Regulus Therapeutics Presents Additional Data from its Autosomal Dominant Polycystic Kidney Disease (ADPKD) Program at PKD Connect 2021

Study demonstrates clinical proof of mechanism with statistically significant increases in polycystin levels following RGLS4326 treatment in the first cohort of patients with ADPKD

Trends indicate further increases in polycystin levels may be achievable with longer term and, potentially, less frequent, dosing

Preclinical proof of mechanism demonstrated in relevant mouse model that harbor Pkd1 mutation equivalent to human ADPKD

miR-17 validated as a target for ADPKD treatment

SAN DIEGO, June 25, 2021 /PRNewswire/ -- Regulus Therapeutics Inc. (Nasdaq: RGLS), a biopharmaceutical company focused on the discovery and development of innovative medicines targeting microRNAs (the "Company" or "Regulus"), today announced the presentation of additional data from the first cohort of patients in the Company's Phase 1b clinical trial of RGLS4326 for the treatment of autosomal dominant polycystic kidney disease (ADPKD), as well as new preclinical data from relevant animal models of the disease. The E-poster presentation, titled "Preclinical Evaluation and Results from the First Cohort of Phase 1b Clinical Trial of RGLS4326 for the Treatment of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)," is available to attendees of the PKD Connect Conference 2021, on Friday, June 25, from 2-3 p.m. CDT.

The poster presents results from the Company's ongoing Phase 1b study evaluating the safety, pharmacokinetics, and effects on pharmacodynamic biomarkers of multiple doses of RGLS4326 in patients with ADPKD. The data demonstrate clinical proof of mechanism by showing target engagement in the kidneys through a statistically significant increase in urinary biomarkers PC1 and PC2, validating miR-17 as a target for ADPKD treatment. Levels of PC1 and PC2 have previously been shown to be inversely correlated with disease severity. RGLS4326 was well-tolerated with no serious adverse events. The poster also describes new data from relevant preclinical models showing treatment with RGLS4326 results in increased gene and polycystin levels *in vitro.* In addition, improvements in key disease markers including serum creatinine and BUN were demonstrated in the *Pkd1*(F/RC) mouse model that harbors *Pkd1* mutation equivalent to human ADPKD.

"These exciting results lend further support to the therapeutic potential of RGLS4326 in ADPKD and also bring us a step closer to our mission to improve the lives of patients suffering from this disease," commented Jay Hagan, President and Chief Executive Officer of Regulus. "The data from the first cohort of patients in this clinical study suggest that further increases in polycystin levels may be achievable with longer term and, potentially, less frequent, dosing and reinforce our belief that RGLS4326 represents an innovative approach to the treatment of underlying genetic drivers of ADPKD."

Clinical study details:

RGLS4326 is currently being evaluated in a Phase 1b, multicenter, open-label, adaptive design dose-ranging study to evaluate its safety, tolerability, pharmacokinetics and pharmacodynamics in patients with ADPKD. In the first cohort of the Phase 1b study, nine patients were enrolled and received 4 doses of 1 mg/kg of RGLS4326 administered every other week.

Clinical study results:

- The data demonstrate clinical proof of mechanism by showing target engagement in the kidneys through statistically significant increases in urinary biomarkers, PC1 and PC2, at study completion compared to baseline.
- In addition, one patient with pre-study levels uNGAL almost twice the upper limit of normal saw their uNGAL levels drop into the normal range during the course of the study.
- Administration of RGLS4326 was well-tolerated with no serious adverse events.

The study is continuing to enroll patients with ADPKD in additional cohorts to evaluate different doses of RGLS4326. The second cohort of patients are receiving a dose of 0.3mg/kg administered every other week and is nearing completion of enrollment.

Preclinical study details:

Pkd1(RC/-) cells were treated with either vehicle, control or RGL4326 for 2 days prior to measuring changes in *Pkd1* and *Pkd2* genes, and for 3 days prior to measuring changes in PC1 and PC2 proteins. In addition, *Pkd1*(F/RC) mice were dosed with either a control or RGLS4326 for four doses prior to assessment of efficacy.

Preclinical study results:

- RGLS4326 treatment led to increased *Pkd1* and *Pkd2* gene expression (>100% increase) and increased levels of their encoded proteins PC1 and PC2 (~50% increase) in *Pkd1*(RC/-) cells *in vitro.*
- RGLS4326 treatment demonstrated improvement in key efficacy parameters including kidney-weight-to-body-weight ratio (~75% decrease), serum creatinine (~50% decrease) and BUN (~60% decrease) in *Pkd*1(F/RC) mice compared to control.

About RGLS4326 Phase 1b

The Phase 1b is an adaptive design, open-label, multiple dose study in up to three cohorts of patients with ADPKD. The study is designed to evaluate the safety, pharmacokinetics, and changes in levels of PC1 and PC2 in patients with ADPKD administered RGLS4326 every other week for a total of four doses. To characterize the effect of RGLS4326 within each cohort, biomarker values at the end of study are compared to baseline values using a two-sided paired t-test. P-values less than 0.05 are considered statistically significant with no adjustment for multiplicity. The dose level for the first cohort is 1mg/kg of RGLS4326 and the dose level for the second cohort is 0.3mg/kg. The third and final cohort will be dosed at a level to be determined based on the results of the first two cohorts.

For more information about the clinical trial design, please visit www.clinicaltrials.gov (NCT04536688).

About RGLS4326

RGLS4326 is a novel oligonucleotide designed to inhibit miR-17 and designed to preferentially target the kidney. Preclinical studies with RGLS4326 have demonstrated direct regulation of *Pkd1* and *Pkd2*, reduction of cyst growth in human *in vitro* ADPKD models, and attenuation of cyst proliferation and improvement of kidney function in mouse models of ADPKD. The RGLS4326 IND is currently on a partial clinical hold for treatment of extended duration by FDA until the second set of requirements outlined by the agency have been satisfactorily addressed. The Company will use information from the Phase 1 clinical studies, including the first cohort of the Phase 1b study together with information from the recently completed additional nonclinical studies generated in 2020, in its plan to address the second set of requirements outlined in the partial clinical hold letter to support studies of extended duration. Regulus plans to discuss its approach to addressing the remaining partial clinical hold requirements with FDA in mid-2021. RGLS4326 has received orphan drug designation from FDA in July 2020.

About ADPKD

ADPKD, caused by the mutations in the *PKD1* or *PKD2* genes, is among the most common human monogenic disorders and a leading cause of end-stage renal disease. The disease is characterized by the development of multiple fluid filled cysts primarily in the kidneys, and to a lesser extent in the liver and other organs. Excessive kidney cyst cell proliferation, a central pathological feature, ultimately leads to end-stage renal disease in approximately 50% of ADPKD patients by age 60.

About Regulus

Regulus Therapeutics Inc. (Nasdaq: RGLS) is a biopharmaceutical company focused on the discovery and development of innovative medicines targeting microRNAs. Regulus has leveraged its oligonucleotide drug discovery and development expertise to develop a pipeline complemented by a rich intellectual property estate in the microRNA field. Regulus maintains its corporate headquarters in San Diego, CA.

Forward-Looking Statements

Statements contained in this press release 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 clinical activities concerning the RGLS4326 program, including the preliminary biomarker, pharmacokinetic and safety data resulting from the first cohort of patients from the ongoing clinical study, the sufficiency of the data required to recommence clinical studies for extended duration dosing, the timing of the Company's interactions with FDA regarding the clinical hold and the timing and 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, 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 feedback from the FDA. In addition, while Regulus expects the COVID-19 pandemic to adversely affect its business operations and financial results, the extent of

the impact on Regulus' ability to achieve its preclinical and clinical development objectives and the value of and market for its common stock, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the U.S. and in other countries, and the effectiveness of actions taken globally to contain and treat the disease. These and other risks are described in additional detail in Regulus' filings with the Securities and Exchange Commission. 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.

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