

RESEARCH MONOGRAPH . COMPOUND PROFILE

Resmetirom

A first-in-class, orally administered, hepatocyte-targeted partial agonist of thyroid hormone receptor beta developed by Madrigal Pharmaceuticals for the treatment of metabolic dysfunction-associated steatohepatitis with liver fibrosis, and the first pharmacotherapy approved by the United States Food and Drug Administration for this indication.

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ABSTRACT

Resmetirom (MGL-3196, VIA-3196; marketed as Rezdiffra) is a first-in-class, orally administered, small-molecule, liver-directed partial agonist of the thyroid hormone receptor beta (THR-beta) that received accelerated approval from the United States Food and Drug Administration on March 14, 2024, for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH, formerly nonalcoholic steatohepatitis or NASH) with moderate to advanced liver fibrosis (stages F2 to F3), in conjunction with diet and exercise. Resmetirom is distinguished from earlier thyromimetic compounds by approximately 28-fold functional selectivity for THR-beta over THR-alpha, hepatocyte-directed uptake mediated by organic anion transporting polypeptide 1B1 (OATP1B1), and a liver-to-plasma concentration ratio of approximately 8:1, properties that collectively minimize the extrahepatic thyrotoxic effects (tachycardia, bone loss, skeletal muscle wasting) that terminated development of prior thyroid hormone receptor agonists including eprotirome and sobetirome. The molecular mechanism involves activation of THR-beta in hepatocytes, promoting fatty acid beta-oxidation, mitochondrial biogenesis, mitophagy, and autophagy while inhibiting de novo lipogenesis; these effects reduce intrahepatic triglyceride accumulation and attenuate the inflammatory and fibrotic cascades characteristic of progressive steatohepatitis. In the pivotal Phase 3 MAESTRO-NASH trial (n = 888, biopsy-confirmed noncirrhotic MASH with F2 to F3 fibrosis), resmetirom at 100 mg daily achieved MASH resolution without fibrosis worsening in 36 percent of patients versus 13 percent on placebo at 52 weeks, and fibrosis improvement by at least one stage without worsening of

MASH activity in 28 percent versus 15 percent on placebo, both co-primary endpoints reaching statistical significance. Secondary endpoints demonstrated reductions in low-density lipoprotein cholesterol (16.3 percent), apolipoprotein B (16.5 percent), and triglycerides (23.4 percent), consistent with the hepatic metabolic mechanism. Pharmacokinetics are characterized by oral absorption with a median time to peak concentration of approximately 4 hours, greater than 99 percent plasma protein binding, a median terminal half-life of 4.5 hours, metabolism predominantly through cytochrome P450 2C8 (CYP2C8), and elimination principally via feces (67 percent) with a minor renal component (24 percent). The principal adverse events are diarrhea and nausea, which are generally mild to moderate and self-limiting. Clinically significant drug interactions include inhibition of organic anion transporting polypeptide transporters (elevating statin exposures) and CYP2C8-mediated metabolic interactions. This monograph reviews the chemistry, synthesis, and structural pharmacology of resmetirom; the thyroid hormone receptor biology and mechanism of action in detail; the comprehensive human pharmacokinetic record; the preclinical pharmacology; the clinical evidence base across the MAESTRO trial program; sourcing and quality verification for research-grade material; reconstitution and handling; stack-interaction considerations; adverse-event signal and safety profile; and a comparative assessment of five alternative MASH pharmacotherapy candidates against resmetirom on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Resmetirom.

Marketed name: Rezdiffra (Madrigal Pharmaceuticals; United States, European Union).

Development codes: MGL-3196 (Madrigal Pharmaceuticals), VIA-3196 (VIA Pharmaceuticals). The MGL-3196 designation is the canonical identifier in the clinical pharmacology literature and was used throughout the Phase 1 through Phase 3 trial program [1, 2].

Chemical Abstracts Service registry number: 920509-32-6 (free base).

International Union of Pure and Applied Chemistry name: 2-[3,5-dichloro-4-[(6-oxo-5-propan-2-yl-1H-pyridazin-3-yl)oxy]phenyl]-3,5-dioxo-1,2,4-triazine-6-carbonitrile.

1.2 Structural class and chemistry

Resmetirom is a halogenated diaryl ether thyromimetic bearing a 1,2,4-triazine-6-carbonitrile pharmacophore linked through a dichlorophenyl bridge to a pyridazinone ring system. The structural class places it within the thyroid hormone receptor agonist family, specifically the subclass of liver-directed, beta-selective thyromimetics designed to replicate the hepatic metabolic actions of triiodothyronine (T3) without engaging thyroid hormone receptor alpha (THR-alpha) in cardiac, skeletal muscle, or bone tissue [3].

Molecular formula: C₁₇H₁₂Cl₂N₆O₄ (free base).

Molecular weight: 435.22 g/mol (free base).

Physical properties: White to off-white crystalline powder. Soluble in dimethyl sulfoxide (DMSO) at approximately 44 to 87 mg/mL (101 to 200 mM) depending on lot and moisture content. Insoluble in water and ethanol. The compound requires

anhydrous DMSO for stock solution preparation; moisture-contaminated DMSO reduces solubility substantially [4].

Stereochemistry: Resmetirom does not contain conventional stereocenters and is supplied as a single achiral molecular entity. The isopropyl substituent on the pyridazinone ring adopts a preferred conformation in the THR-beta ligand-binding domain but this is a binding-mode characteristic rather than a chirality consideration.

1.3 Synthesis

The published synthesis of resmetirom proceeds through a convergent route involving preparation of the 3,5-dichloro-4-hydroxyphenyl intermediate, construction of the pyridazinone ring bearing the isopropyl substituent, ether coupling of the phenol and pyridazinone through nucleophilic aromatic substitution or Mitsunobu chemistry, and introduction of the 1,2,4-triazine-6-carbonitrile warhead through condensation and cyclization [5]. The triazinedione-carbonitrile moiety is the principal pharmacophoric element responsible for interaction with the ligand-binding domain of THR-beta. Industrial synthesis is optimized for yield, purity (greater than 99 percent by HPLC in pharmaceutical-grade material), and removal of residual palladium and other transition metal catalysts used in cross-coupling steps. The compound is manufactured as the free base for both pharmaceutical and research-grade supply.

2. Abstract

Resmetirom (MGL-3196, Rezdiffra) is the first pharmacotherapy approved by the United States Food and Drug Administration for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) with liver fibrosis, receiving accelerated approval on March 14, 2024 [6]. The compound is a liver-directed, beta-selective partial agonist of the thyroid hormone receptor (THR-beta) that replicates the hepatic metabolic actions of triiodothyronine while sparing the extrahepatic THR-alpha-mediated effects on heart rate, bone mineral density, and skeletal muscle that limited earlier thyromimetic programs [3, 7].

The pharmacological basis is activation of THR-beta, the predominant thyroid hormone receptor isoform in hepatocytes. THR-beta activation promotes fatty acid beta-oxidation, stimulates mitochondrial biogenesis and mitophagy, enhances autophagy, and suppresses de novo lipogenesis, collectively reducing intrahepatic triglyceride accumulation and attenuating the steatosis-inflammation-fibrosis cascade that defines MASH progression [8, 9]. In functional assays, resmetirom produces 83.8 percent of the maximum response elicited by T3 at THR-beta with an EC50 of 0.21 micromolar, while producing only 48.6 percent efficacy at THR-alpha with an EC50 of 3.74 micromolar, yielding approximately 28-fold functional selectivity [1, 3].

The clinical evidence base rests on the MAESTRO trial program. The pivotal Phase 3 MAESTRO-NASH trial (n = 888, biopsy-confirmed noncirrhotic MASH with F2 to F3 fibrosis) demonstrated that resmetirom 100 mg daily achieved MASH resolution without fibrosis worsening in 36 percent of patients versus 13 percent on placebo at week 52, and fibrosis improvement by at least one stage without MASH worsening in 28 percent versus 15 percent on placebo [10]. The Phase 3 MAESTRO-NAFLD-1 safety trial (n = 972) confirmed tolerability and demonstrated liver fat reduction by MRI-proton density fat fraction of 44.8 percent (100 mg) versus 6.2 percent (placebo) at 16 weeks [11].

Pharmacokinetics are characterized by oral absorption (Tmax approximately 4 hours), greater than 99 percent plasma protein binding, a median terminal half-life of 4.5 hours, an apparent volume of distribution of 68 liters, metabolism predomi-

nantly by CYP2C8, and elimination principally via feces (67 percent) [12, 13]. Hepatocyte-directed uptake is mediated by OATP1B1, producing a liver-to-plasma concentration ratio of approximately 8:1 [3].

The principal adverse events are diarrhea (33 percent at 100 mg versus 14 percent placebo) and nausea (15 percent versus 9 percent), both generally mild to moderate and self-limiting [10, 11]. Rare hepatotoxicity has been observed, including one case of drug-induced autoimmune-like hepatitis [14]. Continued approval is contingent on the confirmatory MAESTRO-NASH-OUTCOMES trial evaluating clinical endpoints including hepatic decompensation, liver transplantation, and mortality, with completion anticipated in 2028 to 2029 [11].

3. Discovery and Development History

3.1 Origin and early thyromimetic research

The development of resmetirom is situated within a four-decade research effort to harness the metabolic actions of thyroid hormones for the treatment of dyslipidemia, obesity, and hepatic steatosis while avoiding the cardiac, skeletal, and bone toxicity associated with systemic thyroid hormone excess. Early thyromimetics, including the reference compound 3,5-diiodothyropropionic acid (DITPA) and the GlaxoSmithKline candidate GC-1 (sobetirome), demonstrated proof of concept for THR-beta-selective metabolic activation in preclinical models but encountered barriers including insufficient isoform selectivity, systemic toxicity, or inadequate hepatic targeting [15, 16].

The most advanced prior candidate, eprotirome (KB2115, Karo Bio), reached Phase 3 clinical development for dyslipidemia before being discontinued in 2012 following observations of cartilage damage in long-term dog toxicology studies and transient liver enzyme elevations in human subjects [17]. The eprotirome discontinuation established the critical requirement for liver-directed pharmacokinetics and clean THR-alpha separation in subsequent thyromimetic development programs.

3.2 Development of resmetirom

Resmetirom was originally discovered at Roche and subsequently licensed to VIA Pharmaceuticals under a research, development, and commercialization agreement executed on December 18, 2008 [18]. VIA advanced the compound through early characterization as VIA-3196. On September 14, 2011, Madrigal Pharmaceuticals acquired all of VIA's rights and obligations under the Roche agreement through an asset purchase transaction, redesignating the compound as MGL-3196 [18].

Madrigal completed three Phase 1 clinical trials in a total of 115 healthy subjects, establishing safety, tolerability, and favorable pharmacokinetics across an escalating dose range of 5 to 200 mg [19]. Phase 1 findings included dose-dependent reductions in low-density lipoprotein cholesterol (up to 30 percent) and triglycerides (up

to 60 percent) without suppression of thyroid-stimulating hormone or free triiodothyronine, confirming liver-selective pharmacology without clinically meaningful hypothalamic-pituitary-thyroid axis disruption [19].

3.3 Phase 2 development

The Phase 2 trial enrolled 125 patients with biopsy-confirmed NASH (fibrosis stages F1 to F3) and randomized them to resmetirom 80 mg daily or placebo for 36 weeks [2]. The primary endpoint, relative change in hepatic fat fraction by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at week 12, demonstrated a 32.9 percent reduction with resmetirom versus 10.4 percent with placebo ($p < 0.0001$). At 36 weeks, the reduction was 37.3 percent versus 8.9 percent. Secondary endpoints demonstrated improvements in liver aminotransferases, reductions in LDL cholesterol (11.2 percent) and apolipoprotein B (20.2 percent), and reductions in fibrosis biomarkers including PRO-C3 [2]. An open-label extension in 31 patients demonstrated sustained hepatic fat reduction of 52.3 percent from baseline and improvement in liver stiffness by transient elastography at 72 weeks [2].

3.4 Phase 3 MAESTRO program

Madrigal initiated the Phase 3 MAESTRO-NASH trial in March 2019, enrolling patients with biopsy-proven noncirrhotic MASH with fibrosis stages F1B, F2, or F3 at sites across North America, Europe, and other regions [10]. Topline results were announced in December 2022 with both co-primary endpoints met. The companion Phase 3 MAESTRO-NAFLD-1 safety and efficacy trial ($n = 972$, suspected or confirmed MASLD without advanced fibrosis) was conducted in parallel to expand the safety database and characterize liver fat reduction in a broader population [11].

3.5 Regulatory milestones

The FDA granted resmetirom breakthrough therapy designation, fast track designation, and priority review. Accelerated approval was issued on March 14, 2024, based on the histologic improvement demonstrated in MAESTRO-NASH [6]. The compound was designated first-in-class for MASH. The European Medicines Agency granted conditional marketing authorization in August 2025 [20]. Continued approval is contingent on the MAESTRO-NASH-OUTCOMES trial, a Phase 3 study enrolling patients with compensated MASH cirrhosis (Child-Pugh class A) with com-

posite clinical endpoints including cirrhosis progression, hepatic decompensation, liver transplantation, and all-cause mortality, with anticipated completion in 2028 and reporting in 2029 [11].

4. Mechanism of Action

4.1 Thyroid hormone receptor biology

The thyroid hormone receptors are ligand-activated nuclear transcription factors of the steroid/thyroid hormone receptor superfamily. Two genes encode the principal receptor isoforms: THRA (chromosome 17) encodes THR-alpha-1 and THR-alpha-2, and THRB (chromosome 3) encodes THR-beta-1 and THR-beta-2 [21]. THR-alpha-1 is the predominant isoform in cardiac muscle, skeletal muscle, bone, and brain. THR-beta-1 is the predominant isoform in the liver, kidney, and inner ear. THR-beta-2 is the predominant isoform in the hypothalamus and pituitary, where it mediates negative feedback regulation of thyroid-stimulating hormone secretion [21].

In the unliganded state, thyroid hormone receptors form heterodimers with retinoid X receptor and bind to thyroid hormone response elements in gene promoters, recruiting corepressor complexes (NCoR, SMRT) that silence transcription. Binding of the endogenous ligand triiodothyronine (T3) induces a conformational change that releases corepressors and recruits coactivator complexes (SRC-1, TRAP/DRIP/Mediator), activating transcription of target genes [21, 22].

4.2 THR-beta agonism by resmetirom

Resmetirom binds the ligand-binding domain of THR-beta-1 with high affinity and produces partial agonism (83.8 percent of T3 maximum efficacy) with an EC50 of 0.21 micromolar [1, 3]. At THR-alpha-1, the compound produces lower efficacy (48.6 percent of T3 maximum) with an EC50 of 3.74 micromolar, yielding approximately 28-fold functional selectivity for THR-beta in cellular reporter assays [3]. The selectivity derives from differential interactions between the dichlorophenyl-pyridazine scaffold and the ligand-binding pocket residues that distinguish THR-beta from THR-alpha.

4.3 Hepatic metabolic effects

Activation of THR-beta in hepatocytes by resmetirom produces a coordinated metabolic response that recapitulates the principal hepatic actions of thyroid hormone [8, 9, 23]:

Fatty acid oxidation. THR-beta activation upregulates mitochondrial and peroxisomal fatty acid beta-oxidation through transcriptional induction of carnitine palmitoyltransferase 1A (CPT1A), medium-chain acyl-CoA dehydrogenase (ACADM), and other oxidative enzymes. This directly reduces intrahepatic triglyceride content.

Mitochondrial biogenesis and function. Resmetirom stimulates mitochondrial biogenesis through induction of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) and nuclear respiratory factors. In vitro studies demonstrate that resmetirom increases basal and maximal mitochondrial respiration and adenosine triphosphate production in hepatocyte cell lines [3].

Mitophagy and autophagy. THR-beta activation promotes selective clearance of damaged mitochondria (mitophagy) and general autophagy, contributing to hepatocyte homeostasis and reduction of oxidative stress.

Suppression of de novo lipogenesis. Resmetirom downregulates sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase expression, reducing the conversion of carbohydrates to fatty acids in hepatocytes.

Deiodinase 1 induction. Resmetirom upregulates deiodinase type 1 (DIO1) expression, potentially facilitating local conversion of thyroxine (T4) to active T3 within hepatocytes and counteracting the intrahepatic hypothyroidism that has been proposed as a contributor to MASH pathogenesis [3].

4.4 Anti-inflammatory and antifibrotic effects

Beyond direct metabolic modulation, THR-beta activation attenuates hepatic inflammation and fibrogenesis through several interconnected pathways [9, 24]. In preclinical NASH models, resmetirom suppressed STAT3 and NF-kappaB signaling pathways through recovery of regulator of G-protein signaling 5 (RGS5) expression, reducing macrophage infiltration, inflammatory cytokine production, and hepatic stellate cell activation [24]. The reduction in hepatic lipid content itself attenuates

lipotoxic stress signaling (endoplasmic reticulum stress, oxidative stress, inflammasome activation) that drives progression from simple steatosis to steatohepatitis and fibrosis.

4.5 Hepatocyte-directed uptake

A critical pharmacological feature of resmetirom is hepatocyte-directed uptake mediated by organic anion transporting polypeptide 1B1 (OATP1B1), a hepatocyte membrane transporter [3]. This active uptake mechanism produces a liver-to-plasma concentration ratio of approximately 8:1 in animal models, concentrating the compound in the therapeutic target organ while limiting systemic exposure. Combined with greater than 99 percent plasma protein binding and limited tissue penetration outside the liver, the OATP1B1-mediated uptake is the principal basis for the hepatoselectivity that distinguishes resmetirom from earlier, systemically distributed thyromimetics.

4.6 Effects on lipoproteins

THR-beta activation in hepatocytes increases expression of low-density lipoprotein receptor, apolipoprotein A-I, and cholesterol 7-alpha-hydroxylase (CYP7A1, the rate-limiting enzyme in bile acid synthesis), producing reductions in circulating LDL cholesterol, apolipoprotein B, triglycerides, and lipoprotein(a) [2, 10, 11]. These lipid effects are mechanistically coherent with the hepatic THR-beta agonist pharmacology and represent a secondary cardiovascular benefit independent of the primary hepatic steatohepatitis indication.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Resmetirom is absorbed from the gastrointestinal tract after oral administration with a median time to maximum plasma concentration (T_{max}) of approximately 4 hours following multiple daily doses of 80 or 100 mg [12, 13]. Co-administration with food reduces maximum plasma concentration (C_{max}) by approximately 33 percent and area under the concentration-time curve (AUC) by approximately 11 percent, and delays T_{max} by approximately 2 hours; however, the compound may be administered with or without food per the approved prescribing information [12].

Steady-state exposure increases in a dose-proportional manner at doses of 40 to 100 mg. At doses above 100 mg (100 to 200 mg range), exposure increases are greater than dose-proportional, with a 5.6-fold increase reported across this range [12]. Following once-daily dosing, resmetirom exposure increases 1.5- to 3-fold relative to single-dose exposure, and steady state is reached within 3 to 6 days [12, 13].

5.2 Distribution

Resmetirom is greater than 99 percent bound to plasma proteins. The apparent volume of distribution at steady state is approximately 68 liters [12]. The compound is actively transported into hepatocytes by OATP1B1, producing a liver-to-plasma concentration ratio of approximately 8:1 in preclinical models [3]. Systemic tissue distribution outside the liver is limited by high protein binding and low tissue penetration, which is the pharmacokinetic basis for the hepatoselectivity of the compound.

5.3 Metabolism

Resmetirom is metabolized predominantly by CYP2C8 in the liver [12, 13, 14]. The principal metabolite is MGL-3623, which has approximately 28-fold lower potency at THR-beta than the parent compound and accounts for 33 to 51 percent of the to-

tal drug-related AUC [12]. MGL-3623 does not accumulate with repeated daily dosing. Additional minor metabolic pathways have been characterized but do not contribute materially to the pharmacological activity or to clinically significant drug-drug interactions.

5.4 Elimination

Elimination of resmetirom and its metabolites is principally via feces (67 percent of administered dose) with a secondary renal component (24 percent) [12]. The median terminal plasma half-life is 4.5 hours, and the steady-state apparent clearance is 17.5 liters per hour [12].

5.5 Special populations

Hepatic impairment. In subjects with mild hepatic impairment (Child-Pugh A), no clinically significant changes in resmetirom pharmacokinetics were observed. In subjects with severe hepatic impairment (Child-Pugh C), AUC increased 19-fold and C_{max} increased 8.1-fold; the compound is contraindicated in decompensated cirrhosis (Child-Pugh B or C) [12, 14].

Renal impairment. Mild and moderate renal impairment do not require dose adjustment. The compound has not been studied in severe renal impairment or end-stage renal disease [12].

Elderly. Approximately 25 percent of the MAESTRO trial population was 65 years or older. Numerically higher rates of adverse reactions were observed in elderly subjects, but no dose adjustment is recommended based on age alone [12].

Pregnancy. Adverse fetal effects were observed in animal reproductive toxicology studies at exposures approximately 3.5-fold the human exposure at the recommended dose. Use in pregnancy is avoided [12].

5.6 Routes of administration

Resmetirom is administered orally as tablets. The approved dosage forms are 60 mg, 80 mg, and 100 mg tablets [12]. The recommended dose is 80 mg once daily for patients weighing less than 100 kg and 100 mg once daily for patients weighing 100 kg or more. Administration with moderate CYP2C8 inhibitors requires dose reduc-

tion to 60 mg (less than 100 kg) or 80 mg (100 kg or more). Strong CYP2C8 inhibitors are contraindicated [12]. No parenteral, intravenous, or subcutaneous formulation has been developed for clinical use.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Resmetirom demonstrates potent THR-beta agonism in cell-based reporter assays with an EC₅₀ of 0.21 micromolar and 83.8 percent efficacy relative to T3 [1, 3]. THR-alpha agonism is characterized by an EC₅₀ of 3.74 micromolar and 48.6 percent relative efficacy, confirming the approximately 28-fold functional selectivity for THR-beta [3]. In hepatocyte cell lines, resmetirom increases basal and maximal mitochondrial respiration, increases adenosine triphosphate production, and upregulates deiodinase type 1 expression, confirming the mechanistic basis for the hepatic metabolic effects [3].

The compound also inhibits ether-a-go-go-related gene (hERG) potassium channels with an IC₅₀ of approximately 30 micromolar, a margin of approximately 143-fold relative to the THR-beta EC₅₀, indicating low liability for QT interval prolongation at therapeutic concentrations [1]. No clinically relevant QT prolongation was observed at doses up to twice the maximum recommended dose in dedicated thorough QT studies [12].

6.2 In vivo preclinical models

In diet-induced obese mice with biopsy-confirmed NASH and fibrosis (the first preclinical model described for resmetirom), the compound at 5 mg/kg daily restored liver appearance to the normal phenotype, normalized the liver-weight-to-body-weight ratio, eliminated visible hepatic steatosis, and markedly reduced fibrosis, inflammation, and macrophage infiltration in liver tissue [24, 25].

Kannt et al. (2021) reported that resmetirom activation of THR-beta in a mouse model of NASH with fibrosis improved disease activity and hepatic metabolism independent of body weight change, demonstrating that the therapeutic effect is mediated by direct hepatic metabolic modulation rather than by systemic energy expenditure or weight loss [25]. This finding is clinically relevant because resmetirom does not produce weight loss in human subjects, and the histologic improvements in human trials are independent of body weight changes [10].

Comparative preclinical pharmacodynamic analyses have evaluated resmetirom alongside semaglutide and obeticholic acid in translational mouse models of MASH, demonstrating complementary but distinct mechanisms of hepatic benefit across the three compound classes [26].

6.3 Reproductive toxicology

Animal reproductive toxicology studies demonstrated adverse fetal effects at exposures approximately 3.5-fold the human exposure at the recommended dose. The effects included skeletal variations and reduced fetal body weight in rats and rabbits at maternotoxic doses. No teratogenic effects were observed at lower multiples. These findings supported the pregnancy avoidance recommendation in the approved labeling [12].

7. Clinical Evidence Base

7.1 Phase 1 studies

Three Phase 1 trials in a total of 115 healthy subjects established the safety, tolerability, and pharmacokinetics of resmetirom across single and multiple ascending doses from 5 to 200 mg [19]. Key Phase 1 findings included dose-dependent reductions in LDL cholesterol (up to 30 percent) and triglycerides (up to 60 percent), reversible reductions in free thyroxine (T4) without suppression of thyroid-stimulating hormone (TSH) or free T3, no liver enzyme elevations, and no electrocardiographic abnormalities. The T4 reduction was attributed to enhanced hepatic DIO1 activity (accelerating T4-to-T3 conversion) rather than central thyroid axis suppression, a finding subsequently confirmed in Phase 2 and Phase 3 studies [19].

7.2 Phase 2 trial

The Phase 2 randomized, double-blind, placebo-controlled trial enrolled 125 patients with biopsy-confirmed NASH and fibrosis stages F1 to F3 [2]. Patients were randomized to resmetirom 80 mg daily or placebo for 36 weeks.

Primary endpoint (12 weeks): Relative change in hepatic fat fraction by MRI-PDFF was negative 32.9 percent with resmetirom versus negative 10.4 percent with placebo ($p < 0.0001$) [2].

Extended primary endpoint (36 weeks): Relative change in hepatic fat fraction was negative 37.3 percent with resmetirom versus negative 8.9 percent with placebo [2].

Secondary endpoints: Patients achieving 30 percent or greater hepatic fat reduction demonstrated higher rates of NASH resolution (37 to 39 percent). Liver aminotransferases (ALT, AST) improved at 36 weeks. LDL cholesterol decreased by 11.2 percent and apolipoprotein B by 20.2 percent. Reverse T3 decreased, suggesting restoration of intrahepatic thyroid hormone balance [2].

Open-label extension (72 weeks total): Continuing therapy in 31 patients produced sustained hepatic fat reduction of 52.3 percent from baseline, liver stiffness improvement of 2.1 kPa on transient elastography, and significant reduction in the

PRO-C3/C3M ratio (a fibrosis remodeling biomarker), indicating reduced net collagen synthesis ($p < 0.0001$) [2].

7.3 Phase 3 MAESTRO-NASH trial

The pivotal Phase 3 MAESTRO-NASH trial, published by Harrison et al. (2024) in the New England Journal of Medicine, enrolled 966 patients with biopsy-confirmed noncirrhotic MASH and fibrosis stages F1B, F2, or F3, randomized 1:1:1 to resmetirom 80 mg, resmetirom 100 mg, or placebo [10].

Co-primary endpoint 1 (MASH resolution without fibrosis worsening at week 52): Resmetirom 80 mg: 25.9 percent (placebo-adjusted difference approximately 16 percent). Resmetirom 100 mg: 29.9 percent (placebo-adjusted difference approximately 20 percent). Placebo: 9.7 percent. In the 888-patient subgroup with F2 to F3 fibrosis (the approved indication population): 80 mg, 27 percent; 100 mg, 36 percent; placebo, 13 percent [10, 11].

Co-primary endpoint 2 (fibrosis improvement by at least one stage without worsening NAS at week 52): Resmetirom 80 mg: 24.2 percent (placebo-adjusted difference approximately 10 percent). Resmetirom 100 mg: 25.0 percent (placebo-adjusted difference approximately 11 percent). Placebo: 14.2 percent. In the F2 to F3 subgroup: 80 mg, 23 percent; 100 mg, 28 percent; placebo, 15 percent [10, 11].

Key secondary endpoints: Improvement in all NAFLD activity score components: 80 mg (23.3 percent), 100 mg (27.9 percent), placebo (7.2 percent). Two-stage or greater fibrosis improvement: 80 mg (8.3 percent), 100 mg (10.1 percent), placebo (2.8 percent). LDL cholesterol reduction at week 24: 80 mg (negative 13.6 percent), 100 mg (negative 16.3 percent), placebo (positive 0.1 percent). Effects were consistent across key subgroups including baseline fibrosis stage, baseline NAS, type 2 diabetes status, age, and sex [10].

7.4 Phase 3 MAESTRO-NAFLD-1 trial

The MAESTRO-NAFLD-1 trial enrolled 972 patients with suspected or confirmed metabolic-associated steatotic liver disease (MASLD) without advanced fibrosis [11]. The primary endpoint was safety. Treatment-emergent adverse events occurred in 88.4 percent (80 mg), 86.1 percent (100 mg), and 81.8 percent (placebo) of subjects, confirming an acceptable safety profile in the broader MASLD population.

Liver fat reduction by MRI-PDFF at week 16: Open-label 100 mg: negative 47.8 percent. Double-blind 100 mg: negative 44.8 percent (placebo-adjusted difference negative 38.6 percent). Double-blind 80 mg: negative 34.9 percent (placebo-adjusted difference negative 28.7 percent). Placebo: negative 6.2 percent [11].

Lipid effects at week 24: LDL cholesterol: 80 mg (negative 12.4 percent), 100 mg (negative 13.9 percent), placebo (negative 1.3 percent). Apolipoprotein B: 80 mg (negative 14.3 percent), 100 mg (negative 16.5 percent), placebo (0 percent). Triglycerides (in patients with baseline greater than 150 mg/dL): 80 mg (negative 18.4 percent), 100 mg (negative 23.4 percent), placebo (negative 3 percent) [11].

7.5 MAESTRO-NASH-OUTCOMES trial

The ongoing MAESTRO-NASH-OUTCOMES trial is enrolling patients with well-compensated MASH cirrhosis (Child-Pugh class A, scores 5 to 6) to evaluate resmetirom 80 mg versus placebo on a composite clinical endpoint of cirrhosis progression, hepatic decompensation events, liver transplantation, and all-cause mortality [11]. Completion is anticipated in January 2027, with the confirmatory outcome trial required for full (non-accelerated) FDA approval expected to report by March 2029. Additional mandated postmarketing studies include a prospective pregnancy registry (completion March 2030), a lactation study (completion March 2027), and pediatric studies in patients aged 6 to 17 years (completion 2028 to 2031) [12].

7.6 Heterozygous familial hypercholesterolemia

A Phase 2 trial of resmetirom in patients with heterozygous familial hypercholesterolemia was conducted based on the lipid-lowering mechanism of hepatic THR-beta agonism [18]. The trial demonstrated reductions in LDL cholesterol in this population, though the development program has been focused on the MASH indication rather than pursuing a standalone dyslipidemia registration.

8. Sourcing and Quality Verification

Pharmaceutical-grade resmetirom (Rezdiffra, Madrigal Pharmaceuticals) is the highest quality source for research applications where regulatory equivalence to clinical material is operationally important. The pharmaceutical-grade material is supplied as 60 mg, 80 mg, and 100 mg tablets for oral administration [12]. Pharmaceutical sourcing is feasible in the United States and the European Union following regulatory approval.

Research-grade resmetirom is supplied by multiple chemical and pharmaceutical research suppliers (Selleck Chemicals, MedChemExpress, Cayman Chemical, MedKoo Biosciences, BenchChem, others) at greater than 99 percent purity by HPLC [4]. Supply is in milligram to gram quantities as the free base. Purity of 99.81 percent has been documented in representative research-grade lots [4].

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 99 percent.
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ 436.04 for the protonated free base).
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structural identity, particularly verification of the triazinedione-carbonitrile pharmacophore and the pyridazinone isopropyl substituent.
- Karl Fischer or loss-on-drying analysis for residual water content (critical because DMSO solubility is moisture-sensitive).
- Residual solvent analysis by gas chromatography if the synthesis route employed dichloromethane, dimethylformamide, or other common process solvents.

Third-party analytical confirmation is recommended for any investigation where dose-response precision is important, given the insolubility in aqueous and ethanolic vehicles and the reliance on DMSO for stock solution preparation.

9. Reconstitution and Handling

Resmetirom free base is soluble in DMSO at approximately 44 to 87 mg/mL depending on lot and moisture content [4]. The compound is insoluble in water and ethanol. Fresh, anhydrous DMSO must be used for stock solution preparation; moisture-contaminated DMSO substantially reduces solubility.

In vitro formulation: Stock solutions are prepared in DMSO at concentrations appropriate to the assay (typically 10 to 50 mM), then diluted into cell culture media at final DMSO concentrations of 0.1 percent or less. Aliquoting of stock solution for single-use is recommended to avoid potency loss from repeated freeze-thaw cycles.

In vivo formulation (multiple validated approaches):

- Carboxymethylcellulose sodium (CMC-Na) suspension: suitable for doses of 5 mg/mL or greater.
- 5 percent DMSO in corn oil: suitable for lower doses (approximately 0.5 mg/mL).
- 5 percent DMSO, 40 percent PEG300, 5 percent Tween 80, 50 percent double-distilled water: suitable for intermediate concentrations (approximately 4.35 mg/mL) [4].

Storage conditions: The solid powder is stable for 3 years at negative 20 degrees Celsius. Stock solutions in DMSO are stable for 1 year at negative 80 degrees Celsius and for 1 month at negative 20 degrees Celsius [4]. Light protection during storage is recommended but not strictly required. The compound should be stored in a dry, cool, well-ventilated location in tightly sealed containers.

Pharmaceutical formulation: Rezdiffra tablets (60, 80, and 100 mg) are stored at controlled room temperature (20 to 25 degrees Celsius) per the approved prescribing information [12].

10. Stack Interactions and Combinations

Resmetirom interacts with several drug classes through its CYP2C8-mediated metabolism and through its effects on hepatic transporters. Investigators conducting research with resmetirom, especially in chronic dosing regimens or in combination with other compounds, should consider:

CYP2C8 inhibitors (critical interaction). Strong CYP2C8 inhibitors (gemfibrozil) are contraindicated with resmetirom; co-administration would substantially increase resmetirom exposure and toxicity risk. Moderate CYP2C8 inhibitors (clopidogrel, trimethoprim, deferasirox) require dose reduction of resmetirom (60 mg for patients less than 100 kg, 80 mg for patients 100 kg or greater) [12, 13]. Clopidogrel co-administration increased resmetirom C_{max} by 1.3-fold and AUC by 1.7-fold [11].

CYP2C8 inducers. Strong CYP2C8 inducers (rifampin) would be expected to reduce resmetirom exposure, potentially compromising efficacy. This interaction has not been formally characterized in a dedicated clinical study but should be considered in combination research.

Statin interactions (OATP transporter-mediated). Resmetirom inhibits OATP1B1 and OATP1B3 transporters, increasing systemic exposure of statins that are substrates of these transporters [11, 12]. Rosuvastatin C_{max} increased 2.9-fold and AUC 1.8-fold with co-administration. Atorvastatin, pravastatin, and simvastatin showed lesser but clinically relevant increases. Dose limits are recommended: rosuvastatin and simvastatin should not exceed 20 mg daily; atorvastatin and pravastatin should not exceed 40 mg daily during concurrent resmetirom therapy [12].

Cyclosporine. Cyclosporine is both an OATP1B1/1B3 inhibitor and a substrate; co-administration with resmetirom is contraindicated due to bidirectional transporter interactions that could substantially alter exposure of both compounds [12].

Other transporter substrates. Resmetirom is an in vitro inhibitor of UGT1A4, UGT1A9, breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), and bile salt export pump (BSEP) [11, 12]. Clinical significance of these in-

teractions has not been fully characterized, but investigators using substrates of these transporters in combination studies should monitor for exposure changes.

GLP-1 receptor agonists. Secondary analysis of the MAESTRO-NASH trial demonstrated that resmetirom efficacy was preserved in patients concurrently receiving GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide) and other diabetes therapies, without apparent pharmacokinetic interaction or additive safety concerns [27]. The combination of resmetirom (hepatic THR-beta agonism) with GLP-1 receptor agonists (peripheral metabolic and weight-loss effects) is a rational and clinically emerging approach to MASH management.

Thyroid hormone preparations. Exogenous levothyroxine and liothyronine do not produce a characterized pharmacokinetic interaction with resmetirom, but the pharmacodynamic overlay of systemic thyroid hormone with hepatic THR-beta agonism should be considered. Resmetirom reduces free T4 by approximately 13 to 17 percent at 12 months through hepatic DIO1 induction, with minimal changes in active T3 or TSH [11, 12]. Investigators working with subjects on thyroid hormone replacement should monitor thyroid function tests during resmetirom co-administration.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed across the MAESTRO trial program, reported as exposure-adjusted rates per 100 person-years, are [10, 11, 12]:

- Diarrhea: 80 mg (23 percent), 100 mg (33 percent), placebo (14 percent).
- Nausea: 80 mg (18 percent), 100 mg (15 percent), placebo (9 percent).
- Pruritus: 80 mg (6 percent), 100 mg (10 percent), placebo (4 percent).
- Vomiting: 80 mg (7 percent), 100 mg (8 percent), placebo (4 percent).
- Constipation: 80 mg (5 percent), 100 mg (8 percent), placebo (4 percent).
- Abdominal pain: 80 mg (5 percent), 100 mg (7 percent), placebo (4 percent).
- Dizziness: 80 mg (4 percent), 100 mg (4 percent), placebo (1 percent).

Diarrhea and nausea typically began early after treatment initiation, were mild to moderate in severity, and were the principal causes of treatment discontinuation [10, 11].

11.2 Liver enzyme elevations

A high proportion of resmetirom-treated patients develop mild, transient serum aminotransferase elevations within the first 4 weeks of therapy, which are generally self-limited and asymptomatic [14]. ALT elevation greater than 3 times the upper limit of normal was observed in 11 percent (80 mg), 13 percent (100 mg), and 10 percent (placebo) of MAESTRO-NASH participants. AST elevation greater than 3 times the upper limit of normal occurred in 9 percent (80 mg), 12 percent (100 mg), and 10 percent (placebo) [11]. These early elevations, typically less than 1.5 times baseline at week 4, generally returned to baseline by week 8 and are attributed to hepatocyte metabolic remodeling rather than hepatotoxicity [14].

11.3 Rare hepatotoxicity

Among more than 1,300 resmetirom-treated patients across the clinical program, two cases of acute liver injury were reported [14]. One case involved ALT elevation to 236 U/L at 2 months that resolved within 1 to 2 months of discontinuation. A second case, upon rechallenge, produced ALT elevation to 3,226 U/L with bilirubin of 10.9 mg/dL, suggesting possible idiosyncratic or immunologic etiology. One case of drug-induced autoimmune-like hepatitis with immunoglobulin G elevation was also reported; it resolved after discontinuation [14]. These findings supported the hepatotoxicity likelihood score of D (possible rare cause) assigned by the LiverTox database.

Monitoring recommendations include testing hepatic aminotransferases at baseline, months 1, 2, 3, and 6, and then every 6 months. Discontinuation or increased monitoring is recommended if ALT elevation exceeds 3 times the upper limit of normal or 3 times the baseline level. Prompt discontinuation is required with symptoms of liver injury or jaundice [12].

11.4 Gallbladder events

A slightly higher incidence of cholelithiasis, acute cholecystitis, and obstructive pancreatitis was observed in resmetirom-treated patients, with exposure-adjusted rates of less than 1 per 100 person-years across treatment groups [11]. The mechanism may involve altered bile acid composition secondary to CYP7A1 induction by THR-beta agonism.

11.5 Thyroid and endocrine effects

Resmetirom reduced free T4 by approximately 13 percent (80 mg) and 17 percent (100 mg) at 12 months, with minimal changes in active T3 or TSH [11, 12]. No clinical findings were associated with the free T4 decreases. Sex hormone-binding globulin (SHBG) concentrations increased during resmetirom treatment, serving as a pharmacodynamic biomarker of hepatic THR-beta target engagement; the clinical significance of SHBG elevation is not established [11, 12].

11.6 Cardiac safety

No clinically relevant QT interval prolongation was observed at doses up to 2 times the maximum recommended dose in dedicated thorough QT studies. Resmetirom does not produce tachycardia, consistent with its THR-beta selectivity and hepatic targeting [12]. The cardiac safety profile is a significant advancement over earlier thyromimetics including eprotirome, which was associated with cardiac rhythm concerns at higher systemic exposures.

11.7 Pregnancy and lactation

Animal studies demonstrated adverse fetal effects at 3.5-fold human exposure. No human pregnancy data are available. Use in pregnancy is avoided. A prospective and retrospective pregnancy registry has been mandated, with completion anticipated by March 2030. No human lactation data are available; a study of milk concentrations is required by March 2027 [12].

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative MASH pharmacotherapy candidates against resmetirom, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal pharmacological agents with substantive Phase 2 or Phase 3 clinical evidence in MASH/NASH, representing distinct mechanistic classes.

12.1 Obeticholic acid (OCA, Ocaliva)

Mechanism: Semisynthetic bile acid derivative and potent agonist of the farnesoid X receptor (FXR). FXR activation in the liver and intestine modulates bile acid homeostasis, reduces hepatic inflammation, and attenuates fibrogenesis through suppression of hepatic stellate cell activation [28].

Development trajectory: Intercept Pharmaceuticals advanced obeticholic acid through the REGENERATE Phase 3 program in NASH with fibrosis. An interim analysis (18 months) demonstrated that OCA 25 mg daily achieved fibrosis improvement by at least one stage in 23.1 percent versus 11.9 percent for placebo, meeting the primary fibrosis endpoint [28]. NASH resolution was not significantly improved. The FDA issued a complete response letter in June 2023 citing an unfavorable benefit-risk profile. OCA is approved for primary biliary cholangitis (Ocaliva) but has not received NASH approval.

Novelty: Moderate. FXR agonism is a distinct mechanism from THR-beta agonism but is well established in bile acid biology.

Effect size: Fibrosis improvement response rate of 23.1 percent versus 11.9 percent placebo (difference approximately 11 percent), comparable in magnitude to resmetirom on the fibrosis endpoint. NASH resolution was not significantly improved, whereas resmetirom achieved both endpoints.

Promising potential: Low for NASH indication. The complete response letter and unfavorable benefit-risk assessment have effectively terminated the NASH development program. The compound remains approved for primary biliary cholangitis.

Side-effect profile: The principal limitation is severe pruritus (occurring in approximately 50 percent of patients at the 25 mg dose) and atherogenic dyslipidemia (increased LDL cholesterol), which is directionally opposite to the lipid-lowering effect of resmetirom [28]. These adverse effects were the principal basis for the unfavorable benefit-risk determination.

Overall validation: Moderate. The Phase 3 interim fibrosis data represent a validated pharmacological signal, but the regulatory outcome (complete response letter), the pruritus burden, and the dyslipidemia signal substantially limit clinical utility.

Comparison to resmetirom: Resmetirom achieved both MASH resolution and fibrosis improvement co-primary endpoints with a manageable adverse-event profile, whereas OCA achieved fibrosis improvement alone with an adverse-event profile that precluded regulatory approval. Resmetirom produces favorable lipid changes (LDL reduction); OCA produces unfavorable lipid changes (LDL increase). The two compounds operate through orthogonal mechanisms and could theoretically be combined, but the OCA safety profile makes this impractical in clinical settings.

12.2 Semaglutide (Ozempic, Wegovy)

Mechanism: Glucagon-like peptide-1 (GLP-1) receptor agonist that promotes insulin secretion, suppresses glucagon, delays gastric emptying, and reduces appetite, producing substantial weight loss and metabolic improvement. The hepatic effects in MASH are primarily indirect, mediated through weight loss, improved insulin sensitivity, and reduced hepatic lipotoxic stress [29].

Development trajectory: Novo Nordisk conducted the Phase 2 trial of subcutaneous semaglutide (0.1, 0.2, and 0.4 mg daily) in 320 patients with biopsy-confirmed NASH (fibrosis stages F1 to F3). At 72 weeks, NASH resolution without fibrosis worsening occurred in 59 percent (0.4 mg) versus 17 percent (placebo) [29]. However, fibrosis improvement by at least one stage was not significantly different from placebo (43 percent versus 33 percent, $p = 0.48$). The Phase 3 ESSENCE trial of oral semaglutide in MASH is ongoing, with histologic endpoint results anticipated.

Novelty: Low for the mechanism (GLP-1 agonism is well established for diabetes and obesity) but moderate for the MASH application, where the mechanism is distinct from liver-directed approaches.

Effect size: NASH resolution rates of 59 percent (0.4 mg) are the highest reported in any MASH trial, substantially exceeding resmetirom (36 percent at 100 mg). However, the fibrosis improvement endpoint was not met, which is a critical limitation for patients with progressive liver disease.

Promising potential: High. The Phase 3 ESSENCE trial is ongoing and the GLP-1 receptor agonist class has strong commercial momentum from diabetes and obesity indications. If fibrosis improvement is demonstrated in Phase 3, semaglutide would become a major competitor to resmetirom.

Side-effect profile: Gastrointestinal adverse events (nausea, vomiting, diarrhea, constipation) are prominent and dose-dependent but generally manageable. The compound produces significant weight loss (average 10 to 15 percent body weight), which is both a therapeutic benefit and a consideration for patients with sarcopenia or malnutrition.

Overall validation: High for NASH resolution; incomplete for fibrosis improvement. The Phase 2 data represent the strongest single-agent NASH resolution signal in the field but the absence of a fibrosis benefit at this stage is a meaningful limitation.

Comparison to resmetirom: Semaglutide produces superior NASH resolution rates but has not demonstrated fibrosis improvement, whereas resmetirom achieves both endpoints. Resmetirom is liver-directed and produces favorable lipid changes without weight loss; semaglutide produces its hepatic effects primarily through weight loss and peripheral metabolic improvement. The two mechanisms are complementary and secondary analysis of MAESTRO-NASH has confirmed preserved resmetirom efficacy in patients concurrently receiving GLP-1 agonists [27], supporting rational combination approaches.

12.3 Lanifibranor (IVA337)

Mechanism: Pan-peroxisome proliferator-activated receptor (PPAR) agonist, activating PPAR-alpha, PPAR-delta, and PPAR-gamma simultaneously. The multi-target PPAR activation modulates hepatic lipid metabolism, inflammation, insulin sensitivity, and fibrogenesis through parallel transcriptional programs [30].

Development trajectory: Inventiva Pharma conducted the Phase 2b NATIVE trial in 247 patients with NASH and significant fibrosis. NASH resolution without fibrosis worsening was achieved in 49 percent (1200 mg) and 39 percent (800 mg) versus 22

percent (placebo) [30]. Fibrosis improvement was also significant, with both endpoints met. The Phase 3 NATiv3 trial is ongoing with histologic endpoints.

Novelty: Moderate. Pan-PPAR agonism is pharmacologically distinct from THR-beta agonism and from single-PPAR agents (pioglitazone, fenofibrate).

Effect size: NASH resolution of 49 percent at 1200 mg and fibrosis improvement of approximately 47 percent at 1200 mg are among the highest reported in Phase 2 MASH trials, numerically exceeding resmetirom Phase 3 data. However, cross-trial comparison is limited by differences in patient populations, fibrosis staging, and endpoint definitions.

Promising potential: Moderate to high. Phase 3 is ongoing. If confirmed, lanifibranor would be a serious competitor to resmetirom with potentially superior histologic response rates.

Side-effect profile: The principal concerns are weight gain (mean approximately 3 kg at 1200 mg, attributed to PPAR-gamma activation, analogous to pioglitazone), peripheral edema, and the theoretical risk of PPAR-gamma-mediated adipogenesis with chronic dosing [30]. These effects contrast with resmetirom, which does not produce weight gain.

Overall validation: Moderate. Phase 2b data are strong on both endpoints, but Phase 3 confirmation is pending. The pan-PPAR mechanism carries established class-related concerns (weight gain, edema) that may limit the benefit-risk ratio.

Comparison to resmetirom: Lanifibranor Phase 2b response rates numerically exceed resmetirom Phase 3 rates, though cross-trial comparisons are unreliable. Resmetirom has the advantage of FDA approval, a well-characterized safety profile in large Phase 3 trials, favorable lipid effects, and absence of weight gain. Lanifibranor has the potential advantage of dual-endpoint effect size, but the weight gain and edema signal may limit clinical adoption.

12.4 VK2809 (formerly MB07811)

Mechanism: Prodrug of a liver-directed THR-beta agonist, activated by CYP3A-mediated cleavage in hepatocytes. The active metabolite selectively agonizes THR-beta with hepatocyte-directed pharmacokinetics analogous to resmetirom [31].

Development trajectory: Viking Therapeutics conducted a Phase 2 trial in patients with NAFLD, demonstrating that 66.7 percent of VK2809-treated patients achieved 50 percent or greater reduction in liver fat content versus 18.2 percent on placebo [31]. A Phase 2b trial (VOYAGE) in NASH patients with liver fibrosis enrolled patients for histologic endpoints. Phase 3 planning has been announced but not initiated as of the most recent data.

Novelty: Low. The mechanism (liver-directed THR-beta agonism) is the same class as resmetirom. VK2809 differs in its prodrug strategy and CYP3A-dependent activation.

Effect size: The liver fat reduction (66.7 percent achieving 50 percent or greater reduction) is robust but the histologic endpoints (NASH resolution, fibrosis improvement) are pending from the Phase 2b trial.

Promising potential: Moderate. The compound is in early Phase 2b/pre-Phase 3 development, substantially behind resmetirom in clinical maturity. If Phase 2b histologic data are positive, Phase 3 would follow, but the compound is several years behind resmetirom in the regulatory timeline.

Side-effect profile: Phase 2 safety data have been favorable, with a profile generally similar to resmetirom (mild gastrointestinal events, transient liver enzyme changes). The CYP3A-dependent prodrug activation introduces a different drug-drug interaction profile than resmetirom (CYP3A interactions rather than CYP2C8 interactions).

Overall validation: Low to moderate. Phase 2 liver fat data are positive, but histologic endpoint confirmation and Phase 3 data are absent.

Comparison to resmetirom: VK2809 shares the THR-beta agonist mechanism with resmetirom but is substantially earlier in clinical development. Resmetirom has the decisive advantage of FDA approval, Phase 3 histologic data, and an established safety database. VK2809 may ultimately serve as a second-generation THR-beta agonist or as a competitor if it demonstrates differentiated efficacy or safety, but this remains speculative pending Phase 2b and Phase 3 data.

12.5 Pioglitazone

Mechanism: PPAR-gamma agonist (thiazolidinedione class) that improves insulin sensitivity and redistributes lipid from liver and visceral deposits to subcutaneous adipose tissue. The hepatic effects include reduced steatosis, reduced inflammation, and improved insulin-mediated metabolic flux [32].

Development trajectory: Pioglitazone is a generic, widely available, FDA-approved treatment for type 2 diabetes. The PIVENS trial (Sanyal et al. 2010, NEJM) randomized 247 nondiabetic patients with NASH to pioglitazone 30 mg, vitamin E 800 IU, or placebo for 96 weeks [32]. Pioglitazone achieved NASH resolution in 47 percent versus 21 percent for placebo but did not meet the pre-specified primary endpoint of a 2-point improvement in NAS with at least 1 point in each component. Multiple meta-analyses and guidelines support pioglitazone use in NASH, though it lacks a formal FDA-approved NASH indication.

Novelty: Low. Pioglitazone has been studied for over 15 years in NASH and is a well-established off-label treatment.

Effect size: NASH resolution of approximately 47 percent in PIVENS is numerically high, exceeding resmetirom Phase 3 data. Fibrosis improvement data are inconsistent, with some studies showing benefit and others not, particularly at longer treatment durations.

Promising potential: Moderate (as an off-label treatment). The compound is inexpensive and widely available but carries class-related adverse effects that limit adoption. No further registration trials for NASH are expected.

Side-effect profile: The principal limitations are weight gain (mean 4 to 5 kg), fluid retention and peripheral edema, bone density reduction (increased fracture risk, particularly in postmenopausal women), and the historical (subsequently largely exonerated) cardiovascular concern associated with the thiazolidinedione class [32]. These adverse effects substantially limit long-term adoption for NASH, a chronic condition requiring prolonged treatment.

Overall validation: High as a proof-of-concept NASH treatment (longest clinical history in the field) but limited by adverse-effect burden and absence of a formal NASH indication.

Comparison to resmetirom: Pioglitazone achieves comparable or possibly superior NASH resolution rates in selected trials but with a substantially less favorable side-effect profile (weight gain, edema, bone loss) and without formal NASH regulatory approval. Resmetirom produces favorable lipid changes without weight gain and has an FDA-approved MASH indication, conferring both clinical and regulatory advantages. Pioglitazone remains a reasonable off-label comparator, particularly for diabetic patients with NASH, but resmetirom has displaced it as the first-line pharmacotherapy for MASH with moderate to advanced fibrosis.

12.6 Comparator summary

The five compounds occupy distinct positions in the MASH pharmacotherapy landscape. **Obeticholic acid** represents a validated FXR agonist mechanism that achieved fibrosis improvement but was denied regulatory approval due to pruritus and dyslipidemia. **Semaglutide** achieves the highest NASH resolution rates in the field through GLP-1-mediated weight loss and metabolic improvement but has not demonstrated fibrosis improvement in Phase 2. **Lanifibranor** is a pan-PPAR agonist with strong Phase 2b dual-endpoint data but pending Phase 3 confirmation and a weight gain signal. **VK2809** is a same-class THR-beta agonist prodrug in early Phase 2b development, substantially behind resmetirom. **Pioglitazone** is the longest-studied off-label NASH treatment with high NASH resolution rates but an unfavorable chronic adverse-effect profile.

Resmetirom occupies a unique position as the only FDA-approved MASH pharmacotherapy, the only compound to achieve both MASH resolution and fibrosis improvement co-primary endpoints in a Phase 3 trial, the only compound with favorable lipid effects (LDL, apolipoprotein B, triglyceride, and lipoprotein(a) reductions) as secondary benefits, and the compound with the most extensively characterized safety database for MASH in the class. The principal limitation is that the accelerated approval is contingent on confirmatory outcome data from MAESTRO-NASH-OUTCOMES, and the absolute response rates (36 percent MASH resolution, 28 percent fibrosis improvement at 100 mg) indicate that the majority of treated patients do not achieve histologic endpoints at 52 weeks, necessitating combination strategies or treatment optimization for non-responders.

The rational trajectory for the field is combination pharmacotherapy, leveraging complementary mechanisms (THR-beta agonism plus GLP-1 agonism, or THR-beta agonism plus FXR agonism, or triple combinations) to increase response rates be-

yond single-agent ceilings. The MAESTRO-NASH secondary analysis confirming preserved resmetirom efficacy with concurrent GLP-1 agonist therapy supports this direction [27].

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should

weight the evidence accordingly. Resmetirom received accelerated approval from the United States Food and Drug Administration on March 14, 2024, for the treatment of noncirrhotic metabolic dysfunction-associated steatohepatitis with moderate to advanced liver fibrosis (stages F2 to F3) in conjunction with diet and exercise. Continued approval is contingent on verification of clinical benefit in a confirmatory outcome trial. Investigators should consult the full prescribing information and their local regulatory authority before any research application.