Therapeutic targets in MASLD
Dianas terapéuticas en EHmet.

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Conflict of interest

DISCLOSURES

- Consulting for: Alpha-sigma, Allergan, BMS, Boehringer-Ingelheim, Intercept, Innventia, Julius Clinical; Kaleido, MSD, Pfizer, Prosciento, Rubió, Shionogi, Siemens, Sobi, Thera, Zydus.
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Opinions expressed here are solely based on my own personal academic view and are intended to stimulate intelectual debate and not in any direct or indirect way drug prescription, clinical trial enrollment or any investment action.

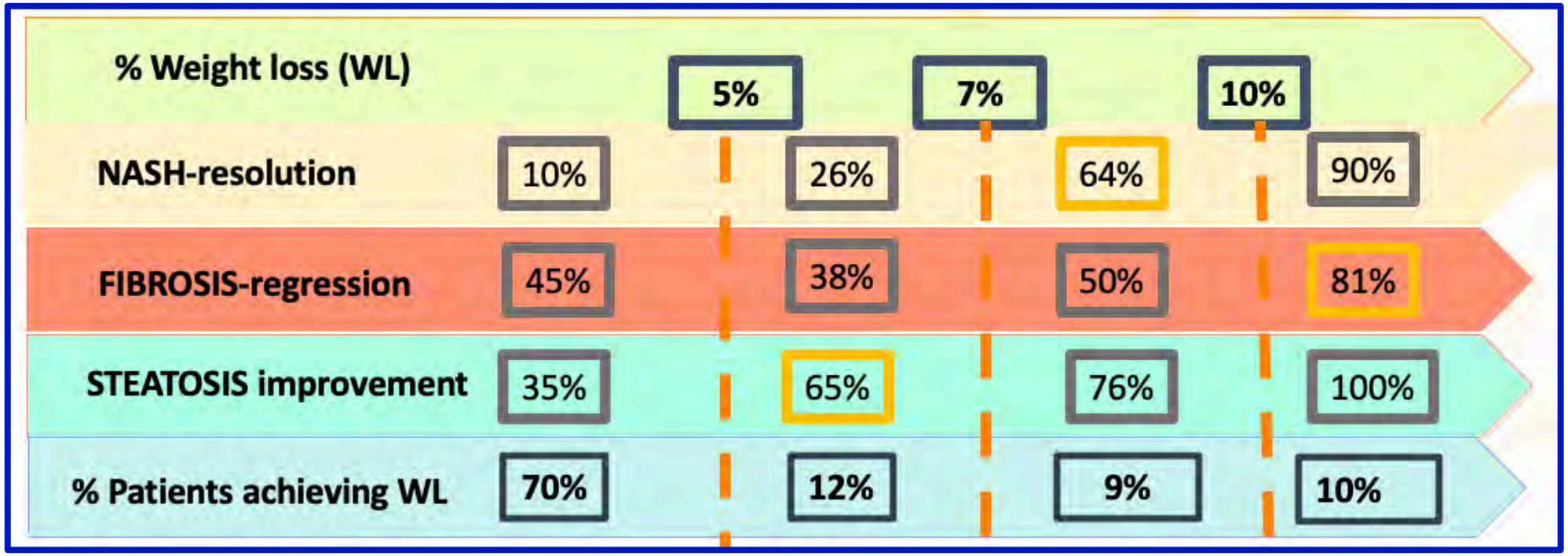
Gastroenterology 2015;149:367–378

CLINICAL—LIVER

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1] Ana Torres-Gonzalez,[1] Bienvenido Gra-Oramas,[3] Licet Gonzalez-Fabian,[3] Scott L. Friedman,[4] Moises Diago,[5] and Manuel Romero-Gomez[2]

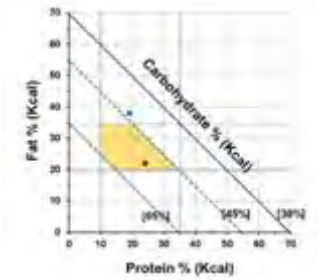
Weight loss by diet and physical activity promotes steatosis and NASH resolution and regression of fibrosis

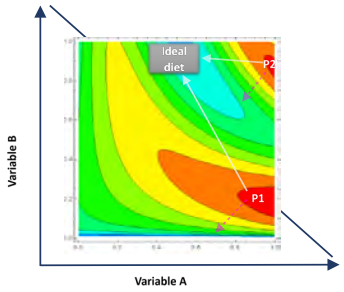


Vilar-Gomez et al. Gastro 2015; Romero-Gómez M, Zelber-Sagi S, Trenell M. J Hepatol 2017

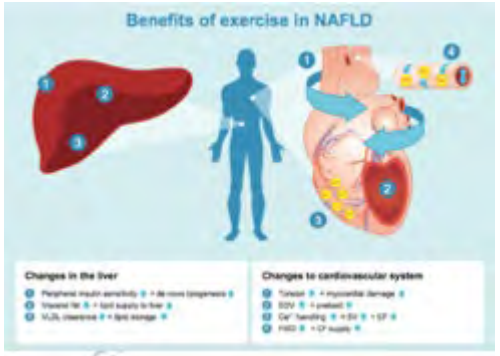
MASLD

Dietary recommendation
Hypocaloric Mediterranean Diet
Nutritional Geometry





LIFE-STYLE INTERVENTION



Aerobic /resistant exercise
150 min/week

RESPONDERS → **Long-term maintenance**

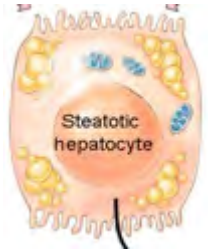
% Weight loss
ALT normalization → **Improvement of Obesity, T2DM, dyslipidemia & AHT**

NON-RESPONDERS → **Drug therapy**

NON-RESPONDERS → **Bariatric surgery/endoscopy**

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

Pharmacological therapy for MAFLD

- **MAFLD therapies**
  - **Liver centered anti-fibrotic**
    - **FXR agonist** → **Obeticholic acid**
    - THbeta → **Resmetiron**
  - 

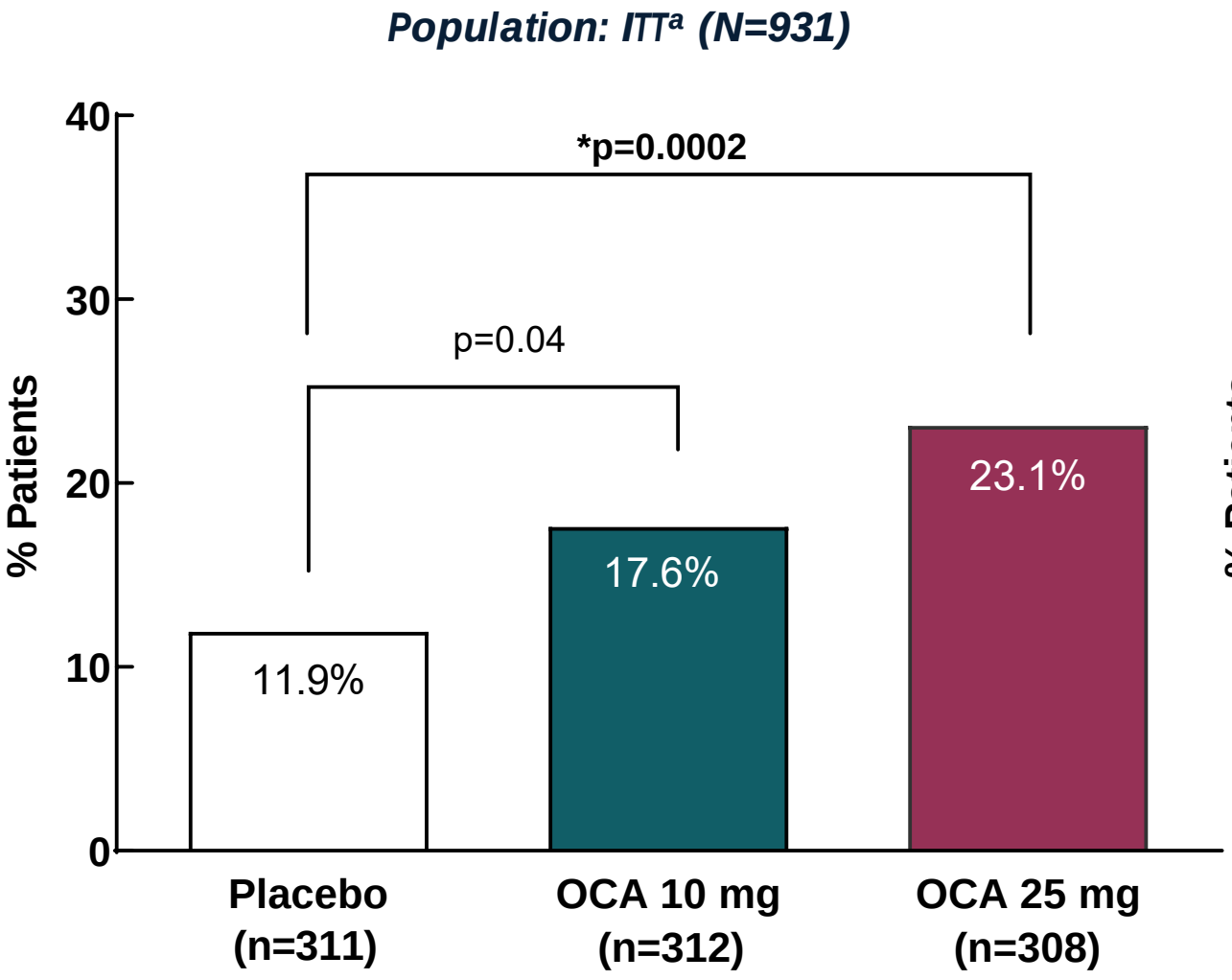
  - **Liver centered Metabolic drugs**
    - **FGF-21 agonists** → **Pegozafermin**, **Efruxifermin**
    - **Semaglutide / dual** → **Efinopegdutide**, **Pemvidutide**, **Survodutide**
    - **PPARs agonist** → **Lanifibranor**, **Saroglitazar**
    - **Denifanstat**

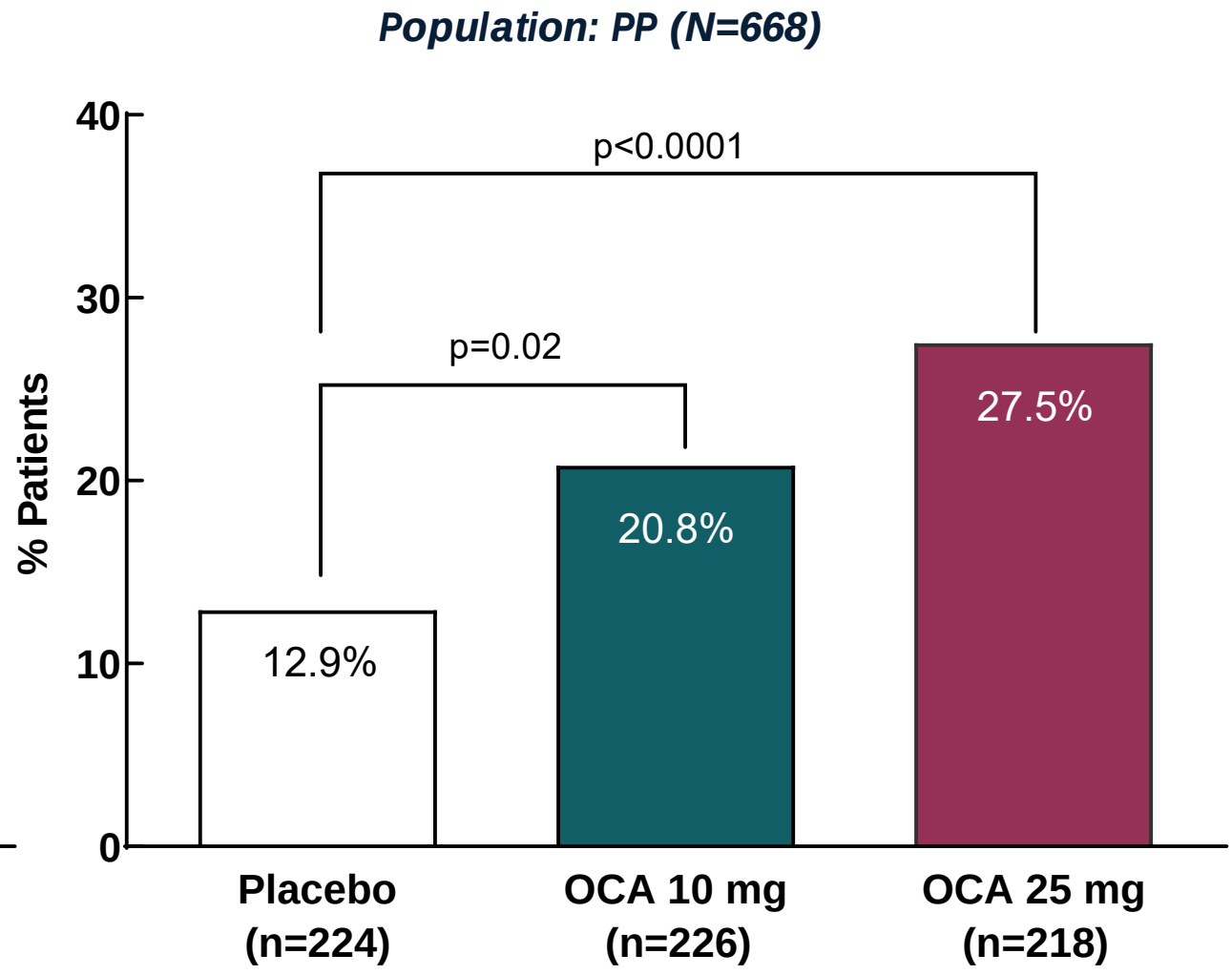
- **Metformin**
- **Pioglitazone**
- **SGLT-2 inh**
- **GLP1RA**
- **Statins**

- Emricasan
- Simtuzumab
- Selonsertib
- Cenicriviroc
- Elafibranor

Modified from Wang & Friedman et al. J Hepatol 2020;73:210-211

Obeticholic acid: Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
(Primary Endpoint: ITT Population)

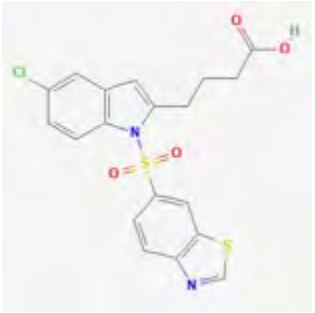


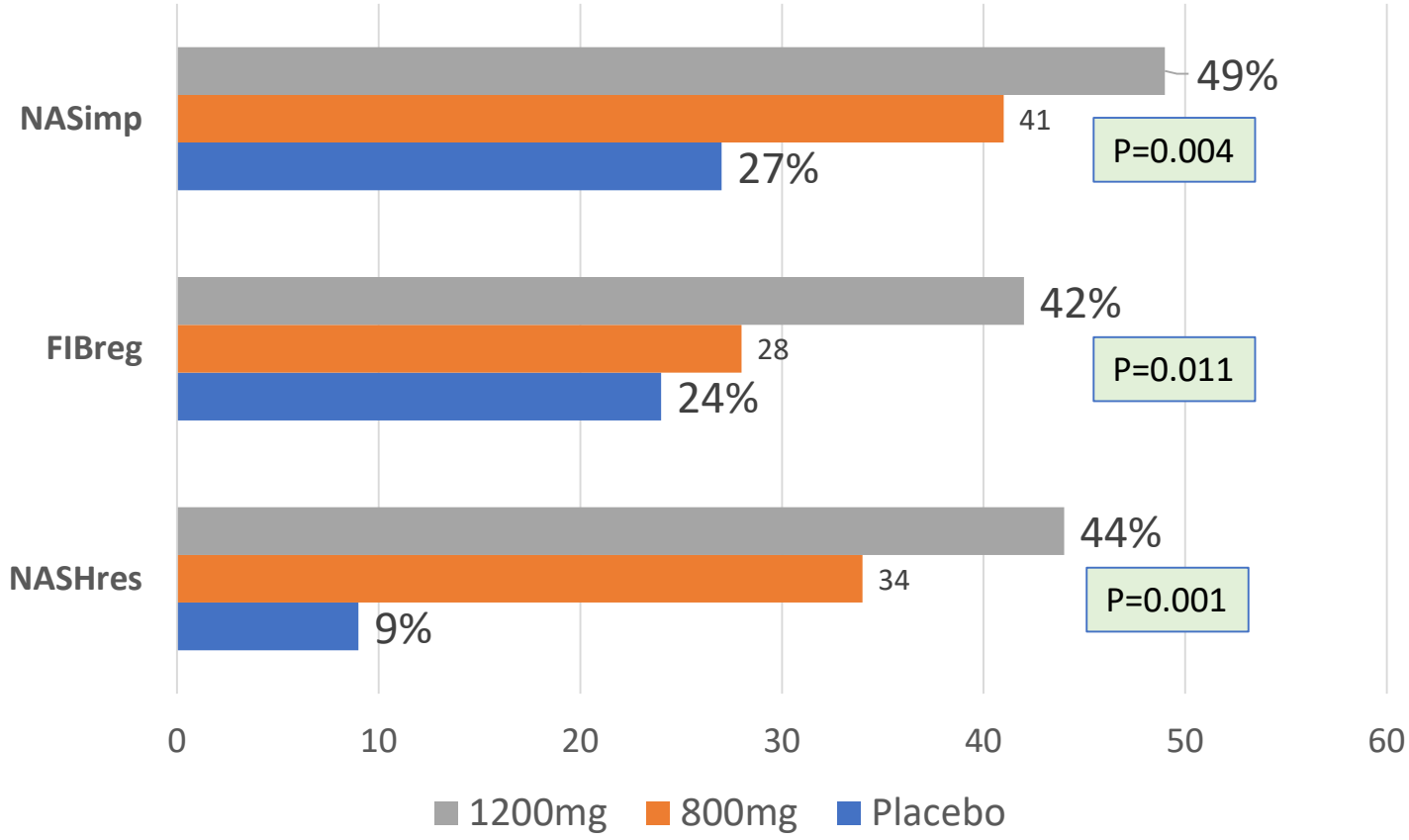


Primary endpoint definition: improvement in fibrosis by ≥1 stage (NASH CRN) with no worsening of lobular inflammation, hepatocellular ballooning or steatosis.
Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.
*Statistically significant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

Lanifibranor in MAFLD
A pan-PPAR agonist

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





Decrease of insulin, fasting glucose and glycated haemoglobin (HB1AC) in patients with type 2 diabetes.

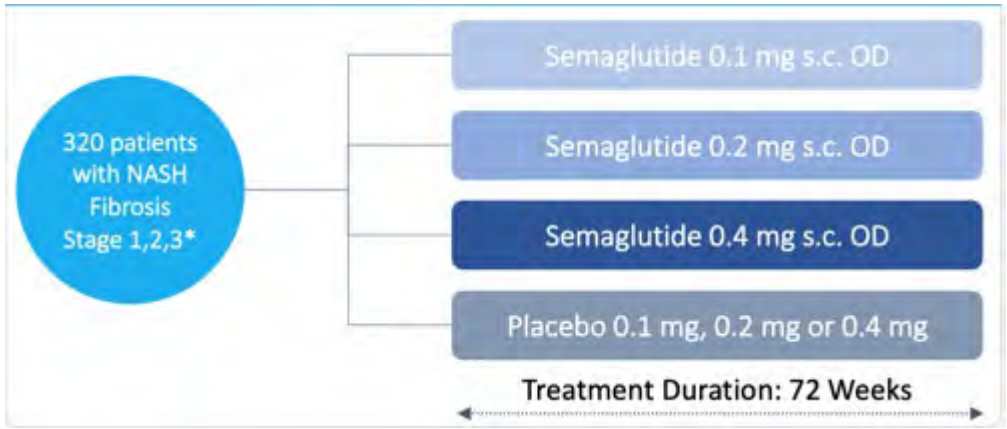
Decrease in triglycerides.

Increase in high density lipoprotein cholesterol (HDL).

Decrease in liver enzymes (ALT, AST and GGT)

Franque S and Abdelmalek M. Native IIb. 2020

Semaglutide in MAFLD



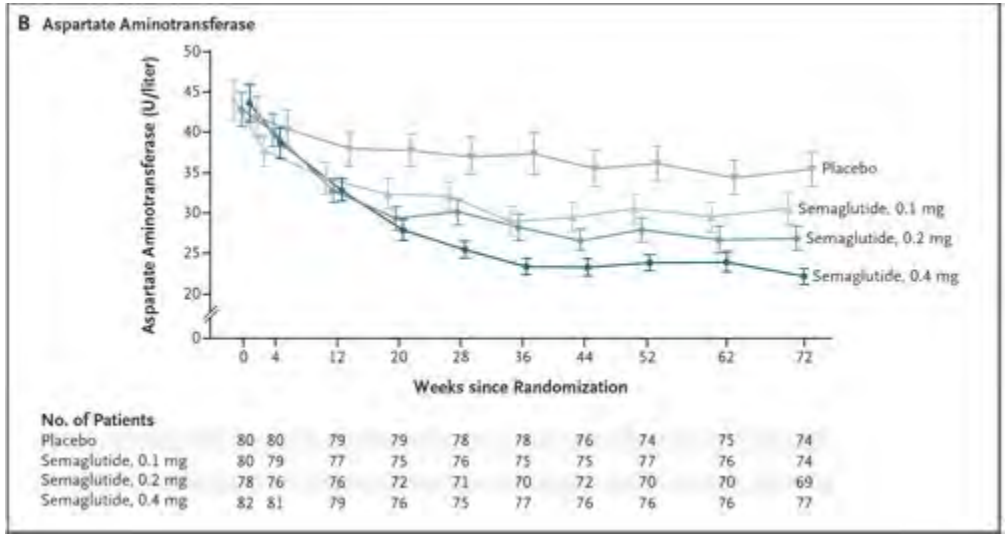
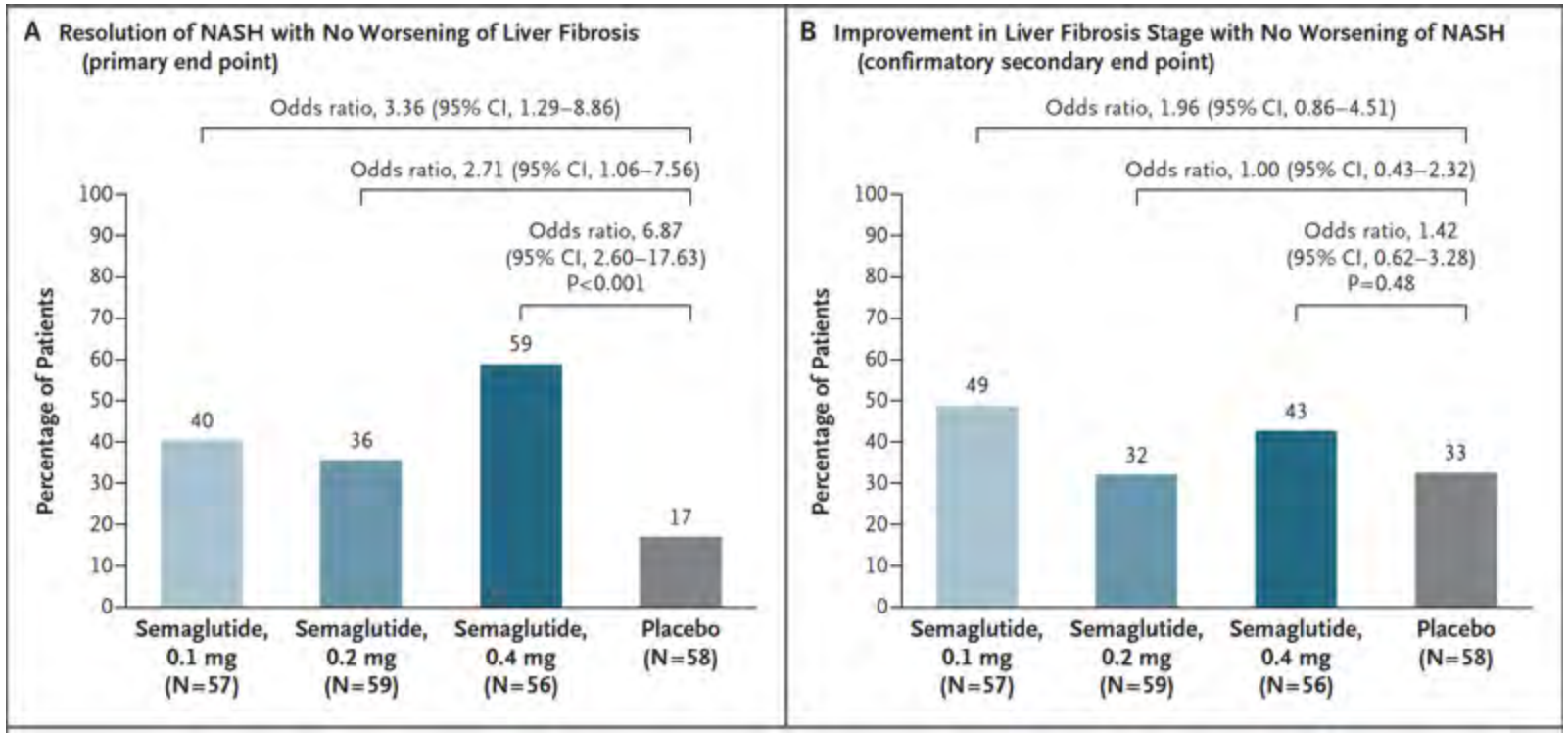


Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

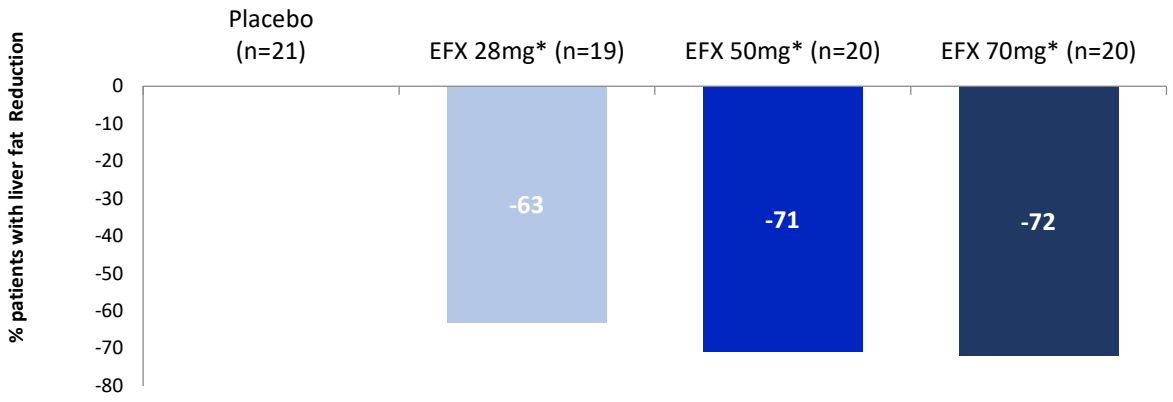
End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment 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

Efruxifermin: FGF21 analog

N=80
4 arms



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 arms

	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

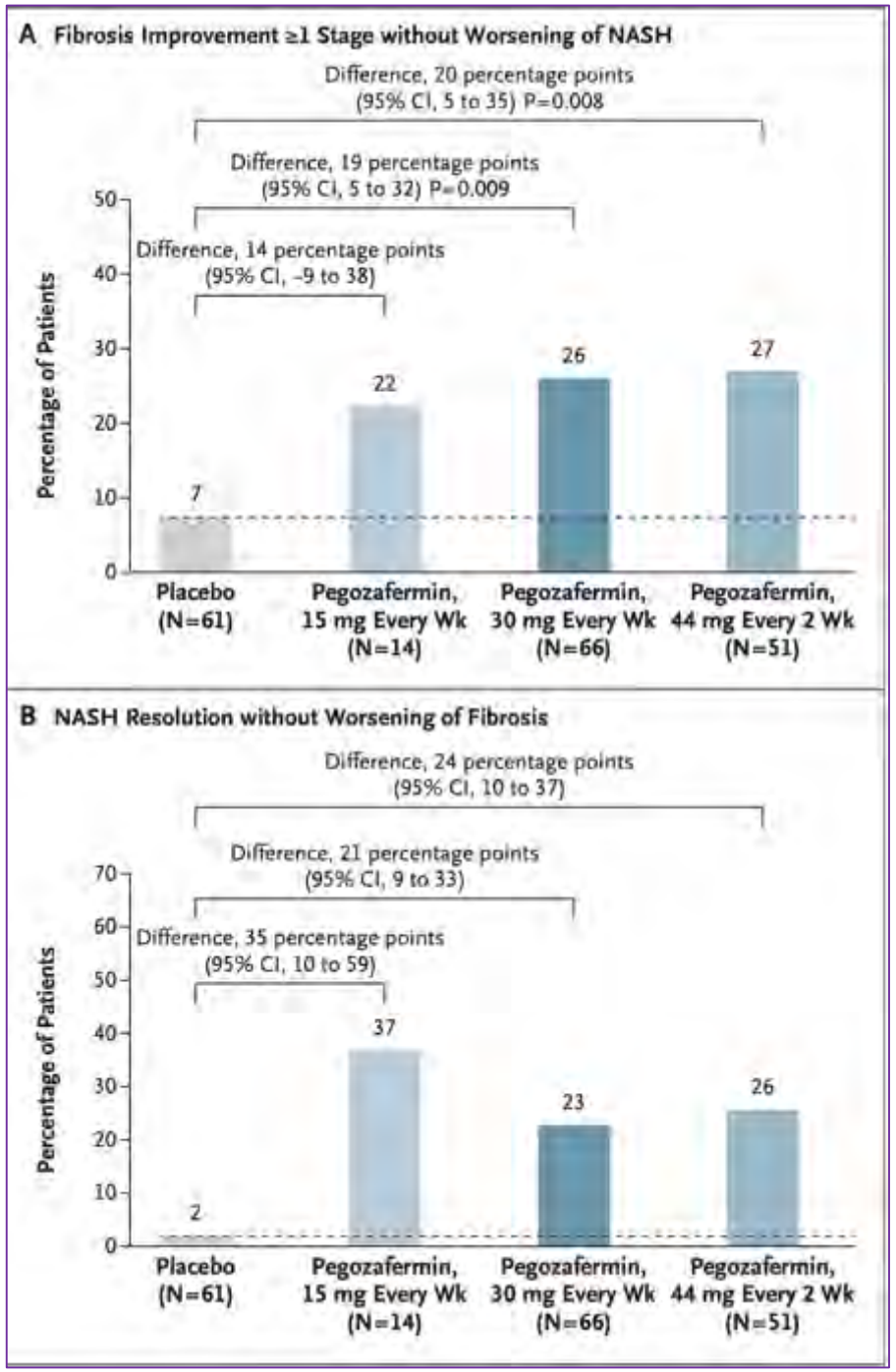
Akero. Akero Announces Strongly Positive Histological Data Across All Efruxifermin Dose Groups in 16-Week Phase 2a BALANCED Study in NASH Patients. 2020 Jun 30. Press Release. https://ir.akerotx.com/news-releases/news-release-details/akero-announces-strongly-positive-histological-data-across-all/

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

Pegozafermin in MASH

Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.*

Characteristic	Placebo (N=71)	Pegozafermin, 15 mg Weekly (N=21)	Pegozafermin, 30 mg Weekly (N=73)	Pegozafermin, 44 mg Every 2 Wk (N=57)	Total (N=222)
Age — yr	56.3±9.0	55.0±10.5	55.3±11.2	55.2±11.2	55.6±10.4
Male sex — no. (%)	32 (45)	12 (57)	23 (32)	20 (35)	87 (39)
White race — no. (%)†	67 (94)	18 (86)	69 (95)	54 (95)	208 (94)
Hispanic or Latino ethnic group — no. (%)†	24 (34)	9 (43)	32 (44)	20 (35)	85 (38)
Body weight — kg	108.7±20.1	108.0±21.0	95.7±20.2	100.2±20.4	102.2±20.9
Body-mass index‡	38.1±5.6	37.8±4.8	35.1±6.4	36.1±5.5	36.6±5.9
Type 2 diabetes — no. (%)	49 (69)	18 (86)	45 (62)	35 (61)	147 (66)
Glycated hemoglobin — %	6.6±1.0	7.0±1.2	6.6±1.2	6.7±1.3	6.7±1.2
Alanine aminotransferase — U/liter	49.6±25.7	61.1±34.8	60.0±32.1	56.3±32.0	55.8±30.6
Aspartate aminotransferase — U/liter	40.6±20.2	47.7±27.9	46.7±25.3	41.7±23.3	43.6±23.5
NASH CRN fibrosis stage — no. (%)§					
F1	2 (3)	3 (14)	2 (3)	0	7 (3)
F2	20 (28)	6 (29)	21 (29)	21 (37)	68 (31)
F3	47 (66)	9 (43)	47 (64)	30 (53)	133 (60)
F4	2 (3)	3 (14)	3 (4)	6 (11)	14 (6)
NAFLD activity score¶	5.0±1.2	4.8±1.2	5.3±1.1	5.2±1.0	5.1±1.1
Liver fat content — %‖	16.7±7.1	15.8±6.4	16.7±7.0	15.8±7.8	16.4±7.2
Liver stiffness — kPa**	14.1±7.7	11.2±2.9	12.5±4.2	13.2±10.3	13.0±7.3
Pro-C3 — ng/ml††	49.8±17.5	61.6±30.7	53.6±22.3	52.3±18.8	52.8±21.1
Triglycerides — mg/ml	170.3±84.6	186.2±118.7	175.0±83.1	164.7±77.7	171.9±85.8



Loomba et al. NEJM 2023;389:998-1008

Dysregulated Lipid Metabolism in NAFLD

Environmental Factors
- Diet and sedentary lifestyle

Metabolic Factors
- Insulin resistance, T2D, obesity, and dyslipidemia

Genetic Factors
- PNPLA3, others

Surplus of FFAs causes
- TG stored as lipid droplets and partially released to circulation as LDL
- Generation of lipotoxic lipid species
- Overwhelmed metabolic capacity - failure of b-oxidation and mitochondrial dysfunction
- Generation of ROS causing cell injury, leads to inflammation and liver fibrosis

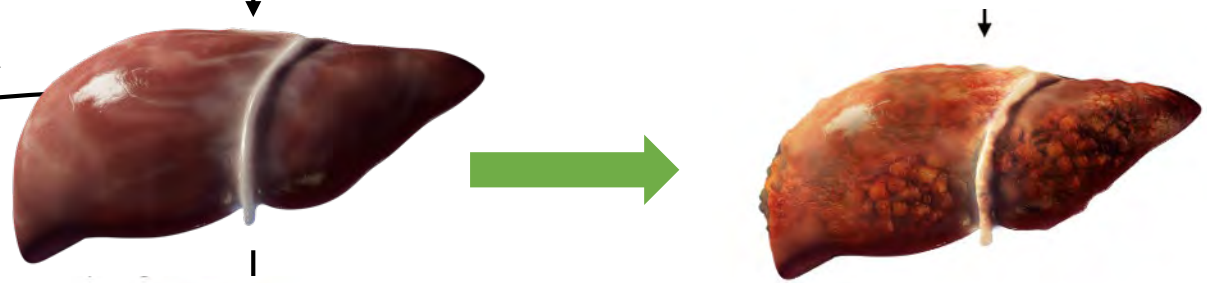
Increased visceral adiposity

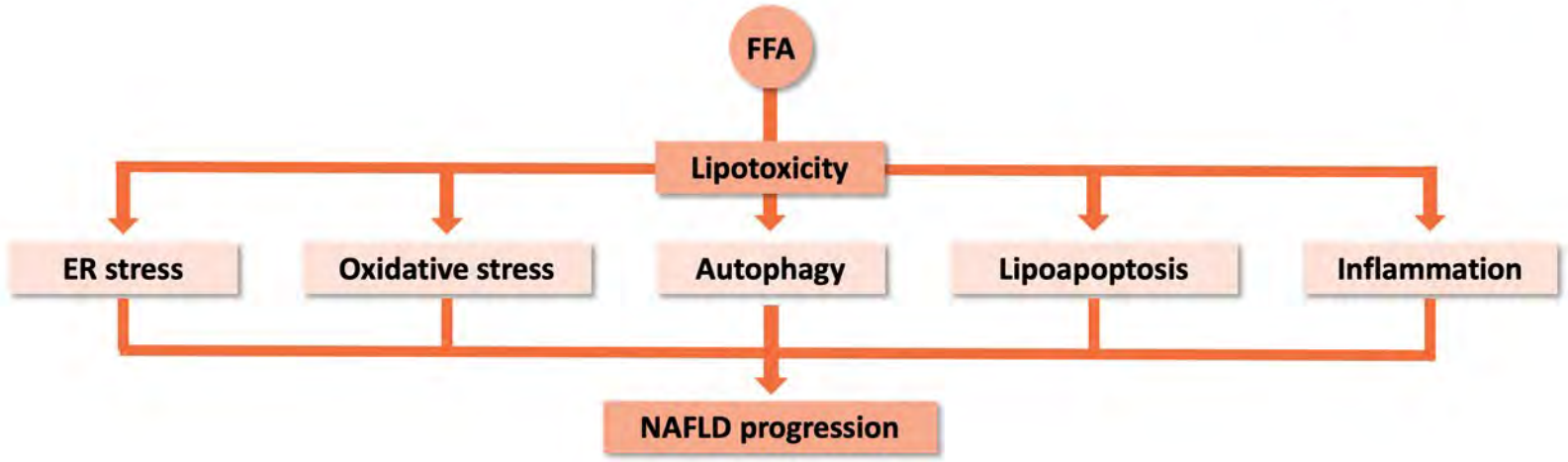
Fate of FFAs in the liver
- Mitochondrial β-oxidation
- Esterification to form TG

FFAs from diet

FFAs from peripheral lipolysis

FFAs from *de novo* lipogenesis





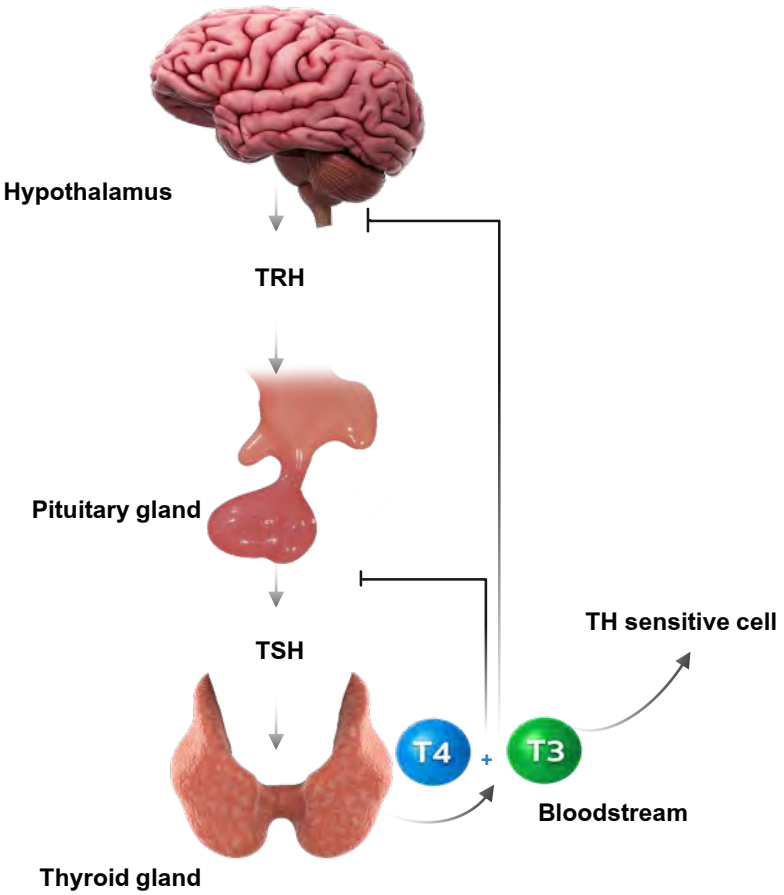
FFA, free fatty acid; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; ROS, reactive oxygen species; T2D, type 2 diabetes; TG, triglycerides.
Adapted from Clare K, et al. *J Clin Transl Hepatol*. 2022;10(5):939-946.

ER, endoplasmic reticulum; FFA, free fatty acid; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Adapted from Rada P, et al. *Cell Death Dis*. 2020;11(9):802.

Thyroid Hormone Pathway: HPT Axis

- Thyroid hormone has important effects on cellular development, growth, and metabolism
  - Necessary for healthy function of almost all tissues
- Synthesis and secretion of thyroid hormone is regulated by a negative feedback loop involving the hypothalamus, pituitary, and thyroid glands (HPT axis)
  - TRH and TSH are both repressed by high thyroid hormone levels
- Two main types of thyroid hormone:
  - T4 (prohormone; main form secreted by thyroid gland; 40-fold higher than T3)
  - T3 (active hormone)

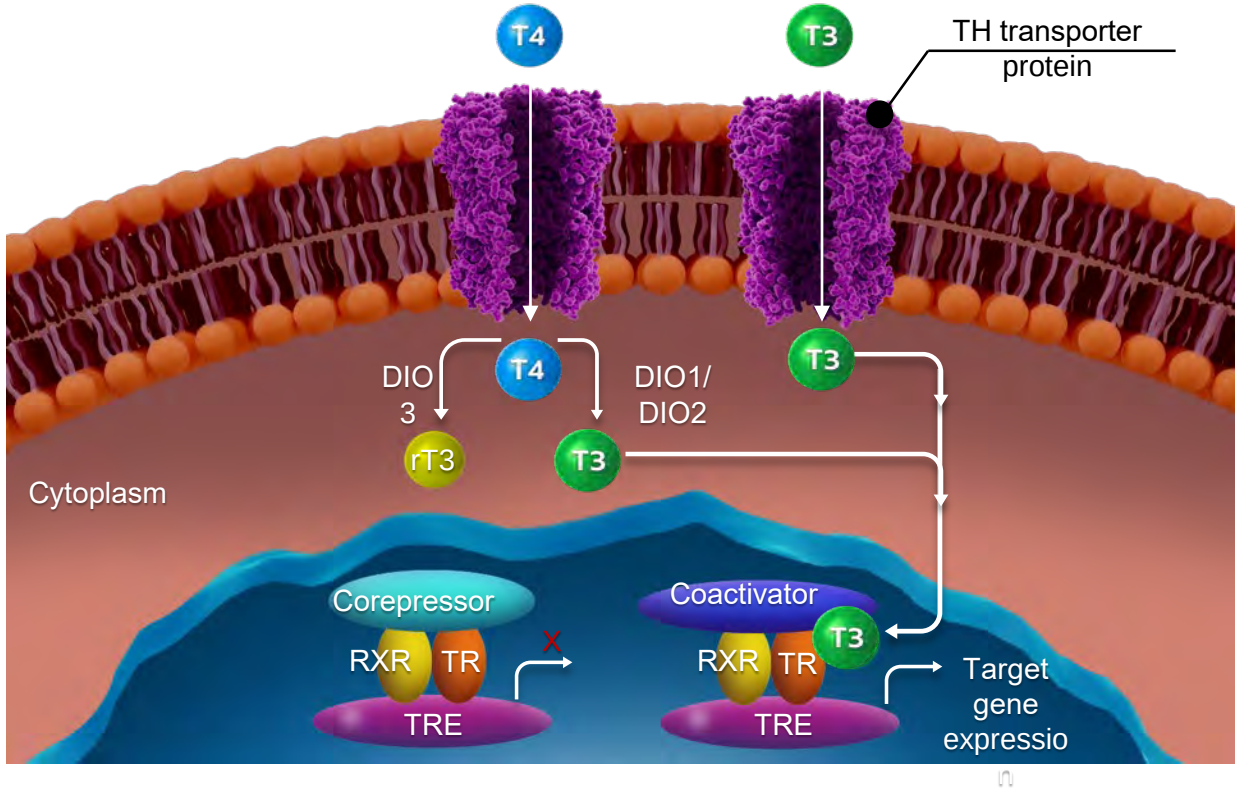


HPT, hypothalamus-pituitary-thyroid; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

1. Jakobsson T, et al. *Drugs*. 2017;77:1613-1621. 2. Ayers S, Webb P. *J Endocrinol Diabetes Obes*. 2014;2:1042.

Thyroid Hormone Mechanism of Action

- Thyroid hormones T4 and T3 are transported into the cell by thyroid hormone transporters
- Prohormone T4 is converted to active hormone T3 by specific enzymes known as deiodinases (DIOs)
- The DIOs work together to maintain homeostasis (DIO1, DIO2, and DIO3)
- Binding of T3 to the ligand-binding domain of nuclear thyroid hormone receptors results in disruption of corepressor binding and promotion of coactivator binding

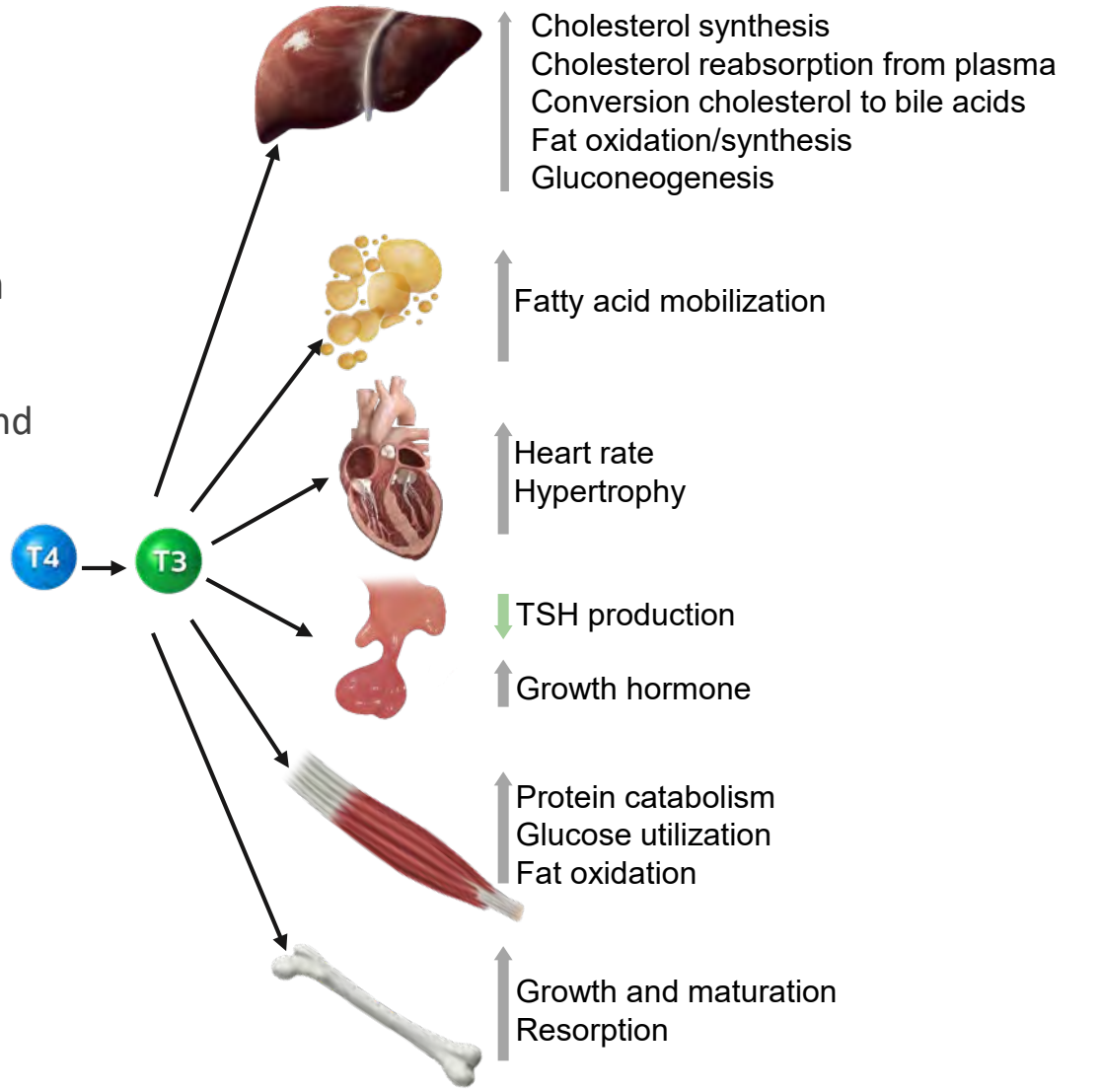


DIO1, deiodinase 1; DIO2, deiodinase 2; DIO3, deiodinase 3; rT3, reverse T3; RXR, retinoid X receptor; TH, thyroid hormone; TR, thyroid hormone receptor; TRE, thyroid hormone response element.

1. Bohinc BN, et al. *Endocrinology.* 2014;155(11):4591-4601. 2. Brent GA. *J Clin Invest.* 2012;122(9):3035-3043. 3. Wu Y, et al. *J Biol Chem.* 2001;276(6):3929-3936.

Thyroid Hormone Pathway: Actions of Thyroid Hormone

- Thyroid hormone status affects body weight, energy expenditure, and lipid metabolism
- Hyperthyroidism (↓TSH, ↑T4)
  - Excess thyroid hormone production results in hyperthyroidism or thyrotoxicosis
    - Marked by tachycardia, muscle wasting, osteoporosis, fatigue, and anxiety
  - However, an increase in thyroid hormone also results in beneficial effects including reductions in LDL-C and body fat
- Hypothyroidism (↑TSH, ↓T4)
  - Symptoms of hypothyroidism, in which too little thyroid hormone is produced, are mostly the opposite of hyperthyroidism
    - Weight gain, high LDL-C, reduced body temperature, and depression

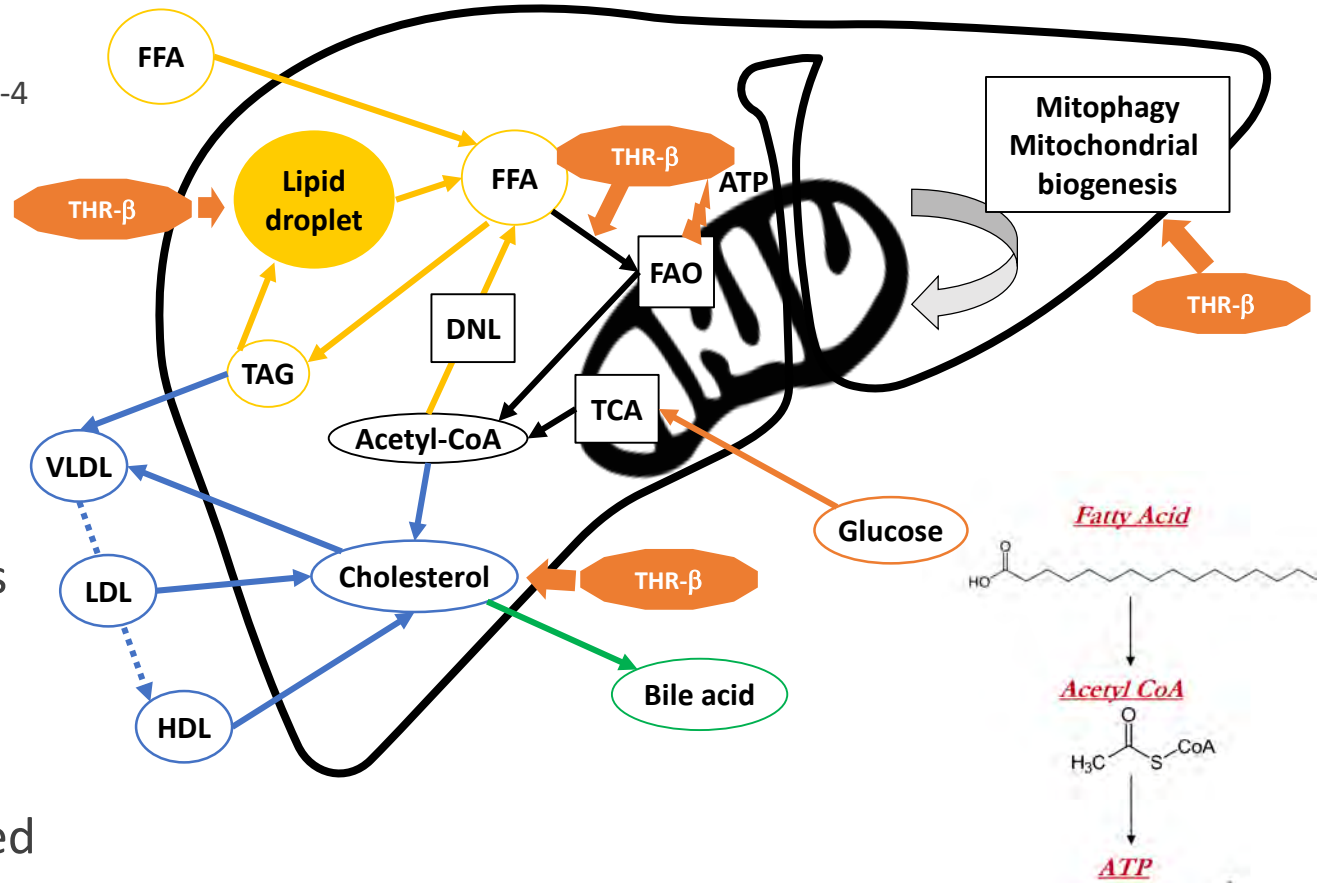


LDL-C, low-density lipoprotein cholesterol; T4, thyroxine; TH, thyroid hormone; TSH, thyroid-stimulating hormone.

1. Jakobsson T, et al. *Drugs*. 2017;77:1613-1621. 2. Baxter JD, Webb P. *Nat Rev Drug Discov*. 2009:8;308-320.

THR-β Pathway Plays a Key Role in Hepatic Lipid Metabolism

- Thyroid hormone acts on multiple pathways to maintain homeostasis in the liver by controlling[1-4]
  - *De novo* lipogenesis
  - Fatty acid beta oxidation
  - Mitophagy and mitochondrial biogenesis
  - Cholesterol metabolism
  - Carbohydrates metabolism
- THR-β is responsible for thyroid hormone effects on metabolism in the liver as determined in preclinical models[2]
- In clinical trials, THR-β agonism has demonstrated beneficial effects on lipid metabolism[5-8]



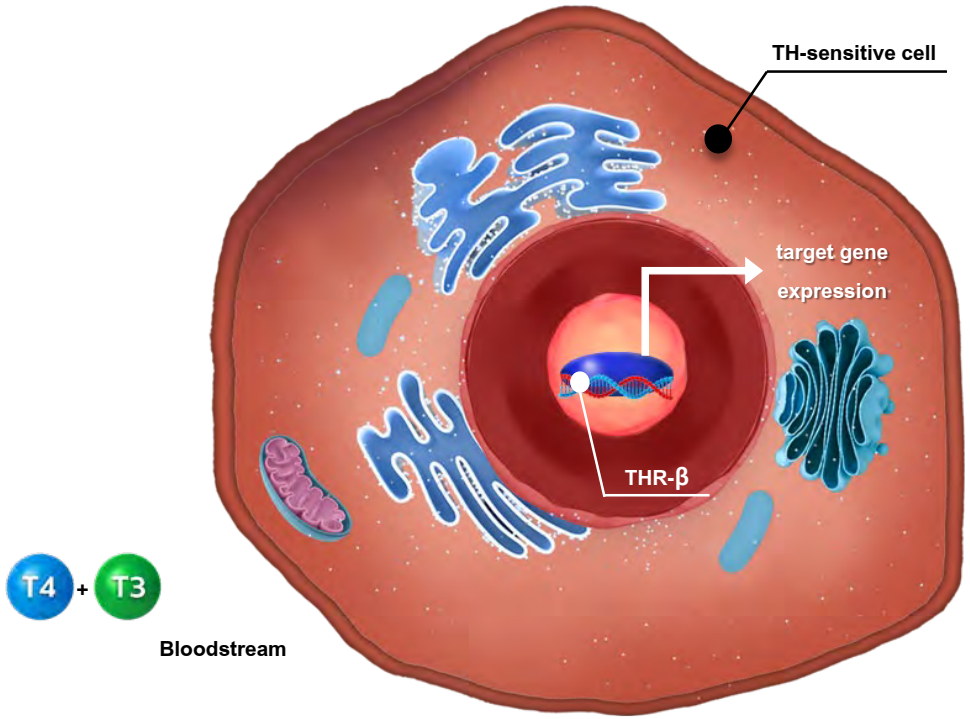
Carbons eliminated through CO_2 respiration (citric acid cycle)

DNL, *de novo* lipogenesis; FAO, fatty acid beta oxidation; FFA, free fatty acid; TAG, triacylglycerol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TAG, triacylglycerol; TCA, tricarboxylic acid; VLDL, very low density lipoprotein. ATP, adenosine triphosphate; TH, thyroid hormone; THR, thyroid hormone receptor.

1. Ritter MJ, et al. *Hepatology*. 2020;72:742-752. 2. Saponaro F, et al. *Front Med (Lausanne)*. 2020;7:331. 3. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269. 4. Taub R, et al. *Atherosclerosis*. 2013;230:373-380. 5. Taub R, et al. Presented at Therapeutic Agents for Non-Alcoholic Steatohepatitis and Liver Fibrosis (NASH-TAG) Conference; 04-06 Jan 2018; Park City, UT. 6. Harrison SA, et al. *Lancet*. 2019;394:2012-2024. 7. Loomba R, et al. EASL 2020 AS073. 8. Nelson CH, et al. EASL 2022. OS123.

Thyroid Hormone Pathway: Thyroid Hormone Receptors

- Two primary isoforms of thyroid hormone receptors mediate the physiological effects of thyroid hormone, both widely expressed
  - **THR-α**, predominant in heart, brain, and bone
    - Responsible for effects in heart and bone, thyrotoxicosis side effects of thyroid hormone excess
  - **THR-β,** predominant in liver, kidney, and pituitary gland
    - Responsible for effects on metabolism
    - Crucial role in the liver, including activation of liver fat oxidation[1]
- The liver is the only organ where THR-β (*THRB*) is expressed higher than THR-α (*THRA*)[2,3]

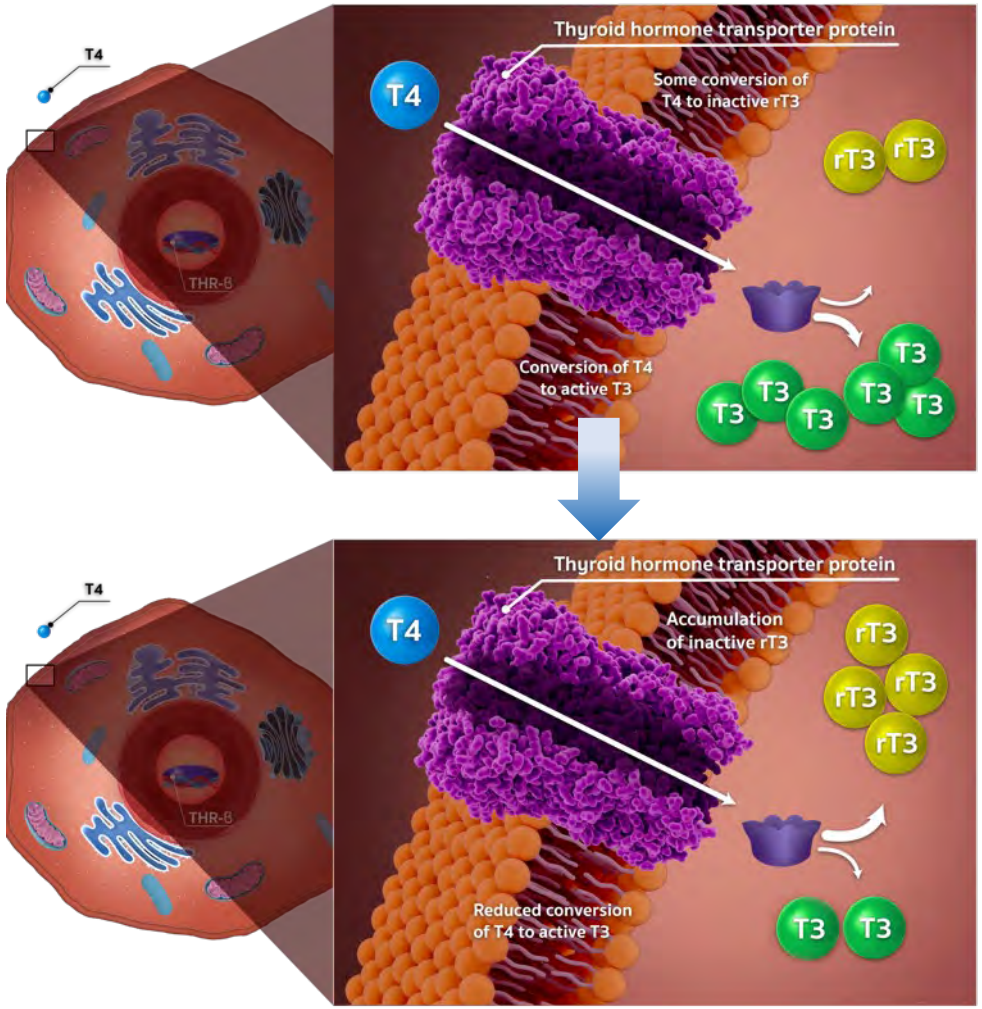


T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; THR, thyroid hormone receptor.

1. Saponaro F, et al. *Front Med (Lausanne).* 2020;7:331. 2. Fagerberg L, et al. *Mol Cell Proteomics*. 2014;13:397-406. 3. Expression Atlas: https://www.ebi.ac.uk/gxa/home. Accessed May 2022.

THR-β Pathway: Chronic Liver Injury Induces Dysfunction

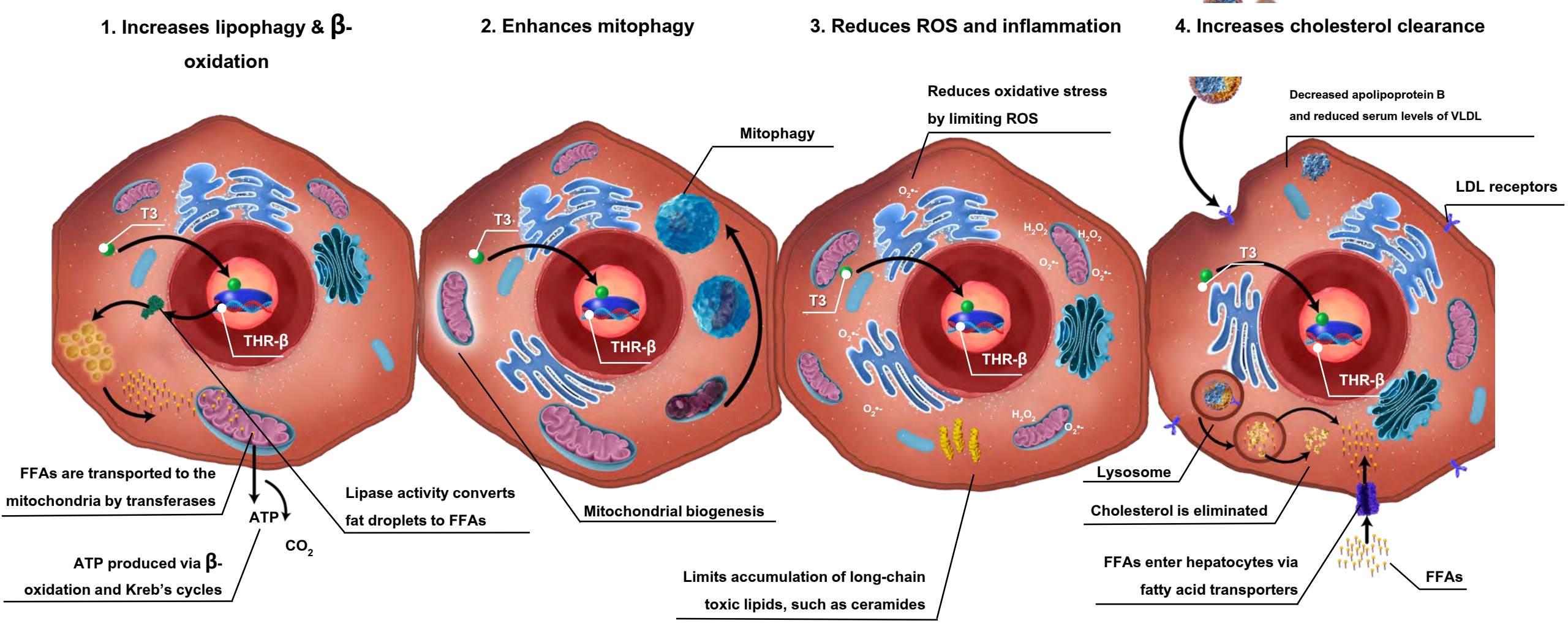
- Local intrahepatic hypothyroidism, observed during chronic liver injury, is caused by:[1]
  - Depressed conversion of prohormone T4 to active hormone T3
  - Decrease in T3/rT3 ratio causes intrahepatic hypothyroidism and downregulation of hepatic thyroid hormone pathway
- Thyroxine treatment does not improve this deficiency; in fact, patients with NASH treated with thyroxine (T4) have more exaggerated elevations of rT3 and reductions in FT3/rT3 [2]
  - Leads to the depressed thyroid hormone signaling in the liver and sets up a vicious cycle leading to additional inflammatory fat and dysfunction



NASH, nonalcoholic steatohepatitis; rT3, reverse T3; T2D, type 2 diabetes; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone.

1. Bohinc BN, et al. *Endocrinology*. 2014;155:4591-4601. 2. Taub R, et al. Presented at American Thyroid Association Annual Meeting; 29 Sept-03 Oct 2021; Scottsdale, AZ.

THR-β Pathway Plays a Role in Hepatic Lipid Metabolism

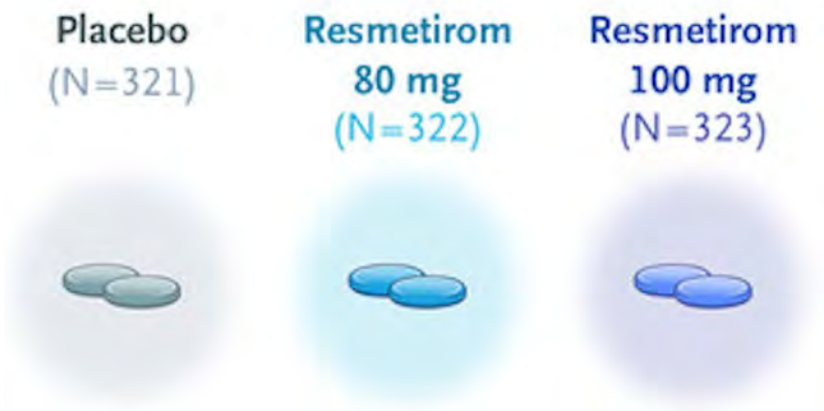


ATP, adenosine triphosphate; CO2, carbon dioxide; FFA, free fatty acid; H2O2, hydrogen peroxide; LDL, low-density lipoprotein; O2•-, oxygen radical; ROS, reactive oxygen species; T3, triiodothyronine; THR, thyroid hormone receptor; VLDL, very-low-density lipoprotein.

1. Ritter MJ, et al. *Hepatology*. 2020;72:742-752. 2. Saponaro F, et al. *Front Med (Lausanne)*. 2020;7:331. 3. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14:259-269.
4. Taub R, et al. *Atherosclerosis*. 2013;230:373-380. 5. Taub R, et al. Presented at Therapeutic Agents for Non-Alcoholic Steatohepatitis and Liver Fibrosis (NASH-TAG) Conference; 04-06 Jan 2018; Park City, UT. 6. Harrison SA, et al. *Lancet*. 2019;394:2012-2024.

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

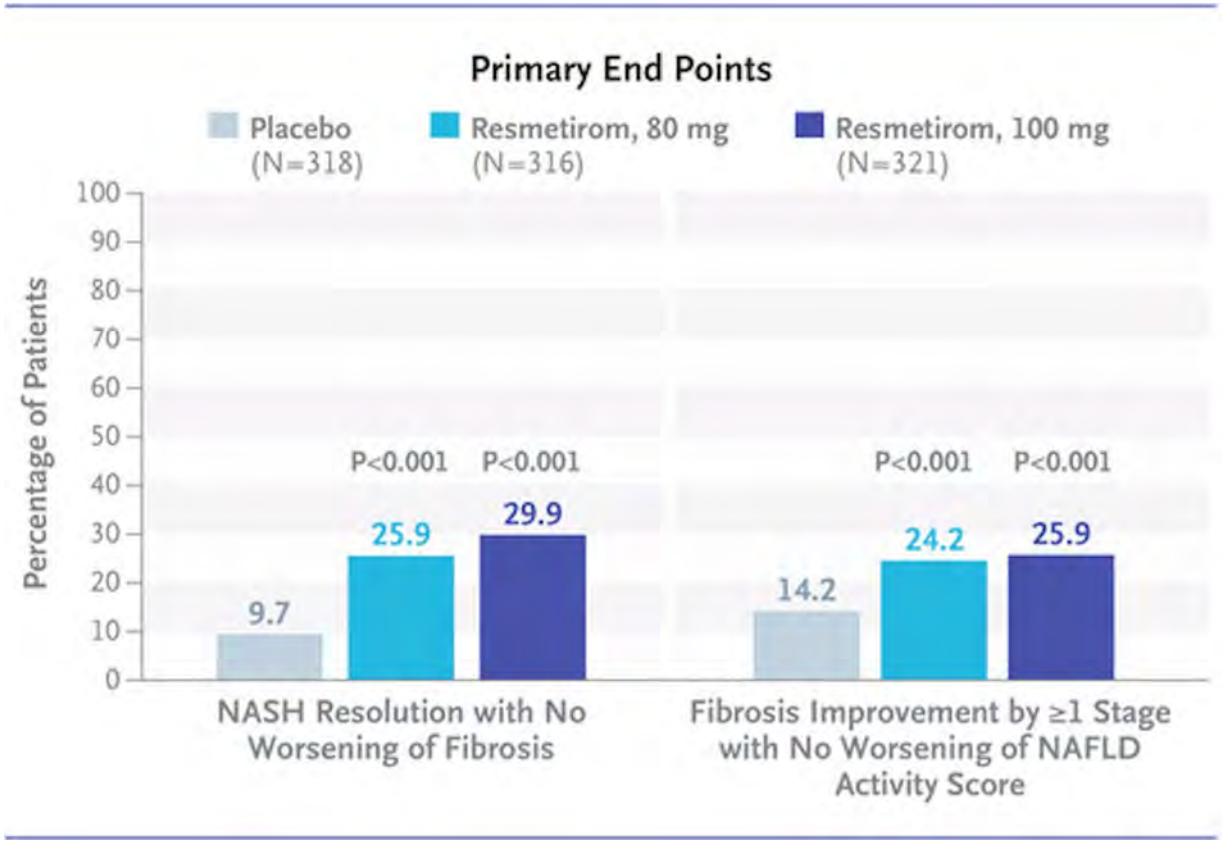
Harrison SA et al. DOI: 10.1056/NEJMoa2309000

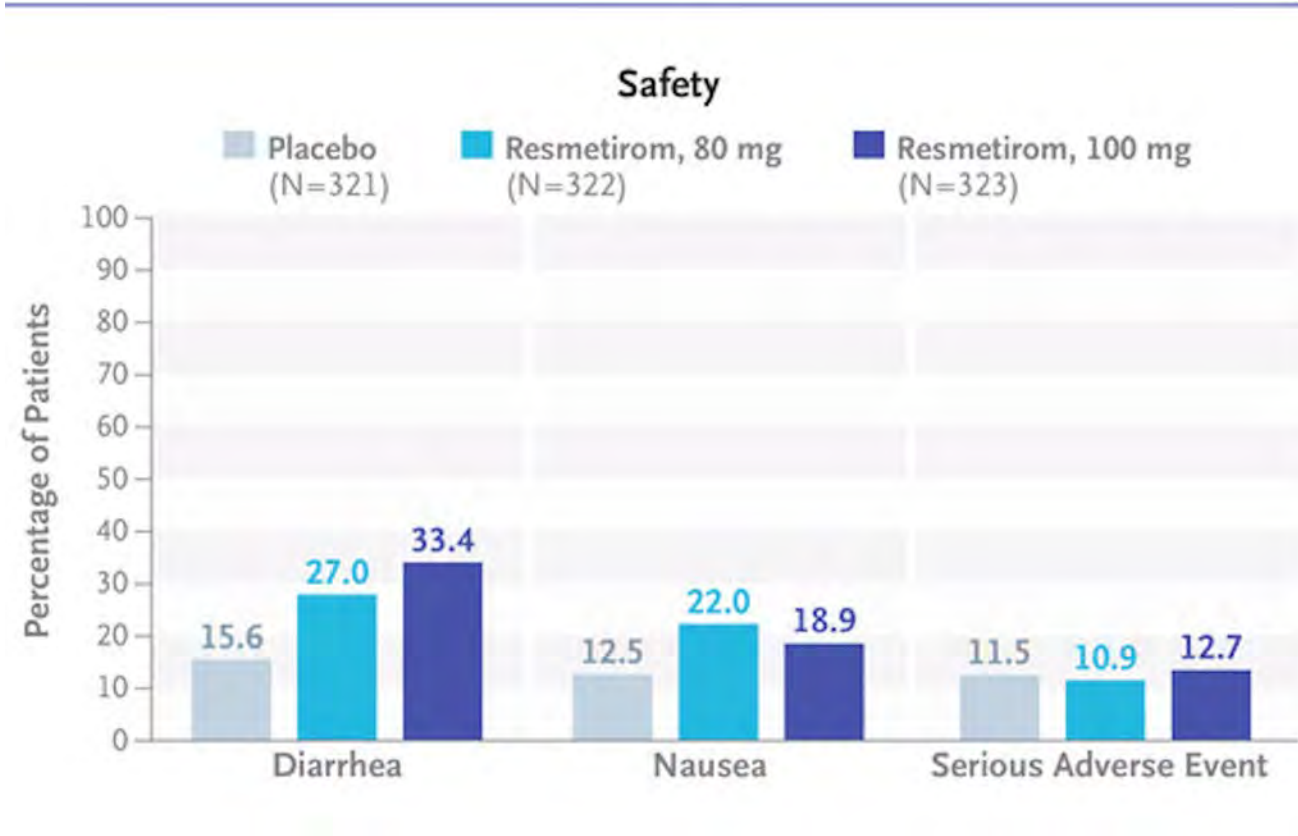


N=966	Resmetirom 80 mg (n=322)	Resmetirom 100 mg (n=323)	Placebo (n=321)	Overall (N=966)
Age, mean (SD), years	56 (12)	57 (11)	57 (11)	**57 (11)**
Sex, female, n (%)	182 (57)	182 (56)	178 (56)	**542 (56)**
White, n (%)	291 (90)	291 (90)	281 (88)	**863 (89)**
Hispanic or Latino, n (%)	71 (22)	81 (25)	52 (16)	**204 (21)**
BMI, mean (SD)	36 (6)	36 (7)	35 (7)	**36 (7)**
Type 2 diabetes, n (%)	224 (70)	213 (66)	210 (65)	**647 (67)**
Hypertension, n (%)	243 (76)	254 (79)	257 (80)	**754 (78)**
Dyslipidemia, n (%)	230 (71)	236 (73)	223 (70)	**689 (71)**
Hypothyroid, n (%)	38 (12)	46 (14)	45 (14)	**129 (13)**
FibroScan VCTE, mean (SD), kPa	13 (7)	14 (7)	13 (6)	**13 (7)**
FibroScan CAP, mean (SD), d/Bm	346 (37)	349 (39)	347 (37)	**348 (38)**
MRI-PDFF, mean (SD)	18 (7)	17 (7)	18 (7)	**18 (7)**
Baseline liver biopsy, n (%)				
NAS ≥5	266 (83)	288 (89)	253 (79)	**807 (84)**
1B	16 (5)	15 (5)	18 (6)	**49 (5)**
2	107 (33)	100 (31)	112 (35)	**319 (33)**
3	199 (62)	208 (64)	191 (60)	**598 (62)**

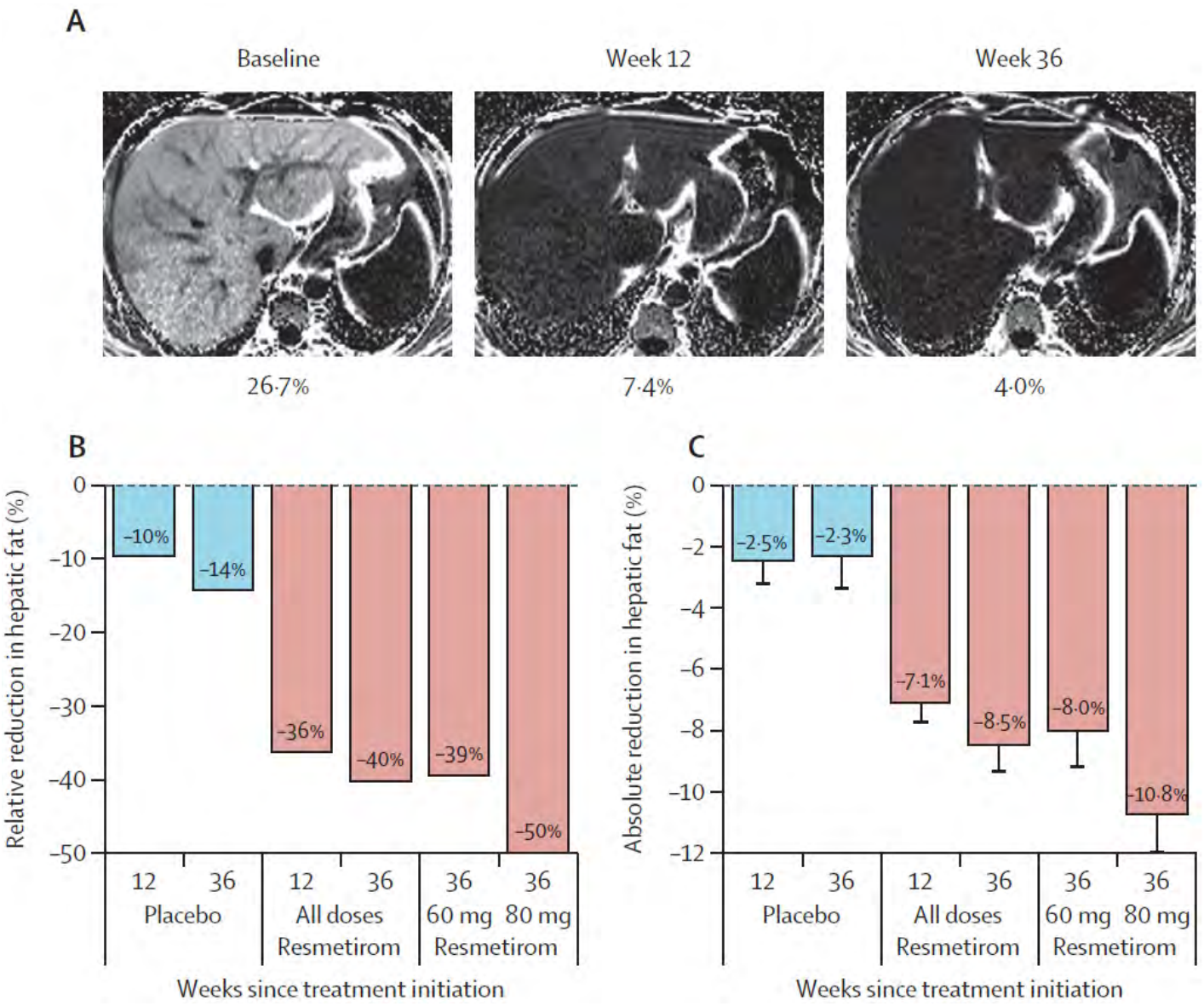
BMI, body mass index; CAP, controlled attenuation parameter; ITT, intent-to-treat; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; SD, standard deviation; VCTE, vibration-controlled transient elastography.

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

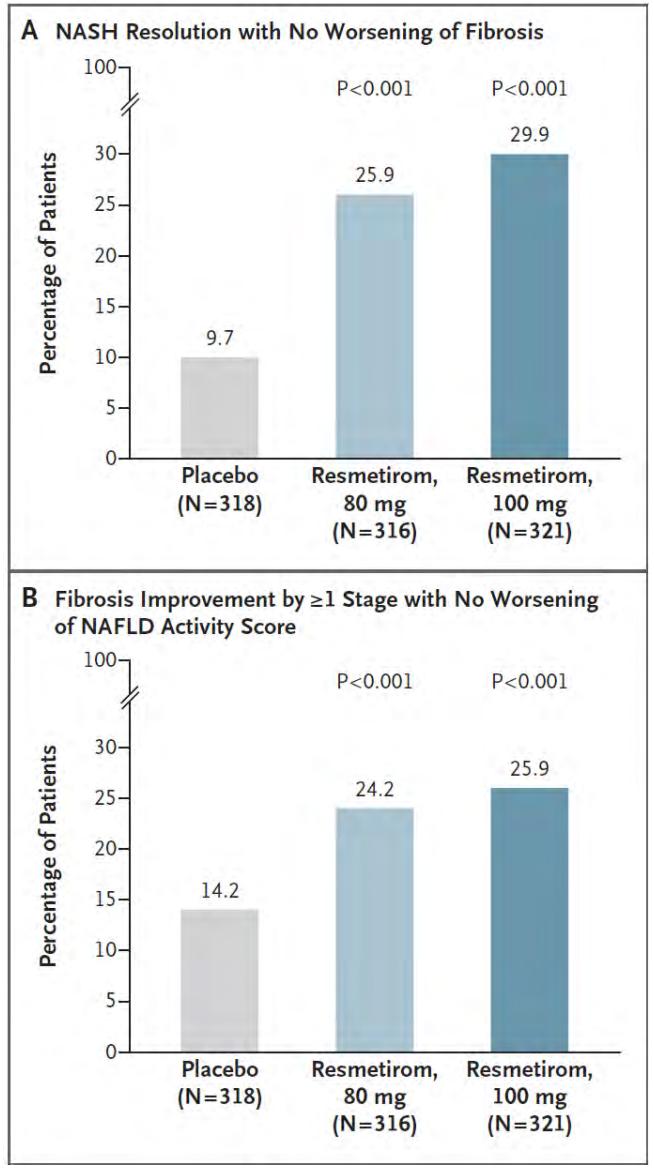




Resmetirom (MGL-3196)



Harrison, S. et al., The Lancet. Volume 394, Issue 10213, 30 November–6 December 2019, Pages 2012-2024



S.A. Harrison. N Engl J Med 390;6 nejm.org February 8, 2024.

Resmetirom (MGL-3196)

Compound	Study	Human study	Serum lipids	Steatosis	Liver function	BW	HPT axis	Other side effects
TRβ receptor agonist								
MGL-3196	Taub *et al.* (167)	48 Subjects with mildly elevated LDL-C and BMI 24.9–27.6 kg/m^2 (2 weeks, 50–200 mg/day, [115–460 μmol])	TC ↓ TAG ↓				fT4 ↓ (100/200 mg/dose), TSH =	Heart rate =, blood pressure =
	Harrison *et al.* meeting abstract (136)	125 Patients with biopsy-proven NASH (9 months, 80 mg/day [184 μmol])	TC ↓ TAG ↓	Liver fat (^{1}H-MRS) ↓	AST, ALT ↓		Only no change reported	Heart rate =

Sinha et al. Thyroid. 2019 September 01; 29(9): 1173–1191.

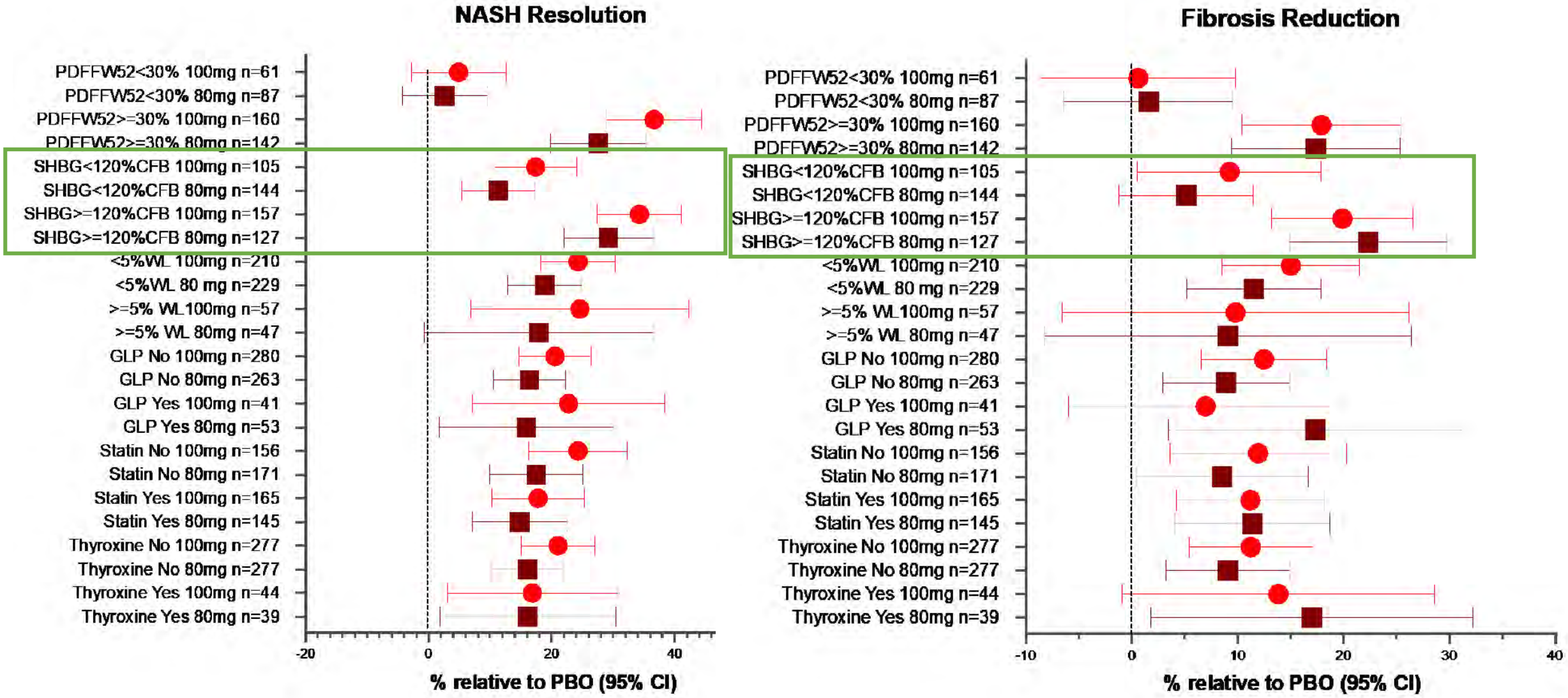
Compound	Mechanism of action	Effects (B, body; L, liver)	Current status
Resmetirom (MGL-3196)	Liver-specific TRβ agonist, low extra-hepatic penetration	↓ L-TAG, peroxidation, inflammation, fibrosis (animals) ↓ L-TAG (humans)	Another large multicenter RCT ongoing

Hatziagelaki, E. et al. Trends in Endocrinology & Metabolism, November 2022, Vol. 33, No. 11

Completed studies with THR-β agonists				
Study	Study design	LDL	Liver fat	LFT
MGL-3196 (phase IIb)[47]	125 patients with biopsy-proven NASH; 36 weeks; 60 or 80 mg daily	LDL-C -11% (placebo +6%)	Liver fat -50% (80 mg) (placebo -14%)	AST, ALT↓

S.A. Harrison. n engl j med 390;6 nejm.org February 8, 2024.

SHBG - Resmetirom (MGL-3196)



S.A. Harrison. n engl j med 390;6 nejm.org February 8, 2024.

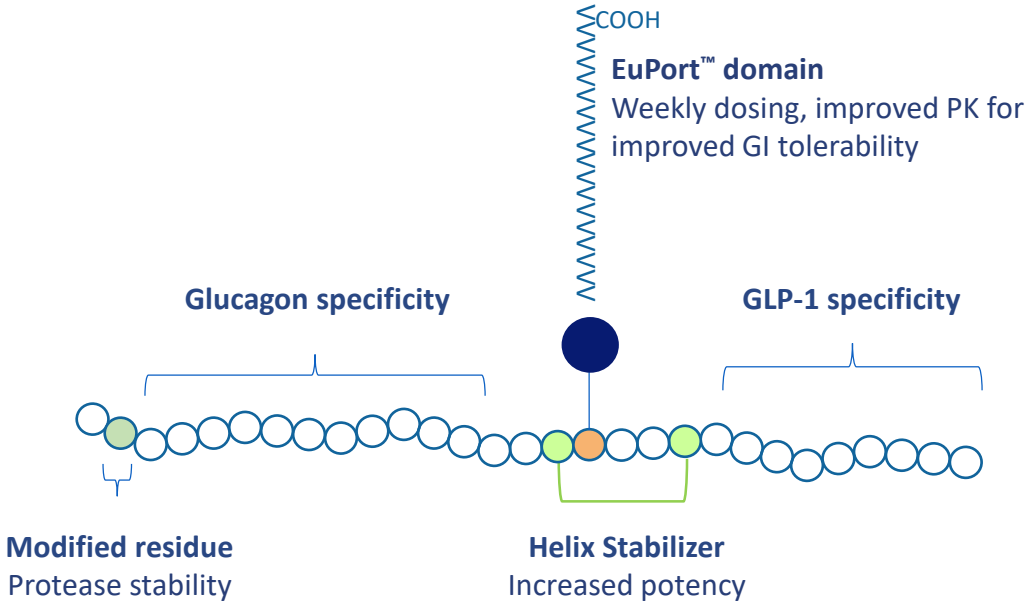
SHBG - Resmetirom (MGL-3196)

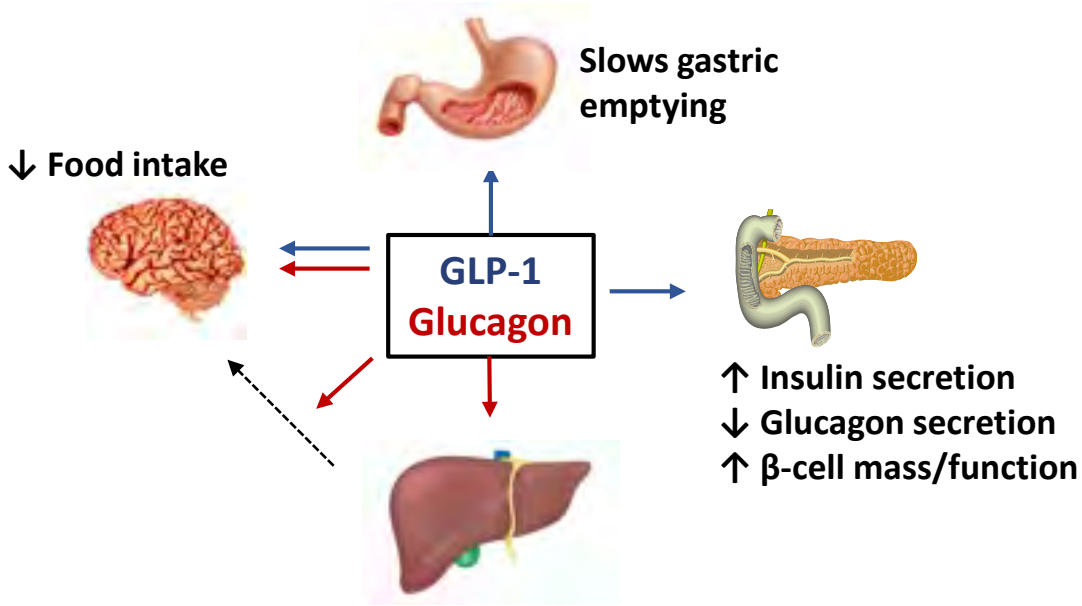
	LS Mean Difference Resmetirom 80 mg from PBO (95% CI)	LS Mean Difference Resmetirom 100 mg from PBO (95% CI)
Estradiol, ng/L (female)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	15.9 (-1.3, 33.1)	28.8 (11.3, 46.3)
Estradiol, ng/L (male)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	9.0 (6.3, 11.8)	11.2 (8.4, 13.9)
FSH, mIU/mL (female)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	0.79 (-1.1, 2.7)	2.0 (0.02, 3.9)
FSH, mIU/mL (male)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	1.1 (0.57, 1.6)	1.7 (1.1, 2.2)
LH, mIU/mL (female)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	-0.33 (-1.8, 1.2)	1.4 (-0.11, 2.9)
LH, mIU/mL (male)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	1.8 (1.1, 2.4)	2.0 (1.4, 2.7)
Testosterone, ug/L (female)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	0.15 (0.10, 0.19)	0.19 (0.14, 0.23)

	LS Mean Difference Resmetirom 80 mg from PBO (95% CI)	LS Mean Difference Resmetirom 100 mg from PBO (95% CI)
Testosterone, ug/L (male)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	2.2 (1.6, 2.8)	3.0 (2.5, 3.6)
Free testosterone, nmol/L (female)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	0	0
Free testosterone, nmol/L (male)		
no.		
Baseline mean (SD)		
Week 52 CFB (SE)	0.02 (0, 0.04)	0.01 (-0.01, 0.03)
SHBG, nmol/L		
no.		
Baseline mean (SD)		
Week 52 %CFB (SE)	148.5 (126.6, 170.4)	208.4 (186.3, 230.5)
Week 52 CFB (SE)	58.9 (50.3, 67.5)	79.4 (70.7, 88.1)
SHBG, nmol/L (female)		
no.		
Baseline mean (SD)		
Week 52 %CFB (SE)	177.4 (144.3, 210.5)	236.2 (202.3, 270.0)
Week 52 CFB (SE)	73.3 (60.3, 86.2)	93.2 (79.9, 106.5)
SHBG, nmol/L (male)		
no.		
Baseline mean (SD)		
Week 52 %CFB (SE)	107.3 (83.4, 131.2)	173.3 (149.4, 197.2)
Week 52 CFB (SE)	40.4 (31.4, 49.4)	59.3 (50.3, 68.3)

S.A. Harrison. N Engl J Med 390;6 nejm.org February 8, 2024.

Pemvidutide (1:1) – Efinopegdutide (2:1) – Cotadutide (5:1) – Survodutide (8:1)



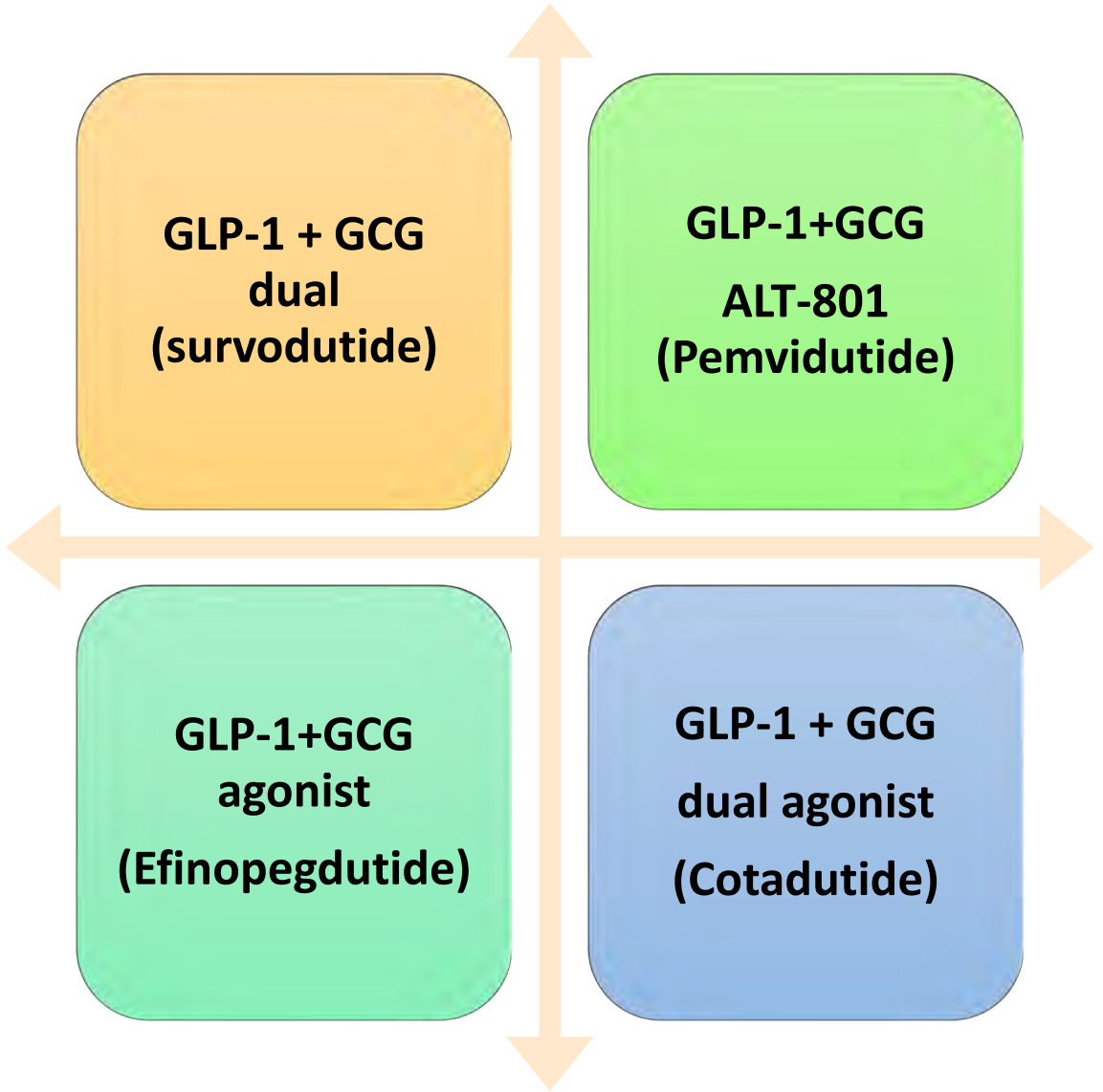


↑ Glucose, FGF21, bile acid production
↑ TG lipolysis, Fatty acid oxidation, ketogenesis
↓ Hepatic *de novo* lipogenesis
↑ LDL receptor activity (↓plasma LDL-C)
↑ Energy expenditure (hepatic, brain: SNS, FGF21, BA-FXR)

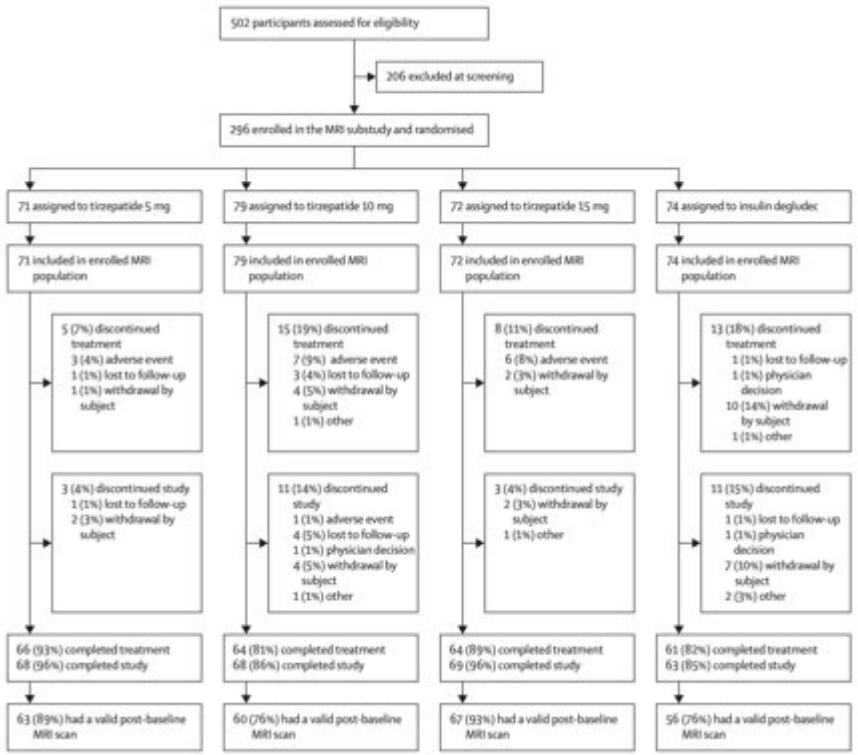
Guarracino DA et al, Chem Rev. 2019 Sep 11;119(17):9915-49; Nestor JJ et al, Peptide Science. 2021;113:e24221
Newsome et al. J Hepatol 2023;79:1557-1565

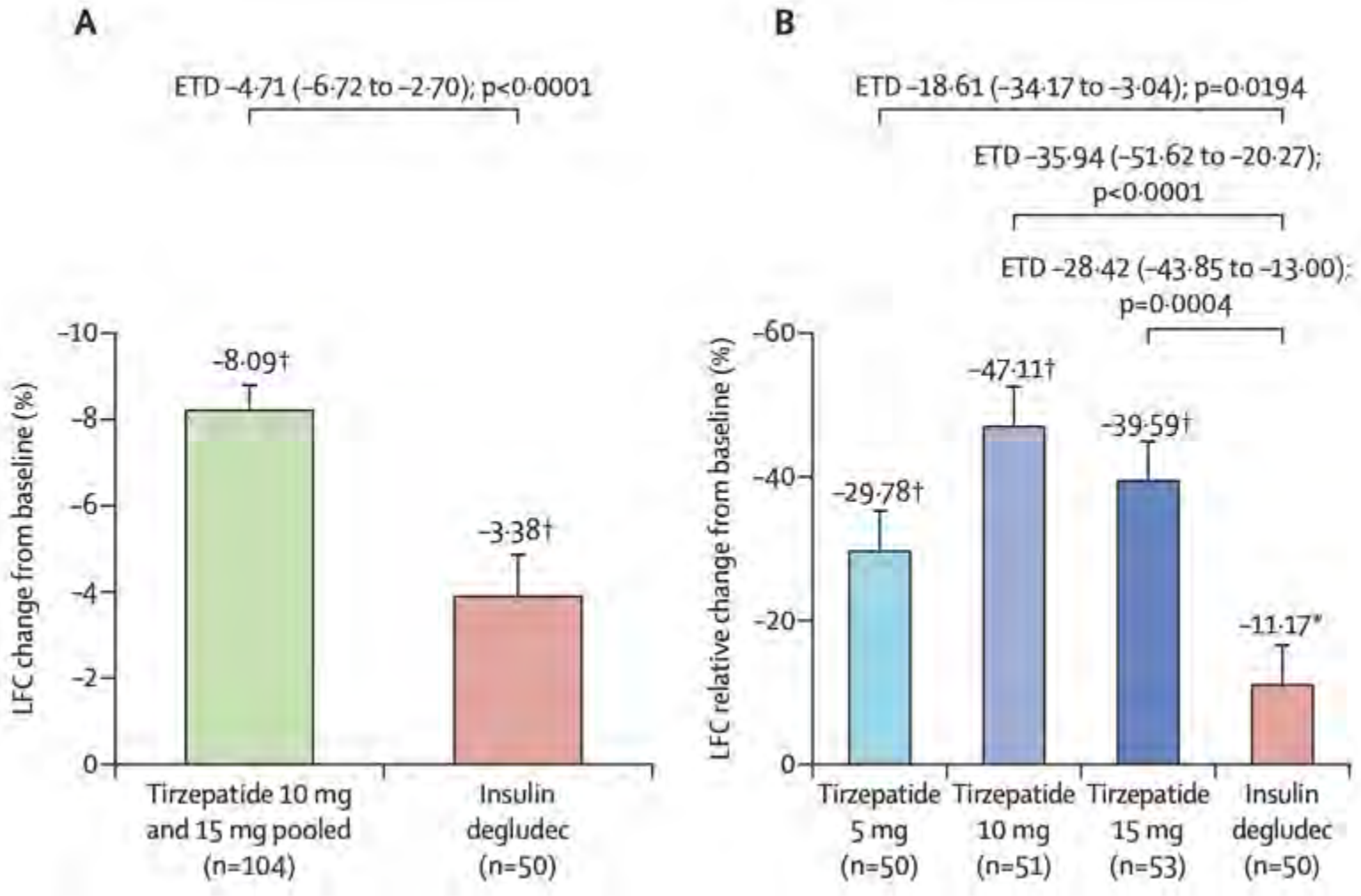
Clinical trials in MASH using dual/triple agonists

GLP-1 + GIP
dual agonist
(Tirzepatide)



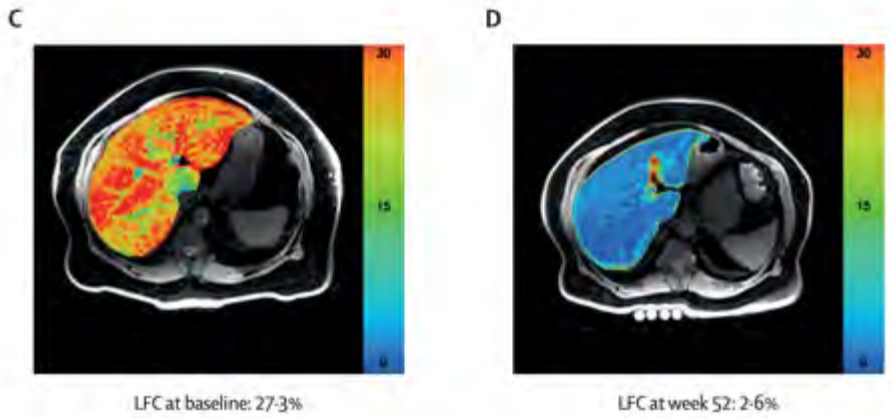
Tirzepatide in MASLD: Removing fat in the liver

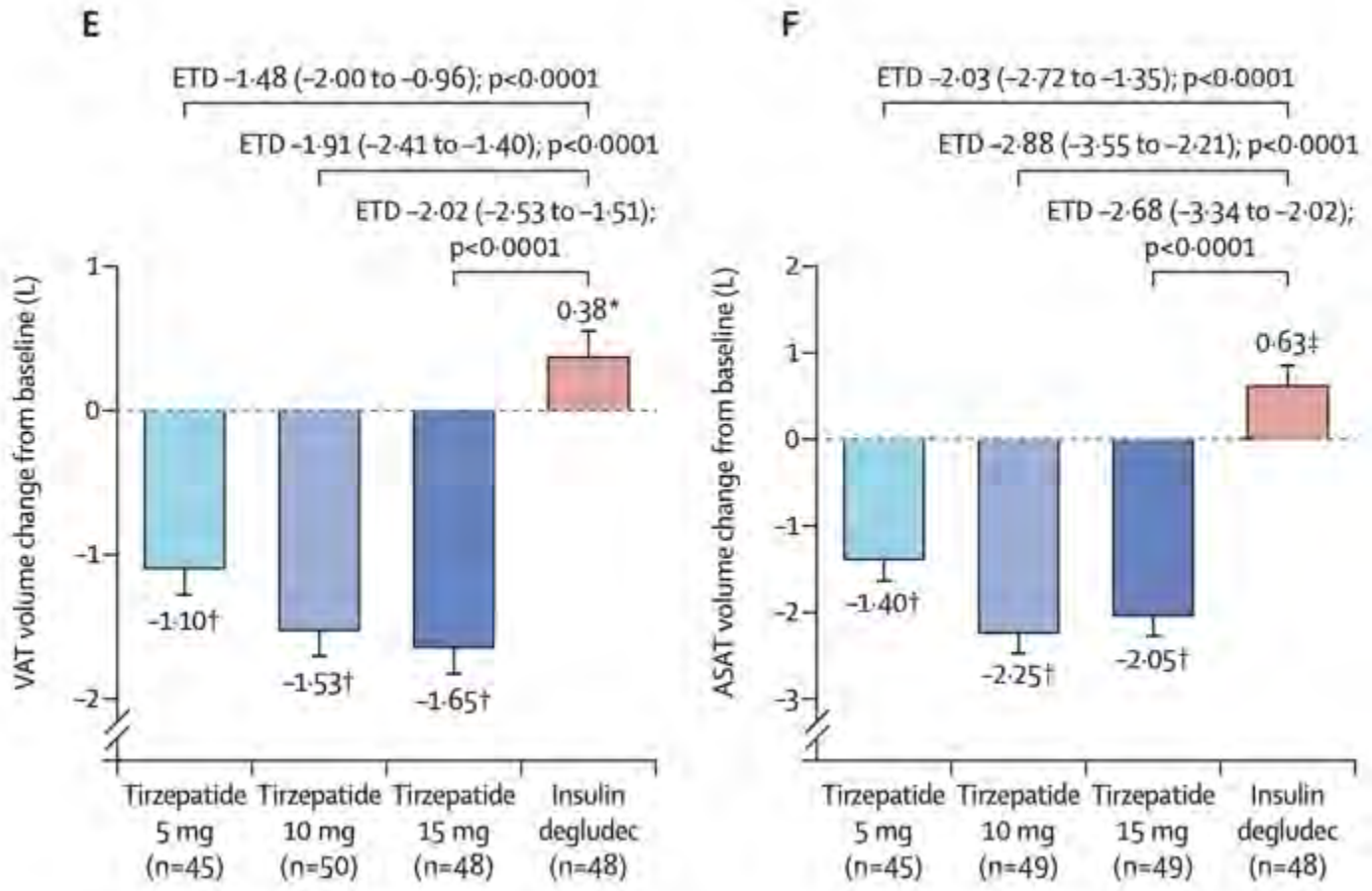




Gastaldelli et al. Lancet Diabetes Endocrinol 2022;10:393-406

Tirzepatide in MASLD: Removing fat in the liver

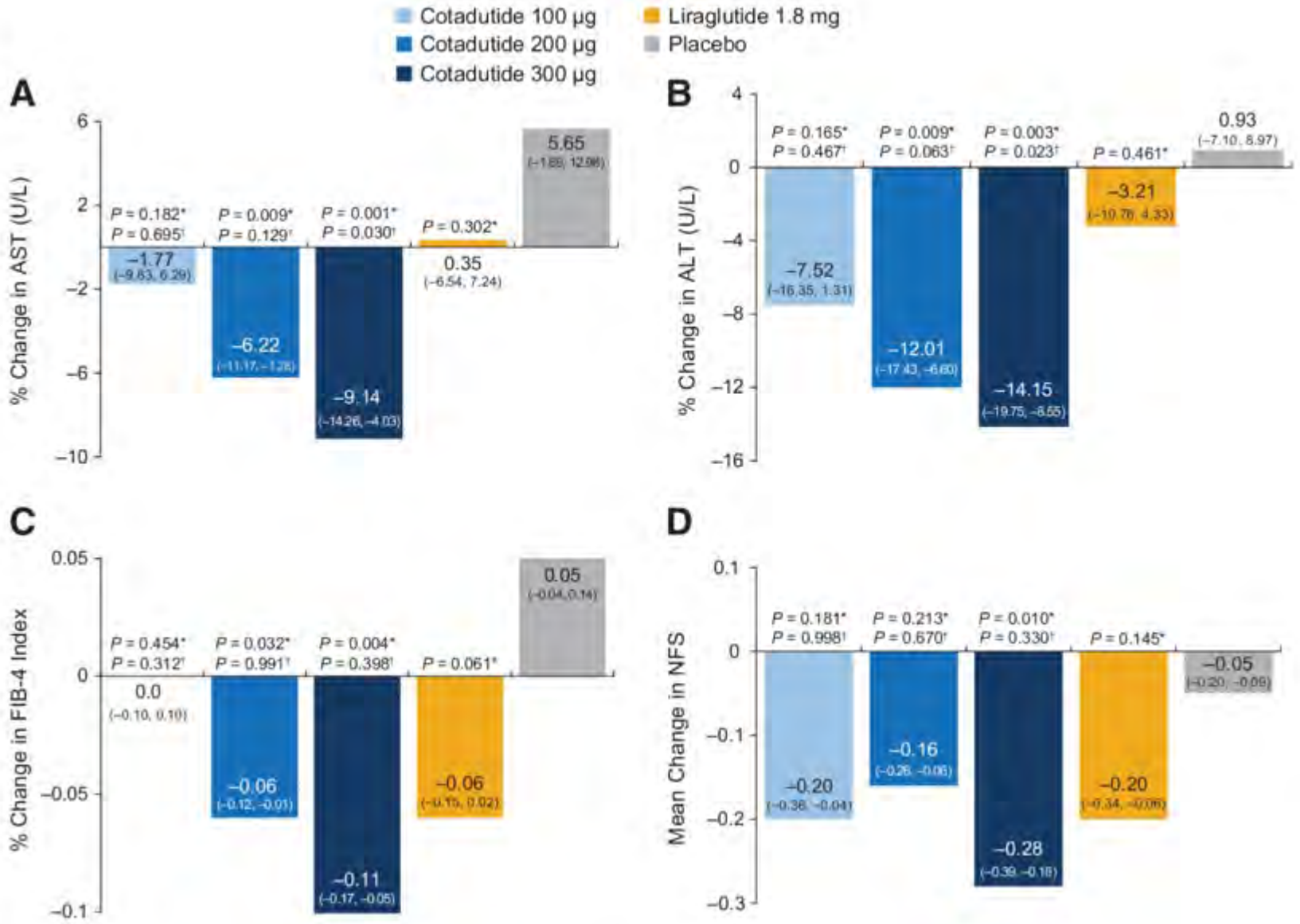




Gastaldelli et al. Lancet Diabetes Endocrinol 2022;10:393-406

N=834

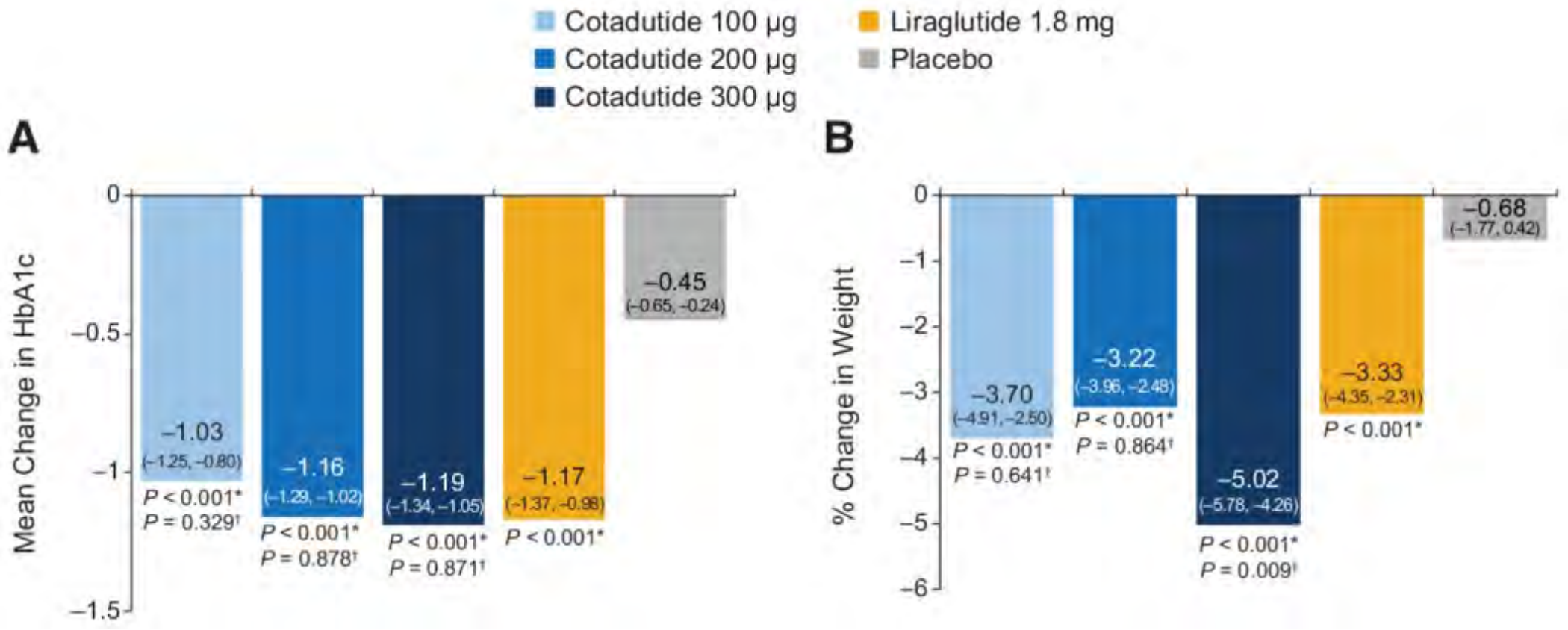
Cotadutide in MASLD: Removing fat in the liver



Nahna et aL. Diabetes care 2021;44:1433-1442

N=834

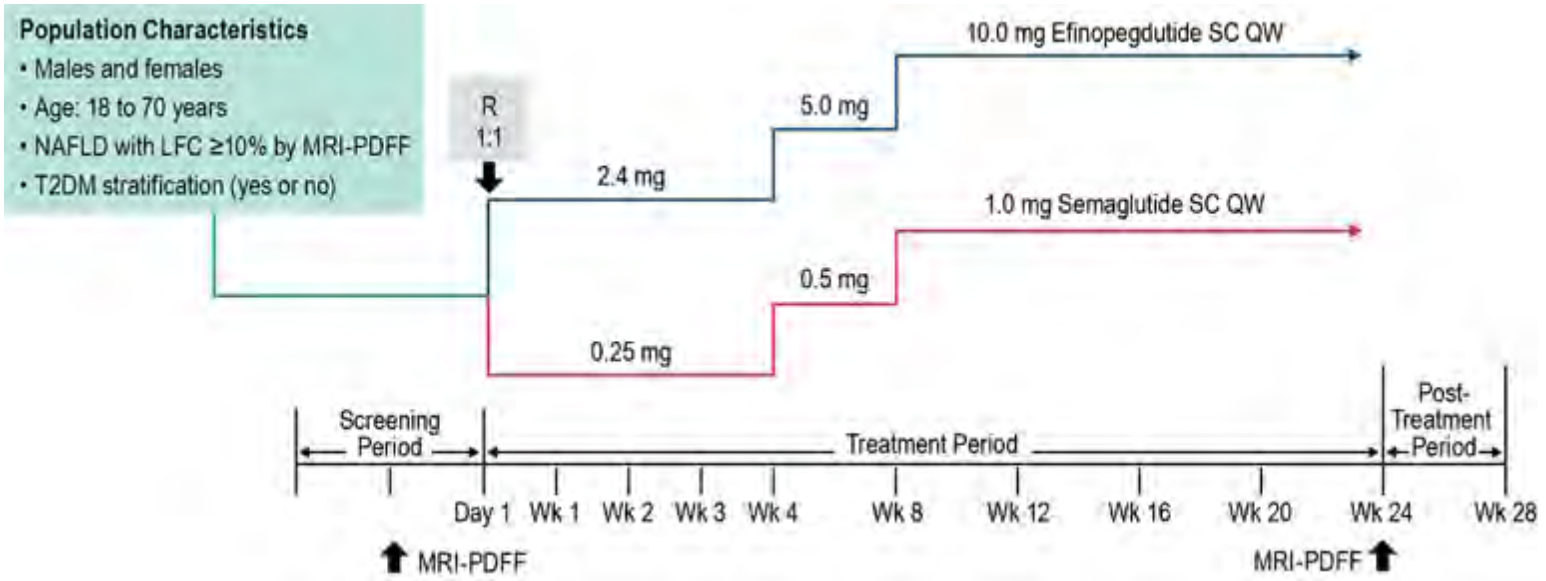
Cotadutide in MASLD: Removing fat in the liver



Nahna et aL. Diabetes care 2021;44:1433-1442

Efinopegdutide and MASLD

- The weight loss associated with GLP-1 agonists has been shown to be associated with decreased hepatic inflammation in patients with MASH
- Glucagon receptor activation has a number of effects that may complement the beneficial effects of GLP-1 receptor agonism for the treatment of MASH
    - Glucagon has been shown to induce weight loss by reducing food intake and increasing energy expenditure
    - Glucagon agonism may also reduce liver fat content (LFC) by acting on the liver directly to stimulate fatty acid oxidation and reduce lipogenesis

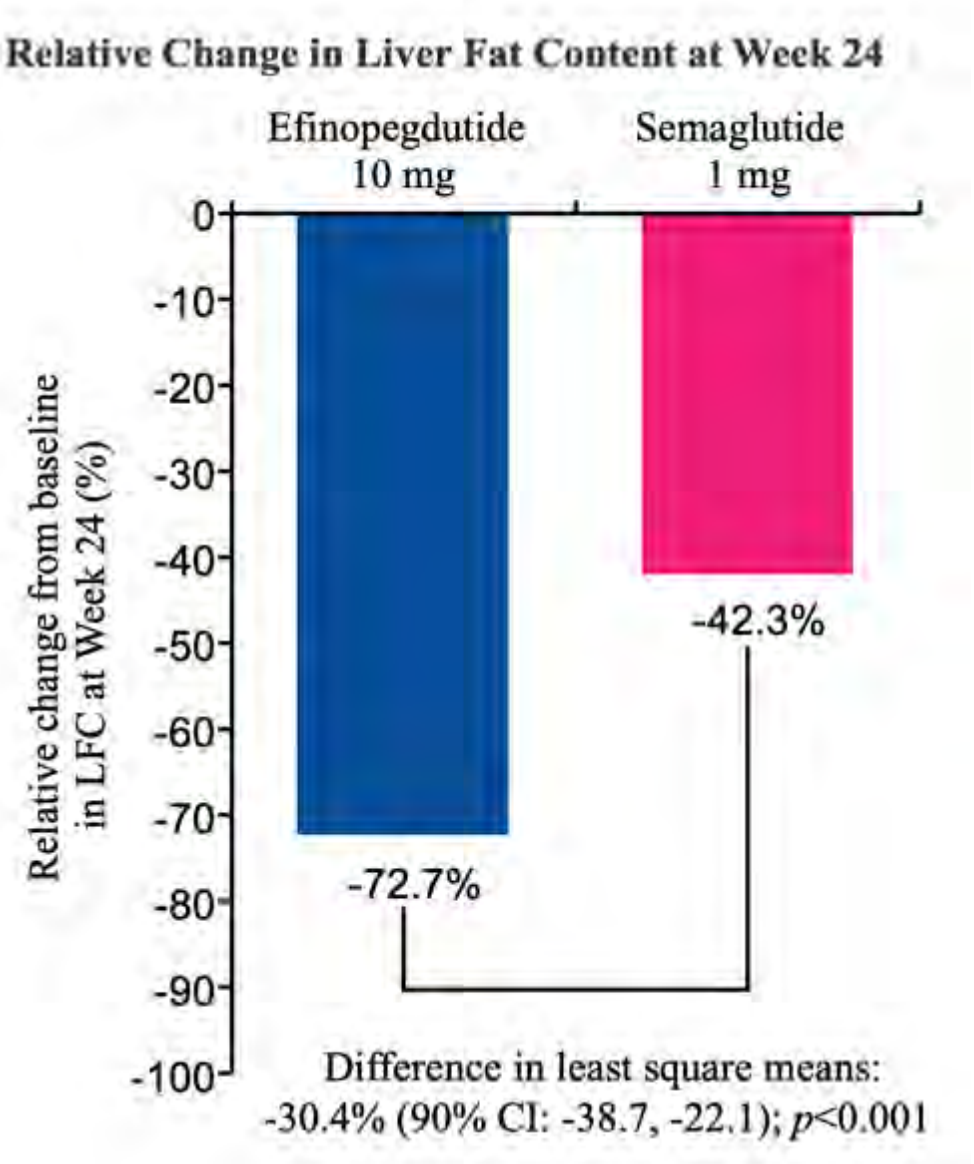


Romero-Gómez et al. J Hepatol 2023

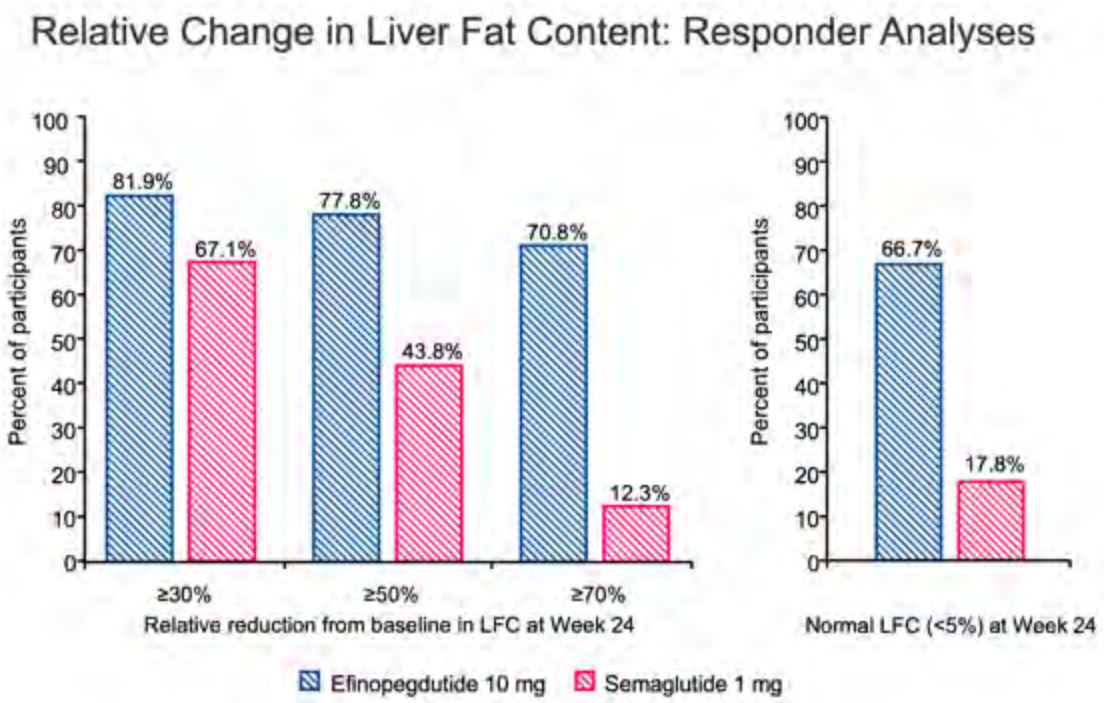
N=145

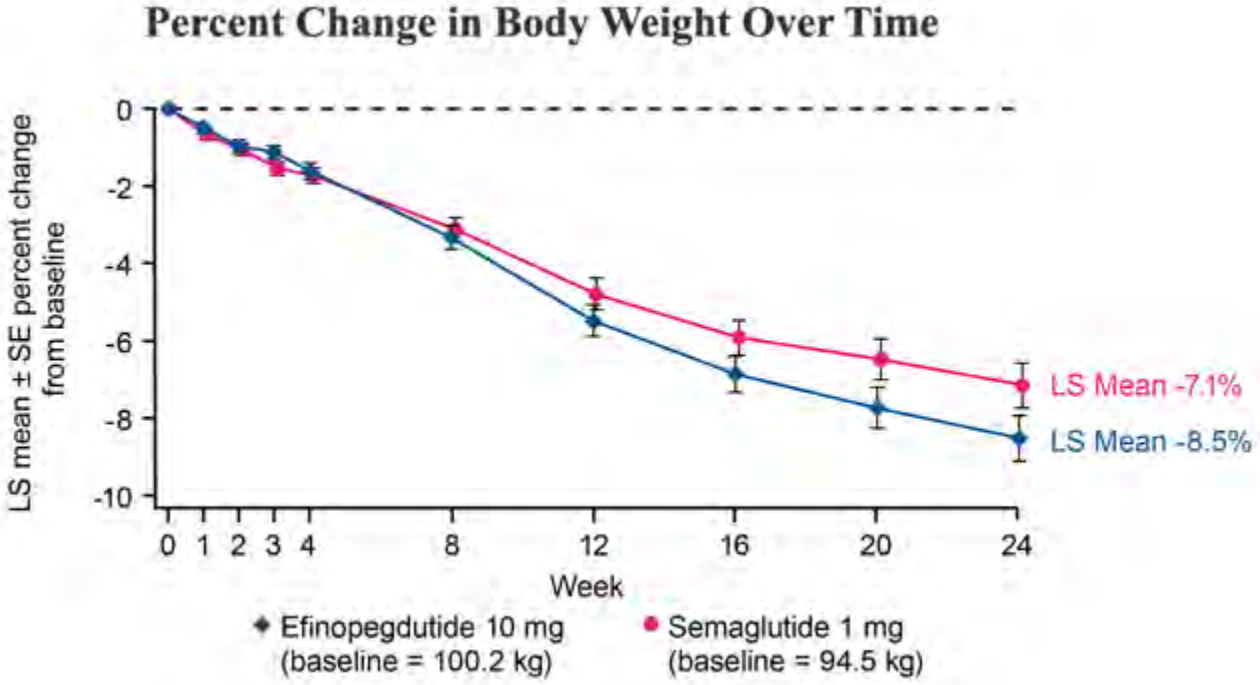
Parameter	Efinopegdutide N=72	Semaglutide N=73
Sex, n (%)		
Male	39 (54.2%)	41 (56.2%)
Race, n (%)		
American Indian	3 (4.2%)	2 (2.7%)
Asian	7 (9.7%)	7 (9.6%)
Black	0	1 (1.4%)
White	62 (86.1%)	63 (86.3%)
Ethnicity, n (%)		
Hispanic Or Latino	25 (34.7%)	26 (35.6%)
Not Hispanic Or Latino	46 (63.9%)	47 (64.4%)
Unknown	1 (1.4%)	0
T2DM, n (%)	24 (33.3%)	24 (32.9%)
Age mean (SD), years	48.1 (11.0)	50.9 (10.9)
BMI mean (SD), kg/m^2	35.2 (5.7)	33.5 (5.0)
Body Weight mean (SD), kg	100.2 (18.9)	94.4 (18.9)
LFC mean (SD), %	21.1 (8.1)	19.4 (8.1)

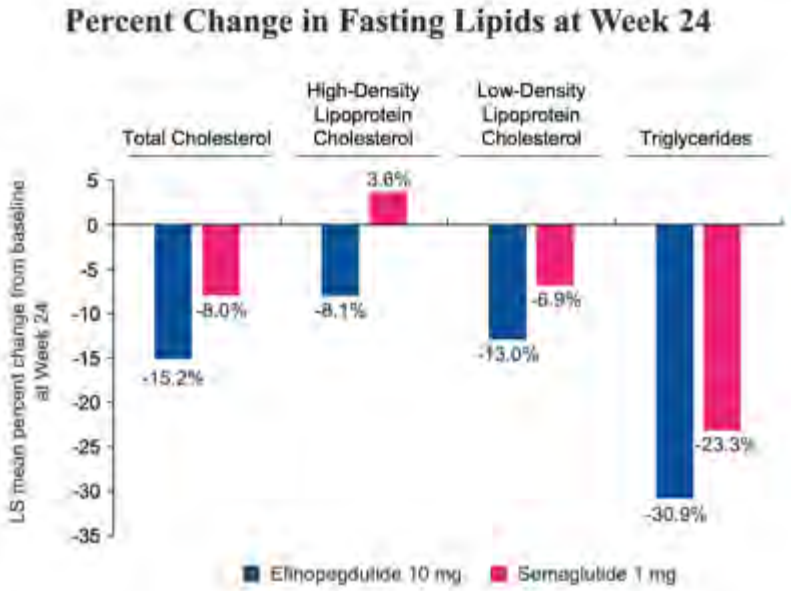
T2DM, type 2 diabetes mellitus; BMI, body mass index; LFC, liver fat content

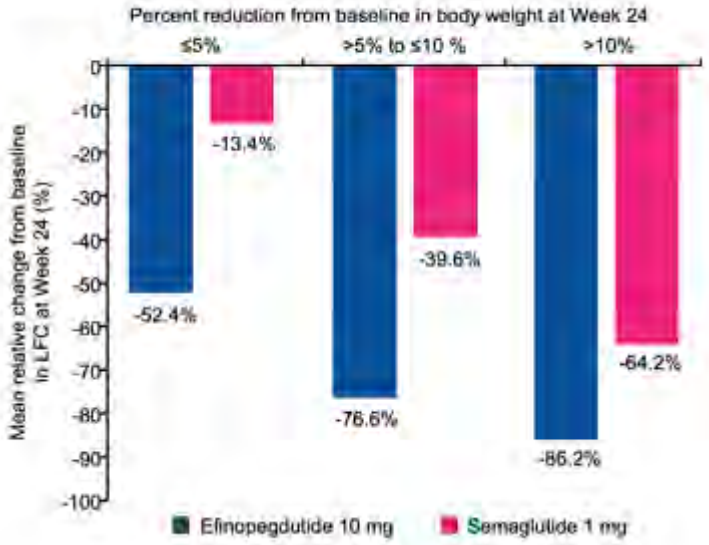


Romero-Gómez et al. J Hepatol 2023









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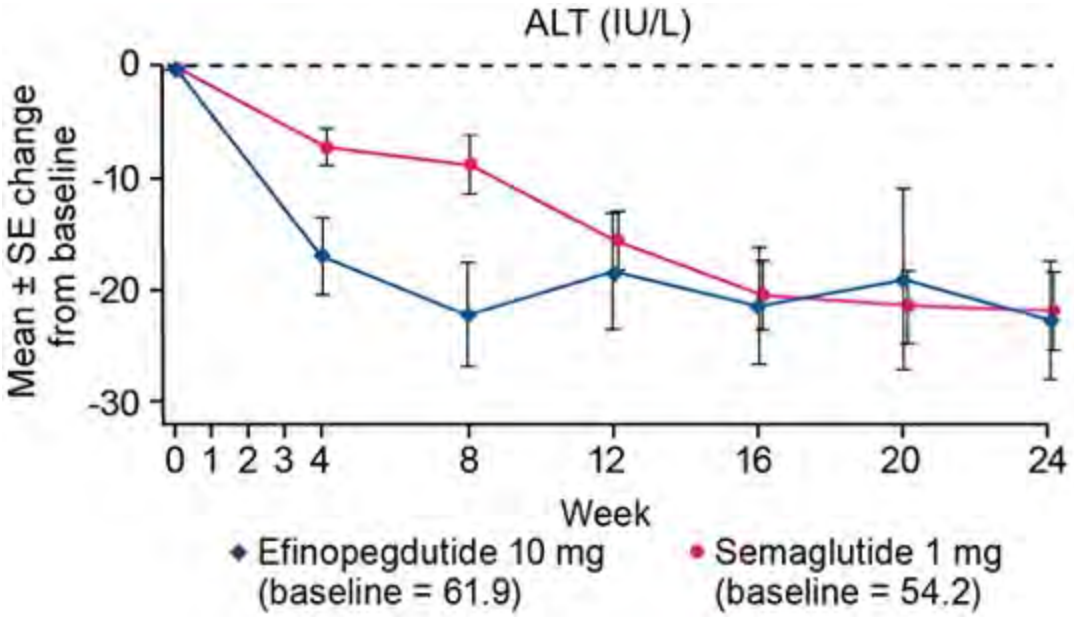
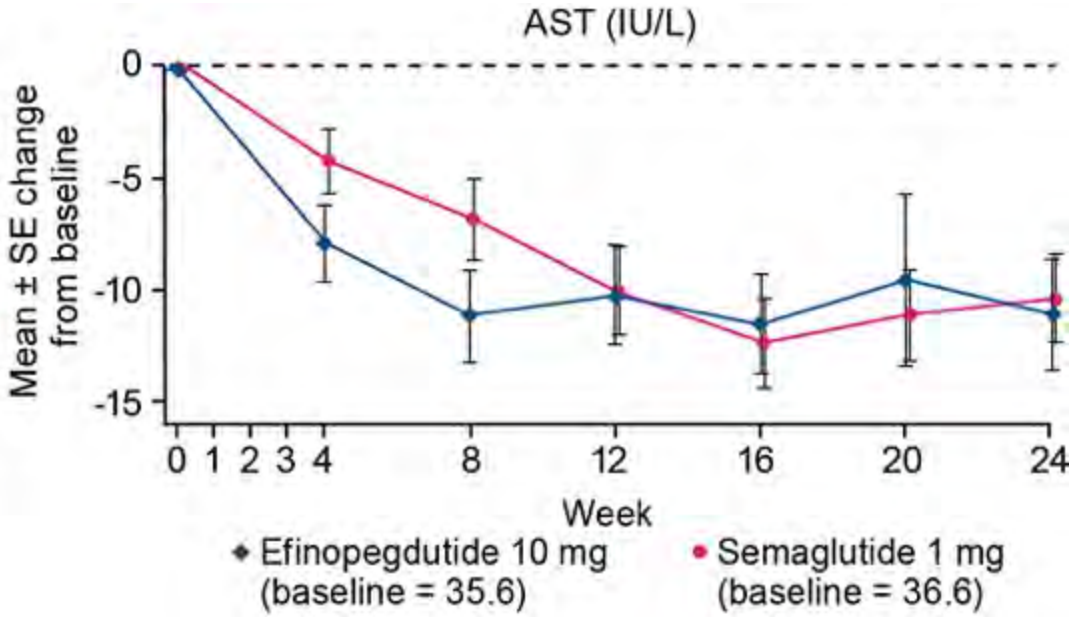
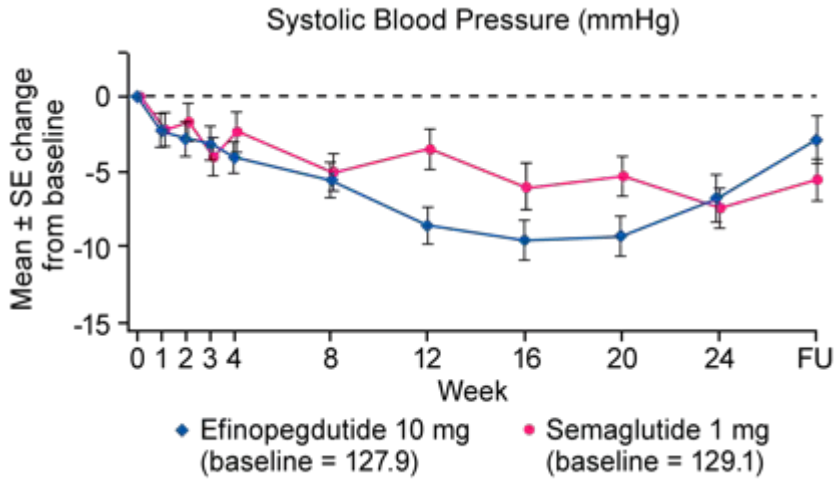
Changes in Liver Transaminases Over Time

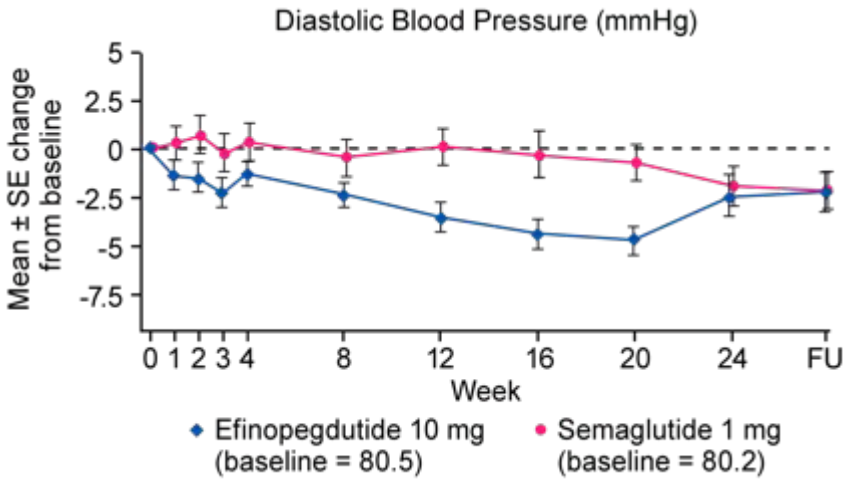




Romero-Gómez et al. J Hepatol 2023

Adverse Events





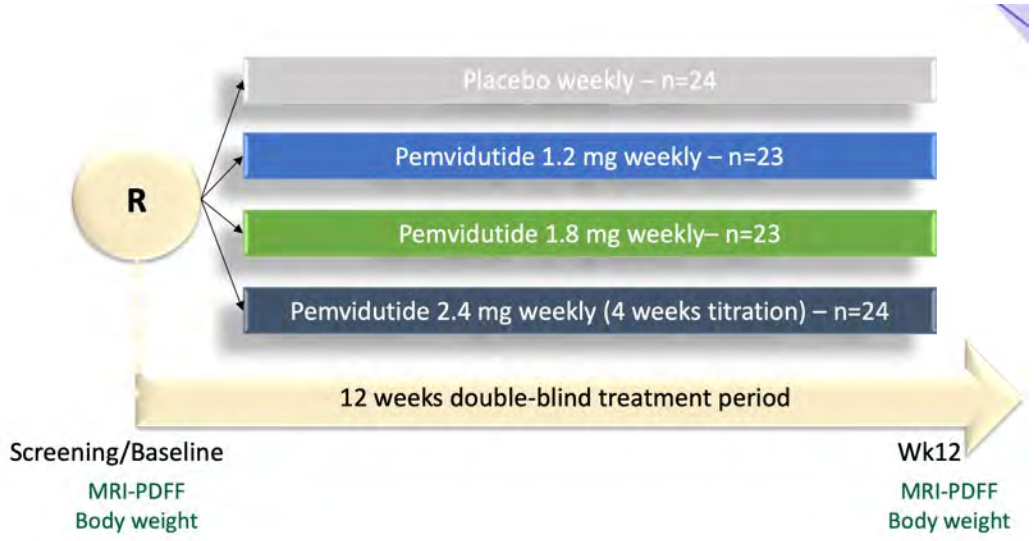
Changes in Blood Pressure Over Time

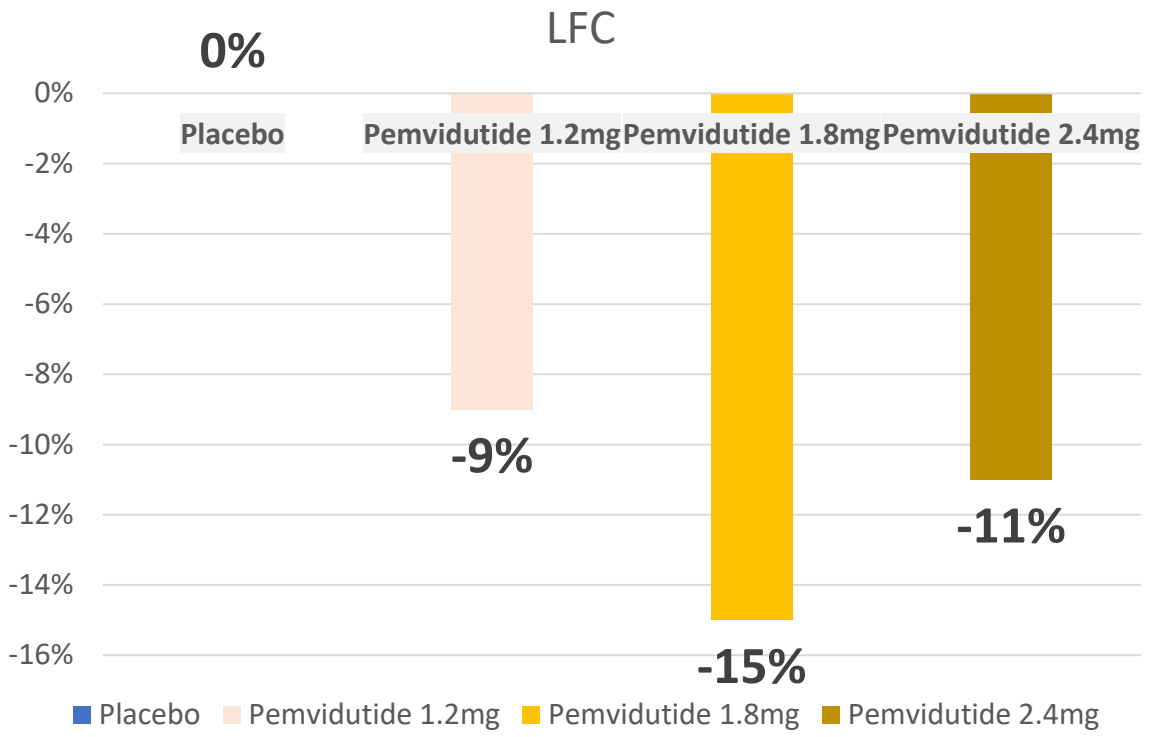
	Efinopegdutide N=72		Semaglutide N=73	
	n	**(%)**	**n**	**(%)**
Adverse events	64	(88.9%)	53	(72.6%)
Drug-related[a] adverse events	46	(63.9%)	35	(47.9%)
Serious adverse events	1	(1.4%)	1	(1.4%)
Serious drug-related adverse events	0		0	
Deaths	0	0	0	
Discontinued drug due to an adverse event	4	(5.6%)	0	
Discontinued drug due to a drug-related adverse event	3	(4.2%)	0	
Discontinued drug due to a serious adverse event	0		0	
Discontinued drug due to a serious drug-related adverse event	0		0	
Gastrointestinal adverse events	41	(56.9%)	38	(52.1%)
Abdominal pain	9	(12.5%)	2	(2.7%)
Constipation	12	(16.7%)	4	(5.5%)

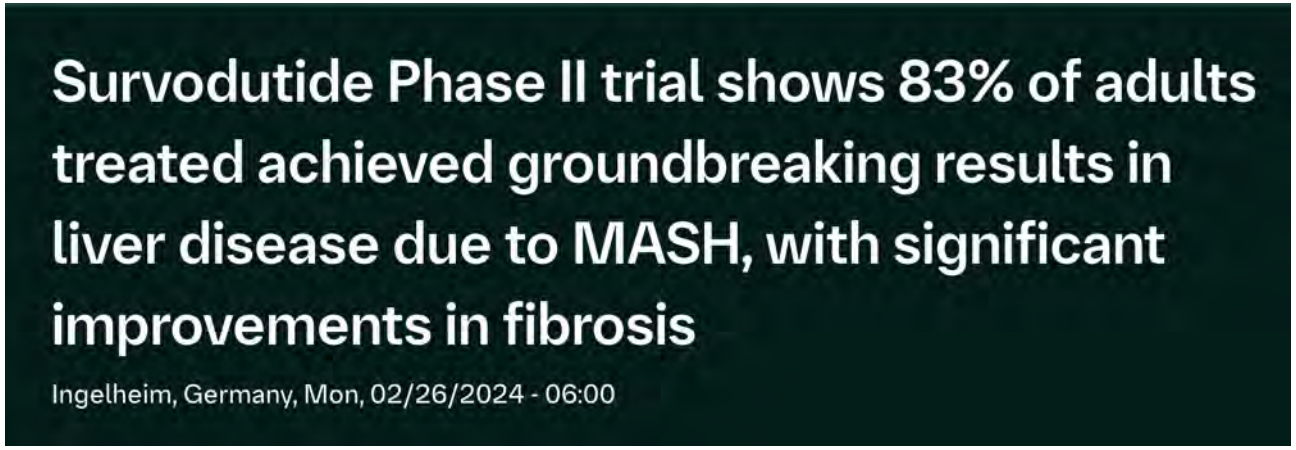
Romero-Gómez et al. J Hepatol 2023

Pemvidutide – NASH Phase 1b NAFLD Study Design

KEY ELIGIBILITY CRITERIA
Liver Fat Content (PDFF) ≥ 10%





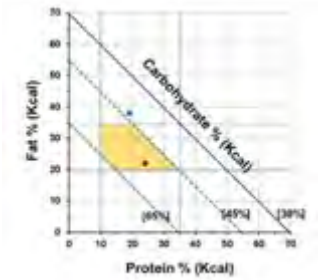


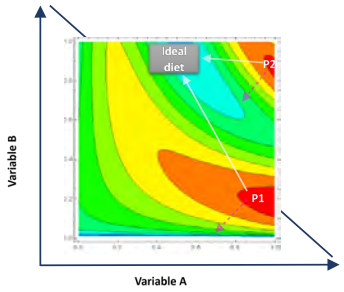
Boehringer Ingelheim today announced that up to **83.0%** of adults treated with survodutide (BI 456906) achieved a statistically significant improvement of metabolic dysfunction-associated steatohepatitis (MASH) versus placebo (**18.2%**) in a Phase II trial [response difference: **64.8% (CI 51.1% - 78.6%), p<0.0001].** The trial met its primary endpoint with survodutide reaching a biopsy-proven improvement in MASH after 48 weeks, without worsening of fibrosis stages F1, F2 and F3 (mild to moderate or advanced scarring). Survodutide also met all secondary endpoints, including a statistically significant improvement in liver fibrosis.

https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/survodutide-top-line-results-mash-fibrosis

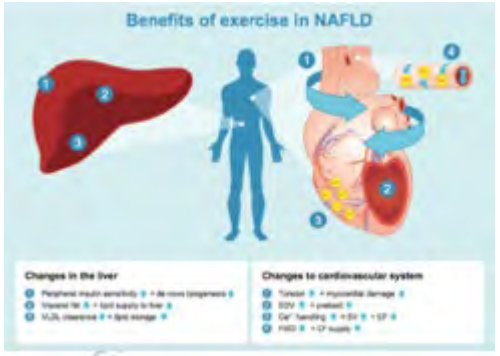
Dietary recommendation
Hypocaloric Mediterranean Diet
Nutritional Geometry

MASLD





LIFE-STYLE INTERVENTION



Aerobic /resistant exercise
150 min/week

RESPONDERS → **Long-term maintenance**

% Weight loss
ALT normalization → **Improvement of Obesity, T2DM, dyslipidemia & AHT**

NON-RESPONDERS → **Drug therapy** → Resmetiron

Lanifibranor
Survodutide
Efinopegdutide
Pegozafermin
Efruxifermin

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Take home message

1. Weight loss is a major target in MASLD-MASH
2. LSI, drugs and bariatric endoscopy/surgery could reach this goal.
3. Pan-PPAR agonist Lanifibranor promoted NASH resolution and improvement of fibrosis in Phase II trials.
4. Semaglutide promote weight loss and MASH resolution but not fibrosis regression
5. Dual agonists GLP1 and GCG promoted larger weight loss and fat removal in the liver with potential improvement of MASH and fibrosis.
6. Resmetiron has been approved for MASH-fibrosis by FDA.
7. Precision medicine and innovative trial designs together with combination therapy might help to improve the overall efficacy and efficiency of treatments for MASLD.

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