at a glance™

REGULUS

Of Note: ***Regulus is moving into a potentially catalyst-rich period with the pending submission of an IND for its new kidney disease drug candidate, the initiation of and subsequent data from a Phase 1 trial in healthy volunteers and in patients with ADPKD, and the potential receipt of a $25 million milestone payment from Sanofi upon successful completion of a Phase 2 trial for a drug candidate developed by Regulus and licensed to Sanofi. At December 31, 2021, Regulus reported $60.4 million of cash and cash equivalents, which is projected to carry it through 2023.***

Key Considerations

- **Regulus is a leading developer of microRNA-based therapies. Its lead candidate is a second-generation compound targeting microRNA-17, named RGLS8429, for the treatment of Autosomal Dominant Polycystic Kidney Disease, or ADPKD, one of the most common monogenic diseases.**
- **The new second-generation compound follows on the work of the first-generation compound (RGLS4326) which showed significant improvement in key biomarkers, polycystin 1 and polycystin 2, associated with ADPKD in a Phase 1b clinical trial but had the potential for dose-limiting side effects.**
- **In pre-IND studies, RGLS8429, has shown equal potency to the first-generation compound for its molecular target (miR-17) in both in-vitro and in-vivo studies and none of the off-target central nervous system (CNS) effects that were observed with the first-generation compound at the top doses tested in chronic preclinical toxicology studies.**
- **In 4Q21, the company held a pre-IND meeting with the FDA to obtain feedback on the proposed preclinical data package as well as the Phase 1 clinical trial design.**
- **On January 20, 2022, the company announced the successful completion of the Pre-IND meeting with FDA for RGLS8429. The FDA provided overall agreement with the trial design and length of the Phase 1 study, as well as sufficiency of the non-clinical package.**

Regulus Therapeutics Inc.

(Nasdaq: RGLS)

52 Week Range:	**$0.19-$1.88**
Shares O/S:	**146 Million**
Approx. Mkt Cap:	**$42 Million**
Avg. Daily Volume:	**1.5 Million**
Fiscal Year Ends:	**Dec. 31**

Analyst Coverage: Cantor Fitzgerald, H.C. Wainwright, Needham & Co., and Wells Fargo Securities

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- **The filing of the IND and start of the Phase 1 clinical trial are on track to occur in 2Q22.**
- **Topline data from the Phase 1a portion in healthy volunteers is expected 2H22, with topline data from the first cohort of patients with ADPKD in the Phase 1b portion of the study expected 1H23.**
- **Regulus' pipeline leverages its expertise in microRNA biology with early programs in other kidney diseases, CNS disorders, and other areas of research interest where microRNAs are implicated in the disease.**
- **Sanofi licensed from Regulus worldwide rights to lademirsen, a drug candidate for treating Alport syndrome, another genetic disease of the kidney. Enrollment in a Phase 2 Sanofi-sponsored trial of lademirsen was recently completed. Topline results are anticipated 1H23. Regulus is eligible to receive $25 million upon successful completion of the study or the initiation of a next phase of clinical development for lademirsen.**

About ADPKD*

ADPKD is caused by a mutation in either the Pkd1 gene or the Pkd2 gene that leads to formation and proliferation of kidney cysts and the eventual loss of kidney function.

As the disease progresses, the cysts expand and begin interfering with normal kidney function. Over time, untreated patients typically advance to kidney failure (in many cases in their mid-50s) and the prospect of a lifetime on dialysis or kidney transplant.

The mechanistic goal of RGLS8429 is to bind to and reduce the level of miR-17, which in turn allows for increased gene expression of Pkd1 and Pkd2, the two genes that are deficient in the disease.

High levels of miR-17 reduce the levels of Pkd1 and Pkd2 and their protein products, polycystin 1 and polycystin 2. Lower levels of these polycystins are correlated with increased disease severity including larger cystic kidneys and reduced kidney function. Left untreated, the cysts grow and lead to serious clinical complications.

Anticipated Events RGLS8429

--2Q22-Filing of IND

--2Q22-Start of Phase 1 clinical trial program

--2H22-Topline results in healthy volunteers in Phase la

--2H22-Initiation of Phase 1b in ADPKD patients

--1H23-Topline results in patients in first cohort of Phase 1b patients

In earlier human trials with the first-generation compound, Regulus demonstrated that targeting and suppressing miR-17 significantly increased polycystin levels in patients with ADPKD, implying overexpressed miR-17 in diseased patients limits Pkd1 and Pkd2 expression, further validating miR-17 as a therapeutic target for ADPKD treatment.

Researchers at Yale recently published results of a mouse model study (Dong, et al, *Nature Genetics*, 2021) that supports the important role of Pkd1 and Pkd2 and the polycystins they produce in treating ADPKD. They showed that low levels of polycystins 1 and 2 correlated with higher cystic expansion, and that by increasing polycystins 1 and 2, cystic expansion is reversed, normalizing kidney weight to body weight.

Regulus CEO Jay Hagan on the Switch to a Second-Generation Compound

"In light of our discussions with FDA and early analysis of data from the second cohort of our Phase 1b trial in ADPKD, we determined that advancing our second-generation compound RGLS8429 is more compelling than further development of RGLS4326. The extensive work and investment we have made in our first-generation compound will directly inform the advancement of our new candidate, and we believe it will make this transition both expeditious and productive. This prioritization of RGLS8429 is supported by both robust data in preclinical models, where we have seen clear improvements in kidney function, size, and other measures of disease severity, as well as the compound's superior pharmacologic profile."

About 160,000 people in the US are diagnosed with ADPKD. Eighty five percent have the more aggressive form where half will advance to end-stage renal disease in their 50s. Kidney failure therapy in the US costs $3.8 billion yearly. Regulus' drug candidate is designed to reduce or delay the likelihood of ADPKD patients requiring kidney failure therapy.

As a point of reference, the only currently FDA-approved drug for ADPKD, Jynarque® from Otsuka Pharmaceuticals of Japan, costs roughly $200,000 a year, despite carrying a Black Box warning due to potentially fatal liver injury or failure requiring transplant. Its sales are approaching $1 billion a year

Planned Phase 1 Protocol

The Phase 1 study will consist of two parts.

Part 1 will consist of a single-ascending dose study in healthy volunteers to assess safety and tolerability of RGLS8429 and characterize its pharmacokinetics. A total of 32 subjects will be randomized to RGLS8429 or placebo into one of four sequential cohorts.

Part 2 will be a multiple ascending dose study in adult patients with ADPKD to assess the safety and tolerability of RGLS8429, to characterize the pharmacokinetics of RGLS8429, and to evaluate the dose response of RGLS8429 treatment on disease parameters including changes in the levels of the disease biomarker polycystin, cystic kidney volume (htTKV), and overall kidney function. A total of 36 subjects will be randomized to RGLS8429 or placebo into one of three sequential cohorts.

Part 2 of the study includes extending dosing to three months in each cohort of patients with ADPKD, inclusion of measurements of changes in height-adjusted total kidney volume (htTKV) by Magnetic Resonance Imaging (MRI) and testing higher doses of the molecule than were tested with the first-generation compound. htTKV, a measure of cystic kidney volume, is a surrogate marker for disease severity and progression to kidney failure in patients with ADPKD.

Increased htTKV occurs prior to loss of kidney function, typically by years or decades, and retrospective evidence from published clinical studies has shown a correlation between improvement in htTKV and improvement in the rate of decline in renal function versus untreated patients.

FDA has indicated that htTKV, a surrogate marker, could be appropriate for use as a primary endpoint for accelerated approval.

ADPKD stands for Autosomal Dominant Polycystic Kidney Disease. **Autosomal means that the gene in question is located on one of the numbered, or non-sex, chromosomes. **Dominant** means that a single copy of the disease-associated mutation is enough to cause the disease. This contrasts with a recessive disorder, where two copies of the mutation are needed to cause the disease. One copy of a mutated (changed) gene from one parent can cause the genetic condition. A child who has a parent with the mutated gene has a 50 percent chance of inheriting that mutated gene.*

Summary

- **Regulus plans to submit an IND application and start a Phase 1 clinical trial of its second-generation candidate for ADPKD in the second quarter of this year.**
- **Data from the healthy volunteer portion of the study is expected to be released in the second half of this year with data from the first cohort of patients expected in the first half of 2023.**
- **In the pre-IND enabling toxicity study, the second-generation compound (RGLS8429) demonstrated a superior pharmacological profile, including the absence of the off-target CNS effects that were seen with the first generation compound at the top doses tested in chronic preclinical toxicology studies.**
- **In addition to measuring changes in polycystin 1 and polycystin 2 levels, the trial will utilize MRI imaging to evaluate if RGLS8429 treatment impacts total kidney volume (htTKV), a surrogate marker.**
- **The first-generation compound showed statistically significant increases in polycystin 1 and polycystin 2 in patients with ADPKD, and in animal models it reduced body weight adjusted total kidney volume by 50 percent by week 14 of treatment.**
- **Topline results from a Sanofi-sponsored Phase 2 clinical trial of lademirsen are expected 1H23. Under terms of the agreement with Sanofi, Regulus is eligible to receive $25 million upon successful completion of the study or initiation of the next phase of development of lademirsen.**
- **Last November, Regulus completed a $34.6 million private offering of common stock at market with no warrants. The financing was led by the Federated Hermes Kaufmann Funds and New Enterprise Associates (NEA), with participation from other new and existing investors. At December 31, 2021, Regulus reported $60.4 million of cash and cash equivalents, which is projected to carry it through 2023.**

For additional information, contact:

Redington, Inc. • CT 203 222-7399 • NY 212 926-1733 • www.redingtoninc.com
Regulus Therapeutics, Inc. • 888 734-8587 • www.regulusrx.com