Phase 2a Study of HU6, Rivus Pharmaceuticals' Investigational Controlled Metabolic Accelerator, Demonstrates Clinical Benefit in Patients with High Body Mass Index and Nonalcoholic Fatty Liver Disease

– Results showing significant reductions in liver fat content and body weight, no loss of lean muscle mass, and improvement in key markers of metabolism and inflammation published in *The Lancet Gastroenterology & Hepatology* –

– HU6 was well tolerated at once-daily oral doses with adverse events mainly mild or moderate in severity –

CHARLOTTESVILLE, Va., and SAN FRANCISCO (October 5, 2023) – Rivus Pharmaceuticals Inc., a clinical-stage biopharmaceutical company dedicated to improving cardiometabolic health, today announced publication in *The Lancet Gastroenterology & Hepatology* of the results of a Phase 2a metabolic study of HU6, an investigational first-in-class controlled metabolic accelerator (CMA), in patients with nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease (MASLD), and a high body mass index (BMI).

Results showed that HU6 significantly reduced liver fat compared with placebo in both the overall study population and in study participants at increased risk of Type 2 diabetes. HU6 also reduced body weight, with no loss of lean muscle mass, and improved measures of metabolism and systemic inflammation. HU6, the company's lead medicine, is an oral, controlled metabolic accelerator in Phase 2 clinical development.

"The positive efficacy and safety results of this Phase 2a metabolic clinical trial of HU6 give us confidence that this first-in-class therapy has the potential to provide an effective, well-tolerated treatment for a broad range of cardiometabolic diseases associated with obesity," said Mazen Noureddin, M.D., hepatologist at Houston Research Institute and Houston Methodist Hospital and lead author of the publication. "A broad range of investigational therapies have been studied in patients with NAFLD/MASLD, but there are still not many options that are able to effectively manage this disease in patients with obesity and elevated liver fat. The significant reductions in liver fat, coupled with greater than expected reductions in inflammatory markers, make HU6 a promising new approach."

"There is growing evidence that HU6 can speed up metabolism in a safe and controlled manner that enables fat-specific weight loss, while lowering inflammation," said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. "We are highly encouraged by the Phase 2a metabolic study results and are continuing to evaluate HU6 broadly to improve cardiometabolic

health in people with obesity, one of the most challenging health issues we face in society today."

The company is presently enrolling patients with obese phenotype of heart failure with preserved injection fraction (HFpEF) in the Phase 2a HuMAIN study (ClinicalTrials.gov, NCT05284617) and patients with obesity and Type 2 diabetes at risk of metabolic dysfunction associated steatohepatitis (MASH) in the Phase 2b M-ACCEL trial (ClinicalTrials.gov, NCT05979779).

Phase 2a Study Design and Results

The 61-day randomized, double-blind, placebo-controlled Phase 2a metabolic trial (ClinicalTrials.gov, NCT04874233) was designed to evaluate the safety and efficacy of once-daily HU6 at three dose levels (150 mg, 300 mg and 450 mg) in 80 patients age 28 to 65 years with NAFLD, elevated liver fat (greater than 8%) and a BMI of 28 to 45 kg/m2. These doses correlate to a 10%, 20% and 30% increase in resting metabolic rate, respectively, all within the range of normal daily fluctuations. A subset of study participants (40%) had elevated HbA1C levels, placing them at increased risk of Type 2 diabetes. The primary efficacy endpoint was the relative change in liver fat content from baseline to day 61 as assessed by MRI-proton density fat fraction (MRI-PDFF). The study was conducted at a single community site in the United States.

The published results demonstrated the following:

- **Liver fat content** (primary endpoint): A significant decrease from baseline to day 61 as assessed by MRI-PDFF was observed with all HU6 doses compared with placebo ($p<0.0001$) in the overall study population and in the elevated HbA1c subgroup ($p<0.0001$).
- **>30% reduction in liver fat:** Overall, 61% of study participants treated with any dose of HU6 had at least a 30% reduction in liver fat from baseline to day 61 as assessed by MRI-PDFF. Among the HU6 150 mg, 300 mg and 450 mg dosing groups, the percentages were 40%, 71% and 72%, respectively, versus 5% of those receiving placebo; all $p<0.0001$). Similar results were observed in study participants in the HbA1c subset (43%, 75% and 86%, respectively, versus 0% of those receiving placebo; all $p<0.0001$).
- **Body weight:** HU6 300 mg and 450 mg were associated with significant weight loss at day 61 and at the follow-up visit, with no loss of lean body mass or skeletal muscle mass. Notably, the elevated HbA1c subgroup had a greater overall weight loss than the total population.
- **Inflammatory and metabolic markers:** HU6 300 mg and 450 mg significantly reduced systemic high sensitivity C-reactive protein (hsCRP), a systemic marker of inflammation, compared with placebo. The hsCRP reductions were four-fold greater than expected for the observed weight loss, due to the independent effect of HU6 on reducing oxidative stress. HU6 also was associated with significant improvement in glycemic control, with glycated albumin significantly reduced by HU6 450 mg versus placebo in the HbA1c subgroup.
- **Safety:** HU6 was well tolerated at once-daily doses of 150 mg, 300 mg and 450 mg for up to 61 days. Treatment-emergent adverse events (TEAEs) occurred in 65% of

participants who received HU6 and in 35% of study participants who received placebo. Adverse events were mainly mild or moderate in severity. No serious TEAEs were reported. In those treated with HU6, the most frequently reported TEAEs were flushing (32% of participants), diarrhea (25% of participants), and palpitations (12% participants). In the placebo arm, 10% of participants had flushing, none had diarrhea, and 5% had palpitations. No effects of HU6 were observed on body temperature or on any of the precursors to an elevated body temperature. Side effects commonly associated with incretin therapies, such as nausea and vomiting, were not observed with HU6. No patients discontinued for any reason at the high dose of 450 mg of HU6.

About Controlled Metabolic Accelerators (CMAs)

Rivus is advancing a new class of therapies, called controlled metabolic accelerators (CMAs). CMAs have the potential to improve metabolic health and reduce cardiovascular risk and mortality. As oral small molecules, CMAs are designed to address excess fat and treat a broad range of cardiometabolic diseases by safely leveraging mitochondrial uncoupling, a natural metabolic process by which the body generates heat. Within the mitochondria, sugars and fats are broken down by biochemical processes to help regulate the body's metabolism. CMAs cue the increased oxidation of sugars and fats by metabolic processes in the mitochondria while maintaining the same baseline production of adenosine triphosphate (ATP), the body's primary source for energy production, resulting in a sustained, imperceivable increase in the resting metabolic rate throughout the day and night. Activating this process results in the reduction of accumulated fat and sugars throughout the body, while preserving, or even improving, lean muscle mass. CMAs provide a novel, measured approach to activating this natural process, resulting in weight loss, reduction of liver fat, improved insulin sensitivity and a significant reduction in oxidative stress and inflammation.

About HU6

HU6 is the most advanced CMA in clinical development and was purposefully designed to control both absorption and metabolism. The proprietary mechanism of HU6 increases the body's resting metabolic rate without any perceived or actual increases in body temperature. In clinical trials, HU6 has shown potential for inducing fat-specific weight loss, preservation of lean muscle mass and significant improvements in measures of metabolic health. Treatment with HU6 could potentially significantly reduce systemic inflammation by decreasing the production of reactive oxygen species within the cell. Rivus is pursuing clinical development programs for HU6 in heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction associated steatohepatitis (MASH), Type 2 diabetes and obesity.

About Rivus Pharmaceuticals

Rivus Pharmaceuticals, Inc., a leader in mitochondrial biology, is dedicated to improving cardiometabolic health by advancing a new class of medicines called controlled metabolic accelerators (CMAs). Rivus' investigational first-in-class small molecule therapy, HU6, represents a tremendous opportunity to empower patients on their journey to better health when facing a broad range of conditions, including obesity, heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction-associated steatotic liver disease (MASLD) / metabolic dysfunction-associated steatohepatitis (MASH), Type 2 diabetes and obesity. For more information, please visit www.rivuspharma.com.

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