Dicerna Announces Interim Results From Phase 1 Trial of Belcesiran for Treatment of Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

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– Interim Results From Phase 1 Study Enabled Initiation and First Patient Dosing in Phase 2 ESTRELLA Study, Which Is Currently Underway –

LEXINGTON, Mass.--(BUSINESS WIRE)--Jul. 21, 2021-- Dicerna Pharmaceuticals, Inc. (Nasdaq: DRNA) (the "Company" or "Dicerna"), a leading developer of investigational ribonucleic acid interference (RNAi) therapeutics, today announced interim results from the four completed active-treatment dose cohorts (0.1, 1.0, 3.0 and 6.0 mg/kg) of its Phase 1 double-blind, placebo-controlled, randomized trial of belcesiran, an investigational GalXC™ RNAi therapeutic in development for the treatment of alpha-1 antitrypsin deficiency-associated liver disease (AATLD). AATLD is a rare genetic condition that can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. Data from this interim analysis showed dose-dependent reductions in serum alpha-1 antitrypsin (AAT) with administration of a single dose of belcesiran. In this analysis, belcesiran was found to have an acceptable safety profile and was generally well tolerated. The primary treatment evaluation period for the final dose cohort (12.0 mg/kg) of belcesiran in the Phase 1 trial is ongoing.

"We are encouraged by the interim results from this first clinical trial of belcesiran, which met our objective, demonstrating an acceptable safety profile and tolerability as well as dose-dependent reductions in AAT levels over the treatment period," said Shreeram Aradhye, M.D., Executive Vice President and Chief Medical Officer at Dicerna. "Given the severity and progressive nature of AATLD, there is a significant need for a therapy that can directly impact the aggregation of mutated AAT protein in the liver. In addition to demonstrating that belcesiran was well tolerated, the results from this study suggest that belcesiran has the potential to meaningfully reduce the production of abnormal AAT protein – a key objective in developing a pharmacological intervention for people with AATLD."

Serum AAT Reductions, Safety and Tolerability Data

The Phase 1 trial is designed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of a single subcutaneous injection of belcesiran 0.1, 1.0, 3.0, 6.0 or 12.0 mg/kg compared to placebo (n=6 per cohort; 2:1 randomization) in adult healthy volunteers.

- In this interim analysis that included belcesiran doses up to 6.0 mg/kg, mean maximum serum AAT reductions from baseline achieved for doses greater than 0.1 mg/kg were: 50% (1.0 mg/kg), 69% (3.0 mg/kg) and 80% (6.0 mg/kg).
- In the four subjects receiving 6.0 mg/kg, maximum AAT reductions of 91%, 87%, 79% and 62% were observed, with the latter participant experiencing a concomitant skin infection (unrelated to belcesiran) and markedly elevated levels of C-reactive protein (CRP; a measure of inflammation in the body). Both CRP and AAT are known to increase in the presence of infection.[1]
- There were no serious adverse events reported. All treatment-emergent adverse events (TEAEs) were mild except for three TEAEs, which were moderate and determined to be unrelated to belcesiran. No clinically significant changes in lung function or laboratory tests were reported during the treatment periods for any of the belcesiran dose cohorts included in this analysis.

The final 12.0 mg/kg dose cohort in this trial is ongoing, and data from this cohort were not available for inclusion in this interim analysis. Dicerna plans to present additional results from all Phase 1 dose cohorts at an upcoming medical congress in 2021, subject to abstract acceptance.

About Alpha-1 Antitrypsin Deficiency and Alpha-1 Antitrypsin Deficiency-Associated Liver Disease (AATLD)

Alpha-1 antitrypsin (AAT) deficiency is a rare genetic condition caused by mutations in the *SERPINA1* gene that results in disease of the liver and lungs. AAT protein is produced in hepatocytes and circulates in the bloodstream; AAT protects the lungs and other parts of the body by neutralizing neutrophil elastase, an enzyme that fights infection but can also damage healthy tissues if not adequately regulated by AAT. The majority of people with severe AAT deficiency are homozygous for the Z allele (PiZZ genotype).[2] In the liver, misfolding of the mutant Z-AAT protein causes the protein to aggregate in liver cells, leading to liver injury, including fibrosis, cirrhosis and hepatocellular carcinoma. An estimated 10% or more of adults with AAT deficiency develop clinically meaningful liver disease.[3,4] People with AAT deficiency may also develop lung disease, including emphysema.

About Belcesiran

Belcesiran is a clinical-stage, subcutaneously administered, investigational GalXC™ RNAi therapy targeting alpha-1 antitrypsin (AAT) that is in development for the treatment of AAT deficiency-associated liver disease (AATLD). Belcesiran is designed to target the gene responsible for production of the abnormal AAT protein in order to reduce AAT production in the liver. Dicerna is currently investigating the use of belcesiran for the treatment of AATLD in the SHINE clinical development program.

About RNAi and Dicerna's GalXC™ RNAi Platform

Ribonucleic acid interference, or RNAi, provides a unique advantage to other disease inhibitor technologies, like small-molecule pharmaceuticals or monoclonal antibodies. Instead of targeting proteins after they have been produced and released, RNAi silences the genes themselves via the specific destruction of the messenger RNA (mRNA) made from the gene. Rather than seeking to inhibit a protein, the RNAi approach can prevent a disease-causing protein's creation, directly impacting disease manifestation.

Dicerna's proprietary GalXC™ RNAi platform aims to advance the development of next-generation RNAi-based therapies. Investigational therapeutics developed using our flagship GalXC technology utilize a proprietary *N*-acetyl-D-galactosamine (GalNAc)-mediated structure of double-stranded RNA

molecules that are designed to bind specifically to receptors on liver cells, leading to selective hepatocyte internalization and access to the RNAi machinery within the cells. Dicerna is continuously innovating and exploring new applications of RNAi technology beyond GalNAc-mediated delivery to the liver, including alternative RNA structures and fully synthetic ligands that target other tissues and cell types and enable new therapeutic applications, referred to as GalXC-Plus™.

About Dicerna Pharmaceuticals, Inc.

Dicerna Pharmaceuticals, Inc. (Nasdaq: DRNA) is a biopharmaceutical company focused on discovering, developing and commercializing medicines that are designed to leverage ribonucleic acid interference (RNAi) to silence selectively genes that cause or contribute to disease. Using our proprietary GalXC™ and GalXC-Plus™ RNAi technologies, Dicerna is committed to developing RNAi-based therapies with the potential to treat both rare and more prevalent diseases. By silencing disease-causing genes, Dicerna's GalXC platform has the potential to address conditions that are difficult to treat with other modalities. Initially focused on disease-causing genes in the liver, Dicerna has continued to innovate and is exploring new applications of its RNAi technology with GalXC-Plus, which expands the functionality and application of our flagship liver-targeted GalXC technology to tissues and cell types outside the liver and has the potential to treat diseases across multiple therapeutic areas. In addition to our own pipeline of core discovery and clinical candidates, Dicerna has established collaborative relationships with some of the world's leading pharmaceutical companies, including Novo Nordisk A/S, Roche, Eli Lilly and Company, Alexion Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH and Alnylam Pharmaceuticals, Inc. Between Dicerna and our collaborative partners, we currently have more than 20 active discovery, preclinical or clinical programs focused on cardiometabolic, viral, chronic liver and complement-mediated diseases, as well as neurodegenerative diseases and pain. At Dicerna, our mission is to interfere – to silence genes, to fight disease, to restore health. For more information, visit www.dicerna.com.

Cautionary Note on Forward-Looking Statements

This press release includes forward-looking statements. Such forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statements. Examples of forward-looking statements include, among others, statements we make regarding the belcesiran development program, including the timeline or outcomes of trials, the potential of belcesiran as a treatment for alpha-1 antitrypsin deficiency-associated liver disease (AATLD), and the submission, acceptance or delivery of results at conferences. The process by which investigational therapies could potentially lead to an approved product is long and subject to highly significant risks. Applicable risks and uncertainties include those relating to Dicerna's clinical research and other risks identified under the heading "Risk Factors" included in the Company's most recent filings on Forms 10-K and 10-Q and in other future filings with the Securities and Exchange Commission. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and clinical trials and other development activities by us and our collaborative partners; the likelihood of Dicerna's clinical programs being executed on timelines provided and reliance on the Company's contract research organizations and predictability of timely enrollment of subjects and patients to advance Dicerna's clinical trials; the reliance of Dicerna on contract manufacturers to supply its products for research and development and the risk of supply interruption from a contract manufacturer; the potential for future data to alter initial, interim and preliminary results of early-stage clinical trials; the impact of the ongoing COVID-19 pandemic on our business operations, including the conduct of our research and development activities; the unpredictability of the duration and results of the regulatory review of Investigational New Drug (IND) applications and Clinical Trial Applications (CTAs) that are necessary to continue to advance and progress the Company's clinical programs and the regulatory review of INDs and CTAs; the timing, plans and reviews by regulatory authorities of marketing applications such as New Drug Applications (NDAs) and comparable foreign applications for one or more of Dicerna's product candidates; the ability to secure, maintain and realize the intended benefits of collaborations with partners; market acceptance for approved products and innovative therapeutic treatments; competition; the possible impairment of, inability to obtain and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in R&D; and general business, financial and accounting risks and litigation. The forward-looking statements contained in this press release reflect Dicerna's current views with respect to future events, and Dicerna does not undertake and specifically disclaims any obligation to update any forward-looking statements.

[1] Sanders CL, Ponte A, Kueppers F. The Effects of Inflammation on Alpha 1 Antitrypsin Levels in a National Screening Cohort. COPD. 2018 Feb;15(1):10-16. doi: 10.1080/15412555.2017.1401600.

[2] Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [updated 2020 May 21]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021. PMID: 20301692.

[3] Tanash & Piitulainen. J Gastroenterol. 2019 Jun;54(6):541-548. doi: 10.1007/s00535-019-01548-y. Epub 2019 Jan 24.

[4] Clark et al. J Hepatol. 2018 Dec;69(6):1357-1364. doi: 10.1016/j.jhep.2018.08.005. Epub 2018 Aug 21.

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