Rivus Pharmaceuticals to Present New Data from Phase 2a HuMAIN Trial of HU6 for the Treatment of Obesity-Related Heart Failure with Preserved Ejection Fraction at Heart Failure Society of America Annual Scientific Meeting 2024

– New data from the HuMAIN study, which met the primary endpoint of weight loss and several efficacy and pharmacodynamic secondary endpoints, will be presented in a Late Breaking Clinical Research Session –

– 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., September 23, 2024 – Rivus Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company dedicated to improving metabolic health, today announced it will present data from the Phase 2a HuMAIN clinical trial of HU6 in patients with obesity-related heart failure with preserved ejection fraction (HFpEF). The data will be shared during a Late Breaking Clinical Research Session at the Heart Failure Society of America (HFSA) Annual Scientific Meeting 2024, taking place September 27-30 at the Georgia World Congress Center in Atlanta.

The HuMAIN trial met its primary endpoint of significant weight reduction and several secondary efficacy and pharmacodynamic measures. 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. Rivus remains on track to engage health authorities to discuss the design of a Phase 3 study of HU6 in obesity-related HFpEF in 2025.

“The HuMAIN study showed that treatment with HU6 resulted in fat-specific weight loss while preserving muscle, an especially important consideration for patients with HFpEF, who often are older and fragile,” said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. “We are excited to share further data from this study at HFSA 2024 that support the potential of HU6 to be the first disease-modifying treatment for patients with HFpEF.”

Oral Presentation Details

Abstract #: 2287
Title: A Novel Controlled Metabolic Accelerator For The Treatment Of Obesity-related Heart Failure With Preserved Ejection Fraction: Humain-hfpef Trial
Presenting Author: Ambarish Pandey, M.D., associate professor, Department of Internal Medicine, UT Southwestern Medical Center, Dallas
Session Title: Monday Plenary Session: Late Breaking Clinical Research Session II
Presentation Date/Time: Monday, September 30, 2024, 10:08 a.m.

Location: Georgia World Congress Center, Signia by Hilton, Atlanta, GA

Rivus previously announced that the HuMAIN study met its primary endpoint of weight reduction, with HU6 treatment resulting in a statistically significant weight reduction. The study also met several key secondary efficacy and pharmacodynamic endpoints. The profile of HU6 was consistent with previous studies. HU6 was generally well tolerated 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]

About the Phase 2a HuMAIN Trial
The randomized, double-blind, placebo-controlled, parallel-group, dose-escalation Phase 2a HuMAIN trial (ClinicalTrials.gov: NCT05284617) evaluated 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 was 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) were also 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 Heart Failure with Preserved Ejection Fraction
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 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 Controlled Metabolic Accelerators
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.