Rivus Pharmaceuticals Announces Publication of Phase 2a HuMAIN Trial of HU6 in Patients with Obesity-Related Heart Failure in *JAMA Cardiology*

–Treatment with HU6 led to significant reductions in body fat and abdominal visceral fat while preserving skeletal muscle in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) –

– HU6, a novel, once-daily, oral therapy in Phase 2 clinical development, is a Controlled Metabolic Accelerator, a new class of investigational therapies designed to selectively reduce body fat while maintaining muscle mass –

CHARLOTTESVILLE, Va., and SOUTH SAN FRANCISCO, Calif., March 12, 2025 – Rivus Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company dedicated to treating cardiometabolic diseases driven by obesity, today announced the publication of results of the Phase 2a HuMAIN clinical trial of HU6 in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) in *JAMA Cardiology*. The study met the primary endpoint of reduction in body weight with HU6 compared to placebo over the 19-week period. This reduction was driven by decreases in fat mass and visceral fat while preserving lean mass, highlighting improved body composition with HU6. Overall rates of serious adverse events (AEs) and treatment discontinuation with HU6 were low.

HU6, a novel, once-daily, oral investigational medicine, is part of Rivus' portfolio of Controlled Metabolic Accelerators (CMAs). HU6, the company's lead program, increases metabolic rate in a controlled manner enabling sustained fat loss while preserving muscle mass, the primary engine of caloric utilization in the body. Excess body fat plays a key role in the underlying pathology of HFpEF, an increasingly common disorder that affects a growing population of patients for whom few effective treatments are available.

"I am excited to see the potential of HU6 in significantly reducing visceral adiposity and total body fat without affecting lean mass in patients with obesity and HFpEF," said Ambarish Pandey, M.D., a cardiologist, lead-author of the publication and member of the HuMAIN study Steering Committee. "As we know, visceral adiposity is causally implicated in the development and progression of HFpEF and having a therapy that can directly target this could be transformative in HFpEF treatment."

The published HuMAIN study results showed that HU6 resulted in a significantly greater reduction in body weight (-6.8 lbs vs -0.5 lbs, p=0.0026), total fat mass (-7.4 lbs vs. -0.88 lbs with placebo, p=0.0003), percent visceral fat (-1.5% vs. -0.2% with placebo, p=0.0028) and percent reduction in body fat percentage (-4.8% vs. -0.45% with placebo, p=0.0002) at 19 weeks compared with baseline. Other measures of body composition showed:

- No significant change in lean body mass or skeletal muscle mass with HU6 vs. placebo or with HU6 at 19 weeks compared with baseline. A reduction in abdominal visceral adipose tissue with HU6 vs. placebo (-0.19 L) in patients whose body composition was assessed by MRI.

Although this Phase 2a study was a short duration of 19 weeks, additional secondary endpoints were assessed to evaluate the impact of HU6 on a number of cardiac markers. The findings showed:

- Significant improvements from placebo in left ventricular systolic function (increased left ventricular ejection fraction [LVEF] of 3.76% and decreased left ventricular end-systolic volume of -5.64 ml) and right ventricular function (right ventricular systolic [RV S'] velocity of 2.10 cm/s) as assessed by echocardiography.
- Significant reductions from placebo in resting systolic blood pressure (-8.7 mm Hg) and diastolic blood pressure (-4.9 mm Hg), which was observed early and persisted throughout the study.
- No significant differences in changes in cardiac safety parameters in participants who underwent a cardiac MRI or in resting heart rate or respiratory rate.
- No significant difference was noted in peak exercise oxygen uptake between HU6 and placebo arms.

The safety profile of HU6 was consistent with previous studies. HU6 was well tolerated in study participants, who were on average elderly, obese, had multiple comorbidities, and were taking 15 concomitant medications. Overall rates of serious AEs were low. Four patients taking HU6 and one patient taking placebo experienced a serious AE, all of which were deemed unrelated to the study drug.

"Although HuMAIN was a small study of short duration powered only for a reduction in body weight, the significant improvements observed in body composition and cardiac and metabolic secondary endpoints are meaningful," said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. "These positive study results, especially the improvements in cardiac structure and function, suggest that HU6 could be the first disease-modifying treatment for HFpEF, a debilitating disorder associated with poor quality of life and physical limitations."

Data from HuMAIN study participants in the compliance population (i.e., those who complied with taking HU6 throughout the study based on a measure of a primary metabolite of HU6) are available on the Rivus website.

In addition to the Phase 2a HuMAIN study, Rivus is evaluating HU6 in the randomized, double-blind, placebo-controlled, parallel-group Phase 2 M-ACCEL trial (ClinicalTrials.gov: NCT05979779) in patients with MASH. The company remains on track to announce topline results from M-ACCEL in the second quarter of 2025.

About the Phase 2a HuMAIN Trial
The multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-escalation Phase 2a HuMAIN trial (ClinicalTrials.gov: NCT05284617) evaluated the efficacy and safety of oral HU6 in patients with chronic, stable obesity-related HFpEF. In the intention-to-treat (ITT)

population, 66 study participants were randomized to HU6 (starting at 150 mg/day and potentially up-titrated to 450 mg/day based on safety and tolerability) or placebo. Study participants were over age 30 (average of 64.5 years; range: 38 to 87 years) with a body mass index (BMI) ≥30 kg/m2 (average of 39.4 kg/m^2) and an average body weight of 110.9 kg (245 pounds). The primary efficacy endpoint was the change in body weight from baseline to Day 134 (19 weeks). The key secondary efficacy endpoint was the change in peak oxygen uptake (VO_2). Exploratory secondary endpoints included changes in body composition, 6-minute walk distance (6MWD), Kansas City Cardiomyopathy Questionnaire (KCCQ) score, N-terminal pro b-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (Hs-CRP) and safety/tolerability. HuMAIN was conducted at 14 clinical sites in the United States.

About Heart Failure with Preserved Ejection Fraction (HFpEF)
Heart failure with preserved ejection fraction (HFpEF) is a chronic debilitating syndrome characterized by severely reduced exercise capacity, which degrades quality of life. Obesity is a strong risk factor for HFpEF and key contributor to the increasing worldwide prevalence of this disorder, with as many as 80% of patients with HFpEF in Western countries either overweight or obese. Specifically, systemic inflammation generated by visceral fat deposits is believed to contribute significantly to the development and progression of HFpEF. Studies have shown that the five-year survival rate in the United States for people hospitalized with HFpEF was 24.3%. Weight loss approaches that involve dieting, bariatric surgery and GLP-1 agonists work by decreasing energy intake rather than by increasing energy expenditure. In addition to loss of fat, these approaches result in marked reductions in muscle mass, which can lead to impaired function in patients with HFpEF, who are typically elderly and frail and already have reduced muscle mass.

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, a novel, oral, once-daily investigational therapy, is Rivus' lead CMA. It is a purposely designed investigational oral small molecule that is intended to be a foundational monotherapy for cardiac, liver, diabetes and obesity indications. HU6 has been demonstrated to promote sustained body fat loss by imperceptibly increasing resting metabolism, which results in fat burn, while preserving muscle mass. The current clinical development of HU6 is focused on metabolic diseases with the most morbidity and greatest treatment needs: 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 400 patients have been treated with HU6 as part of the clinical development program.

Results of a Phase 2 metabolic study in patients with a high body mass index (BMI) and MASLD showed that once-daily HU6 significantly reduced liver fat content and body weight with no loss of lean muscle mass and improved key markers of systemic inflammation and metabolism.[1] HU6 was well tolerated in this trial; side effects were mainly mild or moderate in severity. Results from the Phase 2a HuMAIN study (ClinicalTrials.gov: NCT05284617) of HU6 in patients with obesity-related HFpEF showed the trial met its primary endpoint, demonstrating that treatment with HU6 resulted in statistically significant weight loss. The rationale for the use of HU6 in HFpEF and the design of the HuMAIN trial were published in the European Journal of Heart Failure in June 2024.[2]

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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2. Kitzman DW, Lewis GD, Pandey A, et al. A novel controlled metabolic accelerator for the treatment of obesity-related heart failure with preserved ejection fraction: Rationale and design of the Phase 2a HuMAIN trial. *Eur J Heart Fail*. June 26, 2024.