Regulus Therapeutics Announces Top-Line Data from the First Cohort of Phase 1b Clinical Trial of RGLS4326 for the Treatment of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Demonstrated Pharmacokinetic Profile Similar to Healthy Volunteers
Statistically Significant Increase in Polycystin 1 Biomarker Observed by End of Study
Data Presentation Targeted for American Society of Nephrology (ASN) Kidney Week
Regulus Therapeutics to Host Conference Call Today at 8:30 a.m. ET

LA JOLLA, Calif., May 3, 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 top-line results from the first cohort of patients with ADPKD in its ongoing Phase 1b clinical trial of RGLS4326. The study is evaluating the safety, pharmacokinetics, and effects on pharmacodynamic biomarkers of multiple doses of RGLS4326 in patients with ADPKD.

In the first cohort, nine patients were enrolled and received 1 mg/kg of RGLS4326 subcutaneously every other week for four doses. Safety, pharmacokinetics, and certain disease related biomarkers were evaluated through the course of the study. The biomarkers included: Polycystin 1 (PC1) and Polycystin 2 (PC2) which are the protein products of the PKD1 and PKD2 genes respectively, kidney injury marker 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), as well as urea and creatinine and were chosen to evaluate changes in disease related measures.

RGLS4326 was well tolerated by all nine patients with no serious adverse events reported. All reported adverse events were mild and generally transient in nature.

Overall, the pharmacokinetic profile of RGLS4326 in patients with ADPKD was similar to the pharmacokinetic profile observed in a prior healthy volunteer study with the following observations:

- The half-life of RGLS4326 in plasma was slightly longer in patients with impaired renal function and did not exhibit any signs of accumulation in plasma.
- RGLS4326 plasma concentrations in patients were elevated relative to healthy volunteers with mean plasma AUC levels after the first and fourth dose approximately two-fold higher in patients.
- Higher plasma exposure is anticipated to lead to higher kidney exposure allowing for potential dose reductions needed to achieve desired kidney exposure.

A statistically significant increase in the PC1 biomarker was observed in the first cohort of this study. The mean increase at Day 71 (n=8) compared to baseline was greater than 50% and all patients had double digit increases in PC1 levels with an overall trend showing increasing levels of both PC1 and PC2 over time. Mean PC2 levels increased compared to baseline levels (>20%) however the results did not reach statistical significance. Importantly, at the time of the analysis, mutational status was not known and may further contribute to understanding differences in response rates. Approximately 85% of patients with ADPKD are reported to have a mutation in the PKD1 gene, while the remaining 15% have a mutation in the PKD2 gene. Measured levels of these biomarkers (PC1 and PC2) inversely correlate with disease severity and are believed to be directly linked to the underlying genetic drivers of the disease. Regulus believes these initial data demonstrate that RGLS4326 engages the target miR-17 leading to de-repression of the PKD1 and PKD2 genes and the resultant increases in measured polycystin levels. In addition to polycystin changes, one other notable improvement was observed in NGAL levels for one patient in the first cohort. As anticipated, NGAL levels for nearly all patients in this study were within the normal range. However, one patient had levels that were approximately twice the normal range at baseline and that individual saw NGAL levels drop to within the normal range by the end of study. Further analyses of the data are ongoing to better understand drivers of response and correlations with baseline characteristics and other parameters. Data from this first cohort is planned to be submitted for presentation at Kidney Week, the American Society of Nephrology annual meeting being held in November 2021.

"We are very pleased with these data as it provides the safety and pharmacokinetic data needed to complete the modeled safety margins and engage FDA on the remaining partial clinical hold requirements. We believe it also demonstrates clinical proof of mechanism by showing target engagement through increases in a biomarker that inversely correlates with disease severity with a promising trend of increasing levels over time, suggesting that with extended dosing, further increases in polycystin may be attainable," said Jay Hagan, CEO of Regulus. "These results validate our efforts in targeting miR-17 in the kidney and give us confidence in our overall program, with our lead molecule, RGLS4326, now in the second cohort of this Phase 1b study and our next generation compound in IND preparation. We want to thank all of the patients, investigators and collaborators we continue to work with in advancing this novel program designed to address this significant disease at the

genetic level."

Conference Call & Webcast Information

Regulus will host a conference call and webcast at 8:30 a.m. Eastern Time today to discuss the top-line results from the available data at the time of this analysis from the first cohort of patients in our ongoing Phase 1b study of RGLS4326 in patients with ADPKD. To access the call, please dial (877) 257-8599 (domestic) or (970) 315-0459 (international) and refer to conference ID 9988705. To access the telephone replay of the call, dial (855) 859-2056 (domestic) or (404) 537-3406 (international), passcode ID 9988705. The webcast and telephone replay will be archived on the company's website at www.regulusrx.com for ninety days following the call.

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 polycystin 1 (PC1) and polycystin 2 (PC2) in patients with ADPKD administered RGLS4326 every other week for a total of four doses. 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 La Jolla, 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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