RGLS8429 Increases Urinary PC1 and PC2 and May Reduce Height-Adjusted Total Kidney Volume (htTKV) in Patients with ADPKD

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Background & objectives

ADPKD is caused by mutations in either PKD1 or PKD2, leading to reduced expression or function of PKD-encoded proteins PC1 and PC2. This results in widespread dysregulated gene expression, hyperproliferation of renal tubular epithelia, formation of multiple cysts, progressive enlargement of the kidneys, and declining renal function. The microRNA miR-17 inhibits PKD1 and PKD2 and is implicated in the dysregulated gene expression observed in ADPKD. RGLS8429 is an antimiR-17 oligonucleotide that derepresses miR-17 mRNA targets, including PKD1 and PKD2, leading to increased PC1 and PC2 and amelioration of PKD in multiple mouse models.

Methods

A Phase 1b, randomized, double-blind, placebo-controlled, multiple ascending dose and open-label, fixed dose study in patients with ADPKD to evaluate safety, tolerability, biomarkers and pharmacokinetics of RGLS8429. The 3 weight-based cohorts (1, 2, 3 mg/kg) have completed the study with enrollment completed in 300 mg fixed dose cohort. Key inclusion criteria were Mayo Imaging Class (MIC) 1C, 1D, or 1E, and an eGFR between 30-90 mL/min/1.73 m^2. The treatment duration was 12 weeks with RGLS8429 or placebo subcutaneous injection Q2W x 7 doses, with an end of study visit 4 weeks after the last dose. Urinary PC1 and PC2 levels were measured before and at multiple points after randomization. An exploratory analysis of the change in htTKV from the baseline compared to the end of study (EOS) was conducted. Because the data for PC1, PC2 and htTKV were right skewed and non-normally distributed, these data were log transformed and analyzed using a mixed model with treatment as a class terms and log baseline value as a covariate. The LSM by treatment and differences between RGLS8429 and placebo LSM were back-transformed to present results on the percent change scale.

Results

42 subjects with ADPKD were randomized and baseline characteristics were balance between treatment cohorts. 2 subjects discontinued due to injection site reaction (ISR), 1 due to abdominal pain/diarrhea and 1 due to administrative site closure. RGLS8429 was well tolerated with ISRs being the most common treatment emergent adverse event but not dose limiting.

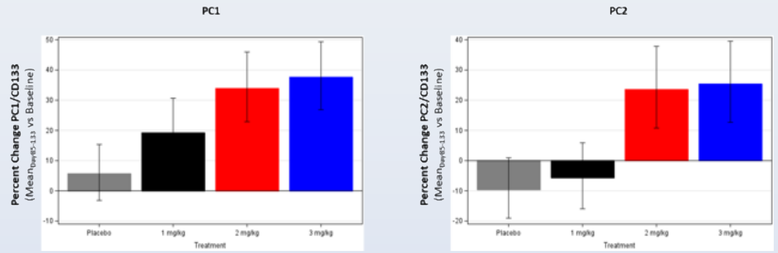
Baseline Characteristics		Placebo (All) N=10	RGLS8429 (1 mg/kg) N=9	RGLS8429 (2 mg/kg) N=11	RGLS8429 (3 mg/kg) N=12	RGSL8429 (All) N=32
Age (years) mean (SD)		45 (12)	52 (12)	46 (12)	48 (11)	48 (11)
Female n (%)		4(40%)	5 (56%)	5 (46%)	4 (33%)	14 (44%)
White n (%)		7 (70%)	9 (100%)	10 (91%)	11 (92%)	30 (94%)
Tolvaptan use in prior 3 months n (%)		1 (10%)	2 (22%)	1 (10%)	2 (17%)	5 (16%)
eGFR (mL/min/1.73m^2) mean (SD)		55 (17)	47 (20)	68 (19)	61 (16)	60 (19)
htTKV (mL/m) mean (SD)		1763 (859)	1698 (737)	1264 (567)	1393 (459)	1437 (599)
MIC n (%)	1C	2 (20%)	5 (56%)	5 (45%)	7 (58%)	17 (53%)
	1D	6 (60%)	3 (33%)	4 (36%)	3 (25%)	10 (31%)
	1E	2 (20%)	1 (11%)	2 (18%)	2 (17%)	5 (16%)
Genetic Mutation n (%)	PKD1	8 (80%)	5 (56%)	9 (82%)	9 (75%)	23 (72%)
	PKD2	0 (0%)	3 (33%)	2 (18%)	1 (8%)	6 (19%)
	Neither	2 (20%)	1 (11%)	0 (0%)	2 (17%)	3 (9%)

Plasma AUC and Cmax generally increased with increasing dose in an approximately dose-proportional manner.

As shown in Figure 1, RGLS8429 increased urinary PC1 and PC2 levels in a dose-dependent manner. The change from baseline to EOS in PC1 and PC2 levels was statistically significant in the 3 mg/kg cohort compared to the placebo cohort (p=0.034 and p=0.038 respectively).

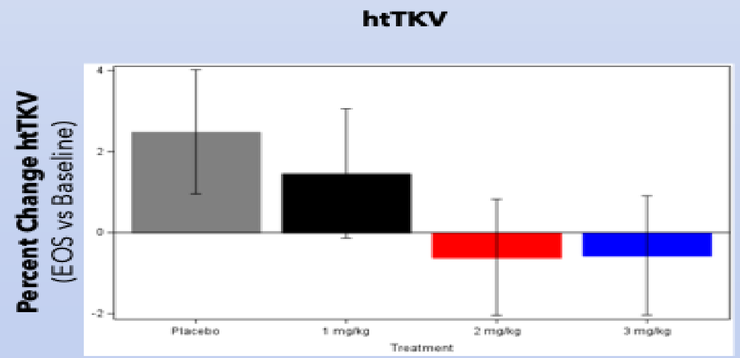
Results

Figure 1: Percent Change in Urinary PC1 and PC2 Ratios from Baseline to EOS in Cohorts 1-3



As shown in Figure 2, 70% of subjects receiving 3 mg/kg had a reduction in htTKV and the geometric least squares mean percent change in htTKV over 16 weeks was 2.5, 1.4, -0.6, and -0.6 for placebo, 1, 2, and 3 mg/kg groups, respectively.

Figure 2: Percent Change in htTKV from Baseline to EOS in Cohorts 1-3



Conclusion

Results provide clinical proof of dose-responsive RGLS8429 mechanistic activity on PC1 and PC2. Exploratory analysis suggests a reduction of htTKV at 2 and 3 mg/kg doses over a relatively short treatment period. Findings validate miR-17 as a potential therapeutic target for ADPKD.

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