Rivus Pharmaceuticals Announces Publication of Phase 2a HuMAIN Trial Rationale and Design in European Journal of Heart Failure

– Study evaluating HU6 in patients with obesity-related heart failure with preserved ejection fraction is on track to report topline data in the second half of 2024 –

– HU6, a novel Controlled Metabolic Accelerator, is a new class of investigational medicines designed to reduce weight while preserving muscle –

CHARLOTTESVILLE, Va., and SAN FRANCISCO, June 26, 2024 – Rivus Pharmaceuticals Inc., a clinical-stage biopharmaceutical company dedicated to improving metabolic health, today announced publication of the rationale and design of the company's Phase 2a HuMAIN trial in the European Journal of Heart Failure. Rivus has completed patient enrollment in this clinical trial of HU6, an investigational Controlled Metabolic Accelerator (CMA), in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) and expects to report topline data in the second half of 2024.

"HuMAIN is the first clinical trial to evaluate the effects of a CMA in patients with obesity-related HFpEF, who have a median survival rate of around two years following hospitalization," said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. "HU6 has the potential to be the first disease-modifying treatment for HFpEF. We look forward to further evaluating the potential benefits of HU6 in this large and growing patient population and sharing topline results in the second half of 2024."

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. 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.

"Given the limitations of current options for patients with obesity-related HFpEF, novel disease-modifying treatments are urgently needed," said Dalane W. Kitzman, M.D., lead author of the publication and professor of internal medicine and cardiovascular medicine at Wake Forest University School of Medicine. "As detailed in this new publication, HU6 reduces fat, which is pivotal to the development of HFpEF, by increasing energy expenditure while preserving muscle. The Phase 2a trial will examine HU6's potential to improve key outcomes in HFpEF,

including increasing exercise capacity and quality of life, reducing systemic inflammation, and improving blood pressure and glucose metabolism."

About the Phase 2a HuMAIN Trial
The randomized, double-blind, placebo-controlled, parallel-group, dose-escalation Phase 2a HuMAIN study (ClinicalTrials.gov: NCT05284617) is evaluating 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 65 study participants (37 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). The key secondary efficacy endpoint is exercise capacity (as measured by the change from baseline in peak VO_2 [mL/kg/min] during a standardized, noninvasive cardiopulmonary exercise test at Day 134). The effects of HU6 on disease-specific quality of life, 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 fat and liver enzymes) are also being evaluated. The study is designed to identify the optimal dose of HU6 for Phase 3 trials. HuMAIN is being conducted at 22 clinical sites in the United States.

About Controlled Metabolic Accelerators (CMAs)
Rivus is advancing a new class of investigational medicines 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 provide fat-selective weight loss, improved insulin sensitivity, and a significant reduction in oxidative stress and inflammation.

About HU6
HU6, an oral, once-daily investigational medicine, 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 promotes sustained weight 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.[1] HU6 was well tolerated; 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: 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 medicines called Controlled Metabolic Accelerators (CMAs). Rivus' lead CMA is the investigational small molecule HU6 in development to treat 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. 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.