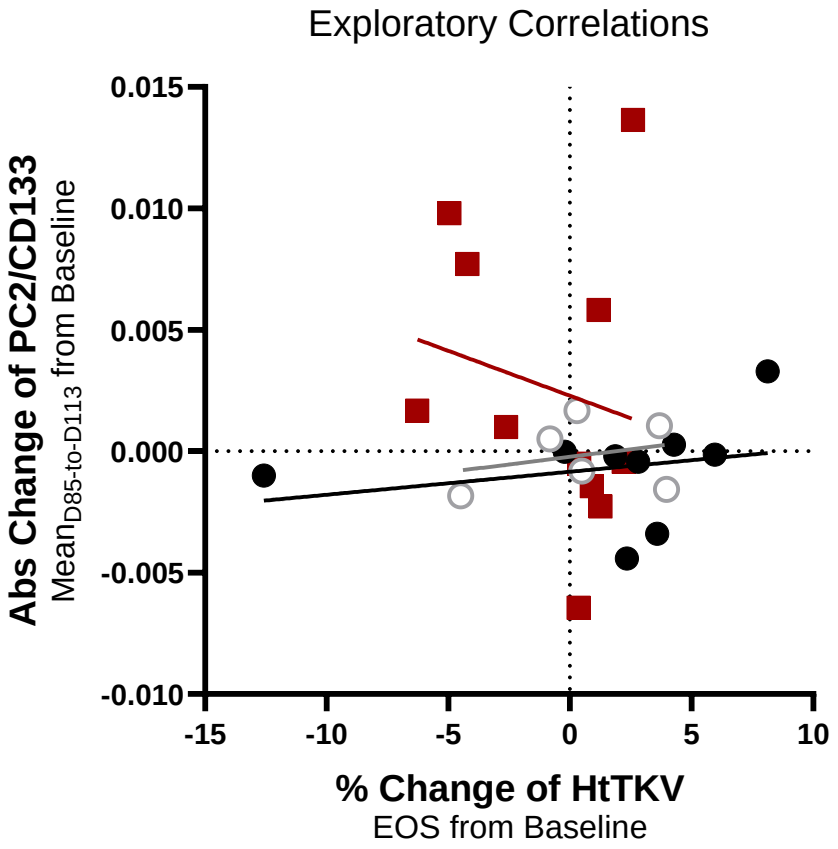
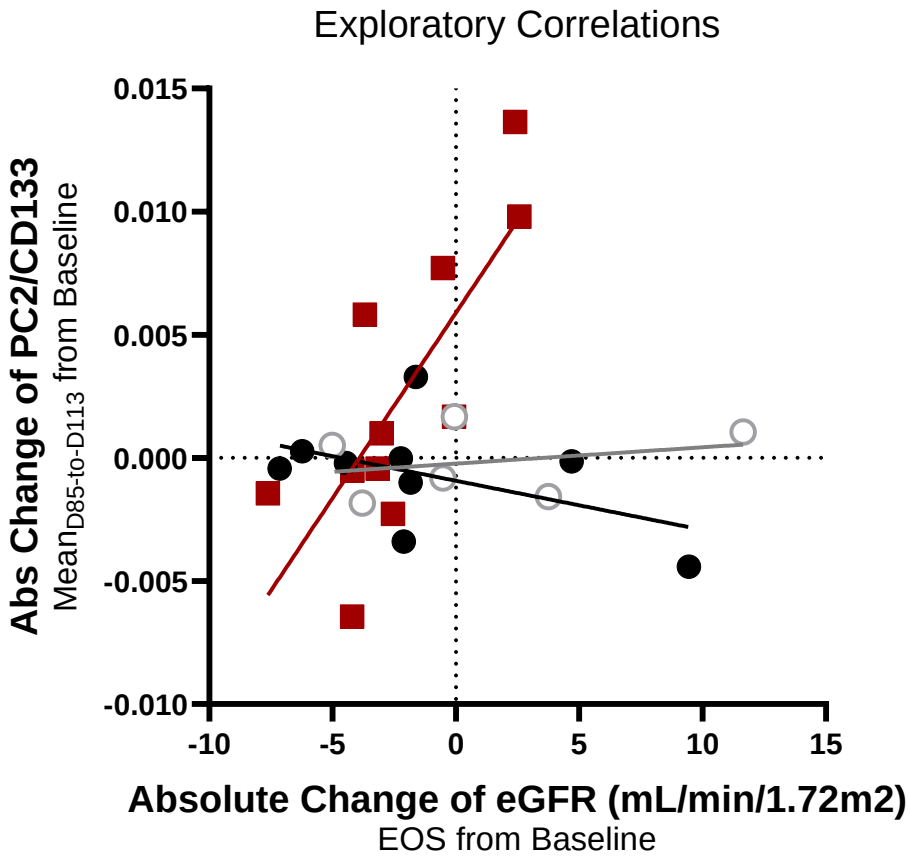
Exploratory Correlation: Change in PC2 compared to Change in HtTKV and eGFR





Simple Linear Regression	R^2	P-value
Placebo	0.0728	0.605
RGLS8429 (1mg/kg)	0.0639	0.570
RGLS8429 (2 mg/kg)	0.0373	0.512

Simple Linear Regression	R^2	P-value
Placebo	0.0766	0.596
RGLS8429 (1mg/kg)	0.5902	0.197
RGLS8429 (2 mg/kg)	0.2249	0.006

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Summary of Findings from Cohort 2

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- Clear evidence of mechanistic dose response at 2mg/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

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htTKV= height-adjusted total kidney volume
TKCV= total kidney cyst volume

Next Steps

- Cohort 3 fully enrolled with data readout anticipated mid 2024
- Cohort 4 on track for initiation of screening in Q2 2024
  - Based on cohort 2 results, Regulus planning to increase sample size of Cohort 4 fixed-dose open label enrollment (up to 30 subjects) to further interrogate potential impact on cystic volume in patients with ADPKD
- On track for an End of Phase 1 meeting with FDA in Q4 2024

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