Arrowhead Pharmaceuticals Begins Dosing in Phase 1 Study of ARO-ANG3 for Treatment of Dyslipidemias and Metabolic Diseases

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PASADENA, Calif.--(BUSINESS WIRE)--Jan. 7, 2019-- Arrowhead Pharmaceuticals Inc. (NASDAQ: ARWR) today announced that it has dosed the first subjects in a Phase 1 clinical study of ARO-ANG3, an RNAi-based investigational medicine targeting angiopoietin like protein 3 (ANGPTL3) being developed for the treatment of dyslipidemias and metabolic diseases.

Bruce Given, M.D., chief operating officer and head of R&D at Arrowhead, said: “We continue to advance our broad pipeline of RNAi therapeutics with the dosing of the first subjects in our Phase 1 study of ARO-ANG3. ANGPTL3 has emerged as a potentially important target to address dyslipidemias, such as elevated cholesterol and triglycerides that are not well-controlled with currently available medicines, and also metabolic diseases, such as NAFLD and NASH. The preclinical data for ARO-ANG3 have been promising, and our prior clinical results from the ARO-HBV and ARO-AAT programs, which also leverage the Targeted RNAi Molecule, or TRiM^{TM}, platform, give us confidence in the potential for ARO-ANG3 to address significant unmet medical needs.”

AROANG1001 (NCT03747224) is a Phase 1 single and multiple dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ARO-ANG3 in adult healthy volunteers and patients with dyslipidemia. The study is designed to enroll up to 70 subjects.

The single-ascending dose (SAD) portion of the study is designed to include up to 4 cohorts of 10 adult healthy volunteers per cohort (6 active: 4 placebo). Each SAD subject will receive a single-dose administration of either placebo or ARO-ANG3 at dose levels of 35, 100, 200, or 300 mg. The multiple-dose portion is designed to include up to 4 patient cohorts, including patients with non-alcoholic fatty liver disease (NAFLD), patients on a stable statin treatment regimen with elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides, patients with heterozygous or homozygous familial hypercholesterolemia, and patients with severe hypertriglyceridemia.

Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease (Kersten, 2017). While the current standard of care is effective at lowering LDL-C, a large unmet medical need for lipid lowering and risk modifying therapies with novel mechanisms of action persists. Hypertriglyceridemia and elevations in triglyceride-rich lipoproteins represent causative risks for atherosclerosis, and elevated triglycerides also manifest in the form of metabolic syndrome, pancreatitis and hepatic steatosis. Metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease and type II diabetes mellitus.

ANGPTL3 has emerged as an important regulator of plasma lipoprotein levels (including triglycerides, LDL-C, high-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol) by inhibition of enzymes including lipoprotein lipase and endothelial lipase. ANGPTL3 may also be involved in regulating apolipoprotein B particle containing synthesis and hepatocyte clearance of LDL-C through mechanisms independent of the low-density lipoprotein receptor (LDLR) (Xu et al., 2018). This LDLR-independent feature makes ANGPTL3 inhibition potentially applicable as a therapeutic for *LDLR*-deficient hypercholesterolemic patients.

Intrahepatic targeting of ANGPTL3 may also improve hepatic steatosis which can progress to nonalcoholic steatohepatitis (NASH). Additionally, human genetic studies indicate that *ANGPTL3*-deficient homozygotes show lower serum insulin, lower serum glucose, and improved measures of insulin resistance compared to non-carriers (Robciuc et al., 2013).

About Arrowhead Pharmaceuticals

Arrowhead Pharmaceuticals develops medicines that treat intractable diseases by silencing the genes that cause them. Using a broad portfolio of RNA chemistries and efficient modes of delivery, Arrowhead therapies trigger the RNA interference mechanism to induce rapid, deep, and durable knockdown of target genes. RNA interference, or RNAi, is a mechanism present in living cells that inhibits the expression of a specific gene, thereby affecting the production of a specific protein. Arrowhead’s RNAi-based therapeutics leverage this natural pathway of gene silencing.

For more information, please visit www.arrowheadpharma.com, or follow us on Twitter @ArrowheadPharma. To be added to the Company's email list and receive news directly, please visit http://ir.arrowheadpharma.com/email-alerts.

Safe Harbor Statement under the Private Securities Litigation Reform Act:

This news release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including the safety and efficacy of our product candidates, the duration and impact of regulatory delays in our clinical programs, our ability to finance our operations, the likelihood and timing of the receipt of future milestone and licensing fees, the future success of our scientific studies, our ability to successfully develop and commercialize drug candidates, the timing for starting and completing clinical trials, rapid technological change in our markets, and the enforcement of our intellectual property rights. Our most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q discuss some of the important risk factors that may affect our business, results of operations and financial condition. We assume no obligation to update or revise forward-looking statements to reflect new events or circumstances.

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