Regulus Therapeutics Announces Incremental Update of Autosomal Dominant Polycystic Kidney Disease (ADPKD) Program

Data to Be Presented Today at the Oppenheimer Rare & Orphan Disease Summit

SAN DIEGO, May 21, 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 an incremental update 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. The mean increase in polycystins 1 and 2 at the end of study compared to baseline levels for all nine patients in the first cohort were 58% (p=.0004) and 38% (p=.026) respectively. As disclosed earlier, treatment with RGLS4326 was generally well-tolerated with no serious adverse events reported. All reported adverse events were mild and generally transient in nature. Regulus believes these data demonstrate that RGLS4326 engages the target miR-17 leading to increased expression of the PKD1 and PKD2 genes and the resultant increases in polycystins' levels. Levels of polycystin 1 (PC1) and polycystin 2 (PC2) have previously been shown to inversely correlate with disease severity and are believed to be directly linked to the underlying genetic drivers of the disease.

As previously announced, these data will be presented at the Oppenheimer Rare & Orphan Disease Summit today, Friday, May 21, 2021 at 11:35am ET. The presentation will be archived on the Company's website. Additional data from this first cohort will be presented at PKD Connect in June 2021, and an abstract will be submitted to the American Society of Nephrology annual meeting in November 2021.

"We are very encouraged by these results and look forward to data from the second cohort in the third quarter" said Jay Hagan, CEO of Regulus. "As previously reported, the ninth and final patient was trending well at the end of the dosing period and saw their polycystin levels continue to rise until study completion, twenty-eight days after the last dose. This pattern was generally consistent across the first cohort and further enhanced the overall mean changes from baseline for both biomarkers."

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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