Treatment: New Drugs

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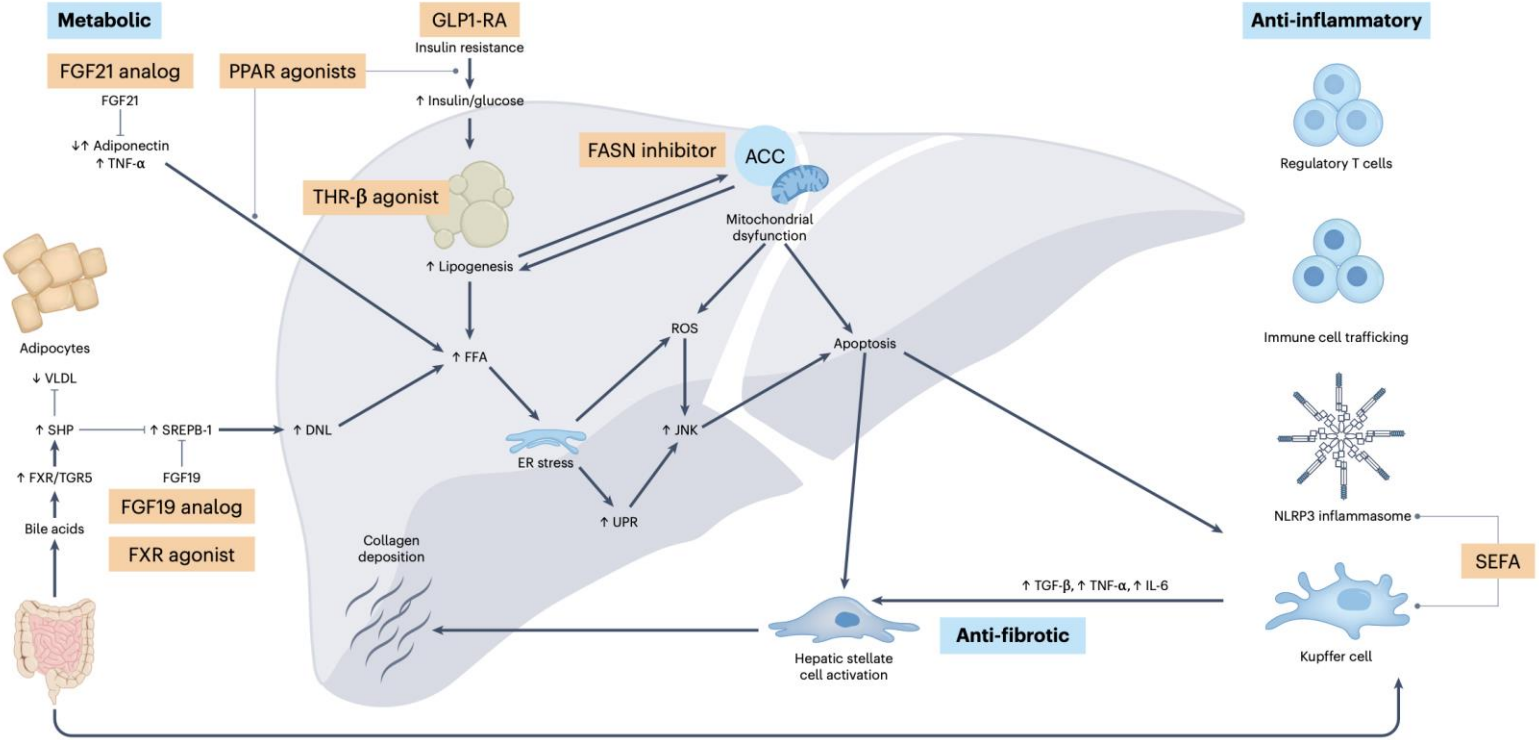
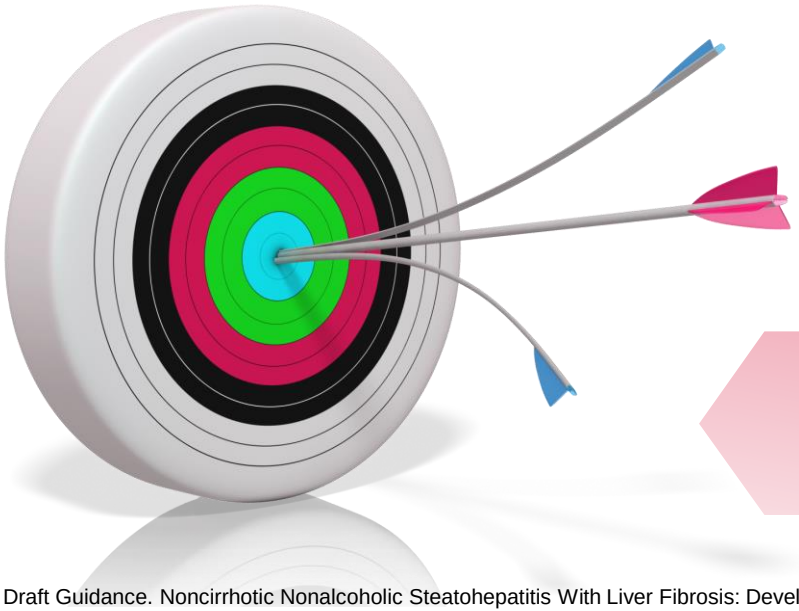
Potential Targets for NASH Treatments



Harrison et al. *Nat Med*. 2023.

Regulatory Framework for Drug Approval

FDA Registration Surrogate Histological Endpoints
=> Conditional Approval pending Long-Term Outcomes Trial



NASH Resolution

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

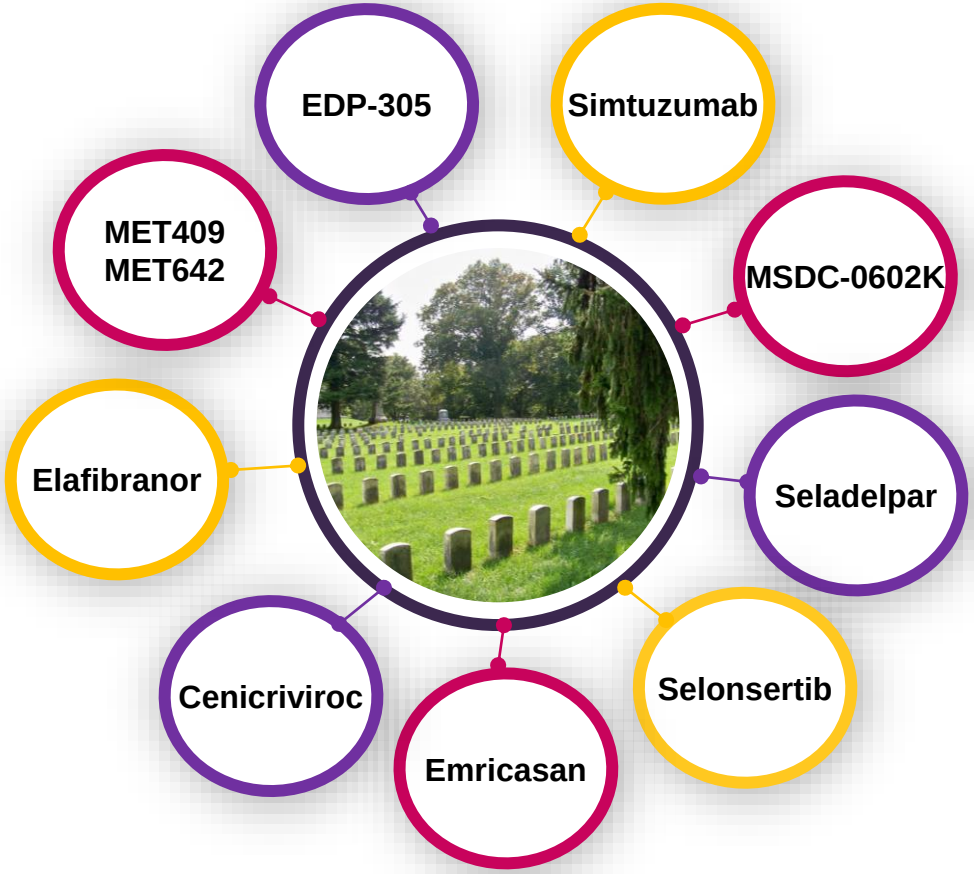
AND/OR

Fibrosis Improvement ≥ 1

Fibrosis stage and no worsening of steatohepatitis

FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

Graveyard Is Full of Failed Drugs for NASH



Agents in Phase 3 Development

Oral Agents

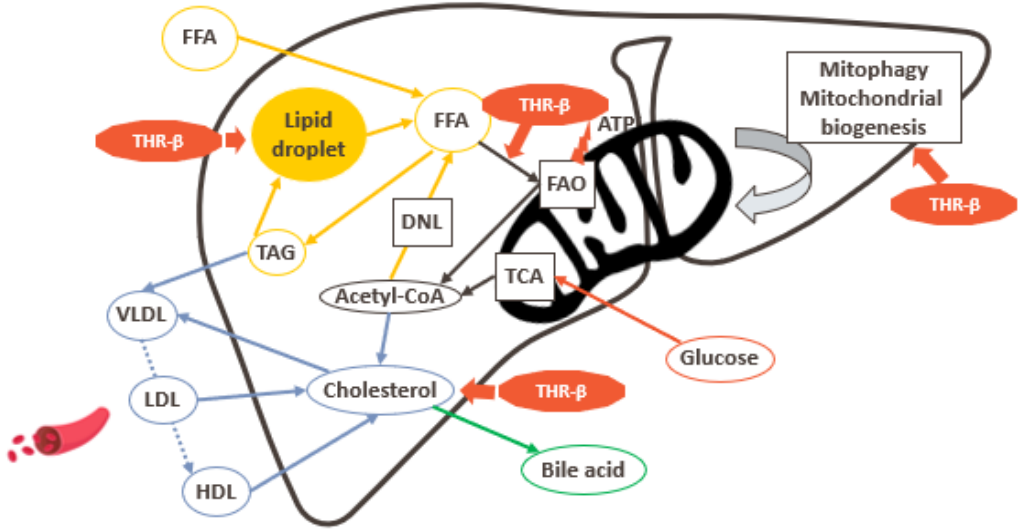
- RESMETIROM
- OBETICHOLIC ACID
- LANIFIBRANOR
- ~~ARAMCHOL~~

Injectable / Infusion

- SEMAGLUTIDE

a. ClinicalTrials.gov. Accessed October 27, 2022. https://clinicaltrials.gov/ct2/show/NCT02548351; b. ClinicalTrials.gov. Accessed October 27, 2022. https://clinicaltrials.gov/ct2/show/NCT04849728; c. ClinicalTrials.gov. Accessed October 13, 2019. https://clinicaltrials.gov/ct2/show/NCT03900429; d. ClinicalTrials.gov. Accessed October 22, 2022. https://clinicaltrials.gov/ct2/show/NCT02279524; e. ClinicalTrials.gov. Accessed October 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04822181.

Resmetirom - Mode of Action



Thyroid hormone, through activation of the THR-β in hepatocytes, plays a central role in liver function impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver

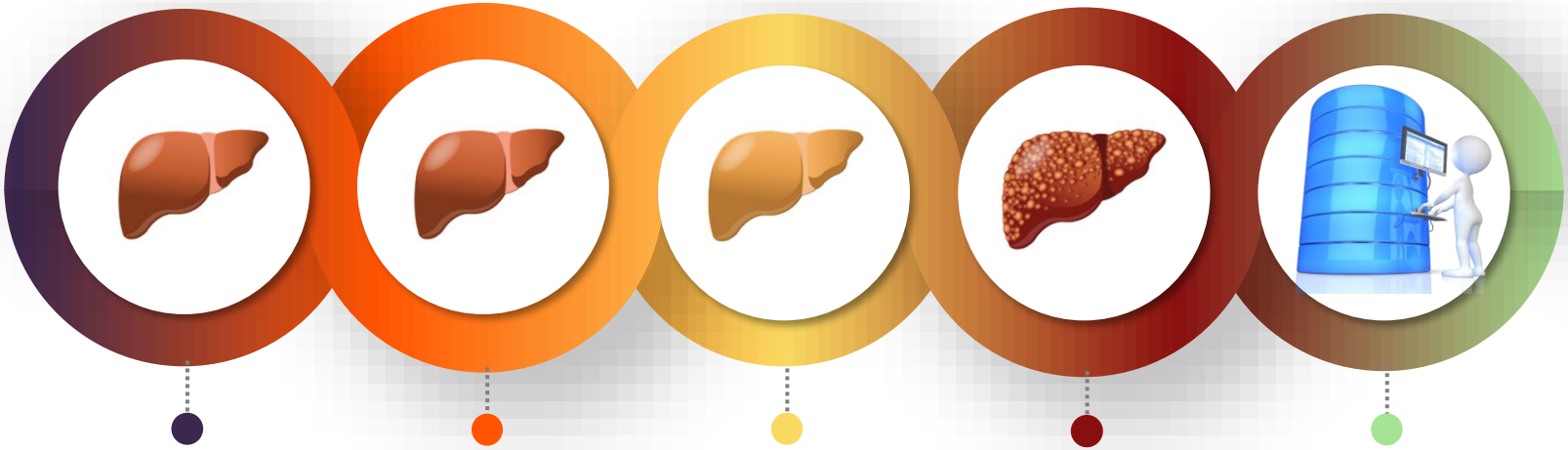
Resmetirom is a THR-β agonist that has shown in clinical trials to,

- 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; THR-β, thyroid hormone receptor beta; VLDL, very low-density lipoprotein.

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

Resmetirom – Phase 3 Program



MAESTRO NAFLD-1

Safety & tolerability as measured by incidence of AEs over 52 weeks in >1200 patients

MAESTRO NAFLD-OLE

52-week extension to MAESTRO-NAFLD-1 in >700 patients: Safety & tolerability by incidence of AEs over 52 weeks

MAESTRO NASH

Subpart H:
NASH resolution or fibrosis improvement on serial liver biopsy at Week 52
Outcomes (54 months – ongoing)

MAESTRO NASH OUTCOMES

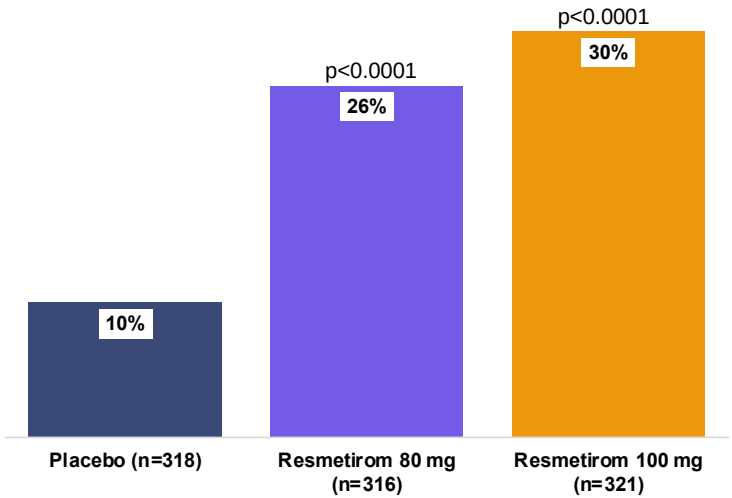
Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis

A total of > 1500 patients at the top dose of 100 mg &
> 2000 patients on at least 80 mg to support accelerated approval

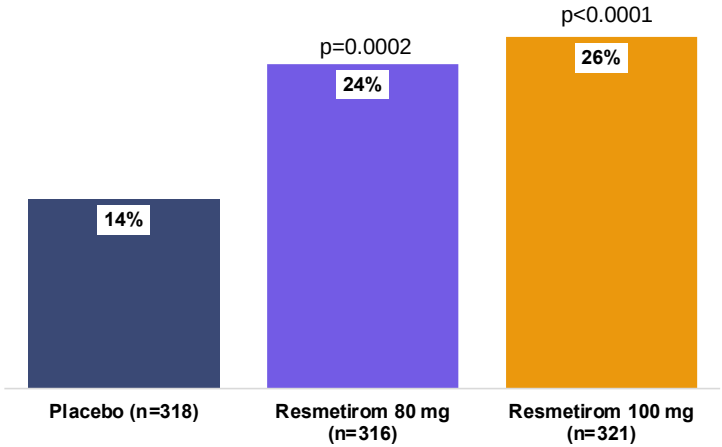
Resmetirom – Phase 3 Results

Liver Biopsy (ITT) at Week 52

NASH Resolution



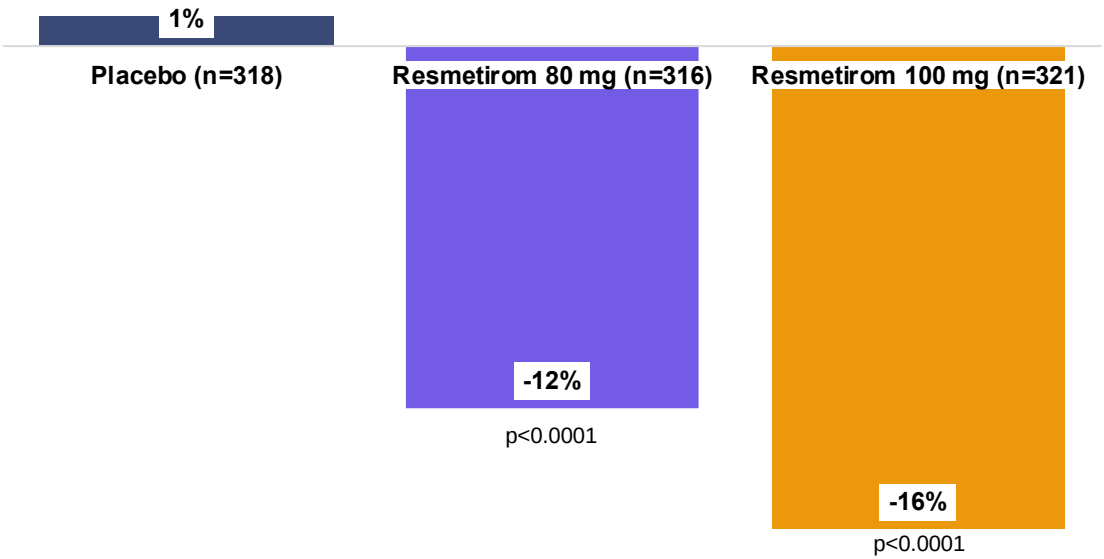
Fibrosis Improvement (≥1 stage)



Harrison S. Oral Presentation. *NASH-TAG*. 2023.

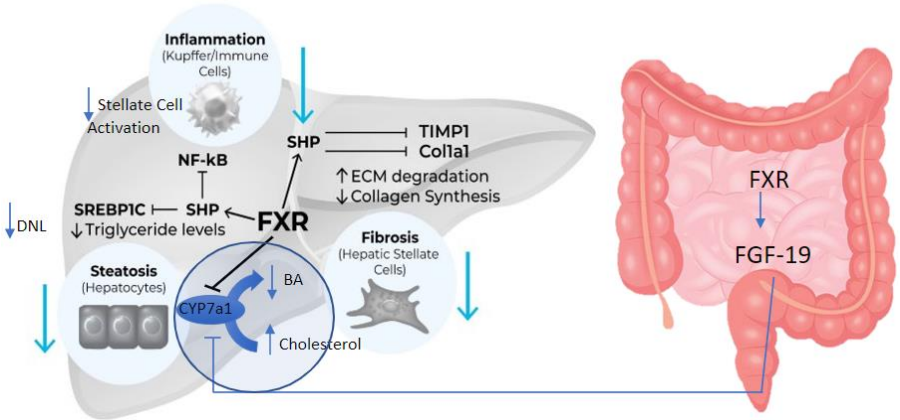
Resmetirom – Phase 3 Results

Key Secondary Endpoint LDL-c at Week 24 (ITT)



Harrison S. Oral Presentation. *NASH-TAG*. 2023.

Obeticholic Acid - Mode of Action



The FXR is a nuclear receptor that plays a central role in the regulation of bile acids and metabolism

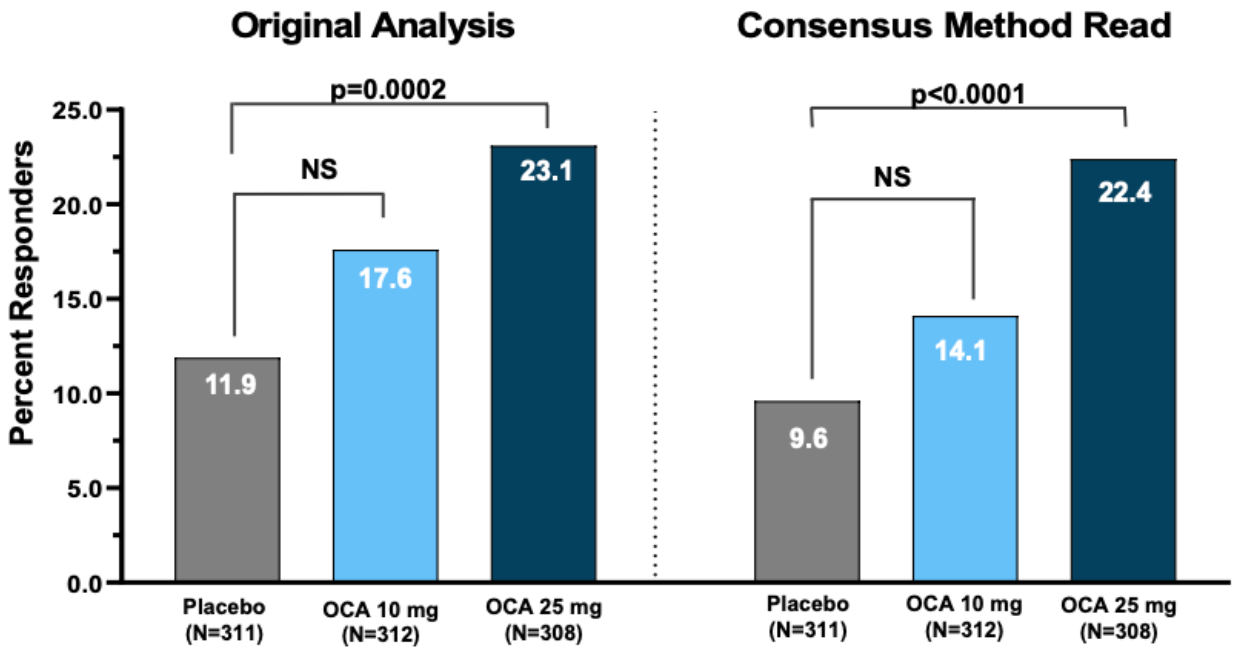
Obeticholic Acid is an FXR agonist and has been shown in clinical trials to affect,

- CYP7A1 Inhibition → decrease BA synthesis
- Inhibit DNL via SREBP-1 inhibition
- Induce intestinal FGF-19
- Reduce FFA and lipotoxicity
- Reduce inflammation and fibrosis

BA, bile acid; FGF-19, fibroblast growth factor 19; FXR, farnesoid X receptor.
Younossi ZM et al. *Lancet*. 2019;394:2184-2196.

Obeticholic Acid - Phase 3 Trial

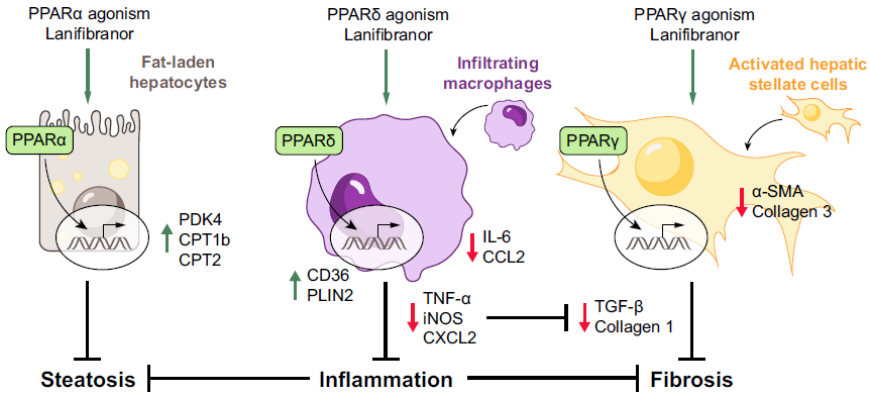
Primary Endpoint: Improvement of Fibrosis by ≥ 1 Stage without Worsening of NASH



No worsening of NASH defined as no increase of hepatocellular ballooning, lobular inflammation, or steatosis

Intercept Pharmaceuticals Press Release-July 2022. REGENERATE topline data presentation-July 2022.

Lanifibranor - Mode of Action



PPARs are nuclear receptors with key regulatory functions in metabolism, inflammation, and fibrogenesis.

Lanifibranor is a pan-PPAR (PPAR α/δ/γ) and has been shown in clinical trials to affect,

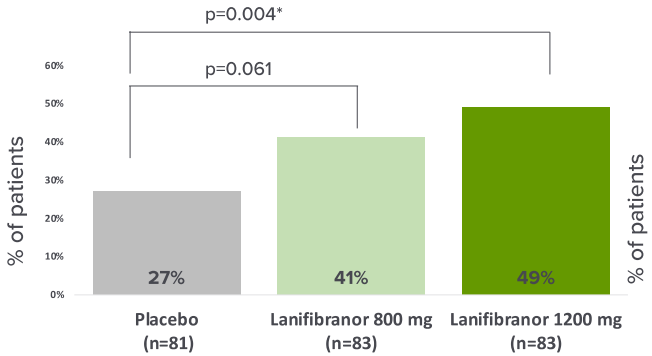
- Steatosis
- Inflammation
- Liver fibrosis
- Macrophage activation

PPAR, peroxisome proliferator–activated receptor.

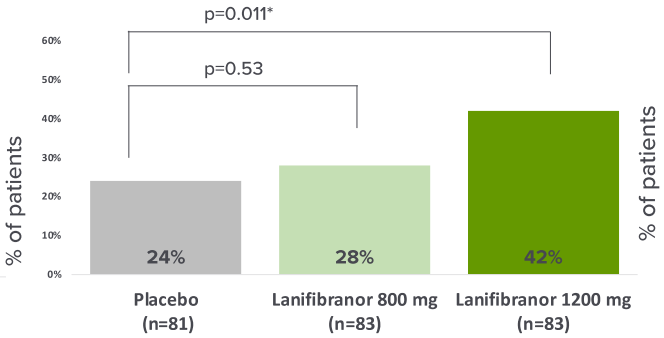
Francque SM et al. *N Engl J Med*. 2021;385:1547-1558; Lefere S et al. *J Hepatol*. 2020;73:757-770.

Lanifibranor - Phase 2B Results

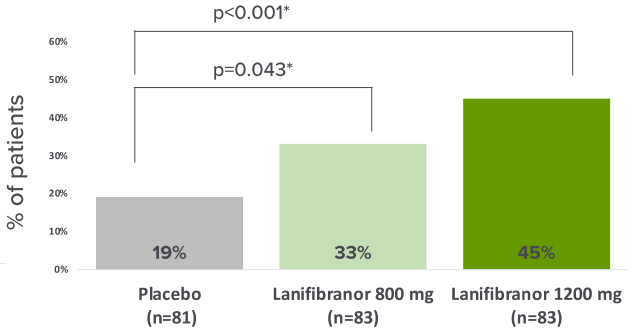
Primary Endpoint: Reduction of ≥ 2 points of SAF Activity Score and no worsening of fibrosis



Secondary Endpoint: Improvement of ≥ 1 Stage of fibrosis and no worsening of NASH

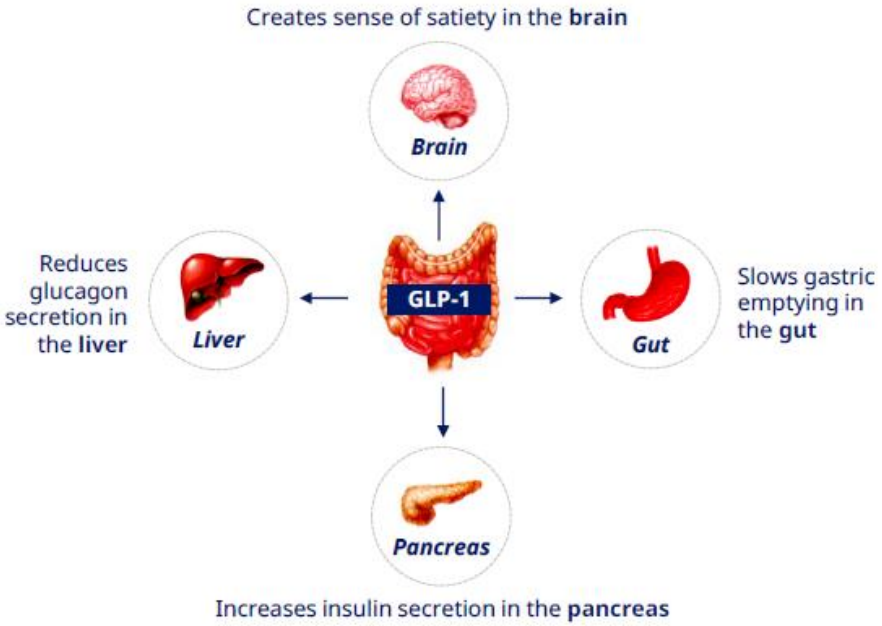


Secondary Endpoint: Resolution of NASH and no worsening of fibrosis



Francque SM et al. *N Engl J Med*. 2021;385(17):1547-1558.

Semaglutide - Mode of Action



GLP-1 released from gut enteroendocrine cells, controls meal-related glycemic excursions through augmentation of insulin and inhibition of glucagon secretion

Semaglutide is a GLP-1 receptor agonist and has shown in clinical trials to,

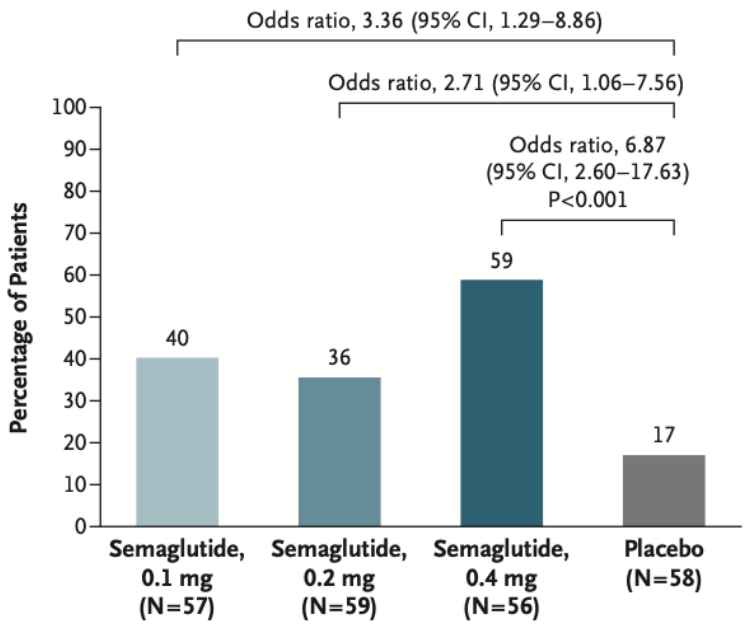
- Induce weight loss
- Improve liver-enzyme levels
- Reduce liver fat
- Have beneficial effect on histologic resolution

GLP-1, glucagon-like peptide 1.

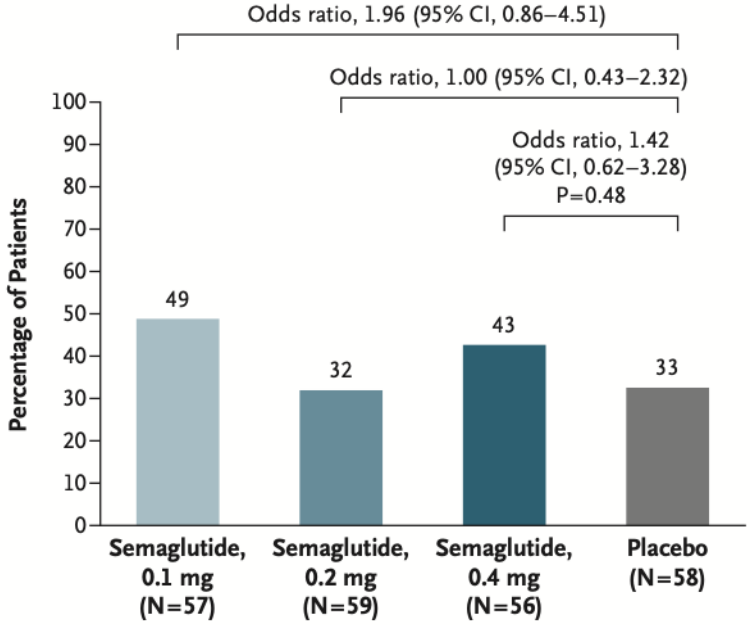
Drucker DJ. *Cell Metab*. 2018;27:740-756; Newsome PN et al. *N Engl J Med*. 2021;25:384:1113-1124.

Semaglutide - NASH Phase 2 Results

Primary Endpoint: Resolution of NASH with no Worsening of Liver Fibrosis

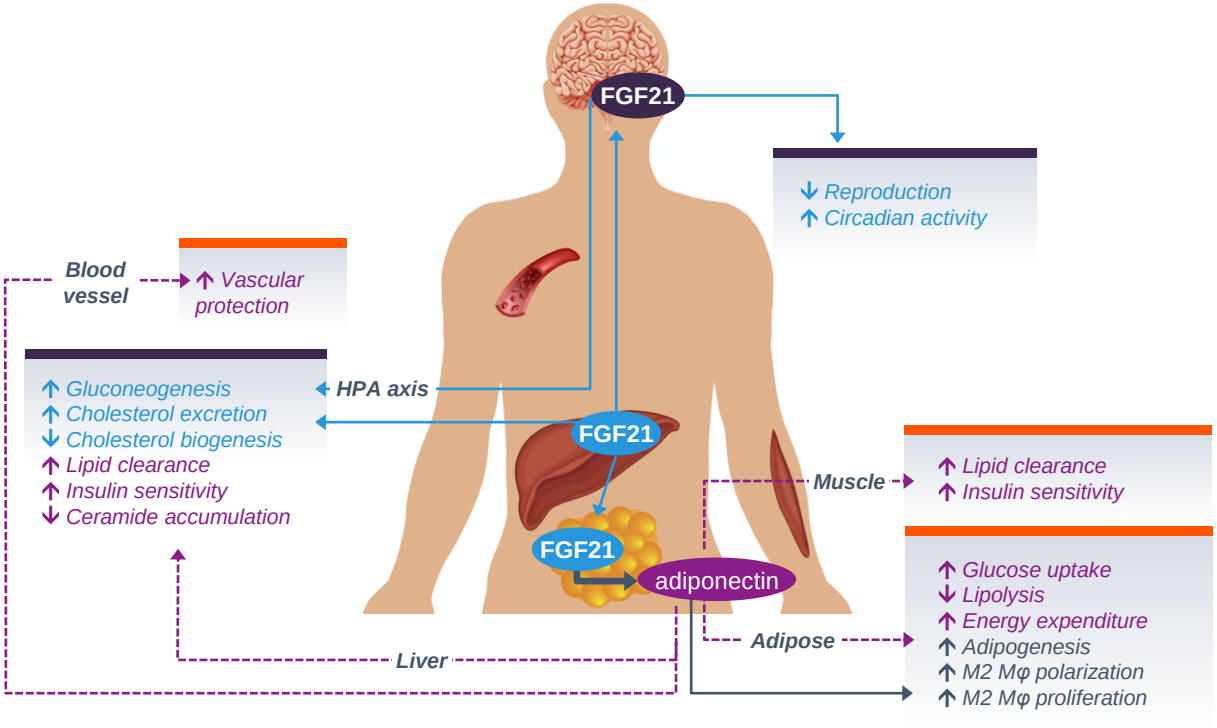


Secondary Endpoint: Improvement in Liver Fibrosis with no Worsening of NASH



Newsome PN et al. *N Engl J Med*. 2021;384:1113-1124.

Efruxifermin – Mode of Action



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

Reduces liver fat by action within liver and from periphery

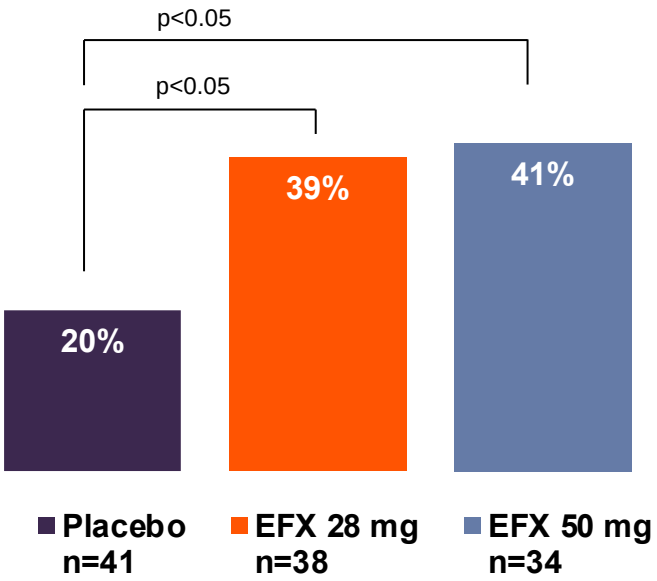
Impacts liver fibrosis via metabolic pathway and upregulation of adiponectin

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

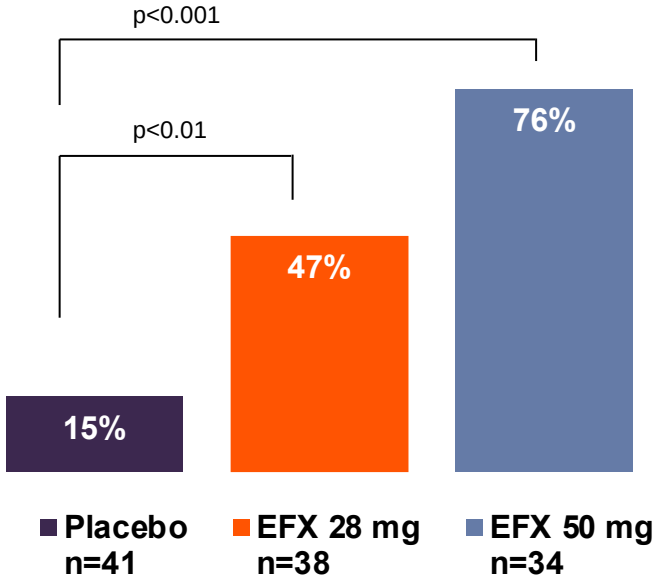
Geng L et al. *Nat Rev Endocrinol*. 2020 Nov;16:654-667.

Efruxifermin – Phase 2B Results

Both EFX Doses Achieved Statistical Significance on Primary Endpoint (Fibrosis Improvement)



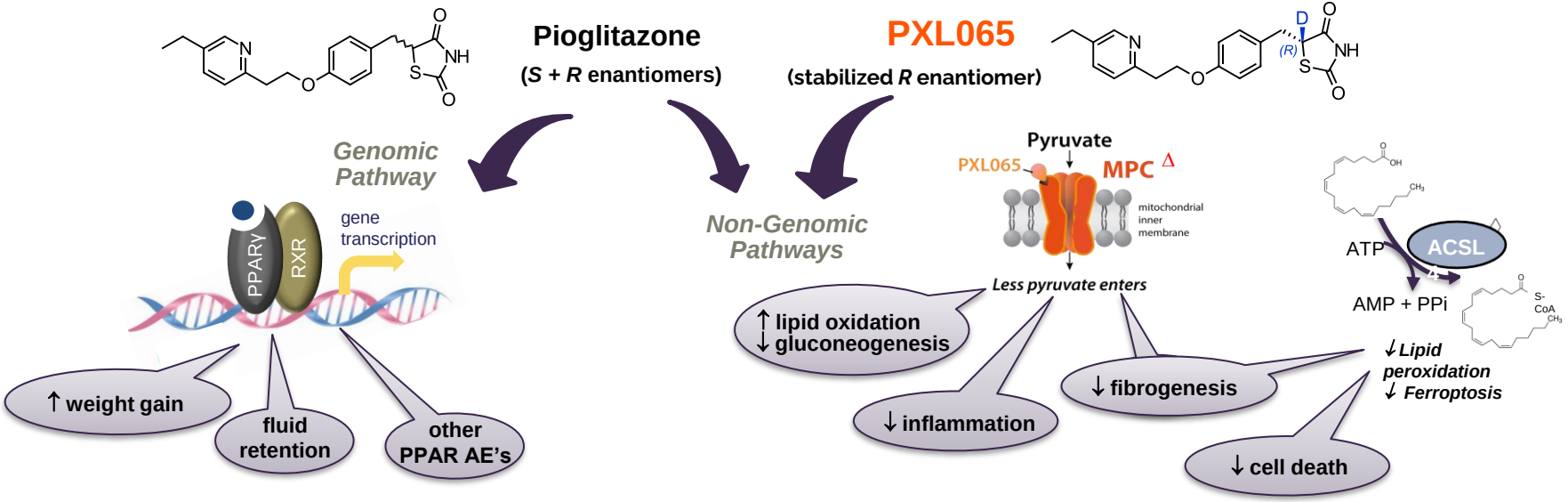
Both EFX Doses Achieved Statistical Significance on Key Secondary Endpoints (NASH Resolution)



Harrison S. Oral Presentation. *AASLD*. 2023.

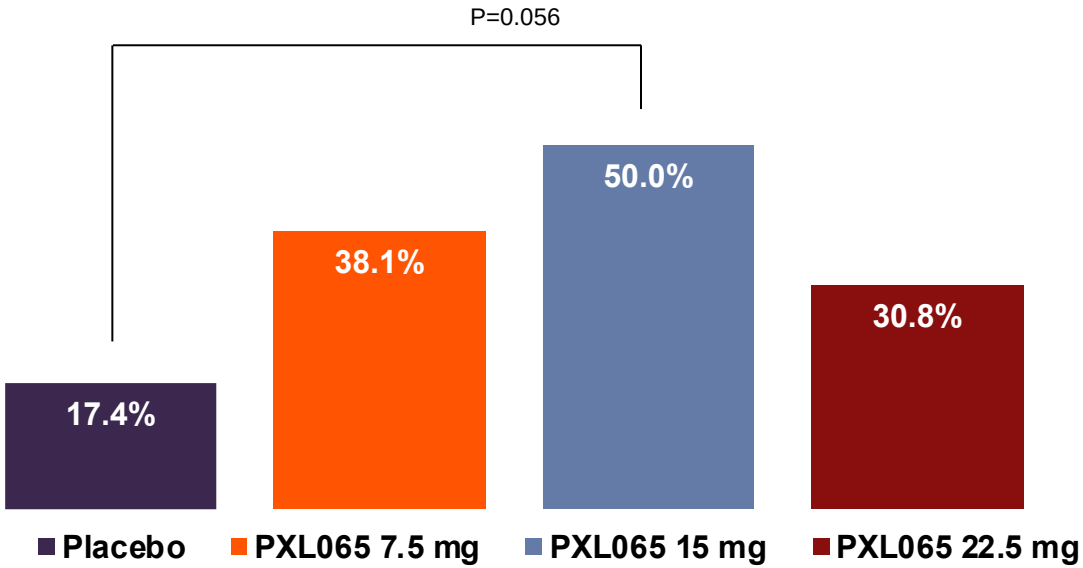
PLX065 – Mechanism of Action

PXL065 is deuterium-stabilized single stereoisomer; selectively mediates non-PPARg effects of pioglitazone (retains efficacy in preclinical NASH models with no significant weight gain-fluid retention)



PLX065 – Phase 2 Results

Secondary Endpoint: Improvement in Liver Fibrosis with no Worsening of NASH



Harrison S. Oral Presentation. *AASLD*. 2023.

My Perspective on Non-cirrhotic NASH Histopathologic and Extrahepatic Profiles

DRUGS in PHASE 3

- Resmetirom
- Obeticholic acid
- Lanifibranor
- Semaglutide

DRUGS with PHASE 2 biopsy results

- PXL065
- Efruxifermin

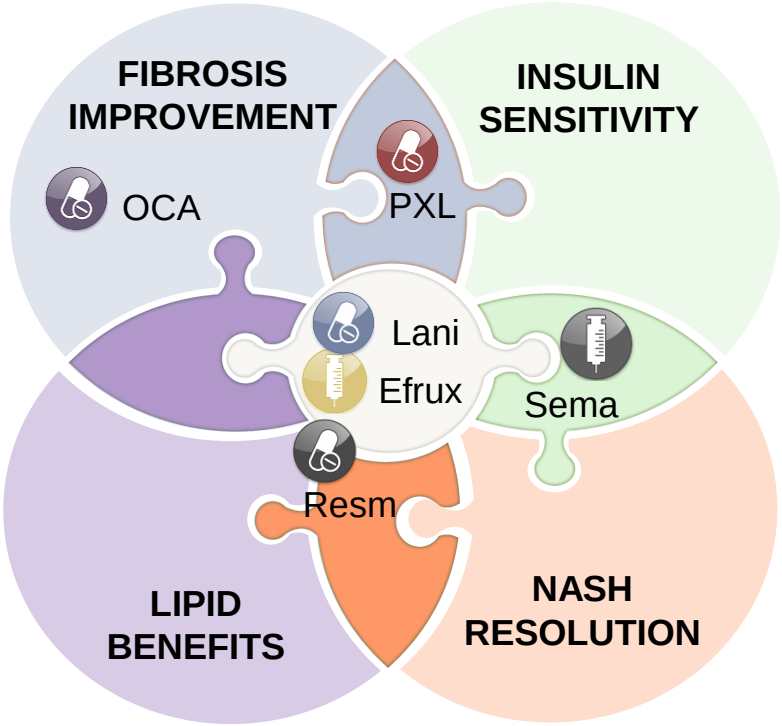
My Perspective on Non-cirrhotic NASH Histopathologic and Extrahepatic Profiles

DRUGS in PHASE 3

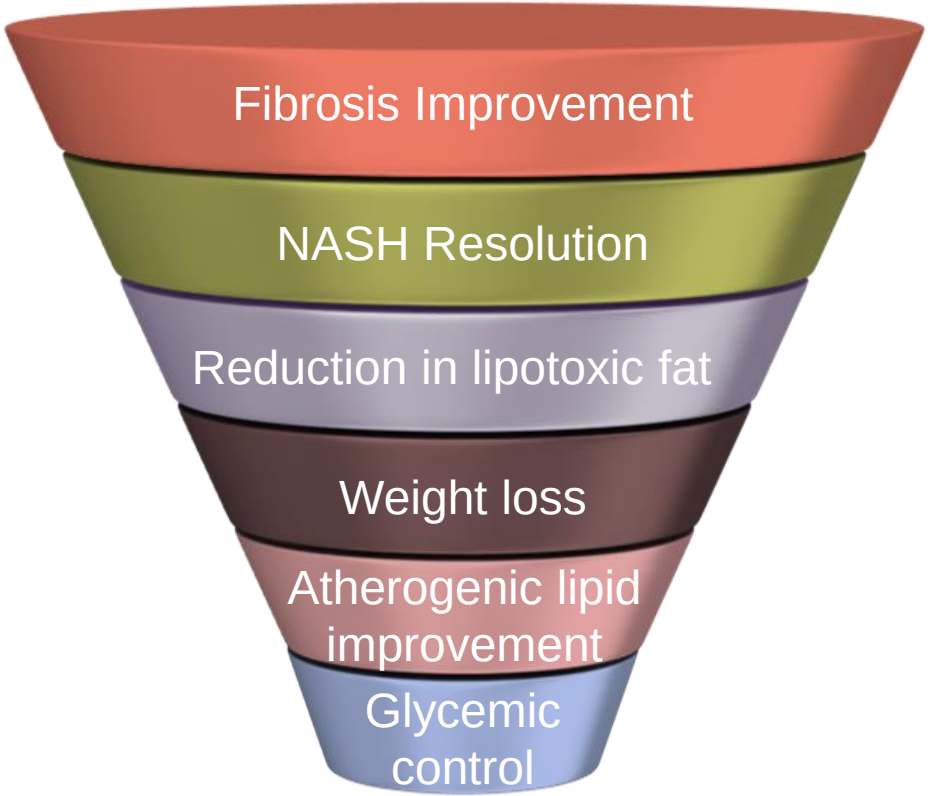
- Resmetirom – safety/tolerability
- Obeticholic acid - safety/tolerability
- Lanifibranor - safety/tolerability
- Semaglutide - safety/tolerability

DRUGS with PHASE 2 biopsy results

- PXL065 – safety/tolerability
- Efruxifermin - safety/tolerability



A Single Therapy Is Not Likely to Be Enough

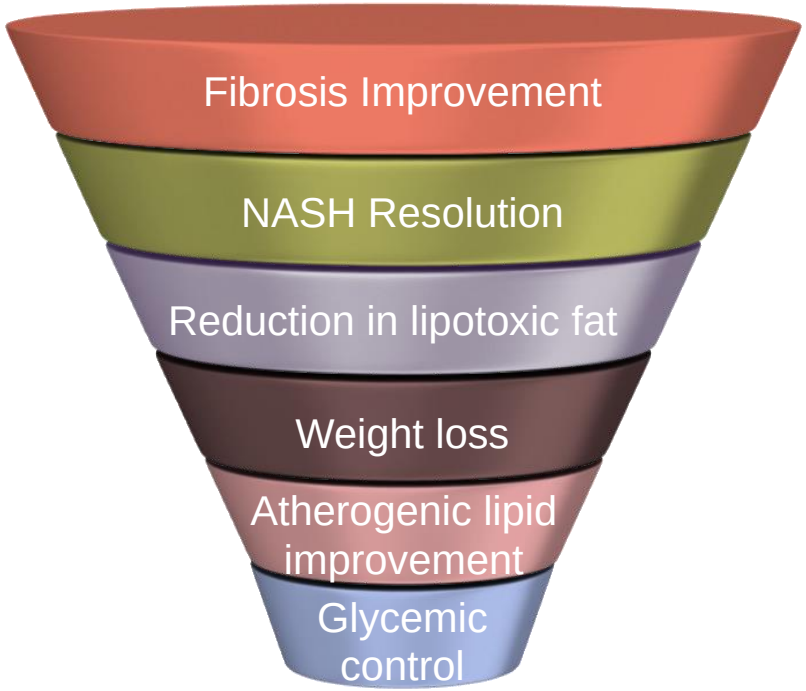


Multifactorial metabolic milieu of NASH warrants potential therapies targeting many pathways

Ideal Combination: Expert Insight

Oral- long-term
Injection- Induction or intermittent use
Well tolerated and safe
Synergistic
- Improves histopathology
- Improves extrahepatic metabolic profiles

Enhances long-term outcomes

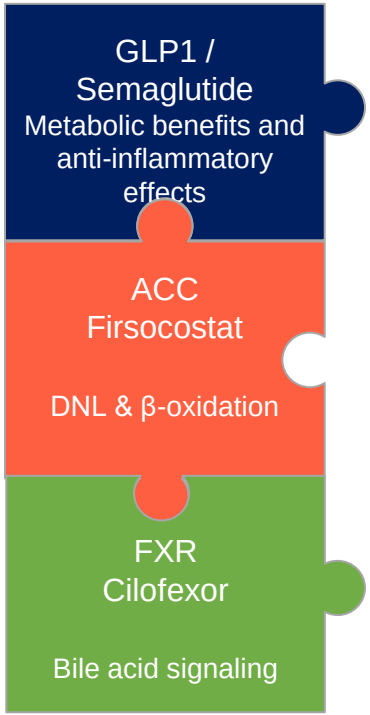


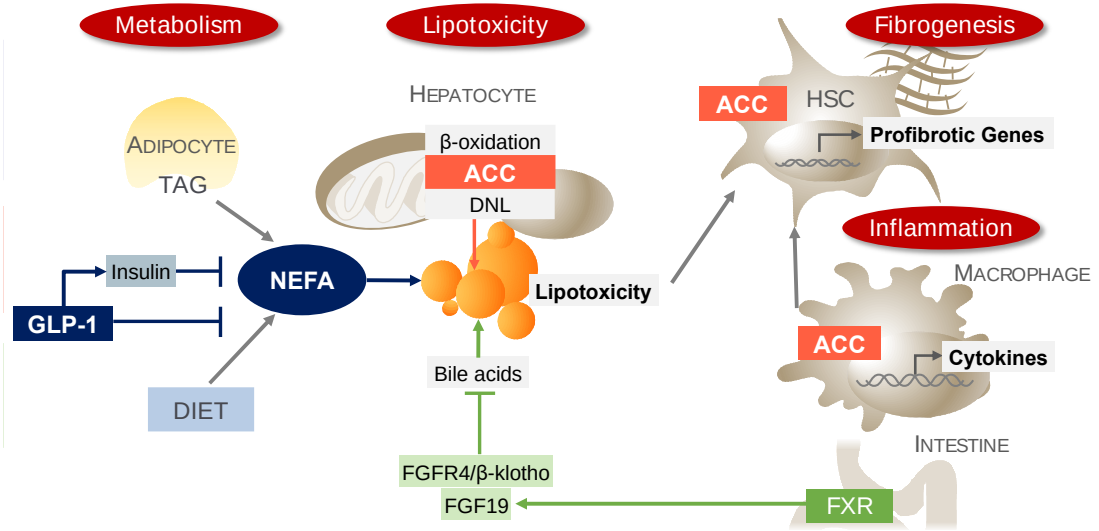
Jamaican 4x100M
Relay World Record Seoul, Sept 4th 2011

All:

- World class sprinters in their own right
- Got along well with each other
- Had complementary strengths
- Similar endurance
- Same home

Semaglutide + Firsocostat + Cilofexor Rationale for the Combination





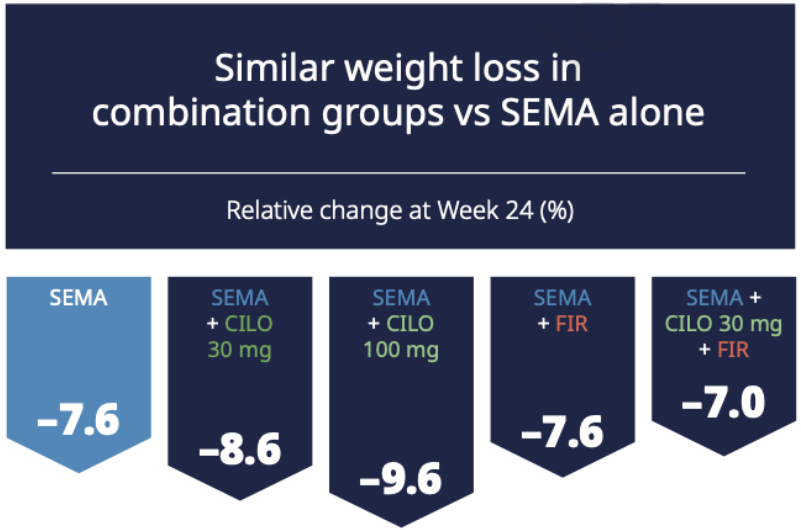
Pathogenesis of NASH is multifactorial and patient population is heterogeneous
Semaglutide, firsocostat, and cilofexor target distinct and complementary mechanisms

ACC, acetyl-CoA carboxylase; DNL, de novo lipogenesis; FGF19, fibroblast growth factor 19; FGFR4, FGF receptor 4; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HSC, hepatic stellate cell; NASH, non-alcoholic steatohepatitis; NEFA, non-esterified fatty acids; TAG, triacylglycerol.

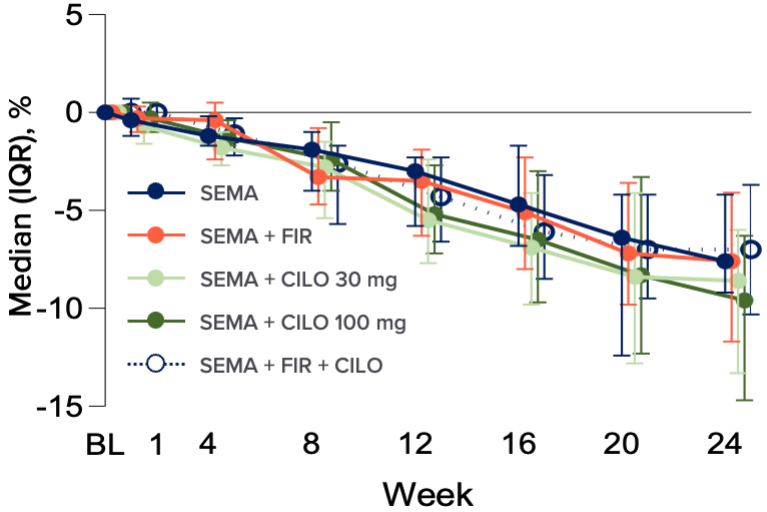
1. Marso SP et al. *N Engl J Med*. 2016;375:1834-44; 2. Rakipovski G et al. *JACC Basic Transl Sci*. 2018;3:844–57; 3. Marra F. *J Hepatol*. 2018;68:280–95; 4. Newsome PN et al. *AASLD*. 2020, abstr 10; 5; Loomba R et al. *Gastroenterology*. 2018;155:1463–73; 6. Patel K et al. *Hepatology*. 2020;72:58–71; 7. Alkhouri N et al. *J Hepatol*. 2022;77(3):607-618.

Semaglutide + Firsocostat + Cilofexor

Relative Change at Week 24



Relative Change from Baseline

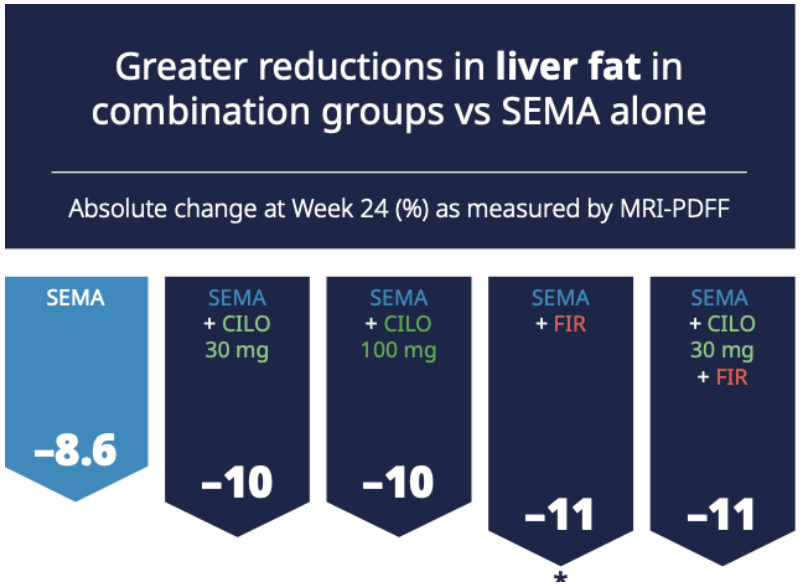


BL, baseline; CILO, cilofexor; FIR, firsocostat; IQR, interquartile range; SEMA, semaglutide.

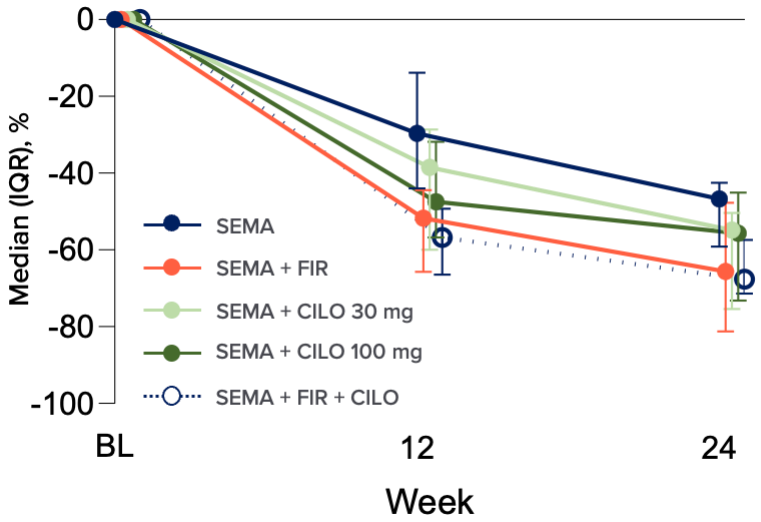
Alkhouri N et al. *J Hepatol*. 2022;77(3):607-618.

Semaglutide + Firsocostat + Cilofexor

Relative Change at Week 24



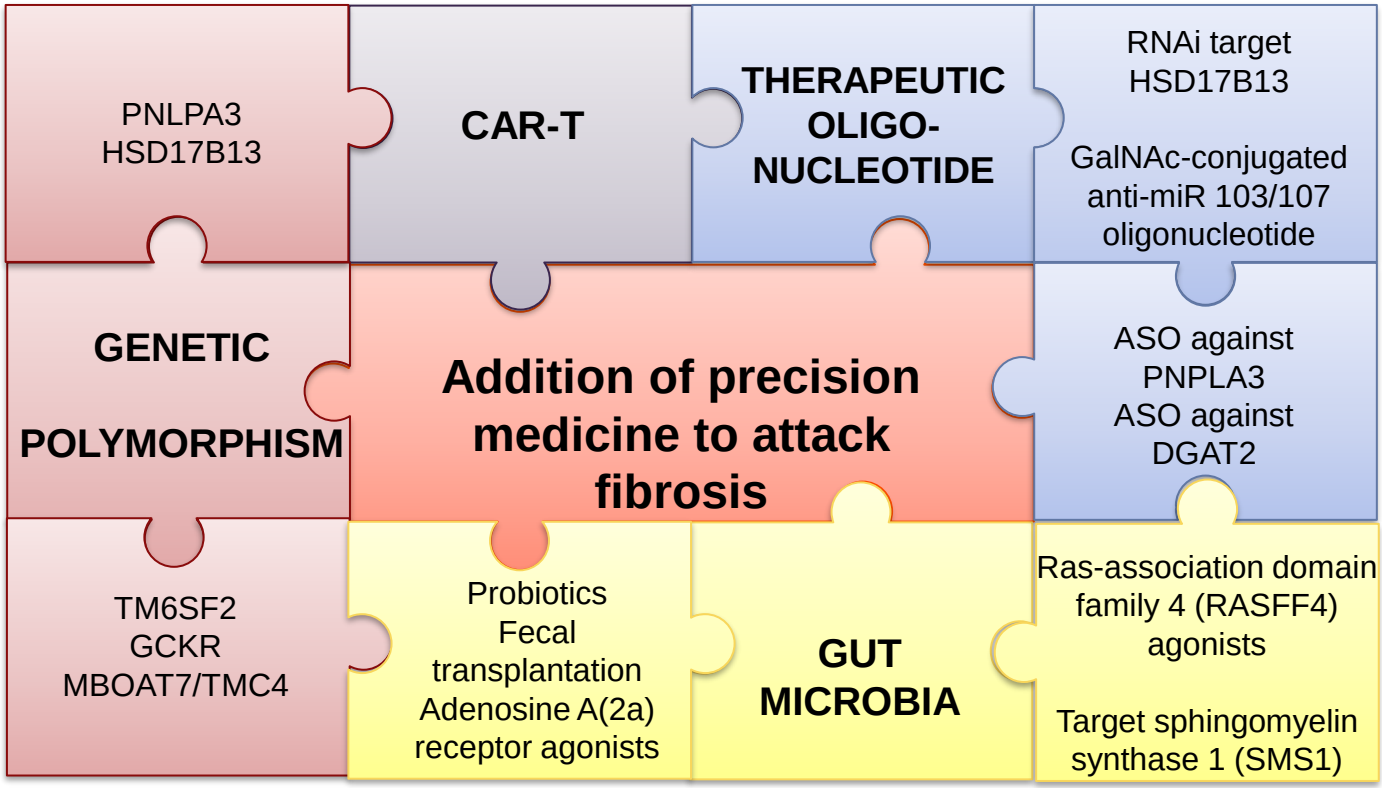
Relative Change from Baseline



Data collected beyond 30 days after last dose of any study drug excluded from analysis. Changes in PDFF based on ANCOVA models adjusted for BL and diabetes status.

* p<0.05 vs SEMA alone. ANCOVA, analysis of covariance; BL, baseline; CAP, Controlled Attenuation Parameter; CI, confidence interval; CILO, cilofexor; FIR, firsocostat; IQR, interquartile range; LSmean, least squares mean; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; SEMA, semaglutide. Alkhouri N et al. *J Hepatol*. 2022;77(3):607-618.

Future Therapeutic Considerations



Amor C. *Nature*. 2020 ; Alkhouri, Exp Opin Invest Drugs, 2021; Xu X, Signal Transduction and Targeted Therapy 2022; Carlsson B, AP&T 2020.

THANK YOU