
2023 SCSG
GI SYMPOSIUM

Update on Novel NASH Treatments and the Clinical Trial Data

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Disclosures

Research / Grants to Institution		
• Hanmi	• Genfit Pharmaceuticals	• Inventiva
• Gilead Sciences	• Galactin	• Intercept
• TaiwanJ	• Galmed	• NGM Biopharma
• Bristol Meyers Squibb	• Conatus	• Madrigal
• Boeringher-Ingelheim	• Enyo	• Allergan
• Progenity	• Genentech	• TARGET-NASH
• Durect	• NovoNordisk	• Poxel
• Viking	• Astra Zeneca	
Consultant/ Scientific Advisory Board		
• Brstol Meyers Squibb	• Inventiva	• Interecept
• NGM Biopharma	• Hanmi Pharma	• NovoNordisk
• SonicIncytes	• Theratherapeutics	• Madrigal
Speaker's Bureau/ Education		
• MedScape	• Terra Firma, LLC	• Fishawack, Inc
• Simply Speaking NASH	• Clinical Care Options	• Chronic Liver Disease Foundation

No off-label use of pharmaceutical products will be discussed.

LEARNING OBJECTIVE

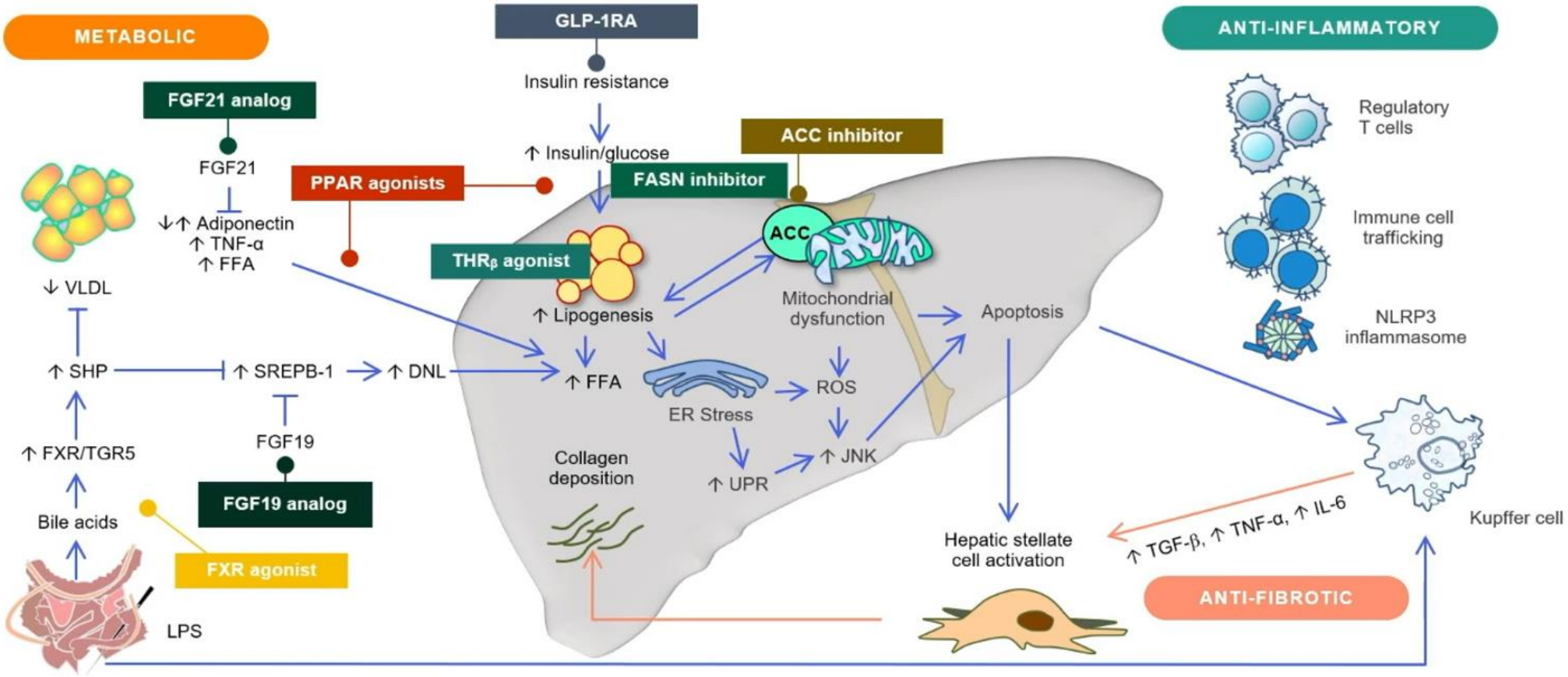
- Discuss the goals of pharmacotherapy for NASH
- Review the landscape of emerging therapies
- Discuss therapies currently in phase 3 clinical studies:
  - FXR agonist (obeticholic acid)
  - Thyroid hormone receptor β agonist (resmetirom)
  - Pan-PPAR (lanifibranor)
  - GLP-1 receptor agonist (semaglutide)

# of NASH Treatment

- Prevent, arrest, or reverse *liver fibrosis—the* primary predictor of liver-related clinical outcomes
- *Liver-directed pharmacotherapy* should generally be limited to those with biopsy-proven NASH and clinically significant fibrosis (i.e., ≥ F2 stage)
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes
- Eventually improve liver-related morbidity/mortality

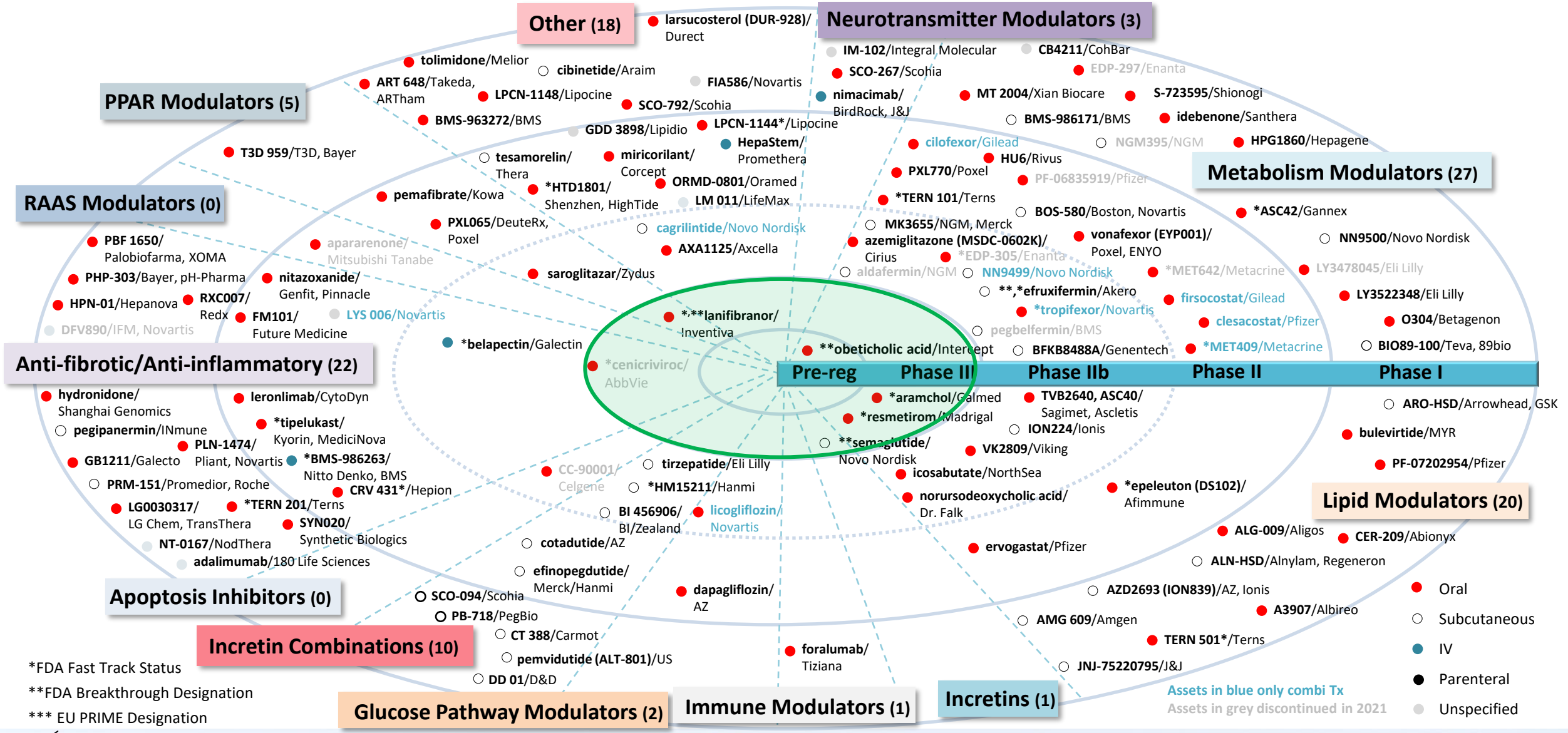
Chalasani N, et al. *Hepatology*. 2018;67328-35.

NAFLD/NASH: Potential Therapeutic Targets



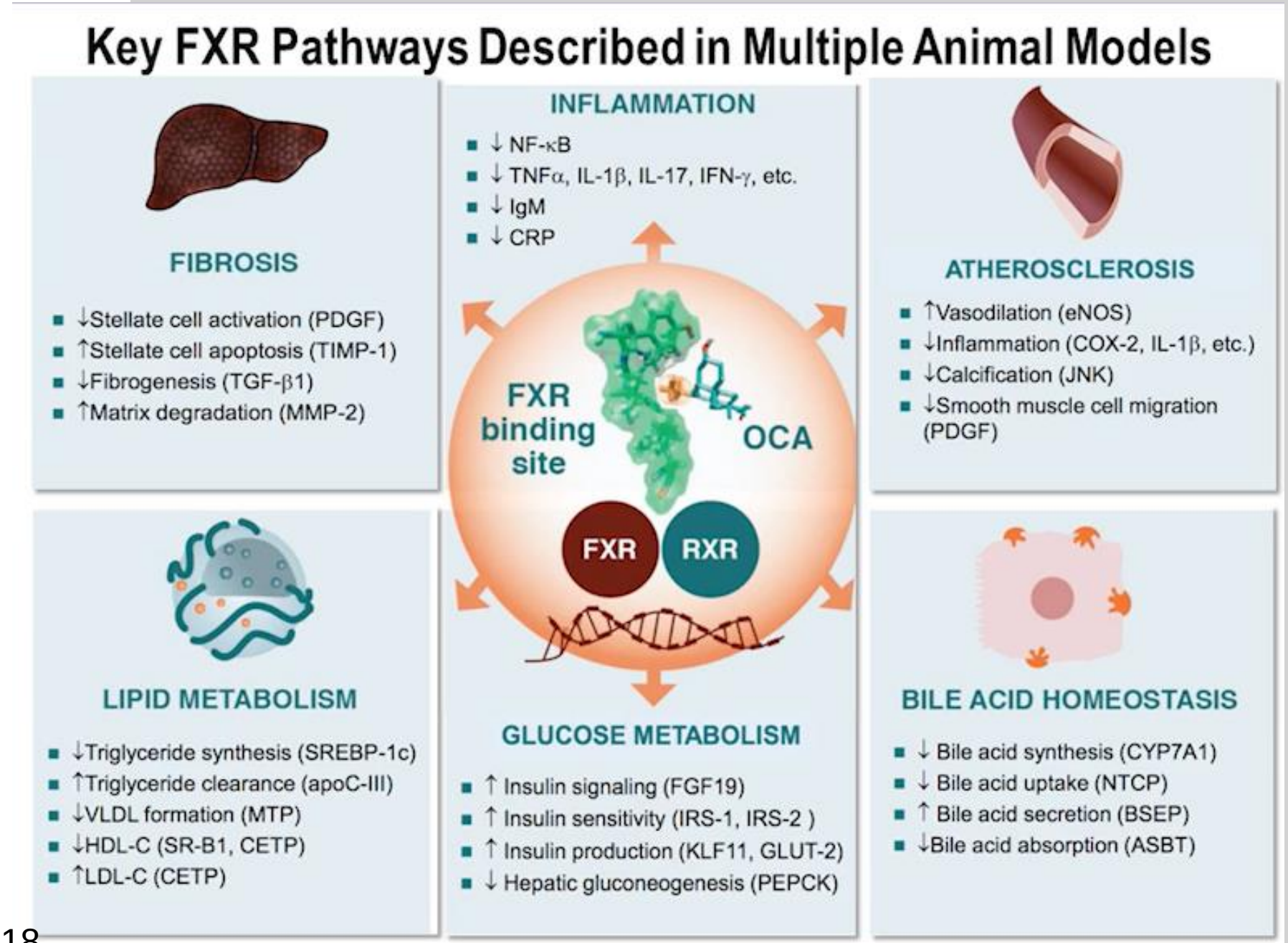
Adapted from Kronerman MA et al. J Hepatol. 2018.

Agents in development for NASH in US, EU, and Japan – Phase I-III



FXR Agonists

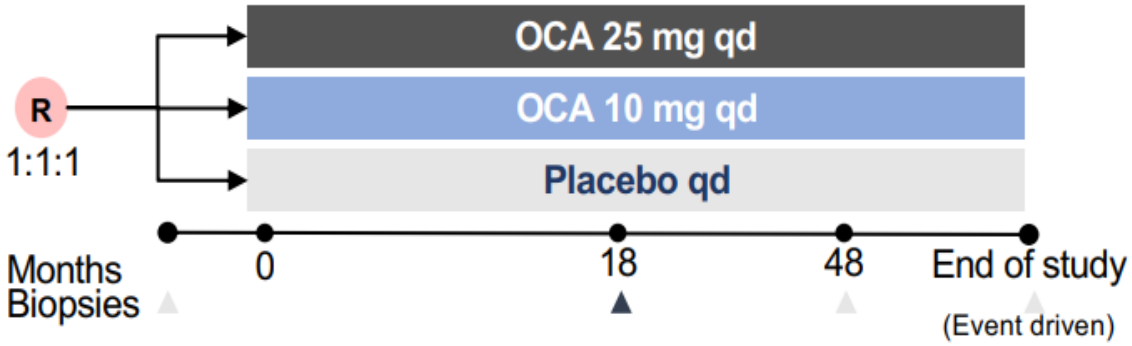
Obeticholic acid (OCA)
under FDA review



West R et al. J Hep. 2017;
Gawrieh S, et al. Clin Liv Dis. 2018.

New Analysis of Topline Results of REGENERATE: OCA for the treatment of NASH

- **REGENERATE:** Phase 3 study of 2477 patients with NASH

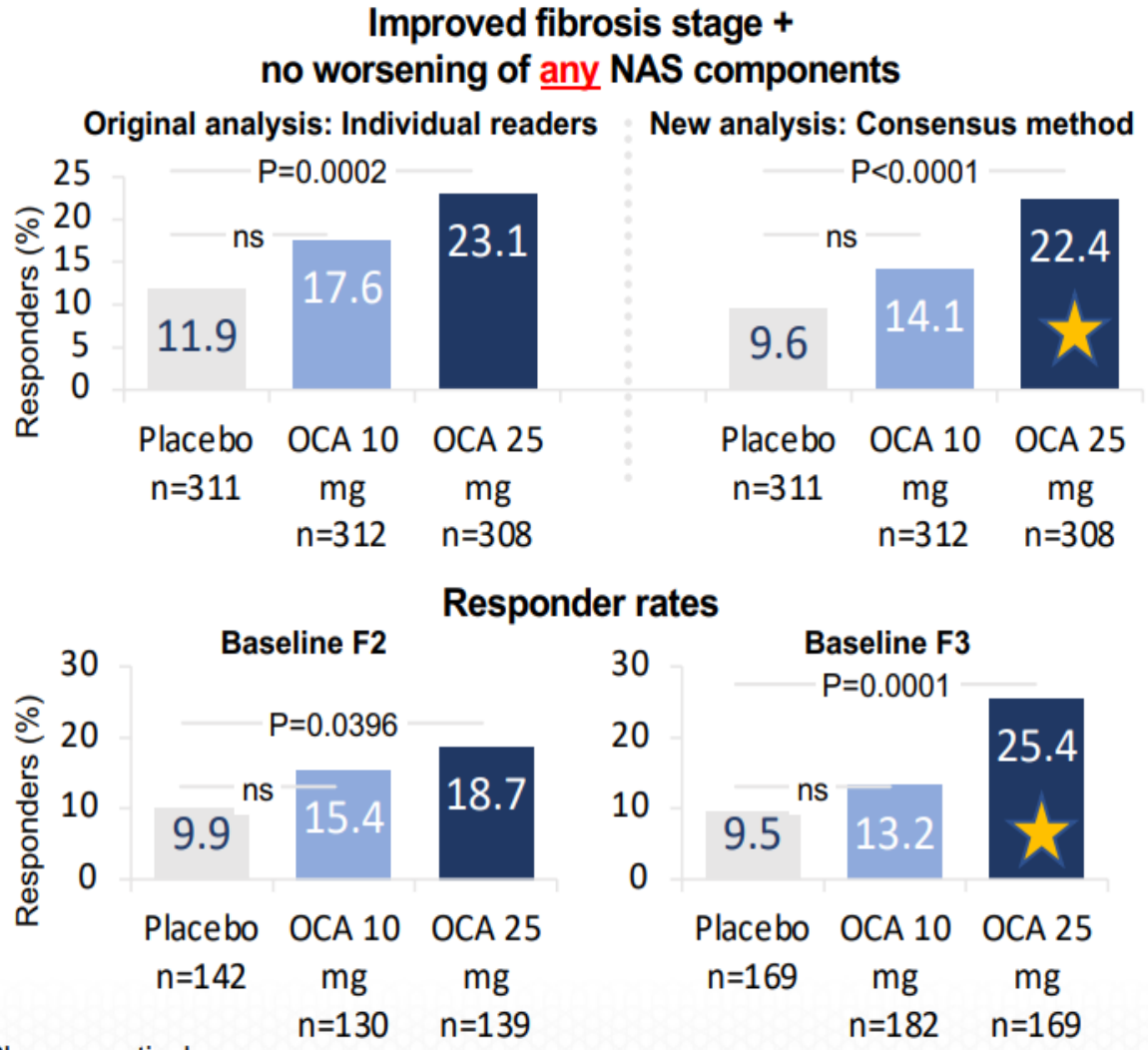


Planned Month 18 interim analysis
Primary endpoints

Fibrosis improvement by ≥1 stage and no worsening of NASH or **NASH resolution and no worsening of fibrosis**

- Reread of 931 M18 biopsies using consensus methodology

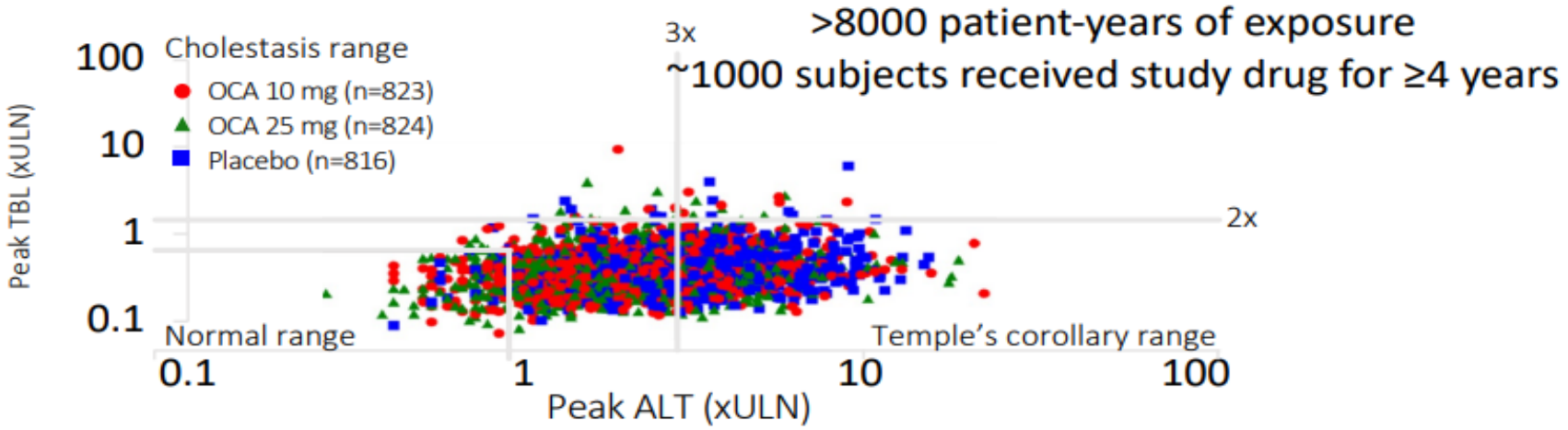
2019: Central pathologist read vs. 2022: Consensus panel read



Sanyal AJ, et al. AASLD 2022. Late-breaking oral #5008. Sponsored by Intercept Pharmaceuticals

New Analysis of Topline Results of REGENERATE: OCA for the treatment of NASH

eDISH plot of total bilirubin vs ALT



Hy's law range
Placebo = 7
OCA 10 mg = 6
OCA 25 mg = 6

	Placebo n=825	OCA 10 mg n=825	OCA 25 mg n=827
Deaths	8 (1.0)	9 (1.1)	10 (1.2)
TEAEs	766 (92.8)	795 (96.4)	807 (97.6)
Serious TEAEs	181 (21.9)	204 (12.4)	216 (26.1)
TEAEs leading to d/c of IP	93 (11.3)	**102 (33.2)**	**179 (21.6)**
Most frequent TEAE: pruritus	200 (24.2)	274 (33.2)	453 (54.8)
TEAE leading to IP d/c	8 (1.0)	**14 (1.7)**	**93 (11.2)**

Sanyal AJ, et al. AASLD 2022. Late-breaking oral #5008. Sponsored by Intercept Pharmaceuticals

New Analysis of Topline Results of REGENERATE: OCA for the treatment of NASH

No increase in adjudicated MACE

Adjudicated liver injury was mostly mild-to-moderate and most cases were unrelated to OCA

	Placebo n=825	OCA 10 mg n=825	OCA 25 mg n=827
All TEAEs			
Gallbladder disease	33 (4.0)	43 (5.2)	63 (7.6)
Serious AEs			
Gallbladder disease	6 (0.7)	8 (1.0)	21 (2.5)
Pancreatitis	4 (0.5)	5 (0.6)	6 (0.7)
Hyperglycemia/diabetes	1 (0.1)	3 (0.4)	9 (1.1)
Diabetic ketacidosis	1 (0.1)	2 (0.2)	2 (0.2)

Data are n (%)

Sanyal A et al. AASLD 2022. Late-breaking oral #5008. Sponsored by Intercept Pharmaceuticals

FDA Public Hearing

Gastrointestinal Drugs Advisory Committee (GIDAC) Meeting [illegible]/19/2023

Table 11.Trial 747-303, Blinded HSAC DILI Assessme[illegible]

Blinded HSAC Assessment Score	OCA 25 mg	(% Within Arm)	Placebo	(% Within Arm)
1 = Definite			0	(0)
2 = Highly likely			0	(0)
3 = Probable			1	(0.6)
4 = Possible		(28.6)	11	(6.8)
5 = Unlikely		(67.3)	150	(92.6)
Total	[illegible]99	(100)	162	(100)

Source: Reviewer genera[illegible]bmitted by the Applicant; blinded HSAC DILI assessments for liver injury events (numbers and percentages within arm[illegible]OCA 25 mg/day and placebo arms.
Abbreviations: DILI, drug-ind[illegible]ced liver injury; HSAC, Hepatic Safety Adjudication Committee; OCA, obeticholic acid

News > Medscape Medical News > FDA Approvals

FDA Advisory Committee Votes Against Approval for NASH Drug

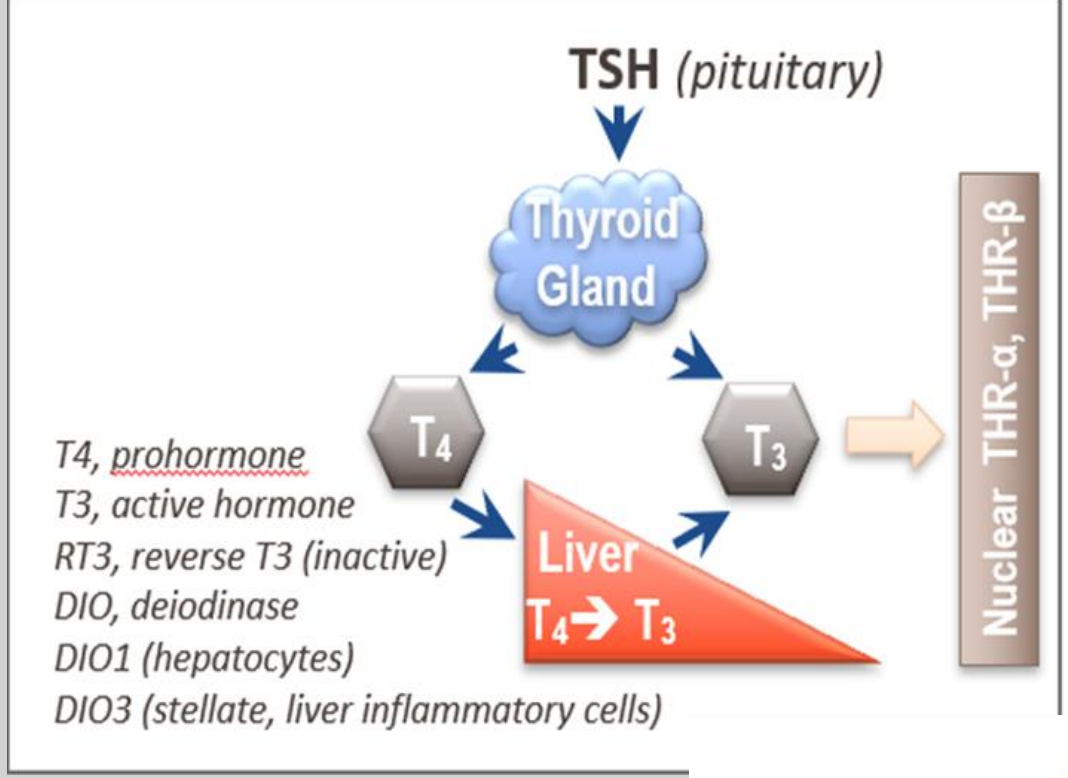
Lucy Hicks
May 19, 2023

www.fda.gov/media/168215/download

Thyroid Hormone β-Receptor Agonist

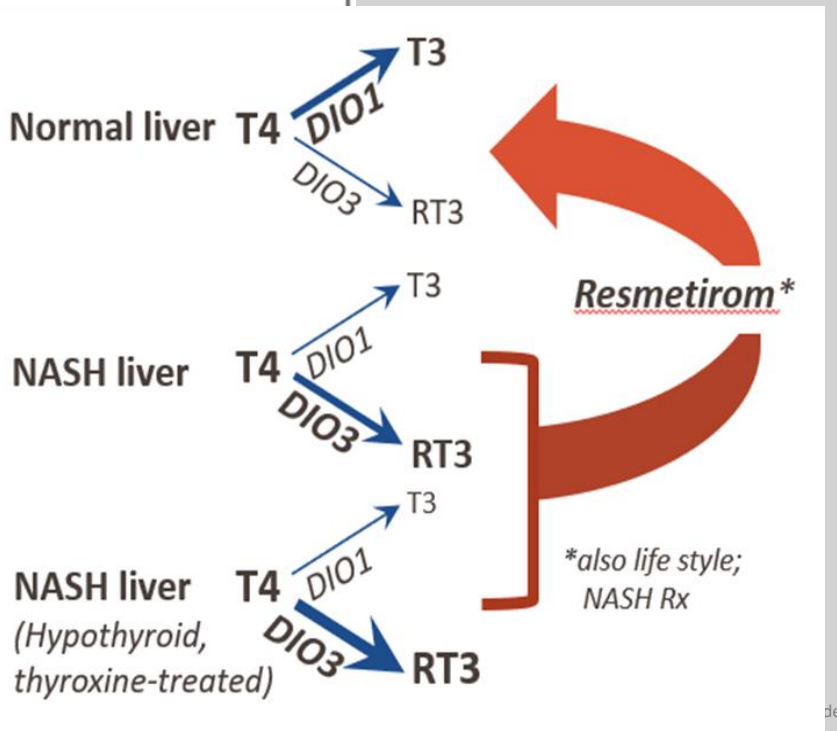
Resmetirom

FDA NDA submission in progress



Correction of intrahepatic hypothyroidism

Normalize T3/RT3 ratio



Resmetirom (THR-β agonist) MEASTRO-NASH Study
Phase 3, placebo-control RTC

Study Design: Randomized, Double-Blind, Placebo Controlled

Inclusion/Exclusion

- ≥3 metabolic risk factors (Metabolic Syndrome)
- FibroScan **kPa consistent with F2-3**
- FibroScan **CAP ≥280**
- **≥8% liver fat** on MRI-PDFF
- **NAS≥4** with fibrosis stage 1A (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, the rest F2

n=966 patients (ongoing)

Patient Characteristics

85% NAS ≥ 5

Fibrosis stage 3: 60%

T2DM= 67%; dyslipidemia 71%; hypertension 78

VCTE kPa = 13 kPa

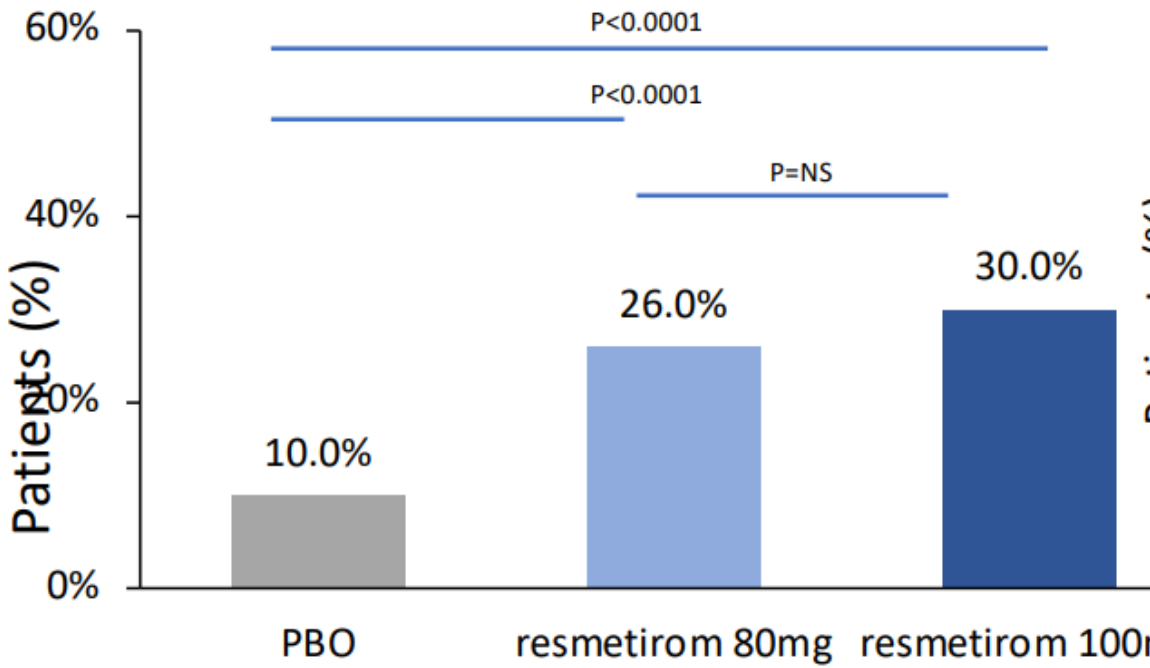
MRI-PDFF = 18%

Madrigal press release: https://ir.madrigalpharma.com/news-releases/news-release-details/positive-topline-phase-3-maestro-nafld-1-data-demonstrate

Efficacy And Safety of Resmetirom vs. PBO In Patients with NASH (MAESTRO-NASH), a Phase 3 Study

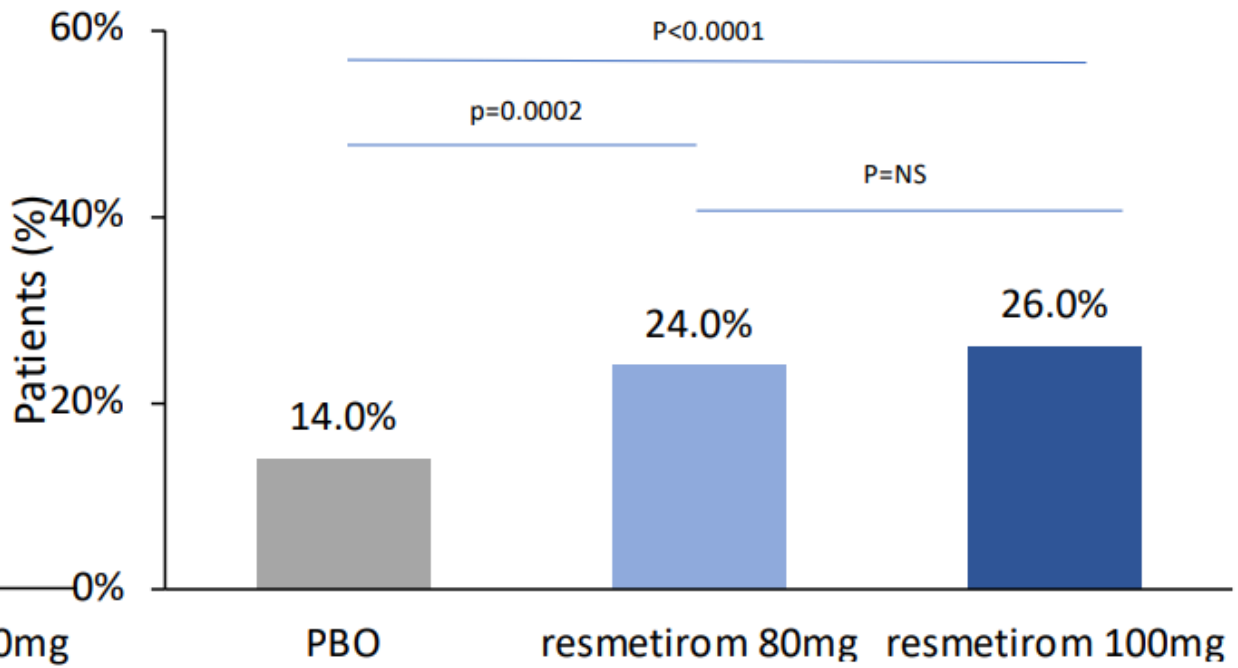
Resolution of NASH and no worsening in liver fibrosis

mITT, n=955, 1:1:1



Improvement in liver fibrosis stage ≥1 and no worsening in steatohepatitis

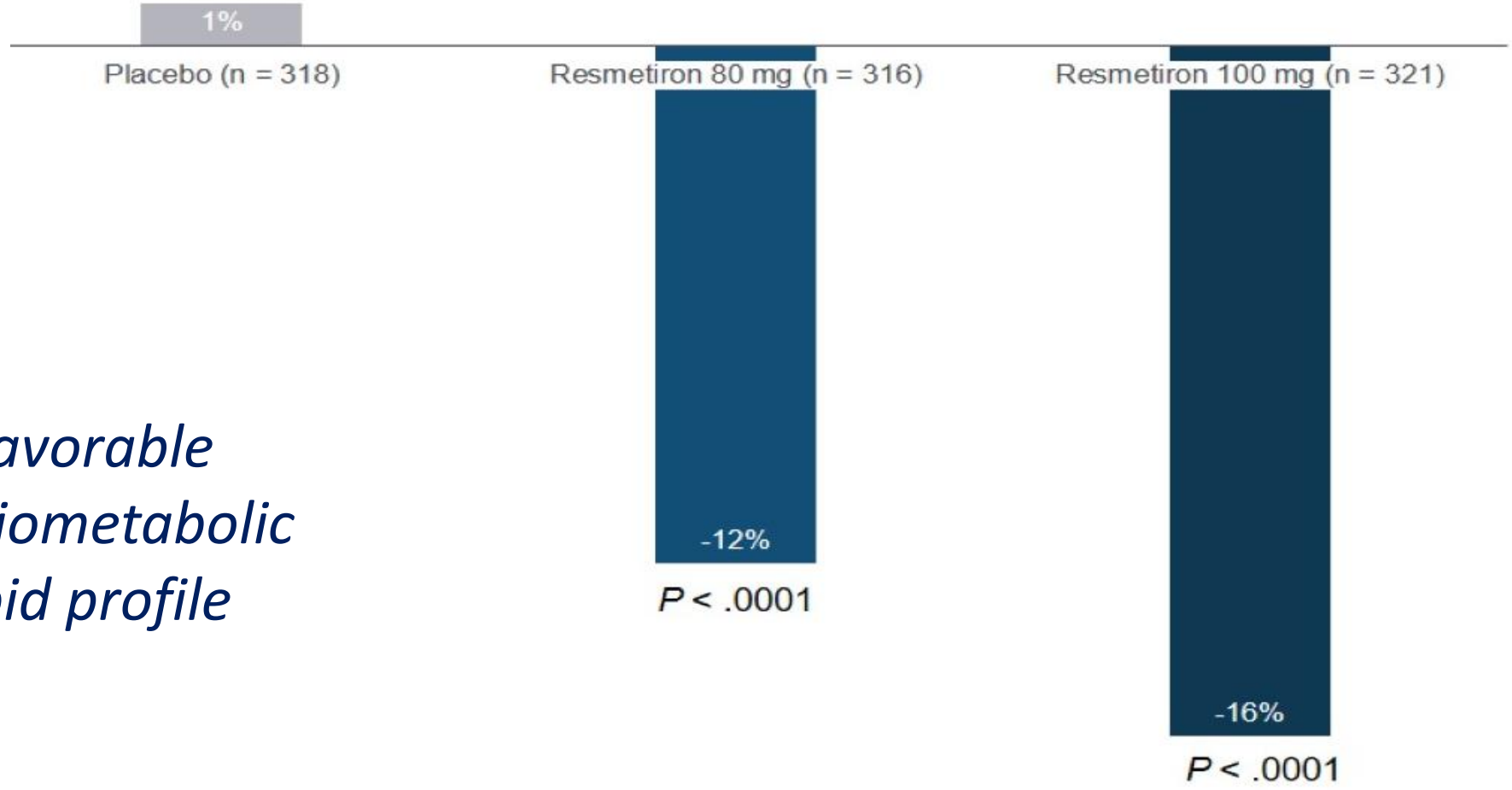
95% with fibrosis Stage 2 or 3 at BL



Madrigal press release: https://ir.madrigalpharma.com/news-releases/news-release-details/positive-topline-phase-3-maestro-nafld-1-data-demonstrate

MEASTRO NASH: Key Secondary Endpoint

LDL Lowering at 24 weeks (ITT)



Favorable cardiometabolic lipid profile

Efficacy And Safety of Resmetirom vs. PBO In Patients with NASH (MAESTRO-NASH), a Phase 3 Study

Safe and well tolerated

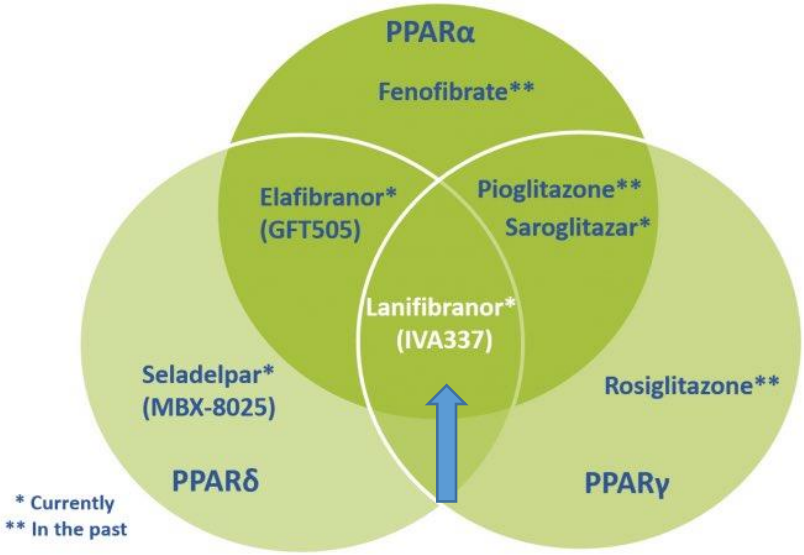
Adverse events consistent with phase 2 study

Transient diarrhea and mild nausea generally at beginning of therapy

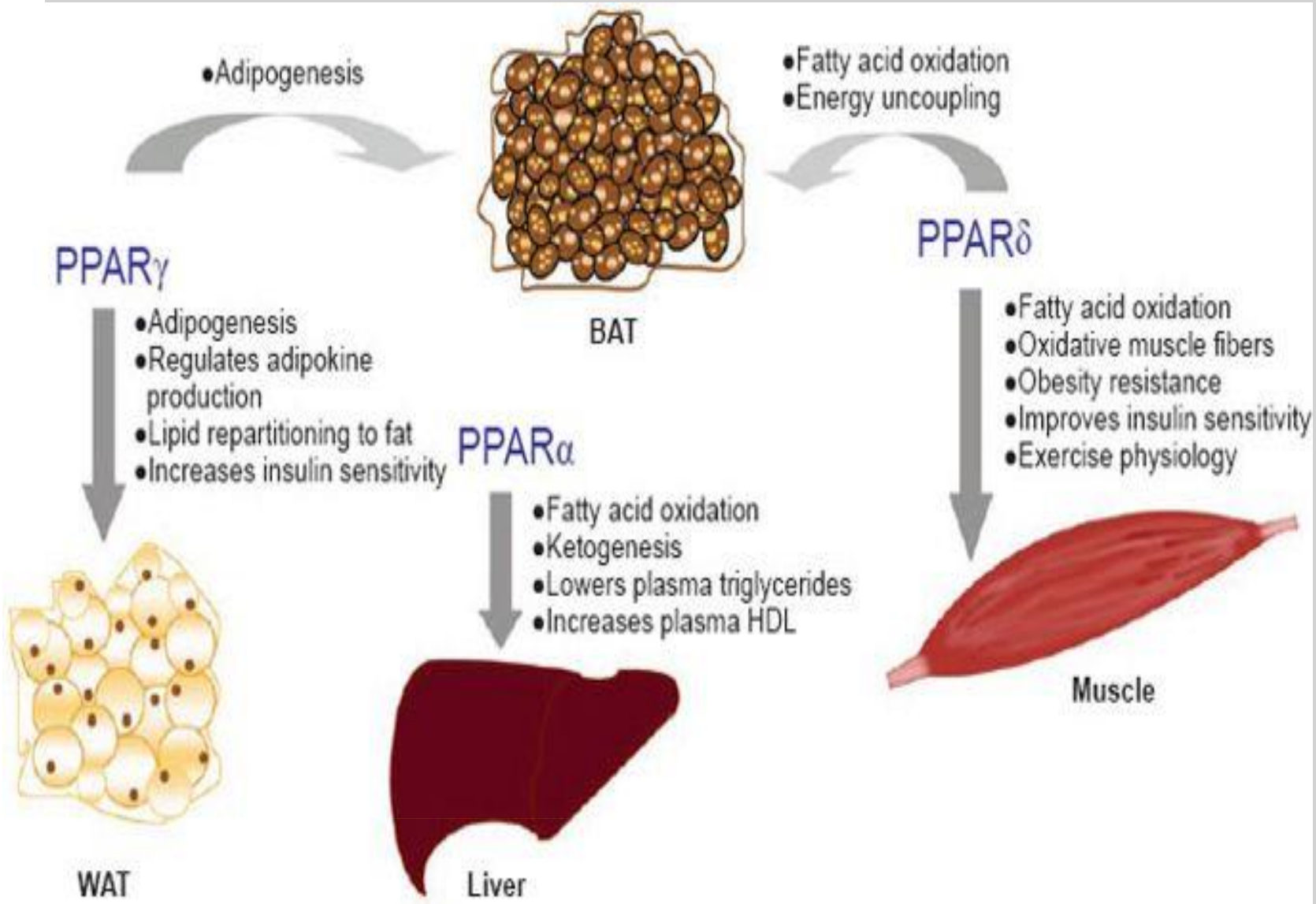
	Placebo	Resmetirom 80 mg	Resmetirom 100 mg
Serious Adverse Events	12.1%	11.8%	12.1%
AE discontinuations from study	3.7%	2.8%	7.7%
AEs over 10%			
Diarrhea	16%	28%	34%
Nausea	13%	22%	19%

Madrigal press release: https://ir.madrigalpharma.com/news-releases/news-release-details/positive-topline-phase-3-maestro-nafld-1-data-demonstrate

Peroxisome ProliferatoR Activated Receptors



Pan-PPAR agonist
Lanifibranor
on-going phase 3 study



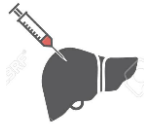
Wang. Cell Research. 2010

Trial design: NATIVE Trial

Clinicaltrials.gov: NCT03008070

24-week treatment + 4-week follow-up
Double blind, randomized, placebo-controlled

Screening
- **Liver biopsy**



- Randomisation 1/1/1
- Stratification on T2DM

Placebo

Lanifibranor, 800 mg once daily

Lanifibranor, 1200 mg once daily

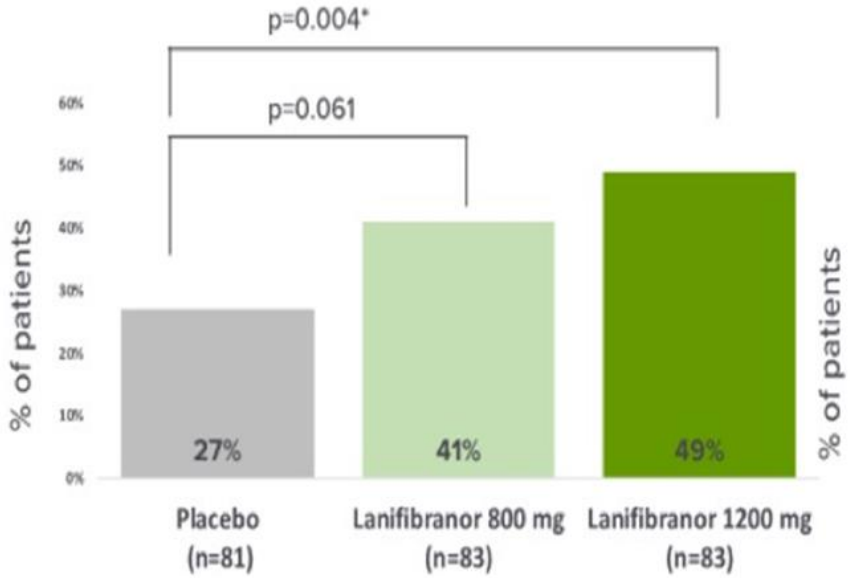
End of treatment
- **Liver biopsy**

- **Main inclusion criteria**: patients with biopsy-proven NASH confirmed by central reader having Steatosis-Activity-Fibrosis (SAF) scores of 1-3 for **S**teatosis, 3-4 for **A**ctivity, and <4 for **F**ibrosis

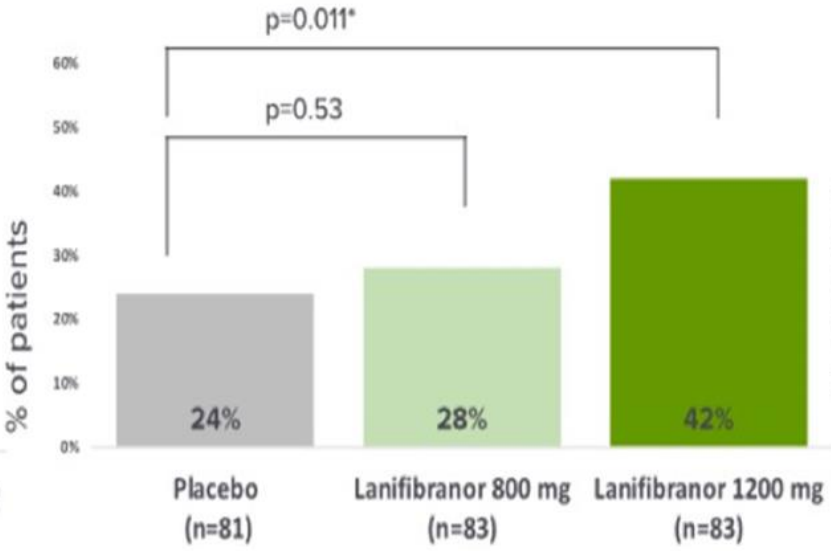
Patient population	# patients	Definition
Full Analysis Set (FAS) = Safety set	247	Patients randomized having received at least one dose of lanifibranor/placebo
Per Protocol (PP)	194	Patients with paired biopsies and without deviation impacting efficacy results

Lanifibranor: Phase 2 Histologic Results

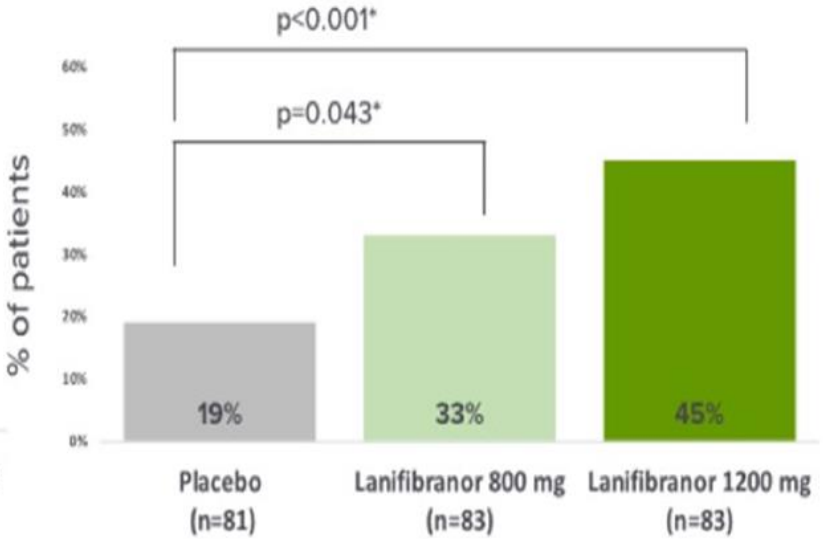
Primary endpoint: reduction of ≥ 2 points of SAF Activity Score and no worsening of fibrosis



Secondary endpoint: improvement of ≥ 1 stage of fibrosis and no worsening of NASH

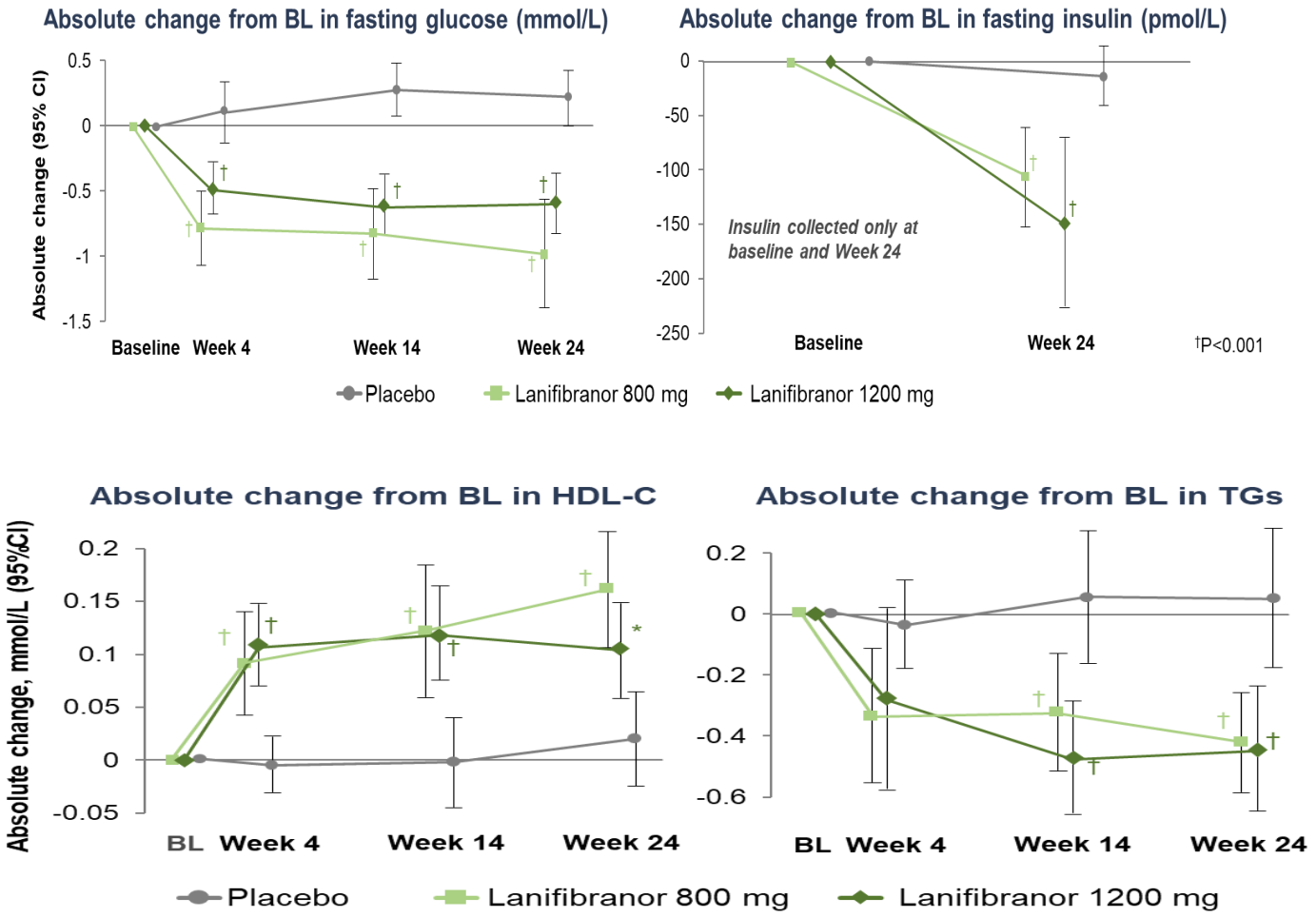


Secondary endpoint: resolution of NASH and no worsening of fibrosis



Francque SM, et al. Presented at: EASL International Liver Congress; June 23-26, 2021; Virtual. Presentation 1044.

Phase 2b NATIVE study – subanalysis: Favorable EFFECT on GLUCOSE and LIPIDS



- Serum markers of lipid metabolism, insulin resistance and glycemic control improved with lanifibranor at Week 24 compared with placebo.
- Lanifibranor also improved markers of inflammation (Hs-CRP, MACK-3 TIMP1/MMP2) compared to placebo
- Well tolerated: mild weight gain in keeping with PPAR- γ effect

Francque S, et al. EASL 2021. #OS-1044

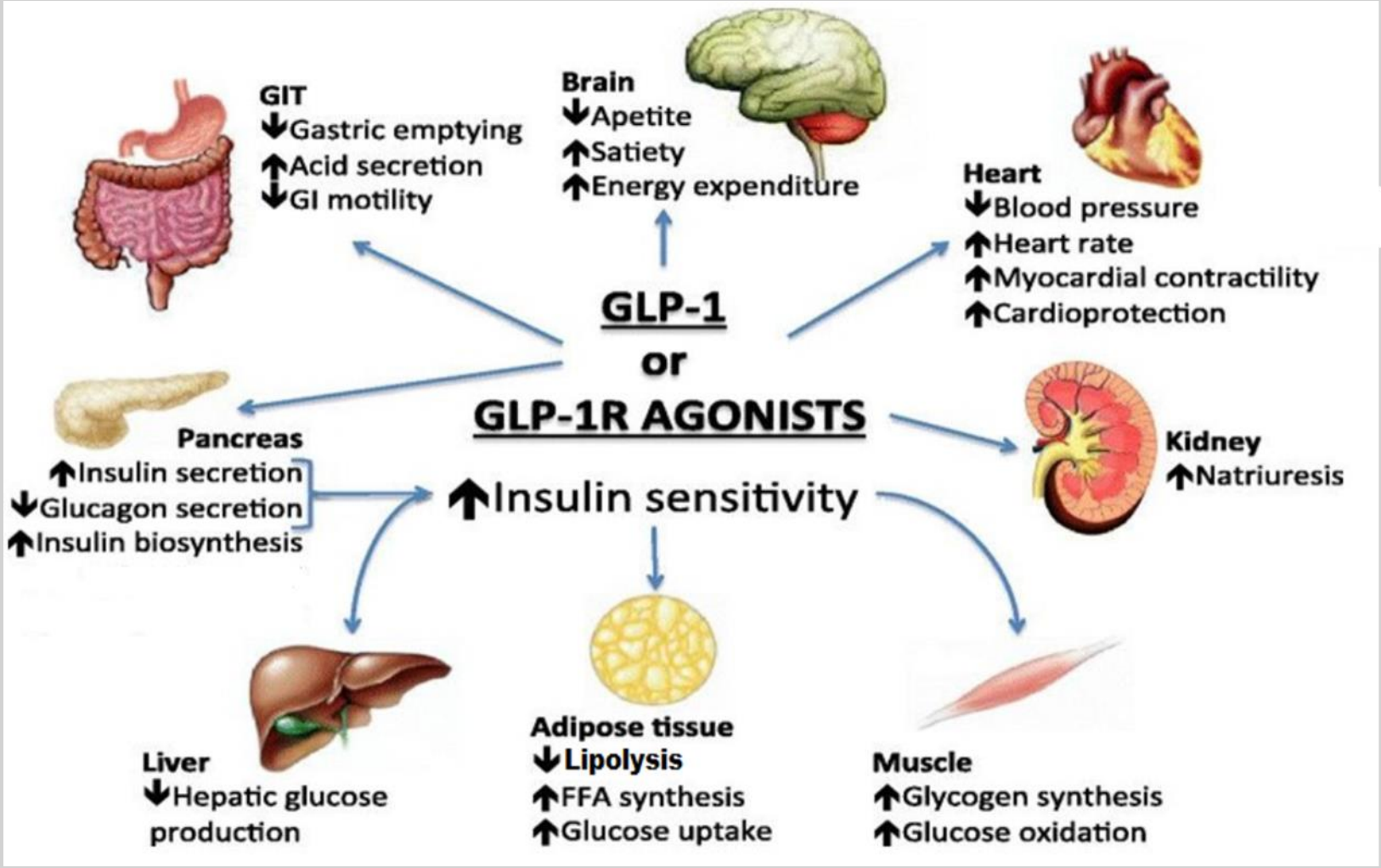
Lanifibranor—PPAR Agonist
Phase 2b Results--Safety

	Lanifibranor 1200 mg (N = 83)	Lanifibranor 800 mg (N = 83)	Placebo (N = 81)
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
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
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;385:1547-1558.

Glucagon-Like Peptide-1 Receptor Agonists

Semaglutide



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.

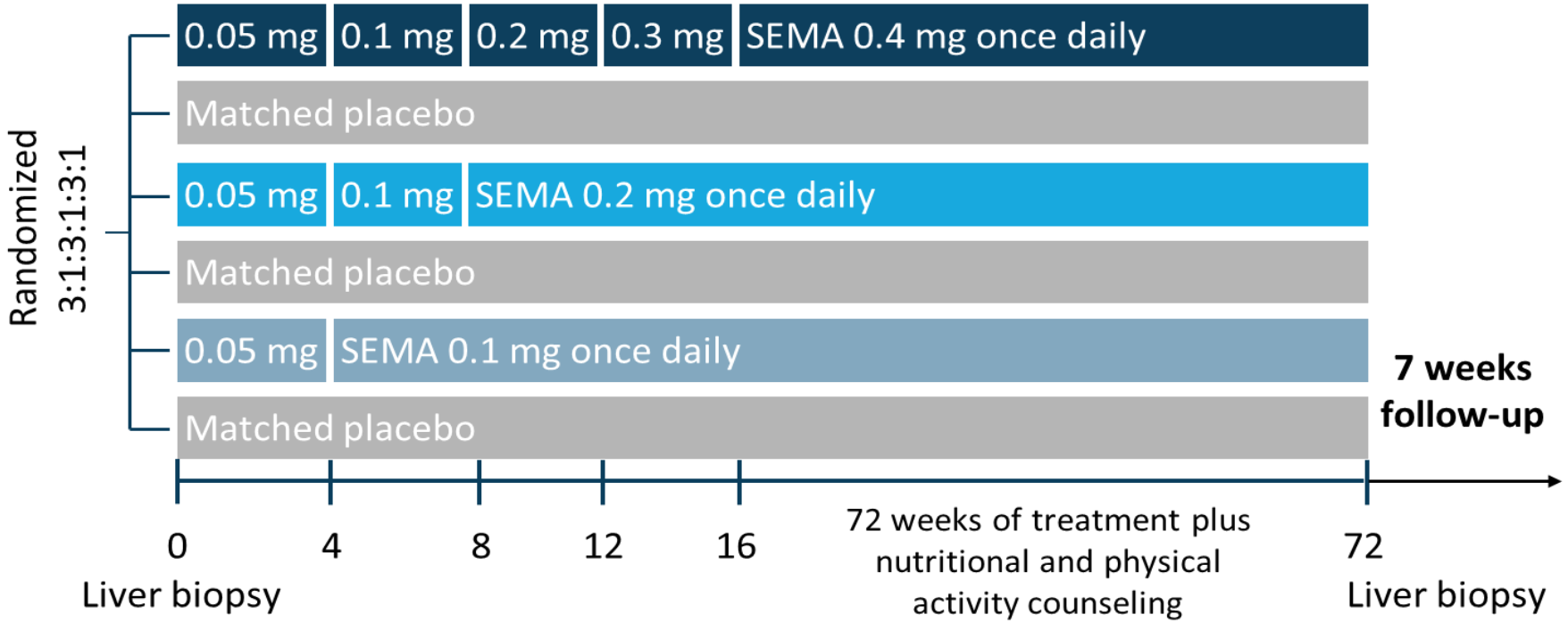
Efficacy and Safety of Subcutaneous Semaglutide Once-Daily vs Placebo in Patients with NASH

***ClinicalTrials.gov, number* NCT02970942**

Objective: compare the effect of 3 different doses of SEMA S.C once daily versus placebo on histological resolution of NASH

Inclusion criteria:

- Biopsy confirmed NASH
- NAS ≥4
- Fibrosis stage 1, 2 or 3
- BMI >25 kg/m^2
- HbA1c ≤10%



Primary endpoint:

- Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

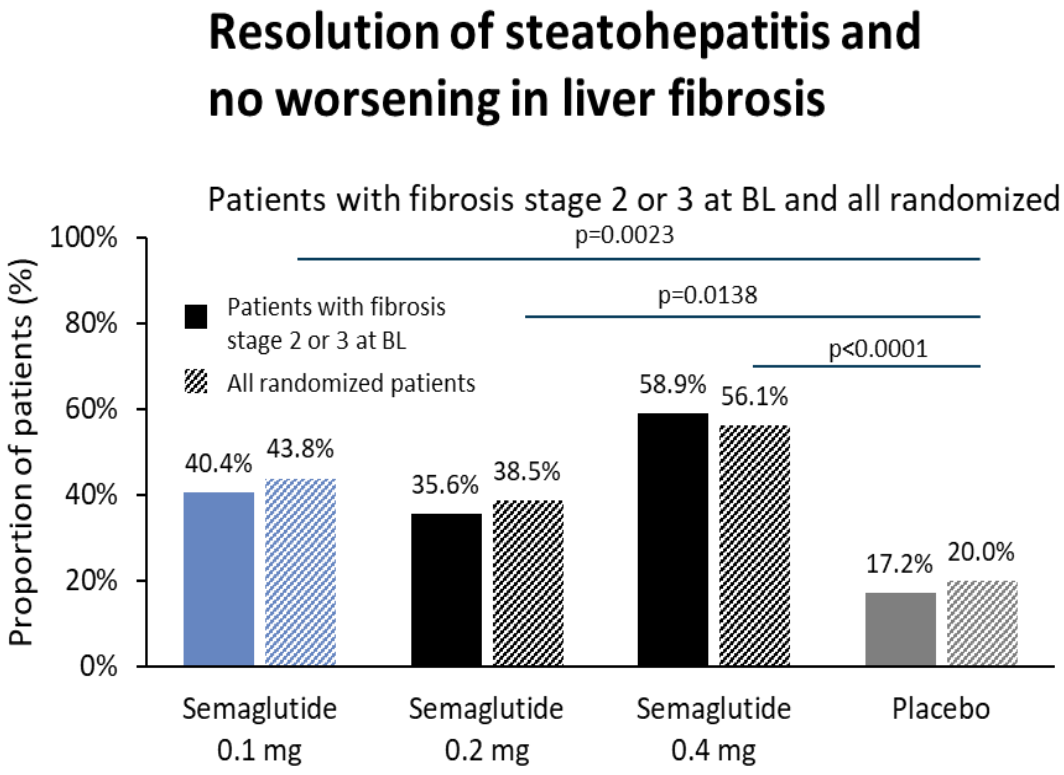
Confirmatory secondary endpoint:

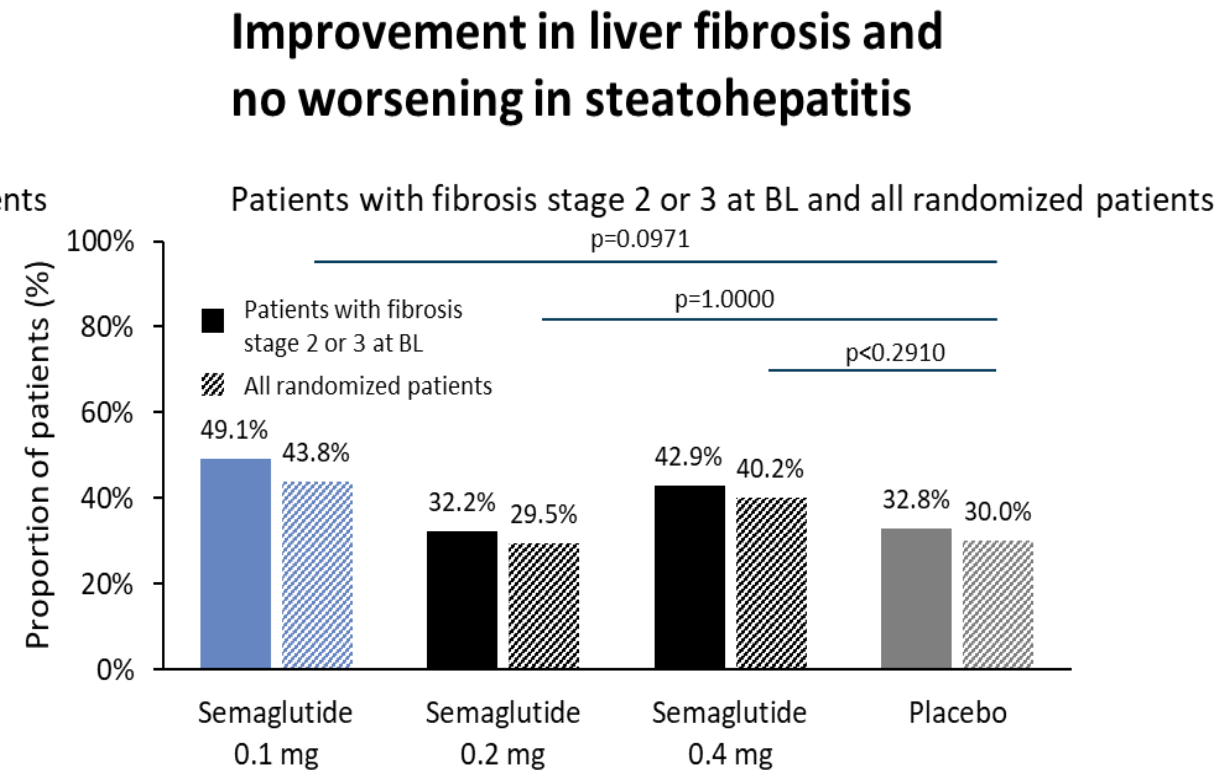
- Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

Newsome P et al. NEJM. 2021 Mar 25;384(12):1113-1124.

Semaglutide for NASH

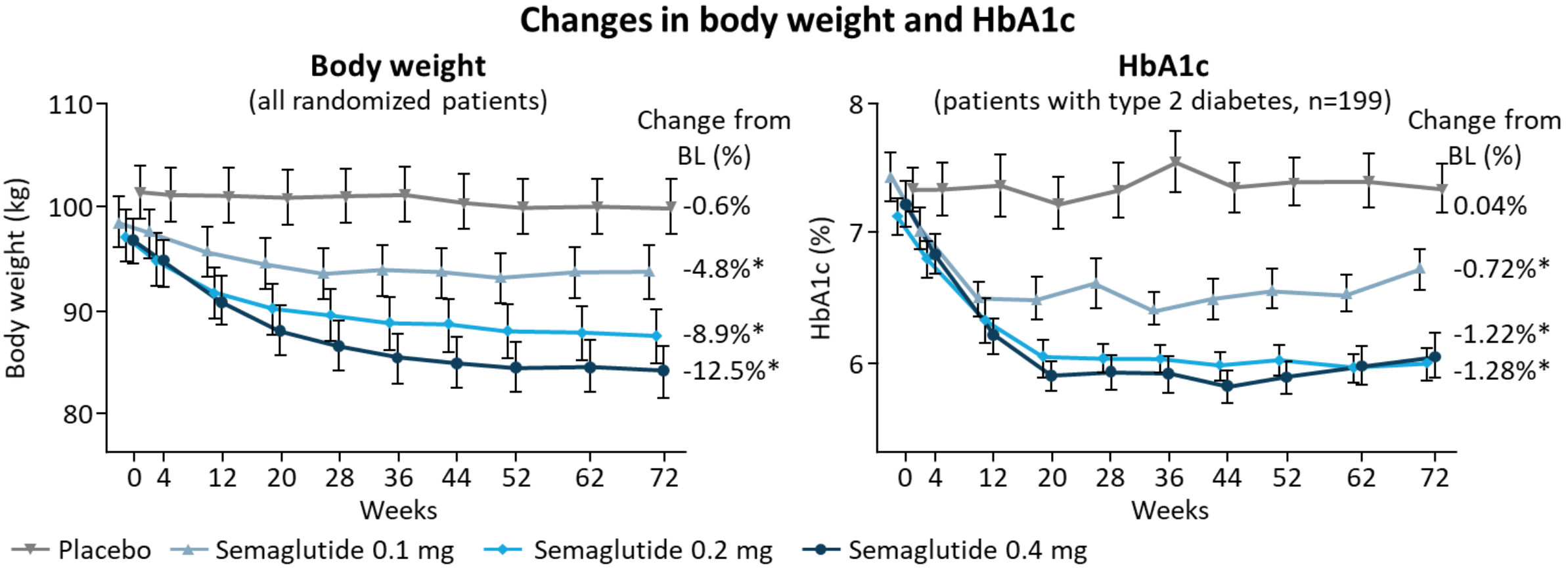
- A 72-week, Phase 2 study of 320 participants with NASH, fibrosis stage 1, 2, or 3
- **Interventions**: Placebo vs semaglutide 0.1 , 0.2 or 0.4 mg subcutaneously daily
- **Primary outcome**: Resolution of NASH and no worsening in liver fibrosis





Newsome PN, et al. NEJM. 2020

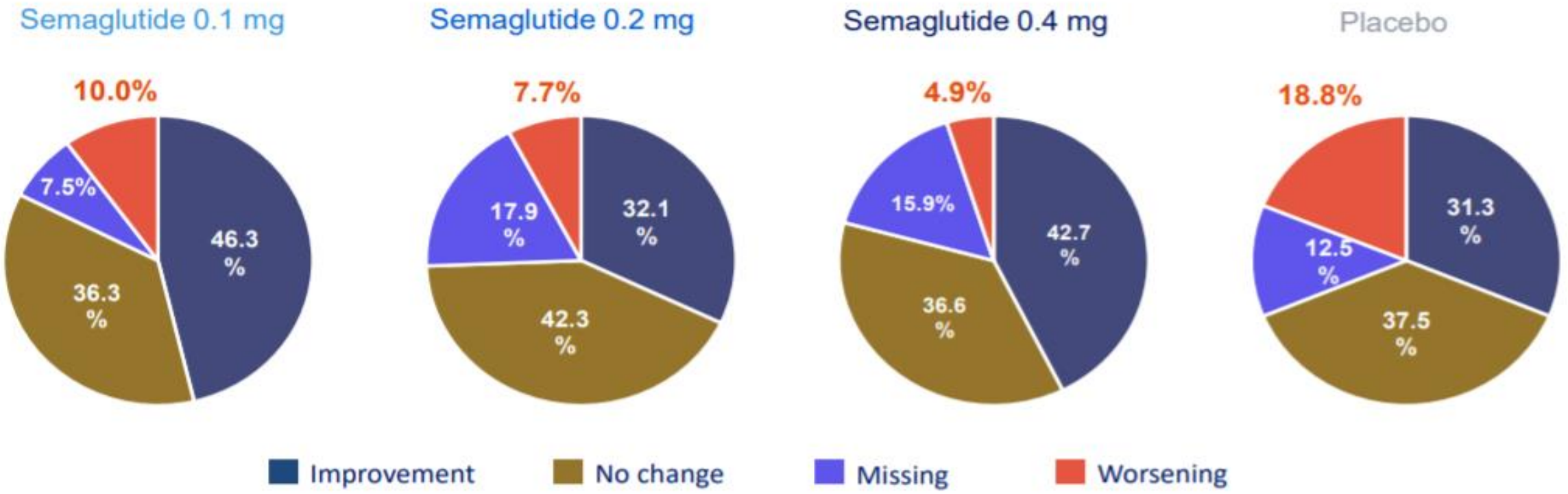
Efficacy and Safety of Subcutaneous Semaglutide Once-Daily vs Placebo in Patients with NASH



Newsome PN, et al. NEJM. 2020.

Semaglutide: Change in Fibrosis Stage

All Patients



Data based on in-trial period.

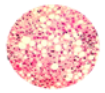
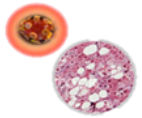
Newsome PN, et al. NEJM. 2020.

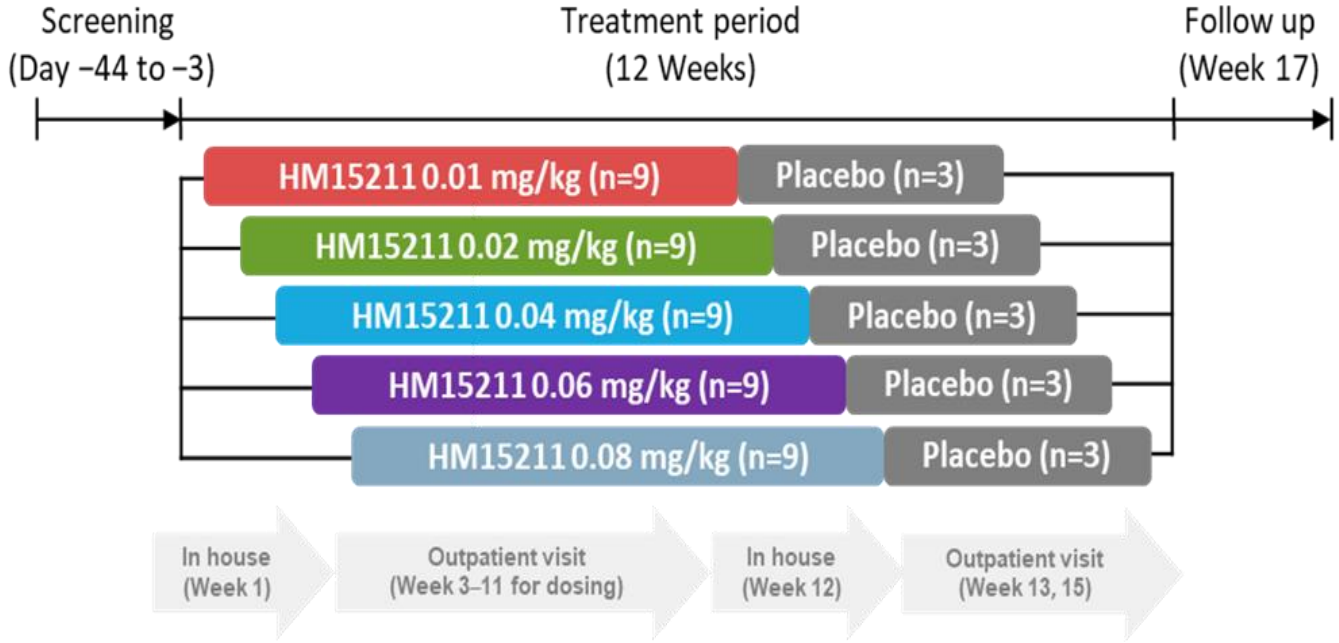
Around the Corner

2nd generation drugs

- FXR agonists
- THR-β agonists
- Dual / triple agonists
  - ✓ GLP-1/GIP
  - ✓ GLP-1/Gluc
  - ✓ GLP-1/GIP/Gluc
- FGF21 agonists
  - ✓ Pegozafermin
  - ✓ Efruxafermin

HM15211, A NOVEL GLP-1/GIP/GLUCAGON TRIPLE-RECEPTOR CO-AGONIST SIGNIFICANTLY REDUCES LIVER FAT AND BODY WEIGHT IN OBESE SUBJECTS WITH NAFLD: A PHASE 1B/2A, MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

	Glucagon	GIP	GLP-1
Steatosis 	Liver TARGETING Unique effect of glucagon Hepatic Fat Reduction ↑ β-oxidation ↓ de novo lipogenesis *"Animal to human translation confirmed"*	Hepatic Fat Reduction ↓ Ectopic fat accumulation	Hepatic Fat Reduction ↓ Excessive calorie intake
Inflammation, ballooning 	Cytokine regulation[1] ↓ Macrophage activation ↓ Immune cell recruiting Liver function improvement ↓ Blood ALT/AST Bile acid production ↓[2] ↓ Liver injury	Cytokine regulation[3] ↓ Macrophage activation ↓ Immune cell recruiting	Cytokine regulation[1] ↓ Macrophage activation ↓ Immune cell recruiting Liver function improvement ↓ Blood ALT/AST
Fibrosis 	Inhibition of TGF-β production ↓ Hepatic stellate cell activation Inhibition of TGF-β signaling ↓ Fibrogenesis in activated hepatic stellate cell *"Glucagon's new finding"*		



Inclusion criteria

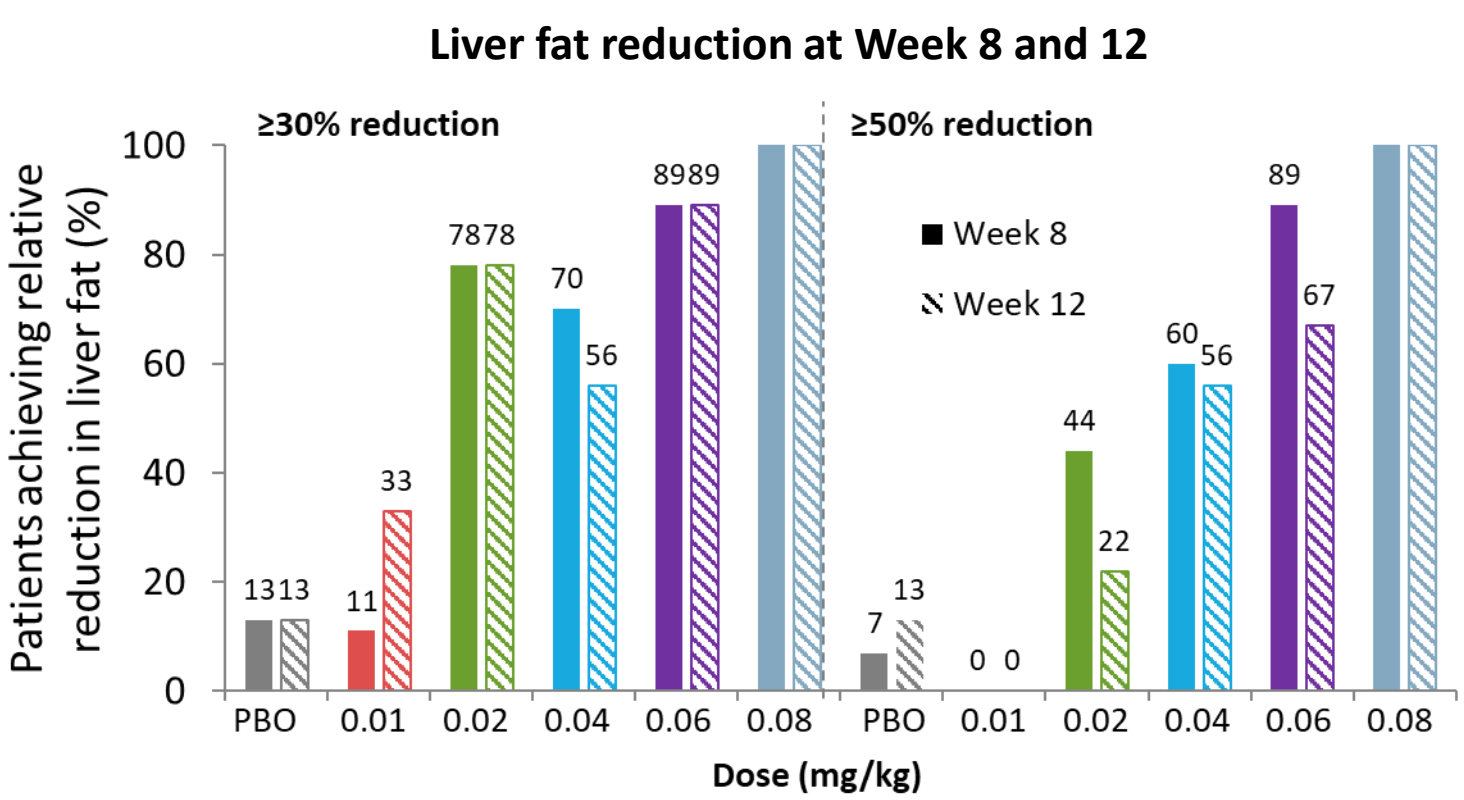
- Adults with NAFLD liver fat by MRI-PDFF (≥10%)
- Non-diabetic (HbA1c <6.5%)
- Obese (BMI ≥30 kg/m^2)

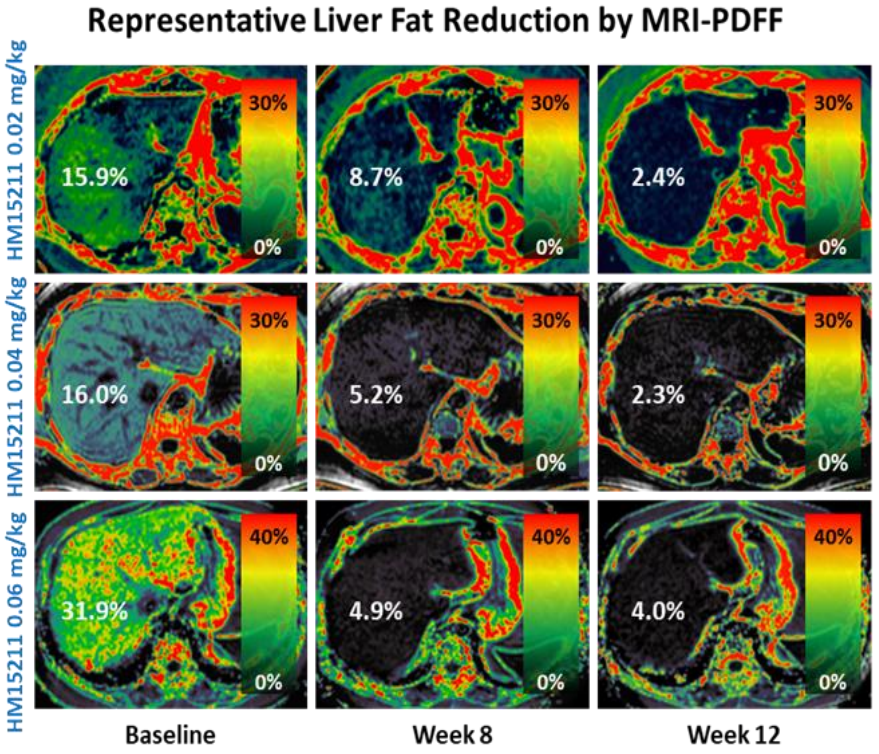
Primary objectives

- Safety and tolerability of HM15211 after administration of multiple SC doses
- Reduction of liver fat after administration of multiple doses

MAYO CLINIC

HM15211, A NOVEL GLP-1/GIP/GLUCAGON TRIPLE-RECEPTOR CO-AGONIST SIGNIFICANTLY REDUCES LIVER FAT AND BODY WEIGHT IN OBESE SUBJECTS WITH NAFLD: A PHASE 1B/2A, MULTI-CENTER, RANDOMIZED, PLACEBO-CONTROLLED TRIAL





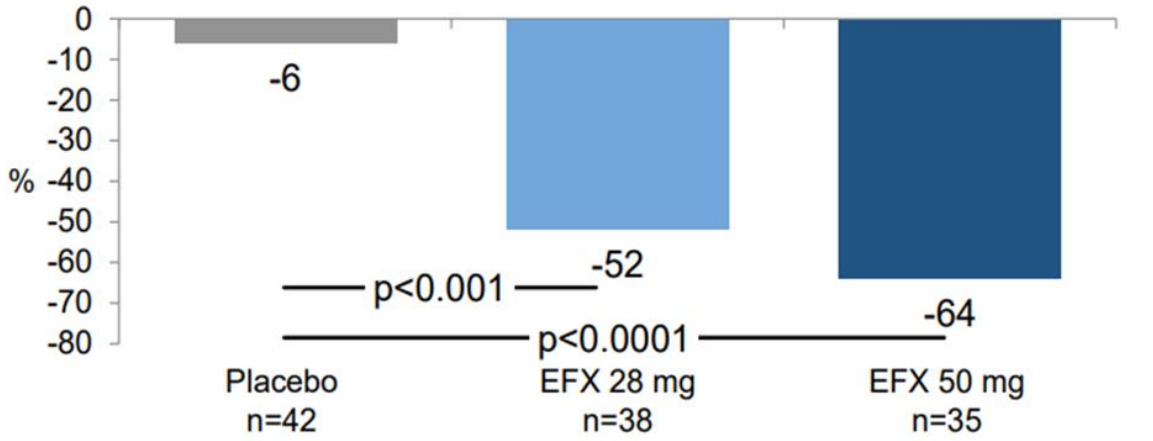
- HM15211 was safe / well tolerated during 12-wk treatment in non-diabetic obese subjects with NAFLD
- Two subjects at different dosing cohorts developed hyperglycemia secondary to glucagon effect.
- Improvement in MRI-PDFF was independent of glycemic control in this early phase study

Efruxifermin (FGF-21) in NASH with fibrosis: HARMONY, a phase 2b placebo-control RCT

Baseline demographics

	Placebo N=43	EFX 28 mg N=42	EFX 50 mg N=43
Age, years	55	57	52
Sex, female	63	69	53
Weight, Kg	108	104	103
Hispanic/Latino.	35	40	47
BMI, kg/m^2	38.7	38.3	37.2
T2DM	65	76	70
F3	70	64	63
ELF score	9.8	9.7	9.8
ProC3, µg/L	16.5	15.3	18.4
Liver stiffness by VCTE, kPa	15	14	16
Hepatic fat fraction by MRI-PDFF	17.1	18.5	17.5
NAS	5.4	5.1	5.6
ALT, U/L	62	50	63
AST, U/L	57	42	52
HbA1c	6.8	6.8	6.7
T2DM	7.2	7.2	7.1
Triglycerides (mg/dL)	170	158	154
LDL cholesterol, mg/dL	94	96	111
Data are mean or %			

LS mean relative % change from baseline in liver fat at Wk 24



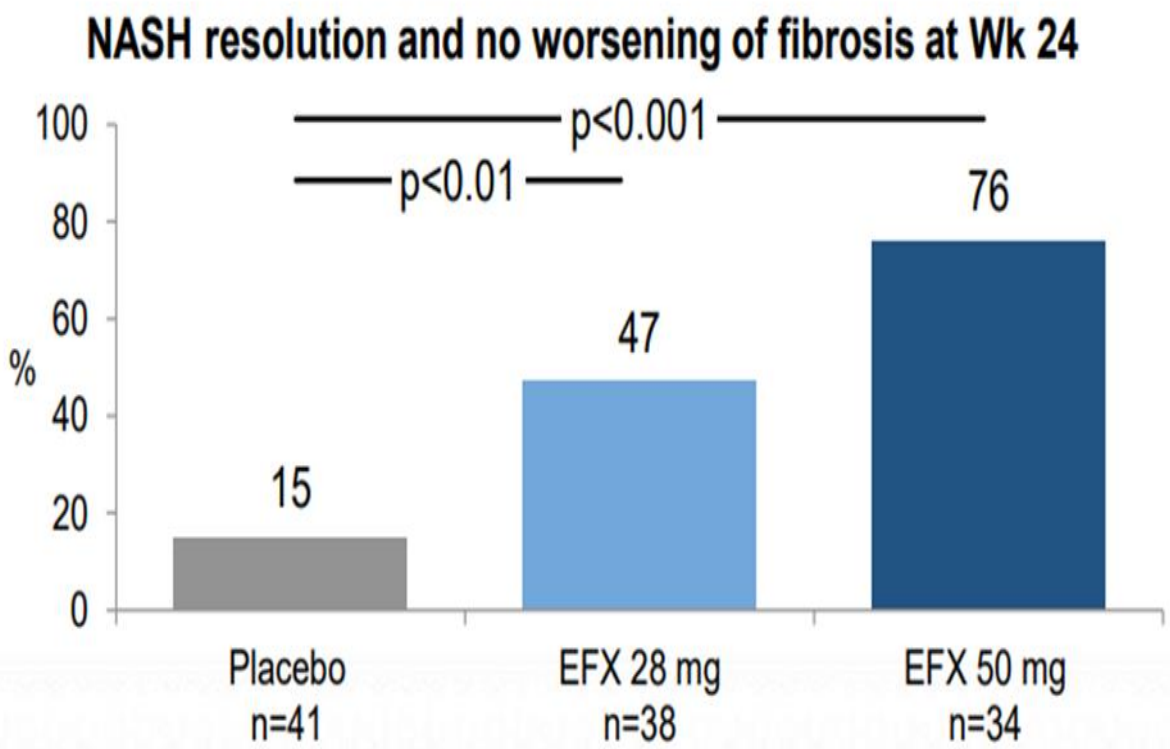
% of patients achieving fat reduction thresholds at Wk 24

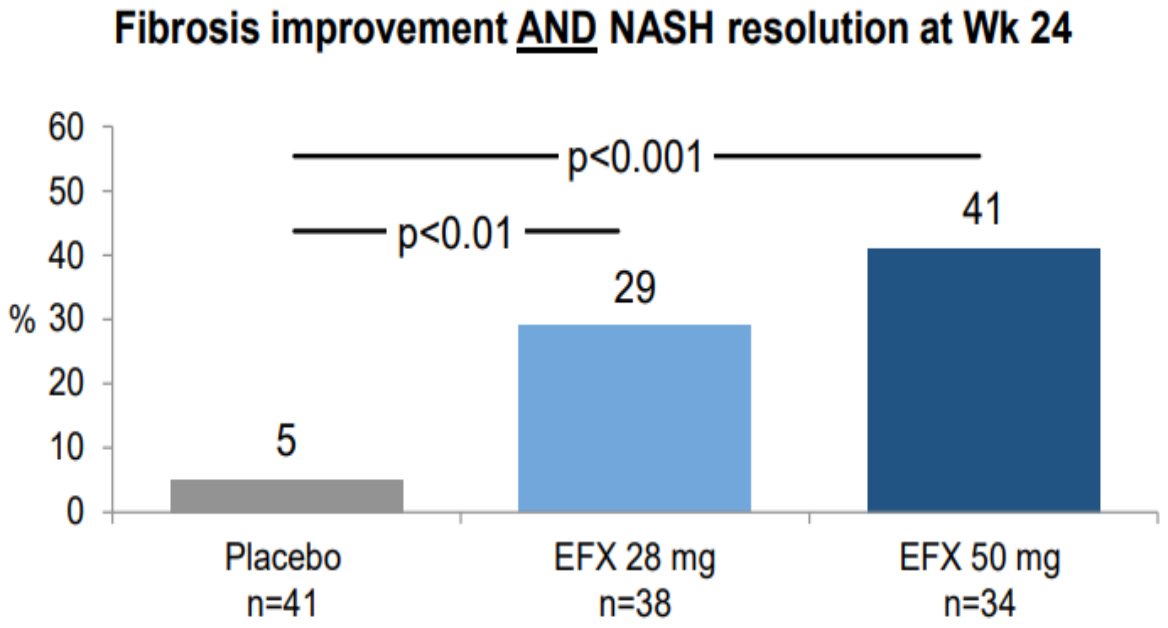
Endpoint	Placebo n=42	EFX 28 mg n=38	EFX 50 mg N=35
Relative reduction in liver fat			
≥50%	2%	63%***	77%***
Normalization of liver fat content (from >5% to <5%)			
≤5%	0%	34%***	51%***

***p<0.001 vs placebo

Harrison SA, et al. AASLD 2022. Late-breaking oral #5006.

Efruxifermin in NASH with fibrosis: HARMONY, a randomized, double-blind, placebo-controlled, phase 2b trial





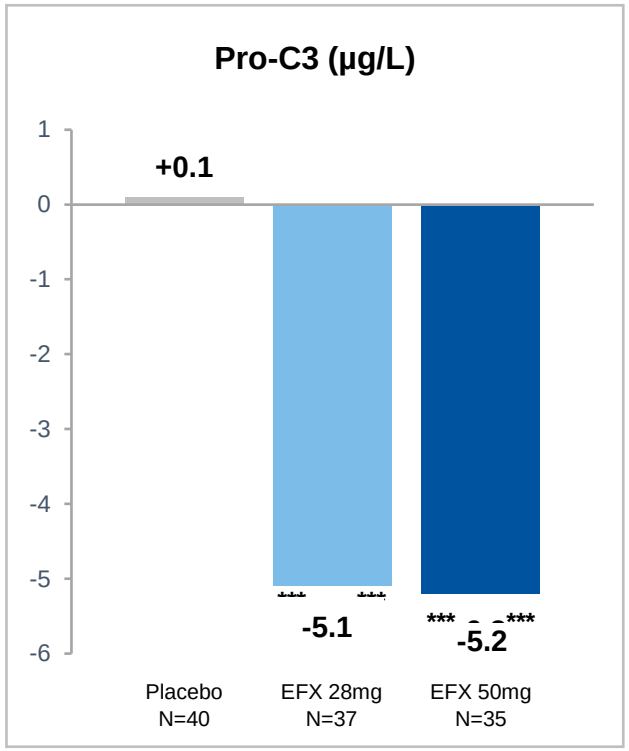
Patients achieving fibrosis improvement ≥2 stages and no worsening of NASH at Wk 24

Placebo n=41	EFX 28 mg n=38	EFX 50 mg N=34
5%	16%	15%

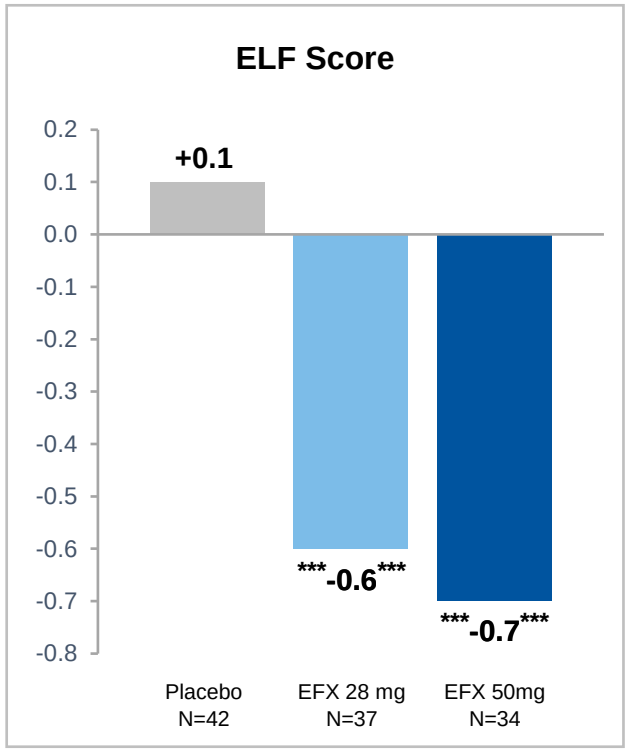
Harrison SA, et al. AASLD 2022. Late-breaking oral #5006.

Statistically Significant Reductions in Non-Invasive Markers Reflect Histological Improvement in Fibrosis

LS Mean Change From Baseline to Week 24

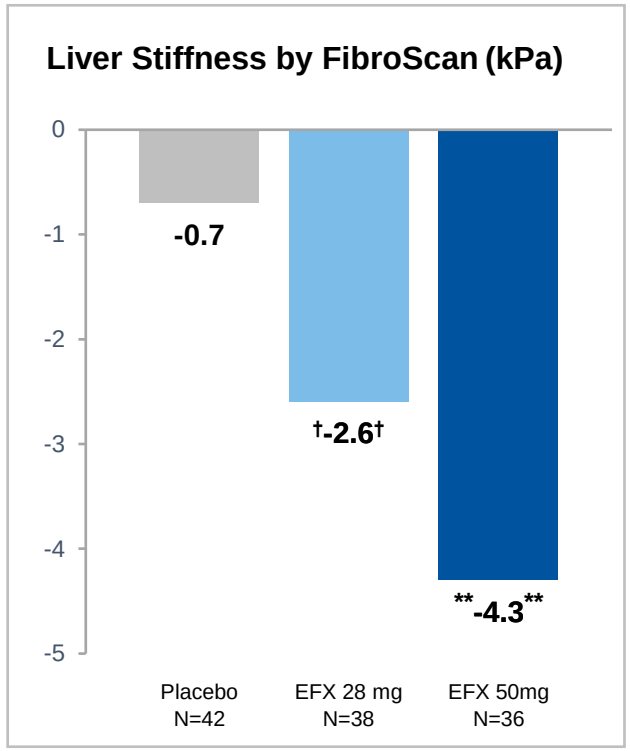


*** p<0.001, versus placebo (MMRM[1])



*** p<0.001, versus placebo (MMRM[1])

[1]Mixed-model repeated-measures
[2]Analysis of Covariance



** p<0.01, versus placebo (ANCOVA[2])
† p<0.01, versus baseline (ANCOVA)

Source Data: Biomarker Analysis Set (Pro-C3 and ELF); Full Analysis Set (Liver Stiffness) (non-missing values only, no imputation)

Harrison SA, et al. AASLD 2022. Late-breaking oral #5006.

Agents in development for NASH in US, EU, and Japan – Phase I-III

Other (18)
- **larsucosterol (DUR-928)/** Durect
- **tolimidone**/Melior
- **cibinetide**/Araim
- **ART 648**/Takeda, ARTham
- **FIA586**/Novartis
- **LPCN-1148**/Lipocine

Neurotransmitter Modulators (3)
- **IM-102**/Integral Molecular
- **CB4211**/CohBar
- **SCO-267**/Scohia
- **EDP-297**/Enanta
- **nimacimab/**
- **MT 2004**/Xian Biocare
- **S-723595**/Shionogi
- **idebenone**/Santhera
- **HPG1860**/Hepagene

PPAR Modulators (5)
- **T3D 959**/T3D, Bayer

RAAS Modulators (0)
- **PBF 1650/** Palobiofarma, XOMA
- **apararenone** Mitsubishi Ta
- **PHP-303**/Bayer, pH-Pharma
- **nitazoxanide/** Genfit, Pinnacle
- **HPN-01**/Hepanova
- **RXC007/** Redx
- **FM101/** Future Medicine
- **LYS 006/N**
- **DFV890**/IFM, Novartis

Metabolism Modulators (27)
- ***ASC42**/Gannex
- **NN9500**/Novo Nordisk
- ***MET642**/Metacrine
- **LY3478045**/Eli Lilly
- **firsocostat**/Gilead
- **LY3522348**/Eli Lilly
- **clesacostat**/Pfizer
- **O304**/Betagenon
- ***MET409**/Metacrine
- **BIO89-100**/Teva, 89bio

Anti-fibrotic/Anti-inflammatory (22)
- **hydronidone/** Shanghai Genomics
- **leronlimab**/CytoDyn
- **pegipanermin**/INmune
- ***tipelukast/** Kyorin, MediciNova
- **PLN-1474/** Pliant, Novartis
- **GB1211**/Galecto
- ***BMS-986263/** Nitto Denko, BMS
- **PRM-151**/Promedior, Roche
- **CRV 431***
- **LG0030317/** LG Chem, TransThera
- ***TERN 201**/Terns
- **SYN020/** Synthetic Biologic
- **NT-0167**/NodThera
- **adalimumab**/180 Life Sciences

Phase II | **Phase I**
- **ARO-HSD**/Arrowhead, GSK
- **bulevirtide**/MYR
- **PF-07202954**/Pfizer

Lipid Modulators (20)
- **ALG-009**/Aligos
- **CER-209**/Abionyx
- **ALN-HSD**/Alnylam, Regeneron

Apoptosis Inhibitors (0)

Incretin Combinations (10)
- **SCO-094**/Scohia
- **PB-718**/PegBio
- **CT 388**/Carmot
- **pemvidutide (ALT-801)**/US
- **DD 01**/D&D

Glucose Pathway Modulators (2)
- **dapagliflozin/** AZ
- **AZD2693 (ION839)**/AZ, Ionis
- **A3907**/Albireo
- **AMG 609**/Amgen
- **TERN 501***/Terns
- **JNJ-75220795**/J&J

Immune Modulators (1)
- **foralumab/** Tiziana

Incretins (1)

*FDA Fast Track Status
**FDA Breakthrough Designation
*** EU PRIME Designation

Assets in blue only combi Tx
Assets in grey discontinued in 2021

- Oral
- Subcutaneous
- IV
- Parenteral
- Unspecified

Take Home Points

- The clinical burden of NAFLD /NASH is huge
- With OCA and resmetirom are under FDA review
- Therapies much lend favorable benefit-risk ratio beyond liver health alone
- Antimetabolic therapies demonstrate benefit against NASH with promise for halting or delaying time to fibrosis progression
- Potent therapies (dual/triple agonists/FGF agonists) are on the horizon.
- Combination therapy using drugs with different mechanisms-of-action (under investigation) are likely the future of NASH treatment.

THANK YOU

Sponsors
Investigators/ Coordinators
Regulatory Authorities
Patients and families who graciously participate in clinical research