DAL DIABETOLOGO ALL'EPATOLOGO: ANDATA E RITORNO

News 1. Le novità farmacologiche: da resmetirom ai GLP1Ra agonisti e oltre

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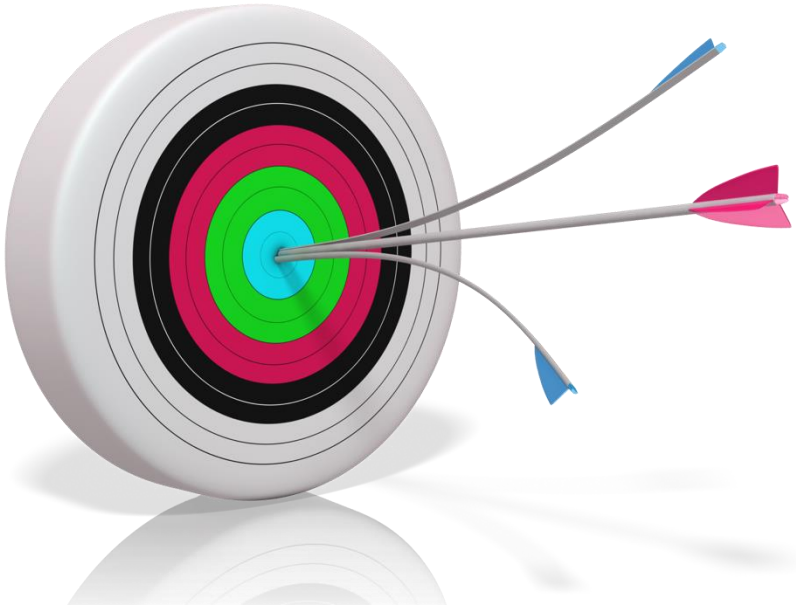
Regulatory Framework for Drug Approval

- FDA Registration Surrogate Histological Endpoints RCTs → Provisional Approval
- Full Approval Pending based on Long-Term Outcomes RCTs



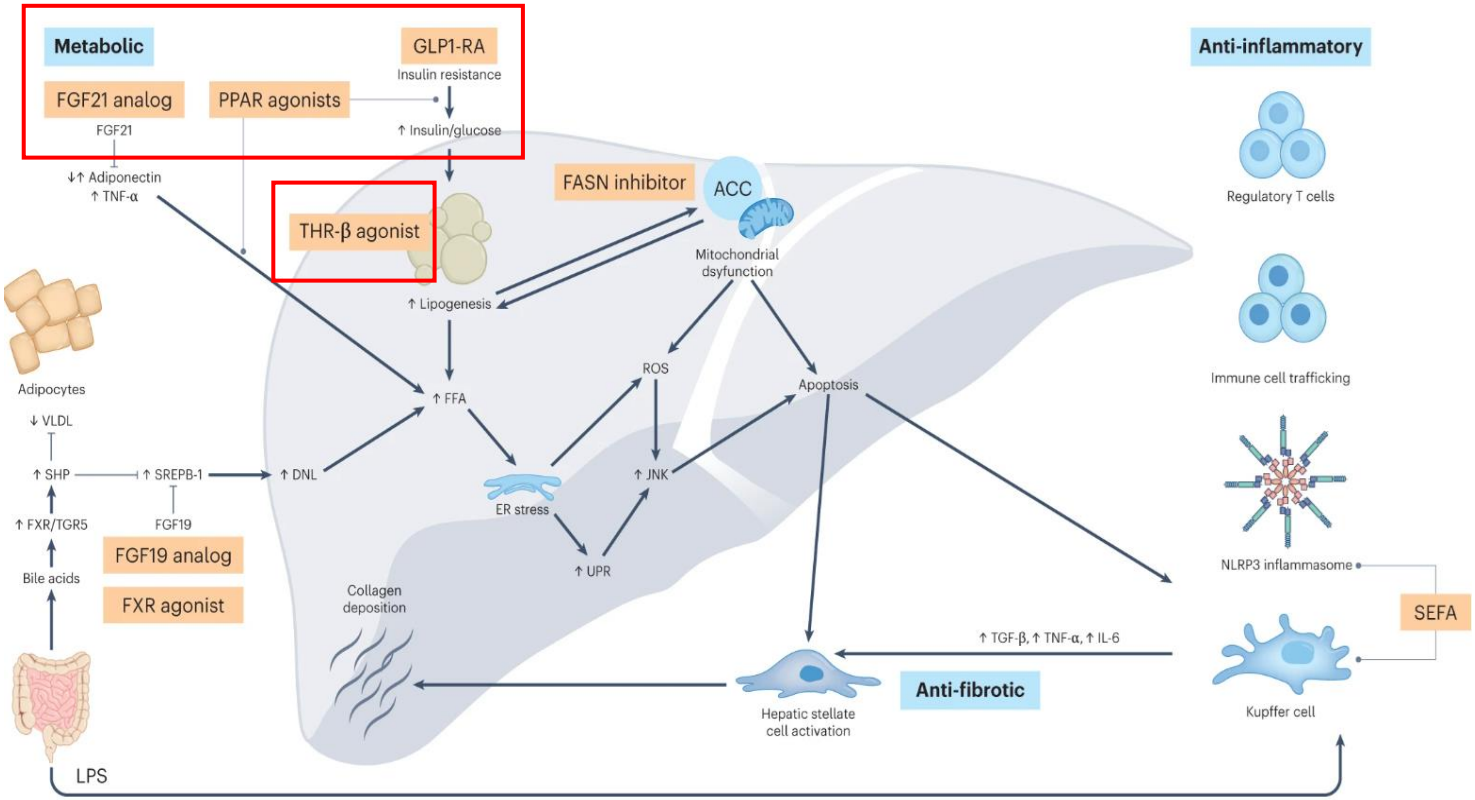
MASH Resolution
Resolution of steatohepatitis on overall histopathologic reading and no worsening of liver fibrosis

And

Fibrosis Improvement ≥ 1
Fibrosis stage and no worsening of steatohepatitis

FDA. 2018. Accessed 1 May 2023. https://www.fda.gov/media/119044/download

Multiple drug targets to treat MASH F2/F3

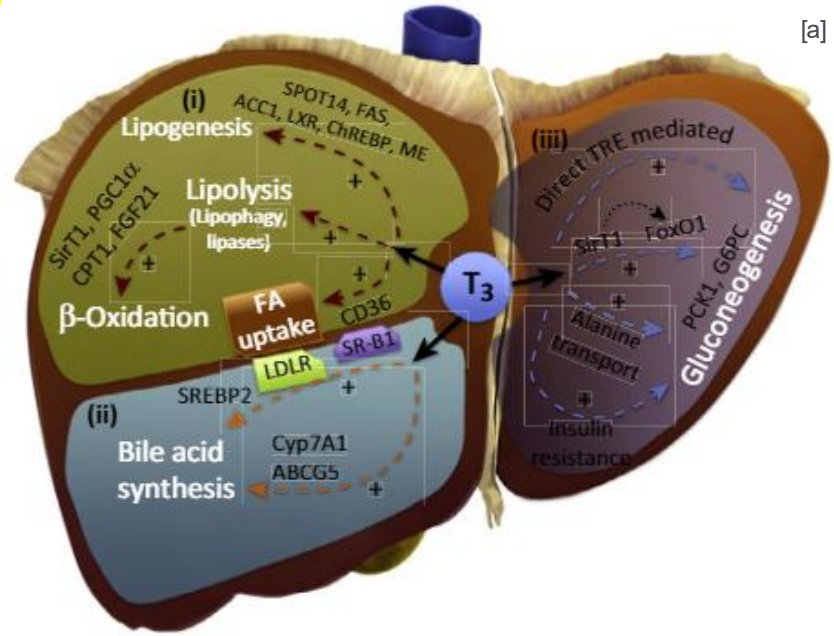


Harrison et al, Nat Med 2023

Resmetirom

Mechanism of Action

Resmetirom Is a THR-β Agonist that has been approved by the FDA for the treatment of MASH F2–F3



Thyroid hormone[b,c]

- Acts via THR-β on the liver and kidneys
- In the liver, impacts de novo lipogenesis and cholesterol metabolism and promotes oxidation of fatty acids by improving mitochondrial function and removing damaged mitochondria

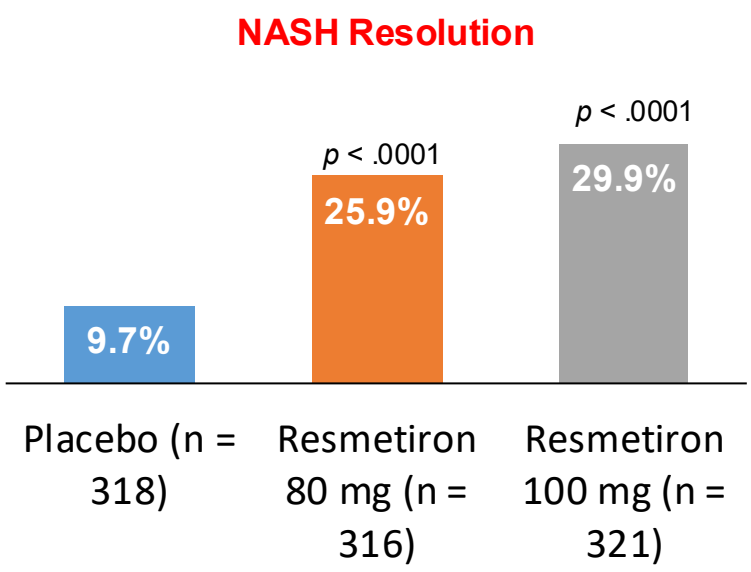
In clinical trial patients, resmetirom has been found to[d]

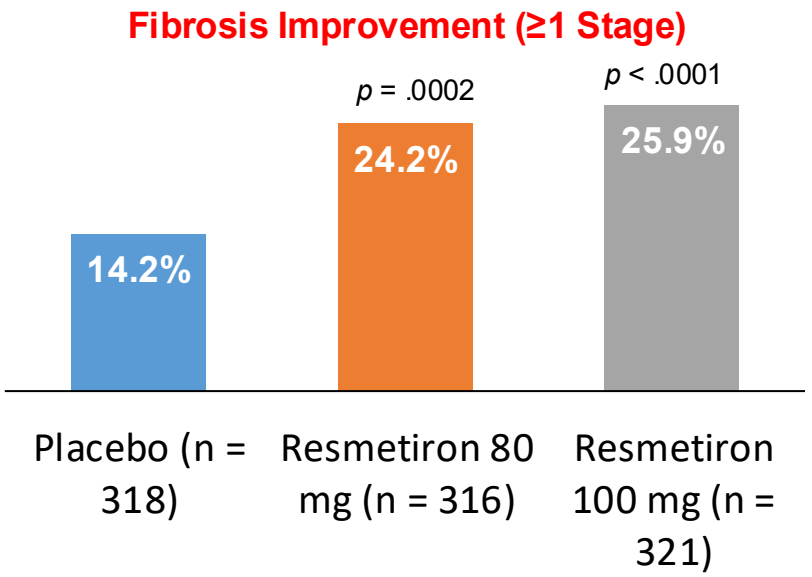
- Lower liver fat
- Resolve NASH
- Lower LDL-C
- Lower triglycerides

- ABCG5, ATP-binding cassette sub-family G member 5; ACC1, acetyl-CoA carboxylase 1; ChREBP, carbohydrate-responsive element-binding protein; CPT1, carnitine palmitoyltransferase-1; FA, fatty acid; FAS, FA synthase; FoxO1 forkhead box O1; G6PC, glucose-6-phosphatase; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; ME, malic enzyme; PCG1α, peroxisome proliferator-activated receptor γ, coactivator 1α; PKC1, phosphoenolpyruvate carboxykinase 1; SirT1, sirtuin 1 (SirT1); SREBP2, sterol regulatory element-binding protein-1c; SR-B1, scavenger receptor class B1; TRE, thyroid hormone response element.
- a. Sinha RA, et al. Trends Endocrinol Metab. 2014;25:538-45; b. Ritter MJ, et al. Hepatology. 2020;72:742-752; c. Sinha RA, et al. Cell Biosci. 2016;6:46; d. Harrison SA, et al. Lancet. 2019;394:2012-2024.

Resmetirom: MAESTRO-NASH Phase III RCT Primary Endpoints

Liver biopsy (ITT) at week 52





Key Secondary Endpoint LDL-C at Week 24 (ITT):
+1% in PLO vs -12% in resmetirom 80 mg vs -16% in resmetirom 100 mg (P<0.0001)

ITT: intention-to-treat.

Harrison S, et al. *N Engl J Med*. 2024;390:497-509.

Resmetirom *MAESTRO-NASH*

Safety

	Resmetirom 80 mg (n = 316), %	Resmetirom 100 mg (n = 321), %	Placebo (n = 318), %
SAEs	**11.8**	**12.7**	**12.1**
Study discontinuation due to AEs	**2.8**	**7.7**	**3.7**
Diarrhea	**28**	**34**	**16**
Nausea	**22**	**19**	**13**

Resmetirom was well tolerated

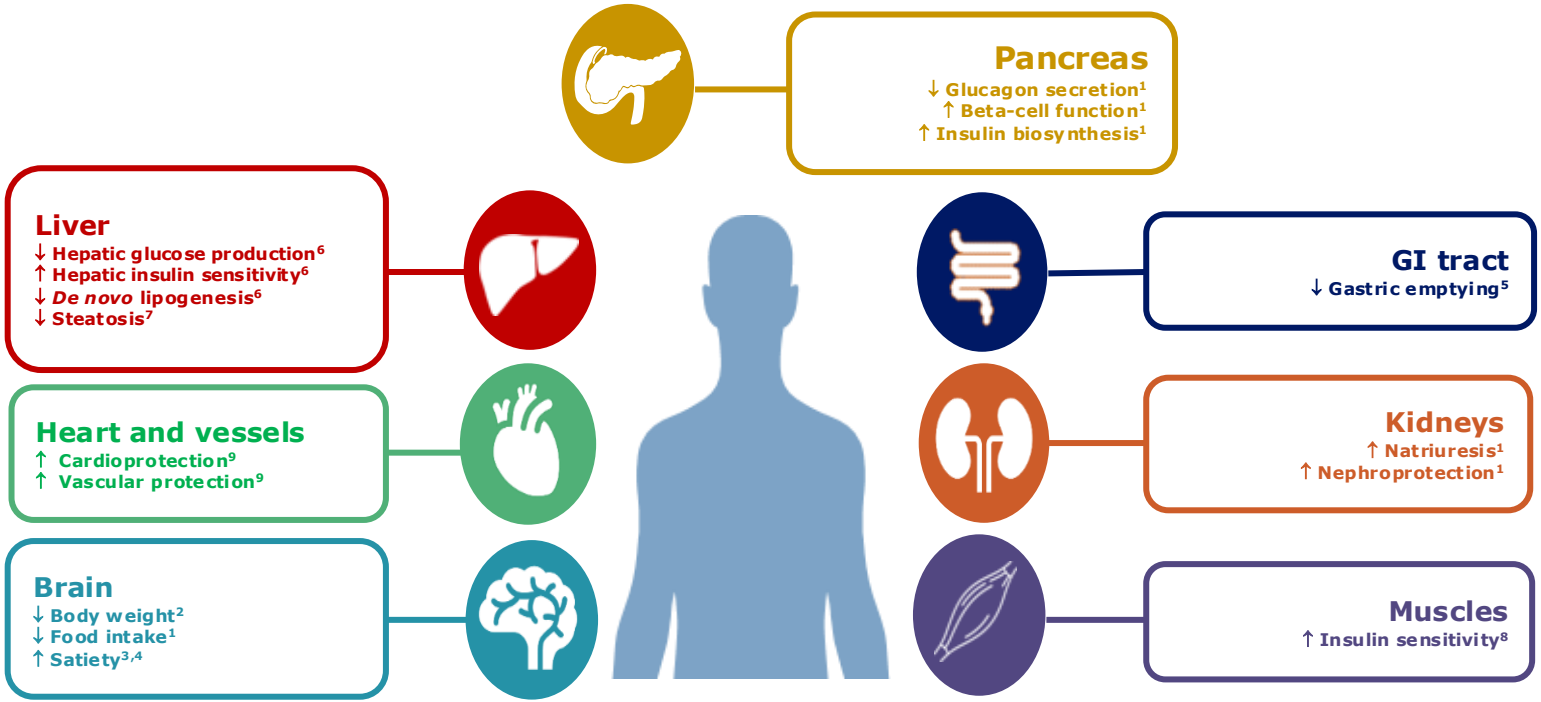
The most common AEs reported with greater frequency in the resmetirom groups vs placebo were

- Excess of generally mild and transient diarrhea
- Generally mild nausea at the beginning of therapy

- SAE, serious adverse event.

Harrison S, et al. Presented at: NASH-TAG, January 5-7, 2023; Park City, UT.

Metabolic Effects of GLP-1 Receptor Agonists



GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell, Drucker. *Cell Metab* 2013;17:819–37; 2. Baggio, Drucker. *J Clin Invest* 2014;124:4223–6; 3. Flint et al. *J Clin Invest* 1998;101:515–20; 4. Blundell et al. *Diabetes Obes Metab* 2017;19:1242–51; 5. Tong, D'Alessio. *Diabetes* 2014;63:407–9; 6. Armstrong et al. *J Hepatol* 2016;64:399–408; 7. Armstrong et al. *Lancet* 2016;387:679–90; 8. MacDonald et al. *Diabetes* 2002;51(Suppl 3):S434–42; 9. Drucker. *Cell Metab* 2016;24:15–30.

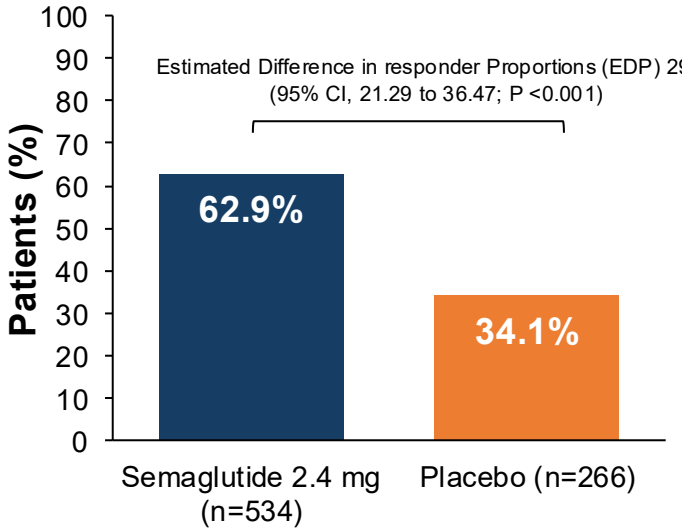
Semaglutide: the ESSENCE Phase III RCT - Primary Endpoints

Semaglutide 2.4 mg was administered once weekly for 72 weeks

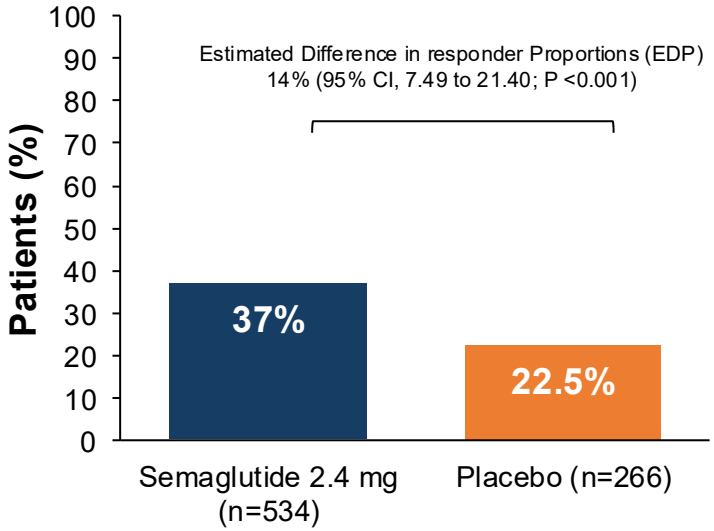
Semaglutide has provisional approval by the FDA for the treatment of MASH F2–F3

The mean percentage change in body weight from baseline at week 72 was −10.51% with semaglutide compared with −2.04% for placebo

MASH Resolution w/o worsening of fibrosis



Fibrosis Improvement (≥1 Stage) w/o worsening of MASH

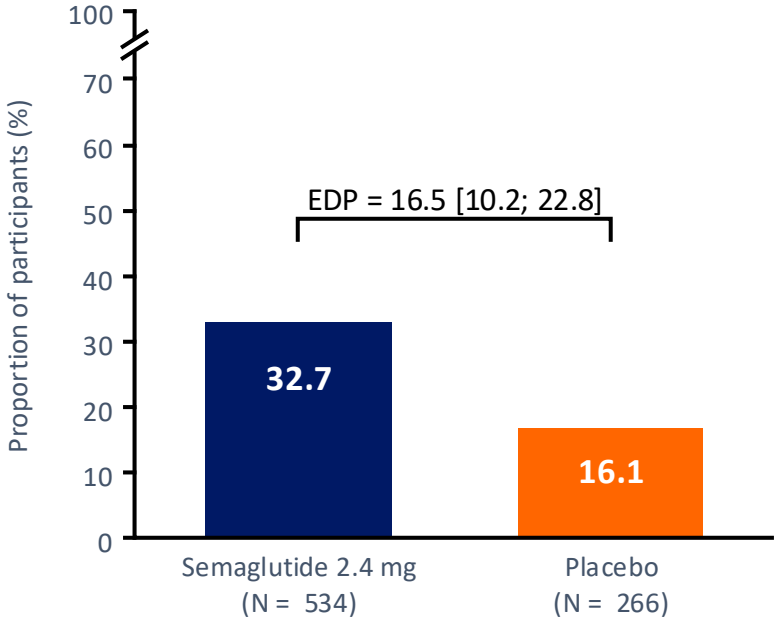


ITT: intention-to-treat. Participants without end-of-treatment biopsies were considered as nonresponders.

Newsome P et al NEJM 2025

Key secondary end point

Resolution of steatohepatitis with improvement in liver fibrosis



ITT: intention-to-treat. Participants without end-of-treatment biopsies were considered as nonresponders.

Newsome P et al NEJM 2025

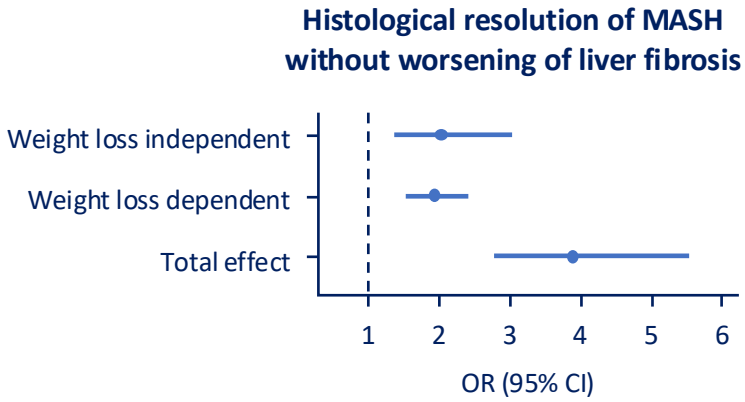
Safety analysis population

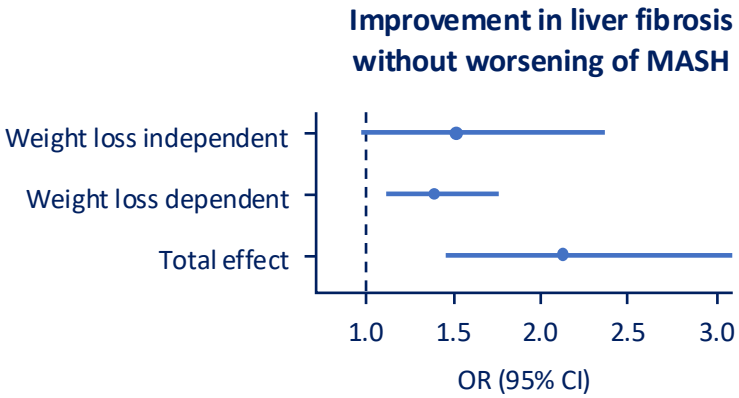
Event	Semaglutide 2.4 mg (n=800)	Placebo (n=395)
Adverse event affecting ≥10% of patients in either group		
Nausea	290 (36.2)	52 (13.2)
Diarrhea	215 (26.9)	48 (12.2)
Constipation	178 (22.2)	33 (8.4)
Vomiting	149 (18.6)	22 (5.6)
Coronavirus disease 2019	134 (16.8)	74 (18.7)
Decreased appetite	112 (14.0)	11 (2.8)
Adverse event within safety focus area†		
Gallbladder-related disorder	20 (2.5)	6 (1.5)
Acute pancreatitis	3 (0.4)	2 (0.5)
Malignant neoplasm	13 (1.6)	9 (2.3)
Hypoglycemia		
Patients with type 2 diabetes (n=446/n=222)‡	33 (7.4)	12 (5.4)
Patients without type 2 diabetes (n=354/n=173)	1 (0.3)	1 (0.6)

ITT: intention-to-treat. Participants without end-of-treatment biopsies were considered as nonresponders.

Newsome P et al NEJM 2025

The effect of semaglutide on MASH-related histological and NIT responder endpoints is only partially mediated by weight loss

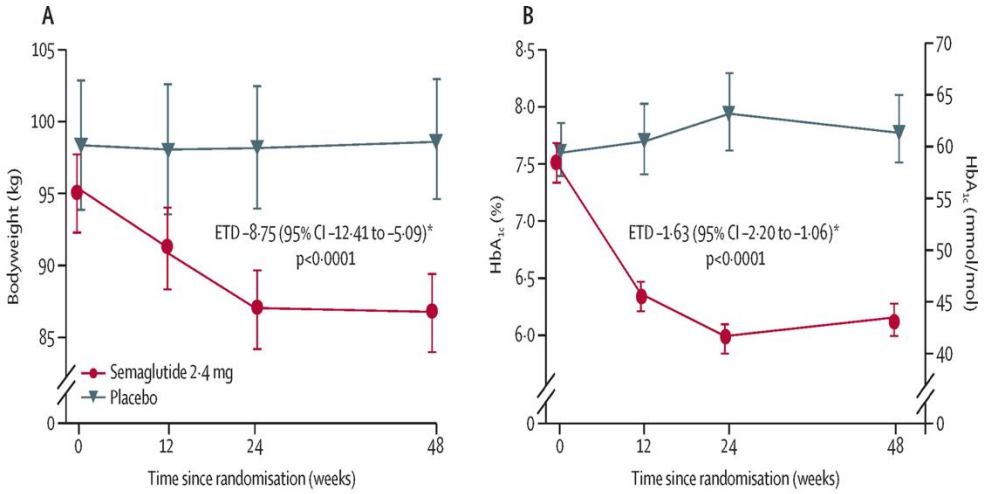




Data are based on the full analysis set from the on-treatment observation period.
All endpoints were assessed for weight loss-independent effects (where the change in the outcome is not attributed to the treatment [semaglutide] effect on the mediator [body weight]) and weight loss-dependent effects (where the change in the outcome is attributed to the treatment effect on the mediator [weight loss]).
Effects were considered statistically significant if the lower bound of the CI exceeded 1.0.

Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial

Rohit Loomba, Manal F Abdelmalek, Matthew J Armstrong, Maximilian Jara, Mette Skalshøi Kjær, Niels Krarup, Eric Lawitz, Vlad Ratziu, Arun J Sanyal, Jörn M Schattenberg, Philip N Newsome*, on behalf of the NN9931-4492 investigators†*

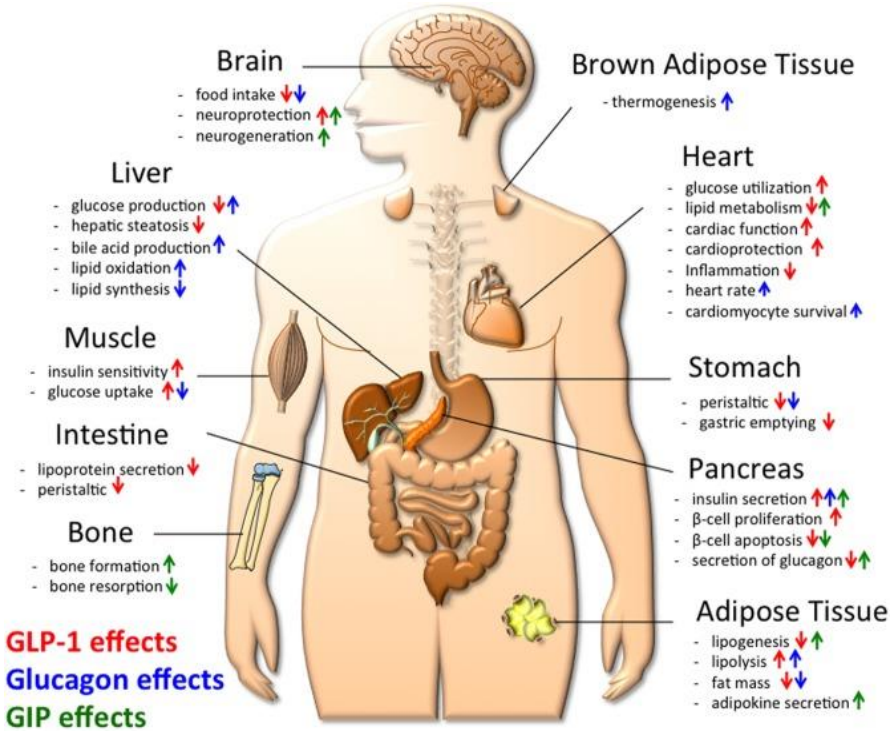


Semaglutide 2·4 mg	47	42	43	46
Placebo	24	23	22	23
Semaglutide 2·4 mg	35	32	33	34
Placebo	18	18	18	18

- RCT phase 2 to assess the efficacy and safety of semaglutide 2·4 mg once weekly in patients with **NASH-related compensated cirrhosis (fibrosis stage 4).**
- **No difference between semaglutide and placebo for fibrosis improvement without worsening of NASH or NASH resolution.**
- However, compared with placebo, semaglutide led to
  - **↓ body weight, liver enzymes, liver steatosis**
  - **↓ in levels of the hepatic collagen biomarker pro-collagen 3 peptide**.
  - **↓ TGC and VLDL cholesterol, HbA1c levels**
  - **No new safety concerns, no decompensating events or deaths**

Loomba et al. Lancet G&H 2023

Twincretin as a Potential Therapeutic for Management of MASLD



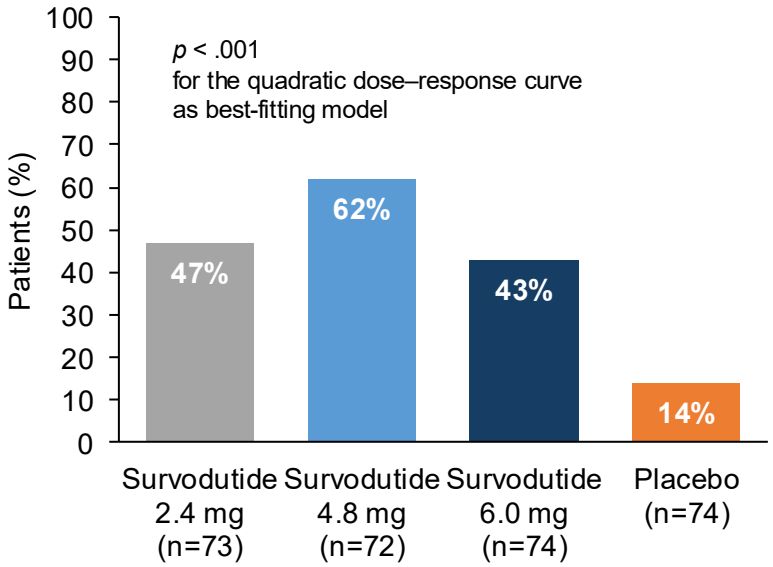
GIP: gastric inhibitory peptide.

Brandt SJ, et al. *J Endocrinol.* 2018;238:R109-R119. Creative https://www.fiercepharma.com/pharma/eli-lilly-touts-tirzepatide-midstage-nash-win-despite-lesser-anti-scarring-effect.

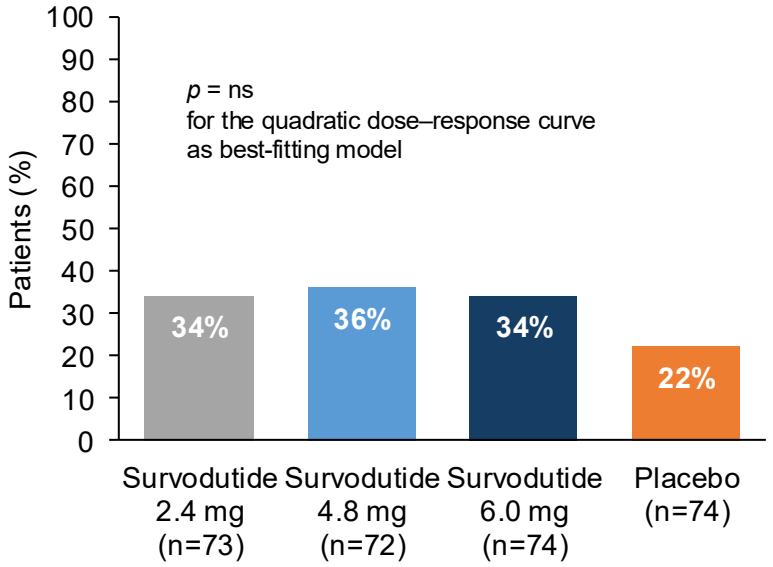
Dual GCGR/GLP-1RA Survodutide: Phase 2b Trial

Subcutaneous doses were administered once weekly for 48 weeks

Primary Endpoint: Histologic Improvement in MASH With No Worsening of Fibrosis



Secondary Endpoint: Improvement in Liver Fibrosis With No Worsening of MASH



All data pertain to participants without end-of-treatment biopsies who were considered as nonresponders.

Sanyal AJ, et al. *N Engl J Med*. 2024;391:311-319.

Incidence of AEs was similar between survodutide and placebo other than for gastrointestinal disorders

AE, n (%)	Survodutide 2.4 mg QW (n=73)	Survodutide 4.8 mg QW (n=72)	Survodutide 6.0 mg QW (n=74)	Total survodutide (n=219)	Placebo (n=74)
Participants with any AE	71 (97.3)	67 (93.1)	70 (94.6)	208 (95.0)	68 (91.9)
AE according to preferred term*					
Nausea	46 (63.0)	49 (68.1)	49 (66.2)	144 (65.8)	17 (23.0)
Diarrhea	30 (41.1)	40 (55.6)	37 (50.0)	107 (48.9)	17 (23.0)
Vomiting	27 (37.0)	33 (45.8)	29 (39.2)	89 (40.6)	3 (4.1)
Constipation	15 (20.5)	12 (16.7)	19 (25.7)	46 (21.0)	11 (14.9)
COVID-19	18 (24.7)	16 (22.2)	7 (9.5)	41 (18.7)	14 (18.9)
Headache	13 (17.8)	16 (22.2)	11 (14.9)	40 (18.3)	12 (16.2)
Decreased appetite	16 (21.9)	9 (12.5)	13 (17.6)	38 (17.4)	7 (9.5)
Fatigue	15 (20.5)	11 (15.3)	11 (14.9)	37 (16.9)	6 (8.1)
Dyspepsia	7 (9.6)	9 (12.5)	15 (20.3)	31 (14.2)	3 (4.1)
Investigator-defined drug-related AE	60 (82.2)	59 (81.9)	60 (81.1)	179 (81.7)	36 (48.6)
AE leading to discontinuation of trial medication†	12 (16.4)	15 (20.8)	17 (23.0)	44 (20.1)	2 (2.7)
Discontinuation due to gastrointestinal AE	10 (13.7)	13 (18.1)	12 (16.2)	35 (16.0)	1 (1.4)
Serious AE	4 (5.5)	7 (9.7)	6 (8.1)	17 (7.8)	5 (6.8)
Drug-related serious AE	1 (1.4)	0 (0)	0 (0)	1 (0.5)	0 (0)

All data pertain to participants without end-of-treatment biopsies who were considered as nonresponders.

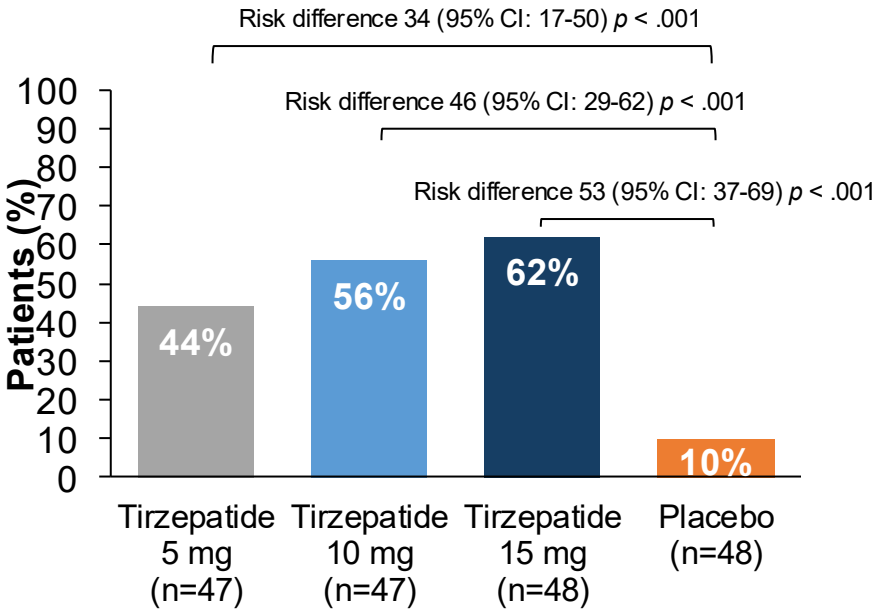
Sanyal AJ, et al. *N Engl J Med*. 2024;391:311-319.

Dual GIP and GLP-1RA Tirzepatide: Phase 2b Trial

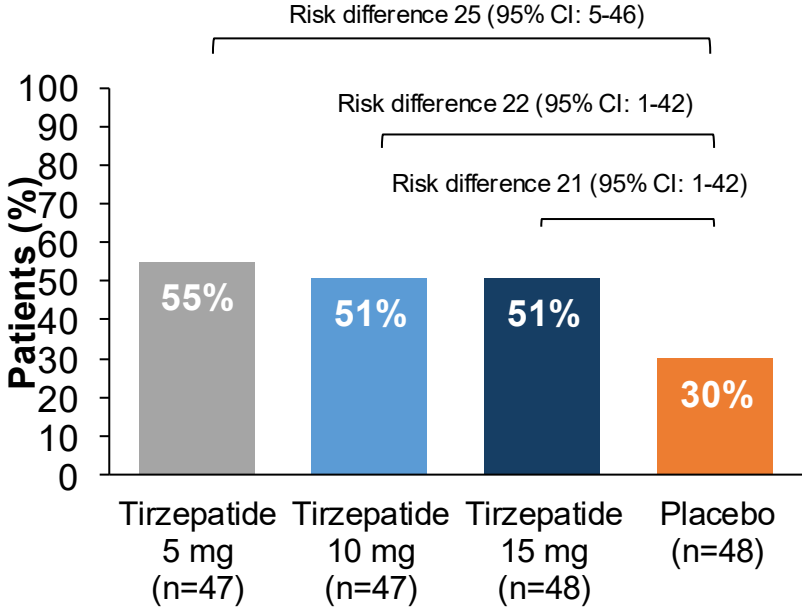
Subcutaneous doses were administered once weekly for 52 weeks

Mean percentage change in body weight was −10.7%, −13.3%, and −15.6% in the 5-mg, 10-mg, and 15-mg tirzepatide groups, respectively, as compared with −0.8% in the placebo group

Primary Endpoint: Resolution of MASH With No Worsening of Liver Fibrosis



Secondary Endpoint: Improvement in Liver Fibrosis With No Worsening of MASH



All data pertain to participants without end-of-treatment biopsies who were considered as nonresponders. Loomba R, et al. *N Engl J Med.* 2024;391:299-310.

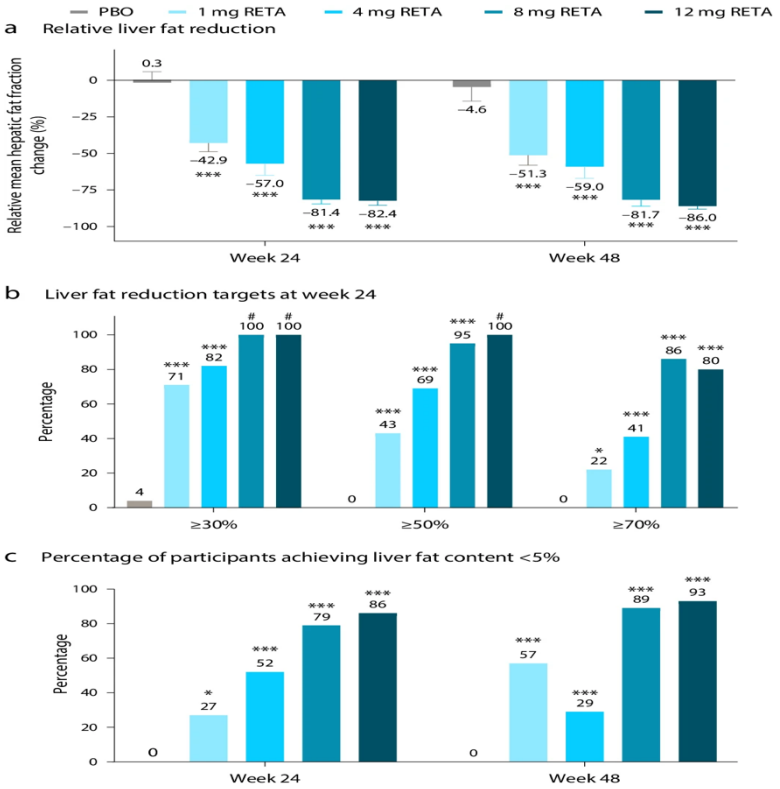
Dual GIP and GLP-1RA Tirzepatide: Phase 2b Trial Adverse events

	Tirzepatide 5 mg N=47	Tirzepatide 10 mg N=47	Tirzepatide 15 mg N=48	Placebo N=48
Participants with any AE	43 (91.5)	44 (93.6)	44 (91.7)	40 (83.3)
Participants with any SAE	5 (10.6)	4 (8.5)	0	3 (6.2)
Participants with AE leading to discontinuation of study drug	2 (4.3)	0	4 (8.3)	2 (4.2)
Participants with Gastrointestinal disorders leading to discontinuation of study drug	2 (4.3)	0	2 (4.2)	1 (2.1)
Participants with ≥1 TEAE	43 (91.5)	44 (93.6)	44 (91.7)	40 (83.3)
Nausea	17 (36.2)	16 (34.0)	21 (43.8)	6 (12.5)
Diarrhea	15 (31.9)	17 (36.2)	13 (27.1)	11 (22.9)
Decreased appetite	9 (19.1)	10 (21.3)	11 (22.9)	1 (2.1)
Constipation	11 (23.4)	9 (19.1)	7 (14.6)	3 (6.2)
COVID-19	5 (10.6)	6 (12.8)	9 (18.8)	4 (8.3)
Headache	3 (6.4)	6 (12.8)	3 (6.2)	5 (10.4)
Abdominal distension	3 (6.4)	3 (6.4)	6 (12.5)	4 (8.3)
Abdominal pain	6 (12.8)	3 (6.4)	4 (8.3)	3 (6.2)
Fatigue	4 (8.5)	4 (8.5)	5 (10.4)	3 (6.2)
Dizziness	2 (4.3)	6 (12.8)	4 (8.3)	2 (4.2)
Dyspepsia	2 (4.3)	8 (17.0)	2 (4.2)	2 (4.2)
Vomiting	3 (6.4)	3 (6.4)	7 (14.6)	1 (2.1)
Weight decreased	5 (10.6)	3 (6.4)	4 (8.3)	0
Urinary tract infection	2 (4.3)	3 (6.4)	2 (4.2)	4 (8.3)
Abdominal pain upper	6 (12.8)	2 (4.3)	0	2 (4.2)
Arthralgia	5 (10.6)	2 (4.3)	2 (4.2)	1 (2.1)
Adjudicated MACE	1 (2.1)	0	0	0
Adjudicated MASH-related clinical events (all progression to cirrhosis)	2 (4.3)	2 (4.3)	0	2 (4.2)

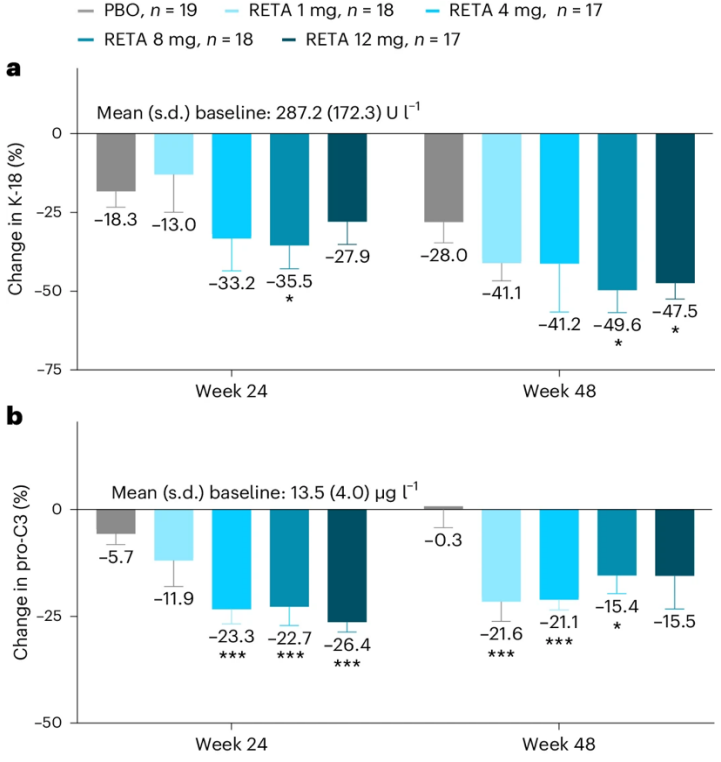
Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial

At 48 weeks, changes in body weight were −8.6%, −16.3%, −23.8% and −25.9% for the 1, 4, 8 and 12 mg once-weekly sc respectively, compared with −0.1% with placebo

Change in Liver fat by PDFF

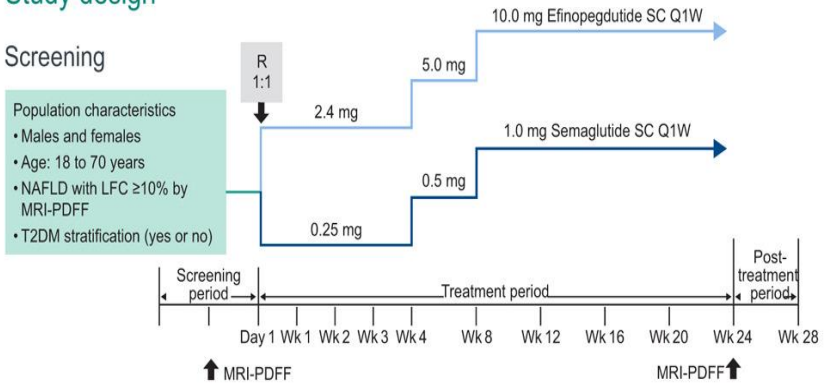


Change in biomarkers of necroinflammation and fibrosis



Dual GCGR/GLP-1R agonist Efinopegdutide in MASH

Study design



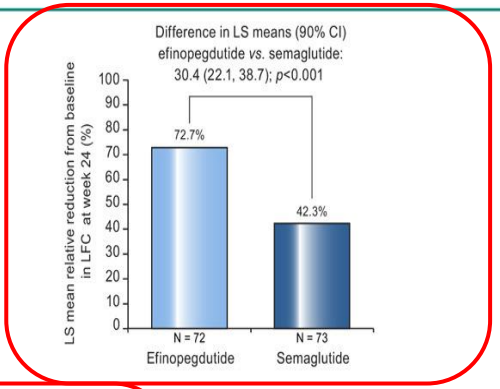
Safety results

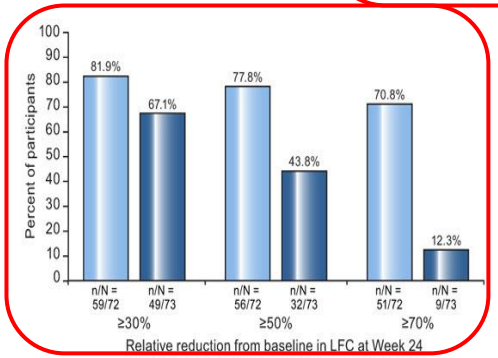
	Efinopegdutide n = 72	Semaglutide n = 73
Participants with an AE, %	88.9%	72.6%
Deaths	0	0
Serious drug-related AEs	0	

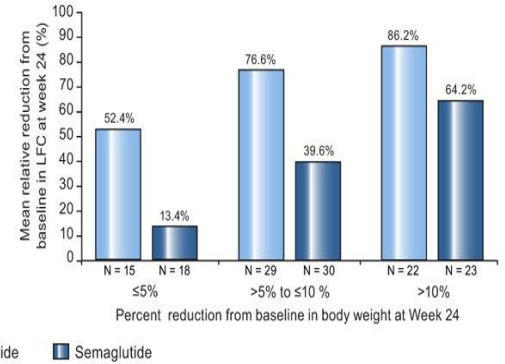
Efficacy results

Primary efficacy endpoint

Relative reduction from baseline in LFC at week 24







Efinopegdutide Semaglutide

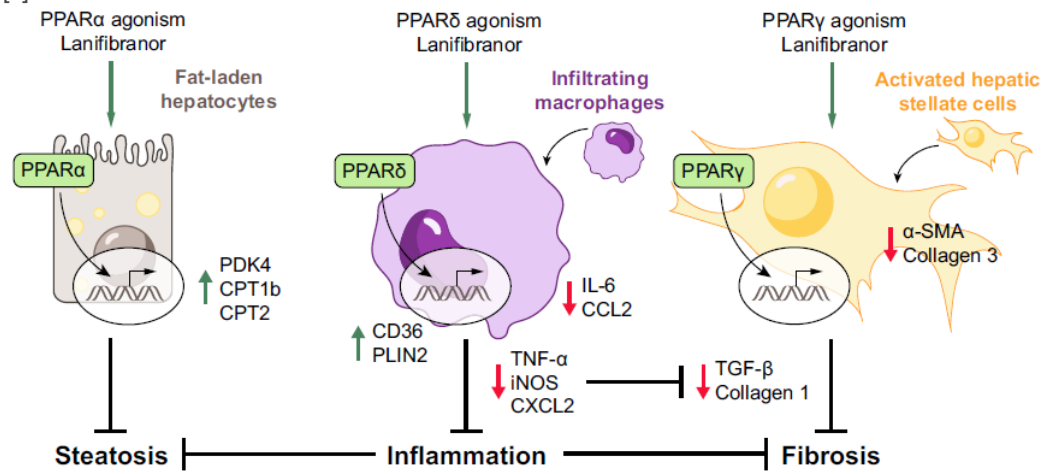
Romero-Gomez et al J Hepatol 2023

Lanifibranor

Mechanism of Action

Lanifibranor Is a Pan-PPAR (PPAR α/δ/γ) Agonist

[a]



PPARs[a]

- Nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis

In clinical trial patients, lanifibranor has been found to affect[b]

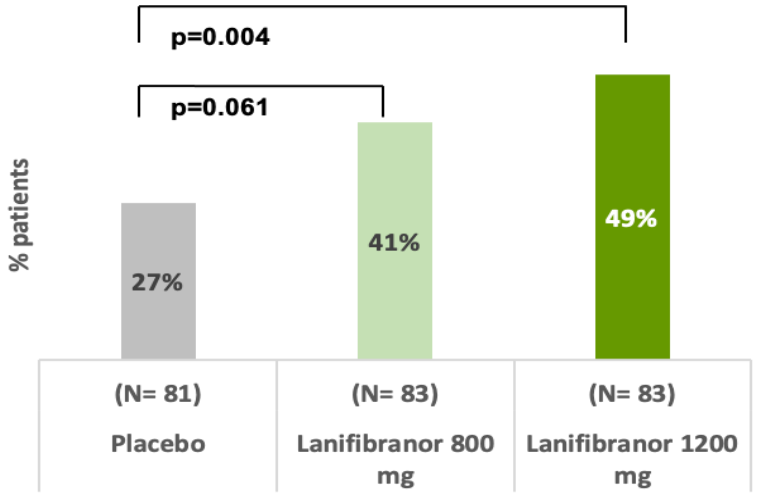
- Steatosis
- Inflammation
- Liver fibrosis
- Macrophage activation was improved in preclinical models

- a. Lefere S, et al. J Hepatol. 2020;73:757-770; b. Francque SM, et al. N Engl J Med. 2021;385:1547-1558.

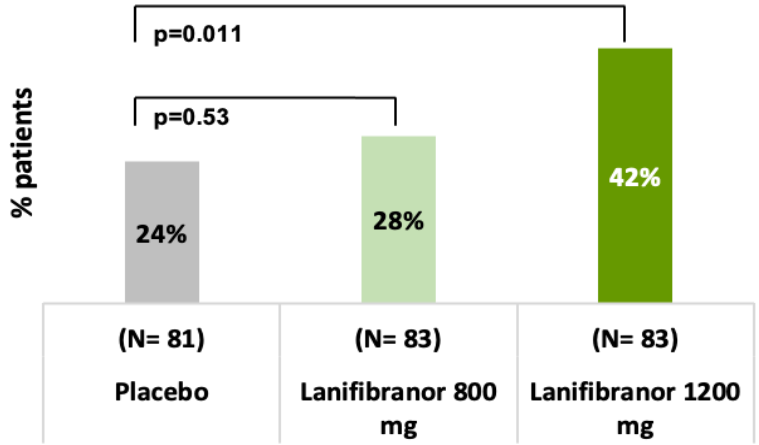
Lanifibranor
phase IIb NATIVE Trial

- A 24-week, Phase 2b study of 247 participants with MASH and SAF activity score ≥2
- **Interventions**: Placebo vs pan-PPAR agonist lanifibranor 800 and 1,200 mg/day oral

Reduction of MASH and no worsening of fibrosis



Improvement of fibrosis by at least one stage and no worsening of MASH



Francque S. et al NEJM 2021

Lanifibranor

Safety NATIVE Trial

Most Frequent AEs	Lanifibranor 1200 mg (N = 83), n (%)	Lanifibranor 800 mg (N = 83), n (%)	Placebo (N = 81), n (%)
Diarrhea	10 (12)	8 (10)	1 (1)
Fatigue	11 (13)	3 (4)	8 (10)
Nausea	7 (8)	8 (10)	3 (4)
Weight gain	7 (8)	8 (10)	0 (0)
Peripheral edema	7 (8)	5 (6)	2 (2)
Headache	7 (8)	4 (5)	4 (5)
Abdominal pain	5 (6)	4 (5)	4 (5)
Dizziness	6 (7)	2 (2)	3 (4)
Anemia	6 (7)	1 (1)	0 (0)
Constipation	5 (6)	3 (4)	6 (7)
Increase in aminotransferase levels	3 (4)	5 (6)	1 (1)

- Francque SM, et al. N Engl J Med. 2021.

Fibroblast growth factor 21 pathway

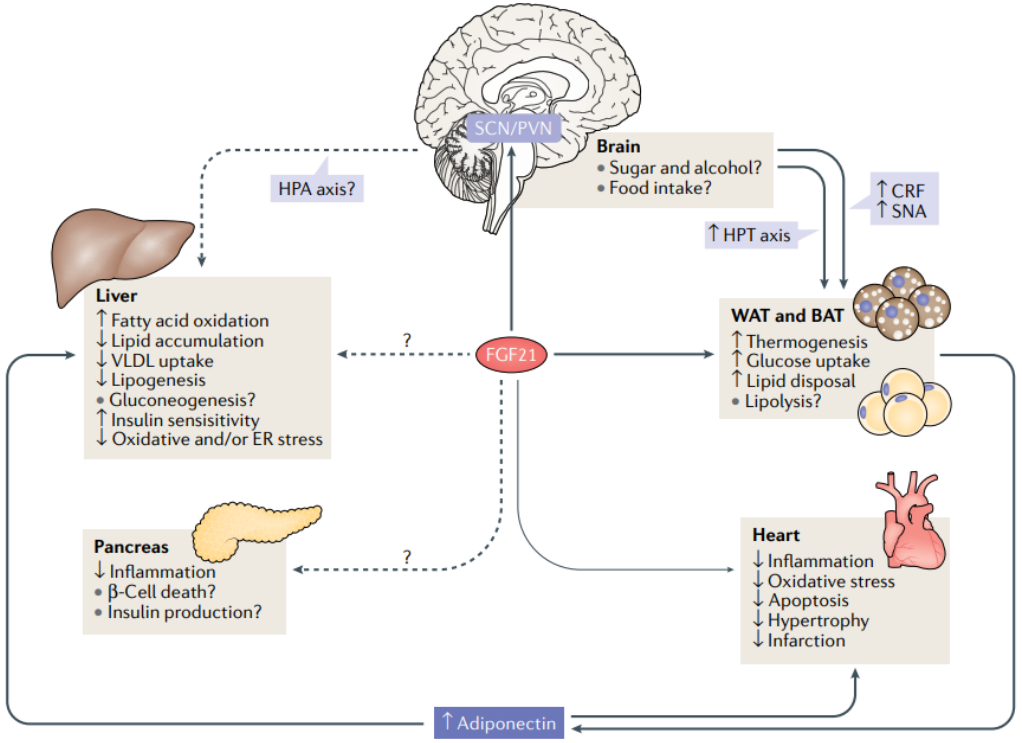
Endogenous metabolic hormone that regulates energy expenditure and glucose and lipid metabolism

Reduces liver fat by action within liver and from periphery

Impacts liver fibrosis via metabolic pathway and upregulation of adiponectin homeostasis.

The pleiotropic effects of FGF21 are mediated by its direct actions in hepatocytes and cardiomyocytes, and/or indirect mechanisms through adipocyte-secreted adiponectin or brain–liver crosstalk.

Native FGF21 has a **short half-life** of < 2 hours



Geng et al, Nat Rev Endocrinol 2020

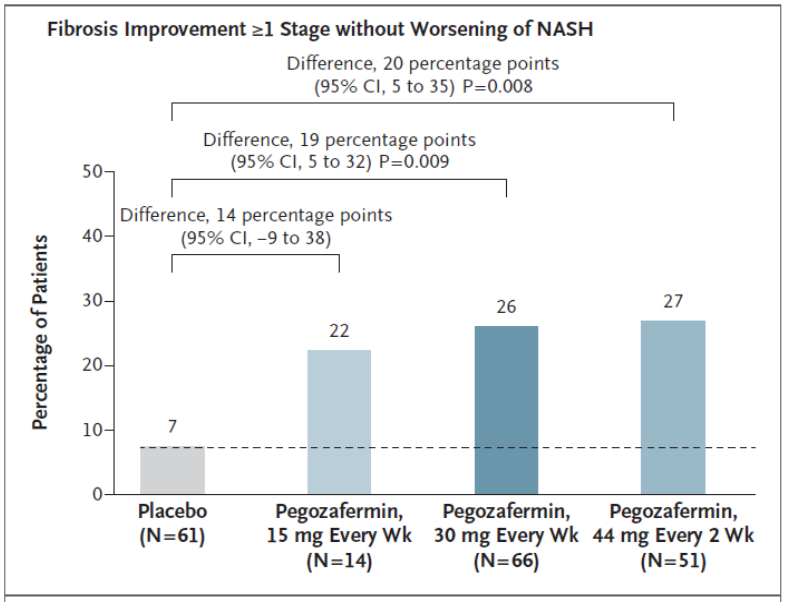
Pegozafermin

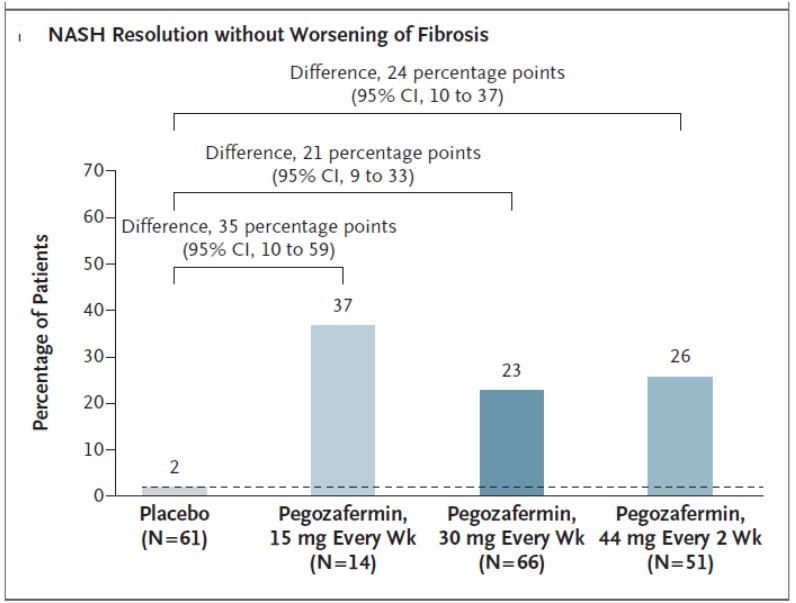
Phase 2b ENLIVEN Trial

Pegozafermin Is a Long-Acting Fc FGF-21 Fusion Protein

A 24-week, RCT in MASH and F2-F3 fibrosis (PLO vs sc 15 mg vs 30 mg weekly vs 44 mg every 2 weeks).

Most common adverse events were nausea and diarrhea. One case of acute pancreatitis in the 44-mg arm.





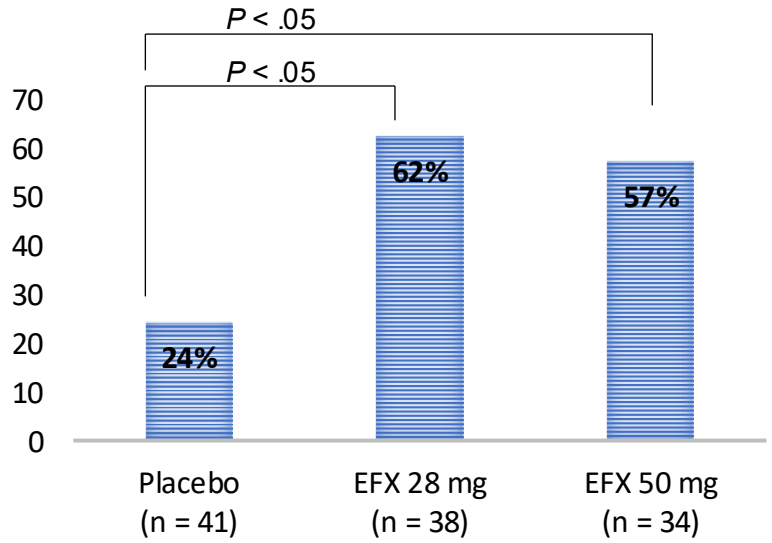
Loomba et al, NEJM 2023

Efruxifermin

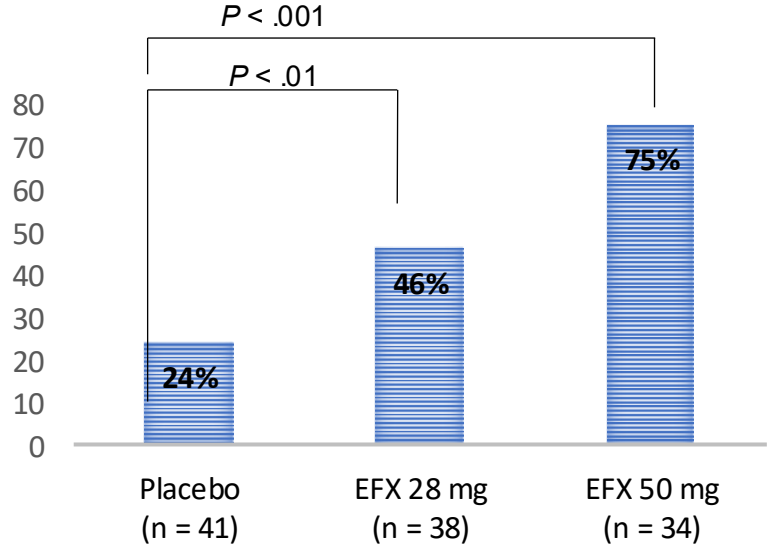
Phase 2b HARMONY Trial

Efruxifermin Is a Long-Acting FGF21 Analog

NASH Resolution
Both EFX Doses Achieved Statistical Significance after 24 wks of tretment



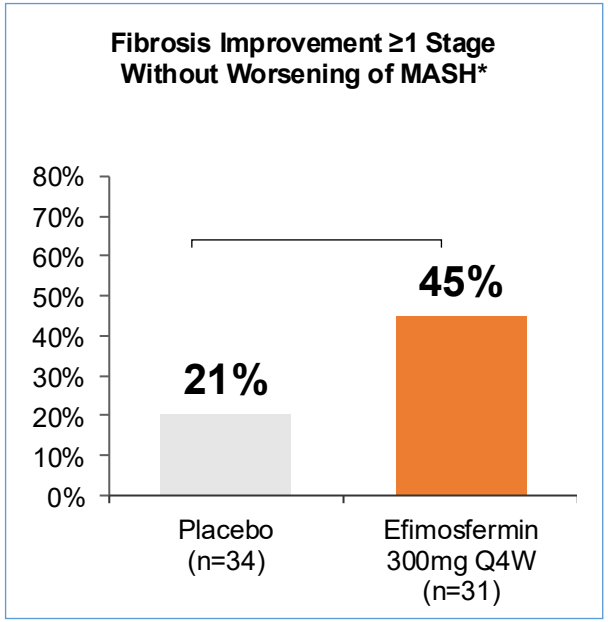
Fibrosis Improvement
Both EFX Doses Achieved Statistical Significance after 24 wks of tretment

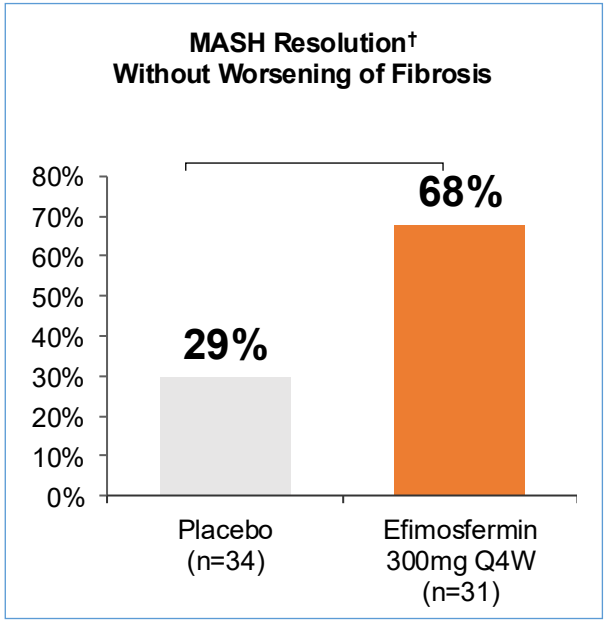


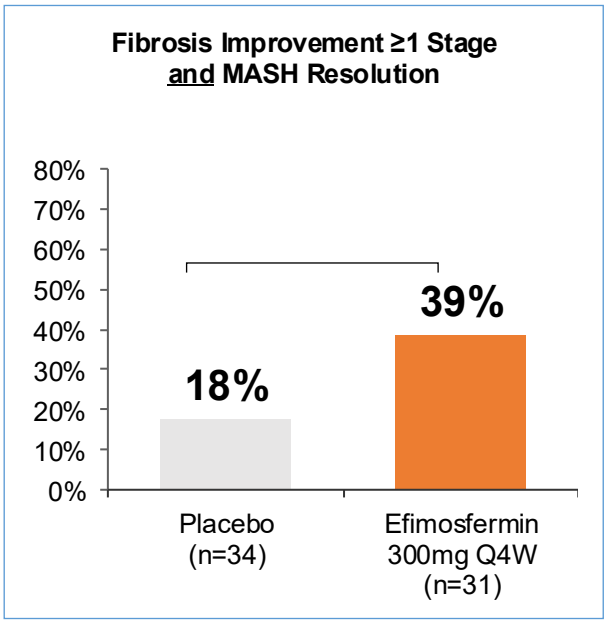
- EFX, efruxifermin. Akero PR. 4 MAR 2024

Once-monthly Efimosfermin Showed Higher Response Rate on Liver Histology After 24 Weeks Treatment vs. Placebo[1]

Proportion of Participants at Week 24, %



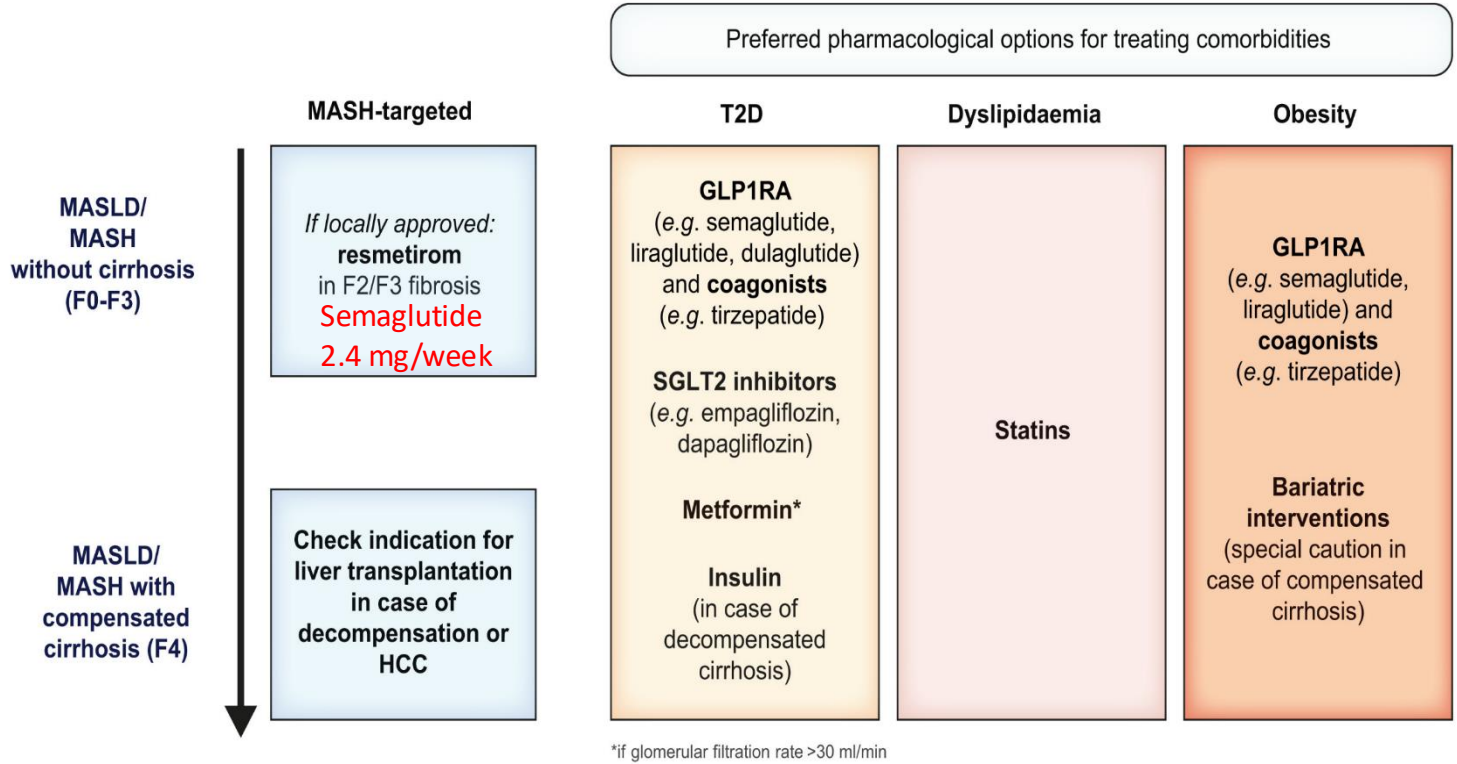




Exploratory endpoint, not adjusted for multiplicity.[2]
Cochran-Mantel-Haenszel (CMH) test stratified by baseline fibrosis stage.
MASH, metabolic dysfunction-associated steatohepatitis; NAS, NAFLD Activity Score; Q4W, every 4 weeks.

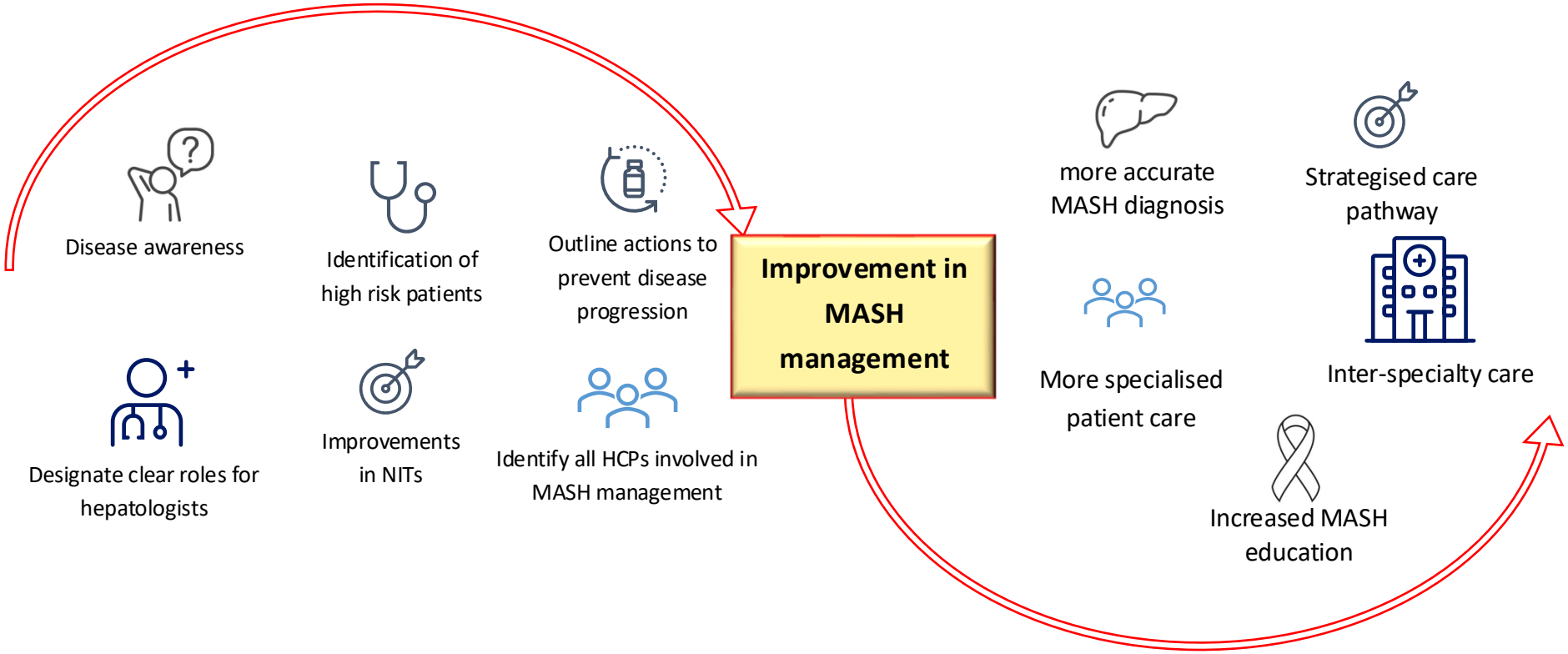
1. Noureddin M et al. DDW 2025. Oral presentation 723; 2. Noureddin M et al. Manuscript in development. Data on file REF-291093.

Treatment recommendations beyond lifestyle modification in MASLD/MASH



EASL-EASD-EASO MASLD clinical practice guideline. *J Hepatol*. 2024

A multidisciplinary approach to improve MASH management



Thank you for your attention!