Rivus Pharmaceuticals' Phase 2a HuMAIN Trial Meets Primary Endpoint of Weight Loss and Secondary Endpoints in Patients with Obesity-Related Heart Failure

– Data from the HuMAIN study in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) will be presented in a Late Breaking Clinical Trial Plenary Session at the Heart Failure Society of America Annual Scientific Meeting –

– Enrollment completed in Phase 2 M-ACCEL trial of HU6 in patients with metabolic dysfunction-associated steatohepatitis (MASH) –

– HU6, a novel oral, once-daily Controlled Metabolic Accelerator, is a new class of investigational therapies designed to reduce body fat while preserving muscle –

CHARLOTTESVILLE, Va., and SAN FRANCISCO, Ca., August 13, 2024 – Rivus Pharmaceuticals Inc., a clinical-stage biopharmaceutical company dedicated to improving metabolic health, today announced its Phase 2a HuMAIN clinical trial of HU6 in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) met its primary endpoint of weight reduction. HU6, an oral, once-daily potentially first-in-class investigational treatment, is a Controlled Metabolic Accelerator (CMA), which is designed to promote sustained body fat loss while preserving muscle mass. Treatment with HU6 resulted in a statistically significant weight reduction. Data from the HuMAIN study will be presented in a Late Breaking Clinical Trial Plenary Session at the Heart Failure Society of America (HFSA) Annual Scientific Meeting, taking place September 27-30, 2024, in Atlanta.

"Inflammation caused by visceral fat is an important driver of obesity-related HFpEF, and reductions in body fat have been shown to lead to improved outcomes in patients. The goal is to reduce body fat while preserving lean muscle mass, especially in this often fragile and elderly patient population," said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. "We believe that the HuMAIN data strongly supports the potential of HU6 to be the first disease-modifying treatment for HFpEF by enabling fat-specific weight loss while preserving muscle, reinforcing the possibility for it to be used in a broad range of cardiometabolic diseases with significant morbidity and limited treatment options."

In addition to meeting the primary endpoint, the HuMAIN study met several secondary efficacy and pharmacodynamic endpoints. The profile of HU6 was consistent with previous studies. HU6 was well tolerated, with a favorable safety profile, in a population of patients who had multiple co-morbidities and were on numerous concomitant medications. The rationale for the use of HU6 in HFpEF and the design of the HuMAIN study were recently published in the European

Journal of Heart Failure.[1] Rivus remains on track to engage health authorities for a Phase 3 study in obesity-related HFpEF in 2025.

Additionally, Rivus has completed patient enrollment in the Phase 2 M-ACCEL trial of HU6 in patients with metabolic dysfunction-associated steatohepatitis (MASH). Rivus remains on track to announce topline results from the M-ACCEL study in the first half of 2025.

To date, more than 400 patients have been treated as part of Rivus' HU6 clinical development program.

About the Phase 2a HuMAIN Trial
The randomized, double-blind, placebo-controlled, parallel-group, dose-escalation Phase 2a HuMAIN trial (ClinicalTrials.gov: NCT05284617) evaluates the safety, tolerability, pharmacodynamics and pharmacokinetics of ascending doses of HU6 (150 mg, 300 mg, 450 mg daily) in patients with obesity-related HFpEF. A total of 66 study participants (38 women and 28 men) age 30 or older with a body mass index (BMI) ≥30 kg/m2 were randomized to 134 days of daily dosing with HU6 or placebo.

The primary efficacy endpoint is weight reduction (as measured by the change from baseline in body weight at Day 134). Secondary endpoints including improvements in exercise capacity, quality of life measures, changes in body composition and cardiac function/structure, and markers of cardiometabolic dysfunction (e.g., changes in blood pressure and pulse, glucose control, inflammation, lipid levels and liver enzymes) are also being evaluated. HuMAIN was conducted at 22 clinical sites in the United States. The HuMAIN trial design and rationale were recently published in the European Journal of Heart Failure.

About HFpEF
HFpEF is a chronic debilitating syndrome characterized by severely reduced exercise capacity, which degrades quality of life. Obesity is a major independent 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. The average survival rate for patients with HFpEF who are hospitalized is about two years. 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 the Phase 2 M-ACCEL Trial
The randomized, double-blind, placebo-controlled, parallel-group Phase 2 M-ACCEL trial (ClinicalTrials.gov: NCT05979779) is evaluating 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 is 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 are 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 will also evaluate safety, tolerability, pharmacodynamics and pharmacokinetics. The study is being conducted at approximately 20 clinical sites in the United States.

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. CMAs are oral small molecules designed to increase resting metabolic rate, which results in increased consumption of energy, primarily from fat. The loss in fat mass addresses multiple cardiometabolic conditions driven by adiposity. CMAs increase metabolism in a continuous and imperceptible manner by leveraging the natural metabolic process of mitochondrial uncoupling. Uncoupling accounts for 20%-40% of resting caloric consumption. A key advantage of this mechanism for increasing energy expenditure is that the resulting weight loss is fat selective with preservation of muscle mass. In contrast, caloric-restriction strategies reduce energy input and result in loss of fat as well as muscle mass. Initial data in humans has demonstrated that CMAs provided fat-selective weight loss, improved insulin sensitivity, and a significant reduction in oxidative stress and inflammation.

About HU6
HU6, an 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 is designed to promote sustained body fat loss by gently, safely and imperceptibly increasing resting metabolism, which results in fat burn, while preserving muscle mass. Phase 2 results in patients with a high body mass index (BMI) and metabolic dysfunction-associated steatotic liver disease (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.[2] HU6 was well tolerated in these trials; side effects were mainly mild or moderate in severity.

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)/MASLD.

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 development to treat obesity-related heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) and Type 2 diabetes. For more information, please visit www.rivuspharma.com.

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References

1. 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.
2. Noureddin M, Khan S, Portell F, et al. Safety and efficacy of once-daily HU6 versus placebo in people with non-alcoholic fatty liver disease and high BMI: a randomised, double-blind, placebo-controlled phase 2a trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1094-1105.