CLOSER LOOK

MEMORANDUM

Rivus Pharmaceuticals announces topline results of phase 2 M-ACCEL trial of oral HU6 for liver fat reduction in MASH – June 25, 2025

Greater than 30% reduction in liver fat observed in the majority of patients; no significant change in lean body mass

Charlottesville, Virginia-based Rivus Pharmaceuticals announced yesterday positive topline results from its phase 2 M-ACCEL trial (n=219) of its leading drug candidate HU6 in people with metabolic dysfunction-associated steatohepatitis (MASH). Recall that MASH is characterized by the accumulation of fat in the liver, with high prevalence in at-risk populations. It is estimated that 16% of people with T2D have MASH, and approximately 34% of people with obesity. MASH may progress to fibrosis, cirrhosis, and hepatocellular carcinoma at highly variable rates, yet progression may be slowed by weight loss. HU6 is administered orally and is a controlled metabolic accelerator (CMA), a novel therapeutic class. The 26-week randomized, double-blind, placebo-controlled, parallel-group phase 2 M-ACCEL trial evaluated the efficacy and safety of HU6 in adults with MASH. The study achieved its primary endpoint of percent change from baseline in liver fat, assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF). The majority of patients achieved over 30% reduction in liver fat, representing a clinically meaningful result, with no significant change in lean mass at any dose. The therapy was well-tolerated with no treatment-related serious adverse events. The company plans to present trial results at an undisclosed upcoming medical meeting.

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Strong improvement achieved in liver fat, body weight, and A1c metrics

The 221 adult participants treated at 22 US clinical sites were randomized 2:1:2:2 into four treatment groups (placebo, HU6 150 mg, HU6 300 mg, and HU6 450 mg, respectively). Two-thirds of patients treated in the study had T2D at baseline. The efficacy of HU6 was similar in this population compared to those without T2D at baseline.

In addition to meeting positive primary endpoints, the study also met secondary endpoints, including reductions in body weight, visceral fat mass, blood pressure, and A1c. Statistical significance of these results was not assessed. Rivus interpreted these results as demonstrating the broad potential for HU6 to address systemic dysmetabolism contributing to MASH. The proportion of responders experiencing a greater than 30% reduction in liver fat also demonstrated statistical significance in all treatment groups.

The company reported fat-specific weight loss, with no significant change to lean mass at any dose. Three-quarters of fat loss was from the visceral fat compartment, which is associated with negative outcomes in overweight and obesity.

Novel CMA therapeutic class provides promise for obesity and related conditions

CMAs are small molecule therapies, also known as mitochondrial uncoupling agents, which increase resting metabolic rate and, therefore, energy consumption. Rivus said that the natural metabolic process of mitochondrial uncoupling, which accounts for 20-50% of daily energy expenditure, may be leveraged to reduce adipose tissue without a loss of muscle mass and while remaining imperceptible to patients. The company also reported fat-selective weight loss, improved insulin sensitivity, and overall reduced oxidative stress and inflammation because of CMA use.

Close Concerns' Questions + Answers from Rivus:

1. How might CMAs such as HU6 be used in combination with other therapeutics?

Rivus: Due to its novel mechanism of action, HU6 can be used in combination with other therapies, such as incretins like GLP-1 medications. Its use may be particularly attractive for patients who stopped treatment with a GLP-1 due to tolerability, ineffectiveness, cost or other reasons. HU6 also has the potential to be used as stand-alone treatment for obesity, liver, cardiac disease, and diabetes. HU6 offers a potential significant advantage over incretins based on its tolerability profile, fat specific weight loss, and ability to preserve muscle mass.

2. How do overall body weight loss results compare to liver fat reductions in HU6? Does the CMA drug class have a particular liver-directed effect?

   Rivus: We are continuing to analyze the data from the M-ACCEL study and look forward to sharing more detailed results on the positive impact of HU6 on weight loss and liver fat reduction at a future medical meeting. Excess weight, particularly abdominal fat, can lead to fat buildup in the liver, which is why reducing fat mass is particularly important. For patients with MASH, weight loss is considered an efficient treatment strategy to reduce liver fibrosis, as even moderate weight loss can benefit a patient's health by reducing fat levels in the liver. The M-ACCEL study demonstrated that HU6 achieved a statistically significant reduction in liver fat content (the primary endpoint of the trial) compared to placebo, with the majority of patients reaching more than a 30% reduction at all doses.

3. Does HU6 provide promise with respect to low manufacturing costs? Could HU6 eventually serve as an affordable weight-loss therapy?

   Rivus: It's too early to speculate what HU6 may cost if it becomes commercially available, but we do believe that manufacturing of an oral therapy may present an opportunity for cost effectiveness when compared to injectable delivery methods.

--by Nour Khachemoune, Esther Min, Monica Oxenreiter, and Kelly Close