Rivus Pharmaceuticals Announces New Clinical Data from Phase 2a HuMAIN Trial Demonstrating Significant Weight Loss with HU6 in Patients with Obesity-Related Heart Failure

– Results from the placebo-controlled study in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) were presented in a Late Breaking Clinical Trial Plenary Session at the HFSA Annual Scientific Meeting 2024 –

– Data showed patients treated with HU6 experienced fat-selective weight loss, reductions in visceral fat, no changes in lean body mass, and a trend toward a reduction in inflammation; HU6 was also generally well tolerated by this often-frail patient population with advanced disease –

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

CHARLOTTESVILLE, Va., and SAN FRANCISCO, September 30, 2024 – Rivus Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company dedicated to improving metabolic health, today announced new clinical data from the Phase 2a HuMAIN study of HU6 in patients with obesity-related heart failure with preserved ejection fraction (HFpEF). The trial met its primary endpoint, demonstrating that treatment with HU6 resulted in statistically significant weight loss. The results were presented by Ambarish Pandey, M.D., a cardiologist and trial investigator, in a Late Breaking Clinical Trial Plenary Session at the Heart Failure Society of America (HFSA) Annual Scientific Meeting 2024 in Atlanta.

In addition to meeting the primary endpoint, the results demonstrated statistically significant reductions in fat mass and visceral fat, with no change in lean body mass after three months of treatment at the HU6 450 mg dose. There were also improvements in key secondary endpoints, including systolic and diastolic blood pressure, and key markers of atherosclerotic cardiovascular disease as well as in echo and MRI measures of cardiac structure and function. There was a trend toward improvement in inflammation in the intention-to-treat (ITT) population, with a 3 mg/L improvement in high sensitivity C-reactive protein (CRP) in the HU6-treated population versus placebo, as well as a trend toward improvement in the 6-minute walk distance (6MWD). HU6 was generally well tolerated, consistent with previous studies.

HU6, a novel, oral, once-daily, potentially first-in-class investigational treatment, is a Controlled Metabolic Accelerator (CMA), which promotes sustained body fat loss while preserving muscle mass.

“The Phase 2a HuMAIN results showing significant reductions in body fat and visceral fat in patients with obesity-related HFpEF, who typically have excess fat throughout their

cardiovascular system and systemic inflammation, are extremely promising given that the study participants had obesity, were older, with multiple medical conditions," said Dr. Pandey, a member of the HuMAIN study Steering Committee. "We were also encouraged to see the preservation of lean muscle mass, which is particularly important for older patients with HFpEF, who are often frail and have low muscle mass."

"With these new clinical data, which highly correlate to the results from our Phase 2 study in MASLD, we have now observed in different populations that HU6, a novel CMA, reduced fat mass and preserved lean body mass, which is especially beneficial in patients with HFpEF," said Jayson Dallas, M.D., chief executive officer, Rivus Pharmaceuticals. "The positive HuMAIN results support the potential differentiating profile of HU6 in HFpEF, which could be the first disease-modifying treatment for this debilitating syndrome. The findings also support advancing our HFpEF clinical program with HU6."

New Clinical Data from Phase 2a HuMAIN Trial

Results from the ITT population of 66 patients with obesity-related HFpEF showed the study met its primary endpoint. After three months, patients taking 450 mg of HU6 experienced significant weight loss from baseline (-6.8 pounds, $p<0.0001$) and significant weight loss compared with placebo-treated patients (-6.3 pounds, $p=0.003$).

Study results also demonstrated improvements with HU6 in secondary efficacy endpoints at three months:

- A significant reduction in fat mass loss from baseline with HU6 (-7.4 pounds, $p<0.0001$) and a significant reduction with HU6 compared with placebo (-6.5 pounds, $p=0.0003$)
- Fat selective weight loss, including a significant reduction in visceral fat from baseline with HU6 (-1.5%, $p<0.0001$) and a significant reduction with HU6 compared with placebo (-1.3%, $p=0.003$), and a trend toward reduction in epicardial fat with HU6 compared with placebo
- No significant reduction in lean body mass with HU6 from baseline or compared with placebo
- Reductions in systolic and diastolic blood pressure from baseline with HU6 (-8.8 mmHg, $p=0.0049$ and -4.1 mmHg, $p=0.0546$, respectively); these reductions occurred without a corresponding increase in heart rate with HU6 versus placebo
- Significant reductions in key markers of atherosclerotic cardiovascular disease from baseline with HU6, including apolipoprotein B, Lp(a) and total cholesterol (all $p<0.05$)
- Improvements in cardiac structure and function from baseline with HU6 versus placebo, including left ventricular mass measured by MRI ($p=0.082$) and left ventricular ejection fraction measured by echocardiography ($p=0.0007$)
- A significant decline in troponin levels, a marker of heart muscle damage, from baseline with HU6 (-84.94 ng/L, $p=0.0473$)
- A trend toward improvement in CRP and in the 6MWD

For 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), HU6 resulted in a significant reduction of 39% in CRP from baseline ($p=0.0238$).

In the ITT population, the safety profile of HU6 was consistent with previous studies. HU6 was well tolerated in the study participants, who were on average elderly, obese, had multiple co-morbidities and were taking an average of 15 concomitant medications. The most common treatment-emergent adverse events (TEAEs) with HU6 (affecting more than 10% of patients) were diarrhea, COVID-19 and dyspnea (shortness of breath). Most TEAEs were mild to moderate in severity. There were no treatment-related serious adverse events and no new or worsening cataracts, metabolic fevers, neutropenia or neuropathy in patients taking HU6.

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. In the ITT population, 66 study participants (38 women and 28 men) were randomized to 134 days of daily dosing with HU6 or placebo. Patients were age 30 or older (range: 38 to 87 years) with a body mass index (BMI) $\geq$30 kg/m2 (average of 39.4 kg/m^2) and an average weight of 245 pounds (range: 157 to 397 pounds).

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 15 clinical sites in the United States. 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.[1]

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. 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 this trial; 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. To date, more than 400 patients have been treated with HU6 as part of the clinical development program.

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 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. The study is being conducted at approximately 20 clinical sites in the United States. Rivus remains on track to announce topline results from M-ACCEL in the first half of 2025.

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. For more information, please visit www.rivuspharma.com.

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