Rivus Pharmaceuticals Announces Positive Topline Results from Phase 2 M-ACCEL Trial of HU6 Showing Significant Reductions in Liver Fat in Patients with MASH

– Study met primary endpoint, with a statistically significant reduction in liver fat observed in all HU6 treatment groups –

– Treatment with HU6 significantly reduced body weight, body fat and abdominal visceral fat with preservation of skeletal muscle mass versus placebo and was well tolerated –

CHARLOTTESVILLE, Va., and SOUTH SAN FRANCISCO, Calif., June 24, 2025 – Rivus Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company dedicated to treating obesity and the resulting cardiometabolic diseases, today announced that its Phase 2 M-ACCEL clinical trial of HU6 in patients with metabolic dysfunction-associated steatohepatitis (MASH) met its primary endpoint, with statistically significant reductions in liver fat content at 6 months compared with placebo ($p<0.01$) in each of the three treatment groups. The proportion of responders, defined as experiencing a greater than 30% reduction in liver fat, was also statistically significant ($p<0.01$) in all treatment groups.

“Obesity is a key driver of poor outcomes in patients with MASH, a progressive and difficult to manage disease that can lead to cirrhosis, liver failure and premature death,” said Mazen Noureddin, M.D., Professor of Medicine at Houston Methodist Hospital and Co-Chairman of the Board of the Summit and Pinnacle Clinical Research Networks. “Patients in the M-ACCEL study achieved a statistically significant reduction in liver fat content with HU6 compared to placebo, with the majority reaching more than a 30% reduction, which has been shown to be a clinically meaningful result associated with MASH resolution and fibrosis improvement. Additionally, given the favorable tolerability profile of HU6, the M-ACCEL study reinforces the potential of this investigational treatment to be a promising approach for the long-term management of MASH.”

The study also met a number of secondary endpoints despite not being powered to do so, including reductions in body weight, visceral fat mass, blood pressure and hemoglobin A1c, which is consistent with HU6 having a broadly beneficial profile to address the dysmetabolism in MASH.

Treatment with HU6 was associated with entirely fat-specific weight loss, with no significant change in lean mass at any dose. This compares favorably to incretin-based therapies, which have been shown in clinical studies to significantly reduce lean muscle mass. Three quarters of the fat loss was from the visceral fat compartment, which is most strongly associated with the harmful consequences of obesity. Approximately two thirds of patients treated in the M-ACCEL study had Type 2 diabetes at baseline, and the efficacy of HU6 was similar in these patients compared to those who were non-diabetic at baseline.

“The topline results from M-ACCEL, the longest study of HU6 to date, indicate that HU6 has a competitive efficacy and safety profile for the treatment of MASH,” said David Grainger, Ph.D., Chairman of Development, Rivus Pharmaceuticals. “Equally important, these data provide continued confirmation of the potential of HU6, and our pipeline of Controlled Metabolic

Accelerators, to deliver entirely fat-specific weight loss with a marked propensity for visceral fat reduction for people with obesity and resulting cardiometabolic disease."

HU6 was well tolerated, and the safety profile was consistent with previous studies, with no treatment-related serious adverse events. The overall safety database for HU6 now includes more than 450 patients.

Rivus will leverage learnings from the M-ACCEL trial to inform next steps in the clinical development of HU6. The company plans to present data from the trial at an upcoming medical meeting.

About the Phase 2 M-ACCEL Trial
The randomized, double-blind, placebo-controlled, parallel-group Phase 2 M-ACCEL trial (ClinicalTrials.gov: NCT05979779) evaluated the safety and efficacy of three dose levels of HU6 in patients with MASH. A total of 221 adult patients were randomized 2:1:2:2 into one of four treatment groups (placebo, HU6 150 mg, HU6 300 mg or HU6 450 mg) and treated for six months (26 weeks). The primary endpoint was percent change from baseline in liver fat as assessed by magnetic resonance imaging liver proton density fat fraction (MRI-Liver PDFF) at six months. Secondary endpoints were the effect of HU6 on body weight, glycemic control as assessed by hemoglobin A1c, liver fibrosis and liver fat, body composition, metabolic and inflammatory parameters, as well as patient-reported outcomes. The M-ACCEL trial also evaluated safety, tolerability, pharmacodynamics and pharmacokinetics. The study was conducted at 22 clinical sites in the United States.

About Metabolic Dysfunction-Associated Steatohepatitis (MASH)
MASH (formerly known as nonalcoholic steatohepatitis or NASH) is a serious liver disease that often progresses to cirrhosis, liver failure, hepatocellular carcinoma, the need for liver transplantation, and premature death. The disease progresses over time, resulting in an increased build-up of fat in the liver and, in many cases, liver fibrosis. Once patients progress to MASH with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), the risk of adverse liver outcomes increases dramatically. Increased body mass index (BMI) is one of the most important risk factors for developing MASH along with cardiovascular disease (CVD) and Type 2 diabetes. MASH is caused by an accumulation of excess fat cells in the liver and is closely linked to obesity. MASH is an independent driver of CVD, the leading cause of mortality for patients, underscoring the close association between MASH and a patient's overall cardiometabolic health.

Approximately 5% of U.S. adults have MASH,[1,2] which is rapidly becoming the leading cause of liver transplantation. With obesity rates rising worldwide, MASH is predicted to have a significant impact on global health.

The treatment goal for patients with MASH is to reduce liver fibrosis. Weight loss is considered an efficient treatment strategy. Even moderate weight loss (3% to 5% of body weight) can benefit a patient's health by reducing fat levels in the liver. The loss of 7% to 10% of body weight can reduce inflammation and lead to MASH resolution.[3] Patients with MASH are in need of novel treatments that not only reduce weight but also target the progression of the disease and the metabolic risk factors that promote the disease – obesity, CVD and Type 2 diabetes.

About Controlled Metabolic Accelerators (CMAs)
Rivus is advancing a new class of investigational therapies called Controlled Metabolic Accelerators (CMAs) that have the potential to improve metabolic health for people with obesity and associated metabolic diseases. Rivus' CMAs are oral small molecules in development to increase resting metabolic rate, which results in increased consumption of energy, primarily

from fat. The loss in fat mass may address multiple cardiometabolic conditions driven by adiposity. CMAs increase metabolism in a manner that is consistent and imperceptible to the patient by leveraging the natural metabolic process of mitochondrial uncoupling. In preclinical studies, mitochondrial uncoupling was shown to account for a significant portion (20% to 50%) of daily energy expenditure. Caloric-restriction strategies, on the other hand, reduce energy input and result in loss of muscle mass as well as fat. Initial data in humans has demonstrated that CMAs provided fat-selective weight loss, improved insulin sensitivity, and significantly reduced oxidative stress and inflammation.

About HU6

HU6 is a novel, oral, once-daily investigational therapy designed to treat obesity and its comorbidities, including liver and cardiovascular disease. HU6 imperceptibly increases resting metabolism resulting in sustained body fat loss while preserving muscle mass. The current clinical development of HU6 is focused on metabolic diseases with the greatest therapeutic need: obesity-related heart failure with preserved ejection fraction (HFpEF) and metabolic dysfunction-associated steatohepatitis (MASH)/metabolic dysfunction-associated steatotic liver disease (MASLD). To date, more than 450 patients have been treated with HU6 as part of the clinical development program.

About Rivus Pharmaceuticals

Rivus Pharmaceuticals, Inc., a leader in mitochondrial biology, is dedicated to improving metabolic health by advancing a new class of investigational therapies called Controlled Metabolic Accelerators (CMAs). Rivus' lead CMA is the investigational small molecule HU6 in clinical development to treat obesity-related heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction associated steatohepatitis (MASH)/metabolic dysfunction-associated steatotic liver disease (MASLD) and Type 2 diabetes. In addition to HU6, Rivus is developing a pipeline of oral small molecule CMAs. For more information, please visit www.rivuspharma.com.

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