Actualización en el tratamiento de la Esteatosis hepática metabólica (EHmet / MASLD)

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Enfermedad hepática esteatósica (SLD)
Esteatosis hepática identificada por imagen o biopsia

¿Presencia de alguno de los criterios cardiometabólicos?

Criterios cardiometabólicos:
- Sobrepeso/obesidad
- Hiperglucemia/Diabetes
- Hipertrigliceridemia > 150
- HDL colesterol < 40 ♂ ó < 50 ♀
- HTA

SI

NO

¿Presencia (historia) de consumo de alcohol > 20 g/día en mujeres y > 30 g/día en hombres ?

NO

Enfermedad hepática esteatósica asociada a disfunción metabólica (MASLD)

Si inflamación y balonización en histología

Esteatohepatitis asociada a disfunción metabólica **(MASH)**

SI

Consumo de alcohol > 50 g/día en mujeres y > 60 g/día en hombres?

NO

MASLD con consumo aumentado de alcohol **(MetALD)**
(20-50 g/día en mujeres y 30-60 g/día en hombres)

SI

Enfermedad hepática relacionada con el alcohol (ALD)
(> 50 g/día en mujeres y > 60 g/día en hombres)

SI

NO

¿Otras causas de esteatosis?

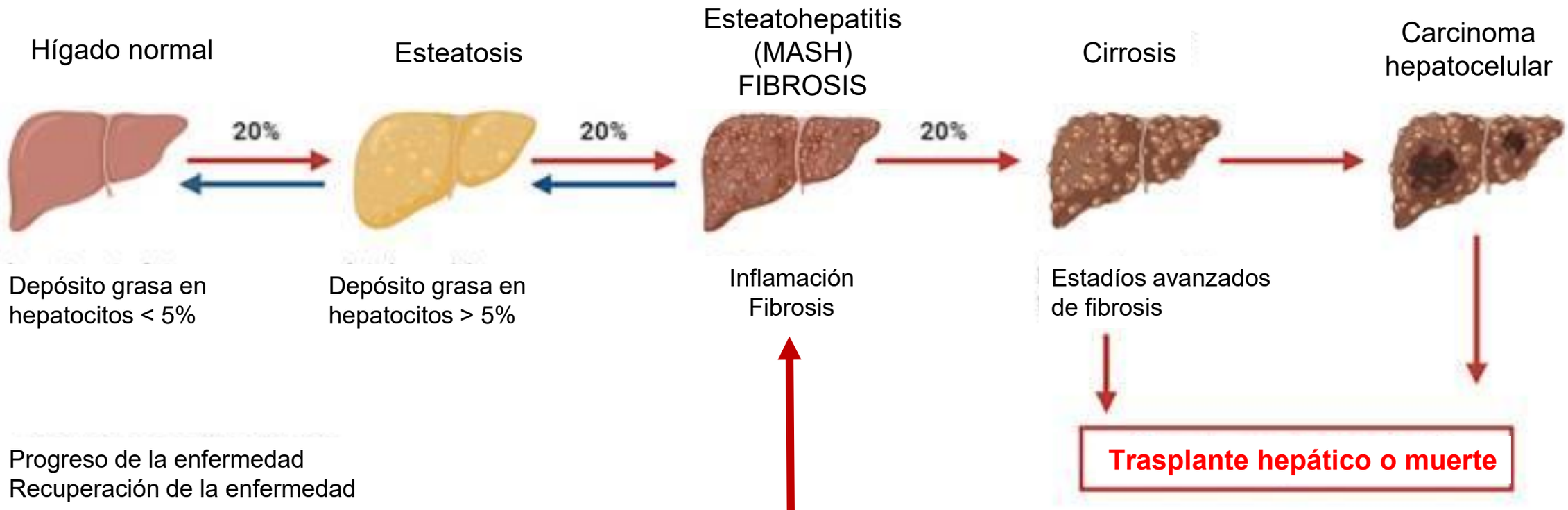
SI

- Enfermedad hepática inducida por fármacos (DILI)
- Enfermedades monogénicas
- Miscelánea

NO

SLD criptogenética

Rinella ME, et al; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol. 2023 Dec;79(6):1542-56.



ESTEATOHEPATITIS **(MASH) EN RIESGO:**

- puntuación elevada de actividad **(NAS≥4)** en la escala del CRN para NAFLD)
- fibrosis significativa **(F ≥ 2)**

Kleiner DE, et al. Diseño y validación de un sistema de puntuación histológica para la enfermedad del hígado graso no alcohólico. Hepatología 2005; 41 : 1313-21

Objetivos terapéuticos actuales

- **Resolución de MASH sin empeoramiento de la fibrosis**
- **Mejoría de la fibrosis** en al menos un estadio **sin empeoramiento de la puntuación de actividad de NAFLD**

Resmetirom 80 o 100 mg/día en EHmet (MASH)

- Agonista selectivo del receptor β de la hormona tiroidea (THR-β), responsable de regular vías metabólicas específicas alteradas en el hígado.
- Actúa específicamente en hígado, sin efectos sistémicos.
- Se administra **una vez al día** por **vía oral**.

4 ensayos de fase III, de los cuales se han publicado resultados de 2: MAESTRO-NAFLD-1 (seguridad) y **MAESTRO-NASH** (eficacia y seguridad).

Los otros 2 en desarrollo son: MAESTRO-NAFLD-OLE, una extensión del MAESTRO-NAFLD-1 a más tiempo de tratamiento activo, y MAESTRO-NASH-OUTCOMES con cirrosis MASH bien compensada para evaluar si retarda la progresión a eventos de descompensación hepática.

Harrison SA, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2019 Nov 30;394(10213):2012-24.

Harrison SA, et al. Design of the phase 3 MAESTRO clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2024 Jan;59(1):51-63.

Harrison SA, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med. 2023 Nov;29(11):2919-28.

Harrison SA, et al; MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024 Feb 8;390(6):497-509.

245 centros de 15 países

Biopsia seriada en adultos con **MASH en riesgo,** en la selección y la semana 52 y se harán en el mes 54.
Sigue en curso con una duración prevista de 54 meses (4,5 años).

Se asignó aleatoriamente a placebo, 80 mg o 100 mg de resmetirom, a **966 pacientes**.

Se publicaron los resultados a las **52 semanas** de tratamiento en febrero de **2024**, precipitando la aprobación del fármaco por la FDA.

En USA se administra en dosis diaria de 80 mg en personas con peso < 100 kg, y de 100 mg en personas con peso > 100 kg.

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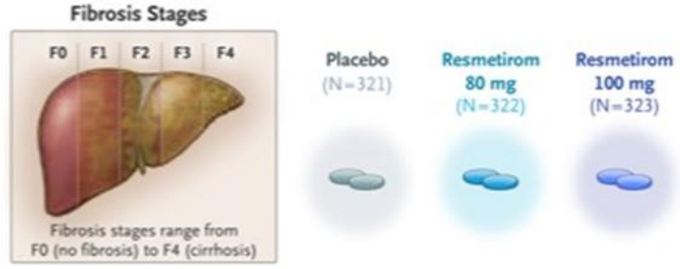
RESEARCH SUMMARY

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

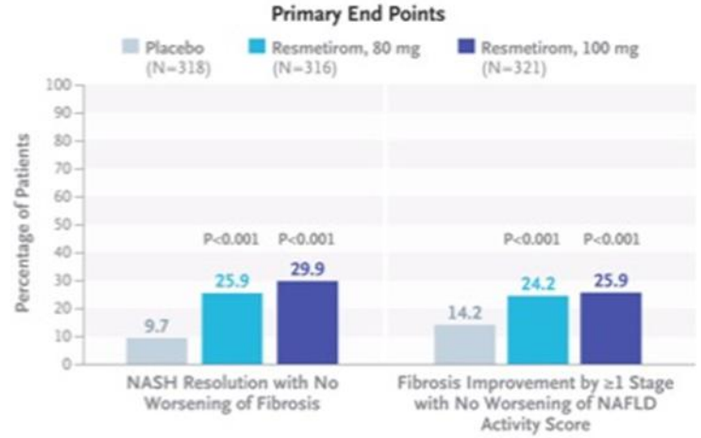
Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.



CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

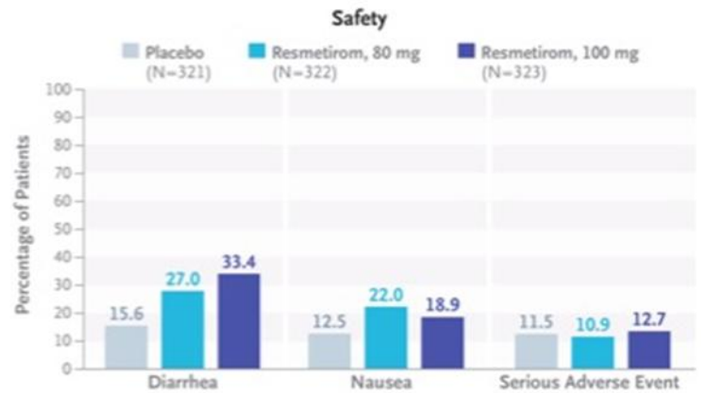
Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.



RESULTS

Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.



LIMITATIONS AND REMAINING QUESTIONS

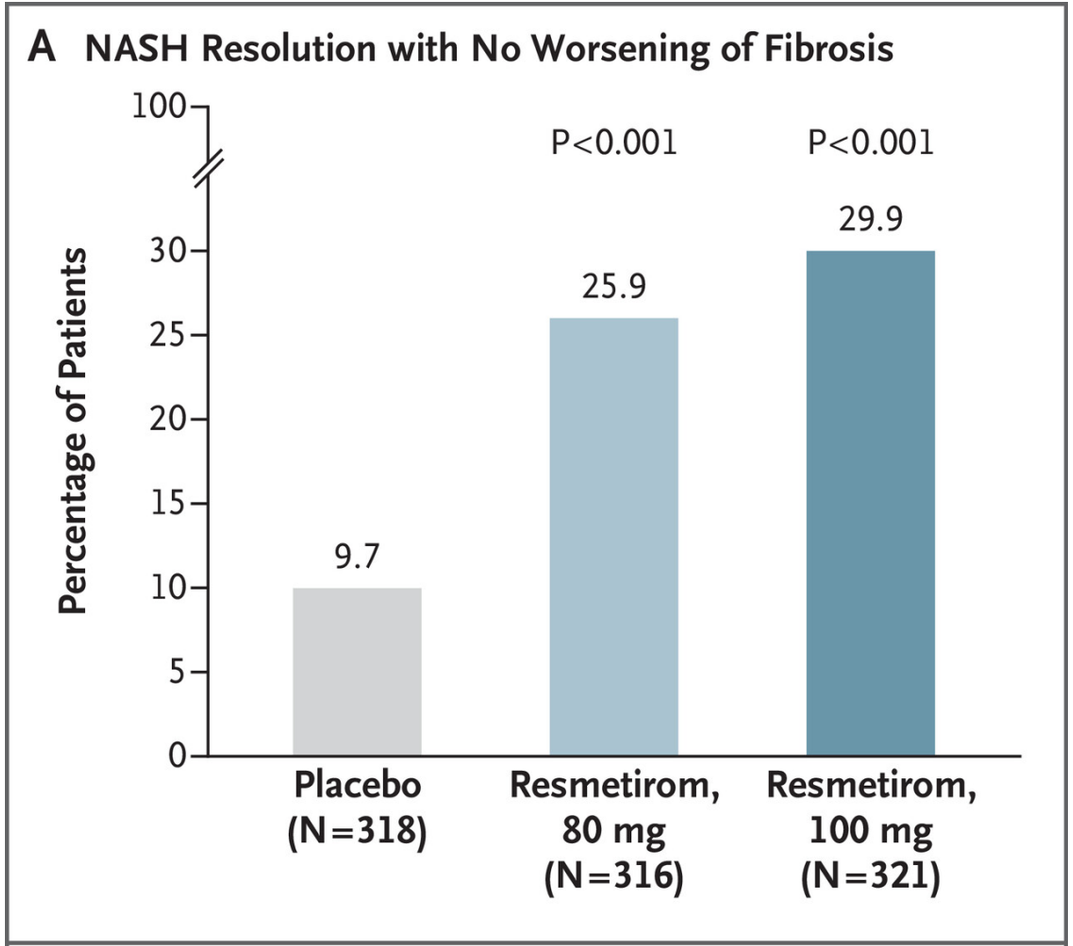
- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.

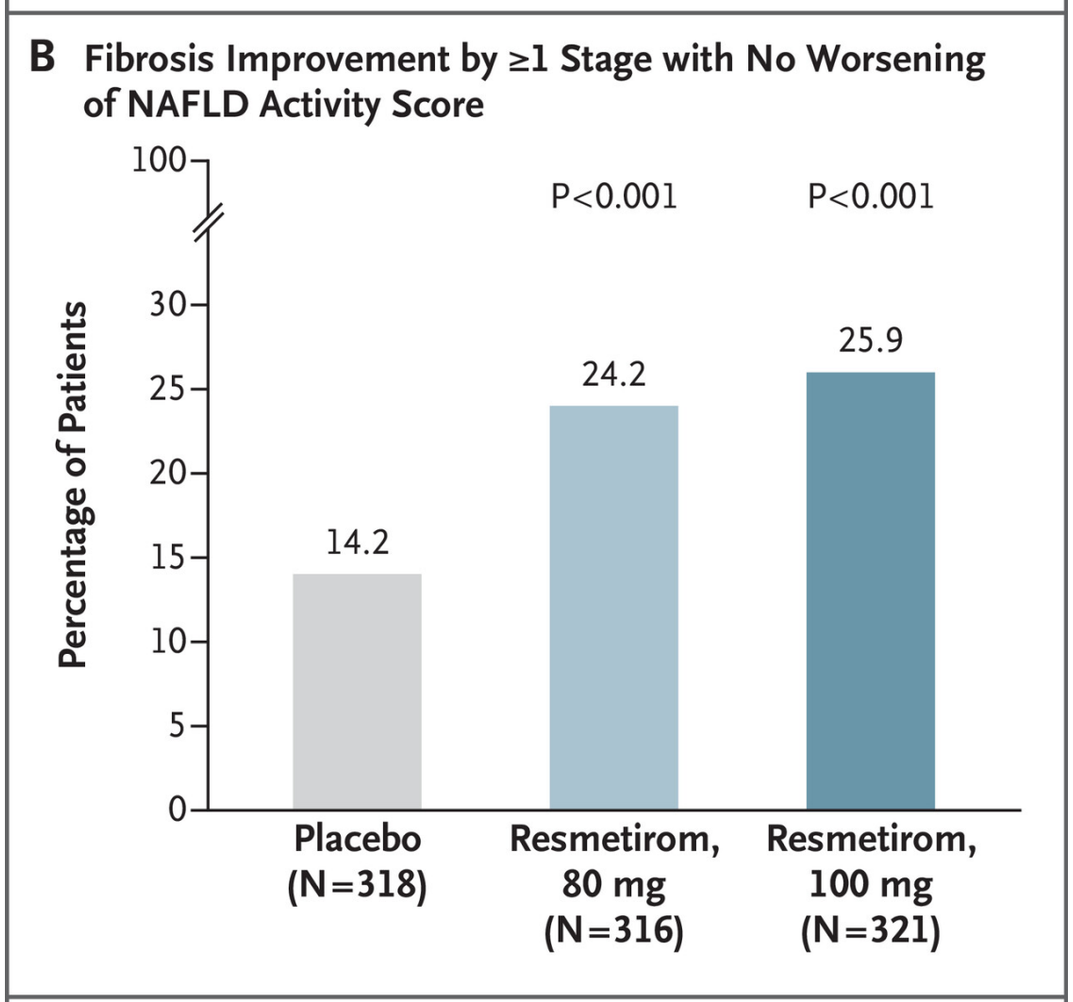
CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

Links: Full Article | NEJM Quick Take | Editorial

Criterios de valoración principales





RESULTADOS TRAS **1 AÑO**

Table 2. Biopsy End Points.*

End Point	Resmetirom, 80 mg (N=316)	Resmetirom, 100 mg (N=321)	Placebo (N=318)	Difference between Resmetirom, 80 mg, and Placebo (95% CI)†	P Value	Difference between Resmetirom, 100 mg, and Placebo (95% CI)†	P Value
	percent with response			*percentage points*		*percentage points*	
Primary end points							
NASH resolution with no worsening of fibrosis	25.9	29.9	9.7	16.4 (11.0–21.8)	<0.001	20.7 (15.3–26.2)	<0.001
Fibrosis improvement by ≥1 stage with no worsening of NAFLD activity score	24.2	25.9	14.2	10.2 (4.8–15.7)	<0.001	11.8 (6.4–17.2)	<0.001
Other end points							
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with no worsening of fibrosis	41.3	44.9	21.2	20.2 (13.8–26.5)		23.8 (17.4–30.2)	
≥2-Point improvement in NAFLD activity score, including ≥1-point improvement in hepatocellular ballooning or lobular inflammation, with improvement in fibrosis	18.8	21.2	8.5	10.5 (5.8–15.3)		13.0 (8.3–17.7)	
Improvement in each component of NAFLD activity score	23.3	27.9	7.2	16.1 (11.1–21.0)		20.9 (15.8–25.9)	
Improvement in fibrosis by ≥2 stages	8.3	10.1	2.8	5.6 (2.5–8.7)		7.4 (3.9–10.8)	
Both NASH resolution and fibrosis improvement by ≥1 stage	14.2	16.0	4.9	9.5 (5.4–13.6)		11.6 (7.5–15.8)	

* Of the 966 patients in the primary population, 11 patients (6 in the 80-mg resmetirom group, 3 in the 100-mg resmetirom group, and 2 in the placebo group) had a delay in their week 52 biopsy for reasons related to coronavirus disease 2019 (Covid-19) and were not evaluated for the end points shown here. NASH resolution was defined as a hepatocellular ballooning score of 0, a lobular inflammation score of 0 or 1, and a reduction in the NAFLD activity score by at least 2 points.

† The widths of the confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing.

Table 4. Safety Summary (Primary Population).

Event	Resmetirom, 80 mg (N = 322)	Resmetirom, 100 mg (N = 323)	Placebo (N = 321)
	number of patients (percent)		
≥1 Adverse event	296 (91.9)	296 (91.6)	298 (92.8)
Grade 1: mild	73 (22.7)	66 (20.4)	77 (24.0)
Grade 2: moderate	180 (55.9)	183 (56.7)	169 (52.6)
Grade 3 or higher: severe	43 (13.4)	47 (14.6)	52 (16.2)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)
Adverse event leading to trial discontinuation before wk 52†	6 (1.9)	22 (6.8)	7 (2.2)
Adverse event leading to trial discontinuation during entire treatment period†	9 (2.8)	25 (7.7)	11 (3.4)
Fatal adverse event	1 (0.3)	2 (0.6)	1 (0.3)
Major adverse cardiovascular event‡	1 (0.3)	1 (0.3)	1 (0.3)
Other cardiovascular event‡	0	1 (0.3)	3 (0.9)
Adverse events affecting >10% of patients in any group			
Diarrhea	87 (27.0)	108 (33.4)	50 (15.6)
Covid-19	69 (21.4)	54 (16.7)	66 (20.6)
Nausea	71 (22.0)	61 (18.9)	40 (12.5)
Arthralgia	48 (14.9)	35 (10.8)	40 (12.5)
Back pain	35 (10.9)	27 (8.4)	38 (11.8)
Urinary tract infection	33 (10.2)	27 (8.4)	27 (8.4)
Fatigue	33 (10.2)	26 (8.0)	28 (8.7)
Pruritus	26 (8.1)	37 (11.5)	22 (6.9)
Vomiting	28 (8.7)	35 (10.8)	17 (5.3)

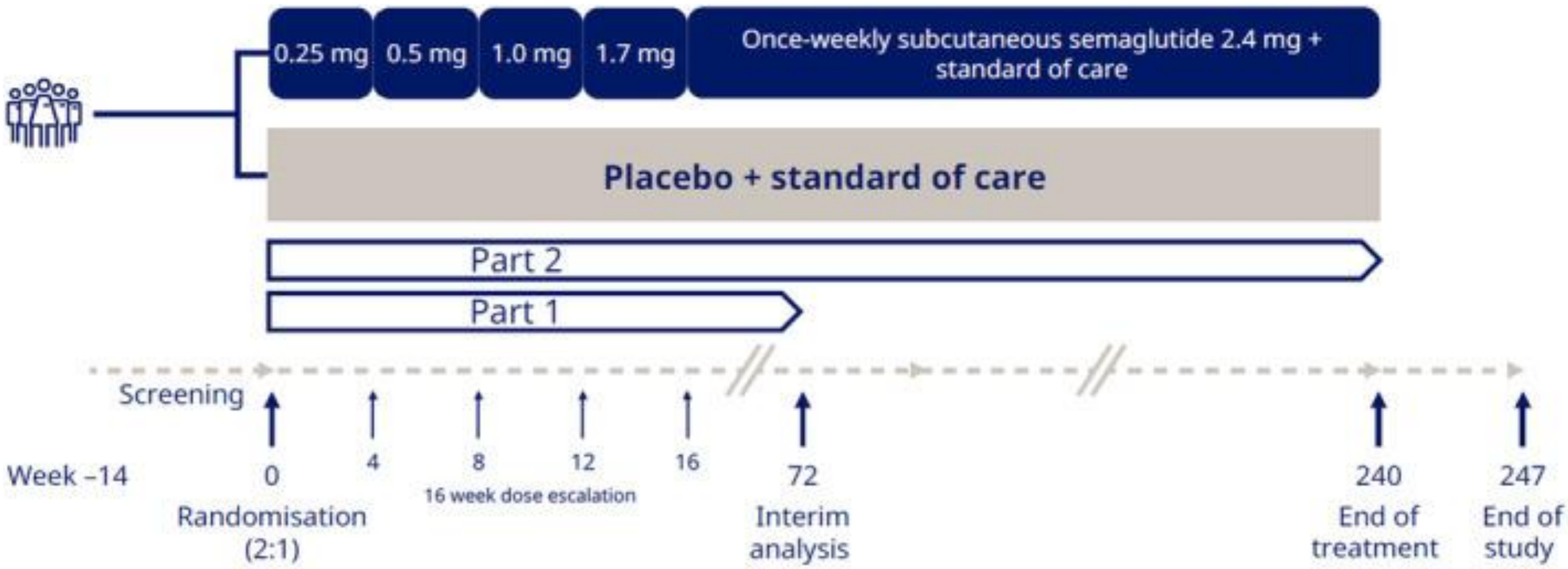
* Shown are events that were considered by investigators to be related to resmetirom or placebo.
† Data are for events that emerged after the first dose of resmetirom or placebo and within 30 days after the last dose.
‡ Major adverse cardiovascular events were defined as nonfatal stroke, nonfatal myocardial infarction, and death from cardiovascular causes. All cardiovascular events were adjudicated.

Situación actual de Resmetirom

- Aprobación FDA marzo 24
- Autorización condicional en la Unión Europea (EMA agosto 2025)
- No está comercializado ni disponible con receta en España a mayo de 2026
- Aunque cuenta con la opinión positiva del Comité de Medicamentos de Uso Humano en Europa y la aprobación de la FDA, el Ministerio de Sanidad español y la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) se encuentran evaluando los procesos de precio y reembolso para el Sistema Nacional de Salud
- Solo es posible acceder a él en España participando en ensayos clínicos controlados o a través de programas de uso compasivo en casos graves supervisados por hepatólogos

SEMAGLUTIDA 2,4 mg/semana en EHmet (MASH)

- ESSENCE



Sanyal AJ, et al; ESSENCE Study Group. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025 Jun 5;392(21):2089-99.

253 centros clínicos de 37 países

Continúa en curso para evaluar los efectos sobre la supervivencia libre de cirrosis tras 240 semanas de seguimiento

Una biopsia al inicio y otra en la semana 72

RESULTADOS a las **72 semanas** de **800 pacientes**

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide in Metabolic-Related Steatohepatitis

A Research Summary based on Sanyal AJ et al. | 10.1056/NEJMoa2413258 | Published on April 30, 2025

WHY WAS THE TRIAL DONE?

Metabolic dysfunction–associated steatohepatitis (MASH) is a severe form of metabolic dysfunction–associated steatotic liver disease characterized by steatosis, hepatocyte damage, and inflammation. In a previous phase 2 trial involving patients with MASH, treatment with semaglutide, a glucagon-like peptide-1 receptor agonist, resulted in better outcomes than placebo.

HOW WAS THE TRIAL CONDUCTED?

1197 adults with biopsy-defined MASH and fibrosis stage 2 or 3 were randomly assigned to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks. The primary end points were the resolution of steatohepatitis with no worsening of liver fibrosis and a reduction in liver fibrosis with no worsening of steatohepatitis.

TRIAL DESIGN

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled
- Location: 253 clinical sites in 37 countries

RESULTS

At a planned interim analysis at week 72 involving the first 800 patients, resolution of steatohepatitis with no worsening of liver fibrosis occurred in a higher percentage of patients treated with semaglutide than with placebo. Reduction in liver fibrosis with no worsening of steatohepatitis was also reported in a higher percentage of patients treated with semaglutide than with placebo. The most common adverse events in both groups were gastrointestinal disorders, including nausea, diarrhea, and constipation.

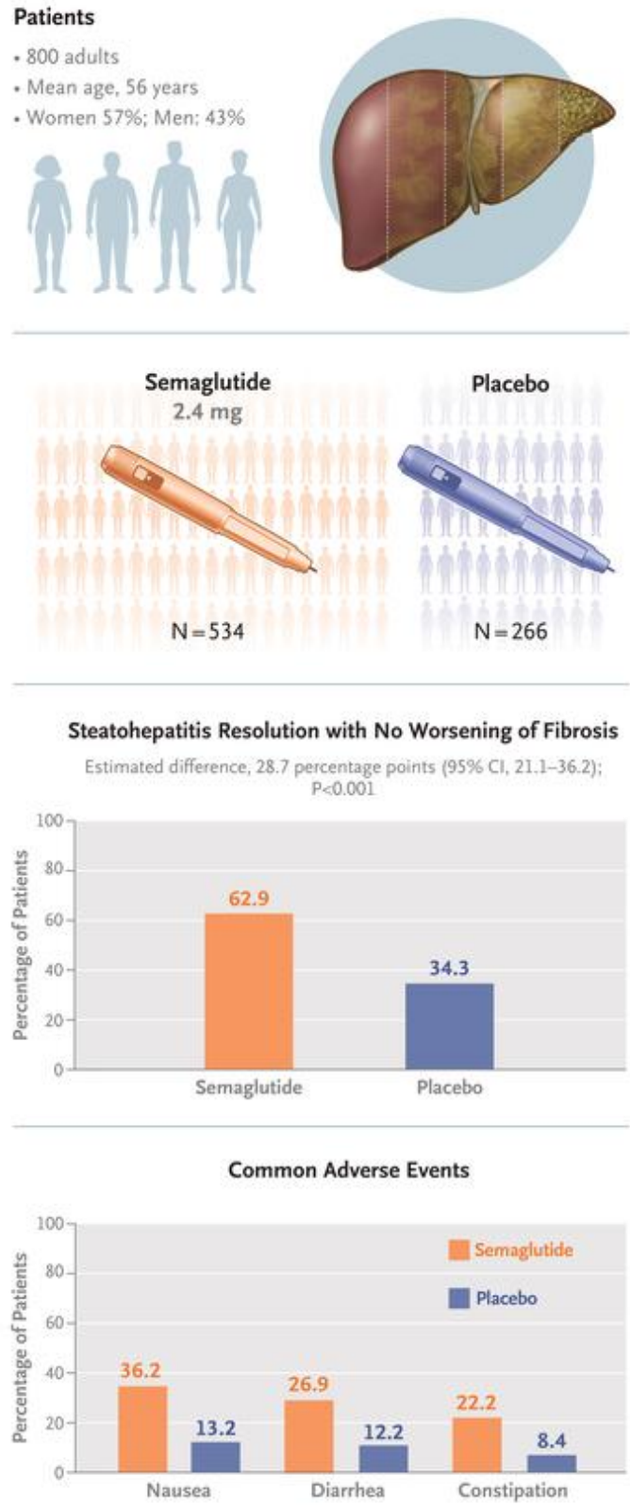
LIMITATIONS AND REMAINING QUESTIONS

- More than two thirds of the patients were White, which may limit the generalizability of the results.
- Data regarding biomarkers of alcohol consumption were lacking.
- Given the small number of lean patients, definitive conclusions about benefit in this population cannot be drawn.

CONCLUSIONS

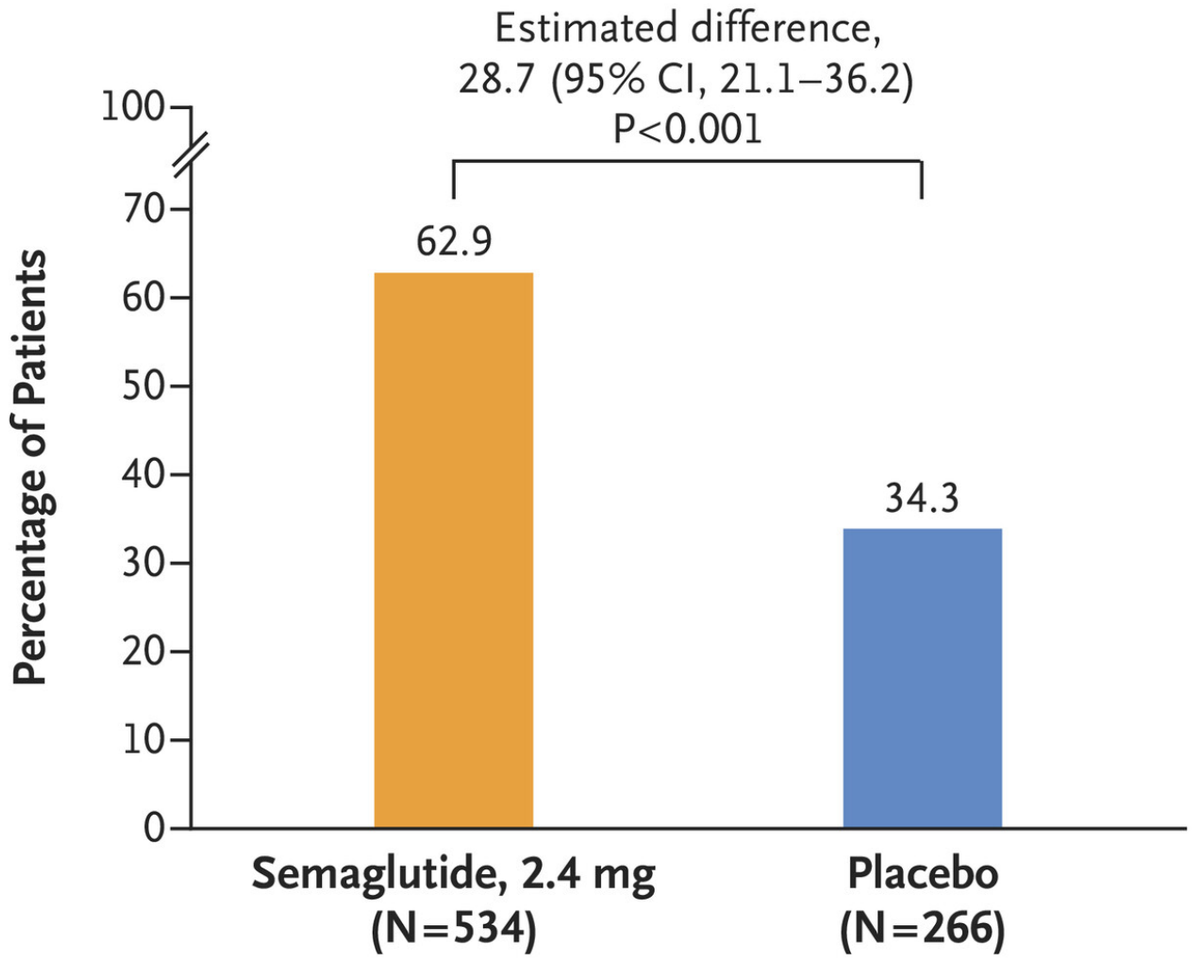
In an interim analysis of a phase 3 trial involving patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide improved liver histologic results over 72 weeks.

NEJM QUICK TAKE | EDITORIAL

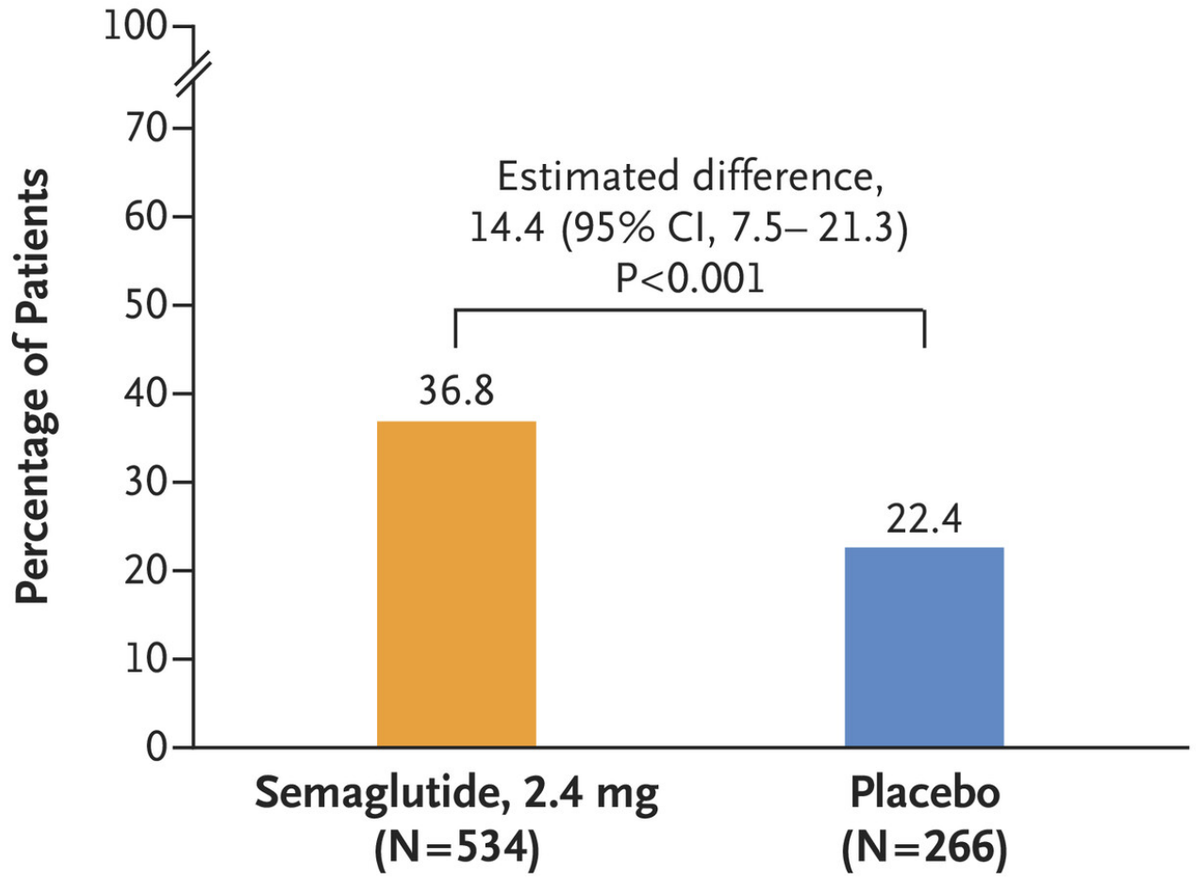


Criterios de valoración principales

A **Resolution of Steatohepatitis with No Worsening of Liver Fibrosis**



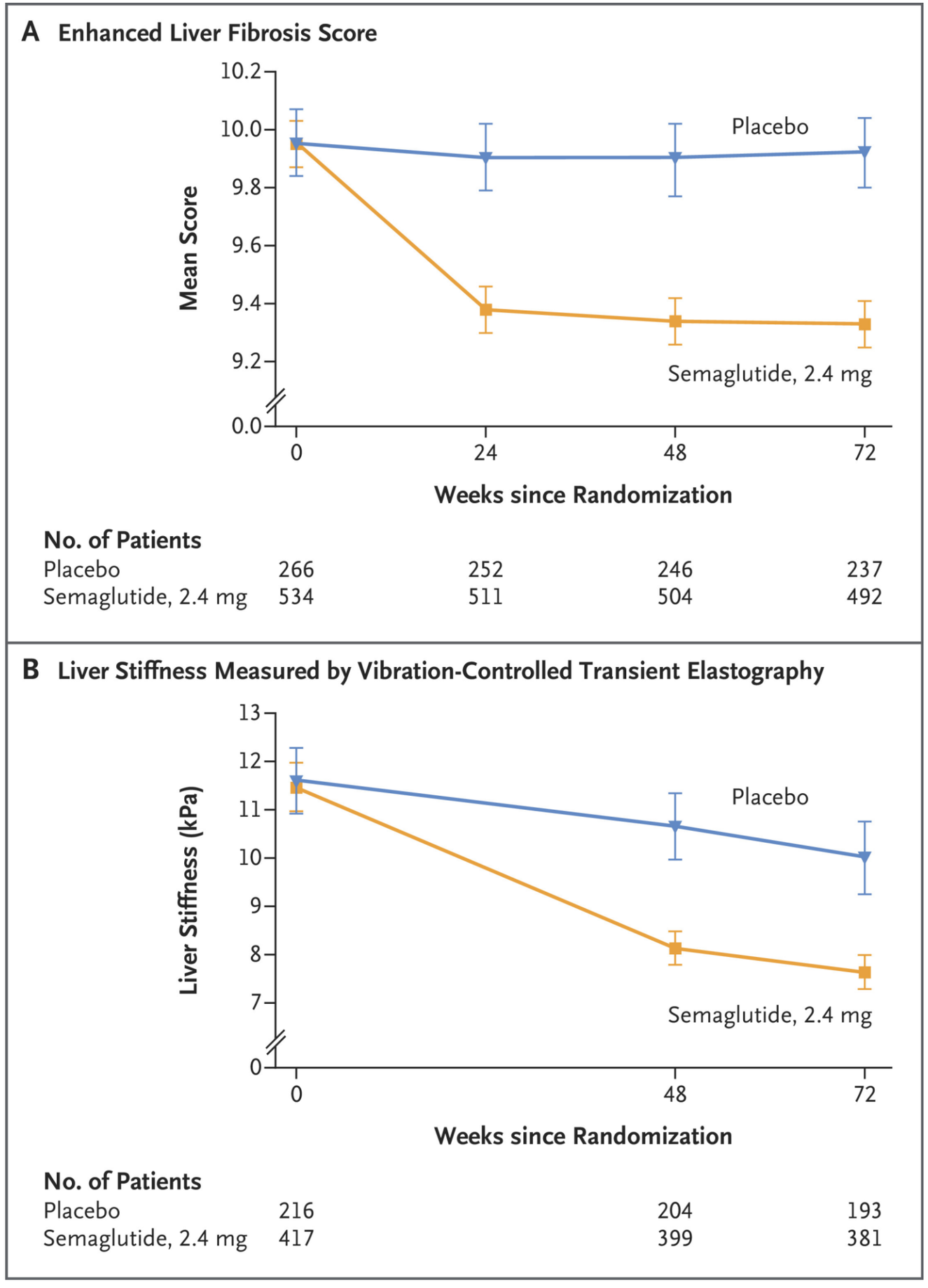
B **Reduction in Liver Fibrosis with No Worsening of Steatohepatitis**



- **La resolución combinada de la esteatohepatitis y de la fibrosis hepática se dio en el 32,7% de los pacientes del grupo de semaglutida y en el 16,1% de los del grupo placebo.**

- El cambio medio en el peso corporal fue de -10,5% con semaglutida y de -2,0% con placebo.

- Mejoró otras características cardiometabólicas, como el control glucémico y la resistencia a la insulina.



El 83,5% de los pacientes del grupo de semaglutida mantuvieron la dosis objetivo de 2,4 mg hasta la semana 72

Table 3. Safety Analysis Population.*

Event	Semaglutide, 2.4 mg	Placebo
	number/total number (percent)	
Any adverse event	690/800 (86.2)	315/395 (79.7)
Fatal adverse event	3/800 (0.4)	6/395 (1.5)
Serious adverse event	107/800 (13.4)	53/395 (13.4)
Infection or infestation	22/800 (2.8)	10/395 (2.5)
Gastrointestinal disorder	20/800 (2.5)	6/395 (1.5)
Musculoskeletal or connective-tissue disorder	14/800 (1.8)	6/395 (1.5)
Injury, poisoning, or procedural complication	11/800 (1.4)	5/395 (1.3)
Nervous system disorder	11/800 (1.4)	5/395 (1.3)
Neoplasm†	11/800 (1.4)	8/395 (2.0)
Adverse event leading to trial discontinuation	21/800 (2.6)	13/395 (3.3)
Adverse event affecting ≥10% of patients in either group		
Nausea	290/800 (36.2)	52/395 (13.2)
Diarrhea	215/800 (26.9)	48/395 (12.2)
Constipation	178/800 (22.2)	33/395 (8.4)
Vomiting	149/800 (18.6)	22/395 (5.6)
Coronavirus disease 2019	134/800 (16.8)	74/395 (18.7)
Decreased appetite	112/800 (14.0)	11/395 (2.8)
Adverse event within safety focus area‡		
Gallbladder-related disorder	20/800 (2.5)	6/395 (1.5)
Acute pancreatitis	3/800 (0.4)	2/395 (0.5)
Malignant neoplasm	13/800 (1.6)	9/395 (2.3)
Hypoglycemia		
Patients with type 2 diabetes§	33/446 (7.4)	12/222 (5.4)
Patients without type 2 diabetes	1/354 (0.3)	1/173 (0.6)

* The safety analysis population included 1195 patients who had undergone randomization. The list includes all events that were reported during follow-up regardless of treatment assignment.
† This category includes all benign and unspecified malignant neoplasms, including cysts and polyps.
‡ Data in this category were reported while patients were receiving their assigned treatment.
§ In these patients, only cases of hypoglycemia of level 2 or 3 were counted.

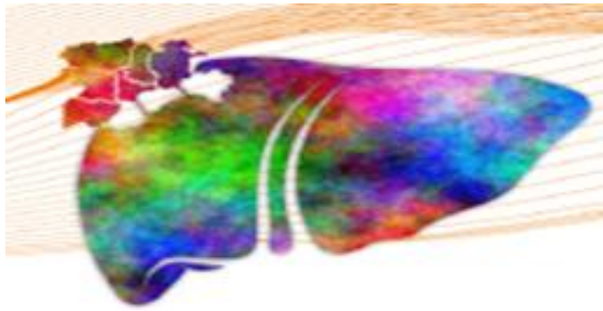
Situación actual de Semaglutida para EHmet

- Aprobación FDA agosto 25
- El Comité de Medicamentos de Uso Humano de la EMA ha recomendado la autorización de su comercialización condicional para esteatohepatitis metabólica a finales de enero de 2026

FUTUROS FÁRMACOS EN EHmet (MASH)

- Tirzepatida (agonista dual de los receptores GLP-1 y GIP): SYNERGY-Outcomes
- Survodutida (agonista dual de los receptores de GLP-1 y glucagon): SYNCHRONIZE-MASLD y Programa LIVERAGE
- Otros ?

- **Las comorbilidades**, como la obesidad, la diabetes y los componentes del síndrome metabólico, **deben tratarse agresivamente para disminuir el riesgo de ECV**
- **Los posibles beneficios hepáticos de cualquier medicamento también deben considerarse al tratar las comorbilidades**



DECÁLOGO PARA UN HÍGADO SALUDABLE:
¡ CUIDA TU HIGADO Y EL CUIDARÁ DE TI !

Siguiendo estos consejos, no solo cuidas de tu hígado, sino que también mejoras tu salud y calidad de vida.

¡ Tu hígado te lo agradecerá !

1. **Come Bien y Controla tu peso:** Mantén una dieta balanceada con frutas, verduras, granos enteros y proteínas magras. Evita los alimentos procesados y las grasas saturadas. Un peso saludable significa menos riesgo de hígado graso.
2. **Haz ejercicio:** Dedica al menos 150 minutos a la semana a actividades moderadas o 75 minutos a actividades intensas. El ejercicio te ayuda a mantenerte en forma y protege tu hígado.
3. **Alcohol cero:** Lo mejor para tu hígado es no beber alcohol. El consumo excesivo puede llevar a cirrosis y otras enfermedades hepáticas.
4. **Vacúnate:** Las vacunas contra la hepatitis A y B son super eficaces y te protegen de infecciones que pueden dañar tu hígado.
5. **Di No a las Drogas Recreativas:** Las drogas pueden ser muy dañinas para tu hígado. Además, compartir agujas puede transmitir hepatitis.
6. **Sé Higiénico y Cuida lo que Comes:** Lávate las manos regularmente y asegúrate de que tus alimentos estén bien cocidos y almacenados.
7. **Usa Medicamentos Responsablemente:** Sólo toma medicinas bajo indicación médica y evita la automedicación. Algunos fármacos pueden dañar tu hígado.
8. **Evita Toxinas:** Mantente alejado de productos químicos tóxicos como solventes y pesticidas que pueden ser perjudiciales para tu hígado.
9. **Practica sexo seguro:** Usa preservativo para prevenir infecciones de transmisión sexual, incluyendo hepatitis B y C.
10. **Hazte Chequeos Médicos:** Realiza exámenes de salud regularmente para detectar cualquier problema hepático a tiempo y tratarlo eficazmente.