

## INPLASY

## Dual and Triple Incretin-Based Receptor Agonists for MASLD and MASH: A systematic review of clinical efficacy and emerging therapeutic roles

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IRCCS.**ADMINISTRATIVE INFORMATION****Support** - No support.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100061**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 October 2026 and was last updated on 13 October 2026.**INTRODUCTION**

**Review question / Objective** Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide, ranging from steatosis to steatohepatitis, fibrosis, and cirrhosis. Pharmacological options remain limited and single GLP-1 receptor agonists (GLP-1 RAs) show limited efficacy in controlling liver fibrosis. Dual and triple incretin receptor agonists may offer a clinical benefit if compared to the available therapies. To exploit the clinical efficacy of these agents, compared with placebo or active comparators in the MASLD spectrum we have systematically synthesized the evidence from randomized clinical trials on the effect of these drugs on hepatic fat content, liver enzymes, resolution of MASH, and improvement in fibrosis.

**Rationale** Dual- and triple-incretin-based receptor agonists (RAs), combining GLP-1 with GIP and/or glucagon receptor agonism, may offer greater

benefit. We aimed to systematically review clinical evidence on these agents across the MASLD spectrum.

**Condition being studied** MASLD, Metabolic Associated Steatotic Liver Disease.

**METHODS**

**Search strategy** We systematically searched PubMed, Scopus, Cochrane Library, Web of Science, and ClinicalTrials.gov (Jan 1, 2020-March 31, 2026) for randomised controlled trials of dual- or triple-incretin-based RAs, compared with placebo or active comparators.

**Participant or population** Of 2795 records initially identified, 17 trials, including a total of 4237 participants, were eligible.

**Intervention** Seven different agents were tested over a mean of 35 weeks (SD 15 weeks).

**Comparator** Placebo or active comparator.

**Study designs to be included** Systematic review.

**Eligibility criteria** Eligible studies were required to meet the following inclusion criteria: i) randomised clinical trials (RCTs) with dual-triple incretin RAs ii) studies conducted with a placebo or an active-comparator group iii) RCTs with primary, secondary or exploratory outcomes, including the assessment of the improvement in hepatic steatosis by Liver Fat Composition (LCF), Hepatic Fat Fraction (HFF) or liver enzymes, iv) studies with outcomes evaluating resolution of MASH, improvement in liver fibrosis by histological scoring systems or by fibrosis biomarkers.

**Information sources** PubMed, Scopus, Cochrane, Web of Science databases and ClinicalTrials.gov.

**Main outcome(s)** Main outcomes measured were liver fat content, liver enzymes, and histological fibrosis endpoints.

**Additional outcome(s)** Changes in LFC from baseline and normalisation of liver fat ( $\leq 5\%$ ), changes in liver stiffness measured by vibration-controlled transient elastography (FibroScan), and improvement in liver fibrosis stage. Among secondary and exploratory outcomes, it emerged changes in liver fibrosis and inflammatory biomarkers including N-terminal type III collagen pro-peptide (Pro C3), corrected T1 mapping (cT1), Cytokeratin-18 M30 fragment (CK-18 M30) and changes in liver fibrosis and inflammatory scores including Enhanced Liver Fibrosis score (ELF), Fibrosis-4 Index (FIB-4), NAFLD Activity Score (NAS), FibroScan-AST score (FAST), AST-to-Platelet Ratio Index (APRI), Non-Invasive Score-4 (NIS-4) and NAFLD Fibrosis Score (NFS).

**Data management** Article selection was performed independently by two authors, and any discrepancies were resolved through discussion with a third investigator. For each eligible study, the following variables were retrieved: publication year, study phase, sample size, treatments and dosages, participant characteristics (i.e., age, sex, BMI, T2DM, and diagnosis of MASLD/MASH), and follow-up duration. Due to heterogeneity among the included studies in reported biomarkers, outcome definitions, and analytical approaches, a formal meta-analysis was not performed. Descriptive statistics were used to characterise the included studies, and analyses were performed using GraphPad Prism (11.0.2-92). Graphs were created to summarize the endpoints and characteristics of the studies. Main outcomes

extrapolated from the studies were synthesised narratively and a comment for the clinical use of dual and triple incretin-based therapies was provided.

**Quality assessment / Risk of bias analysis** The risk of bias for each eligible RCT was assessed using the Cochrane Collaboration tool<sup>34</sup> by two independent authors (AL and FG). Any scoring disagreements were reviewed, and a consensus was reached after discussion. The Cochrane Collaboration's tool assesses seven potential sources of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. For each domain, we categorised each eligible RCT into one of three risk-of-bias levels: low, unclear, or high.

**Strategy of data synthesis** Article selection was performed independently by two authors (RP and FG), and any discrepancies were resolved through discussion with a third investigator (LP). For each study meeting the inclusion criteria, the following variables were retrieved: publication year, study phase, sample size, treatments and dosages, participant characteristics (i.e., age, sex, Body Mass Index (BMI), pre-existing T2DM, and diagnosis of MASLD/MASH), and follow-up duration. Due to heterogeneity among the included studies in biomarkers, outcome definitions, and analytical approaches, a formal meta-analysis was not performed. Descriptive statistics were used to characterise the included studies, and analyses were performed using GraphPad Prism (11.0.2-92).

**Subgroup analysis** No formal subgroup analyses were performed. Owing to clinical and methodological heterogeneity, findings were narratively stratified first according to the relevance of liver-related endpoints (primary vs secondary or exploratory), and subsequently according to receptor-agonist class, individual agent, study population, clinical development phase, and type of liver-related outcome.

**Sensitivity analysis** Not applicable due to the nature of this scientific work.

**Language restriction** No.

**Country(ies) involved** Italy.

**Other relevant information** No.

**Keywords** MASLD; MASH; dual incretin receptor agonists; triple incretin receptor agonists; clinical trial; liver outcome.

**Dissemination plans** The findings of this systematic review will be published in a peer-reviewed, open-access scientific journal to ensure broad and unrestricted access for researchers, clinicians, policymakers, and other relevant stakeholders. Following publication, the article will be disseminated through professional and academic social media platforms, including LinkedIn and ResearchGate, as well as through the authors' institutional networks. Where appropriate, the results may also be presented at relevant national and international scientific conferences and shared through institutional communication channels to increase visibility and encourage scientific discussion.

#### Contributions of each author

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