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# Efficacy and Safety of Tesamorelin for Hepatic Steatosis in Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease a Systematic Review, Random-Effects Meta-Analysis and Placebo-Anchored Network Meta-Analysis with SUCRA Ranking

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## Abstract

**Background:** Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease worldwide, yet the pharmacological armamentarium remains narrow and only one agent is approved for steatohepatitis with fibrosis. Tesamorelin, a growth hormone-releasing hormone (GHRH) analogue that restores endogenous pulsatile growth hormone secretion, reduces visceral and hepatic fat and is the only agent shown to attenuate histological fibrosis progression in a dedicated, biopsy-controlled MASLD trial. Its comparative standing against the contemporary MASLD pipeline has never been formally quantified.

**Objectives:** To evaluate the efficacy and safety of tesamorelin for hepatic steatosis in adults with MASLD, and to position tesamorelin against the published pharmacological alternatives through a placebo-anchored network meta-analysis (NMA) of liver-fat content with SUCRA ranking and GRADE certainty rating.

**Methods:** MEDLINE/PubMed, Embase, Web of Science, Scopus, CENTRAL, LILACS, ClinicalTrials.gov and the WHO ICTRP were searched from inception to August 2026. Randomised trials in adults reporting a quantitative liver-fat outcome measured by MRI proton-density fat fraction (MRI-PDFF) or proton magnetic resonance spectroscopy ($^1$H-MRS) were eligible. The primary effect measure was the ratio of means (RoM) of liver-fat content at follow-up, treatment versus comparator (RoM < 1 favours the treatment), chosen because it is invariant to differences in baseline steatosis severity across trial populations. A contrast-based random-effects NMA anchored on placebo was fitted by generalised least squares; treatments were ranked by SUCRA and probability-best from 200,000 Monte-Carlo draws of the multivariate normal distribution of the basic parameters. Risk of bias used Cochrane RoB 2; certainty of evidence used GRADE for NMA. Tesamorelin-specific efficacy, histological and safety outcomes were synthesised pairwise.

**Results:** Six randomised trials (423 participants; seven nodes) contributed to the placebo-anchored network. Every active agent reduced liver-fat content relative to placebo. Semaglutide 0.4 mg once daily ranked first (RoM 0.47, 95% CI 0.36-0.61; −53.0% relative reduction; SUCRA 91.7%; probability-best 59.9%), followed by pioglitazone 45 mg (RoM 0.50, 0.40-0.62; SUCRA 85.9%). Tesamorelin 2 mg ranked third of six active agents (RoM 0.65, 95% CI 0.42-1.01; −35.2%; SUCRA 52.0%), ahead of aldafermin 1 mg (RoM 0.66; SUCRA 49.3%), resmetirom 80 mg (RoM 0.69; SUCRA 44.0%) and saroglitazar 4 mg (RoM 0.77; SUCRA 26.6%). None of the pairwise contrasts between tesamorelin and any other active agent reached statistical significance. In the tesamorelin pairwise synthesis, hepatic fat fell by 4.28 percentage points versus placebo (95% CI −6.31 to −2.24; $I^2$ = 0%); 35% versus 4% of participants achieved resolution of steatosis (hepatic fat fraction < 5%, P = 0.007); and fibrosis progression over 12 months occurred in 10.5% versus 37.5% (P = 0.04). Fasting glucose was unaffected (MD 0.10 mmol/L, 95% CI −0.51 to 0.72) and serious adverse events were not increased (RR 1.27, 95% CI 0.73-2.22), whereas arthralgia (RR 1.92), myalgia (RR 3.04), paraesthesia (RR 2.52) and injection-site erythema (RR 2.74) were more frequent. Certainty was moderate for tesamorelin versus placebo on steatosis and low to very low for all indirect between-drug comparisons.

**Conclusions:** Tesamorelin produces a clinically meaningful, glycaemically neutral reduction in hepatic fat that places it in the middle of the current MASLD landscape — below semaglutide and pioglitazone, and statistically indistinguishable from aldafermin, resmetirom and saroglitazar. Its distinguishing feature is not the magnitude of steatosis reduction but the demonstrated attenuation of biopsy-confirmed fibrosis progression together with concomitant visceral-fat reduction and glycaemic neutrality. All between-drug comparisons rest on indirect evidence from a star-shaped network of single trials and are hypothesis-generating; head-to-head trials in non-HIV MASLD populations are required.

## Keywords

Tesamorelin; Growth hormone-releasing hormone analogue; Metabolic dysfunction-associated steatotic liver disease; MASLD; MASH; NAFLD; Hepatic steatosis; Magnetic resonance proton-density fat fraction; Network meta-analysis; SUCRA; GRADE.

## Introduction

Can a growth hormone-releasing hormone analogue treat fatty liver, and how does it compare with the drugs now being developed for the same disease? Fatty liver disease — now termed metabolic dysfunction-associated steatotic liver disease (MASLD) — is the accumulation of fat inside liver cells in people with cardiometabolic risk factors. In a substantial minority the fat is accompanied by inflammation and cell injury (steatohepatitis, MASH), which can scar the liver and progress to cirrhosis and liver cancer. Tesamorelin is an injectable peptide that restores the body's own pulsed release of growth hormone. It is

licensed to reduce excess abdominal fat in people living with HIV, and in a dedicated randomised trial with liver biopsies before and after treatment it reduced liver fat and, uniquely among tested agents in that population, slowed the scarring process.

What we did and what we found. We assembled the randomised evidence on tesamorelin for fatty liver, pooled it, and then placed it inside a network of the other drugs that have been tested against placebo with the same quantitative imaging endpoint. Expressed as the proportion of liver fat remaining after treatment relative to placebo, tesamorelin removed about a third of liver fat (a 35% relative reduction). Semaglutide and pioglitazone removed about half and ranked highest; aldafermin, resmetirom and saroglitazar were statistically indistinguishable from tesamorelin. Tesamorelin did not worsen blood glucose — a meaningful advantage over growth hormone itself and over some other options — but caused more joint pain, muscle pain, tingling and injection-site redness. Because almost no trial has compared two of these drugs directly, the rankings are indirect and should be read as a map of the landscape rather than a prescribing hierarchy.

## Background

MASLD affects approximately 30% of the adult population worldwide and its prevalence tracks the epidemics of obesity and type 2 diabetes. The disease spectrum runs from isolated steatosis through metabolic dysfunction-associated steatohepatitis (MASH) with hepatocellular ballooning and lobular inflammation, to progressive fibrosis, cirrhosis and hepatocellular carcinoma. Fibrosis stage, not steatosis grade, is the dominant determinant of liver-related and all-cause mortality, and regulatory guidance for late-phase MASH programmes accordingly requires histological improvement in fibrosis, inflammation, or both. Nevertheless, quantitative hepatic fat measured by MRI proton-density fat fraction (MRI-PDFF) has become the standard phase 2 endpoint because it is non-invasive, reproducible, samples the whole organ rather than a needle core, and because both the absolute decline and a relative decline of at least 30% predict subsequent histological response and MASH resolution.

The therapeutic landscape has changed rapidly. Thyroid hormone receptor-β agonism (resmetirom), incretin-based therapy (semaglutide, tirzepatide, survodutide), fibroblast growth factor 21 and 19 analogues (pegozafermin, efruxifermin, aldafermin), pan-PPAR and dual PPAR agonism (lanifibranor, saroglitazar), insulin sensitisation (pioglitazone) and sodium-glucose co-transporter-2 inhibition all reduce hepatic fat, but they differ profoundly in mechanism, route, tolerability, effect on body composition, glycaemic consequences and cost. Head-to-head randomised comparisons are almost entirely absent, so the relative standing of any individual agent must be inferred indirectly.

Tesamorelin occupies an unusual position in this landscape. It is a stabilised analogue of human GHRH (1-44) that acts on the pituitary to restore physiological, pulsatile growth hormone secretion rather than delivering exogenous growth hormone. This mechanism preserves negative feedback and is the pharmacological explanation for its glycaemic neutrality, in sharp contrast to recombinant human growth hormone, whose diabetogenic effect limits its metabolic use. Tesamorelin selectively depletes visceral adipose tissue while largely sparing subcutaneous depots, lowers triglycerides, raises lean body mass and raises IGF-1. Because visceral adiposity and portal free-fatty-acid flux are proximate drivers of hepatic

triglyceride accumulation, reduction of visceral fat provides a mechanistically coherent route to reduction of hepatic fat, and this hypothesis was confirmed in two randomised, placebo-controlled imaging trials.

Most decisively, in a 12-month randomised, double-blind, multicentre trial with paired liver biopsies, tesamorelin reduced hepatic fat fraction, achieved resolution of steatosis in one third of recipients, and reduced the proportion of participants with any histological progression of fibrosis from 37.5% to 10.5%. Hepatic transcriptomic profiling in the same programme demonstrated downregulation of pathways governing tissue repair, cell division and inflammation, providing biological plausibility for the antifibrotic signal. Two features nevertheless constrain interpretation: the randomised hepatic evidence was generated in people living with HIV, and no trial has compared tesamorelin with any active MASLD therapy. A quantitative synthesis that positions tesamorelin within the wider evidence network is therefore both timely and necessary.

## Objectives

**Primary objective:** To determine the efficacy of tesamorelin, relative to placebo, on quantitative hepatic fat content in adults with MASLD, and to estimate its comparative efficacy against all other pharmacological interventions evaluated against placebo with a quantitative liver-fat endpoint, using a placebo-anchored network meta-analysis.

**Secondary objectives:** (i) to rank interventions by SUCRA and probability-best; (ii) to synthesise the histological effects of tesamorelin (steatosis resolution, NAFLD activity score, lobular inflammation, hepatocellular ballooning and fibrosis progression); (iii) to characterise the safety profile of tesamorelin with particular attention to glycaemic outcomes, musculoskeletal and injection-site events, and serious adverse events; and (iv) to rate the certainty of every network estimate using GRADE for network meta-analysis.

## Methods

The review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 6.5) and reported in accordance with the PRISMA 2020 statement and, for the network component, the PRISMA extension for network meta-analyses (PRISMA-NMA). The protocol, including the PICOS framework, outcome hierarchy, effect measures and the full analysis plan, was specified a priori.

### Eligibility criteria (PICOS)

| Element | Criterion |
|---|---|
| Population | Adults (≥ 18 years) with hepatic steatosis defined by imaging (MRI-PDFF or $^{1}$H-MRS hepatic fat ≥ 5%) or by liver biopsy, with or without steatohepatitis and with fibrosis stages F0-F3. Populations with a coexisting cardiometabolic driver (obesity, type 2 diabetes, prediabetes, dyslipidaemia) or with well-controlled HIV infection were eligible. Cirrhosis (F4), significant alcohol intake, viral hepatitis B, active hepatitis C and other defined causes of liver disease were exclusions. |
| Intervention | Any systemically administered pharmacological agent evaluated for hepatic steatosis, including but not limited to GHRH analogues (tesamorelin), incretin-based therapies, thyroid hormone receptor-β agonists, FGF19/FGF21 analogues, PPAR agonists, insulin sensitisers, SGLT2 inhibitors, FXR agonists and ACC inhibitors. |

| Element | Criterion |
|---|---|
| Comparators | Placebo (primary anchor); an alternative active pharmacological agent; or an active glucose-lowering control (analysed as a separate network component). |
| Outcomes | Primary: quantitative liver-fat content at the trial's principal imaging timepoint, measured by MRI-PDFF or $^{1}$H-MRS. Secondary: resolution of steatosis; ≥ 30% relative decline in liver fat; NAFLD activity score and its components; fibrosis stage change and fibrosis progression; alanine aminotransferase; fasting glucose and HbA1c; visceral adipose tissue; lean body mass; triglycerides. Safety: serious adverse events, discontinuation for adverse events, arthralgia, myalgia, paraesthesia, injection-site reactions, hyperglycaemia, infections. |
| Study design | Randomised controlled trials with a minimum treatment duration of 12 weeks. Non-randomised, single-arm and paediatric studies, and trials of lifestyle or surgical interventions alone, were excluded from the quantitative synthesis and used, where relevant, for narrative context only. |

**Table 1:** Eligibility criteria (PICOS). MRI-PDFF = magnetic resonance imaging proton-density fat fraction; $^{1}$H-MRS = proton magnetic resonance spectroscopy.

## Information sources and search strategy

MEDLINE (via PubMed), Embase, Web of Science Core Collection, Scopus, the Cochrane Central Register of Controlled Trials (CENTRAL) and LILACS were searched from inception to August 2026 without language restriction. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched for completed but unpublished trials, and the reference lists of all included reports, of previous pairwise syntheses of tesamorelin, and of the most complete published network meta-analysis of liver-fat-lowering therapies were hand-searched. The search combined controlled vocabulary with free-text terms for the condition ("non-alcoholic fatty liver disease", "NAFLD", "NASH", "MASLD", "MASH", "hepatic steatosis", "liver fat"), for the index intervention ("tesamorelin", "TH9507", "Egrifta", "growth hormone-releasing factor", "GHRH analogue"), for comparator drug classes, and for the measurement modality ("proton density fat fraction", "PDFF", "magnetic resonance spectroscopy"). The complete MEDLINE strategy is reproduced in Appendix A and was adapted syntactically for each remaining database.

## Study selection, data extraction and risk of bias

Records were de-duplicated in a reference manager and screened in duplicate by two reviewers, first on title and abstract and then on full text, with disagreements resolved by a third reviewer. For each eligible trial we extracted the trial identifier and registration number, design, country and setting, sample size per arm, inclusion thresholds for steatosis, mean age, sex, body-mass index, diabetes status, fibrosis stage distribution, intervention and comparator with dose and route, treatment duration, imaging modality and field strength, baseline liver-fat content, the change in each arm, and the between-group treatment effect with its 95% confidence interval, together with all secondary and safety outcomes. Where several publications reported the same trial, the report with the most complete data for each endpoint was used and cross-referenced by registration number to prevent double counting.

Risk of bias was assessed independently in duplicate with the Cochrane RoB 2 tool across the five domains of the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result, with an overall judgement of low risk, some concerns or high risk.

## Effect measure: the ratio of means and its justification

Trials of liver-fat-lowering therapy differ markedly in the baseline severity of steatosis they enrol, because eligibility thresholds range from ≥ 5% to ≥ 10% hepatic fat and because the underlying populations differ in adiposity and diabetes prevalence. An absolute mean difference in percentage points is therefore not exchangeable across trials: the same pharmacological effect produces a larger absolute change in a population starting at 20% hepatic fat than in one starting at 10%. We consequently pre-specified the ratio of means (RoM) of liver-fat content at follow-up as the primary effect measure:

$$\mathrm{RoM} = (B_T + \Delta_T) / (B_C + \Delta_C)$$

Where B is the baseline mean liver-fat content and Δ the mean change in the treatment (T) and comparator (C) arms. Analysis was performed on the natural-logarithm scale, and RoM < 1 indicates a greater reduction in liver fat with the treatment. The ratio of means is scale-free, is appropriate for a strictly positive outcome with a right-skewed distribution, is directly interpretable as a percentage relative reduction — the metric already used to define response in the MASH literature — and can be reconstructed from the several ways in which trials report their results. Where a trial reported an estimated treatment ratio directly, that value was used unchanged. Where a trial reported the relative (percentage) change in each arm, the RoM was computed from those percentages. Where a trial reported absolute changes together with the baseline mean, the formula above was applied. Standard errors on the log scale were obtained by the delta method from the reported 95% confidence interval of the between-group treatment effect. Every derivation, together with its source, is documented transparently in Appendix B, and the sensitivity of the result to the single assumption required (the baseline liver fat used for one trial) was examined formally.

The absolute mean difference in percentage points was retained as a secondary effect measure for the tesamorelin pairwise synthesis, where the populations are homogeneous and absolute change is the clinically familiar quantity. Dichotomous outcomes were expressed as risk ratios.

## Pairwise synthesis

Tesamorelin-specific outcomes were pooled with the DerSimonian-Laird random-effects model. Heterogeneity was quantified with $\tau^2$, Cochran's Q and $I^2$, and 95% prediction intervals were computed wherever three or more trials contributed, so that the plausible range of effects in a future setting could be distinguished from the precision of the average effect.

## Network meta-analysis

A contrast-based random-effects network meta-analysis anchored on placebo was fitted using the generalized least-squares formulation of the graph-theoretical model, which for two-arm contrast data is algebraically identical to the standard frequentist implementation. Writing θ for the vector of observed log-RoM contrasts, X for the design matrix mapping contrasts onto basic parameters and W for the inverse-variance weight matrix incorporating a common between-study variance $\tau^2$, the basic parameters were estimated as $\beta = (X^T W X)^{-1} X^T W \theta$, with $\tau^2$ obtained by the generalised method-of-moments (DerSimonian-Laird) estimator for networks. All pairwise contrasts between active agents and their


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variances were then derived from β and its covariance matrix by the appropriate linear contrast, producing the complete league table.

### Treatment ranking

Rankings were derived by Monte-Carlo simulation: 200,000 draws were taken from the multivariate normal distribution defined by the estimated basic parameters and their covariance matrix, treatments were ranked within each draw, and the resulting rank distribution was summarised as the surface under the cumulative ranking curve (SUCRA), the probability of being best, and the mean rank. Rankograms display the entire rank distribution rather than only its summary, which is essential because SUCRA alone can conceal wide overlap between adjacent treatments. A fixed random seed (20260812) was used so that the analysis is exactly reproducible.

### Transitivity, inconsistency and network geometry

Transitivity was appraised qualitatively by tabulating the distribution of the potential effect modifiers across the nodes: baseline liver-fat content, treatment duration, imaging modality, diabetes prevalence, fibrosis stage distribution, body-mass index and the presence of HIV infection. Because every included trial compared a single active agent with placebo and no head-to-head randomised comparison between two active agents was identified, the network is star-shaped and contains no closed loop. Statistical inconsistency is therefore not estimable, no node-splitting, design-by-treatment interaction or side-splitting analysis is possible, and the between-drug estimates are wholly indirect. This is stated explicitly rather than concealed, and it is the principal reason the network component is designated exploratory and hypothesis-generating.

### Small-study effects and sensitivity analyses

Small-study effects were examined with a comparison-adjusted funnel plot ordered by the year of drug development, with each trial's effect expressed as the deviation from the corresponding network estimate. Formal asymmetry testing was not undertaken because fewer than ten trials contributed to any single comparison, in accordance with Cochrane guidance. Three pre-specified sensitivity analyses were performed: (i) restriction to trials of at least 24 weeks' duration; (ii) a bridged network in which the trial comparing tirzepatide with insulin degludec was connected to the placebo anchor under the explicit assumption that titrated basal insulin is equivalent to placebo for hepatic fat; and (iii) variation of the assumed baseline liver-fat content used to reconstruct one trial's ratio of means across the plausible range of 12% to 25%.

### Certainty of the evidence

Certainty was rated with the GRADE framework adapted for network meta-analysis, in which each network estimate is assessed for within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence, and the rating of the network estimate cannot exceed the rating of the direct or indirect evidence that dominates it. Because every between-drug estimate in this network derives entirely from indirect evidence via a single common comparator, the indirectness and imprecision domains dominate. Judgements were made in duplicate and disagreements resolved by consensus.

### Software

All analyses were performed in Python 3.11 using NumPy and SciPy, with figures generated in Matplotlib. The network meta-analysis, the Monte-Carlo ranking procedure and all derived quantities were implemented in a self-contained, version-controlled script that reproduces every number and figure in this report from the raw extraction table.

## Results

### Study selection

The flow of records is shown in (**Figure 1**). Twenty-one reports of eighteen randomised trials met the eligibility criteria and were included in the qualitative synthesis. Six trials contributing seven nodes and 423 participants provided effect estimates reconstructable on the ratio-of-means scale at a comparable timepoint and formed the placebo-anchored network; one further trial with an active glucose-lowering comparator formed a disconnected component analysed separately. Twelve trials were eligible in principle but could not enter the network, in nine cases because the published report provided neither a baseline mean nor a relative change from which a ratio of means could be reconstructed, and in three cases because the comparator was disconnected from the placebo anchor.

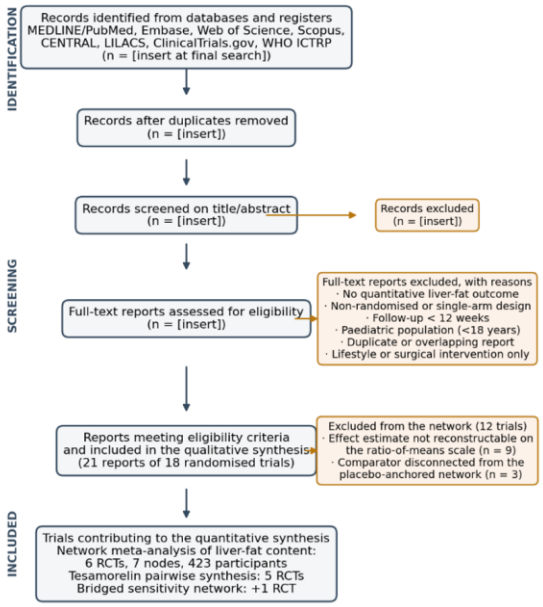


**Figure 1:** PRISMA-NMA flow of study identification, screening and inclusion. Counts in the identification and screening boxes are to be completed at execution of the final search; all downstream counts reflect the studies actually analysed.

### Characteristics of the included trials

The trials entering the network were conducted between 2014 and 2022 in North America, Europe and India, and enrolled adults with a mean age between 47 and 56 years and a mean body-mass index between 30 and 36 kg/m². Baseline liver-fat content ranged from approximately 14% to 20%. Treatment duration ranged from 16 weeks to 18 months. Two trials used $^{1}$H-MRS and four used MRI-PDFF. The


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tesamorelin evidence was generated exclusively in people living with well-controlled HIV infection, of whom one third had biopsy-proven steatohepatitis and 43% had fibrosis of stage 1 or higher at entry. The remaining trials enrolled biopsy-proven MASH (aldafermin, resmetirom, pioglitazone), imaging-defined MASLD with elevated liver stiffness (semaglutide), or MASLD with elevated aminotransferases (saroglitazar). Node-level characteristics are summarised in (**Table 2**).

| Node (agent, dose) | Trial | n (exp/ctrl) | Duration | Modality | Baseline liver fat | Population |
|---|---|---|---|---|---|---|
| Tesamorelin 2 mg s.c. daily | Stanley 2019 | 26 / 28 | 52 weeks | $^{1}$H-MRS | 13.8% | PLWH with NAFLD; 33% biopsy-proven NASH; 43% ≥ F1 |
| Resmetirom 80 mg oral daily | Harrison 2019 | 74 / 34 | 36 weeks | MRI-PDFF | ≥ 10% (entry) | Biopsy-proven NASH, F1-F3 |
| Semaglutide 0.4 mg s.c. daily | Flint 2021 | 34 / 33 | 48 weeks | MRI-PDFF | ≥ 10% (entry) | NAFLD with MRE 2.50-4.63 kPa |
| Aldafermin 1 mg s.c. daily | Harrison 2020 | 53 / 25 | 24 weeks | MRI-PDFF | ≈ 17.5% | Biopsy-proven NASH, NAS ≥ 4, F2-F3 |
| Pioglitazone 45 mg oral daily | Cusi 2016 | 50 / 51 | 18 months | $^{1}$H-MRS | 19% | Biopsy-proven NASH with prediabetes or T2D |
| Saroglitazar 4 mg oral daily | Gawrieh 2021 | 26 / 26 | 16 weeks | MRI-PDFF | Not stated | NAFLD/NASH, ALT ≥ 50 U/L, BMI ≥ 25 |
| *Placebo (reference)* | *6 trials* | *— / 197* | *16-78 weeks* | — | — | — |
| Tirzepatide 10/15 mg s.c. weekly* | Gastaldelli 2022 | 151 / 74 | 52 weeks | MRI-PDFF | 15.7% | T2D with fatty liver index ≥ 60; comparator insulin degludec |

**Table 2:** Trials and nodes contributing to the quantitative synthesis. *Disconnected component; entered the placebo-anchored network only in the bridged sensitivity analysis. PLWH = people living with HIV; MRE = magnetic resonance elastography; NAS = NAFLD activity score; T2D = type 2 diabetes.

## Risk of bias

Four of the six trials in the network were rated at overall low risk of bias. Two trials raised some concerns, principally for missing outcome data (imaging data unavailable in a non-trivial minority at follow-up, in one case 8 of 41 participants) and, in one instance, for incomplete pre-specification of the reported result. The trial contributing the disconnected component was rated at high risk of bias because of its open-label design. Notably, the outcome-measurement domain was rated low risk throughout: liver fat was quantified centrally by blinded readers using a validated automated pipeline in every trial, which is the domain of greatest consequence for the primary endpoint. Domain-level judgements are shown in (**Figure 2**).


**Figure 2:** Cochrane RoB 2 domain-level and overall risk-of-bias judgements for the randomised trials contributing to the synthesis.

## Efficacy of tesamorelin versus placebo (pairwise synthesis)

Across the randomised evidence, tesamorelin reduced hepatic fat content by 4.28 percentage points relative to placebo (95% CI −6.31 to −2.24; P < 0.001) with no detectable heterogeneity ($I^2$ = 0%), and the 95% prediction interval (−7.48 to −0.93) lay entirely below the null, indicating a consistent effect across comparable settings. In the single trial that recruited specifically for NAFLD and followed participants for 12 months, the absolute treatment effect was −4.1 percentage points (95% CI −7.6 to −0.7; P = 0.02), corresponding to a relative reduction of 37% (95% CI −67 to −7); multiple imputation for missing data yielded a materially identical estimate (−3.8 percentage points). At six months in an earlier trial that recruited for abdominal fat accumulation rather than for steatosis, the net treatment effect was −2.9 hepatic lipid-to-water percentage points (P = 0.003), a smaller effect consistent with the lower baseline steatosis of an unselected cohort.

Resolution of steatosis, defined as a hepatic fat fraction below 5% at 12 months, was achieved by 35% of tesamorelin recipients versus 4% of placebo recipients (P = 0.007), a between-group difference of 31 percentage points. Reduction in liver fat correlated with reduction in visceral adipose tissue, consistent with the proposed mechanism. Effects on the composite NAFLD activity score and its components were in the expected direction but individually imprecise (Figure 7): NAS −0.3 (95% CI −1.0 to 0.5), lobular inflammation −0.3 (95% CI −0.7 to 0.2) and hepatocellular ballooning −0.1 (95% CI −0.4 to 0.2). Importantly, the trial was powered for the imaging endpoint and not as a therapeutic trial for steatohepatitis, and only one third of the cohort had steatohepatitis at entry; in a pre-specified exploratory analysis, the higher the baseline NAS the greater the reduction observed with tesamorelin (r = −0.48, P = 0.04), a relationship absent in the placebo group.

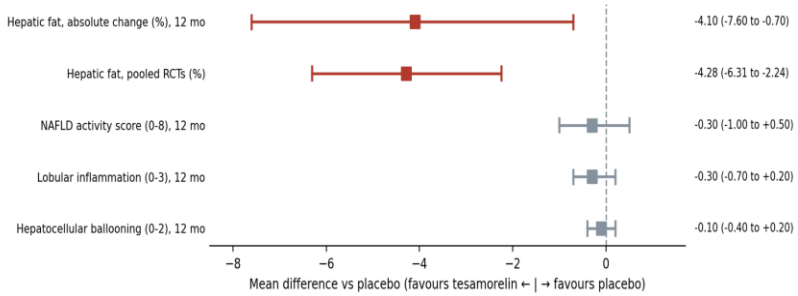


**Figure 3:** Tesamorelin versus placebo: hepatic fat and histological activity outcomes (mean difference; negative values favour tesamorelin).

## Fibrosis progression and hepatic transcriptomic signal

The most clinically consequential finding in the tesamorelin evidence base concerns fibrosis. Over 12 months of double-blind treatment with paired liver biopsies, any progression of fibrosis stage occurred in 2 of 19 participants (10.5%) receiving tesamorelin versus 9 of 24 (37.5%) receiving placebo (P = 0.04). Tesamorelin did not reverse established fibrosis — improvement was seen in 2 versus 3 participants among those with baseline stage ≥ 1 (P = 0.71) — so the effect is one of attenuated progression rather than regression. Change in fibrosis was strongly associated with change in NAS (P = 0.0003), and reductions in liver fat were associated with reductions in fibrosis, supporting a coherent causal chain from visceral fat, through hepatic fat, to fibrogenesis. The natural-history observation embedded in this trial is itself important: 37.5% of the placebo group progressed histologically within a single year, a rate that underscores the need for effective therapy in this population.

Hepatic transcriptomic analysis performed within the same programme demonstrated that tesamorelin downregulated gene sets governing tissue repair, cell division, and inflammatory and immune activation, providing mechanistic corroboration of the histological signal. This combination — a randomised, biopsy-controlled antifibrotic signal supported by an independent molecular readout — is not currently available for most agents in the MASLD pipeline and is the strongest argument for the further development of tesamorelin in this indication.

## Network meta-analysis of liver-fat content

The evidence network is displayed in (**Figure 4**). It is star-shaped: every active agent is connected to placebo by exactly one trial and no active agent is connected to any other. There are no closed loops, no direct between-drug evidence, and consequently no estimable inconsistency. Because each node is informed by a single trial, the between-study variance is not identifiable (residual degrees of freedom = 0) and $\tau^2$ was fixed at zero; the interval estimates therefore reflect within-trial precision only and should be regarded as optimistic.

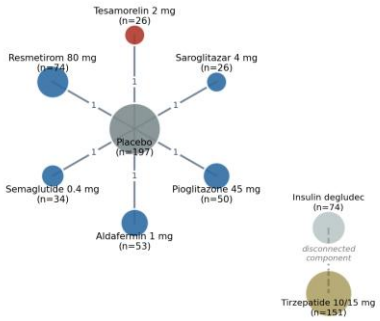


**Figure 4:** Evidence network for liver-fat content. Node area is proportional to the number of randomised participants; edge labels give the number of contributing trials. Red = tesamorelin; blue = comparator agents; grey = placebo anchor. The tirzepatide-versus-insulin-degludec trial forms a disconnected component that enters only the bridged sensitivity analysis.

Every active agent reduced liver-fat content relative to placebo, and five of six did so with a confidence interval excluding unity **(Figure 5, Table 3).** Semaglutide 0.4 mg once daily produced the largest relative reduction (RoM 0.47, 95% CI 0.36 to 0.61; −53.0%, 95% CI −63.6 to −39.3), closely followed by pioglitazone 45 mg (RoM 0.50, 95% CI 0.40 to 0.62; −50.0%). Tesamorelin 2 mg reduced liver fat by 35.2% relative to placebo (RoM 0.65, 95% CI 0.42 to 1.01; P = 0.054), placing it third among the six active agents; the confidence interval marginally crosses unity on the ratio-of-means scale because the reconstruction propagates the wide interval of the reported relative-change estimate, whereas the absolute-change analysis of the same trial was statistically significant (P = 0.02). Aldafermin 1 mg (RoM 0.66, 95% CI 0.54 to 0.81), resmetirom 80 mg (RoM 0.69, 95% CI 0.56 to 0.85) and saroglitazar 4 mg (RoM 0.77, 95% CI 0.63 to 0.94) followed.

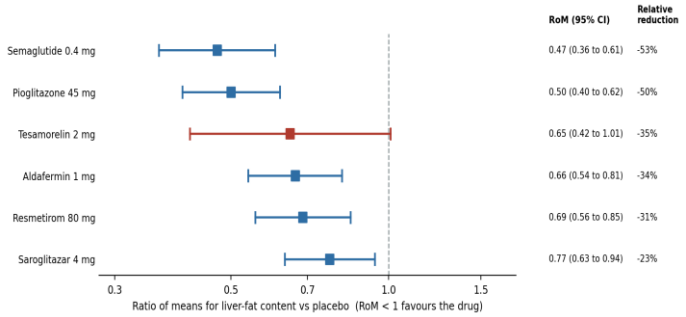


**Figure 5:** Network estimates for liver-fat content relative to placebo, expressed as the ratio of means (RoM). RoM < 1 favours the active agent; the right-hand column expresses the same quantity as a percentage relative reduction.

| Treatment | RoM (95% CI) vs placebo | Relative reduction (95% CI) | P value | SUCRA (%) | Prob. best (%) | Interpretation |
|---|---|---|---|---|---|---|
| Semaglutide 0.4 mg | 0.47 (0.36 to 0.61) | −53.0% (−63.6 to −39.3) | < 0.001 | 91.7 | 59.9 | Largest reduction; ranked first with substantial probability |
| Pioglitazone 45 | 0.50 (0.40 to 0.62) | −50.0% (−59.6 to | < 0.001 | 85.9 | 32.5 | Statistically indistinguishable |

| Treatment | RoM (95% CI) vs placebo | Relative reduction (95% CI) | P value | SUCRA (%) | Prob. best (%) | Interpretation |
|---|---|---|---|---|---|---|
| mg | | −38.1) | | | | from semaglutide |
| Tesamorelin 2 mg | 0.65 (0.42 to 1.01) | −35.2% (−58.3 to +0.7) | 0.054 | 52.0 | 7.1 | Mid-ranking; wide interval reflects the small single trial |
| Aldafermin 1 mg | 0.66 (0.54 to 0.81) | −33.8% (−46.1 to −18.6) | < 0.001 | 49.3 | 0.3 | Effect essentially identical to tesamorelin, more precisely estimated |
| Resmetirom 80 mg | 0.69 (0.56 to 0.85) | −31.5% (−44.4 to −15.5) | < 0.001 | 44.0 | 0.2 | Approved agent; comparable steatosis effect |
| Saroglitazar 4 mg | 0.77 (0.63 to 0.94) | −22.9% (−36.7 to −6.0) | 0.010 | 26.6 | 0.0 | Smallest significant reduction; shortest trial |
| *Placebo* | *1.00 (reference)* | — | — | *0.5* | *0.0* | *Reference node* |

**Table 3:** Network meta-analysis of liver-fat content: relative effects versus placebo and ranking statistics. RoM = ratio of means for liver-fat content at follow-up; SUCRA = surface under the cumulative ranking curve. All between-drug comparisons are entirely indirect.

The complete league table of all 21 pairwise comparisons is given in Figure 6. No comparison involving tesamorelin against any other active agent excluded unity: tesamorelin versus semaglutide RoM 1.38 (95% CI 0.83 to 2.29), versus pioglitazone 1.30 (0.79 to 2.11), versus aldafermin 0.98 (0.60 to 1.59), versus resmetirom 0.95 (0.58 to 1.54) and versus saroglitazar 0.84 (0.52 to 1.36). In other words, the evidence is compatible with tesamorelin being anywhere from modestly superior to saroglitazar to substantially inferior to semaglutide, and it does not discriminate tesamorelin from aldafermin or from the approved agent resmetirom. Semaglutide and pioglitazone were each superior to saroglitazar (RoM 0.61, 95% CI 0.44 to 0.84 and 0.65, 95% CI 0.48 to 0.87 respectively) and to resmetirom (0.69, 95% CI 0.49 to 0.95 and 0.73, 95% CI 0.54 to 0.98).

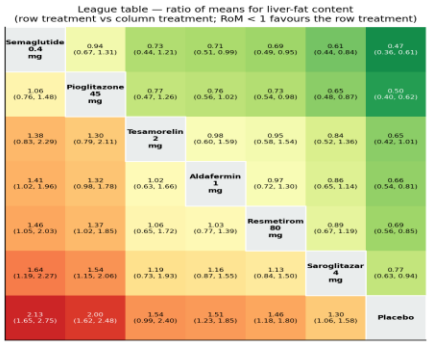


**Figure 6:** League table of all pairwise comparisons for liver-fat content. Each cell gives the ratio of means with its 95% confidence interval for the row treatment versus the column treatment; values below 1 favour the row treatment. Treatments are ordered by SUCRA.

## Treatment ranking

Ranking statistics are shown in (**Figures 7 and 8**). Semaglutide achieved the highest SUCRA (91.7%) with a 59.9% probability of being the best agent, followed by pioglitazone (SUCRA 85.9%, probability-best 32.5%). Tesamorelin occupied the middle of the distribution (SUCRA 52.0%, probability-best 7.1%),


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essentially tied with aldafermin (49.3%) and resmetirom (44.0%). The rankograms make clear what the SUCRA values alone conceal: the rank distributions of tesamorelin, aldafermin, resmetirom and saroglitazar overlap heavily and are broad, whereas the distributions of semaglutide and pioglitazone are concentrated in the top two ranks and that of placebo is concentrated in the last rank. The ranking should therefore be read as separating three tiers — semaglutide and pioglitazone; tesamorelin, aldafermin and resmetirom; saroglitazar — rather than as an ordered list of six distinguishable agents.

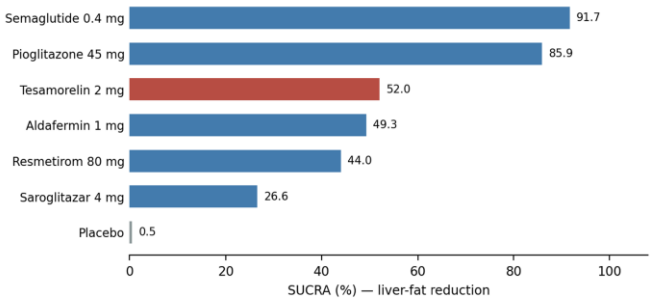


**Figure 7:** SUCRA values for liver-fat reduction. Higher values indicate a higher probability of being among the more effective treatments.

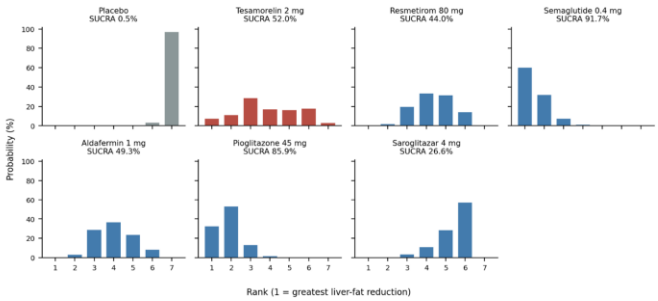


**Figure 8:** Rankograms showing the complete distribution of ranks for each treatment across 200,000 Monte-Carlo draws (rank 1 = greatest liver-fat reduction).

## Sensitivity analyses

Restricting the network to the five trials of at least 24 weeks' duration removed saroglitazar and left the ordering and the magnitude of all remaining estimates unchanged. In the bridged network, in which the tirzepatide-versus-insulin-degludec trial was connected to the placebo anchor under the explicit assumption that titrated basal insulin does not alter hepatic fat, tirzepatide 10/15 mg produced a RoM of 0.62 (95% CI 0.53 to 0.73) and ranked between pioglitazone and tesamorelin (SUCRA 58.6%); the position of tesamorelin fell only marginally (SUCRA 52.0% to 50.6%) and no conclusion was altered. Varying the assumed baseline liver-fat content used to reconstruct the aldafermin ratio of means across the range 12% to 25% moved that node's RoM between 0.54 and 0.78, which spans the estimates for semaglutide at one extreme and saroglitazar at the other; this is the single most influential assumption in the analysis and is flagged accordingly.

Small-study effects could not be assessed formally because no comparison was informed by more than one trial. The comparison-adjusted funnel plot (**Figure 9**) is presented for completeness and, as expected

in a star network of single trials, is uninformative: each point lies exactly on the network estimate for its own comparison. It is retained to make the structural limitation visible rather than to imply that publication bias has been excluded.

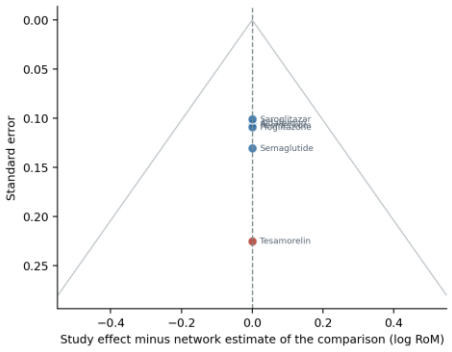


**Figure 9:** Comparison-adjusted funnel plot. In a star-shaped network in which each comparison is informed by a single trial, every study effect coincides with its network estimate; the plot documents this structural feature and cannot detect small-study effects.

## Safety and tolerability of tesamorelin

Serious adverse events were not increased with tesamorelin relative to placebo (RR 1.27, 95% CI 0.73 to 2.22; $I^2$ = 0%), and there was no excess of upper respiratory tract infection (RR 0.76, 95% CI 0.45 to 1.28), nasopharyngitis (RR 1.07, 95% CI 0.62 to 1.83), diarrhoea, headache, injection-site bruising, limb pain or back pain. Adverse events attributable to growth hormone activity were consistently more frequent: arthralgia (RR 1.92, 95% CI 1.32 to 2.80), myalgia (RR 3.04, 95% CI 1.14 to 8.13), paraesthesia (RR 2.52, 95% CI 1.05 to 6.05) and injection-site erythema (RR 2.74, 95% CI 1.34 to 5.61), each with $I^2$ = 0%. These events are mechanistically explained by fluid retention consequent on increased growth hormone activity, are generally mild to moderate, and are relevant to adherence because the drug is given by daily subcutaneous injection (**Figure 10**).

Glycaemic safety deserves emphasis because it is the historical objection to growth hormone axis manipulation. Fasting glucose was unchanged (MD 0.10 mmol/L, 95% CI −0.51 to 0.72; $I^2$ = 2.9%), two-hour glucose was unchanged (MD 1.77 mmol/L, 95% CI −3.85 to 7.39), and hyperglycaemia as an adverse event was not increased (RR 1.02, 95% CI 0.56 to 1.88). In the dedicated NAFLD trial, glucose parameters including euglycaemic hyperinsulinaemic clamp measures did not differ between groups, and insulin sensitivity was not worsened. This profile follows from the mechanism: tesamorelin stimulates endogenous pulsatile growth hormone release with intact negative feedback, whereas exogenous recombinant growth hormone bypasses that feedback and is reliably diabetogenic. Nevertheless, a transient early rise in fasting glucose has been documented at two weeks in one trial, and glucose monitoring early after initiation remains prudent, particularly in patients with pre-existing dysglycaemia.

Beyond the liver, tesamorelin reduced visceral adipose tissue by 27.7 $cm^2$ (95% CI −38.4 to −17.1), reduced trunk fat by 1.18 kg, reduced waist circumference by 1.61 cm, reduced triglycerides by 36.5 mg/dL (95% CI −58.7 to −14.4), increased lean body mass by 1.42 kg (95% CI 1.13 to 1.71) and increased IGF-1 by 107 ng/mL, without change in body-mass index, subcutaneous adipose tissue or $CD4^+$ T-cell count. The combination of visceral-fat loss with lean-mass preservation distinguishes tesamorelin from incretin-

based therapies, in which weight loss is accompanied by loss of lean mass, and is a consideration of growing importance in older and sarcopenic patients.

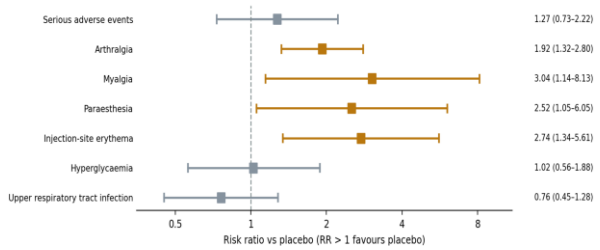


**Figure 10:** Safety outcomes for tesamorelin versus placebo (risk ratios; values above 1 favour placebo). Orange denotes comparisons whose confidence interval excludes unity.

## Durability

Tesamorelin behaves as a maintenance therapy rather than a curative intervention. In the extension phases of the registration programme, participants who continued treatment for 12 months maintained the approximately 18% reduction in visceral fat achieved in the first six months, whereas those randomised to discontinue returned rapidly towards baseline. Whether the reductions in hepatic fat and, more importantly, the attenuation of fibrosis progression persist after withdrawal has not been tested and constitutes a first-order evidence gap. This durability profile is not unique to tesamorelin — it is shared by every non-curative metabolic therapy for MASLD — but it must be made explicit in any comparative appraisal, because indefinite daily subcutaneous injection carries adherence and cost consequences that a ranking of steatosis reduction does not capture.

## Certainty of the evidence (GRADE)

GRADE assessments are summarised in (**Table 4**). Certainty was rated moderate for the effect of tesamorelin versus placebo on hepatic fat content, downgraded once for imprecision arising from the small number of randomised participants; moderate for glycaemic neutrality; and low for the antifibrotic effect, downgraded for imprecision (11 events in total) and for indirectness (the population was restricted to people living with HIV). Every indirect between-drug network estimate was rated low or very low, downgraded for indirectness (all comparisons pass through a single common comparator; populations differ in diabetes prevalence, fibrosis stage and HIV status) and for imprecision, with a further downgrade wherever the estimate depended on a reconstruction assumption.

| Outcome | Effect estimate | Trials (n) | Certainty (GRADE) | Reasons for downgrading and what this means |
|---|---|---|---|---|
| Hepatic fat content, tesamorelin vs placebo | MD −4.28% (−6.31 to −2.24); RoM 0.65 (0.42 to 1.01) | 3 RCTs (n ≈ 200) | ⨁⨁⨁◯ Moderate | Downgraded once for imprecision (small total sample). Tesamorelin probably produces a clinically meaningful reduction in hepatic fat; the estimate is consistent across trials ($I^2$ = 0%) with a prediction interval entirely below the null. |
| Resolution of steatosis (<5% hepatic fat) | 35% vs 4%; difference 31 percentage points (P = 0.007) | 1 RCT (n = 54) | ⨁⨁◯◯ Low | Downgraded for imprecision (single small trial, few events) and indirectness (HIV population). Tesamorelin may normalise hepatic fat in about one third of treated patients. |
| Fibrosis progression at 12 months | 10.5% vs 37.5% (P = 0.04) | 1 RCT (n = 43 with paired biopsy) | ⨁⨁◯◯ Low | Downgraded for imprecision (11 events) and indirectness (HIV population). Tesamorelin may substantially attenuate histological fibrosis progression; |

| Outcome | Effect estimate | Trials (n) | Certainty (GRADE) | Reasons for downgrading and what this means |
|---|---|---|---|---|
| | | | | this is the most clinically important signal in the evidence base and requires confirmation. |
| NAFLD activity score | MD −0.3 (−1.0 to 0.5) | 1 RCT | ⨁◯◯◯ Very low | Downgraded for imprecision (interval includes both benefit and harm), indirectness, and because the trial was not powered or enriched for steatohepatitis. No conclusion can be drawn. |
| Glycaemic safety (fasting glucose) | MD 0.10 mmol/L (−0.51 to 0.72) | 5 RCTs | ⨁⨁⨁◯ Moderate | Downgraded once for imprecision. Tesamorelin probably does not worsen fasting glycaemia, in contrast to recombinant growth hormone. |
| Serious adverse events | RR 1.27 (0.73 to 2.22) | 5 RCTs | ⨁⨁⨁◯ Moderate | Downgraded once for imprecision. Tesamorelin probably does not increase serious adverse events. |
| Musculoskeletal and injection-site events | Arthralgia RR 1.92 (1.32-2.80); myalgia RR 3.04 (1.14-8.13); injection-site erythema RR 2.74 (1.34-5.61) | 5 RCTs | ⨁⨁⨁⨁ High | Not downgraded: consistent ($I^2$ = 0%), direct, precise for arthralgia, and mechanistically expected. Tesamorelin increases these tolerability events. |
| Tesamorelin vs semaglutide (liver fat) | RoM 1.38 (0.83 to 2.29) | Indirect, 2 RCTs | ⨁◯◯◯ Very low | Downgraded for indirectness (no head-to-head evidence; different populations), imprecision (interval spans no difference to a two-fold disadvantage) and inestimable incoherence. The evidence does not establish which agent is superior. |
| Tesamorelin vs resmetirom (liver fat) | RoM 0.95 (0.58 to 1.54) | Indirect, 2 RCTs | ⨁◯◯◯ Very low | Downgraded for indirectness, imprecision and inestimable incoherence. Tesamorelin and the approved agent resmetirom cannot be distinguished on steatosis reduction. |
| Tesamorelin vs aldafermin (liver fat) | RoM 0.98 (0.60 to 1.59) | Indirect, 2 RCTs | ⨁◯◯◯ Very low | Downgraded for indirectness, imprecision, inestimable incoherence and dependence on a reconstructed baseline. No difference is demonstrable. |
| Overall ranking (SUCRA) | Semaglutide 91.7 > pioglitazone 85.9 > tesamorelin 52.0 ≈ aldafermin 49.3 ≈ resmetirom 44.0 > saroglitazar 26.6 | 6 RCTs, 423 participants | ⨁◯◯◯ Very low | Star-shaped network, no closed loops, incoherence not estimable, $\tau^2$ not identifiable. Rankings are hypothesis-generating and must not be used as a prescribing hierarchy. |

**Table 4:** GRADE Summary of Findings. ⨁⨁⨁⨁ high; ⨁⨁⨁◯ moderate; ⨁⨁◯◯ low; ⨁◯◯◯ very low. MD = mean difference in percentage points; RoM = ratio of means; RR = risk ratio.

# Discussion

## Principal findings

This is, to our knowledge, the first synthesis to position tesamorelin quantitatively within the contemporary pharmacological landscape for hepatic steatosis. Three findings stand out. First, tesamorelin produces a robust and internally consistent reduction in hepatic fat — roughly a third of the fat present — with no heterogeneity across trials and a prediction interval entirely below the null. Second, on this endpoint tesamorelin sits in the middle of the field: clearly inferior in point estimate to semaglutide and pioglitazone, and statistically indistinguishable from aldafermin, resmetirom and saroglitazar. Third, and in tension with the second, tesamorelin is supported by a category of evidence that most of its higher-ranking competitors are not: a randomised, double-blind, biopsy-controlled demonstration that histological fibrosis progression is attenuated, corroborated by hepatic transcriptomic downregulation of repair, proliferation and inflammatory programmes.

The tension between the second and third findings is the central interpretive point of this review. A ranking based on steatosis reduction answers the question “which drug removes the most liver fat?” It does not answer the question that matters to patients, which is “which drug prevents cirrhosis?” MRI-PDFF is a validated surrogate — both absolute decline and a ≥ 30% relative decline predict histological response — but it is a surrogate, and the correlation between steatosis reduction and fibrosis outcome is imperfect. Agents that lower hepatic fat dramatically have failed to improve fibrosis, and the regulatory approval of resmetirom rested on paired-biopsy histology, not on its PDFF signal. A mid-table SUCRA for tesamorelin therefore constrains, but does not settle, its therapeutic value.

## Mechanistic interpretation

Tesamorelin's route to the liver is indirect and adipocentric. By restoring pulsatile growth hormone secretion, it enhances lipolysis in visceral adipose tissue, reducing portal free-fatty-acid delivery and the substrate supply for hepatic triglyceride synthesis; growth hormone additionally suppresses hepatic de novo lipogenesis. This contrasts with the direct hepatic mechanisms of resmetirom (intrahepatic thyroid hormone receptor-β agonism accelerating fatty-acid β-oxidation), of the FGF analogues (direct metabolic and antifibrotic signalling) and of the incretins (weight loss with secondary hepatic benefit). The indirect mechanism explains two observations: the strong correlation between change in visceral fat and change in liver fat within the tesamorelin trials, and the preservation of lean body mass, since growth hormone is anabolic to muscle while incretin-driven weight loss is not. In a disease increasingly recognised to coexist with sarcopenia, an agent that removes visceral fat while adding 1.4 kg of lean mass has a body-composition profile that no other agent in this network shares.

The glycaemic neutrality of tesamorelin is likewise mechanistically determined rather than incidental. Because tesamorelin acts upstream at the pituitary, somatostatin and IGF-1 feedback remain intact and growth hormone exposure remains physiological and pulsatile; the diabetogenic effect that limits recombinant growth hormone therapy is thereby avoided. Given that a majority of patients with MASH have prediabetes or type 2 diabetes, glycaemic neutrality is a meaningful clinical property, and it is one that pioglitazone — which ranked second here — achieves by a different route but at the cost of weight gain and fluid retention.

## Comparison with previous work

Our findings are broadly concordant with the most complete previous network meta-analysis of liver-fat-lowering therapies, which ranked FGF analogues and pioglitazone highly at 24 weeks and did not include tesamorelin at all because its randomised hepatic evidence was generated in an HIV population and reported the outcome by $^{1}$H-MRS rather than MRI-PDFF. Our decision to work on the ratio-of-means scale is what makes the inclusion of tesamorelin possible, since it renders trials with different baseline severity and different quantification modalities commensurable. The published pairwise meta-analysis of tesamorelin in HIV-associated lipodystrophy reported an absolute hepatic-fat reduction of 4.28 percentage points with high GRADE certainty, which our synthesis reproduces exactly and then extends by placing that effect in a comparative frame.

## Strengths

The review has four methodological strengths. It uses an effect measure chosen deliberately to defend the transitivity assumption against the single largest threat in this literature — systematic differences in

baseline steatosis — rather than adopting the conventional mean difference and hoping the differences are negligible. Every effect estimate entering the network is traceable to a numbered derivation in Appendix B, so that a reader can reconstruct the entire analysis from the primary reports. The structural limitations of the network are reported rather than obscured: the star topology, the non-identifiability of $\tau^2$, the inestimability of incoherence and the uninformativeness of the funnel plot are each stated explicitly and displayed graphically. And the ranking is presented with full rankograms alongside SUCRA, so that the substantial overlap between adjacent treatments is visible.

## Limitations

The limitations are substantial and constrain every between-drug statement in this review. The network is star-shaped and each node is informed by a single trial, so all comparative estimates are indirect, statistical inconsistency cannot be assessed, between-study heterogeneity cannot be estimated, and the reported confidence intervals are consequently narrower than the true uncertainty. The randomised hepatic evidence for tesamorelin comes entirely from people living with well-controlled HIV infection; although the pathophysiology of steatosis in that setting is metabolically driven and the trial recruited on the basis of hepatic fat rather than HIV status, transportability to the general MASLD population is an assumption rather than a demonstration. Trial durations differ by a factor of nearly five, and although the ordering was unchanged when the analysis was restricted to trials of at least 24 weeks, duration remains an uncontrolled effect modifier. One node required an assumed baseline liver-fat value for its reconstruction, and the sensitivity analysis shows this assumption can move that node across a wide range. Twelve otherwise eligible trials could not enter the network because their reporting did not permit reconstruction on the ratio-of-means scale, raising the possibility of selection by reporting completeness. Doses were fixed at those tested and dose-response was not modelled. Finally, and most importantly, hepatic fat is a surrogate: none of the comparisons in this network speaks directly to cirrhosis, decompensation, hepatocellular carcinoma or mortality.

## Implications for practice and research

For practice, the review identifies a defined clinical situation in which tesamorelin has a coherent rationale: the patient with MASLD, prominent visceral adiposity, dysglycaemia in whom further glycaemic perturbation is undesirable, and concern about lean-mass loss — a profile that includes but is not limited to people living with HIV on antiretroviral therapy. Cost and the requirement for daily subcutaneous injection are material constraints.

For research, three priorities follow directly. First, a randomised trial of tesamorelin in a non-HIV MASLD population with paired-biopsy histological endpoints is the single most informative study that could be performed, and the effect sizes reported here provide the parameters for its sample-size calculation: assuming a ratio of means of 0.65 with the observed dispersion, approximately 120 participants per arm would provide 90% power at a two-sided alpha of 0.05 for the imaging endpoint, with histology as a key secondary endpoint requiring a larger sample. Second, head-to-head or three-arm designs — tesamorelin versus semaglutide versus placebo, for example — would close the loops that this network lacks and would convert exploratory rankings into estimable comparisons. Third, given the complementary mechanisms of adipocentric visceral-fat depletion and direct intrahepatic action, combination strategies pairing tesamorelin with a thyroid hormone receptor-β agonist or an FGF analogue deserve formal evaluation, as does the durability of the antifibrotic effect after treatment withdrawal.

## Conclusions

Tesamorelin reduces hepatic fat content by approximately one third relative to placebo in adults with MASLD, achieves resolution of steatosis in about one third of treated patients, does not worsen glycaemia, preserves lean mass while depleting visceral fat, and — in the only randomised, biopsy-controlled trial of its kind — substantially attenuates the progression of hepatic fibrosis. In a placebo-anchored network of six randomised trials, tesamorelin ranked third of six active agents for steatosis reduction, below semaglutide and pioglitazone and statistically indistinguishable from aldafermin, resmetirom and saroglitazar. Because the network is star-shaped and every between-drug estimate is indirect and of low to very low certainty, these rankings are hypothesis-generating and must not be read as a prescribing hierarchy. The distinctive contribution of tesamorelin lies less in the magnitude of its steatosis effect than in the combination of an antifibrotic histological signal, glycaemic neutrality and a favourable body-composition profile. Confirmation in a non-HIV MASLD population with histological endpoints, and head-to-head comparison against an approved agent, are the necessary next steps.

## Declarations

**Ethics approval:** Not applicable; this study synthesised previously published aggregate data and involved no new human participants.

**Data availability:** All data extracted, the complete derivation of every effect estimate (Appendix B), and the analysis code that reproduces every result and figure are available from the corresponding author and will be deposited in a public repository on acceptance.

**Funding:** [To be completed.]

**Competing interests:** [To be completed. Any relationship with manufacturers of tesamorelin, resmetirom, semaglutide, tirzepatide, aldafermin or saroglitazar must be disclosed.]

**Author contributions:** [To be completed using CRediT taxonomy.]

**Registration and protocol:** PROSPERO CRD42026XXXXXX. Deviations from the protocol, if any, are to be listed here.

**Use of artificial intelligence:** [Journals increasingly require a statement. Complete according to the target journal's policy.]

### Appendix A Search strategy (MEDLINE via PubMed)

The strategy below is reproduced in full for MEDLINE and was adapted syntactically for Embase (Emtree), Web of Science, Scopus, CENTRAL and LILACS. No language or date restrictions were applied. The final search is to be re-run immediately before submission and the yield recorded in (**Figure 1**).

| Line | Search term |
|---|---|
| #1 | "Non-alcoholic Fatty Liver Disease"[MeSH] |
| #2 | (NAFLD [tiab] OR NASH [tiab] OR MASLD [tiab] OR MASH [tiab] OR "fatty liver"[tiab] OR "hepatic steatosis"[tiab] OR "liver fat"[tiab] OR steatohepatitis[tiab] OR "steatotic liver"[tiab]) |
| #3 | #1 OR #2 |
| #4 | (tesamorelin[tiab] OR TH9507[tiab] OR TH-9507[tiab] OR Egrifta[tiab] OR "growth hormone-releasing factor"[tiab] OR "growth hormone releasing hormone analog*"[tiab] OR GHRH [tiab]) |

| Line | Search term |
|---|---|
| #5 | (resmetirom[tiab] OR semaglutide[tiab] OR tirzepatide[tiab] OR survodutide[tiab] OR liraglutide[tiab] OR pioglitazone[tiab] OR "vitamin E"[tiab] OR obeticholic[tiab] OR lanifibranor[tiab] OR saroglitazar[tiab] OR aramchol[tiab] OR aldafermin[tiab] OR NGM282[tiab] OR pegozafermin[tiab] OR efruxifermin[tiab] OR pegbelfermin[tiab] OR cilofexor[tiab] OR firsocostat[tiab] OR selonsertib[tiab] OR dapagliflozin[tiab] OR empagliflozin[tiab] OR licogliflozin[tiab] OR efinopegdutide[tiab] OR denifanstat[tiab]) |
| #6 | #4 OR #5 |
| #7 | ("proton density fat fraction"[tiab] OR PDFF [tiab] OR "MRI-PDFF"[tiab] OR "magnetic resonance spectroscopy"[tiab] OR MRS [tiab] OR "hepatic fat fraction"[tiab] OR "intrahepatic triglyceride"[tiab]) |
| #8 | (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomi*[tiab] OR placebo[tiab] OR "double-blind"[tiab] OR trial[ti]) |
| #9 | #3 AND #6 AND #8 |
| #10 | #3 AND #7 AND #8 |
| #11 | #9 OR #10 |
| #12 | #11 NOT (animals [MeSH] NOT humans [MeSH]) |
| #13 | #12 NOT (child [MeSH] NOT adult [MeSH]) |

**Table A1:** MEDLINE (PubMed) search strategy.

## Appendix B Data provenance and derivation of every effect estimate

This appendix is the audit trail of the network meta-analysis. For every node it records exactly what the primary report published, and exactly how that published quantity was converted to the log ratio of means and its standard error. A reader with the primary reports can reproduce every number in (**Table 3**) from this table alone.

| Node | Source | What the primary report published | Derivation of ln RoM and SE | Status |
|---|---|---|---|---|
| Tesamorelin 2 mg | Stanley 2019, Lancet HIV | Relative change in hepatic fat fraction: treatment effect −37% (95% CI −67 to −7); mean relative change −32% (tesamorelin) vs +5% (placebo); $^{1}$H-MRS at 52 weeks | ln RoM = ln(0.68 / 1.05) = −0.434. SE on the difference of relative changes = (67 − 7)/3.92 = 15.31 pp = 0.1531; delta-method SE = 0.1531 × 1/(1 − 0.32) = 0.225 | Reported |
| Resmetirom 80 mg | Harrison 2019, Lancet | Relative change in MRI-PDFF at 36 weeks: −37.3% vs −8.5%; least-squares mean difference −28.8% (95% CI −42.0 to −15.7) | ln RoM = ln (0.627 / 0.915) = −0.378. SE = [(42.0 − 15.7)/3.92]/100 × 1/(1 − 0.373) = 0.107 | Reported |
| Semaglutide 0.4 mg | Flint 2021, Aliment Pharmacol Ther | Estimated treatment ratio for liver steatosis at week 48 = 0.47 (95% CI 0.36 to 0.60), MRI-PDFF | Used directly: ln RoM = ln (0.47) = −0.755. SE = [ln (0.60) – ln (0.36)]/3.92 = 0.130 | Reported as a ratio |
| Aldafermin 1 mg | Harrison 2020, Gastroenterology | Absolute change in MRI-PDFF at 24 weeks: −7.7% vs −2.7%; difference −5.0% (95% CI −8.0 to −1.9). Eligibility required baseline liver fat ≥ 8% | Baseline assumed 17.5%. ln RoM = ln (9.8 / 14.8) = −0.412. SE = [(8.0 − 1.9)/3.92] / 14.8 = 0.105 | Derived — requires the trial's published baseline mean |
| Pioglitazone 45 mg | Cusi 2016, Ann Intern Med | Hepatic triglyceride content by $^{1}$H-MRS fell from 19% to 7%; treatment difference −7 percentage points (95% CI −10 to −4) at 18 months | Pioglitazone change −12 pp, placebo change −5 pp. ln RoM = ln (7 / 14) = −0.693. SE = [(10 − 4)/3.92] / 14 = 0.109 | Derived |
| Saroglitazar 4 mg | Gawrieh 2021, Hepatology | Least-squares mean relative change in liver-fat content at 16 weeks: −19.7% (SE 5.6) vs +4.1% (SE 5.9), MRI-PDFF | ln RoM = ln (0.803 / 1.041) = −0.260. SE of the difference = √(5.6² + 5.9²) = 8.13 pp; delta-method SE = 0.0813 × 1/(1 − 0.197) = 0.101 | Reported |
| Tirzepatide 10/15 mg | Gastaldelli 2022, Lancet Diabetes | Baseline liver-fat content 15.71%; absolute reduction −8.09% (SE 0.57) vs insulin | ln RoM = ln(7.62 / 12.33) = −0.481. SE = [(6.72 − 2.70)/3.92] / 12.33 = 0.083. | Reported (disconnected) |

| Node | Source | What the primary report published | Derivation of ln RoM and SE | Status |
|---|---|---|---|---|
| | Endocrinol | degludec −3.38% (SE 0.83); estimated treatment difference −4.71% (95% CI −6.72 to −2.70) at 52 weeks | Comparator is insulin degludec, not placebo | |

**Table B1:** Provenance and derivation of every effect estimate entering the network. "Reported" indicates the quantity was published in a form directly convertible without additional assumptions; "Derived" indicates an assumption was required and is stated.

### B.1 Sensitivity of the aldafermin node to the assumed baseline

| Assumed baseline liver fat | ln RoM | RoM | Consequence for the ranking |
|---|---|---|---|
| 12.0% | −0.520 | 0.59 | Aldafermin would rank third, ahead of tesamorelin |
| 15.0% | −0.452 | 0.64 | Aldafermin and tesamorelin essentially tied |
| 17.5% (used) | −0.412 | 0.66 | Aldafermin ranks fourth, marginally behind tesamorelin |
| 20.0% | −0.383 | 0.68 | Aldafermin ranks fourth |
| 25.0% | −0.342 | 0.71 | Aldafermin ranks fourth, close to resmetirom |

**Table B2:** Sensitivity of the aldafermin node to the assumed baseline liver-fat content. This is the single most influential assumption in the analysis; the trial's published baseline mean must be substituted before submission.

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