IL PESO DELLA GLICEMIA
DIABETE E OBESITÀ TRA RISCHIO CARDIO-RENALE, EPATICO E NEUROLOGICO

Diabete e MASLD: nuove prospettive terapeutiche

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Il dott Stefano Ciardullo dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- AstraZeneca
- Boheringer Ingelheim
- Echosens
- Eli Lilly
- Guidotti
- MSD
- Novo Nordisk

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

4.26 In adults with type 2 diabetes, MASLD, and overweight or obesity, consider using a glucagon-like peptide 1 (GLP-1) receptor agonist (RA) or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA for the treatment of obesity with potential benefits in MASH as an adjunctive therapy to lifestyle interventions for weight loss. **B**

4.27a In adults with type 2 diabetes and biopsy-proven MASH or those at high risk for liver fibrosis (based on noninvasive tests), pioglitazone, a GLP-1 RA, or a dual GIP and GLP-1 RA is preferred for glycemic management

4.27b Combination therapy with pioglitazone plus GLP-1 RA can be considered for the treatment of hyperglycemia in adults with type 2 diabetes with biopsy-proven MASH or those at high risk of liver fibrosis (identified with noninvasive tests) because of potential beneficial effects on MASH.**B**

4.28 For consideration of treatment with a thyroid hormone receptor-β agonist in adults with type 2 diabetes or prediabetes with MASLD with moderate (F2) or advanced (F3) liver fibrosis on liver histology, or by a validated imaging-based or blood-based test, refer to a gastroenterologist or hepatologist with expertise in MASLD management. **A**

4.30b Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis. **C**

Diabetes Care 2025;48(Suppl. 1):S59–S85

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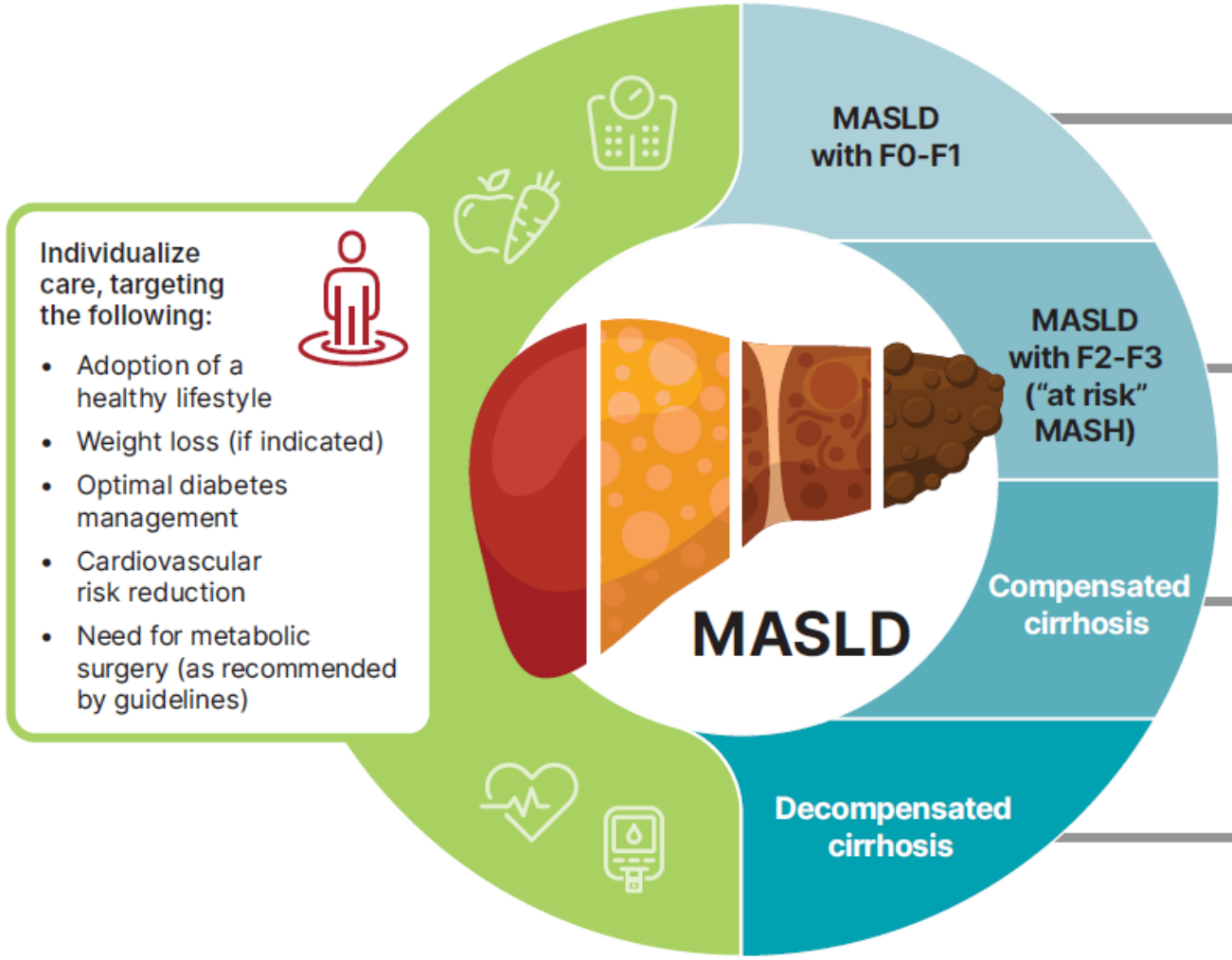


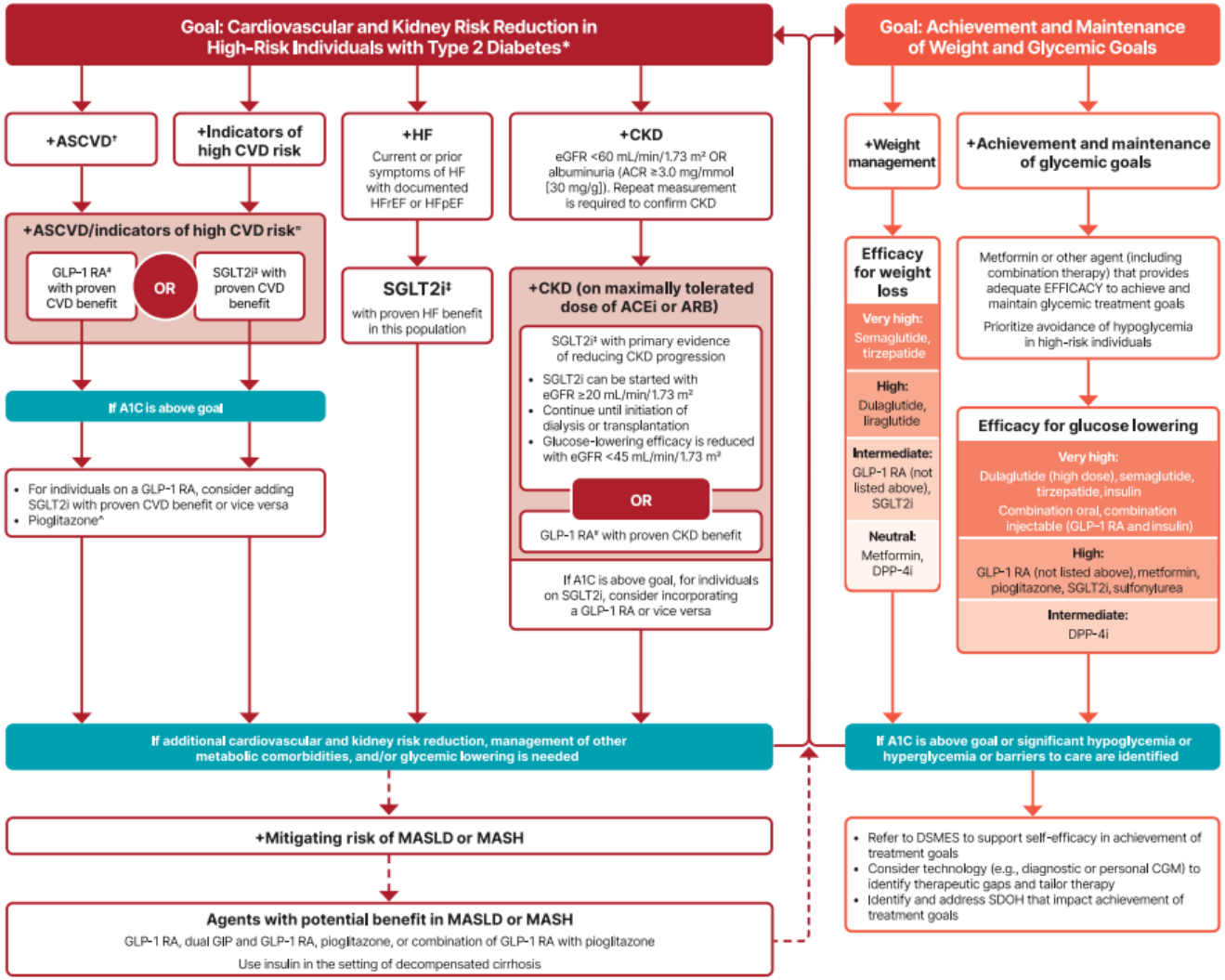
Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone, SGLT2i	Not indicated

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
Prefer GLP-1 RA, dual GIP and GLP-1 RA	Prefer GLP-1 RA, dual GIP and GLP-1 RA, pioglitazone	Resmetirom

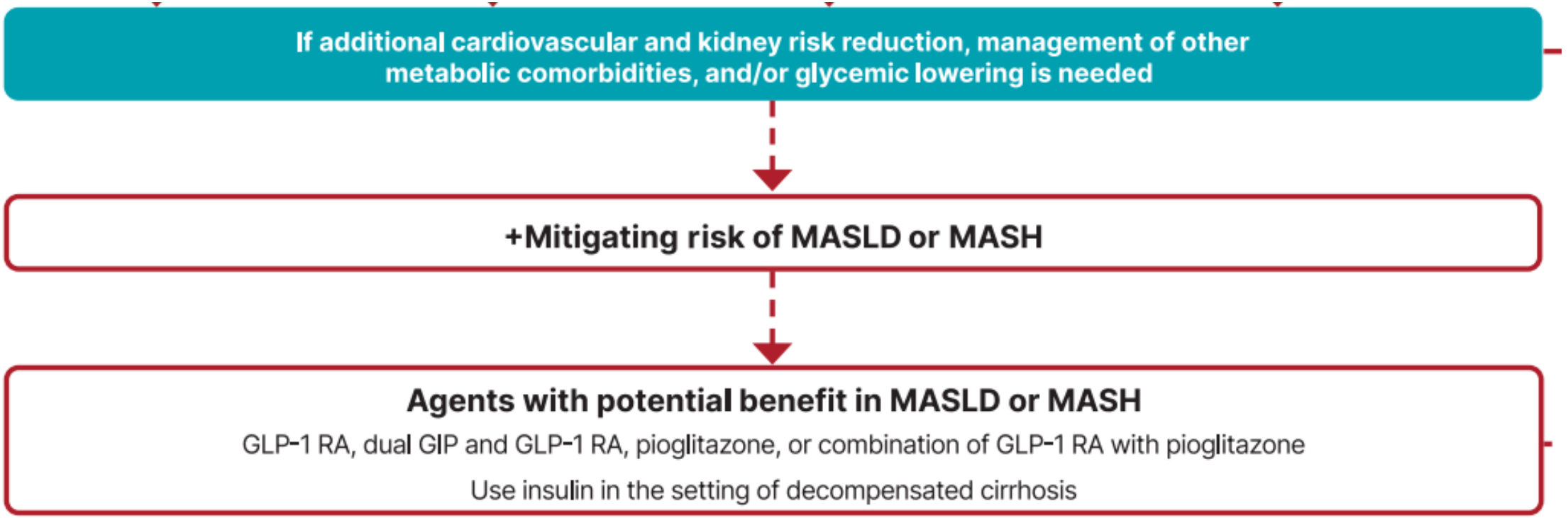
Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
As with F2-F3 with caution*	As with F2-F3 with caution*	ⓘ AVOID

Obesity pharmacotherapy	Diabetes pharmacotherapy	MASH pharmacotherapy
ⓘ AVOID	Only use insulin	ⓘ AVOID

Diabetes Care 2025;48(Suppl. 1):S59–S85



Diabetes Care 2025;48(Suppl. 1):S59–S85



Diabetes Care 2025;48(Suppl. 1):S59–S85

2025 ADA standards

- MASLD terminology
- Four (precise) recommendations on MASLD screening
- Reliance on FIB-4 and VCTE/ELF
- Specific screening algorithm proposed
- Eight recommendations on MASLD treatment
- Presence of MASLD in Chapter 9 (Pharmacologic approaches to glycemic treatment)

MASH Development

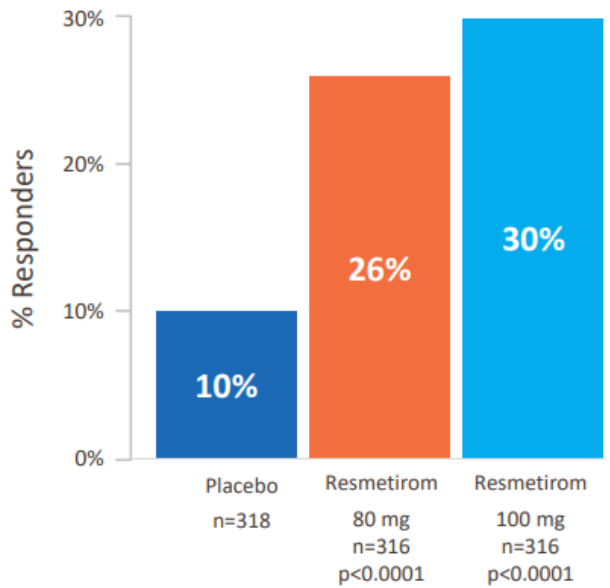
A Climb to the Goal

The Pivotal Phase 3 MAESTRO-NASH Trial

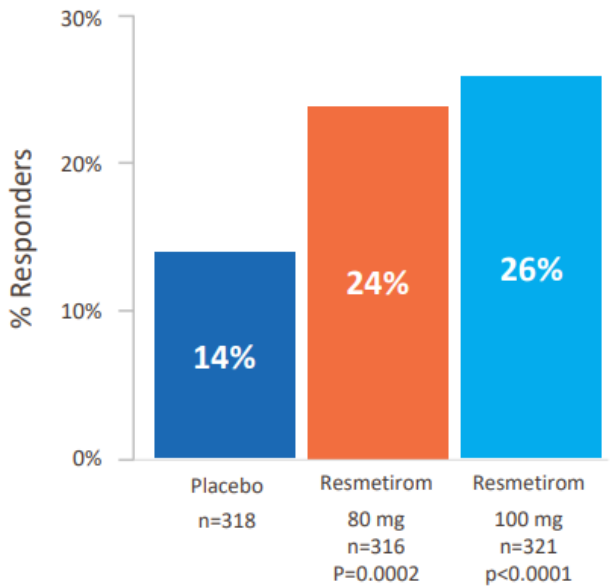
FIRST Phase 3 Trial to Achieve NASH Resolution and Fibrosis Improvement Primary Endpoints

Primary Endpoints

NASH Resolution[1]

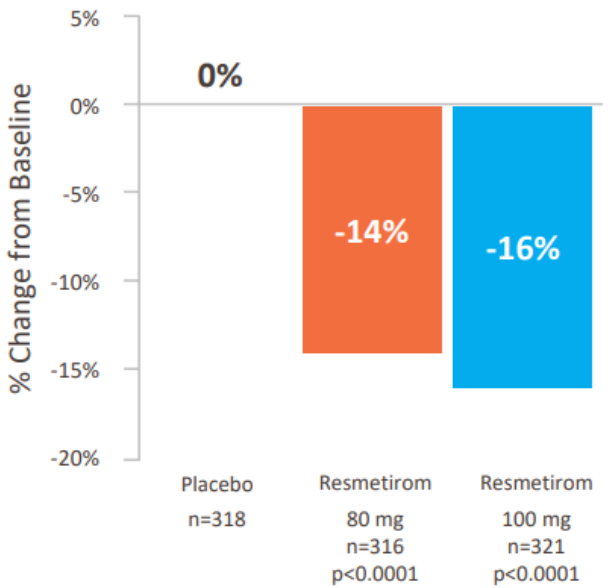


≥1 Stage Fibrosis Improvement[1]



Secondary Endpoint[2]

LDL Cholesterol



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

Resmetirom FDA approval: March 14, 2024

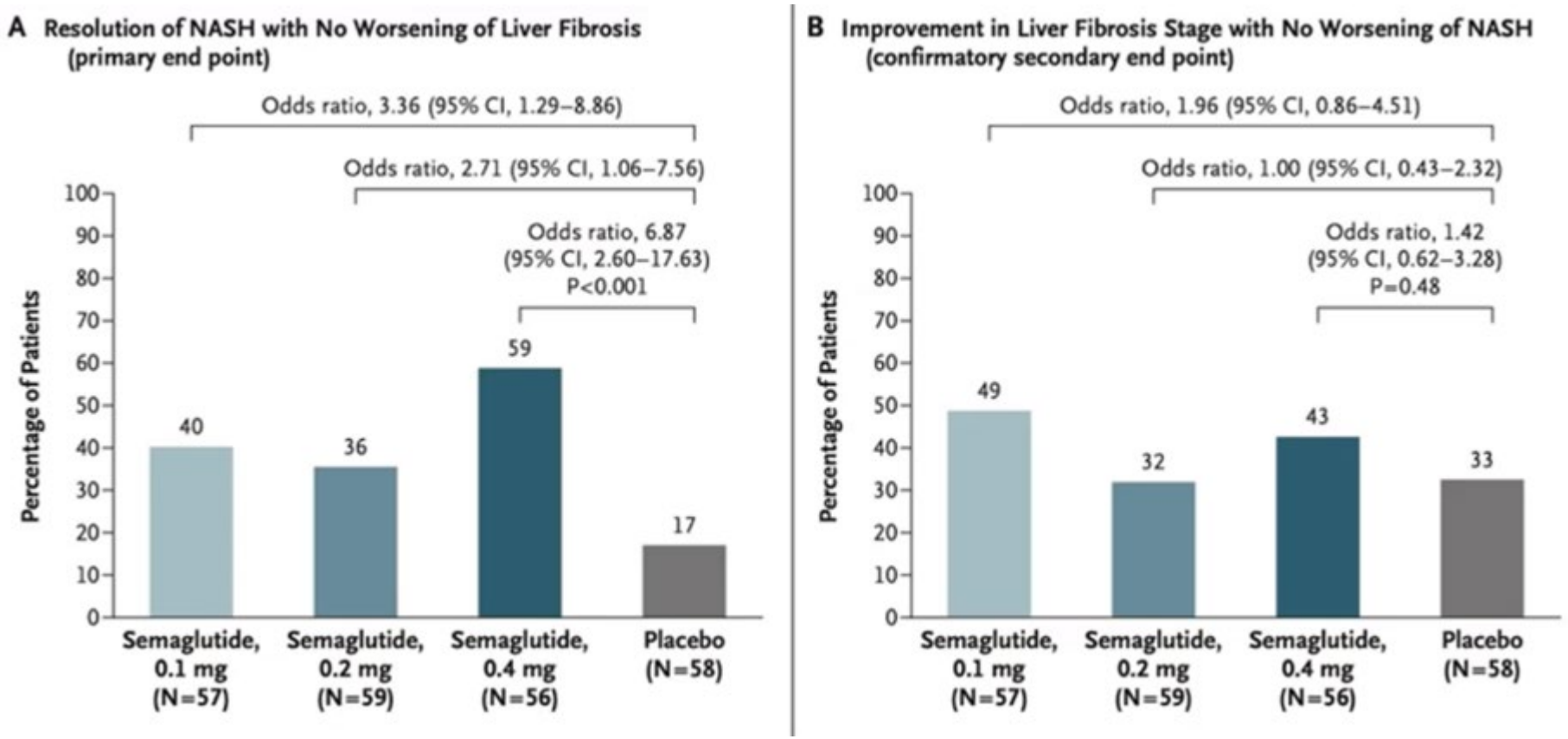
FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease

Resmetirom EMA approval: August 19, 2025

Resmetirom approvato in Europa per il trattamento della MASH con fibrosi epatica da moderata ad avanzata

Semaglutide Phase 2 b



Newsome et al. N Engl J Med. 2021;384:1113-1124

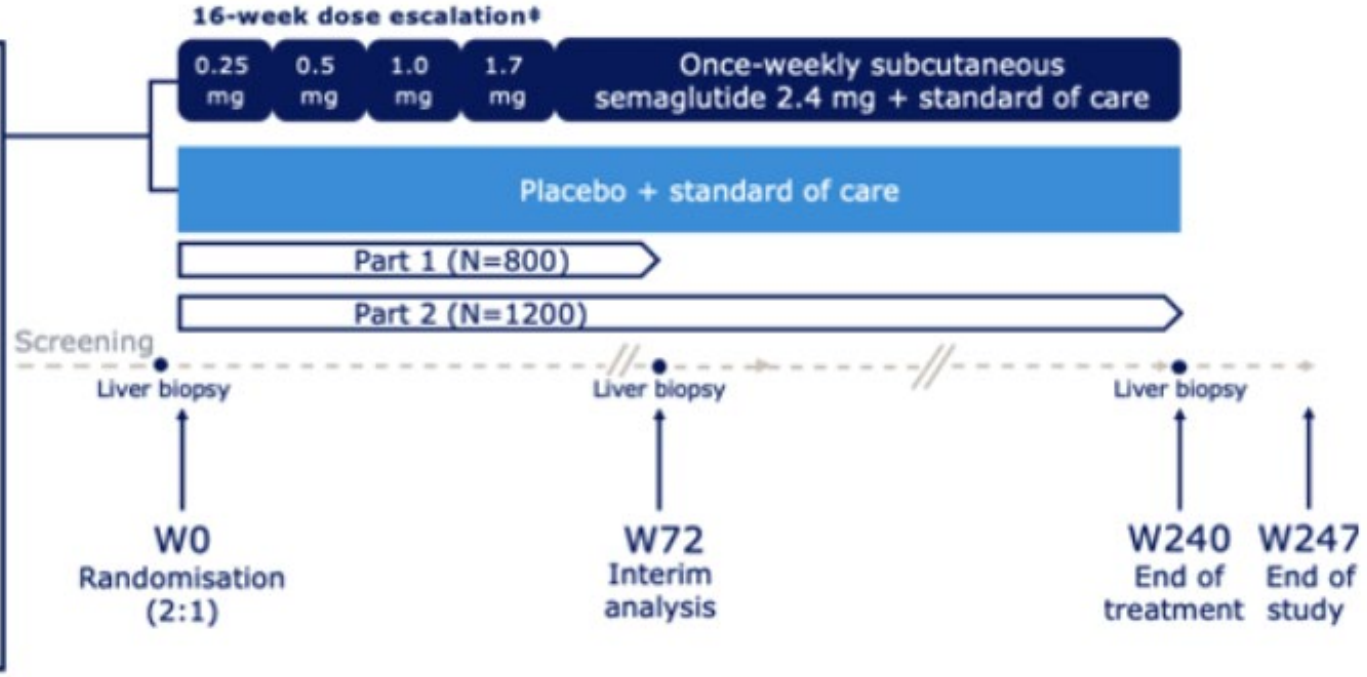
ESSENCE – SEMAGLUTIDE PHASE 3

Methods

Trial design

Key inclusion criteria
- Age ≥18 years old
- Histological evidence of fibrosis stage 2 or 3*
- NAS ≥4†

Key exclusion criteria
- Chronic liver diseases other than MASLD
- Known or suspected excessive consumption of alcohol (>20 g/day for women or >30 g/day for men)
- Treatment with GLP-1RAs or unstable use of other glucose-lowering, lipid-lowering or weight loss medications within 90-days prior to screening

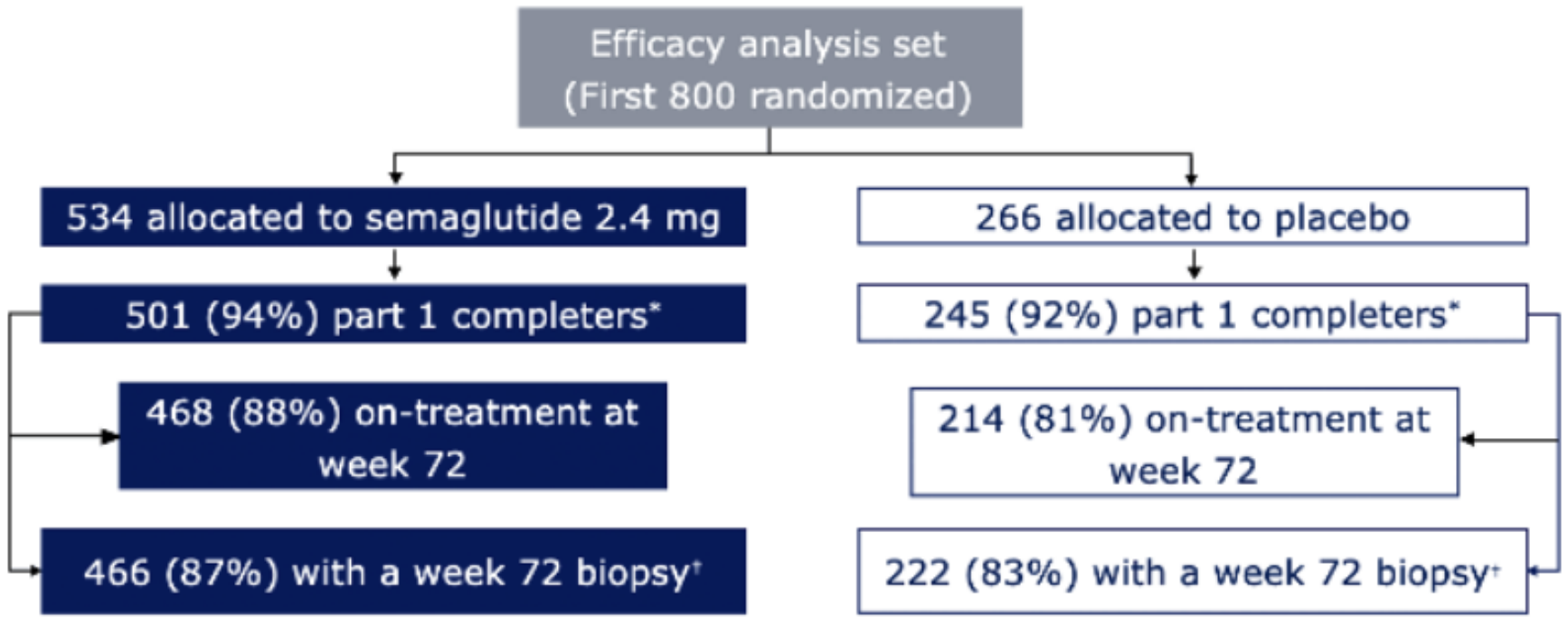


*According to NASH Clinical Research Network classification. †With a score of ≥1 in steatosis, lobular inflammation and hepatocyte ballooning, based on central pathologist evaluation. ‡Uptitration every 4 weeks. One or more dose steps can be prolonged, or the dose lowered if the actual dose is not tolerated. If the designated target dose of once-weekly subcutaneous semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose level. GLP-1RA, glucagon-like peptide-1 receptor agonist; g, gram; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, non-alcoholic fatty liver disease activity score; W, week.

Presented at The Liver Meeting 2024, November 15-19, San Diego, USA.

Methods

Trial flow



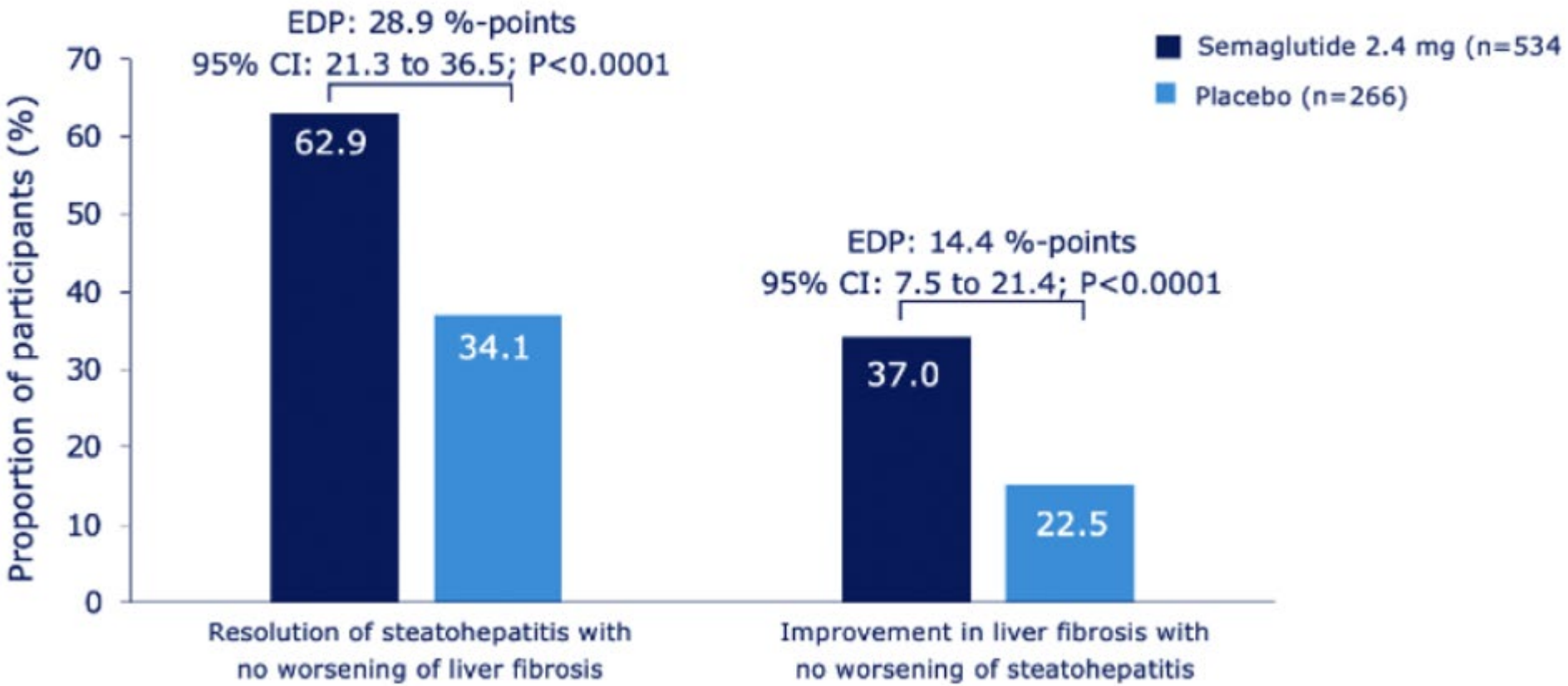
*A trial completer for part 1 is defined as a participant that either attended the week 72 visit or died before the visit.
†Participants with a pathologist consensus result for all 4 liver histology parameters for the week 72 biopsy.

Baseline characteristics

Characteristic	Semaglutide 2.4 mg (N=534)	Placebo (N=266)
Age, years, mean (SD)	56.3 (11.4)	55.4 (12.0)
Sex, female, n (%)	313 (58.6)	144 (54.1)
Type 2 diabetes, n (%)	296 (55.4)	151 (56.8)
HbA_{1c}, %, mean (SD)	6.6 (1.1)	6.4 (1.0)
HbA_{1c}, %, mean (SD) — with type 2 diabetes	7.2 (1.1)	6.9 (1.0)
Body mass index, kg/m^2, mean (SD)	34.3 (7.2)	35.0 (7.1)
Alanine aminotransferase, U/L, mean (SD)	67.8 (42.3)	67.9 (44.7)
Fibrosis stage 3, n (%)	365 (68.4)	185 (69.5)
Liver stiffness by VCTE, kPa, mean (SD)	12.8 (6.6)	12.9 (7.6)
ELF score, mean (SD)	10.0 (0.9)	10.0 (1.0)
PRO-C3, ng/ml, mean (SD)	52.9 (24.9)	52.9 (28.1)

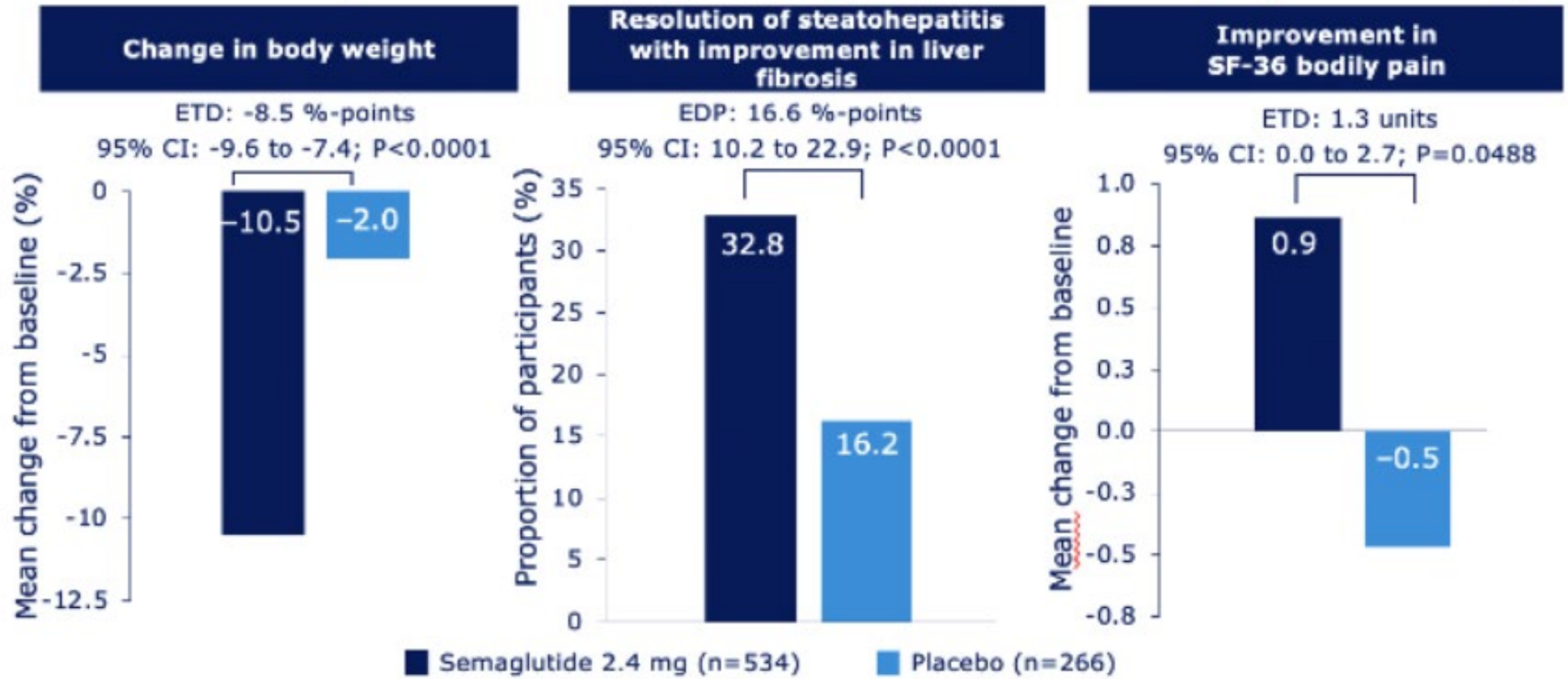
ELF, Enhanced Liver Fibrosis; HbA_{1c}, glycated hemoglobin; IQR; PRO-C3, N-terminal type III collagen; SD, standard deviation; VCTE, vibration-controlled transient elastography.

Primary endpoints (ITT population)



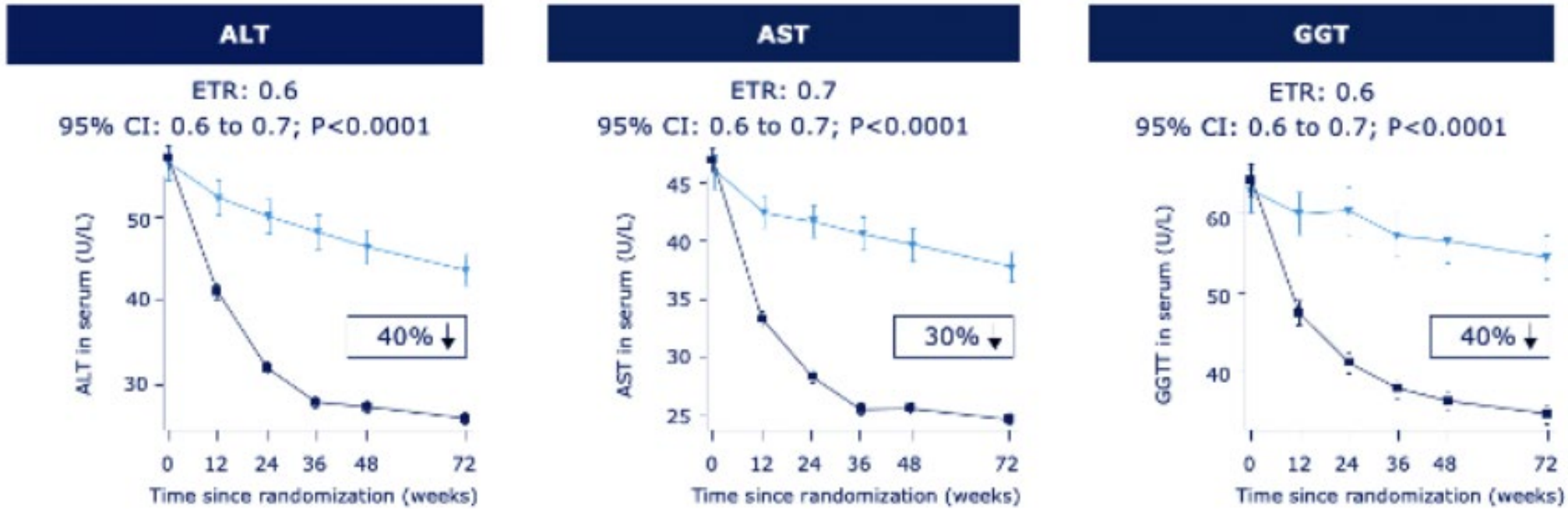
CI, confidence interval; EDP, estimated difference in responder proportions; ITT, intention-to-treat..

Confirmatory secondary endpoints (ITT population)



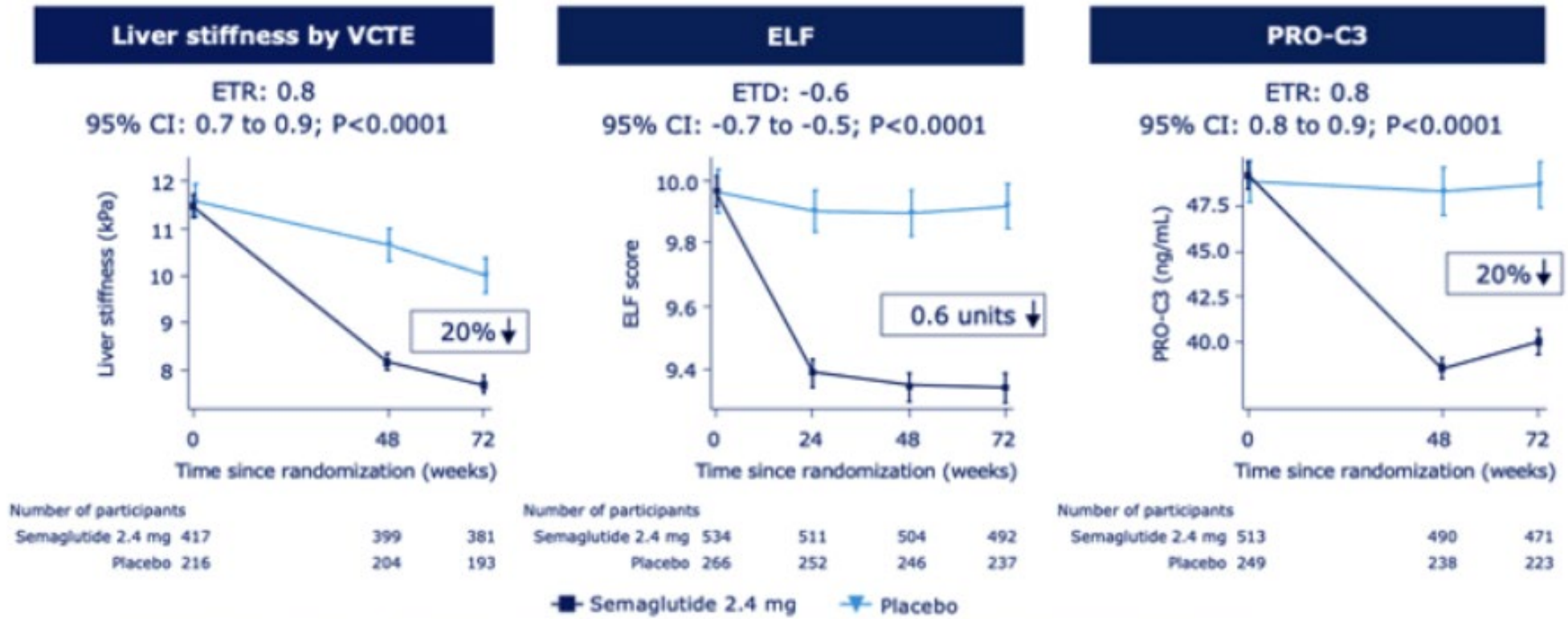
CI, confidence interval; EDP, estimated difference in responder proportions; ETD, estimated treatment difference; ITT, intention-to-treat; SF-36, Short Form-36.

Change in liver enzymes



Data are geometric mean with error bars, derived from the exponential of the standard error on the logarithm scale. P-values not adjusted for multiplicity.
ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; ETR, estimated treatment ratio; GGT, gamma-glutamyl transferase.

Change in non-invasive fibrosis tests



Data are mean ± standard error of the mean back transformed from the logarithm scale. P-values not adjusted for multiplicity.
CI, confidence interval; ELF, Enhanced liver fibrosis; ETD, estimated treatment difference; ETR, estimated treatment ratio; PRO-C3, N-terminal type III collagen; VCTE, vibration controlled transient elastography.

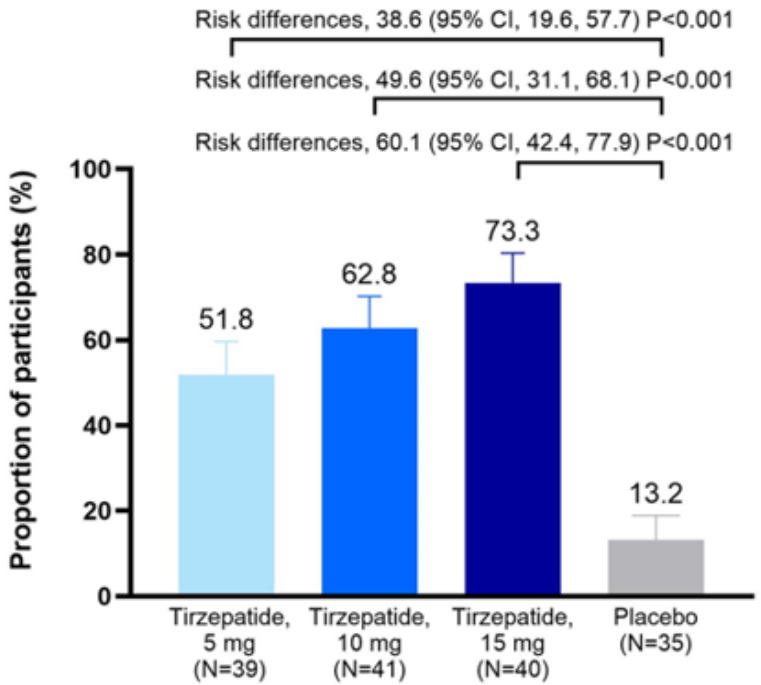
Semaglutide FDA approval: August 15, 2025

FDA Approves Treatment for Serious Liver Disease Known as 'MASH'

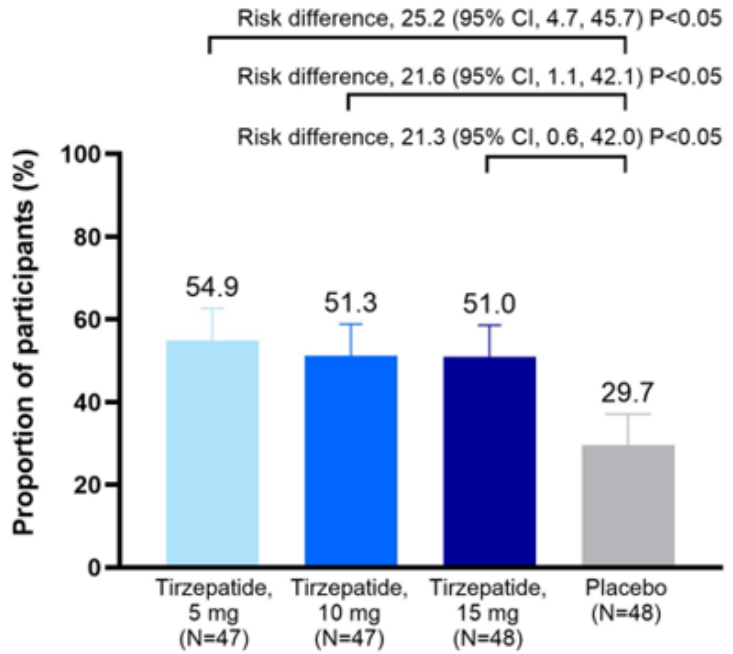
Action Will Provide New Therapy for Growing Public Health Issue

Tirzepatide – SYNERGY NASH (Phase 2)

Primary:
resolution of MASH and no worsening of fibrosis



Secondary:
≥1 stage decrease in fibrosis and no worsening of MASH

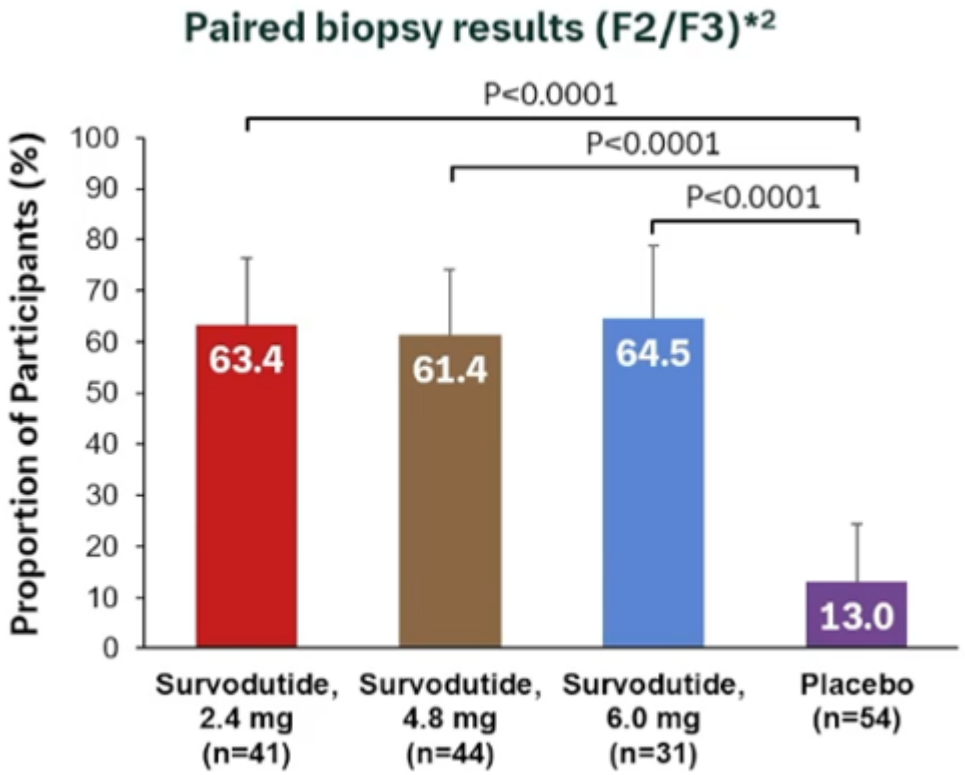


Loomba R et al., N Engl J Med . 2024 Jun 8. doi: 10.1056/NEJMoa2401943

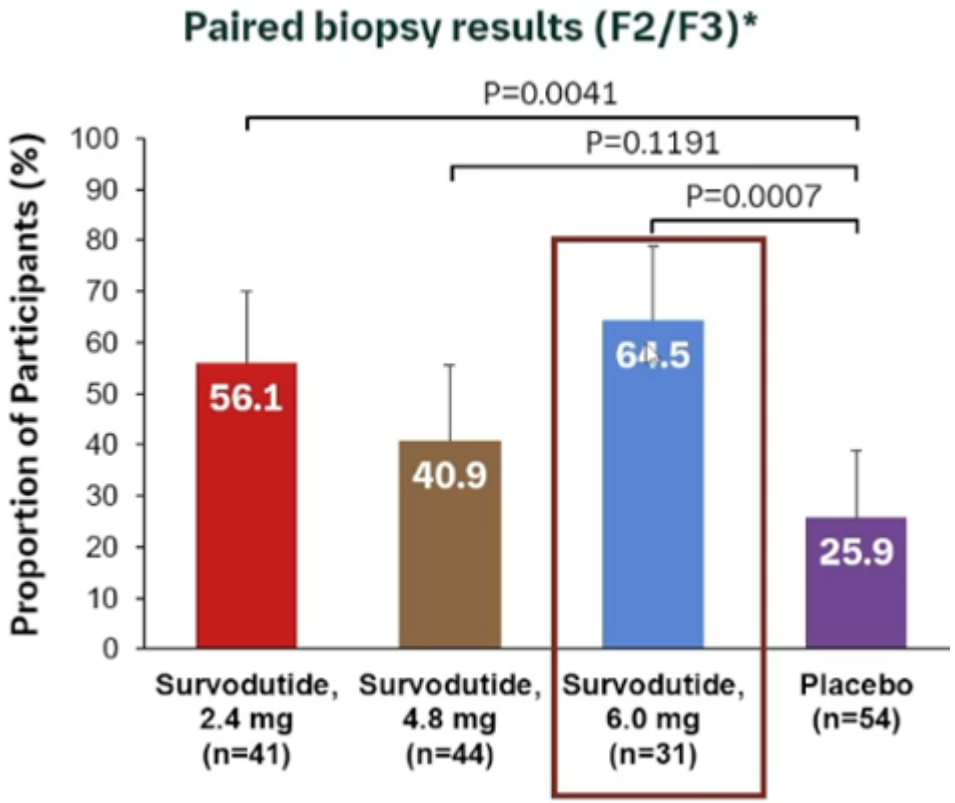
Loomba R et al NEJM 2024

Survodutide (Phase 2)

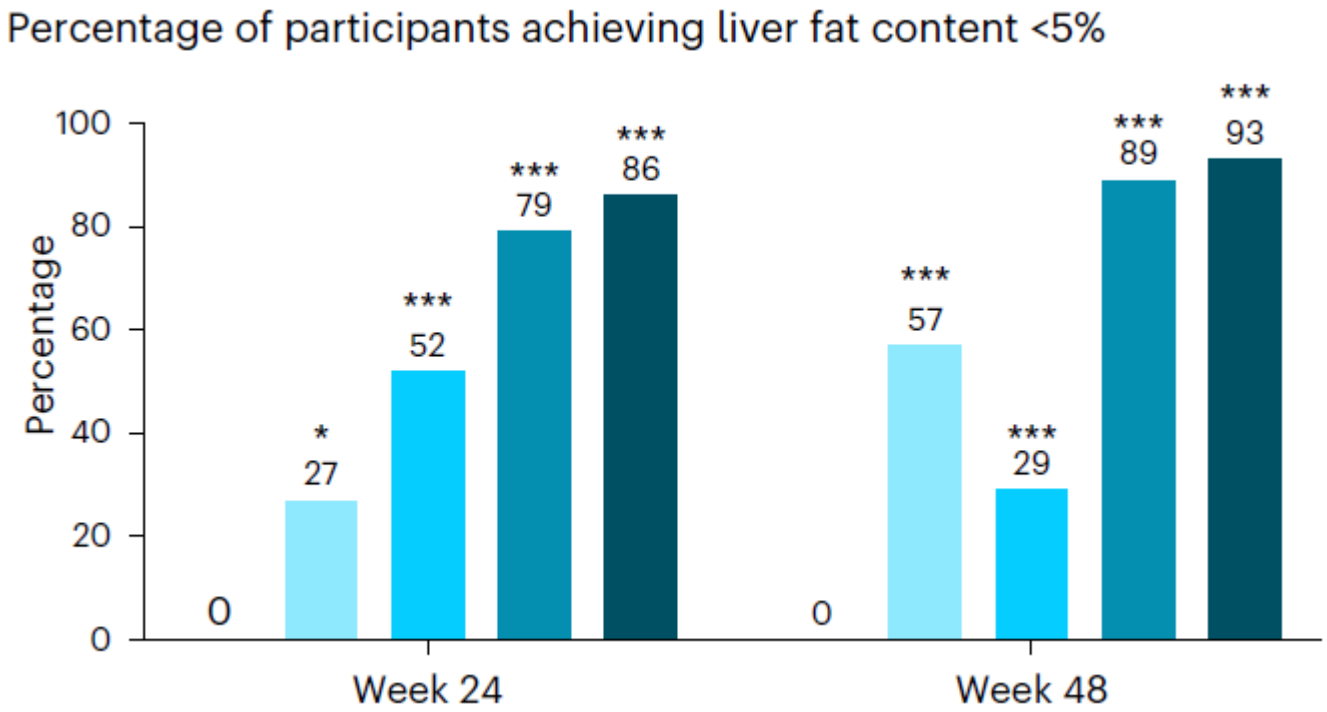
MASH resolution

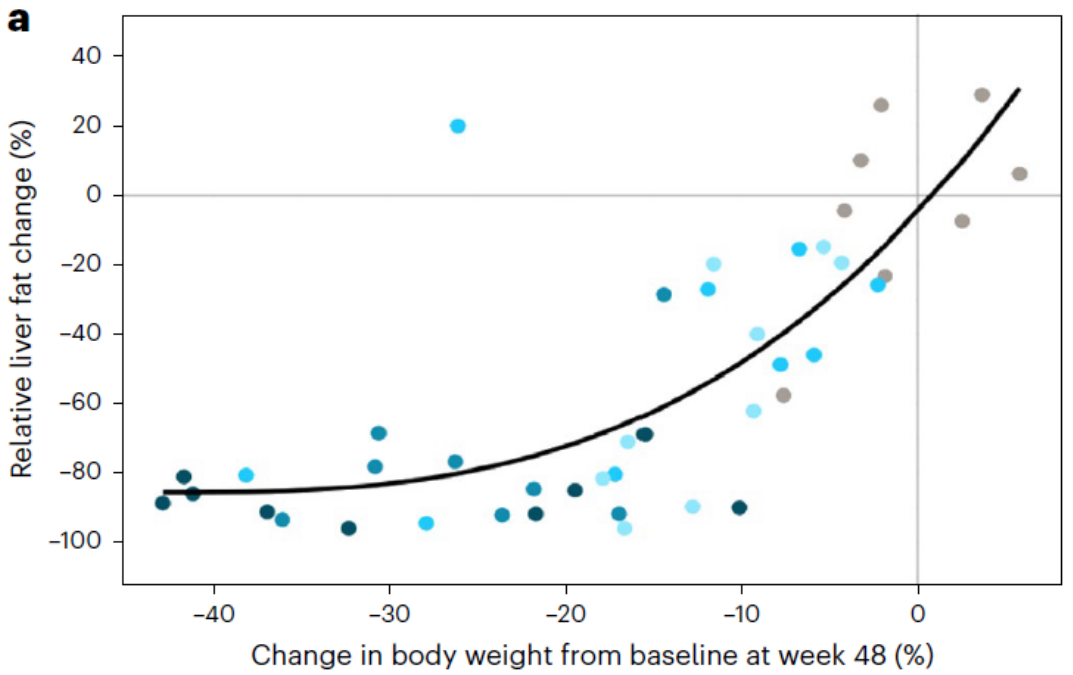


Fibrosis improvement



Retatrutide – MRI data





PBO · 1 mg RETA · 4 mg RETA · 8 mg RETA · 12 mg RETA

Sanyal A et al Nature Med 2024

FDA accepts proposal for reasonably likely surrogate endpoint for 'MASH' all-cause mortality or liver-related events

This acceptance represents the first step in the Drug Development Tool qualification process, where the company will work with FDA to develop a comprehensive qualification plan for data and validation requirements to support the specific context of use.

August 27, 2025

Grazie dell’attenzione