

RESEARCH MONOGRAPH . COMPOUND PROFILE

HU6

A first-in-class controlled metabolic accelerator developed by Rivus Pharmaceuticals as a liver-targeted prodrug of 2,4-dinitrophenol, designed to exploit mitochondrial uncoupling for the treatment of metabolic dysfunction-associated steatohepatitis, obesity-related heart failure with preserved ejection fraction, and related cardiometabolic disorders while mitigating the systemic toxicity historically associated with the parent uncoupler.

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ABSTRACT

HU6 (dinifedriton; 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitroimidazole; CAS 2231311-68-3) is a first-in-class controlled metabolic accelerator (CMA) developed by Rivus Pharmaceuticals as an oral prodrug of the mitochondrial uncoupler 2,4-dinitrophenol (DNP). The compound is designed to undergo hepatic bioactivation to release DNP within the liver, thereby increasing proton leak across the inner mitochondrial membrane via activation of the adenine nucleotide translocase (ANT) channel. This controlled mitochondrial uncoupling increases substrate oxidation, preferentially consuming hepatic and systemic fat stores while reducing reactive oxygen species production and preserving lean skeletal muscle mass. The prodrug strategy addresses the principal limitation of DNP itself, which was withdrawn from clinical use in 1938 owing to a narrow therapeutic index characterized by dose-dependent hyperthermia, cataracts, agranulocytosis, and death at supratherapeutic exposures. By restricting DNP release to the hepatic first-pass compartment and minimizing systemic peak concentrations, HU6 achieves a substantially wider therapeutic index than the parent uncoupler while retaining its metabolic efficacy.

The scientific foundation for HU6 derives from the seminal work of Perry et al. (2015), published in *Science*, demonstrating that a controlled-release mitochondrial protonophore (CRMP) formulation of DNP reversed diabetes, hypertriglyceridemia, hepatic steatosis, and liver fibrosis in rat models of metabolic syndrome and nonalcoholic steatohepatitis (NASH) without systemic toxicity [1]. This proof of concept was extended to

dysmetabolic nonhuman primates by Goedeke et al. (2019), who reported that CRMP produced 20 to 30 percent reductions in fasting plasma triglycerides and low-density lipoprotein cholesterol with concurrent resolution of hepatic steatosis [2]. Rivus Pharmaceuticals was founded in 2019 to advance these findings into clinical development, selecting HU6 as the lead clinical candidate from a portfolio of controlled metabolic accelerator assets.

Three Phase 2 clinical trials have been completed or are in progress. The first Phase 2a trial in 80 patients with nonalcoholic fatty liver disease (NAFLD) and body mass index (BMI) of 28 to 45 kg/m² demonstrated dose-dependent reductions in liver fat content of 26.8 to 35.6 percent from baseline over 61 days at doses of 150, 300, and 450 mg once daily, compared with a 5.4 percent increase in the placebo group, with concurrent body weight reductions of 0.52 to 2.75 kg; results were published in *The Lancet Gastroenterology and Hepatology* [3]. The Phase 2a HuMAIN trial in 66 patients with obesity-related heart failure with preserved ejection fraction (HFpEF) met its primary endpoint of body weight reduction (2.86 kg versus placebo over 19 weeks), with fat-selective weight loss preserving skeletal muscle mass and producing significant improvements in left ventricular ejection fraction (3.76 percent) and end-systolic volume; results were published in *JAMA Cardiology* [4, 5]. The Phase 2 M-ACCEL trial in 228 patients with biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH) and fibrosis stages F2 to F3 demonstrated statistically significant liver fat reductions of 27.0 to 31.2 percent versus 6.7 percent with placebo over 26 weeks, with approximately 50 to 58 percent of treated patients achieving the clinically meaningful threshold of 30 percent or greater liver fat

reduction associated with MASH resolution and fibrosis improvement [6].

Across all three trials, HU6 demonstrated a favorable safety profile with no treatment-related serious adverse events in a cumulative safety database exceeding 500 patients. The most commonly reported treatment-emergent adverse events were flushing (32 percent in early trials, reduced in later formulations), diarrhea (25 percent), and palpitations (12 percent), with discontinuation rates due to adverse events below 5 percent. Gastrointestinal adverse event rates in the M-ACCEL trial were comparable to placebo (14 versus 16 percent). The compound is currently advancing through the AMPLIFY Phase 2 trial for MASH with plans for late-stage clinical development. This monograph reviews the chemistry, mechanism of action, pharmacokinetics, preclinical and clinical evidence, safety profile, and comparative positioning of HU6 against five alternative therapeutic approaches to MASH and metabolic liver disease.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name (proposed): Dinifedriton.

Development code: HU6 (Rivus Pharmaceuticals). The development code is the canonical identifier in the clinical pharmacology literature and in all completed and ongoing registration trials [3, 4, 5, 6].

Chemical Abstracts Service registry number: 2231311-68-3.

PubChem CID: 135205989.

ChemSpider ID: 128784125.

Unique Ingredient Identifier (UNII): 2U87AJU2ZZ (United States Food and Drug Administration Substance Registration System).

International Union of Pure and Applied Chemistry name: 5-[(2,4-dinitrophenoxy)methyl]-1-methyl-2-nitroimidazole.

1.2 Structural class and chemistry

HU6 is a nitroimidazole-linked prodrug of 2,4-dinitrophenol (DNP). The compound consists of a 1-methyl-2-nitroimidazole ring connected through a methylene ether linkage to the phenolic oxygen of 2,4-dinitrophenol. The nitroimidazole moiety serves as the prodrug carrier, providing metabolic stability during gastrointestinal absorption and enabling hepatic bioactivation through cytochrome P450-mediated cleavage of the ether bond, releasing DNP within the hepatocyte. The structural class places HU6 among the nitrobenzene derivatives and nitroimidazole compounds, with the critical distinction that it is not pharmacologically active in its intact form but functions exclusively as a delivery vehicle for the active metabolite DNP.

Molecular formula: C₁₁H₉N₅O₇.

Molecular weight: 323.22 g/mol.

Physical properties: The compound is supplied as a solid for oral formulation. Specific melting point, solubility, and optical rotation data have not been disclosed in published literature as of the most recent monograph revision, consistent with the investigational status of the compound and the proprietary nature of the formulation.

1.3 Synthesis

The synthetic route for HU6 has not been disclosed in full detail in peer-reviewed literature. The compound is proprietary to Rivus Pharmaceuticals and is manufactured under current Good Manufacturing Practice (cGMP) conditions for clinical supply. The general structural logic of the synthesis involves construction of the methylene ether linkage between the 1-methyl-2-nitroimidazole carrier and the phenolic oxygen of 2,4-dinitrophenol, a transformation achievable through standard Williamson ether synthesis or equivalent nucleophilic displacement chemistry. The 2,4-dinitrophenol starting material is a commodity chemical; the 1-methyl-2-nitroimidazole precursor is a known heterocycle accessible through established nitroimidazole chemistry. Patent literature associated with Rivus Pharmaceuticals (over 100 medical patents identified in public databases) likely discloses specific synthetic routes, purification methods, and polymorphic form characterization, but detailed synthetic review is beyond the scope of this compound profile [7].

2. Abstract

HU6 (dinifedriton) is an orally administered, liver-targeted prodrug of the mitochondrial uncoupler 2,4-dinitrophenol (DNP) that functions as a controlled metabolic accelerator (CMA) by increasing proton leak across the inner mitochondrial membrane via activation of the adenine nucleotide translocase (ANT) channel [1, 2, 3]. The compound represents a pharmacological strategy to harness the established metabolic effects of mitochondrial uncoupling (increased substrate oxidation, reduced hepatic lipid accumulation, decreased reactive oxygen species production) while avoiding the systemic toxicity that removed DNP from clinical use in 1938 [8, 9].

The therapeutic rationale is grounded in the observation that mitochondrial uncoupling accounts for approximately 20 to 40 percent of average daily energy expenditure under physiological conditions [10]. By augmenting this endogenous process in a controlled, liver-targeted manner, HU6 increases the oxidation of fat and other carbon substrates, producing fat-selective weight loss, reduction in hepatic steatosis, and improvements in systemic metabolic and inflammatory markers. The fat-selective mechanism distinguishes HU6 from appetite-suppression therapies (including GLP-1 receptor agonists), where approximately 25 to 40 percent of weight loss is attributable to lean mass including skeletal muscle [11].

Three Phase 2 clinical trials have demonstrated consistent efficacy across metabolic dysfunction-associated steatotic liver disease (MASLD), MASH with fibrosis, and obesity-related heart failure with preserved ejection fraction (HFpEF). The Phase 2a NAFLD trial (n = 80) reported liver fat reductions of 26.8 to 35.6 percent over 61 days [3]. The Phase 2a HuMAIN trial (n = 66) in HFpEF reported fat-selective weight loss of 2.86 kg versus placebo over 19 weeks with improvements in left ventricular systolic function [4, 5]. The Phase 2 M-ACCEL trial (n = 228) in MASH with F2-F3 fibrosis reported liver fat reductions of 27.0 to 31.2 percent versus 6.7 percent with placebo over 26 weeks, with 50 to 58 percent of patients achieving clinically meaningful responses [6]. In all three trials, weight loss was entirely fat-selective with preservation of skeletal muscle mass and approximately 2:1 selectivity for abdominal visceral versus subcutaneous fat.

The safety profile across more than 500 treated patients has been favorable, with no treatment-related serious adverse events. The compound is currently advancing through the AMPLIFY Phase 2 trial for MASH, with plans for late-stage development. Rivus Pharmaceuticals is additionally developing RV-8451, a non-peptide oral GLP-1 receptor agonist, as a potential combination partner designed to address both energy intake (through appetite suppression) and energy expenditure (through mitochondrial uncoupling).

3. Discovery and Development History

3.1 Historical context: 2,4-dinitrophenol

The pharmacological history of HU6 begins with 2,4-dinitrophenol (DNP), a substituted phenol first identified as a mitochondrial uncoupler by Loomis and Lipmann in 1948 [8]. DNP was used as an oral weight-loss agent in the United States from 1933 to 1938, during which period it produced substantial weight loss through increased basal metabolic rate. However, the therapeutic index was narrow: dose-dependent adverse effects included hyperthermia (potentially fatal), cataract formation, agranulocytosis, and peripheral neuropathy. Multiple deaths were reported, and the United States Food and Drug Administration classified DNP as "extremely dangerous and not fit for human consumption" under the newly enacted Federal Food, Drug, and Cosmetic Act of 1938. DNP has remained an unapproved substance since that date, although illicit use for weight loss has persisted and continues to produce sporadic fatalities in the 21st century [9].

Despite the clinical toxicity, the fundamental pharmacology of mitochondrial uncoupling remained of substantial scientific interest. The physiological process of regulated proton leak (uncoupling protein 1 in brown adipose tissue, uncoupling proteins 2 through 5 in other tissues, and the adenine nucleotide translocase across all mitochondria-bearing cells) accounts for 20 to 40 percent of basal metabolic rate and is a major determinant of energy expenditure, thermogenesis, and reactive oxygen species production [10]. The scientific question was whether the metabolic benefits of uncoupling could be achieved at doses below the threshold for systemic toxicity.

3.2 Controlled-release mitochondrial protonophore (CRMP)

The critical advance toward clinical translation was the demonstration by Perry et al. (2015) in *Science* that a controlled-release oral formulation of DNP (designated CRMP) could achieve hepatic mitochondrial uncoupling at doses that did not produce measurable systemic DNP concentrations or systemic toxicity in rats [1]. In a methionine/choline-deficient rat model of NASH and in Zucker diabetic fatty rats,

CRMP treatment reversed hypertriglyceridemia, insulin resistance, hepatic steatosis, diabetes, and liver fibrosis. Critically, chronic administration was not associated with hyperthermia, cataracts, or any of the systemic adverse effects that had ended DNP's clinical career in 1938. The mechanistic basis was that the controlled-release formulation restricted DNP absorption to the hepatic portal circulation, achieving therapeutic concentrations in hepatocytes while maintaining subtoxic systemic exposure.

This work was extended by Goedeke et al. (2019) in *Science Translational Medicine* to dysmetabolic nonhuman primates, where CRMP treatment produced 20 to 30 percent reductions in fasting plasma triglycerides and LDL cholesterol and reversed hepatic steatosis without systemic toxicity [2]. The nonhuman primate data provided the translational bridge to human clinical development and represented the most advanced preclinical validation of liver-targeted mitochondrial uncoupling as a therapeutic strategy for metabolic disease.

Gerald I. Shulman of the Yale School of Medicine was the senior investigator on both the Perry et al. and Goedeke et al. studies and is a co-inventor on associated intellectual property [1, 2].

3.3 Founding of Rivus Pharmaceuticals

Rivus Pharmaceuticals was founded in March 2019 by Allen Cunningham (President and Chief Executive Officer) and Shaharyar Khan (Chief Scientific Officer), who had previously established a mitochondrial therapeutics company with early-stage uncoupling programs [12]. The company was capitalized with a Series A investment from Longitude Capital and Medicxi, followed by a \$132 million Series B round that enabled advancement of HU6 into Phase 2 clinical trials. Rivus is headquartered in Charlottesville, Virginia.

HU6 was selected as the lead clinical candidate from a portfolio of controlled metabolic accelerator assets on the basis of its hepatic bioactivation profile, oral bioavailability, and therapeutic index in preclinical models. The compound advanced through Phase 1 ascending-dose studies demonstrating target engagement and dose-dependent increases in metabolic rate, followed by the Phase 2a, HuMAIN, and M-ACCEL trials described in subsequent sections.

3.4 Clinical development timeline

Phase 1 single ascending dose and multiple ascending dose studies established the safety, pharmacokinetic, and pharmacodynamic profile of HU6 in healthy volunteers [3]. The Phase 2a trial in NAFLD patients (NCT04874233) was initiated in 2021 and reported positive topline results in 2022, with full results published in *The Lancet Gastroenterology and Hepatology* in 2023 [3]. The Phase 2a HuMAIN trial in obesity-related HFpEF was designed and initiated in 2023, with the trial design published in the *European Journal of Heart Failure* in 2024 and full results published in *JAMA Cardiology* in 2025 [4, 5]. The Phase 2 M-ACCEL trial in MASH (approximately 228 patients in the modified intent-to-treat analysis) reported positive topline results in June 2025, with detailed data presented at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting in November 2025 as a late-breaker oral presentation [6]. The AMPLIFY Phase 2 trial in MASH is currently enrolling, with plans for late-stage clinical development.

4. Mechanism of Action

4.1 Mitochondrial uncoupling: physiological basis

Under normal oxidative phosphorylation, the electron transport chain pumps protons from the mitochondrial matrix into the intermembrane space, generating an electrochemical gradient (proton motive force) across the inner mitochondrial membrane. This gradient drives ATP synthesis through ATP synthase (Complex V). In coupled mitochondria, the rate of substrate oxidation is tightly linked to ATP demand through respiratory control.

Mitochondrial uncoupling refers to the dissipation of the proton motive force through pathways other than ATP synthase, allowing protons to re-enter the matrix without generating ATP. The energy of the proton gradient is instead released as heat. Physiological uncoupling occurs through uncoupling protein 1 (UCP1) in brown and beige adipose tissue (the basis of non-shivering thermogenesis), through UCPs 2 through 5 in various tissues, and through the adenine nucleotide translocase (ANT) in all mitochondria-bearing cells [10]. Under resting conditions, proton leak through these endogenous pathways accounts for approximately 20 to 40 percent of basal metabolic rate, making it the single largest non-ATP-linked component of energy expenditure.

4.2 HU6 prodrug activation and liver targeting

HU6 is administered orally and absorbed from the gastrointestinal tract in its intact prodrug form. The compound undergoes hepatic first-pass bioactivation, during which cytochrome P450-mediated metabolism cleaves the methylene ether linkage connecting the nitroimidazole carrier to the 2,4-dinitrophenol moiety, releasing active DNP within the hepatocyte [3, 7]. Because bioactivation occurs predominantly in the liver, hepatic DNP concentrations substantially exceed systemic concentrations. This liver-targeting property is the pharmacological basis for the improved therapeutic index relative to DNP itself: the liver receives therapeutic uncoupling concentrations while systemic tissues (brain, heart, skeletal muscle) are exposed to subtoxic levels.

The active metabolite DNP acts as a protonophore, a lipophilic weak acid that shuttles protons across the inner mitochondrial membrane in its protonated form, releasing the proton on the matrix side and returning to the intermembrane space in its deprotonated (anionic) form. The net effect is dissipation of the proton gradient and stimulation of compensatory substrate oxidation to maintain membrane potential. In the liver, this manifests as increased oxidation of hepatic triglycerides, free fatty acids, and glucose, directly reducing hepatic lipid stores [1, 2].

4.3 Adenine nucleotide translocase activation

The molecular target of DNP-mediated uncoupling in the context of HU6 is the adenine nucleotide translocase (ANT), the most abundant protein in the inner mitochondrial membrane. ANT functions physiologically as an ADP/ATP exchanger but also mediates a substantial fraction of basal proton leak. DNP activates the ANT-mediated proton leak pathway, increasing proton conductance in a dose-dependent manner [10]. This mechanism is distinct from UCP1-mediated uncoupling (which is restricted to brown and beige adipose tissue and is activated by free fatty acids and adrenergic signaling) and provides a tissue-ubiquitous target for metabolic acceleration.

4.4 Downstream metabolic consequences

The proximal consequence of hepatic mitochondrial uncoupling by HU6 is increased hepatic substrate oxidation. Fat (triglycerides, free fatty acids) and glucose are oxidized at accelerated rates to compensate for the dissipated proton gradient. The downstream metabolic consequences include:

Reduction in hepatic triglyceride content (hepatic steatosis), the primary pathological substrate of MASLD and MASH [1, 2, 3]. Reduction in hepatic lipotoxicity, oxidative stress, and inflammatory signaling pathways that drive progression from simple steatosis to steatohepatitis and fibrosis [6]. Reduction in systemic triglycerides and LDL cholesterol through increased hepatic clearance and oxidation of circulating lipids [2]. Improvement in hepatic and peripheral insulin sensitivity through reduction of hepatic diacylglycerol content and protein kinase C epsilon activation, the established mechanism linking hepatic lipid accumulation to insulin resistance [1]. Reduction in reactive oxygen species (ROS) production, as mild uncoupling reduces the mitochondrial membrane potential below the threshold at which electron transport chain complexes generate superoxide [1]. Preferential oxi-

dation of pathogenic adipose tissue (visceral fat) with preservation of skeletal muscle mass, reflecting the systemic redistribution of substrate utilization toward lipid oxidation [4, 5, 6].

4.5 Differentiation from appetite-suppression mechanisms

The HU6 mechanism operates on the energy expenditure side of the energy balance equation, increasing caloric consumption through substrate oxidation rather than reducing caloric intake through appetite suppression. This is a fundamental mechanistic distinction from GLP-1 receptor agonists (semaglutide, tirzepatide), which produce weight loss predominantly through reduced food intake. The clinical consequence is that HU6-mediated weight loss is fat-selective and muscle-preserving, whereas GLP-1 receptor agonist-mediated weight loss includes approximately 25 to 40 percent lean mass loss [11]. In the HuMAIN and M-ACCEL trials, body composition analysis confirmed that HU6 weight loss was entirely attributable to fat mass reduction with preservation of lean and skeletal muscle mass and approximately 2:1 selectivity for abdominal visceral fat versus subcutaneous fat [4, 5, 6].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

HU6 is administered orally as a once-daily solid dosage form. The compound is absorbed from the gastrointestinal tract in its intact prodrug form. Specific bioavailability data have not been disclosed in published literature, consistent with the investigational status of the compound and the proprietary nature of the pharmacokinetic characterization. Phase 1 ascending-dose studies established linear pharmacokinetics across the therapeutic dose range (150 to 450 mg) [3].

5.2 Distribution and metabolism

Following absorption, HU6 undergoes first-pass hepatic metabolism, releasing the active metabolite 2,4-dinitrophenol within the hepatocyte. The liver-first activation is the critical pharmacokinetic feature: hepatic DNP concentrations are substantially higher than systemic concentrations, providing the therapeutic index advantage over systemic DNP exposure [1, 2, 3]. Liver-specific metabolism of HU6 also increases DNP exposure in the liver relative to the oral dose, such that lower total doses are required to achieve therapeutic hepatic uncoupling compared to what would be needed with systemic DNP administration.

The parent compound (intact HU6) has a pharmacokinetic profile consistent with a liver-extracted prodrug: high hepatic extraction, rapid hepatic metabolism, and low systemic exposure of the intact form. The active metabolite DNP is further metabolized through hepatic conjugation pathways (glucuronidation, sulfation) and excreted renally.

5.3 Elimination

Detailed elimination pharmacokinetics (terminal half-life, renal clearance, fecal excretion) have not been disclosed in published literature. The once-daily dosing regimen employed in all Phase 2 trials is consistent with a pharmacodynamic duration

of effect sufficient for sustained hepatic uncoupling across the 24-hour dosing interval [3, 4, 5, 6].

5.4 Routes of administration

HU6 is administered exclusively by the oral route. All clinical trials have employed once-daily oral dosing at 150, 300, or 450 mg. No parenteral, intravenous, or alternative-route formulations have been described.

5.5 Special populations

Specific pharmacokinetic studies in renal impairment, hepatic impairment, pediatric, and geriatric populations have not been disclosed in published literature. The Phase 2a NAFLD trial enrolled patients aged 28 to 65 years with BMI 28 to 45 kg/m² [3]. The HuMAIN trial enrolled patients with obesity-related HFpEF [4, 5]. The M-ACCEL trial enrolled patients with biopsy-confirmed MASH and fibrosis stages F2 to F3 [6]. Approximately two-thirds of M-ACCEL patients had type 2 diabetes at baseline, and efficacy was similar between diabetic and non-diabetic subgroups [6].

6. Preclinical Pharmacology

6.1 Rat models of metabolic syndrome and NASH

The foundational preclinical evidence was the Perry et al. (2015) demonstration in *Science* that controlled-release DNP (CRMP) reversed multiple features of metabolic syndrome in rat models [1]. In Zucker diabetic fatty rats, CRMP treatment reduced hypertriglyceridemia, improved insulin sensitivity, and resolved hepatic steatosis. In a methionine/choline-deficient rat model of NASH, CRMP normalized plasma transaminase concentrations, ameliorated liver fibrosis (histological scoring), and improved hepatic protein synthetic function. Chronic treatment was not associated with hyperthermia, changes in core body temperature, cataracts, or any systemic toxicity attributable to DNP.

The mechanistic studies within the Perry et al. report demonstrated that CRMP increased hepatic mitochondrial fat oxidation rates (measured by palmitate oxidation in isolated hepatic mitochondria), reduced hepatic diacylglycerol and ceramide content (the lipid intermediates that mediate hepatic insulin resistance through protein kinase C epsilon activation), and reduced hepatic reactive oxygen species production [1]. These mechanistic data established the causal chain from mitochondrial uncoupling through lipid oxidation to disease reversal.

6.2 Nonhuman primate studies

Goedeke et al. (2019) in *Science Translational Medicine* extended the CRMP proof of concept to dysmetabolic nonhuman primates, a translational model with greater pharmacokinetic and metabolic similarity to humans than rodent models [2]. CRMP treatment produced 20 to 30 percent reductions in fasting plasma triglycerides and LDL cholesterol, resolved hepatic steatosis by magnetic resonance spectroscopy, and improved insulin sensitivity. No systemic toxicity, hyperthermia, or ophthalmologic findings were observed. The nonhuman primate data provided the critical translational bridge for human clinical development and confirmed that the liver-targeting strategy was maintained across species with substantially different metabolic rates and hepatic enzyme activities.

6.3 DIAMOND mouse model of NASH

Additional preclinical work has demonstrated that HU6 (the clinical candidate, not the earlier CRMP formulation) reduces hepatic oxidative stress in the DIAMOND mouse model of NASH, abrogating NASH development [13]. The DIAMOND model recapitulates the progression from steatosis through steatohepatitis to fibrosis observed in human disease and is considered among the more translationally relevant murine NASH models. The finding that HU6 prevented NASH development (not merely reversed established disease) supports a potential disease-modifying role in early metabolic liver disease.

7. Clinical Evidence Base

7.1 Phase 1 studies

Phase 1 single ascending dose and multiple ascending dose studies in healthy volunteers established the safety, tolerability, pharmacokinetic, and pharmacodynamic profile of HU6 [3]. The studies demonstrated dose-proportional pharmacokinetics across the tested dose range, target engagement (as measured by increases in metabolic rate), and an adverse-event profile consistent with mild mitochondrial uncoupling (transient flushing, mild gastrointestinal effects). No serious adverse events or dose-limiting toxicities were reported. Specific numerical pharmacokinetic parameters from Phase 1 have not been disclosed in published peer-reviewed literature.

7.2 Phase 2a NAFLD trial (NCT04874233)

The first Phase 2a trial was a 61-day randomized, double-blind, placebo-controlled study evaluating once-daily HU6 at 150, 300, and 450 mg in 80 patients with NAFLD (defined as liver fat content greater than 8 percent by magnetic resonance imaging proton density fat fraction, MRI-PDFF), BMI 28 to 45 kg/m², and age 28 to 65 years [3].

Primary endpoint: Change in liver fat content from baseline to day 61 by MRI-PDFF.

Results: Participants treated with HU6 150 mg, 300 mg, and 450 mg experienced mean changes in liver fat content of -26.8 percent, -35.6 percent, and -33.0 percent from baseline, respectively, compared with a +5.4 percent change (increase) among those treated with placebo. All three dose groups achieved statistically significant separation from placebo.

Secondary endpoints: HU6 reduced total body weight by 0.52 to 2.75 kg across the dose groups, with weight loss attributable to fat mass reduction and preservation of lean mass. Improvements in metabolic markers (fasting triglycerides, liver enzymes) and systemic inflammatory markers were observed.

Safety: HU6 was well tolerated at all dose levels with no serious adverse events. The most commonly reported treatment-emergent adverse events were intermittent diarrhea and transient flushing. Discontinuation due to adverse events was below 5 percent. Results were published in The Lancet Gastroenterology and Hepatology [3].

7.3 Phase 2a HuMAIN trial (HFpEF)

The HuMAIN trial was a Phase 2a randomized, double-blind, placebo-controlled study evaluating HU6 in 66 patients with obesity-related heart failure with preserved ejection fraction (HFpEF) over 19 weeks [4, 5]. The trial rationale was that excess adipose tissue contributes directly to the pathophysiology of obesity-related HFpEF through increased cardiac loading, systemic inflammation, and metabolic dysfunction. A therapy that selectively reduces pathogenic adipose tissue while preserving lean mass could address the underlying disease mechanism rather than the symptoms alone.

Primary endpoint: Change in body weight from baseline to week 19.

Results: Treatment with HU6 produced a statistically significant weight reduction of 2.86 kg versus placebo. Body composition analysis confirmed that weight loss was entirely fat-selective, with preserved lean and skeletal muscle mass. Fat loss showed approximately 2:1 selectivity for abdominal visceral versus subcutaneous fat.

Cardiac endpoints: Significant improvements were observed in left ventricular systolic function, including an increase in left ventricular ejection fraction of 3.76 percent and a decrease in left ventricular end-systolic volume of 5.64 mL compared with placebo [5].

Safety: HU6 was well tolerated with no treatment-related serious adverse events. Results were published in JAMA Cardiology [5]. The trial design was published in the European Journal of Heart Failure [4].

7.4 Phase 2 M-ACCEL trial (MASH)

The M-ACCEL trial was a Phase 2 randomized, double-blind, placebo-controlled, parallel-group study evaluating HU6 at 150, 300, and 450 mg once daily over 26 weeks in approximately 228 patients (modified intent-to-treat analysis) with biopsy-

confirmed MASH and liver fibrosis stages F2 to F3, liver fat greater than 8 percent by MRI-PDFF, and vibration-controlled transient elastography (VCTE) score of 7 to 15 kPa [6].

Primary endpoint: Change in liver fat content from baseline to 6 months by MRI-PDFF.

Results: HU6 demonstrated statistically significant reductions in liver fat compared with placebo: least-squares mean differences of -29.4 percent (150 mg), -31.2 percent (300 mg), and -27.0 percent (450 mg) versus -6.7 percent with placebo ($p < 0.005$ for all treatment groups versus placebo). Responder analysis showed that approximately 57 percent (150 mg), 58 percent (300 mg), and 50 percent (450 mg) of patients achieved 30 percent or greater liver fat reduction, compared with 22 percent of placebo patients ($p < 0.005$ for all treatment groups). This threshold is a clinically meaningful result associated with MASH resolution and fibrosis improvement in longitudinal studies [6].

Body composition: Body weight was significantly reduced at the 300 mg and 450 mg doses. The 450 mg group showed a mean total body weight reduction of 2.4 percent (2.6 kg). Weight loss was entirely fat-selective with preserved lean and skeletal muscle mass and approximately 2:1 selectivity for abdominal visceral versus subcutaneous fat.

Subgroup analysis: Efficacy was similar between diabetic and non-diabetic patients. Approximately two-thirds of enrolled patients had type 2 diabetes at baseline.

Safety: No treatment-related serious adverse events were reported. Gastrointestinal adverse events occurred in 14 percent of HU6-treated patients versus 16 percent of placebo-treated patients. Discontinuation due to adverse events was below 5 percent. Topline results were announced in June 2025, with detailed data presented as a late-breaker oral presentation at AASLD The Liver Meeting in November 2025 [6].

7.5 Ongoing and planned trials

The AMPLIFY Phase 2 trial in MASH is currently enrolling, representing an extension of the M-ACCEL program with longer treatment duration and additional histological endpoints. Plans for late-stage (Phase 3) clinical development have been an-

nounced but specific trial designs have not been publicly disclosed as of the most recent monograph revision. Over 500 patients have been treated with HU6 across all clinical trials [6].

8. Sourcing and Quality Verification

HU6 is an investigational compound that is not commercially available. The compound is manufactured by Rivus Pharmaceuticals under cGMP conditions for clinical trial supply. There is no pharmaceutical-grade commercial product, no generic competition, and no research-grade supply from independent chemical vendors as of the most recent monograph revision.

Investigators seeking to study HU6 or its mechanism must either participate in Rivus-sponsored clinical trials or use surrogate compounds that share the mitochondrial uncoupling mechanism. Surrogate options include:

Research-grade 2,4-dinitrophenol (DNP), which is available from multiple chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical) at greater than 98 percent purity for in vitro and preclinical in vivo research. DNP is the active metabolite of HU6 and is appropriate for mechanistic studies, though it lacks the liver-targeting pharmacokinetic properties of the intact prodrug. DNP must be handled with appropriate precautions owing to its narrow therapeutic index in vivo and its classification as a hazardous substance.

BAM15, a selective mitochondrial uncoupler available from research suppliers, is an alternative mechanistic tool compound for in vitro and preclinical uncoupling studies. BAM15 has a different mechanism of selectivity (preferential action in lipid-rich tissues) and does not require hepatic bioactivation [14].

FCCP (carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone), a classical mitochondrial uncoupler used extensively in bioenergetics research, is available from standard suppliers but has substantial cytotoxicity and poor in vivo pharmacokinetics.

Investigators should note that none of these surrogate compounds replicate the liver-targeted pharmacokinetic profile of HU6 and that in vivo results with surrogate uncouplers may not predict HU6 clinical outcomes.

9. Reconstitution and Handling

HU6 is supplied in clinical trials as an oral solid dosage form (capsule or tablet formulation; specific formulation details have not been publicly disclosed). The compound does not require reconstitution for clinical use.

For research applications using the active metabolite DNP or surrogate uncouplers:

2,4-Dinitrophenol is supplied as a yellow crystalline solid. Stock solutions are typically prepared at 10 to 100 mM in dimethyl sulfoxide (DMSO) or ethanol for in vitro applications. Aqueous solubility of DNP is moderate (approximately 5.6 g/L at 20 degrees Celsius). Stock solutions should be stored at -20 degrees Celsius, protected from light, and used within 6 months of preparation. Working dilutions in cell culture media or physiological buffers should be prepared fresh.

BAM15 is supplied as a solid and is soluble in DMSO (stock concentration typically 10 to 50 mM). Storage at -20 degrees Celsius in sealed, desiccated containers is recommended.

For all mitochondrial uncouplers, investigators should be aware that these compounds have steep dose-response curves and that excessive concentrations in vitro will produce cytotoxicity through complete dissipation of the mitochondrial membrane potential. Dose-response characterization with appropriate viability controls is essential for any in vitro uncoupling study.

10. Stack Interactions and Combinations

HU6 has not been studied in formal drug-drug interaction trials in published literature. However, the following pharmacological interactions are anticipated or have been noted in clinical trial contexts:

CYP enzyme interactions: HU6 is metabolized hepatically through cytochrome P450 pathways. Specific CYP isoform identification (which CYP enzymes activate the prodrug, which metabolize the released DNP) has not been disclosed. Strong CYP inhibitors or inducers could theoretically alter the rate of prodrug activation and the systemic-to-hepatic ratio of DNP exposure, potentially affecting both efficacy and safety. Investigators should exercise caution with concurrent strong CYP inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin) and inducers (rifampin, carbamazepine, phenytoin) until formal interaction data are available.

GLP-1 receptor agonists: The combination of HU6 with GLP-1 receptor agonists (semaglutide, tirzepatide, liraglutide) is of particular clinical interest because the two mechanisms are complementary: GLP-1 agonists reduce energy intake through appetite suppression while HU6 increases energy expenditure through mitochondrial uncoupling. In the M-ACCEL trial, efficacy was similar between diabetic and non-diabetic patients, many of whom were on stable GLP-1 or SGLT2 inhibitor therapy [6]. Rivus Pharmaceuticals is developing RV-8451, a non-peptide oral GLP-1 agonist, as a potential combination partner for HU6, explicitly targeting both sides of the energy balance equation [12].

Thyroid hormone receptor agonists: Resmetirom (Rezdiffra), a selective thyroid hormone receptor-beta agonist approved for MASH, also increases hepatic lipid metabolism and mitochondrial function through a distinct mechanism [15]. The combination of HU6 and resmetirom has not been studied but could produce additive or synergistic effects on hepatic fat reduction. Theoretical concerns include excessive hepatic metabolic stimulation and hyperthyroid-like effects; formal interaction studies would be needed.

Insulin and oral hypoglycemic agents: HU6 improves insulin sensitivity through reduction of hepatic lipid intermediates that cause insulin resistance. In patients on insulin or sulfonylurea therapy, improved insulin sensitivity could increase the risk of hypoglycemia. The M-ACCEL trial enrolled patients on stable diabetes therapy without requiring dose adjustment, and no significant hypoglycemia signals were reported [6].

Thermogenic agents: Concurrent use with other thermogenic or metabolic-rate-increasing agents (thyroid hormones, sympathomimetics, other mitochondrial uncouplers) could theoretically produce additive increases in energy expenditure and body temperature. Although HU6 has not produced clinically significant hyperthermia at studied doses, combination with additional thermogenic agents should be approached with caution.

Hepatotoxic agents: Concurrent use with known hepatotoxic medications (acetaminophen at high doses, methotrexate, certain statins) warrants monitoring, as the liver is both the site of HU6 activation and the primary target organ for therapeutic effect.

11. Adverse Events and Safety

11.1 Common adverse events

The adverse-event profile of HU6 has been characterized across three Phase 2 clinical trials encompassing more than 500 treated patients [3, 4, 5, 6].

In the Phase 2a NAFLD trial (n = 80, 61 days), the most frequently reported treatment-emergent adverse events were flushing (approximately 32 percent), diarrhea (approximately 25 percent), and palpitations (approximately 12 percent) [3]. The flushing is attributed to the vasodilatory effect of DNP metabolite on cutaneous vasculature and is typically transient, self-limiting, and mild in severity. Diarrhea is attributed to the local effect of uncoupling on intestinal epithelial energy metabolism and was generally mild and intermittent.

In the Phase 2 M-ACCEL trial (n = 228, 26 weeks), the adverse-event profile improved substantially: gastrointestinal disorders occurred in 14 percent of HU6-treated patients versus 16 percent of placebo-treated patients, indicating that gastrointestinal effects were not clearly attributable to study drug at the tested doses and durations [6]. The reduction in flushing and gastrointestinal event rates between the earlier and later trials may reflect formulation optimization and patient selection.

Discontinuation due to adverse events was below 5 percent across all three trials.

11.2 Serious adverse events

No treatment-related serious adverse events have been reported across the cumulative clinical database of more than 500 patients [6]. This safety record is notable given the historical toxicity of the parent compound DNP and represents the principal evidence that the prodrug liver-targeting strategy has achieved its design objective of separating therapeutic efficacy from systemic toxicity.

11.3 DNP-related safety considerations

The principal safety concern with any DNP-based therapeutic is the risk of systemic uncoupling leading to hyperthermia, the mechanism by which DNP produced fatalities in the 1930s [8, 9]. The HU6 prodrug strategy addresses this concern through liver-targeted activation that limits systemic DNP exposure. Across all completed clinical trials, no cases of clinically significant hyperthermia have been reported with HU6. However, the theoretical risk remains relevant at supratherapeutic doses or in the setting of impaired hepatic function (which could alter the systemic-to-hepatic DNP exposure ratio), and long-term safety monitoring for temperature-related adverse events should continue through late-stage development.

A Lancet Gastroenterology and Hepatology editorial commentary noted that flushing, which occurred in approximately 32 percent of patients in the Phase 2a NAFLD trial, may represent a clinically relevant biomarker of systemic DNP exposure and warrants continued monitoring as a potential harbinger of dose-dependent systemic uncoupling effects [16].

Cataract formation, a known complication of chronic DNP exposure in the 1930s literature, has not been reported in any HU6 clinical trial. However, the treatment durations studied to date (61 days to 26 weeks) may not be sufficient to detect this delayed adverse effect, and ophthalmologic monitoring in long-term studies is appropriate.

11.4 Cardiovascular safety

No clinically significant cardiovascular adverse events have been reported with HU6. In the HuMAIN trial, cardiac imaging showed favorable changes including increased left ventricular ejection fraction and decreased end-systolic volume [5]. Palpitations were reported in approximately 12 percent of patients in the Phase 2a NAFLD trial but were transient and did not require intervention or discontinuation [3].

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative therapeutic approaches against HU6, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected to represent the principal pharmacological classes under development or approved for MASH and metabolic liver disease, providing context for the positioning of HU6 within the evolving therapeutic landscape.

12.1 Resmetirom (Rezdiffra; Madrigal Pharmaceuticals)

Mechanism: Selective thyroid hormone receptor-beta (THR-beta) agonist. Liver-directed oral agent that increases hepatic lipid metabolism, fatty acid oxidation, and mitochondrial function through activation of the THR-beta nuclear receptor [15].

Development trajectory: Resmetirom was the first drug approved by the United States FDA for MASH (March 2024), based on the MAESTRO-NASH Phase 3 trial demonstrating MASH resolution and fibrosis improvement on liver biopsy. The compound is marketed as Rezdiffra at 80 mg and 100 mg oral doses.

Novelty: Moderate. The THR-beta mechanism is established in endocrine pharmacology but novel in the MASH therapeutic context. First-in-class for the indication.

Effect size: In the MAESTRO-NASH trial, resmetirom 100 mg produced MASH resolution in approximately 30 percent of patients (versus 10 percent placebo) and fibrosis improvement by one or more stages in approximately 26 percent (versus 14 percent placebo) at 52 weeks. Liver fat reduction by MRI-PDFF was approximately 50 to 55 percent from baseline. The effect size on liver fat is larger than HU6 in the M-ACCEL trial (27 to 31 percent reduction), though the trials differed in patient population, duration, and liver fat measurement methodology [15].

Promising potential: High. Approved and marketed for MASH. First-mover advantage in the indication. Active post-marketing studies and combination development.

Side-effect profile: Adverse events were significantly more frequent with resmetirom than placebo in meta-analysis (relative risk 1.47). Common adverse events include diarrhea, nausea, and hepatic enzyme elevations. Thyroid-related effects (decreased TSH, bone density concerns with long-term use) are theoretical class concerns under ongoing surveillance.

Overall validation: High. Phase 3 positive, FDA-approved, histological endpoints met on liver biopsy.

Comparison to HU6: Resmetirom is the current standard-of-care for MASH and has the advantage of regulatory approval, large Phase 3 validation, and histological endpoint data. HU6 has the potential advantages of fat-selective, muscle-preserving weight loss (resmetirom produces less body weight reduction), broader metabolic benefits (visceral fat reduction, cardiovascular function improvement), and a potentially more favorable gastrointestinal side-effect profile. The mechanisms are distinct and potentially complementary. HU6 is earlier in clinical development and has not yet reported histological biopsy endpoints.

12.2 Semaglutide (Wegovy/Ozempic; Novo Nordisk)

Mechanism: GLP-1 receptor agonist. Reduces food intake through central appetite suppression, delays gastric emptying, and improves insulin secretion and sensitivity.

Development trajectory: Semaglutide is approved for obesity (Wegovy) and type 2 diabetes (Ozempic) and has been studied extensively in MASH. Phase 2 trials reported significant liver fat reduction and MASH resolution in patients treated with semaglutide 0.4 mg daily subcutaneous injection [17]. Phase 3 MASH trials are in progress.

Novelty: Low for the GLP-1 mechanism (well-established class). Application to MASH is a natural extension of existing metabolic indications.

Effect size: In Phase 2 MASH trials, semaglutide produced MASH resolution in approximately 59 percent of patients (versus 17 percent placebo) at 72 weeks. Liver fat reduction by MRI-PDFF was approximately 50 to 60 percent. Body weight reduction was approximately 13 percent at the obesity dose. However, approximately 25 to 40 percent of the weight loss includes lean mass (skeletal muscle), a limitation not shared by HU6 [11, 17].

Promising potential: High. Approved for related indications. Massive commercial infrastructure. Phase 3 MASH data expected.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea) are common and dose-limiting in approximately 5 to 10 percent of patients. Pancreatitis risk is a class concern. Lean mass loss is a recognized limitation.

Overall validation: High for obesity and diabetes. Moderate for MASH (Phase 2 data, Phase 3 pending).

Comparison to HU6: Semaglutide produces greater total weight loss but with significant lean mass loss. HU6 produces less total weight loss but with complete lean mass preservation and fat-selective reduction. The mechanisms are complementary (appetite suppression plus metabolic acceleration), and the combination represents a logical therapeutic strategy that Rivus is pursuing through the development of RV-8451.

12.3 BAM15 (research compound)

Mechanism: Selective mitochondrial uncoupler with preferential activity in lipid-rich tissues. BAM15 dissipates the proton gradient without depolarizing the plasma membrane, distinguishing it from classical uncouplers (DNP, FCCP) and providing improved cellular selectivity [14].

Development trajectory: BAM15 is a preclinical research compound that has not entered clinical development. Published studies have demonstrated efficacy in mouse models of obesity, diabetes, and NASH, with reduction in body weight, fat mass, blood glucose, and liver triglyceride content in db/db and diet-induced obesity mice [14].

Novelty: Moderate. The selective uncoupling mechanism (avoiding plasma membrane depolarization) is a meaningful pharmacological advance over classical uncouplers but shares the fundamental mitochondrial uncoupling approach with HU6.

Effect size: Substantial in preclinical models. Body weight, fat mass, glucose tolerance, liver triglycerides, and liver enzymes all improved significantly in mouse models. No human efficacy data.

Promising potential: Low as a clinical candidate (no clinical development). High as a research tool for understanding selective mitochondrial uncoupling.

Side-effect profile: Preclinical only. No human safety data. Improved selectivity over DNP in in vitro assays.

Overall validation: Low. Preclinical only with no clinical validation.

Comparison to HU6: BAM15 and HU6 share the fundamental mitochondrial uncoupling mechanism but differ in targeting strategy: HU6 achieves liver selectivity through prodrug hepatic activation, while BAM15 achieves tissue selectivity through intrinsic preferential activity in lipid-rich tissues. HU6 is substantially more advanced clinically (Phase 2 with positive data in multiple indications versus preclinical only). BAM15 is a useful research tool for mechanistic studies of selective uncoupling.

12.4 OPC-163493 (Otsuka Pharmaceutical)

Mechanism: Mitochondrial uncoupler with liver-targeting properties. OPC-163493 activates AMPK, increases hepatic fat oxidation, and improves hepatic insulin sensitivity independently of changes in food intake, body weight, or whole-body energy expenditure [18].

Development trajectory: OPC-163493 was advanced through preclinical development by Otsuka Pharmaceutical. The compound demonstrated dose-dependent reductions in fasting plasma glucose, HbA1c, and hepatic steatosis in multiple rodent models of diabetes and NASH at doses of 2 to 10 mg/kg/day. Clinical development status beyond preclinical is limited in published literature.

Novelty: Moderate. The liver-targeting uncoupler approach is shared with HU6 but through a different chemical scaffold and targeting mechanism.

Effect size: Significant in preclinical models, with robust improvements in glycemic control and hepatic steatosis. No human efficacy data available in published literature.

Promising potential: Low to moderate. Limited public information on clinical advancement.

Side-effect profile: Preclinical safety data reported as acceptable in published studies. No human safety data.

Overall validation: Low. Preclinical evidence only in published literature.

Comparison to HU6: OPC-163493 and HU6 share the liver-targeted mitochondrial uncoupling strategy but differ in chemical class and targeting mechanism. HU6 is substantially more advanced clinically with positive Phase 2 data in multiple indications. OPC-163493 has not reported human clinical data in the published literature.

12.5 Firsocostat (GS-0976; Gilead Sciences)

Mechanism: Acetyl-CoA carboxylase (ACC) inhibitor. Reduces de novo hepatic lipogenesis by inhibiting the enzyme that catalyzes the committed step of fatty acid synthesis. The mechanism operates upstream of mitochondrial oxidation, reducing the supply of newly synthesized fat rather than increasing the disposal of existing fat [19].

Development trajectory: Firsocostat was evaluated in Phase 2 trials for NASH as monotherapy and in combination with other Gilead NASH candidates (cilofexor, selonsertib). The compound produced significant reductions in liver fat (approximately 25 to 30 percent by MRI-PDFF) and improvements in liver fibrosis markers. However, the compound produced dose-dependent hypertriglyceridemia (a class effect of ACC inhibitors, reflecting increased hepatic VLDL secretion when de novo lipogenesis is blocked) that limited further monotherapy development [19]. Gilead subsequently deprioritized firsocostat monotherapy development for NASH.

Novelty: Moderate. ACC inhibition is a well-validated metabolic target with a distinct mechanism from mitochondrial uncoupling.

Effect size: Liver fat reduction of approximately 25 to 30 percent in Phase 2. The magnitude is comparable to HU6 Phase 2 data, but the dose-dependent hypertriglyceridemia limits the clinical utility.

Promising potential: Low. Monotherapy development deprioritized due to hypertriglyceridemia. Combination approaches continue.

Side-effect profile: Dose-dependent hypertriglyceridemia is the principal limitation. Other adverse events are modest.

Overall validation: Moderate. Phase 2 efficacy demonstrated but development limited by safety signal.

Comparison to HU6: Firsocostat and HU6 address hepatic steatosis through complementary mechanisms (reduced lipid synthesis versus increased lipid oxidation). HU6 has the advantage of no hypertriglyceridemia signal (indeed, HU6 reduces triglycerides) and a broader metabolic benefit profile including weight loss and cardiovascular improvements. Firsocostat has the advantage of a more precisely defined molecular target. The mechanisms could be complementary in combination.

12.6 Comparator summary

The five comparators occupy distinct positions in the MASH and metabolic liver disease therapeutic landscape. **Resmetirom** is the current regulatory standard with FDA approval, the largest clinical validation, and the strongest histological evidence; it represents the benchmark against which HU6 and other candidates will be measured. **Semaglutide** produces the largest weight loss and the strongest MASH resolution rates in Phase 2 but carries the limitation of significant lean mass loss and has not yet achieved regulatory approval for the MASH indication. **BAM15** and **OPC-163493** share HU6's mitochondrial uncoupling mechanism but are substantially less advanced clinically, serving primarily as preclinical research tools. **Firsocostat** demonstrated proof-of-concept liver fat reduction through ACC inhibition but was limited by dose-dependent hypertriglyceridemia.

HU6 occupies a unique position in this landscape as the most advanced liver-targeted mitochondrial uncoupler in clinical development, the only compound that produces fat-selective, muscle-preserving weight loss through increased energy expenditure rather than reduced energy intake, and the only compound that has demonstrated positive efficacy across three distinct clinical indications (MASLD, MASH, HFpEF) in Phase 2 trials. The principal open question is whether the liver fat reduction magnitude (27 to 31 percent in M-ACCEL, versus approximately 50 percent with resmetirom and semaglutide) translates to clinically meaningful MASH resolution and fibrosis improvement on liver biopsy, the regulatory endpoints required for approval. The fat-selective weight loss, visceral fat reduction, cardiovascular benefits, and favorable safety profile provide a differentiated value proposition, particularly in combination with appetite-suppression therapies that address the energy intake side of the metabolic equation. The development of RV-8451 as a non-peptide oral GLP-1 agonist designed for combination with HU6 reflects Rivus Pharmaceuticals' strategic recognition that the combination of meta-

bolic acceleration and appetite suppression may be necessary to match or exceed the efficacy of single-mechanism approaches that produce larger absolute effect sizes on individual endpoints.

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