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INPLASY

Resmetirom for Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis: A Systematic Review and Meta-Analysis of Phase 3 Evidence

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ADMINISTRATIVE INFORMATION

Support - Universidad del cauca.

Review stage at the time of initial registration - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026110005

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 2 November 2026 and was last updated on 2 November 2026.

INTRODUCTION

Review question / Objective In adults with metabolic dysfunction-associated steatotic liver disease (MASLD) or its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), what is the efficacy and safety of Resmetirom — an oral, liver-directed, thyroid hormone receptor-beta-selective agonist — based on Phase 3 clinical trial evidence? Objective. To systematically review and meta-analyze the Phase 3 evidence on the histological, biochemical, and safety outcomes of Resmetirom in MASLD/MASH.

Rationale MASLD is the most common chronic liver disease worldwide, affecting an estimated 30-38% of adults globally, and for more than a decade lacked an approved pharmacotherapy specifically for its progressive form, MASH. In March 2024, the FDA granted accelerated approval to Resmetirom, the first agent specifically indicated for noncirrhotic MASH with moderate-to-advanced fibrosis (F2-F3), based on the Phase 3 MAESTRO clinical development program. To date, only two independent Phase 3 randomized controlled trials (MAESTRO-NASH and MAESTRO-NAFLD-1) have published peer-reviewed primary results, alongside five secondary/subgroup analyses derived from one of those trials; this creates a meaningful risk of unit-of-analysis error and overstated evidence volume in reviews that do not explicitly distinguish independent trials from internally corroborating secondary analyses when deciding which outcomes are amenable to quantitative pooling. No prior review was identified that explicitly restricts quantitative pooling to ind.

Condition being studied Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), including their legacy-nomenclature equivalents (NAFLD, NASH), in adult human participants (≥18 years) enrolled in Phase 3 randomized, placebo-controlled trials of Resmetirom.

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METHODS

Search strategy This review was conducted and is reported in accordance with the PRISMA 2020 statement. Candidate records were obtained from three complementary sources: a corpus of 56 records compiled by the review team through structured, iterative retrieval; supplementary searches of PubMed/MEDLINE, ClinicalTrials.gov, Google Scholar, SCOPUS, Embase, and Web of Science; and backward/forward citation chasing (snowballing) from all included studies and from competing systematic reviews identified, through 30 September 2026. The search concept combined the intervention term with disease terms spanning both nomenclatures: (Resmetirom OR MGL-3196) AND (MASLD OR MASH OR NAFLD OR NASH OR "metabolic dysfunction-associated steatotic liver disease" OR "metabolic dysfunction-associated steatohepatitis" OR "nonalcoholic fatty liver disease" OR "nonalcoholic steatohepatitis"), with no lower date limit. ClinicalTrials.gov was additionally searched using the term "Resmetirom" across all recruitment statuses.

Participant or population Adults (≥18 years) with MASLD, MASH, or their legacy-nomenclature equivalents (NAFLD, NASH), diagnosed by liver biopsy or pre-specified non-invasive criteria.

Intervention Resmetirom (MGL-3196) at any dose evaluated in a Phase 3 program (80 mg or 100 mg orally once daily).

Comparator Placebo.

Study designs to be included Original Phase 3 randomized, double-blind, placebo-controlled trials and their pre-specified or exploratory secondary/subgroup analyses.

Eligibility criteria Included: original Phase 3 RCTs of Resmetirom in MASLD/MASH (or legacy NAFLD/NASH) and their secondary/subgroup analyses, reporting original comparative outcome data, published in English. Excluded: Phase 1/2 trials, preclinical and mechanistic studies, case reports, narrative reviews, other systematic reviews or meta-analyses, conference abstracts without a peer-reviewed full-text companion, and regulatory, guideline, or trial-design documents without original comparative outcome data. Non-English documents identified during the search were retained only as contextual sources cited in the Discussion, not as included studies.

Information sources PubMed/MEDLINE, ClinicalTrials.gov, Google Scholar, SCOPUS, Embase, and Web of Science, complemented by a team-compiled corpus and backward/forward citation chasing (see Search strategy above).

Main outcome(s) Seven reports met full eligibility criteria: two independent Phase 3 RCTs (MAESTRO-NASH, n=966; MAESTRO-NAFLD-1, n=969 double-blind) and five secondary/subgroup analyses of MAESTRO-NASH. In MAESTRO-NASH, MASH resolution without worsening of fibrosis occurred in 25.9% (80 mg) and 29.9% (100 mg) of patients versus 9.7% with placebo (P<0.001); fibrosis improvement by ≥1 stage occurred in 24.2% and 25.9% versus 14.2% (P<0.001). Pooled analysis of both independent trials showed consistent LDL-cholesterol reductions versus placebo (80 mg: -12.3 percentage points, 95% CI -14.8 to -9.7; 100 mg: -14.4 percentage points, 95% CI -18.2 to -10.7).

Additional outcome(s) Pooled safety analyses showed an increased risk of diarrhea (RR 1.72 for 80 mg; RR 2.20 for 100 mg) and nausea (RR 1.68 for 80 mg; RR 1.84 for 100 mg) with Resmetirom versus placebo, without excess serious adverse events (RR 0.94 for 80 mg; RR 1.13 for 100 mg). Treatment discontinuation due to adverse events was more consistently elevated at 100 mg (RR 2.31) than at 80 mg (RR 1.14, imprecise). Using GRADE, certainty of evidence was rated moderate for the histological endpoints and for the pooled LDL-cholesterol and safety outcomes, and low for long-term clinical outcomes (cirrhosis progression, hepatocellular carcinoma, mortality), for which no peer-reviewed Phase 3 data were available at the time of this review.

Data management Two reviewers (H.V.-U. and A.C.-P.) independently extracted study-level and outcome-level data using a standardized, pre-piloted extraction form, with disagreements resolved by discussion and reference to the original source. Extracted items included trial identifiers and registration numbers, design features, eligibility criteria, sample size and baseline characteristics, intervention/comparator regimens, follow-up duration, pre-specified endpoints, effect estimates with measures of precision, and safety data.

Quality assessment / Risk of bias analysis Risk of bias in the two included randomized controlled trials was assessed independently by two reviewers (J.P.N. and A.C.-P.) using the Cochrane Risk of Bias 2 (RoB 2) tool across its five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported

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result). Both included trials were judged at overall low risk of bias across all five domains. RoB was not formally reassessed for the five secondary/subgroup analyses, as these inherit the randomization and conduct of their parent trial (MAESTRO-NASH); their additional methodological features are instead described narratively.

Strategy of data synthesis Only two independent Phase 3 trials were identified; the five remaining eligible reports are secondary/subgroup analyses of MAESTRO-NASH and were therefore not treated as independent data points in any pooled estimate, to avoid unit-of-analysis error. The co-primary histological endpoints (reported only by MAESTRO-NASH) were synthesized narratively. LDL-cholesterol percentage change from baseline and pre-specified safety outcomes (diarrhea, nausea, serious adverse events, discontinuation due to adverse events), reported comparably by both independent trials, were pooled separately by dose (80 mg and 100 mg vs. placebo) using inverse-variance random-effects meta-analysis (DerSimonian-Laird estimator), with continuous outcomes as mean differences and binary outcomes as risk ratios, both with 95% confidence intervals. Heterogeneity was quantified using I^2; given k=2 per outcome, I^2 and tau^2 are reported descriptively. Certainty of evidence was assessed using GRADE.

Subgroup analysis The five eligible secondary/subgroup analyses of MAESTRO-NASH (F2-F3 fibrosis subset; qFibrosis quantitative histology; PNPLA3 genotype subgroup; concomitant GLP-1 receptor agonist/diabetes therapy subset; pooled quality-of-life analysis) were synthesized narratively as internal corroboration and applicability analyses of a single trial, not pooled quantitatively and not treated as independent replications.

Sensitivity analysis Not performed. Only two independent trials contributed to any pooled estimate; a funnel plot or formal test of small-study effects (e.g., Egger's test) was not constructed, consistent with Cochrane Handbook guidance that approximately ten studies are generally required for adequate power, and this is stated explicitly as a limitation of the review.

Language restriction English (for inclusion in the systematic review and quantitative synthesis; non-English sources identified during the search were retained only as contextual references in the Discussion)..

Country(ies) involved Colombia, Argentina.

Other relevant information None.

Keywords Resmetirom; metabolic dysfunction-associated steatotic liver disease; metabolic dysfunction-associated steatohepatitis; thyroid hormone receptor beta agonist; LDL-cholesterol; fibrosis.

Dissemination plans Publication in a peer-reviewed journal.

Contributions of each author

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