MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura:
Esteatosis Hepática Metabólica (EHmet)

Tratamiento farmacológico EHmet: Ensayos en Fase 3

Hospital Universitario Virgen del Rocío

Universidad de Sevilla

ciberehd

IBiS Instituto de Biomedicina de Sevilla

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SeLiver Group. Institute of Biomedicine of Seville.
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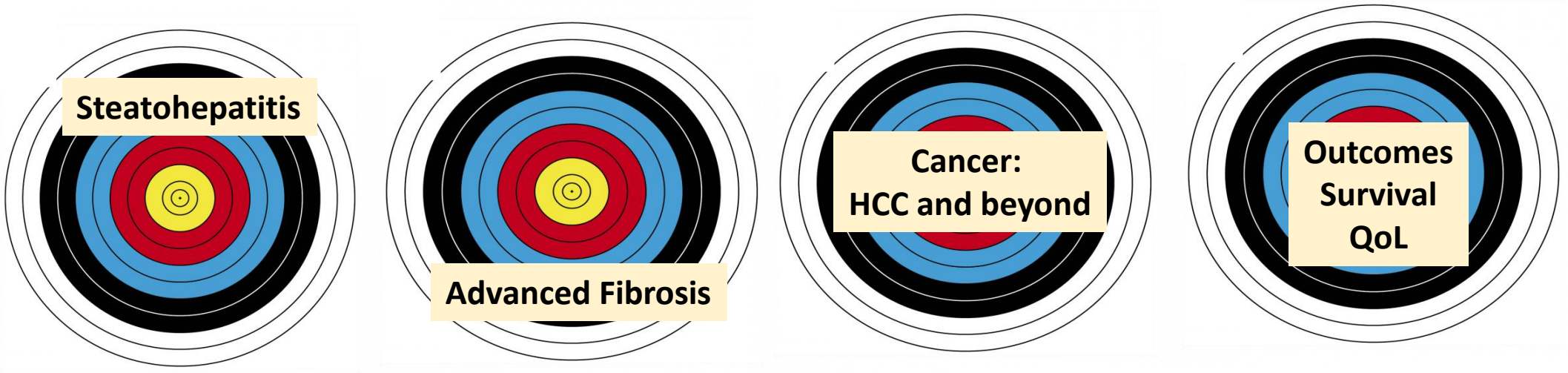
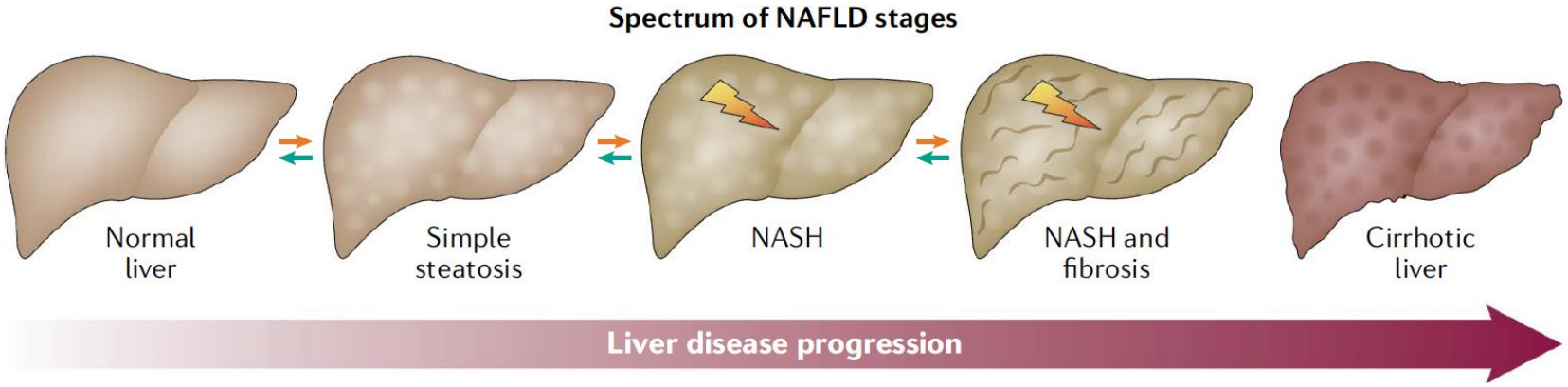
Selección de objetivos terapéuticos en EHmet

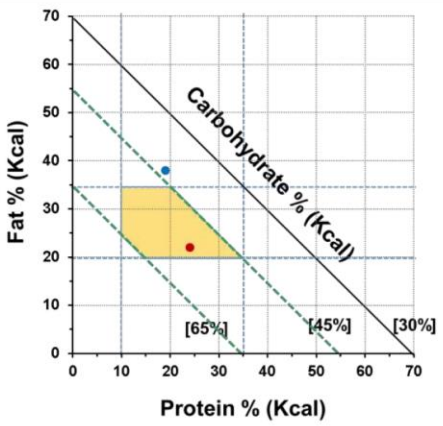




1 Vilar-Gomez E, et al. Gastroenterology. 2015;149:367-78. 2 Promrat K, et al. Hepatology. 2010;51:121-9; 3 Harrison SA, et al. Hepatology. 2009;49:80-6. 4 Wong VW, et al. J Hepatol. 2013;59:536-42

Esteatosis Hepática Metabólica (EHmet)

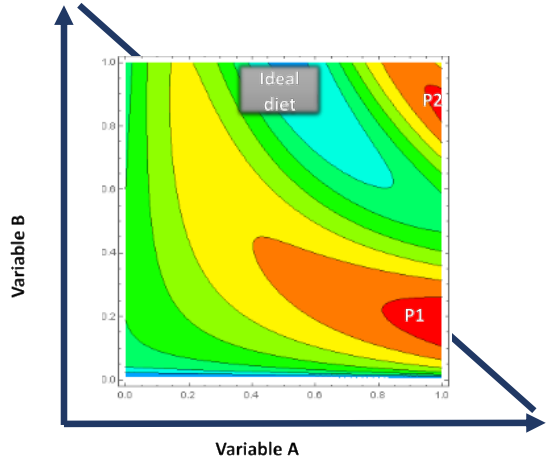
Dietary recommendation
Hypocaloric Mediterranean Diet



DIET
GENES
SEX
AGE

NAFLD

LIFE-STYLE INTERVENTION



Nutritional Geometry

RESPONDERS → **Long-term maintenance**

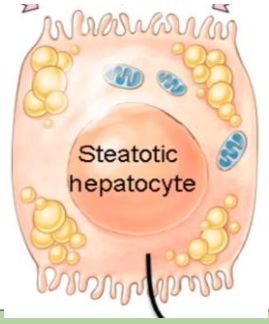
% Weight loss
ALT normalization

NON-RESPONDERS → **Lead-in phase** → **Clinical Trials**

Romero Gómez M, Aller R, Martín-Bermudo F. Semin Liver Dis 2022

Terapia farmacológica para EHmet

Terapias EHmet

- Anti-fibrótica centrada en el hígado
  - **Obeticholic acid**
- 

- Fármacos metabólicos centrados en el hígado
  - **Efruxifermin**
  - **Resmetiron**
  - **Semaglutide**
  - **Lanifibranor**

EMERGING PHARMACOLOGICAL TREATMENT OPTIONS FOR MAFLD

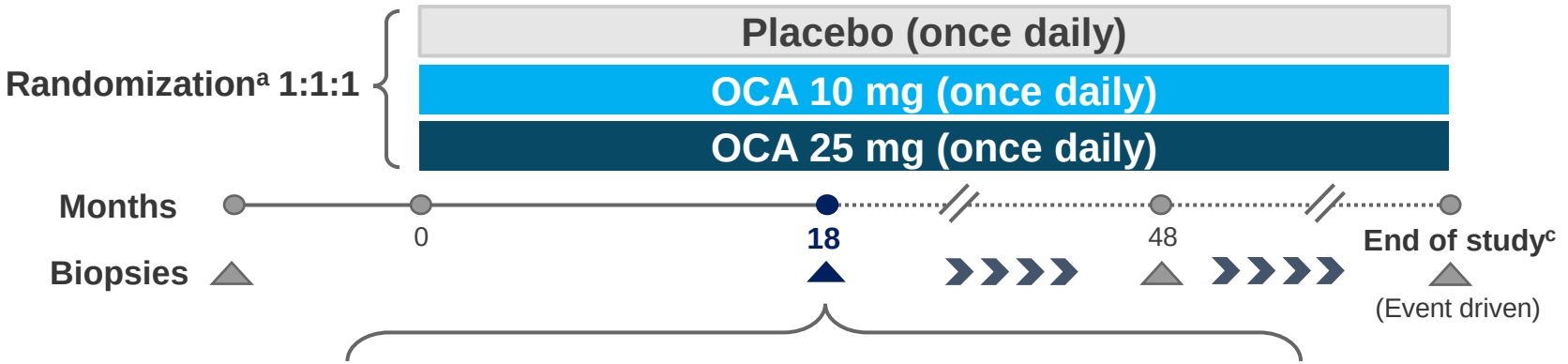
Rojas A, Lara-Romero C, Muñoz R, Gato S, Ampuero J, Romero-Gómez M. Ther Adv Endocrinol Metab 2023 (In Press)

- **Metformina**
- **Pioglitazona**
- **SGLT-2 inh**
- **GLP1RA**
- **Estatinas**

- Emricasan
- Simtuzumab
- Selonsertib
- Cenicriviroc
- Elafibranor

REGENERATE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study (N=2477)

ITT=F2/F3 (n=2187)
Exploratory F1 Cohort
n=290



Planned month 18 interim analysis[b] primary endpoints

Fibrosis improvement by ≥1 stage and no worsening of NASH[d]

OR

NASH resolution[e] and no worsening of fibrosis

Success at 18 months was defined as achievement of at least one of these 2 primary endpoints

Abbreviations: F1, fibrosis stage 1; F2, fibrosis stage 2; F3, fibrosis stage 3; ITT, intent-to-treat; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.
[a]Plus counseling on lifestyle modification with regard to diet and exercise; stratification by presence of type 2 diabetes at enrollment (yes/no) and use of thiazolidinediones/glitazones or vitamin E at baseline (yes/no). [b]The preplanned interim analysis was conducted after 931 randomized patients with stage 2 or 3 liver fibrosis had or would have reached their actual/planned month 18 visit (ITT population). [c]End of study analysis of clinical outcomes to confirm clinical benefit.
[d]No worsening of NASH defined as no increase of hepatocellular ballooning, lobular inflammation, or steatosis. [e]NASH resolution was defined as (i) overall pathologist assessment of "no steatohepatitis" and (ii) hepatocellular ballooning=0 and lobular inflammation=0 or 1.
Intercept Pharmaceuticals [Protocol v11].

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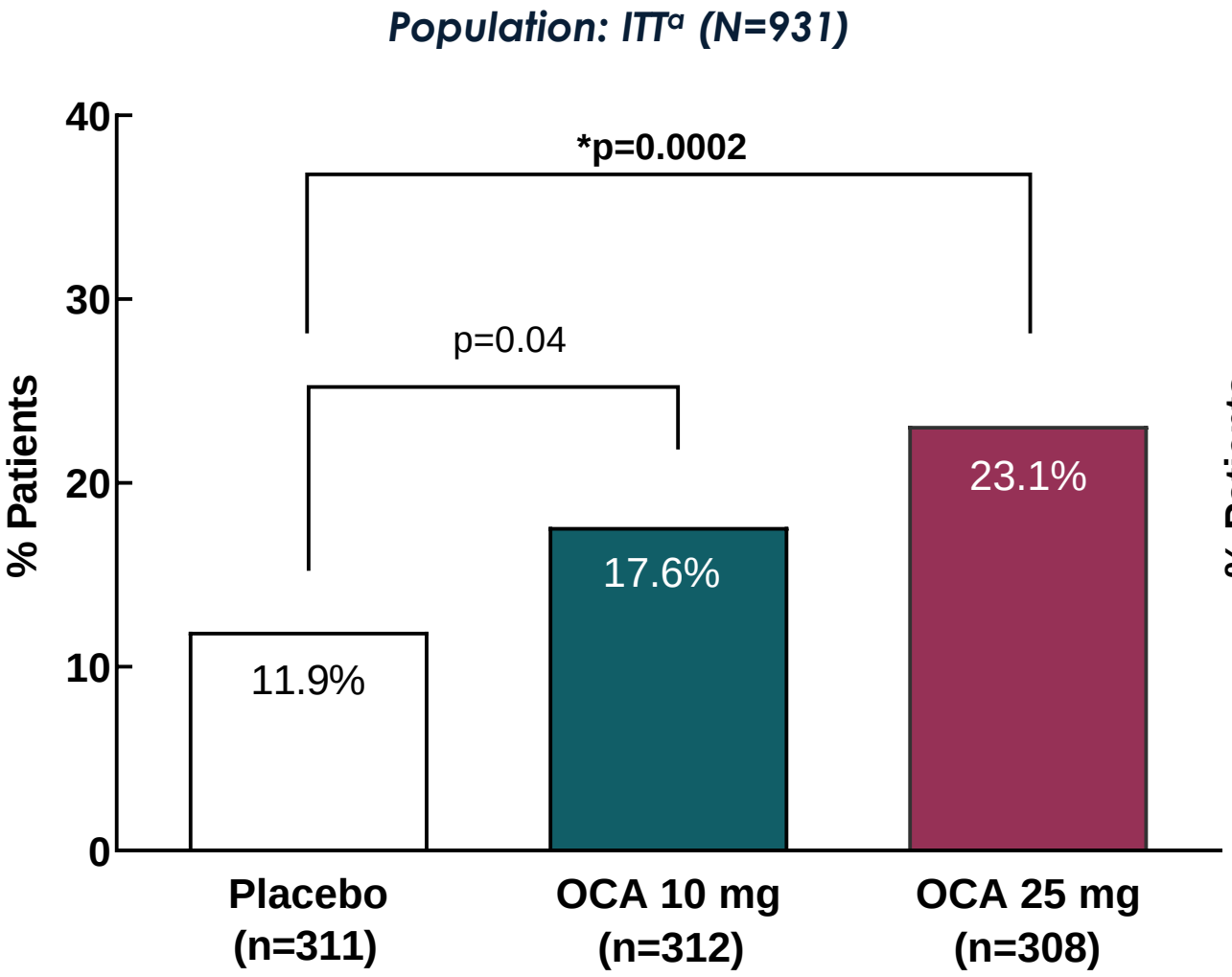
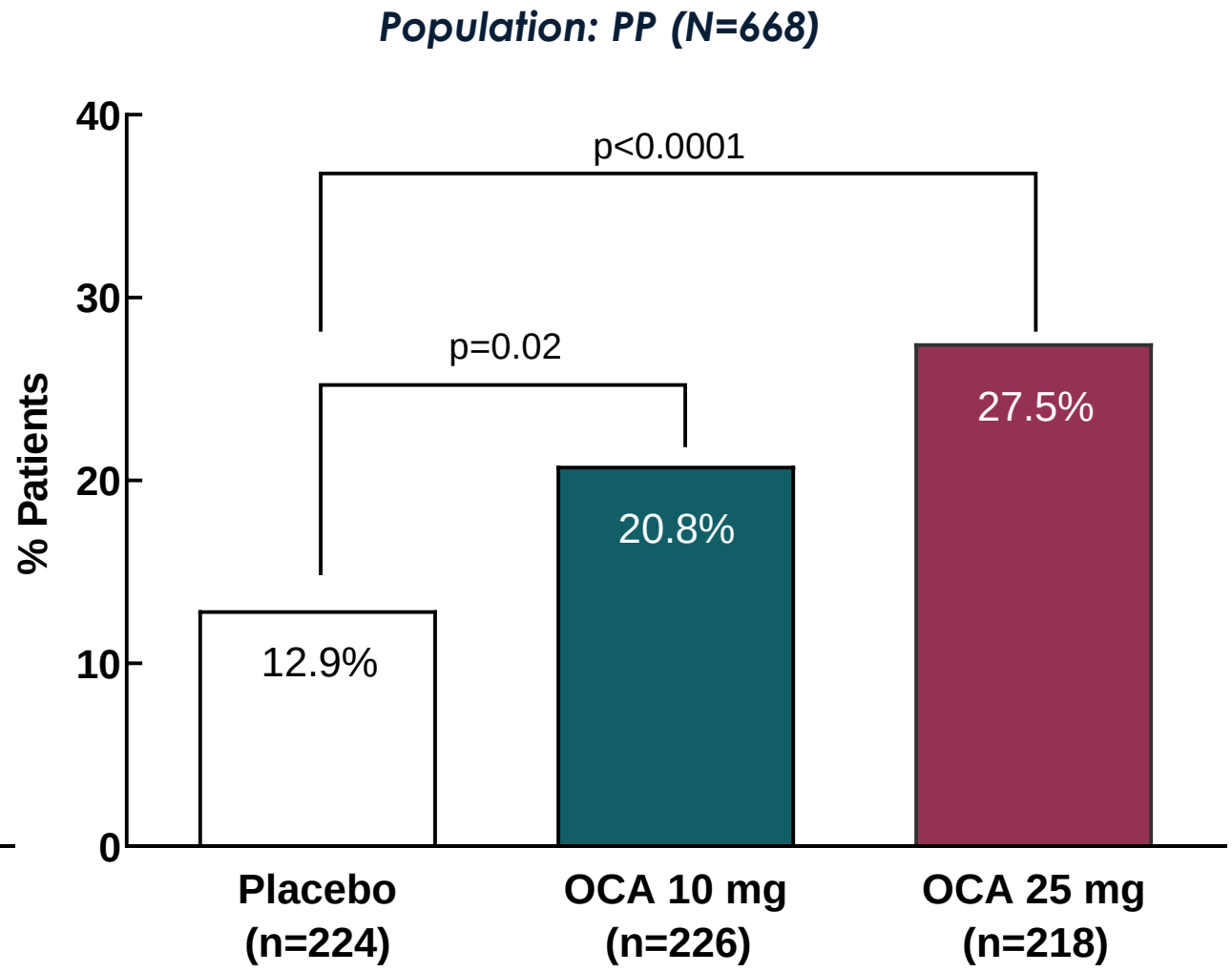
Ácido obeticólico: Mejora de la fibrosis en un estadio ≥1 con ausencia de empeoramiento de la EHNA (criterio de valoración principal: población ITT)



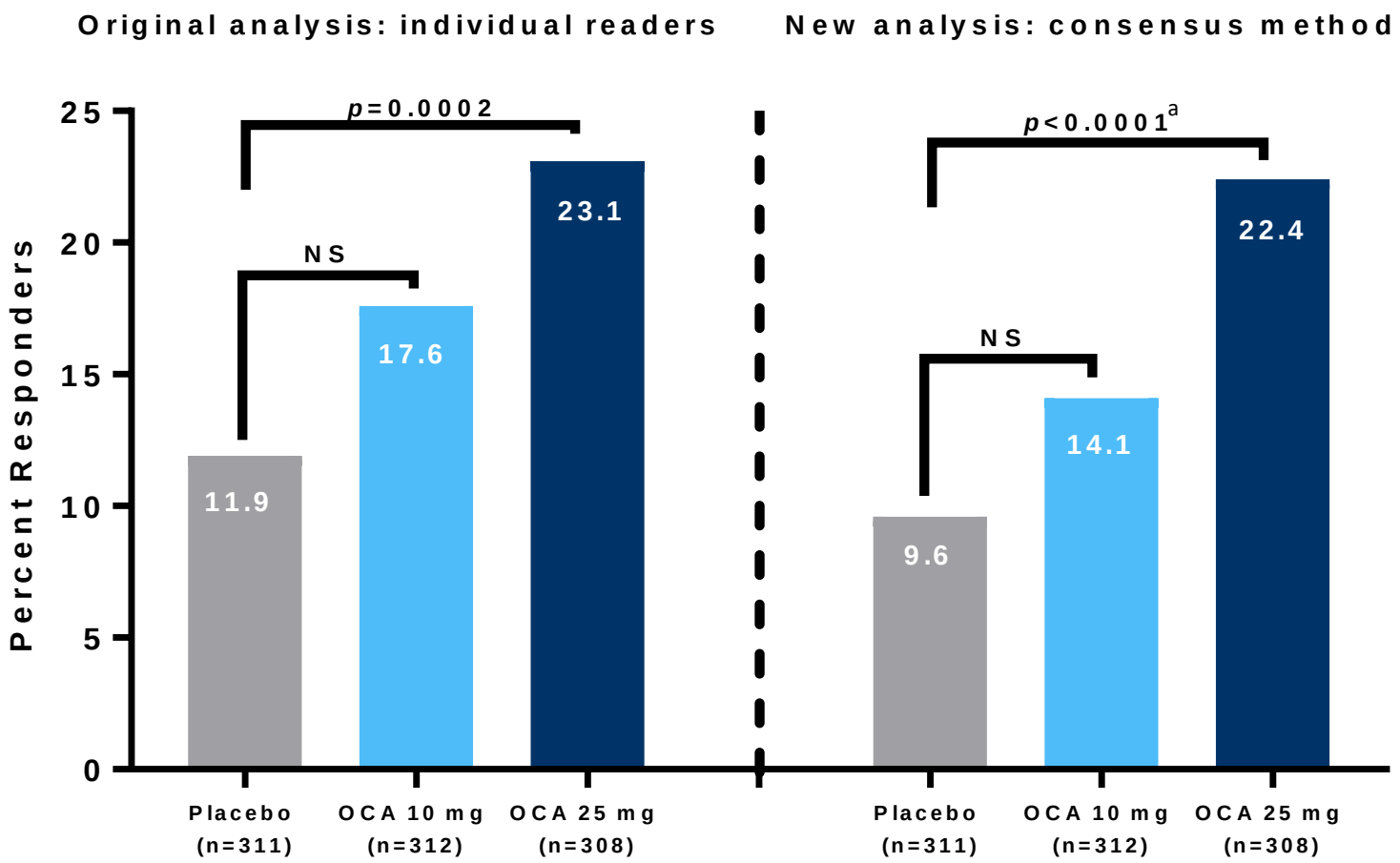


Primary endpoint definition: improvement in fibrosis by ≥1 stage (NASH CRN) with no worsening of lobular inflammation, hepatocellular ballooning or steatosis.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.
*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

Presented at EASL, April 10-14, 2019; Vienna, Austria

Younossi ZM et al. Lancet 2019;394(10215):2184-2196.

Consistent Dose-Dependent Fibrosis Improvement (ITT Population=931)



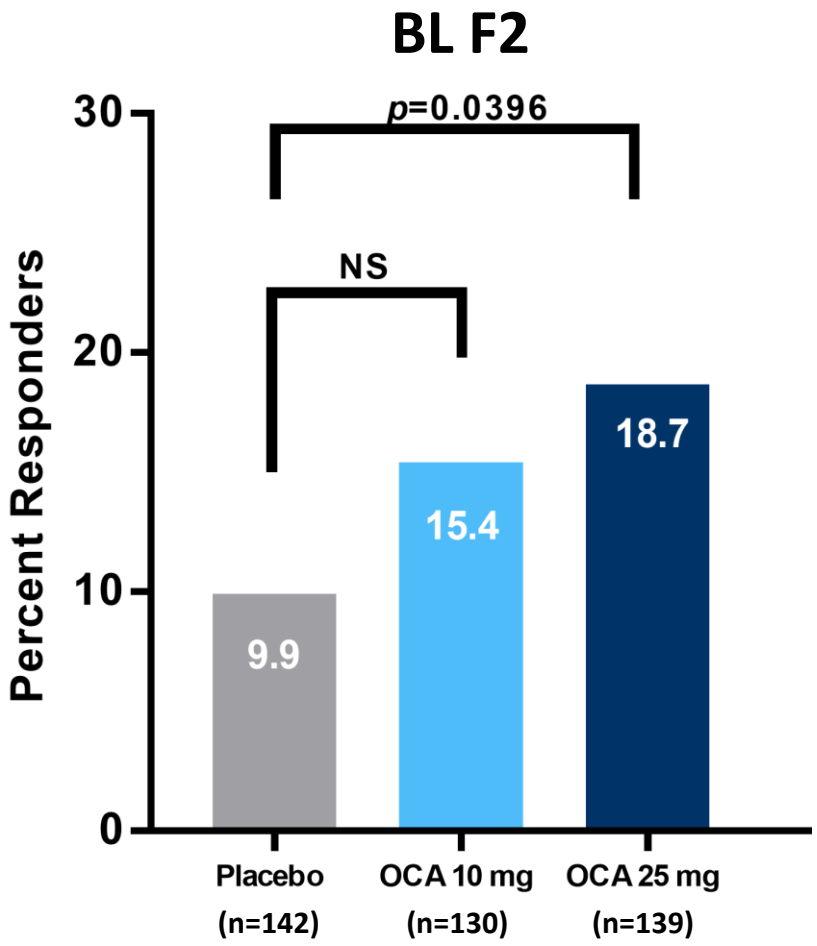
Primary Endpoint:

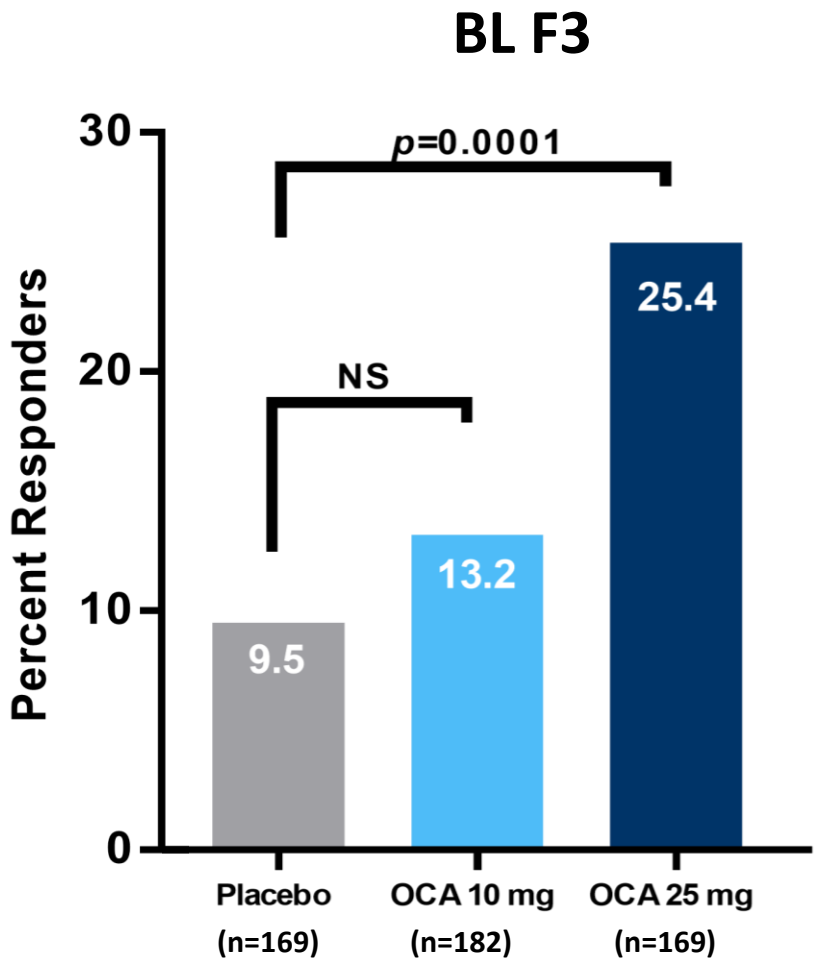
- **Improved fibrosis stage**

  +

- **No worsening on ANY of 3 NAS components**

Higher Responder Rate in Subjects With F3 at Baseline





p-values are nominal.
Abbreviations: BL, baseline; F2, fibrosis stage 2; F3, fibrosis stage 3; ITT, intention-to-treat; NS, not significant; OCA, obeticholic acid.

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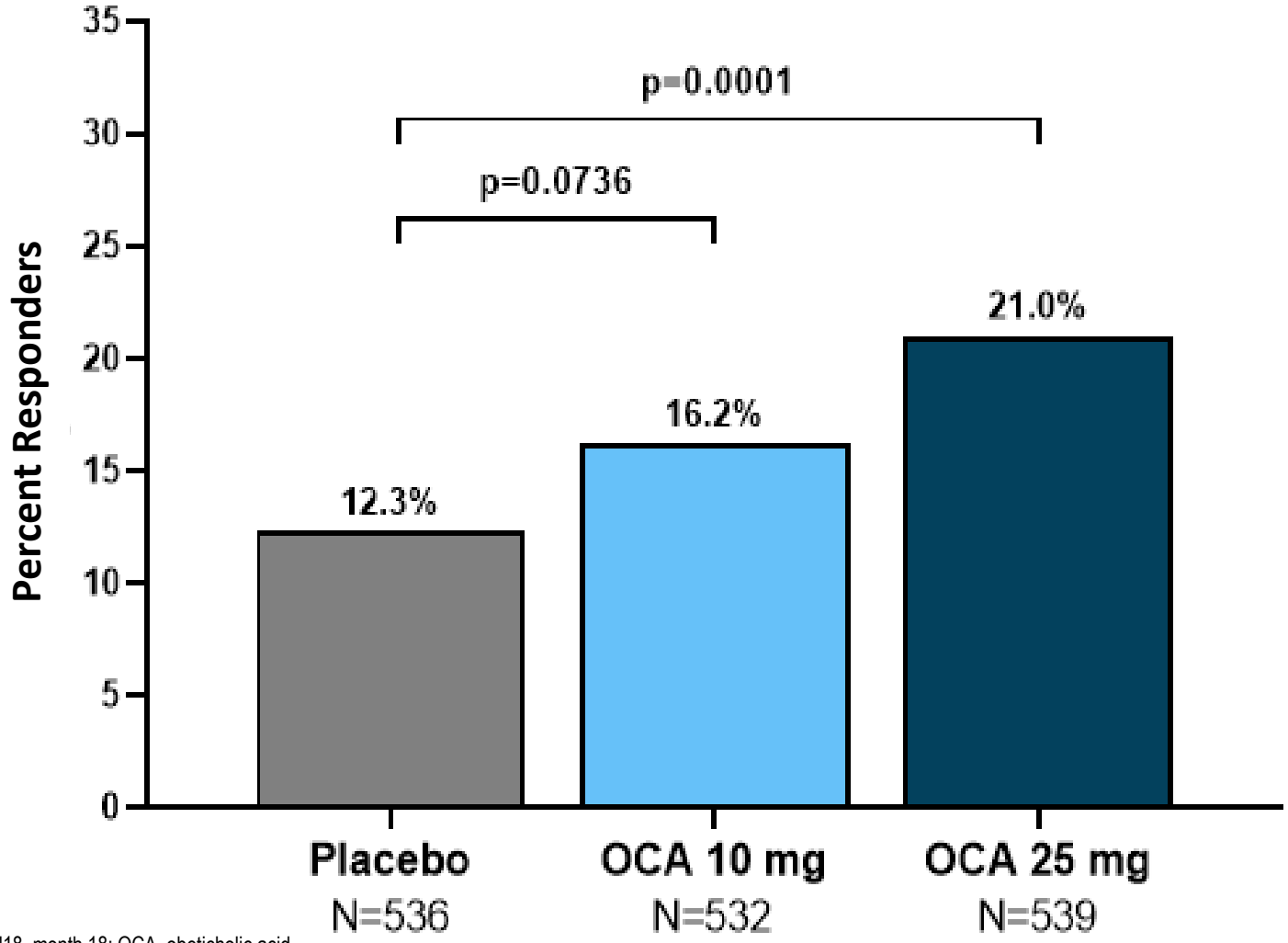
Consistent Responder Rate in Entire ITT Population at M18 Fibrosis Primary Endpoint (N=931+676=1607)[1]



Abbreviations: ITT, intention-to-treat; M18, month 18; OCA, obeticholic acid.

[1]ITT_histology: For Month 18 histology endpoints, the analysis will be conducted in a subset of ITT_all that includes subjects who had or were expected to have completed Month 18 visit (including the Month 18 biopsy) per protocol Version 8 (08 Jan 2019) or earlier.

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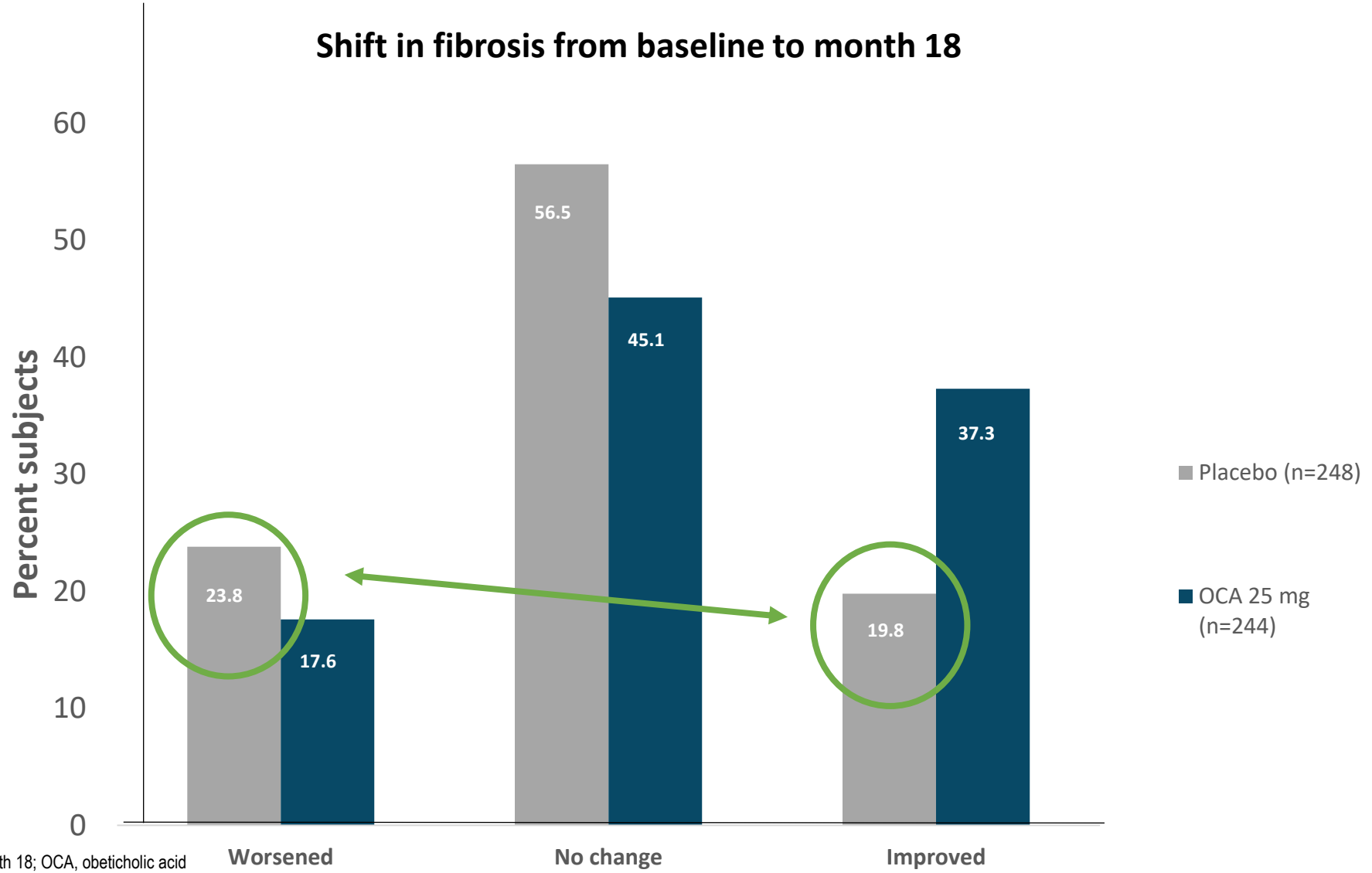
Shift in Fibrosis Stage at M18 in Subjects With Available Baseline and M18 Liver Biopsy



Abbreviations: M18, month 18; OCA, obeticholic acid

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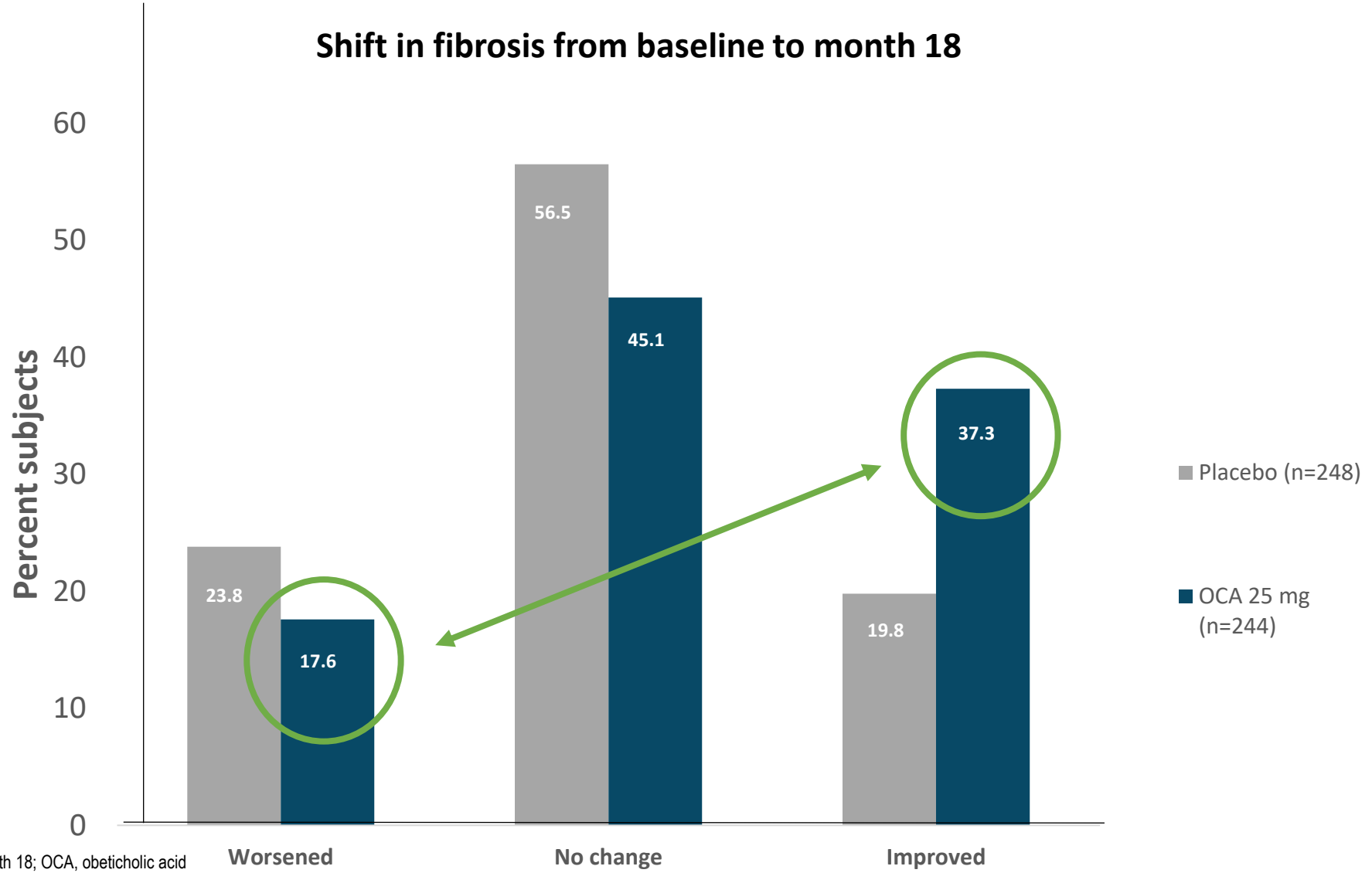
Shift in Fibrosis Stage at M18 in Subjects With Available Baseline and M18 Liver Biopsy



Abbreviations: M18, month 18; OCA, obeticholic acid

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- For OCA 25 mg, improvement of liver fibrosis was observed in 37% of subjects with available BL and M18 liver biopsies
- The OCA 25 mg response rate was double that of placebo for the regulatory primary endpoint of *fibrosis improvement by ≥1 stage without worsening of NASH*
  - Higher responder rate in subjects with F3 at baseline
- OCA demonstrated a favorable safety profile based on a robust safety assessment including more than 8000 patient-years and ~1000 subjects at year 4
- The confirmed antifibrotic effect, together with extended exposure, supports a positive benefit:risk in patients with advanced fibrosis due to NASH

Abbreviations: BL, baseline; F3, fibrosis stage 3; M18, month 18; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

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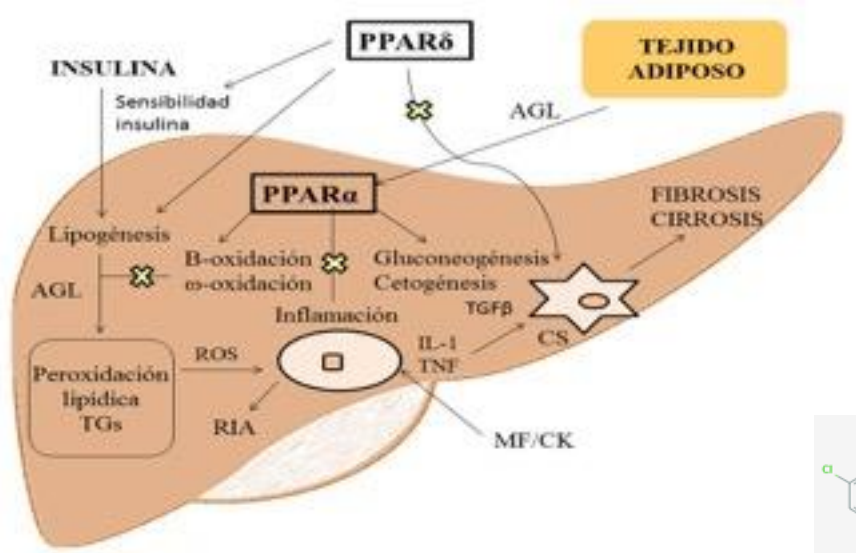
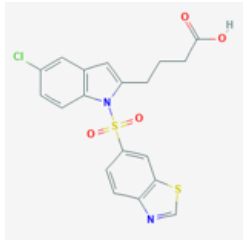
Agonistas PPAR y la fisiopatología de la enfermedad del hígado graso no alcohólico





Metabolism
PPARα,δ,γ
- Insulin sensitivity
- HDLc
- TG

Steatosis
PPARγ
- FA uptake
- FA catabolism
- Lipogenesis

Inflammation and Ballooning
PPARα,δ,γ
- NFkB-dependent gene activation
- Inflammasome
- Ballooning

Fibrosis
PPARγ,δ
- Stellate cell proliferation and activation
- Collagen and fibronectin production

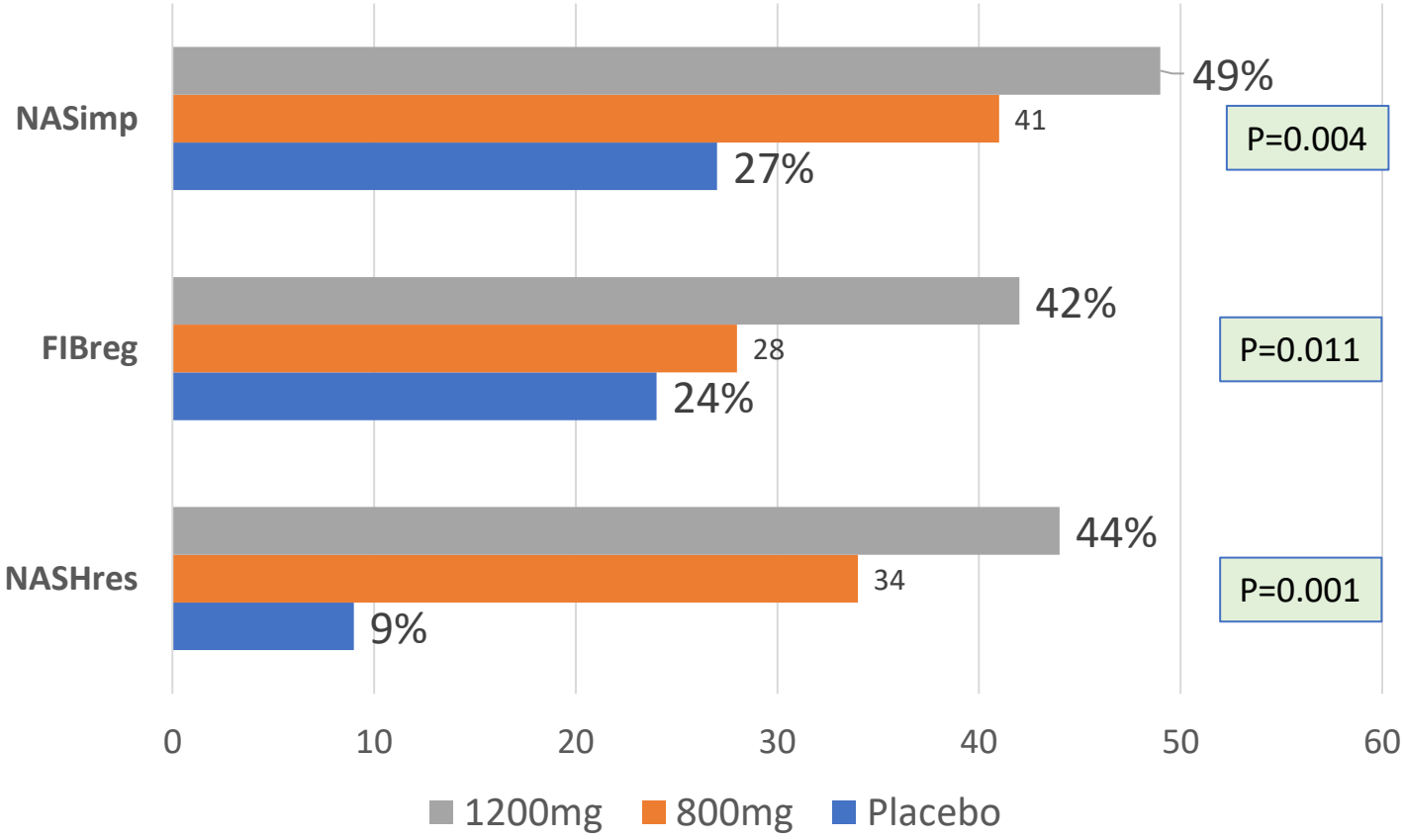
Vascular
PPARα,γ
- Portal pressure
- LSEC capillarization
- Intrahepatic vascular resistance

PPARα (por ejemplo, bezafibrato)
Ensayos pequeños, sin conclusión definitiva, sin histología
PPARγ (por ejemplo, pioglitazona)
Ensayo PIVENS: reducción de la gravedad de NASH, sin efecto sobre la fibrosis, efectos secundarios
PPARδ (por ejemplo, seladelpar)
Mejora de la esteatosis hepática y las enzimas hepáticas en ensayos más pequeños
No hay reducción de la grasa hepática (n=171, MRI-PDFF, peor que el placebo)

Gross B. *Nat Rev Endocrinol*. 2017;13(1):36-49

Lanifibranor en MAFLD
Un pan-PPAR agonista

N=247 F2-F3 pacientes NASH
Placebo (n=81)
Lanifibranor 800 mg (n=83)
Lanifibranor 1200 mg (n=83)



Disminución de la insulina, la glucosa en ayunas y la hemoglobina glicosilada (HB1AC) en pacientes con diabetes tipo 2.

Disminución de los triglicéridos.

Aumento del colesterol de las lipoproteínas de alta densidad (HDL).

Disminución de las enzimas hepáticas (ALT, AST y GGT)

Franque S and Abdelmalek M. Native IIb. 2020

A Phase 3 Study Evaluating Long-term Efficacy and Safety of Lanifibranor in Adult Patients With (NASH) and Fibrosis 2 (F2)/Fibrosis 3 (F3) Stage of Liver Fibrosis (NATiV3)

- Drug: IVA337

  A total of 2000 patients will be randomised to receive lanifibranor (800 mg/day) or lanifibranor (1200 mg/day), or matching placebo, employing a 1:1:1 randomisation scheme, respectively, without interruption between Part 1 and Part 2.

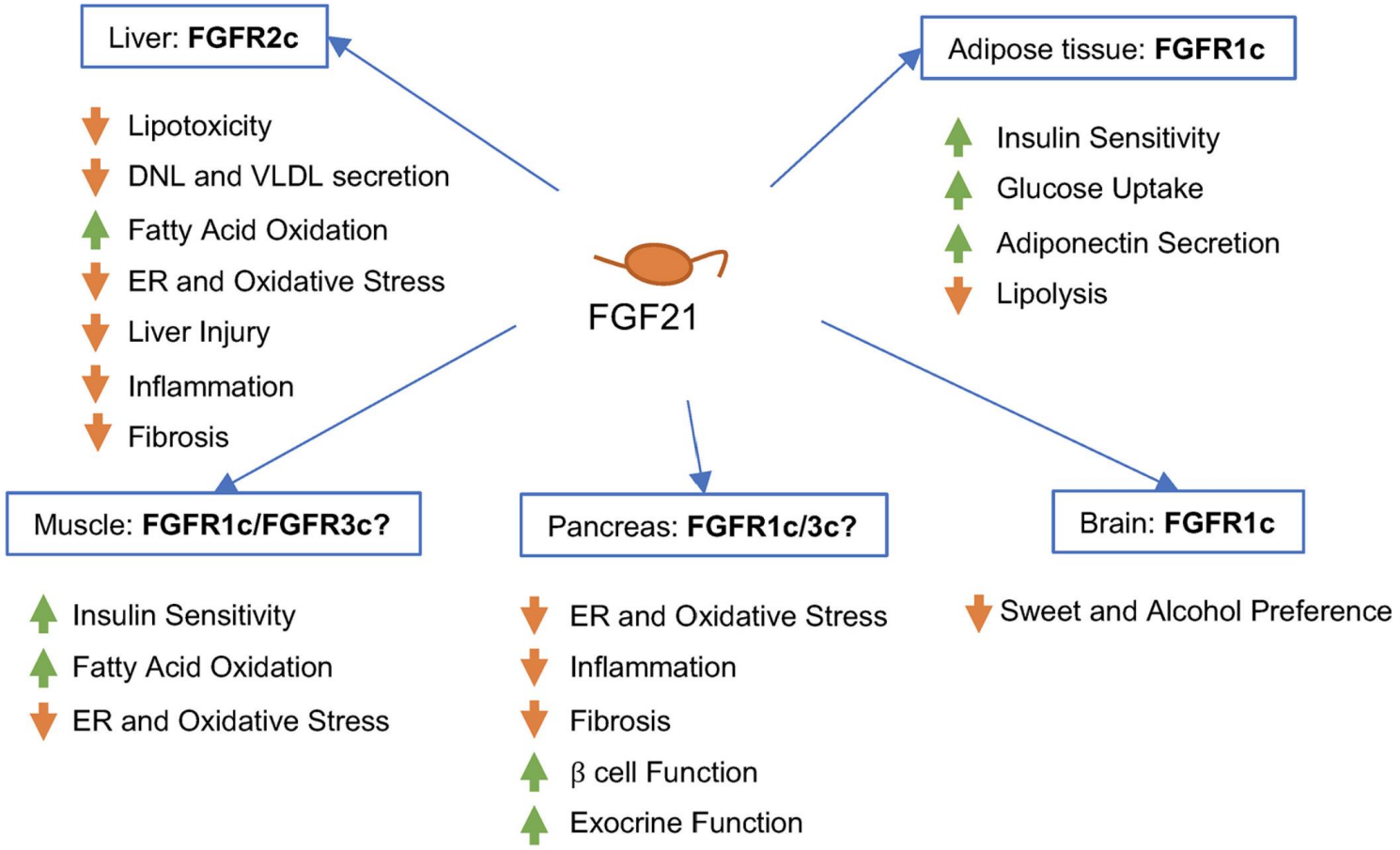
  Other Name: Lanifibranor

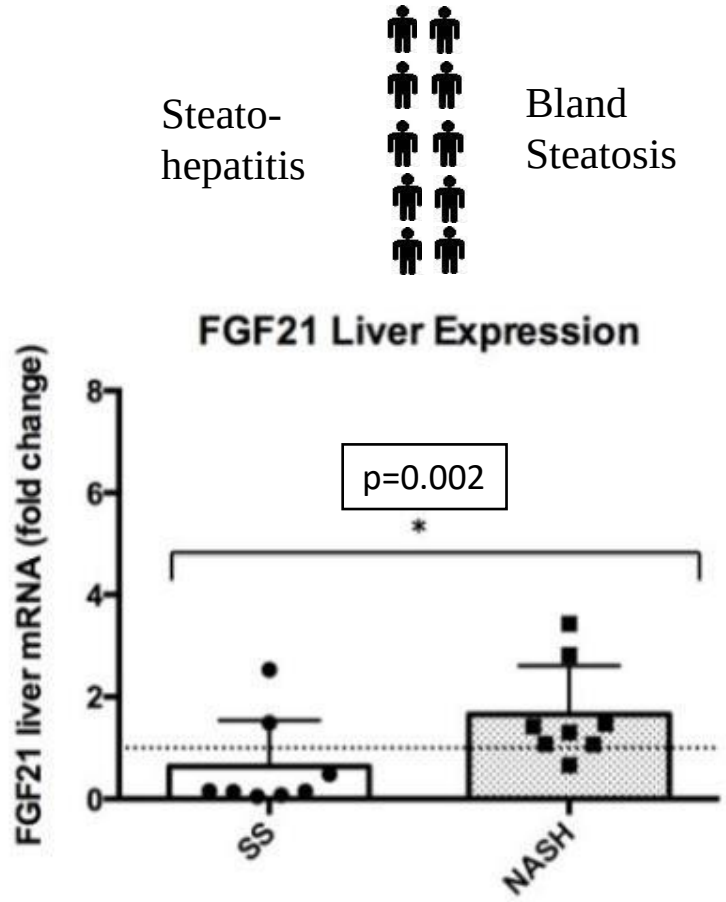
- Drug: Placebo

  A total of 2000 patients will be randomised to receive lanifibranor (800 mg/day) or lanifibranor (1200 mg/day), or matching placebo, employing a 1:1:1 randomisation scheme, respectively, without interruption between Part 1 and Part 2.

ClinicalTrials.gov Identifier: NCT04849728

Efruxifermin – Mechanism of Action



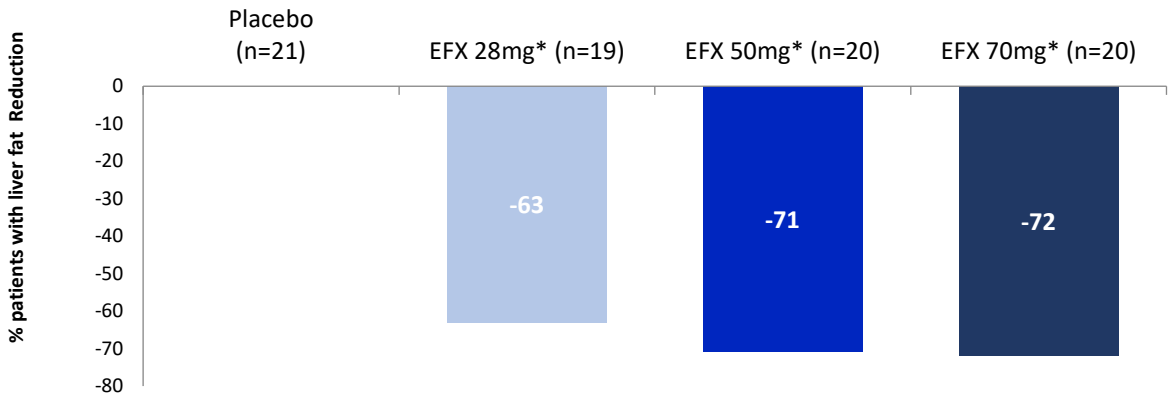


Gallego-Durán & Romero-Gómez, Manuscript in preparation

Tillman E. 2020 Front. Endocrinol;11:601290

Efruxifermin: análogo FGF21

N=80
4 brazos



Measure (Mean)	Placebo (n=21)	EFX (Once Weekly Dose) p<0.001		
		28mg (n=19)	50mg (n=20)	70mg (n=20)
Absolute Reduction in Liver Fat (%)	-0.3	-12.3	-13.4	-14.1
Reduction in ALT (U/L)	-6	-24	-30	-32

N=52
4 brazos

	NASH resolution	Fibrosis regression 1 stage	Fibrosis regression 2 stages
Placebo (n=2)	1/2 (50%)	0/2 (0%)	0%
EFX 28 mg (n=13)	6/3 (46%)	6/13 (46%)	4/13 (31%)
EFX 50 mg (n=13)	7/13 (54%)	8/13 (62%)	5/13 (38%)
EFX 70 mg (n=14)	6/14 (43%)	6/14 (43%)	1/14 (14%)

Efruxifermin

Akero. Akero Announces Strongly Positive Histological Data Across All Efruxifermin Dose Groups in 16-Week Phase 2a BALANCED Study in NASH Patients. 2020 Jun 30. Press Release. https://ir.akerotx.com/news-releases/news-release-details/akero-announces-strongly-positive-histological-data-across-all/

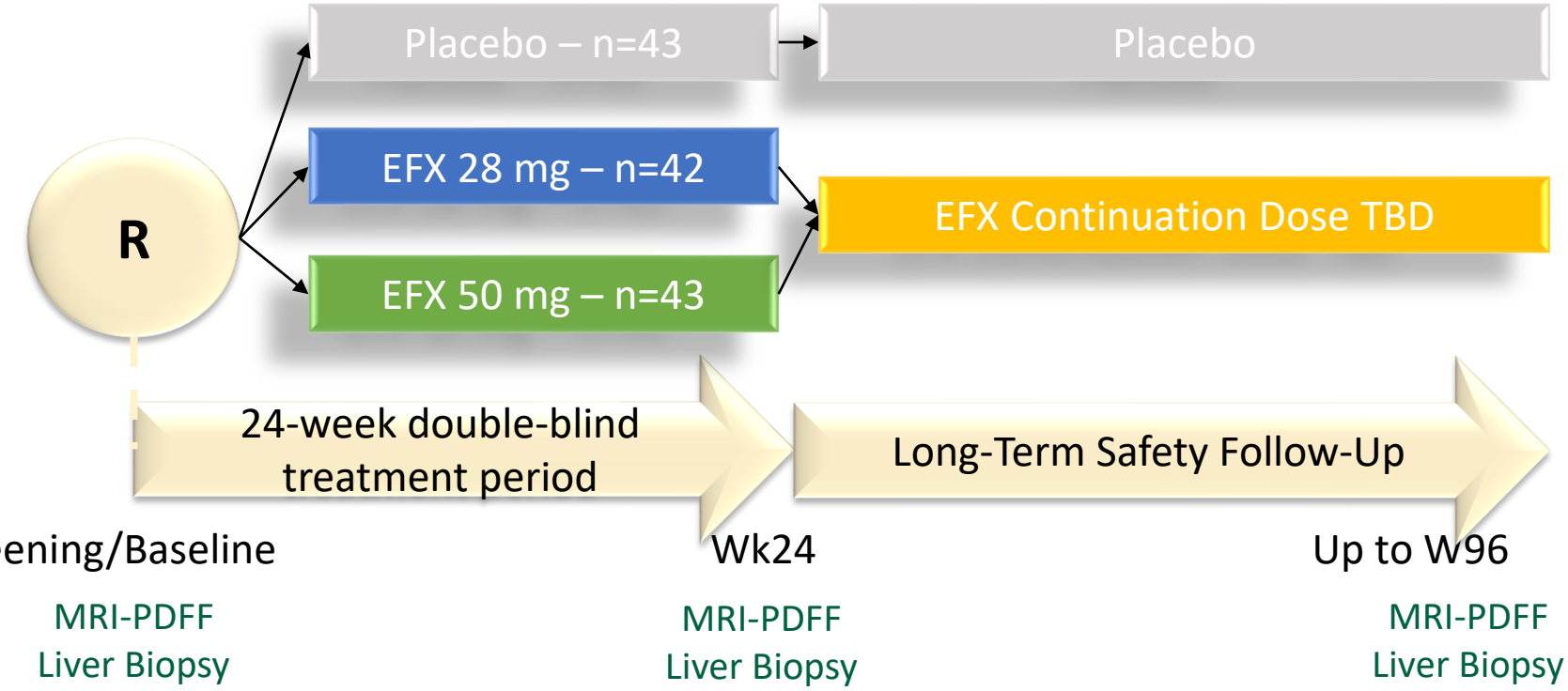
Harrison et al. Nature Medicine 2021;27:1262-1271

Efruxifermin – NASH Phase 2b Study Design

KEY ELIGIBILITY CRITERIA

F2-F3 NASH
NAS ≥ 4

Liver Fat Content (PDFF) ≥ 8%



Primary Endpoint:

- ≥ 1-stage fibrosis improvement without worsening of NASH

Key Secondary Efficacy Endpoints

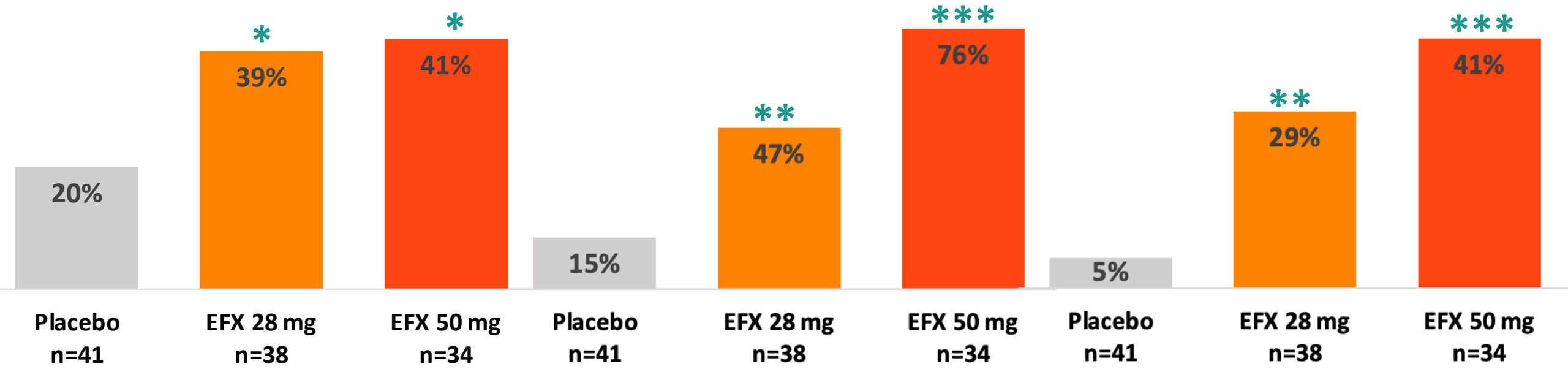
- NASH Resolution & No Worsening of Fibrosis
- MRI-PDFF, Fibrosis Markers, Lipoproteins, Glycemic control, Weight change, Liver Injury Markers

Efruxifermin – NASH Phase 2b Study Results
Histological Endpoints – Week 24

Primary Endpoint:
Fibrosis Improvement ≥ 1 Stage & No Worsening of NASH

Key Secondary Endpoint:
NASH Resolution & No Worsening of Fibrosis

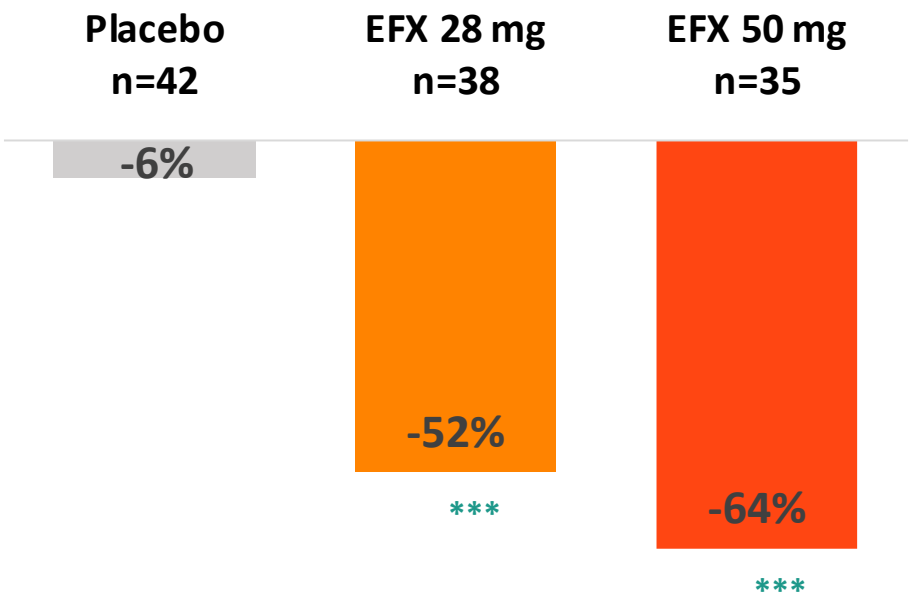
Composite Endpoint:
NASH Resolution AND Improvement of Fibrosis



*p-value <0.05, **p-value<0.01, *** p-value<0.001

Efruxifermin – NASH Phase 2b Study Results
MRI-PDFF & Safety – Week 24

LS Mean Relative Percent Change from Baseline (ANCOVA)



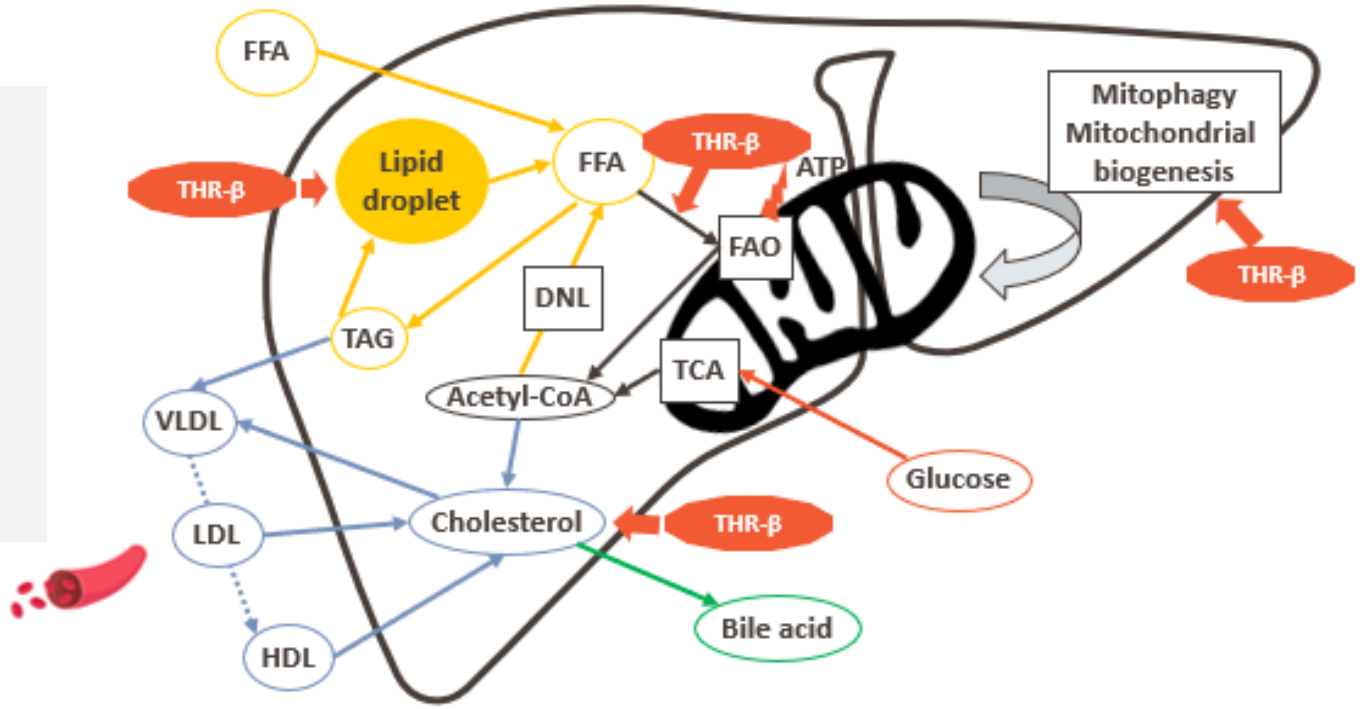
TEAE Overview	Placebo (N=43)	EFX 28mg (N=40)	EFX 50mg (N=43)
TEAE Leading to Death	0 (0%)	0 (0%)	0 (0%)
Drug-Related Serious Adverse Event (SAE)	0 (0%)	0 (0%)	1 (2%)
Drug-Related TEAE Leading to Discontinuation	0 (0%)	2 (5%)[c]	2 (5%)
Most Frequent (≥15%) Drug-Related TEAEs			
Diarrhea	6 (14%)	14 (35%)	14 (33%)
Nausea	5 (12%)	10 (25%)	14 (33%)
Increased Appetite	2 (5%)	7 (18%)	10 (23%)
Frequent Bowel Movements	1 (2%)	8 (20%)	0 (0%)
Injection Site Erythema	5 (12%)	6 (15%)	7 (16%)
Injection Site Bruising	1 (2%)	6 (15%)	3 (7%)

*p-value <0.05, **p-value<0.01, *** p-value<0.001

Resmetirom – Mechanism of Action

Resmetirom is a **THR-β agonist** that has shown in clinical trials to,

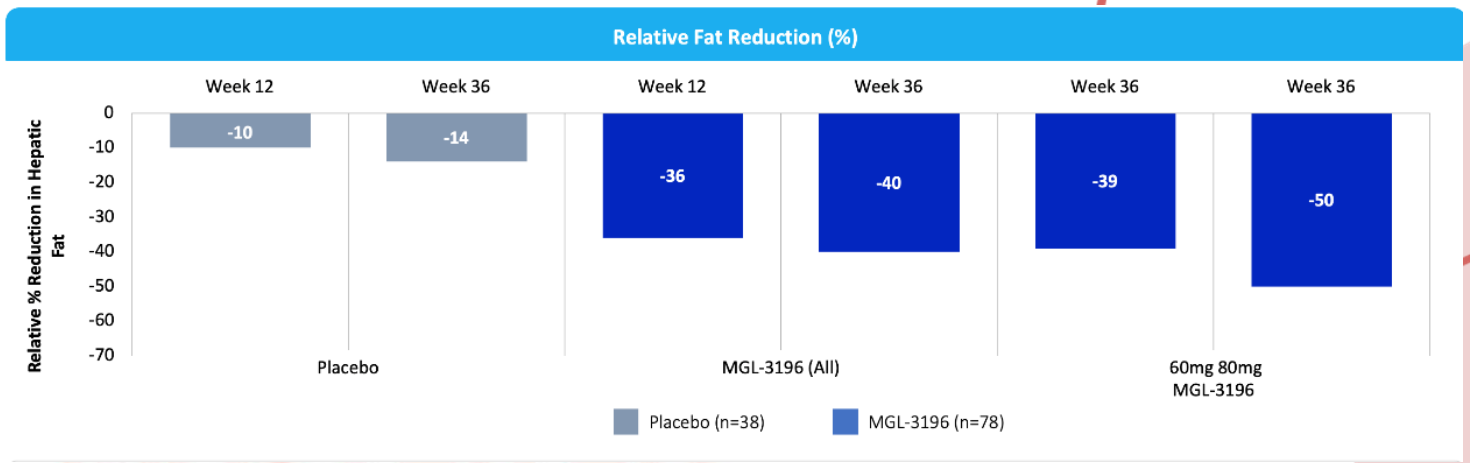
- Lower liver fat, potentially reducing lipotoxicity
- Resolve NASH
- Lower LDL-C
- Lower triglycerides

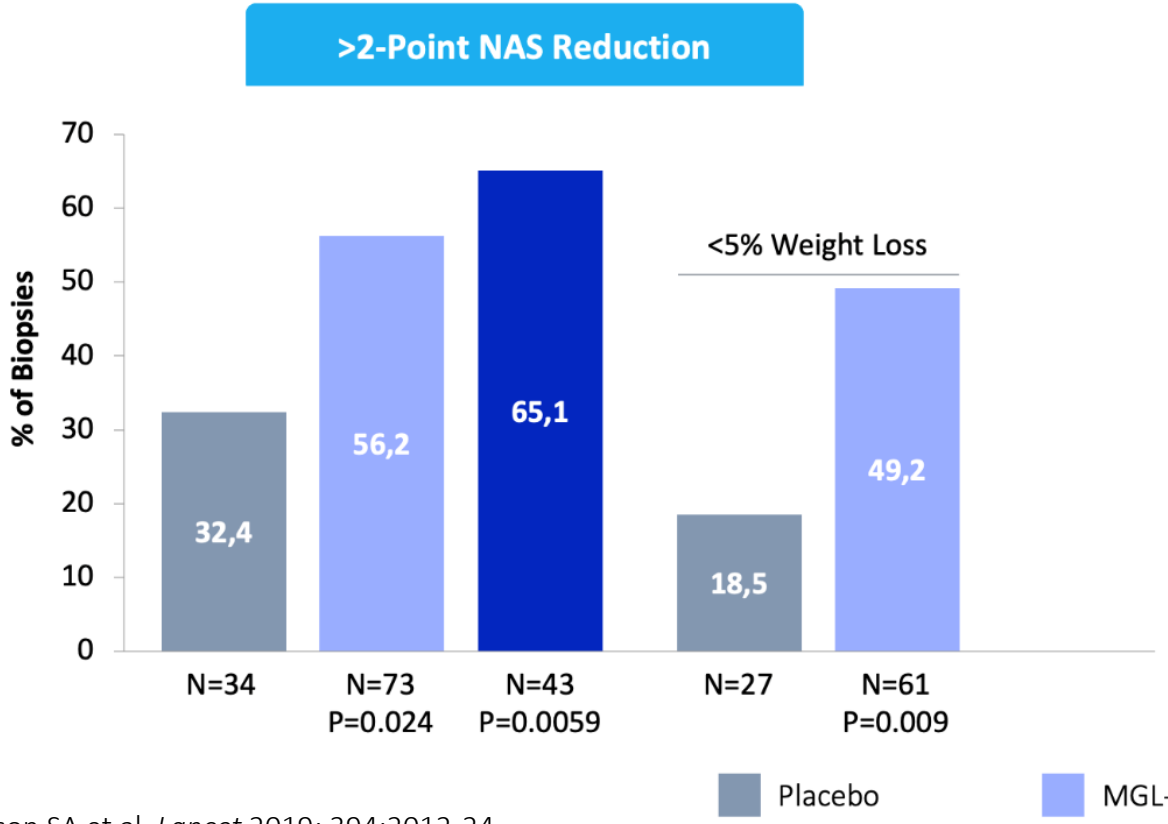


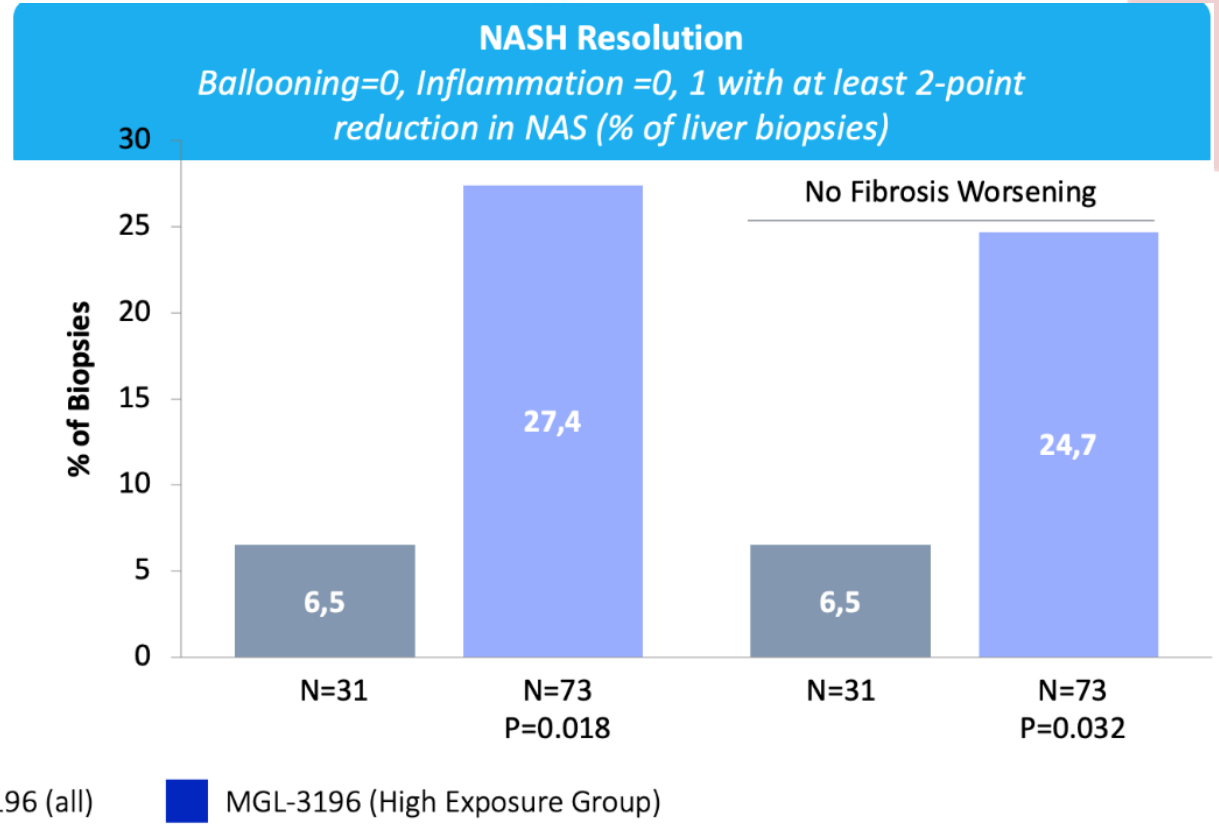
DNL, de novo lipogenesis; FAO, fatty acid oxidation; FFA, free fatty acid; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; THR-β, thyroid hormone receptor beta; VLDL, very low-density lipoprotein.

Ritter MJ, et al. *Hepatology*. 2020;72(2):742-752; Saponaro F, et al. *Front Med*. 2020;7:331; Sinha RA, et al. *Nat Rev Endocrinol.* 2018;14(5):259-226; Taub R, et al. *Atherosclerosis*. 2013;230(2):373-380; Taub R, et al. NASHTAG 2018 poster; Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024; Sinha RA, Yen PM. *Cell Biosci*. 2016;6:46; Sinha, et al. *Autophagy*. 2019;11:8:1341-1357.

Resmetirom: Reducción sostenida de la grasa hepática relacionada con la dosis en la MRI-PDFF y en los criterios de valoración histológicos







Placebo MGL-3196 (all) MGL-3196 (High Exposure Group)

Harrison SA et al. *Lancet* 2019; 394:2012-24.

Resmetirom – NASH Cirrhosis Phase 3 Study Design

KEY ELIGIBILITY CRITERIA

Well-compensated NASH Cirrhosis (Child-Pugh 5-6)

≥ 3 metabolic risk factors

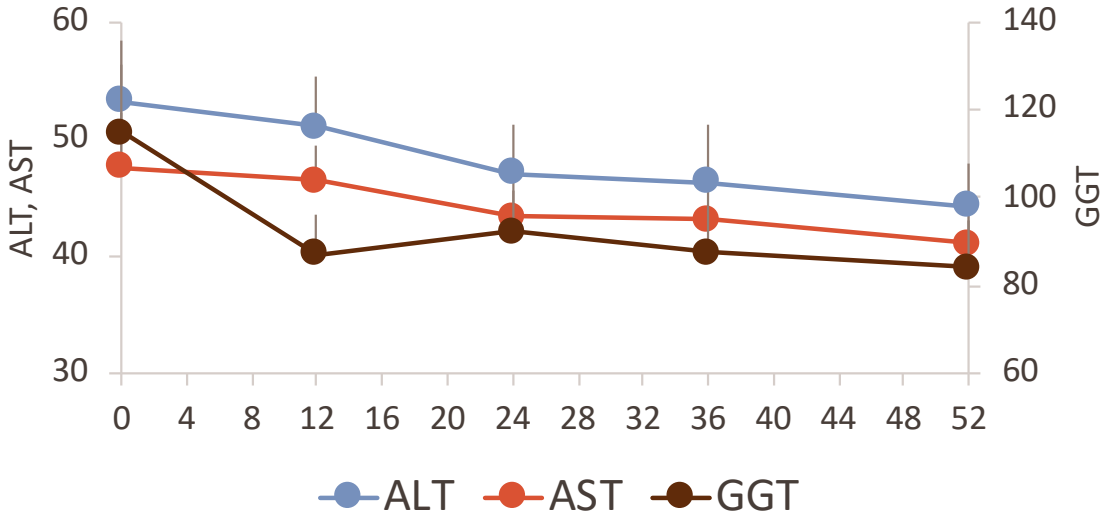
OL

Resmetirom 80 mg (possible up-titration to 100 mg) – n=180

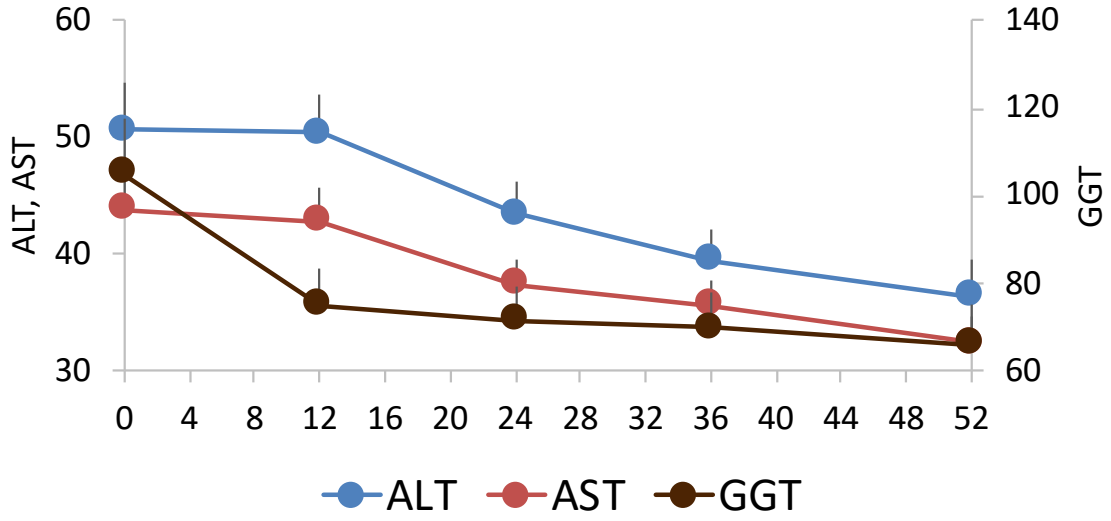
52-week open-label treatment period

Screening/Baseline	Wk 16	Wk24	W52
MRI-PDFF MRE FibroScan Lipids	MRI-PDFF MRE	Lipids	MRI-PDFF MRE FibroScan Lipids

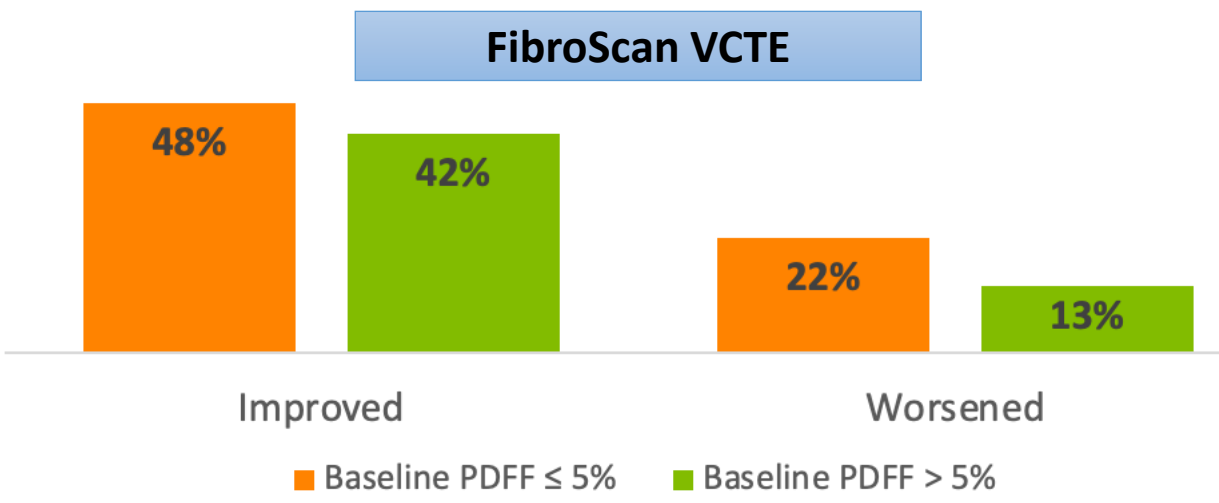
Cohort 1

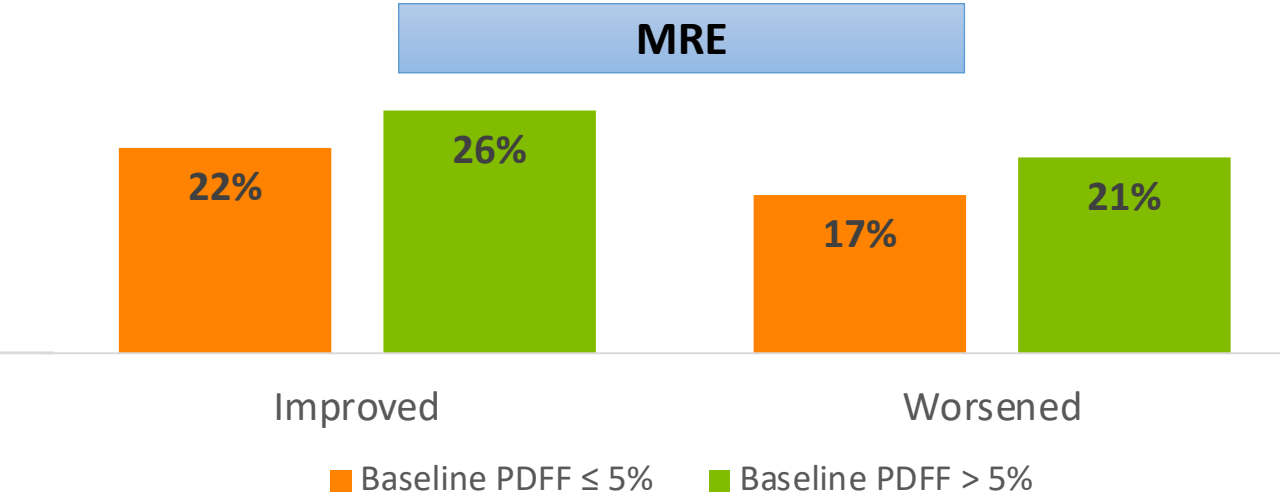


Cohort 2



Resmetirom – NASH Cirrhosis Phase 3 Study Results FibroScan & MRE



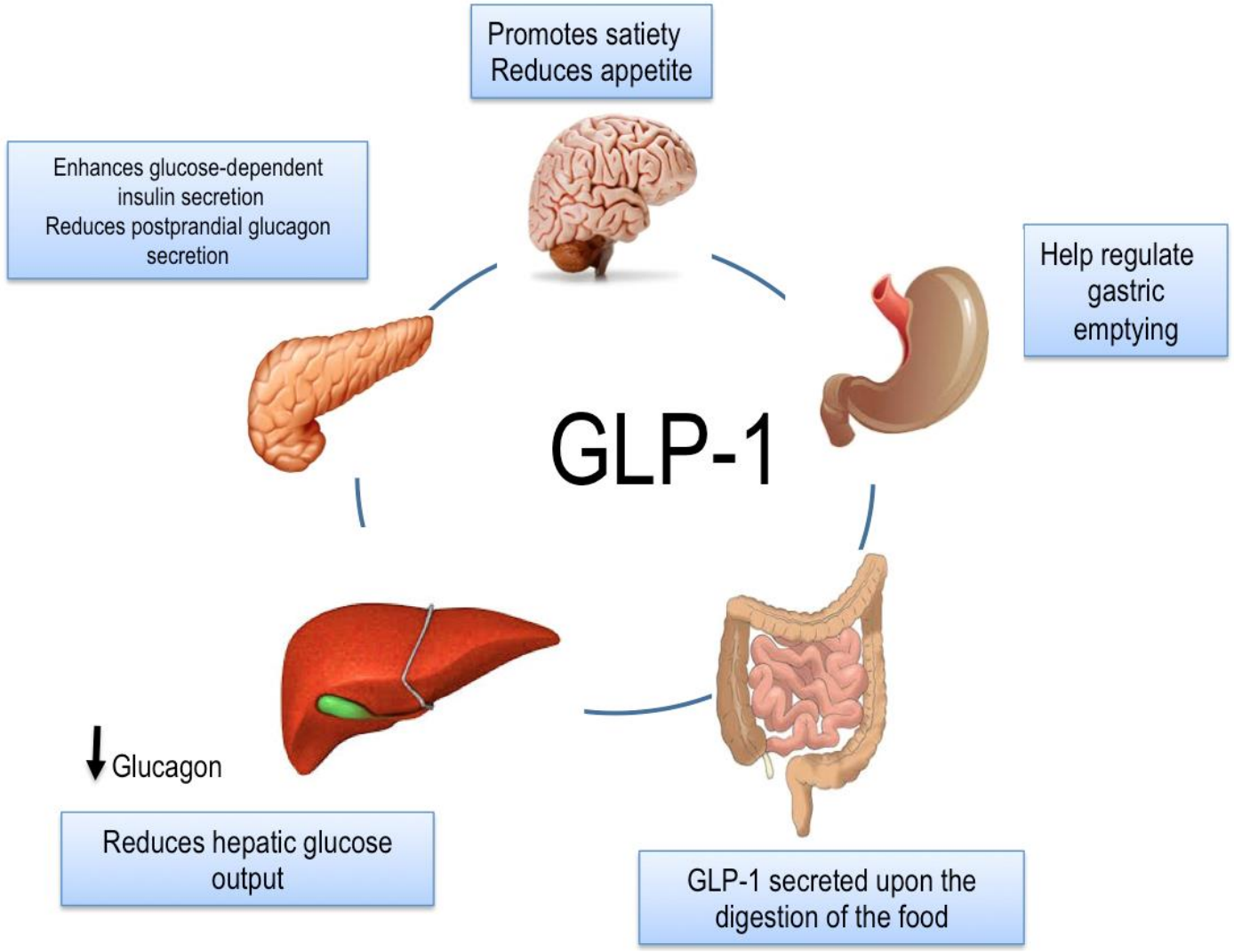


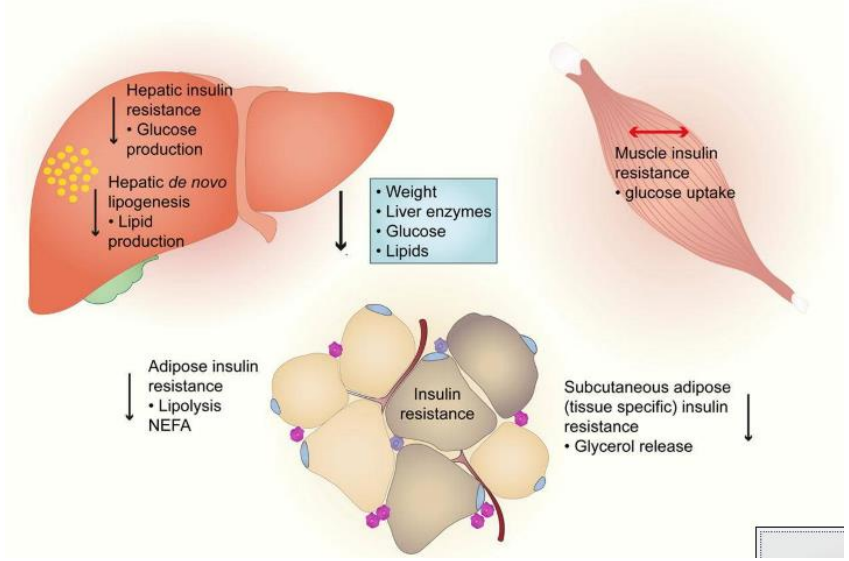
Cohort 1	% of Patients
Any TEAE	**94***
Severity	
Grade 1	23.1
Grade 2	56.5
≥ Grade 3	11.4
Preferred Term	
Diarrhea	33.3
Nausea	25.0
Urinary tract infection	16.7
COVID-19	12
Arthralgia	10.2
Fatigue	12.3
TEAE Leading to Study Discontinuation	**2.8**
Drug-related TEAE Leading to Study Discontinuation	**0**

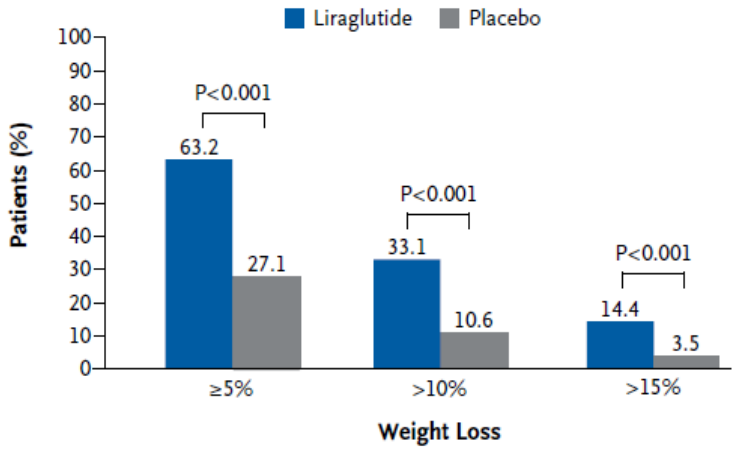
No difference between cirrhosis severity groups or compared with noncirrhotic NASH patients

No central thyroid axis changes

Doble efecto antiobesidad y anti-NASH de los agonistas del GLP-1

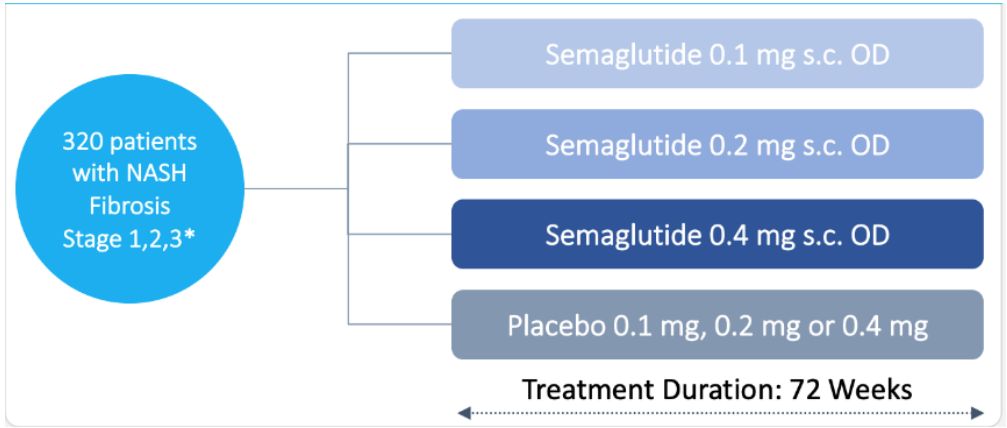






Van Gaal L. European Congress on Obesity (ECO) 2015. Abstract 0S2.1.

Semaglutida en MAFLD



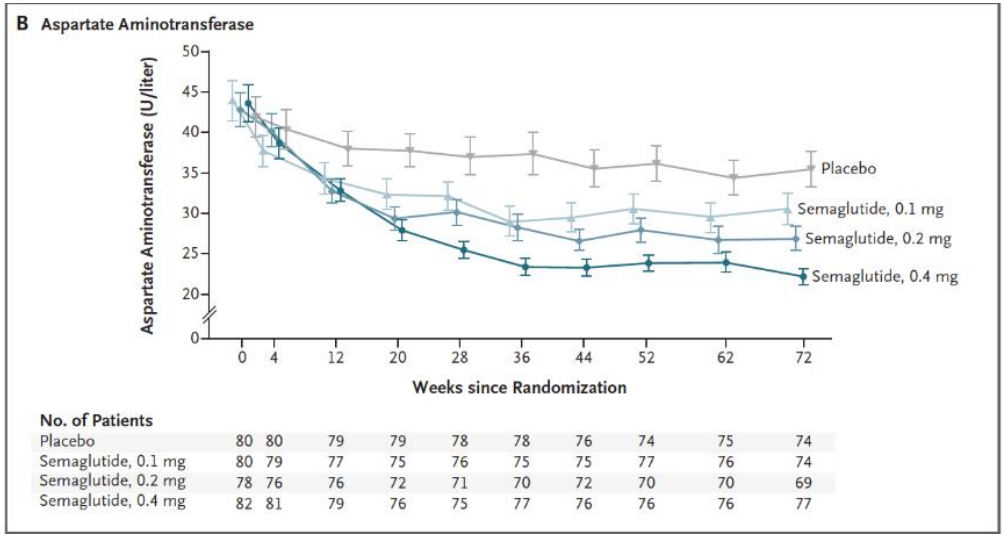
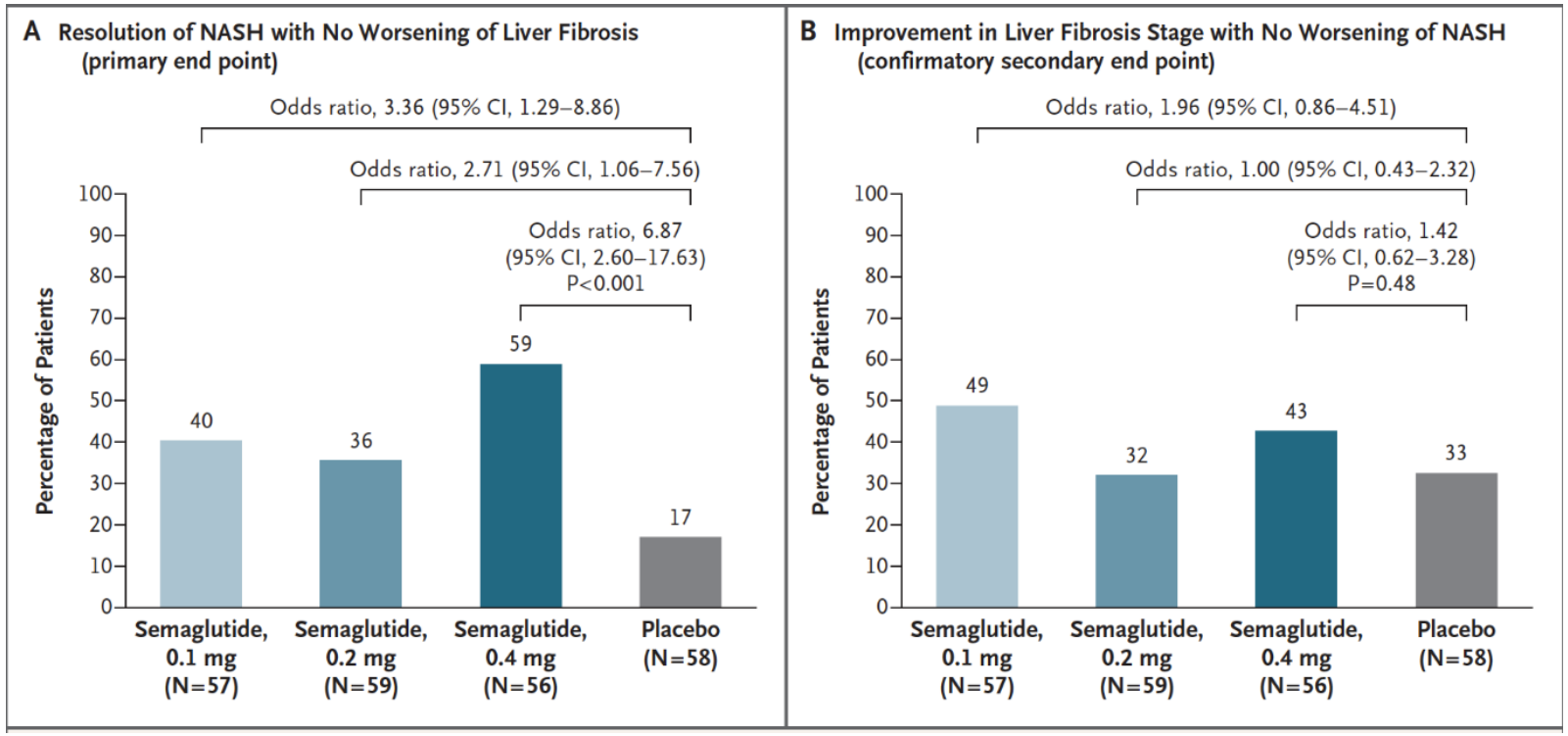


Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	−0.34	−0.39	−0.56	0.01
Body weight — %	−4.84	−8.91	−12.51	−0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	−0.63	−1.07	−1.15	−0.01



Newsome P et al. NEJM 2020

Improved outcomes with semaglutide: NASH & QoL

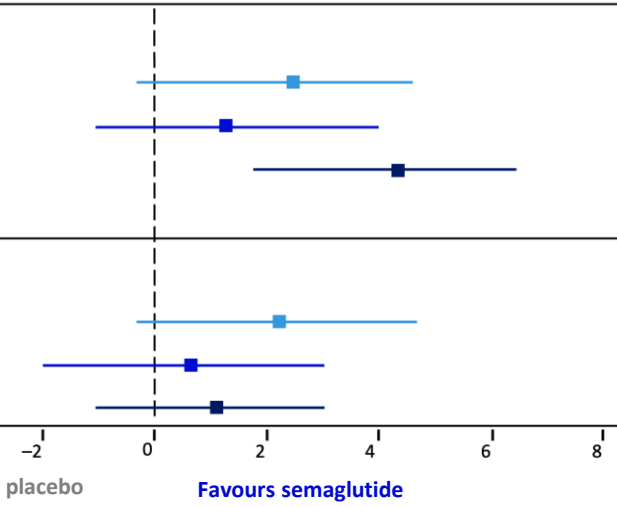
Compared with placebo semaglutide resulted in:

- More patients achieving NASH resolution without worsening of fibrosis
- No significant difference in number of patients with improvement in fibrosis
- Fewer patients with progression of fibrosis
- Improvements in fibrosis biomarkers

Improvements in multiple metabolic characteristics, including body weight, HbA_{1c}, and lipid profile

Safety profile consistent with that seen in patients with type 2 diabetes with no new safety concerns

Estimated treatment differences in **SF-36** component summary scores	Estimated treatment difference	95% CI	p-value
Physical component			
Sema 0.1 mg OD	2.12	-0.17; 4.41	0.0696
Sema 0.2 mg OD	1.56	-0.81; 3.93	0.1965
Sema 0.4 mg OD	4.26	1.96; 6.55	0.0003
Mental component			
Sema 0.1 mg OD	2.05	-0.55; 4.66	0.1224
Sema 0.2 mg OD	0.45	-2.22; 3.13	0.7400
Sema 0.4 mg OD	1.02	-1.59; 3.62	0.4441



ETDs with 95% CIs are from a MMRM with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline value of analysed parameter as covariate, all nested within visit. All scheduled post-baseline assessments during the on-treatment period were used in the model. MMRM, mixed model for repeated measures; ETD, Estimated treatment difference; CI, confidence interval.

Newsome PN, et al. N Engl J Med 2021;384:1113–24.
Romero-Gómez et al. CGH 2023 (Submitted)

Changes in SF-36 individual sub-domains and component summary scores

	Change at week 72		MID	ETD	95% CI	p-value
	Placebo	Sema 0.4 mg				
Physical component	−0.22	4.03	2	4.26	1.96, 6.55	**0.0003**
Physical functioning	−0.34	3.17	3	3.51	1.16, 5.86	**0.0034**
Bodily pain	−1.39	3.68	3	5.07	2.15. 7.99	**0.0007**
General health	1.63	3.92	2	2.29	−0.11, 4.69	0.0615
Role-physical	−0.34	2.46	3	2.80	0.28, 5.33	**0.0294**
Mental component	−0.17	0.84	3	1.02	−1.59, 3.62	0.4441
Role-emotional	−0.02	0.50	4	0.51	−2.04, 3.07	0.6932
Mental health	0.03	1.23	3	1.20	−1.45, 3.85	0.3747
Social functioning	−1.12	2.04	3	3.16	0.53, 5.78	**0.0183**
Vitality	−0.41	4.06	2	4.47	1.63, 7.32	**0.0021**

Data for all randomised patients during the in-trial period, analysed using an ANCOVA model with missing data derived by multiple imputation from placebo group. Data for semaglutide 0.1 mg and 0.2 mg doses not shown (ETD versus placebo all non-significant, except social functioning for 0.1 mg dose, p = 0.0022). MIDs, which are defined as the smallest difference in score which patients perceive as beneficial, are from the SF-36 Manual and Interpretation Guide and refer to mean group differences rather than responder definitions for individuals. ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; MID, minimum important difference; sema, semaglutide; SF-36, Short Form-36.

Newsome PN, et al. N Engl J Med 2021;384:1113–24.
Romero-Gómez et al. CGH 2023 (Submitted)

Relationship between SF-36 and NASH parameters

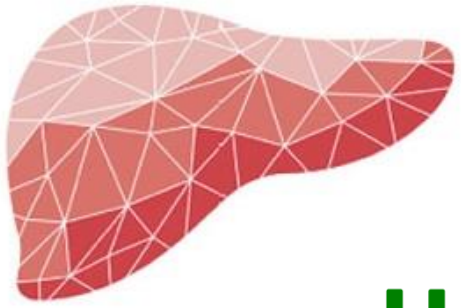
Weak correlation between **baseline SF-36 domains** and baseline lobular inflammation

No correlation between **baseline SF-36 domains** and baseline steatosis or ballooning

No correlations between **changes in SF-36 domains** and changes in body weight, ELF score, FibroScan-LSM, or NASH biopsy components

Once-daily subcutaneous semaglutide 0.4 mg has a clinically important effect on HRQoL in patients with NASH and stage F1–3 fibrosis

MÁSTER EN HEPATOLOGÍA



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