Positive Preclinical Profile of RG-101, a GalNAc-conjugated anti-miR Targeting microRNA-122, Supports Clinical Development for the Treatment of HCV

- Late-Breaking Poster to be Presented at AASLD -
- Regulatory Application for RG-101 to be Filed in the Near Term: Clinical Studies in Man Expected to Commence in Early 2014 -

LA JOLLA, Calif., Nov. 4, 2013 /PRNewswire/ -- Regulus Therapeutics Inc. (NASDAQ: RGLS), a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, today announced that data demonstrating the positive preclinical profile of RG-101 will be presented in a late-breaking poster session at the 64th Annual Meeting of the American Association for the Study of Liver Disease (AASLD) being held in Washington, D.C. on Monday, November 4, 2013 from 8:00 a.m. Eastern Standard Time (EST) to 5:30 p.m. EST. The poster is available on the Company's website at http://www.regulusrx.com.

"RG-101 utilizes a unique mechanism of action by targeting microRNA-122, a liver-specific host factor for stability, replication and translation of HCV. We believe that therapies that target host-encoded factors essential for HCV replication may act as attractive combination agents because they may demonstrate activity across all HCV genotypes and may have a high barrier to resistance," said Neil W. Gibson, Ph.D., Chief Scientific Officer of Regulus. "We continue to be encouraged by the preclinical data seen to date and believe that RG-101 has the potential to be a best-in-class host factor agent. In the near term, we expect to file our application with regulatory authorities and look forward to commencing clinical trials in man in early 2014."

Late-Breaking Poster on RG-101 – Monday, November 4, 2013, 8:00 a.m. EST – 5:30 p.m. EST

- RG-101, a GalNAc-conjugated anti-miR Employing a Unique Mechanism of Action by Targeting Host Factor MicroRNA-122 (miR-122), Demonstrates Potent Activity and Reduction of HCV in Preclinical Studies-

In the late-breaking poster, Regulus will present positive data from completed preclinical studies evaluating RG-101 for *in vitro* and *in vivo* potency, pharmacokinetic/pharmacodynamics, toxicology and safety pharmacology and inhibition of HCV replication.

Potency and Pharmacokinetics/Pharmacodynamics of RG-101

Pharmacologic potency of RG-101 was significantly enhanced by approximately 20 fold *in vivo* in both mice and non-human primates, relative to the unconjugated oligonucleotide of RG-101 (RG-101-N). RG-101 is rapidly taken up in the liver and metabolized to the active oligonucleotide, which has an approximately 14 day tissue half-life. Additionally, potency as measured by AldoA (a miR-122 target gene) de-repression in the liver is achieved at significantly lower liver concentrations of oligonucleotide following efficacious doses of RG-101 of 1mg/kg-10mg/kg, compared to similar doses of RG-101-N. In addition to the potency studies, Regulus tested the efficacy of RG-101 to reduce HCV viral load titer in a human chimeric liver mouse model infected with HCV, as these mice are estimated to contain greater than 80 percent human hepatocytes. Genotype 1a HCV infected mice were subcutaneously administered a single dose of RG-101 at 3 mg/kg, 10mg/kg or 30 mg/kg and monitored for up to 36 days. Up to a 2 log reduction in HCV viral load titer was observed, which is similar to that observed for oral direct-acting antivirals as monotherapy in this mouse model. Additionally, the duration of action observed for RG-101 supports the potential for a once-a-month dosing regimen.

Regulus believes these preclinical data will assist the Company in determining the most efficacious dose of RG-101, including optimal dosing frequency, for clinical studies in man.

Toxicology and Safety Pharmacology of RG-101

RG-101 has demonstrated an excellent preclinical safety profile to date, with no findings observed up to 450 mg/kg in mice and 45 mg/kg in non-human primates. AldoA levels in non-human primates were maximally elevated at 1 mg/kg. These data demonstrate that RG-101 is safe and well tolerated with a high therapeutic index. Additionally, these data provide support that the chemistry and conjugation approach for RG-101 may mitigate the potential for pro-inflammatory effects.

Currently, additional preclinical toxicology and safety pharmacology studies are ongoing in which multiple doses of RG-101 are being evaluated.

About RG-101 for the Treatment of HCV

RG-101 is a key program in Regulus' 'Road to the Clinic' Strategy for 2013, in which the Company expects to nominate two microRNA candidates for clinical development, be positioned to file its first applications with

regulatory authorities by the first half of 2014 and maintain a strong year-end cash position to support these goals. RG-101 was the first microRNA candidate nominated for clinical development under this strategy.

microRNA-122 (miR-122) is the most abundant microRNA in hepatocytes and is a critical host factor for survival and replication of all know HCV genotypes. RG-101 is a novel anti-miR-122 oligonucleotide therapeutic that is effectively targeted to hepatocytes for the treatment of HCV through conjugation to GalNAc, a carbohydrate-based chemistry approach for asialoglycoprotein receptor-mediated delivery of oligonucleotides to hepatocyte cells of the liver. Utilizing the GalNAc conjugate chemistry has significantly improved the potency of the active oligonucleotide of RG-101 by achieving targeted delivery of the oligonucleotide to the infected hepatocytes. Given its attractive properties and positive preclinical profile seen to date, Regulus believes that RG-101 may be an attractive agent to add to existing HCV therapeutic regimens. The Company plans to develop RG-101 as a key component of an HCV combination regimen for patients who have failed, or are intolerant of, the current standard of care and specific patient populations such as HCV/HIV co-infection. In the near term, Regulus expects to submit an application with regulatory authorities and to commence clinical studies in man in early 2014.

About Regulus

Regulus Therapeutics Inc. (*NASDAQ:RGLS*) is a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs. Regulus is uniquely positioned to leverage a mature therapeutic platform that harnesses the oligonucleotide drug discovery and development expertise of Alnylam Pharmaceuticals, Inc. and Isis Pharmaceuticals, Inc., which founded the company. Regulus has a well-balanced microRNA therapeutic pipeline entering clinical development, an emerging microRNA biomarkers platform to support its therapeutic programs, and a rich intellectual property estate to retain its leadership in the microRNA field. Regulus intends to focus its proprietary efforts on developing microRNA therapeutics for oncology indications and orphan diseases and is currently advancing several programs toward clinical development in oncology, fibrosis and metabolic diseases. Regulus is also developing RG-101, a GalNAc-conjugated anti-miR targeting microRNA-122, for the treatment of chronic hepatitis C virus infection. Regulus' commitment to innovation and its leadership in the microRNA field have enabled the formation of strategic alliances with AstraZeneca, GlaxoSmithKline and Sanofi. In addition, Regulus has formed a research collaboration with Biogen Idec around its emerging microRNA biomarkers platform.

For more information, please visit http://www.regulusrx.com.

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 Regulus' expectations regarding future therapeutic and commercial potential of Regulus' business plans, including the belief that RG-101 is the best-in-class anti-HCV host factor agent and its expectations regarding future clinical studies, and technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus. 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. These and other risks concerning Regulus' programs are described in additional detail in Regulus' SEC filings. 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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