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The Evolving Landscape of MASH Combination Therapy

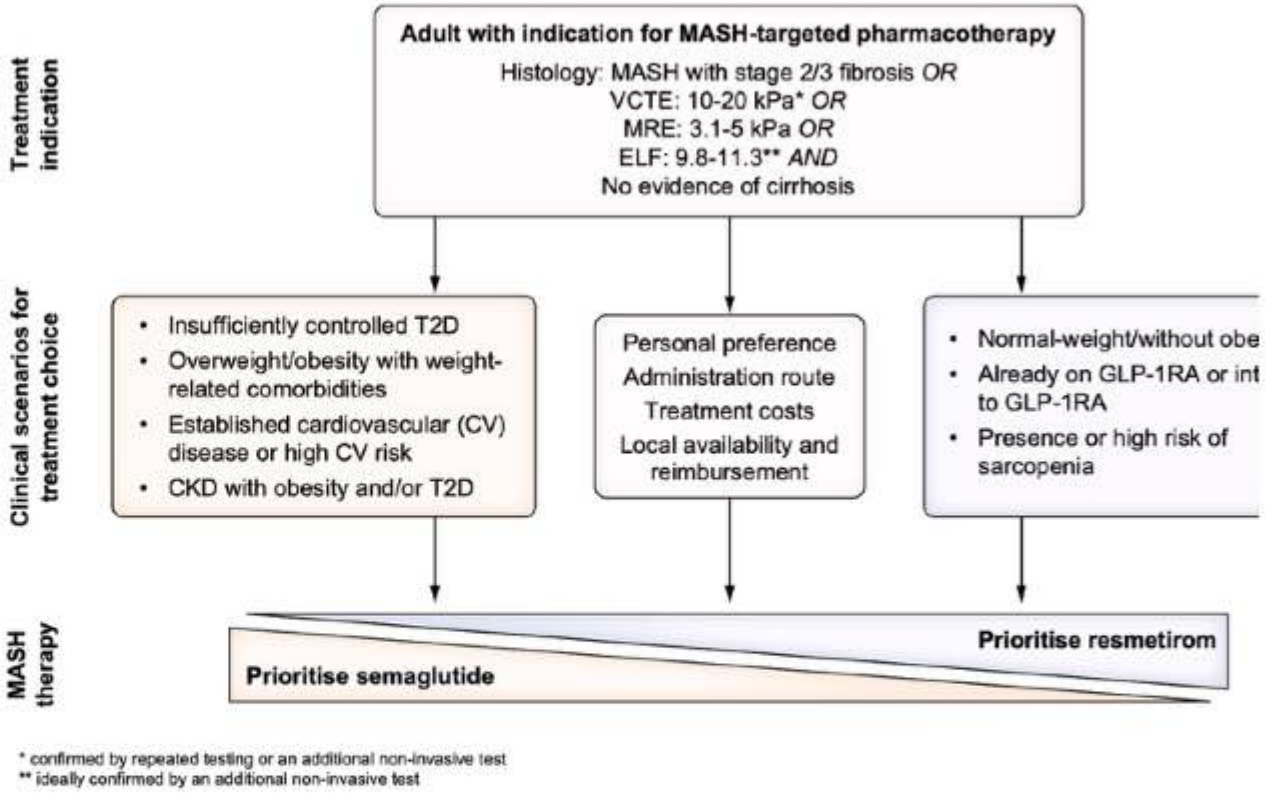
Resmetirom at the center of an expanding treatment landscape



Sources: FDA approvals (2024, 2025); European Commission (2025); EASL–EASD–EASO Guidance (2026); Noureddin et al., APT (2025).

When to consider GLP-1 RAs in MASH-related Fibrosis

In patients with more dominant cardiometabolic burden, GLP-1 RAs are prioritized.



Why Combine Resmetirom with GLP-1 RAs?

Complementary hepatic and metabolic effects

Resmetirom + Background GLP-1 RA Therapy

Greater liver efficacy

Resmetirom directly targets THR-β in the liver and addresses steatosis and fibrosis pathways.

Metabolic support

GLP-1 RAs improve weight, glycemic control, and cardiometabolic drivers that influence

Whole-patient benefit

The combination may help address liver disease alongside obesity, type 2 diabetes, and

Complementary mechanisms provide a rationale

[redacted]

Key takeaway: The focus is not on GLP-1 RAs alone, but on when resmetirom should be added in patients already receiving metabolic therapy.

MAESTRO-NASH: Background GLP-1 RA Use

Trial design and the size of the concomitant-therapy subgroup

PANEL 03

STUDY DESIGN

Phase 3, randomized, double-blind, placebo-controlled

Week 52 secondary analysis

966 randomized patients

CONCOMITANT USE

≈14.7%

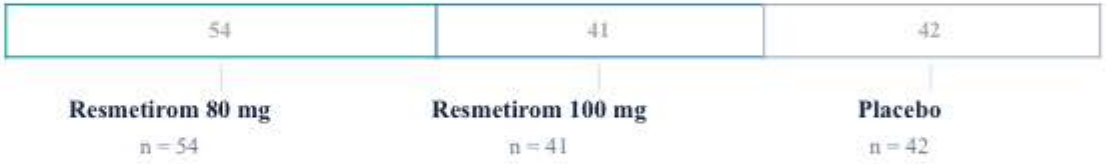
of resmetirom-treated participants

95 patients were already receiving a stable GLP-1 RA when assigned to resmetirom.

GLP-1 RA USE AT BASELINE

137 / 966

14.2% of the overall study population



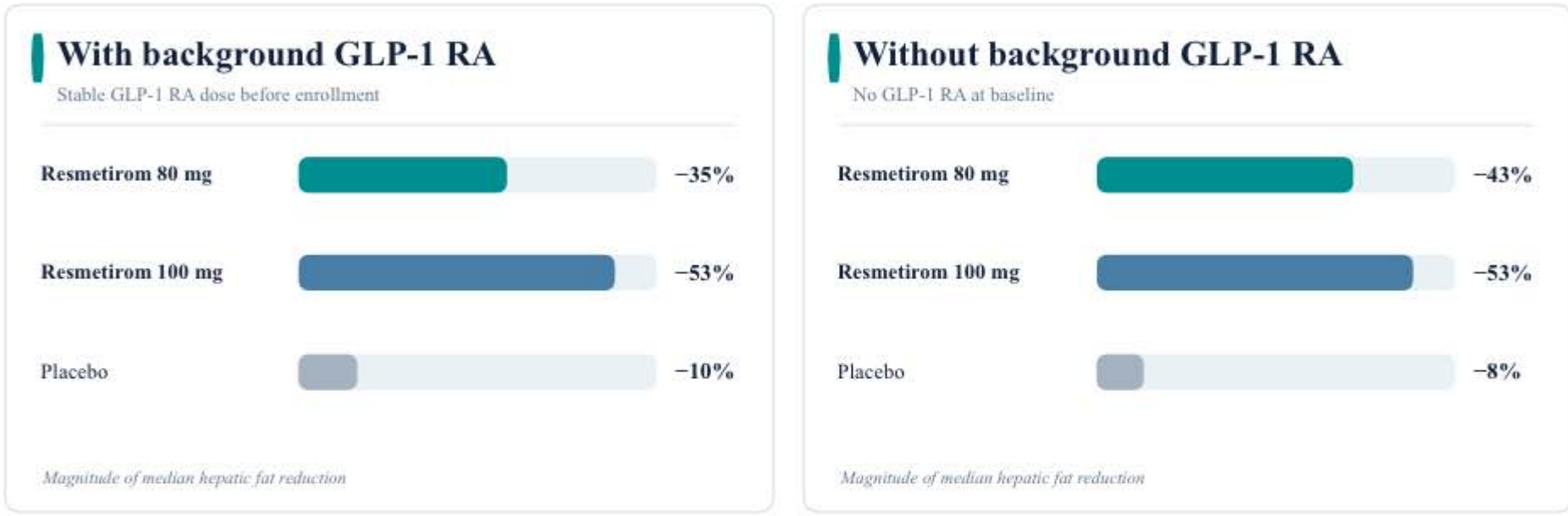
Important: GLP-1 RA was pre-existing therapy (stable ≥6 months), not a randomized trial intervention; all GLP-1 RA users had T2D.

Source: Noureddin M, et al. Aliment Pharmacol Ther. 2025;62:1089–1099. doi:10.1111/apt.70382; Mironova M, et al. Gut. 2026.

Resmetirom Reduces Liver Fat With or Without GLP-1 RA

MAESTRO-NASH secondary analysis | Week 52 | MRI-PDFF median relative change

STABLE BACKGROUND THERAPY



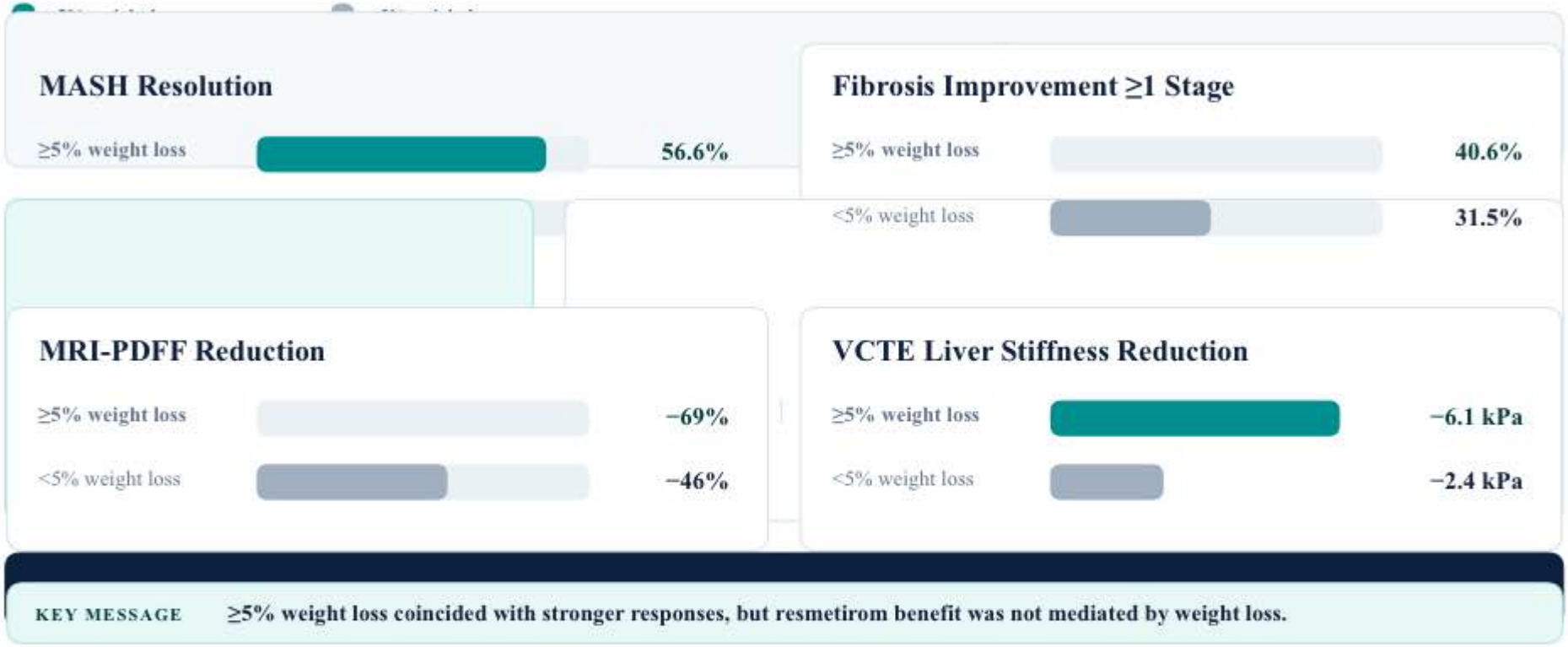
KEY MESSAGE **Resmetirom showed substantial hepatic fat reduction in both background-therapy subgroups.**

Descriptive analysis only: GLP-1 RA status was not randomized; results do not establish added efficacy of the combination.

Noureddin M, et al. Aliment Pharmacol Ther. 2025;62:1089–1099. doi:10.1111/apt.70382.

Weight Loss Is Associated with Better Resmetirom Response

MAESTRO-NASH secondary analysis | Resmetirom 100 mg | Week 52



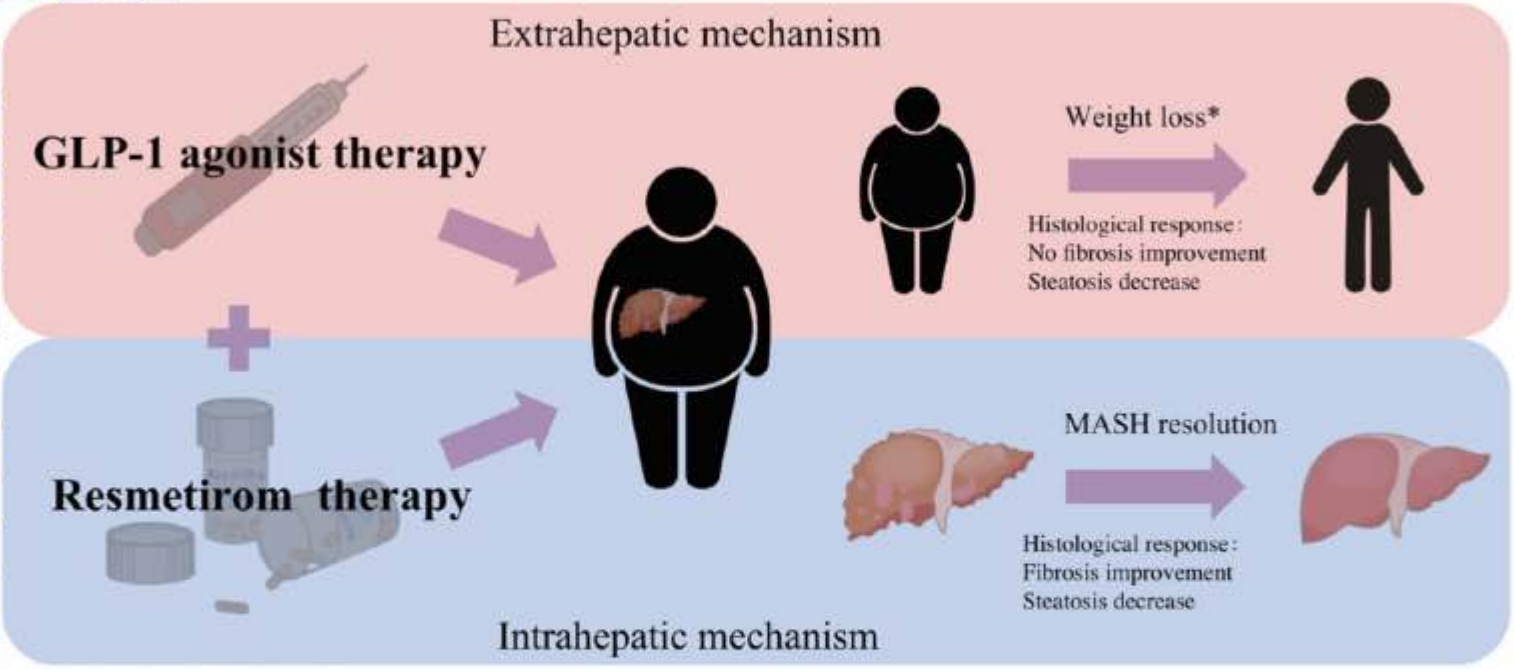
KEY MESSAGE **≥5% weight loss coincided with stronger responses, but resmetirom benefit was not mediated by weight loss.**

Values are within resmetirom 100 mg subgroups (not GLP-1 RA-specific). VCTE: Figure 5A; other measures: Figures 3–4.

Noureddin M, et al. Aliment Pharmacol Ther. 2025;62:1089–1099. doi:10.1111/apt.70382.

Complementary Mechanisms of Resmetirom and GLP-1 RA in MA

Resmetirom directly targets hepatic THR-β receptors, improving hepatic lipid metabolism and reducing liver fat, while GLP-1 receptor agonists primarily address cardiometabolic drivers through weight loss and improved glycemic control

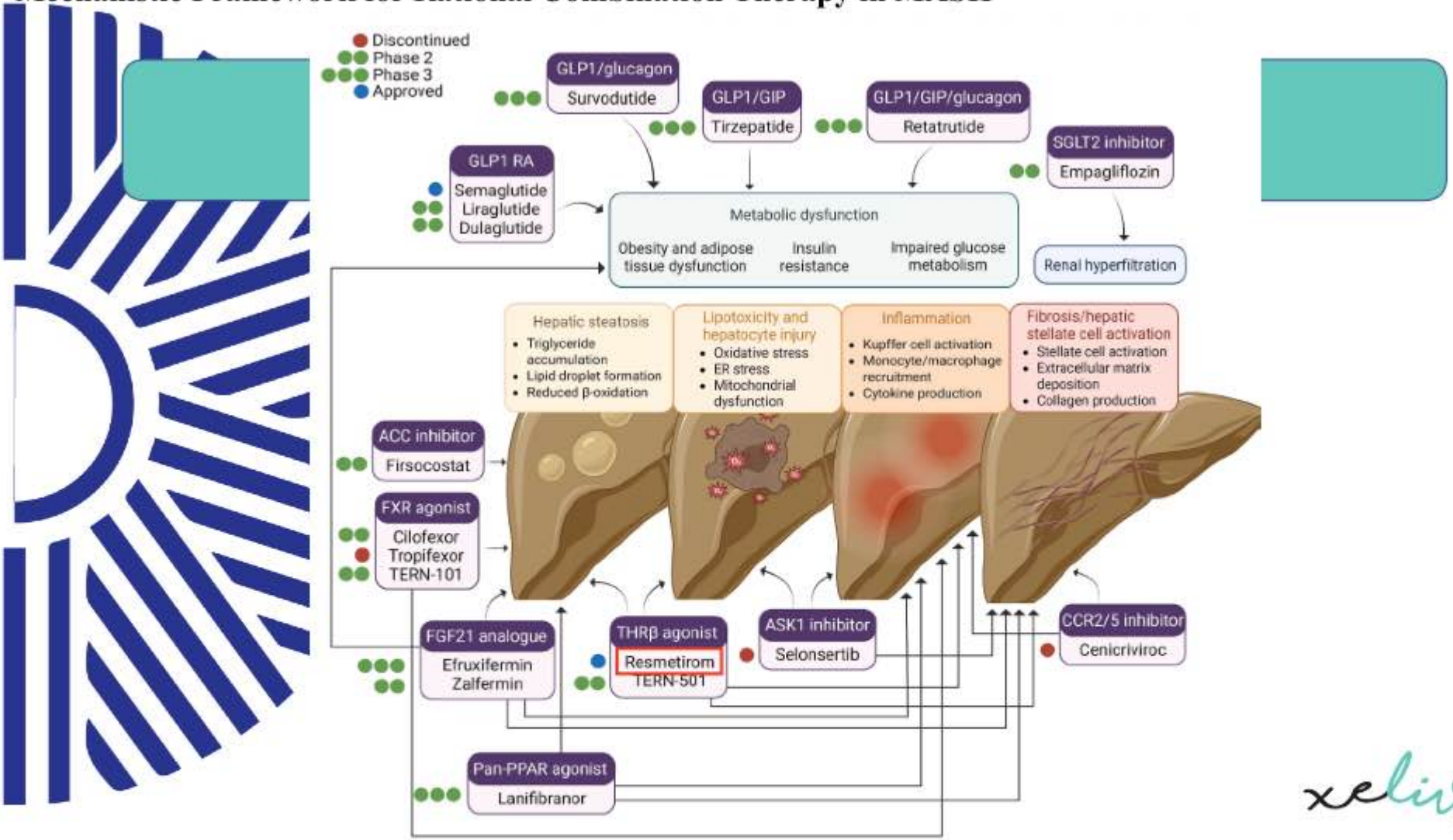


*indirect effect on MASH resolution

The New England Journal of Medicine vol. 390,6 (2024): 497-509.

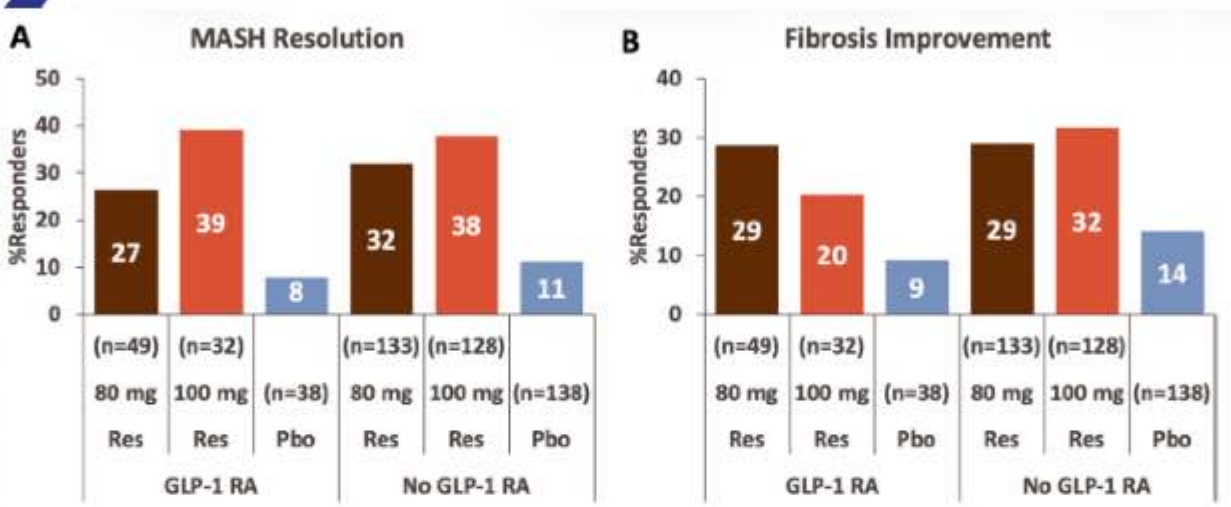
xeliver® Resmetirom

Mechanistic Framework for Rational Combination Therapy in MASH



xeliver®
Resmetirom

Xelivex®, positioning itself as a complementary, mechanism-distinct therapy in the evolving MASH landscape.



Xelivex® demonstrates consistent improvement in both MASH and fibrosis resolution across patients receiving GLP-1 receptor agonists

The New England Journal of medicine vol. 390,6 (2024): 497-509.

xelivex® Resmetirom

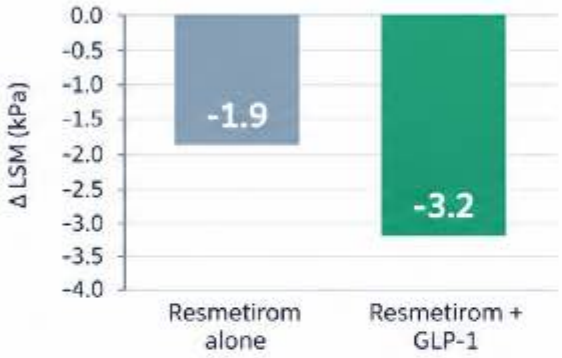
Real-World Experience With Resmetirom and GLP-1 Therapy

Observational cohorts presented in 2026 | Early practice patterns and outcome signals

REAL-WORLD DATA · PRELIMINARY

Liver Stiffness Change

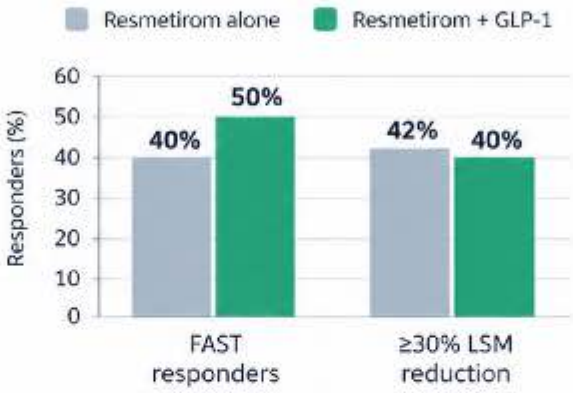
Kim et al., ADA 2026 · subgroup comparison



- Greater LSM reduction was observed in the combination subgroup.

Response Rates at 6 Months

Kim et al., ADA 2026 · percentage of responders



Additional Real-World Reports

Observational cohorts in routine practice

- **Saab et al., ISPOR 2026:** Among 599 patients starting resmetirom, 38.7% had GLP-1 exposure during follow-up.
- **Munteanu et al., ADA 2026:** In 86 patients, 46% were on GLP-1; LIVERFAST, FIB-4, VCTE, and CAP were tracked over time.

CAVEATS | Retrospective analyses; groups not matched; limited VCTE data in the combination subgroup.

KEY MESSAGE | **Concomitant GLP-1 use is already common in practice; early real-world signals are encouraging but remain hypothesis-generating.**

Observational data should not be interpreted as proof of additive efficacy of combination therapy.

Clinical Takeaways From the Current Evidence Base

Resmetirom in the presence of GLP-1 RA therapy | What can and cannot be concluded today

What is supported

In MAESTRO-NASH secondary analyses, resmetirom maintained histologic and MRI-PDFF benefit in patients already on stable GLP-1 RA therapy.

What looks promising

Greater weight loss coincided with stronger responses, and observational cohorts suggest combination use is already frequent in routine care.

Secondary analyses → observational cohorts → prospective trials needed

What is not proven

These analyses were not randomized by GLP-1 status, and real-world cohorts were retrospective; additive efficacy of combination therapy is not established.

Who may be most relevant

Patients with MASH plus obesity or type 2 diabetes may be practical candidates when metabolic indications for GLP-1 RA coexist with a need for liver-directed therapy.

KEY MESSAGE **Use combination thoughtfully when a metabolic indication for GLP-1 RA exists; current data support compatibility, but not definitive synergy.**

Interpretive summary based on MAESTRO-NASH secondary analyses and 2026 observational reports in the reference library.

EASL 2026: Recommendations on Combination Therapy

Three guideline statements that frame resmetirom use alongside pre-existing GLP-1 RA therapy

EASL–EASD–EASO · 2026

agents together

LoE 5 · Weak

rapy cannot currently be recommended.

02

ground treatment

LoE 2 · Strong

Continue existing GLP-1 RA and other cardiometabolic therapies when starting MASH-targeted treatment, with appropriate adjustments

03

Consider adding resmetirom in selected eligible patients

LoE 3 · Weak

When MASH-specific pharmacotherapy remains indicated despite a stable GLP-1 RA dose, resmetirom may be added.

EVIDENCE STATEMENT **Resmetirom retains efficacy in patients on stable GLP-1 RA background therapy (LoE 2; consensus).**

KEY TAKEAWAY **Continuing GLP-1 RA for metabolic indications is different from routinely initiating dual MASH therapy.**

EASL–EASD–EASO. Guidance on resmetirom and semaglutide as MASH-targeted therapy. J Hepatol. 2026; pp. 14–15.

Complementary Mechanisms of Resmetirom and GLP-1 RAs

Distinct biological targets in MASH treatment | EASL–EASD–EASO 2026

Primary target

Selective activation of hepatic THR-β

Primary effects

Reduced appetite and weight; improved glycemic control

Metabolic effects

Reduced hepatic fat; improved atherogenic lipid profile

Beyond the liver

Established cardiometabolic benefits in indicated populations

Histological evidence

MASH resolution and fibrosis improvement in phase III trial

MASH-specific evidence

Semaglutide 2.4 mg improved MASH and fibrosis in phase III trial

CLINICAL MESSAGE

Distinct mechanisms may complement care, but clinical synergy is not yet proven.

Source: EASL–EASD–EASO. J Hepatol. 2026; pp. 4–7, 14–15. doi:10.1016/j.jhep.2026.08.028

Add Resmetirom or Switch GLP-1 RA?

EASL 2026 | Individualized decisions in treatment-eligible, non-cirrhotic MASH

OPTION A · ADD-ON

ADD RESMETIROM

Continue the indicated GLP-1 RA; consider adding resmetirom for MASH-targeted liver treatment.

Weak recommendation

SWITCH TO SEMAGLUTIDE 2.4 MG

Switch the existing GLP-1 RA to semaglutide 2.4 mg once weekly as an alternative MASH-targeted a ch.

LoE 3 · Weak recommendation

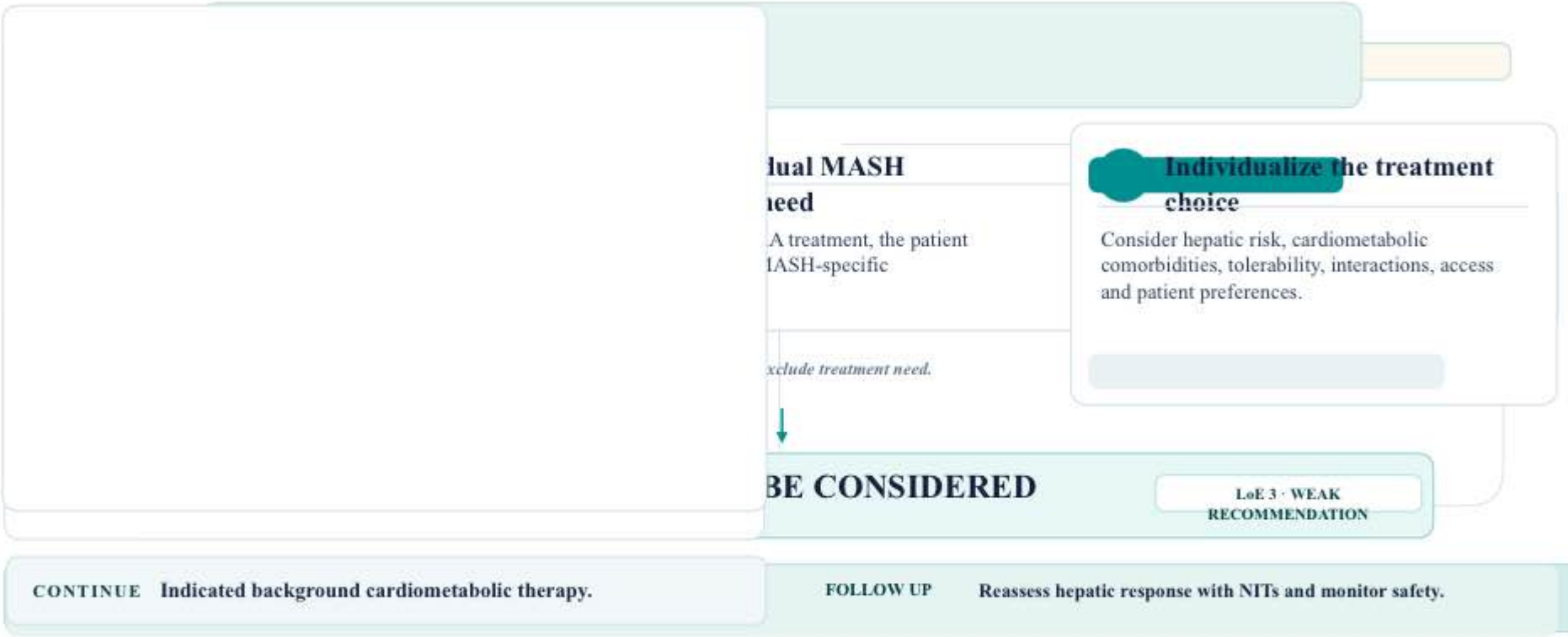
NOT ROUTINE FIRST-LINE **Do not routinely co-initiate resmetirom + semaglutide as initial MASH therapy (LoE 5; weak).**

REVERSE SEQUENCE In patients already on resmetirom, additional MASH efficacy from initiating semaglutide remains unproven.

Source: EASL–EASD–EASO. J Hepatol. 2026; Combination Therapy, pp. 14–15. doi:10.1016/j.jhep.2026.08.028

When Should Resmetirom Be Added to Existing GLP-1 RA Therapy?

A practical, resmetirom-centered pathway for individualized MASH-targeted treatment

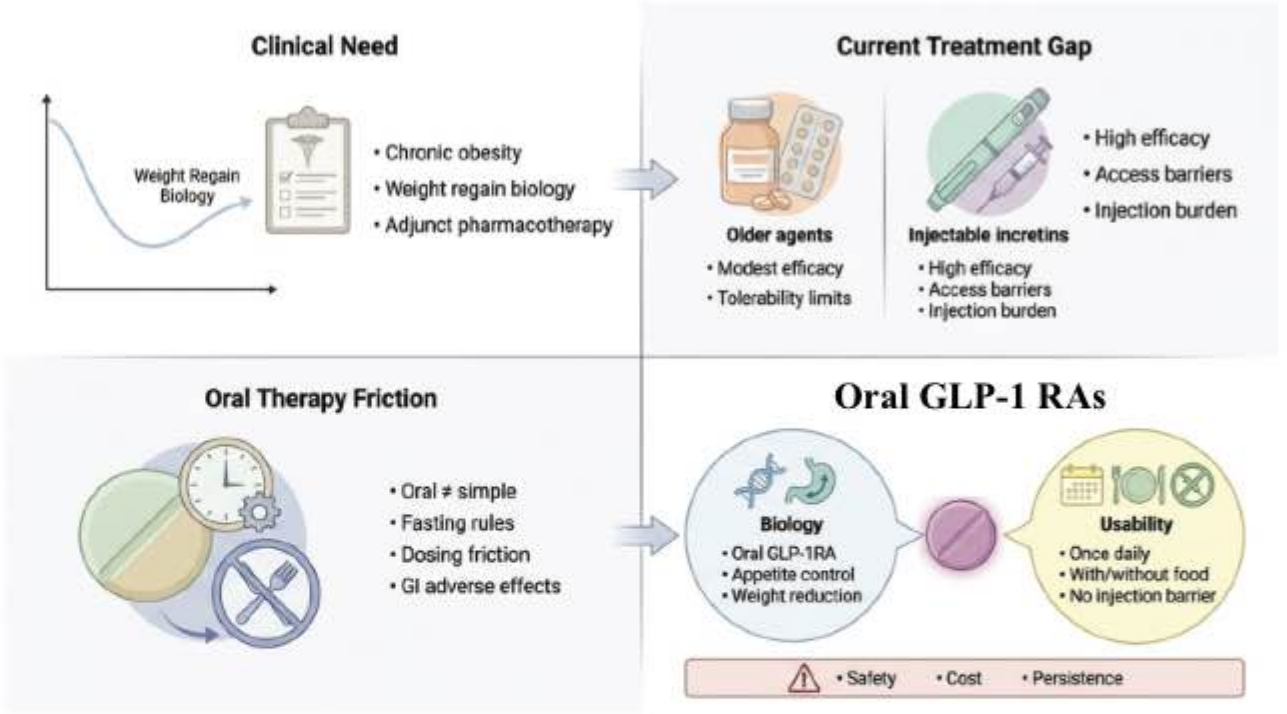


The guidance also provides an alternative MASH-targeted treatment option; the pathway shown focuses on resmetirom.

Adapted from EASL–EASD–EASO Guidance. J Hepatol. 2026; selection, combination and monitoring sections.

Oral GLP-1 RAs: A New Horizon in the CKLM Syndrome Care

Oral GLP-1 RAs bridges this gap by combining GLP-1–mediated metabolic benefits with once-daily oral administration.



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"Orforglipron and the emergence of oral GLP-1 therapy for obesity" 2026: *Expert Opinion on Pharmacotherapy*

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Thank you!