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2020 Third Annual National Conference

November 19-21, 2020

Red Rock Hotel – Las Vegas, NV

Annenberg Center For Health Sciences at Eisenhower
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New and Developmental Agents for NASH

Disclosures

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- Speakers Bureau: Intercept Pharmaceuticals, Clinical Area-NASH, PBC
- Speakers Bureau: Salix, Clinical Area-IBS, HE

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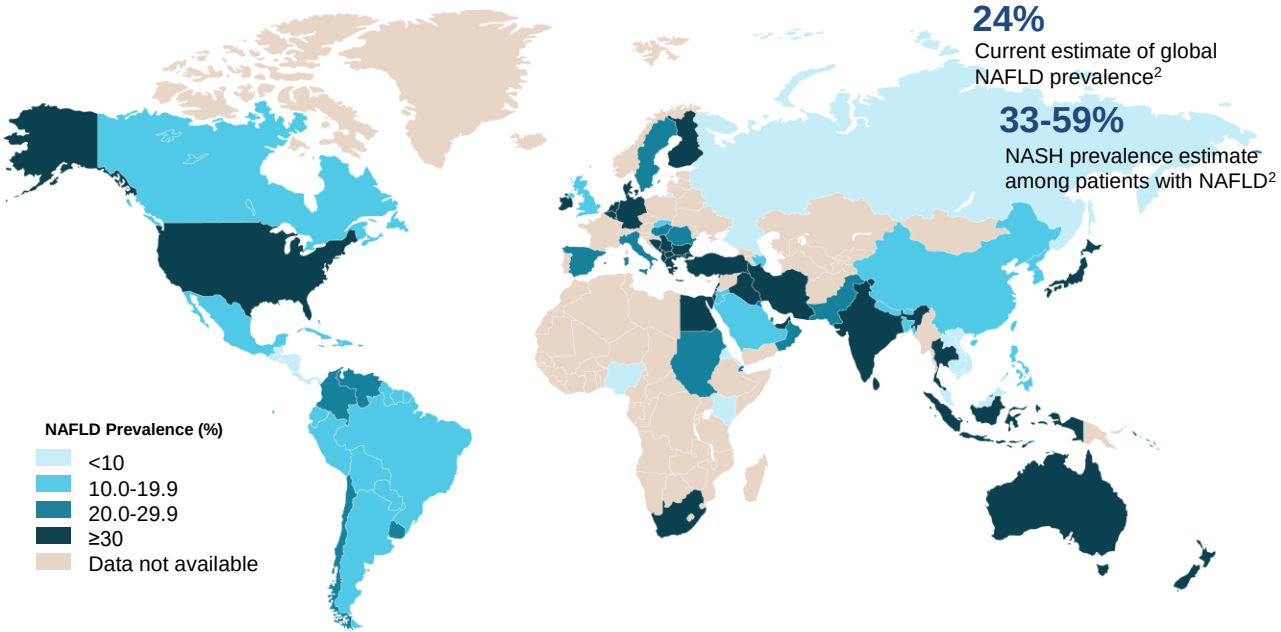
Why Is Drug Development for NASH Important?

NAFLD Is Among the Most Important Causes of Liver Disease Worldwide



1. Younossi Z, et al. *Nat Rev Gastroenterol Hepatol.* 2017;15:11-20; **2**. Younossi ZM, et al. *Hepatology*. 2016;64(1):73-84.

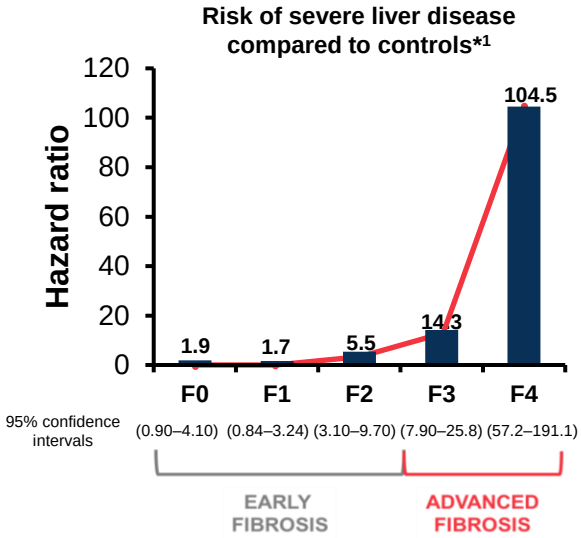
Patients With NAFLD/NASH Have Increased Mortality

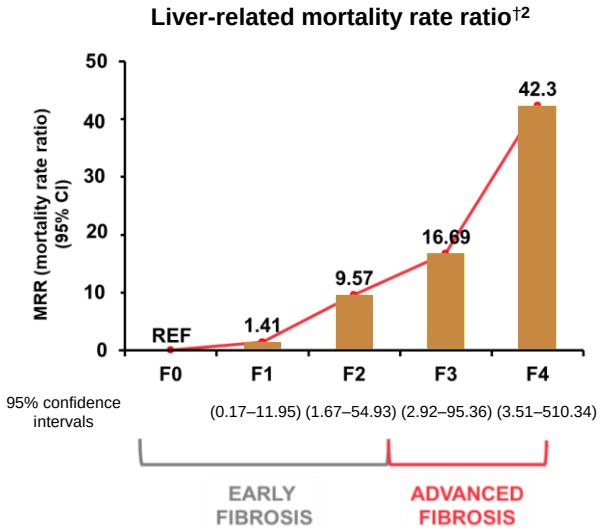
- Although both overall mortality and **liver-specific** mortality are increased in NAFLD, **cardiovascular (CV)** disease remains the most common cause of death ranging from **12.7%–38.3%**[2-7]

Author	N	FU (yr)	CVD Death	Findings
Angulo	619	12.6	38.3%	CVD most common COD Fibrosis predicts death
Söderberg	118	24	30%	↑Death in NASH, CVD most common COD
Ekstedt	129	13.7±1.3	16%	↑CVD death NASH CVD most common COD in NASH but no ss
Dam-Larsen	170	20.4	38%	No difference between SS and control
Rafiq	173	18.5	12.7%	CVD most common COD
Stepanova	289	12.5	27.8%	CVD most common COD

1. Targher G, et al. *Diabetes*. 2005;54(12):3541-3546; 2. Angulo, et al. *Gastroenterology*. 2015;149(2):389-397;
3. Söderberg, et al. *Hepatology*. 2010;51(2):595-602; 4. Ekstedt M, et al. *Hepatology*. 2006;44(4):865-873;
5. Dam-Larsen S, et al. *Scand J of Gastroenterol*. 2009;44(10);1236-1243; 6. Rafiq N, et al. *Clin Gastro Hep*. 2009;7(2):
234 -238; 7. Stepanova M, et al. *Digestive Diseases and Sciences*. October 2013, Volume 58, Issue 10, pp 3017–3023.

Advanced Fibrosis Exponentially Increases the Risk of Liver-Related Morbidity and Mortality





Risk of liver-related morbidity and mortality increases exponentially with increasing fibrosis stage and patients with advanced fibrosis are at the greatest risk[1,2]

1,*From a retrospective cohort study of 646 biopsy-proven NAFLD patients, each matched to 10 controls;
2, †From a meta-analysis of 5 multinational cohorts (17,452 PYF).
CI, confidence interval; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PYF, patient years of follow-up.
Adapted from Hagström H, et al. *J Hepatol.* 2017;67:1265 –1273; Adapted from Dulai PS, et al. *Hepatology.* 2017;65(5):1557–1565;
1. Hagström H, et al. *J Hepatol.* 2017;67:1265 –1273; 2. Dulai PS, et al. *Hepatology.* 2017;65(5):1557–1565.

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Clinical Trial Endpoints: What Are We Looking at?

FDA Efficacy Endpoints for Phase 3 Trials: Liver Histologic Improvement

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- No worsening of steatohepatitis

1. US FDA. Draft Guidance. Noncirrhotic NASH With Liver Fibrosis. December 2018.

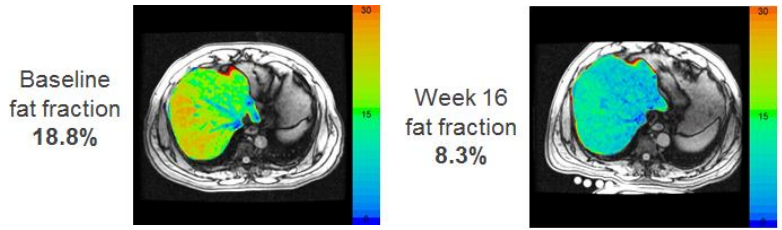
FDA Efficacy Endpoints for Early Phase 2 Trials

Liver Fat Fraction (MRI-PDFF)

- **≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAFLD**

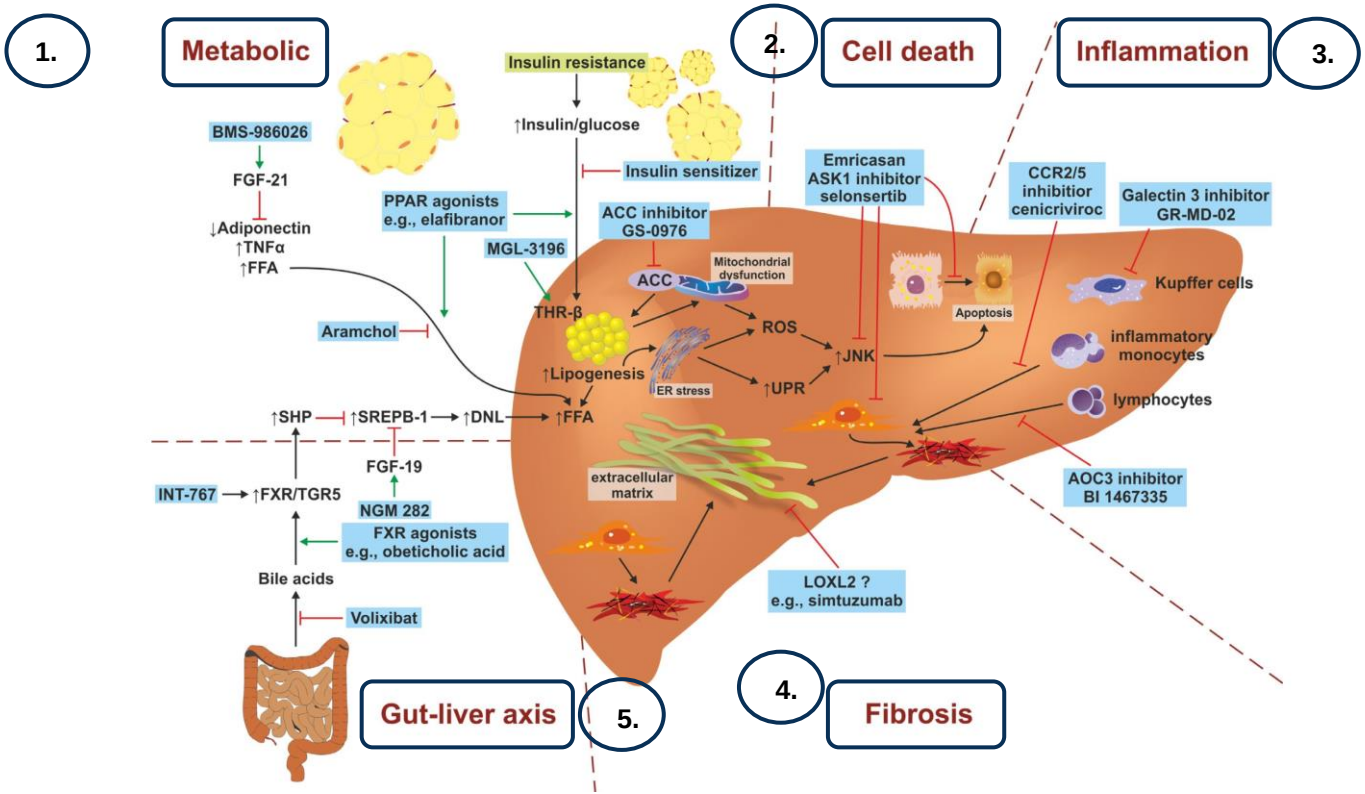
ALT

- **10 U/L reduction in ALT associated with histologic improvement or resolution of NASH[1]**



1. Vuppalanchi. *Clin Gastroenterol Hepatol*. 2014;12:2121; 2. Patel. *Therap Adv Gastro.* 2016;9:692.

Therapeutic Targets in NAFLD/NASH



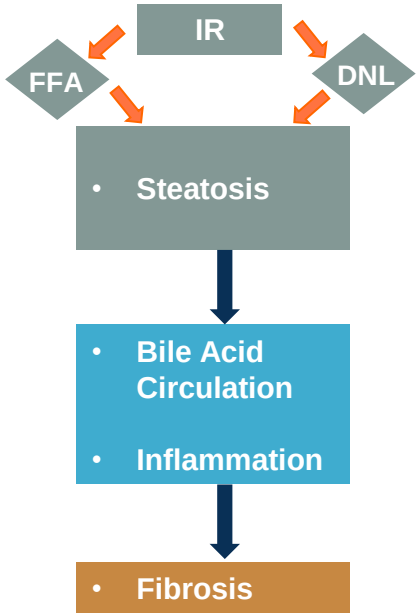
Tacke F, et al. *Exp Rev Gastroenterol Hepatol*. 2018.

NASH Agents in Phase 3 Clinical Development

Agent	Target (mechanism)	Trial, patients and primary endpoint(s)
Cenicriviroc	Inflammation/ immune activation (CCR2/5 antagonist)	**AURORA (n=2000*, fibrosis stage 2–3)** • Fibrosis improvement ≥1 stage without NASH worsening • Composite of progression to cirrhosis, liver-related clinical outcomes and all-cause mortality
Elafibranor	Lipotoxicity/ oxidative stress (PPARα/δ agonist)	**RESOLVE-IT (n=2000*, fibrosis stage 1–3)** • NASH resolution without worsening of fibrosis • Long-term composite of all-cause mortality, cirrhosis and liver-related events
Obeticholic acid	Lipotoxicity/oxidative stress (FXR agonist)	**REGENERATE (n=2065*, fibrosis stage 1–3)** • Fibrosis improvement ≥1 stage without NASH worsening • NASH resolution without fibrosis worsening • All-cause mortality and liver-related events **REVERSE (n=540*, compensated cirrhosis)** • Fibrosis improvement ≥1 stage without NASH worsening
Selonsertib	Apoptosis/necrosis (ASK1 inhibitor)	**STELLAR-4 (n=883, compensated cirrhosis)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival **STELLAR-3 (n=808, fibrosis stage 3)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival
Resmetirom (MGL-3196)	Lipotoxicity (TRß agonist)	**Phase 3 study (n=2000*, fibrosis stage 2–3)** • NASH resolution and 2 point improvement in NAS without worsening of fibrosis
Aramchol	Lipotoxicity (FABAC)	**Phase 3 study (n=2000*, fibrosis stage 2–3)** • NASH resolution without worsening of fibrosis or fibrosis improvement without worsening of NASH

The Race to Cure NASH: Medications in Phase 3 Trials

- **Resmetirom:** TRHb agonist **(MAESTRO)**
- **Obeticholic acid (OCA):** FXR agonist **(REGENERATE)**
- **Cenicriviroc (CVC):** CCR2/CCR5 inhibitor **(AURORA)**



Alkhouri, et al. *Clinical Liver Disease*. 2018.

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Metabolic Targets: Resmetirom

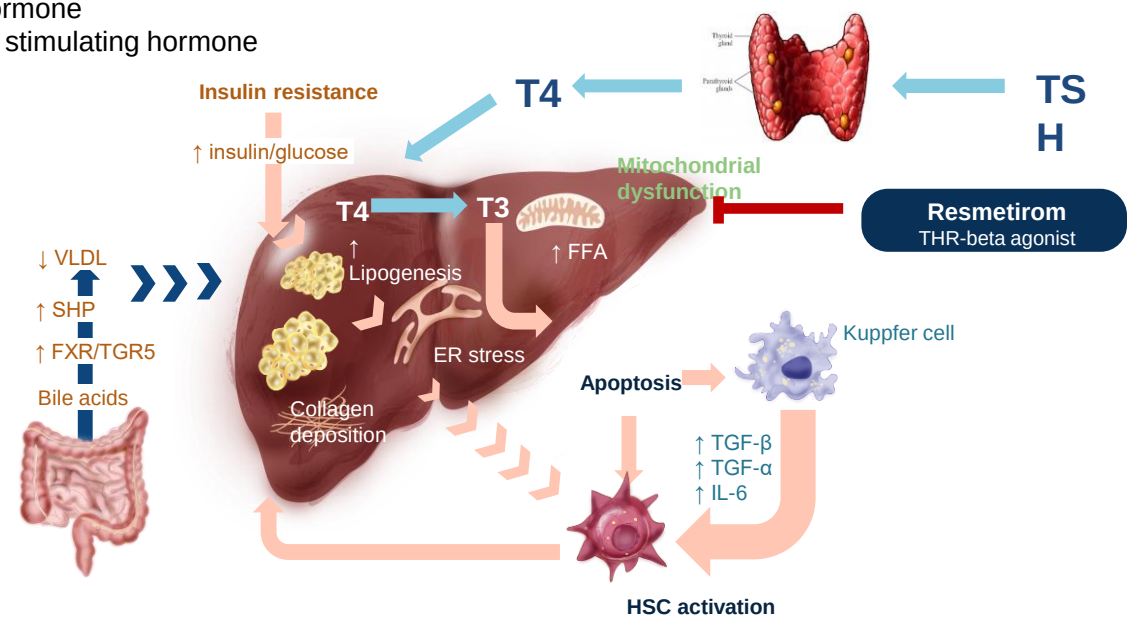
Phase 3 NASH Clinical Trials, Ongoing: MAESTRO-NASH and MAESTRO-NAFLD-1

Compound/ Indication	Clinical Trial	Pre-Clinical	Phase 1	Phase 2	Phase 3	Description
Resmetirom (MGL-3196) **Thyroid Hormone Receptor-beta (THR-B) Agonist**	**Phase 2** MGL-3196-05	Completed				❑ MRI-PDFF, biopsy: positive • 36 week with 36 week open-label extension *Harrison Lancet. 2019 Nov 30;394(10213):2012-2024. doi: 10.1016/S0140-6736(19)32517-6*
Treatment of NASH	**Phase 3** MAESTRO-NASH	Recruiting →				❑ Treatment of NASH with Fibrosis Stage 2-3 • Serial liver biopsy • 52 week phase 3; • 54 month Phase 4
	Phase 3 MAESTRO-NAFLD-1 (presumed NASH)	Recruiting →				❑ Treatment of NASH (recent inclusion of compensated cirrhotic/renal impairment) • 52 week • *Safety, Lipids and NASH biomarker and imaging study*

Harrison, Stephen. Resmetirom for the Treatment of NASH. https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/.

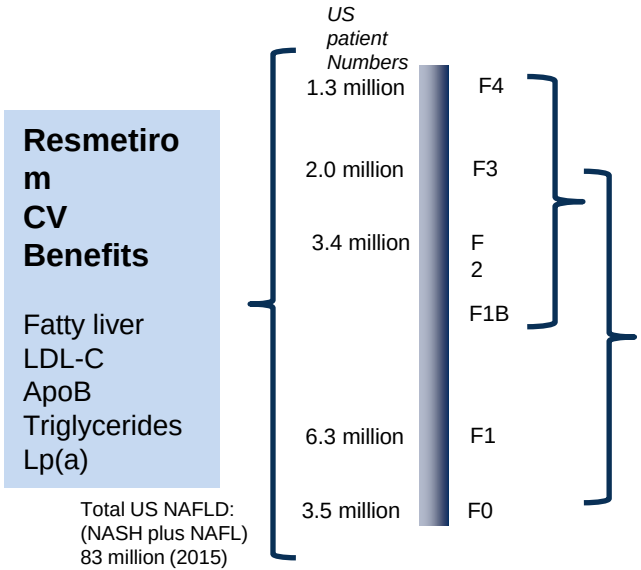
Mechanisms of Late-Stage Investigational Agents for NASH: Resmetirom

T4 prohormone
T3, active hormone
TSH, thyroid stimulating hormone



ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Adapted from Konerman MA, et al. *J Hepatol*. 2018;68:362-365.

Resmetirom Development Path Across the Spectrum of NAFLD/NASH



NASH/NALFD Spectrum

Phase 3 MAESTRO-NASH study:

- F2/F3 NASH with Metabolic Syndrome
- NASH Resolution (primary), LDL-C, fibrosis (key secondary);
- **Phase 4 (post-approval):** cirrhosis and MACE

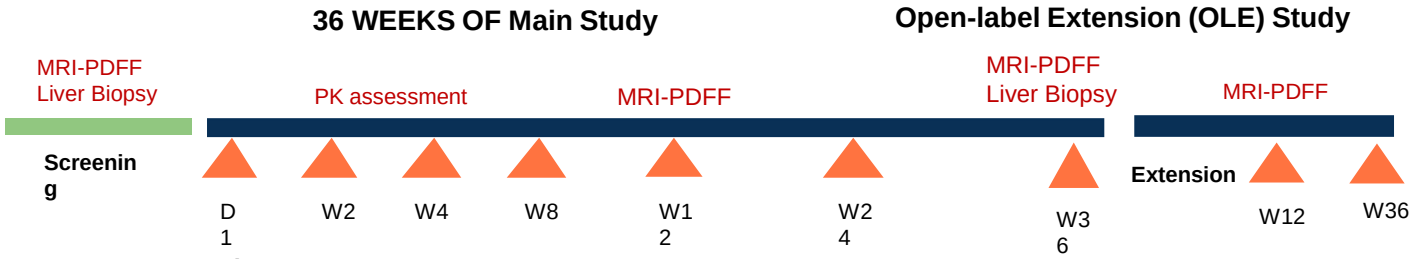
Phase 3 MAESTRO-NAFLD-1 study:

- F1-F3 NASH with Metabolic Syndrome diagnosed non-invasively (no liver biopsy required)
- 100mg Open label arm
- Recent addition of compensated cirrhosis and renal impairment for safety analysis
- Endpoints: Safety, LDL-C, lipids, MRI-PDFF, PRO-C3

Data show that NASH with fibrosis is associated with high CV risk.

Estes, et al; *Hepatology*. Vol. 67, No. 1, 2018; Henson. *Aliment Pharmacol Ther*. 2020,51(7): 728-736; Harrison, Stephen. Resmetirom for the Treatment of NASH.
https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/

Phase 2 NASH Study Design: Randomized, Double Blind, Placebo Controlled

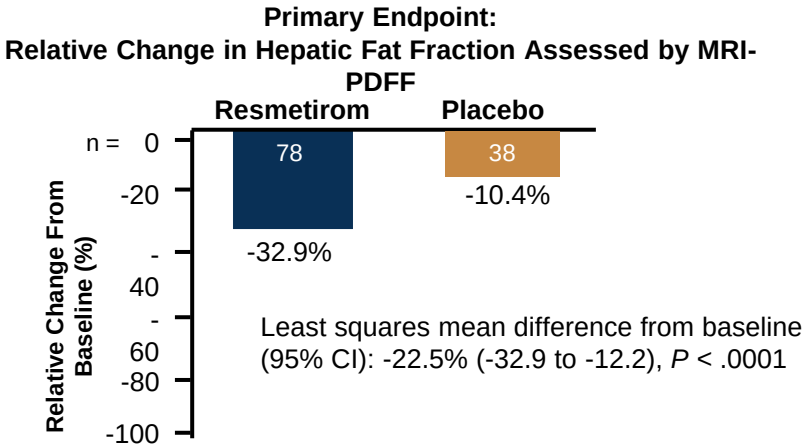


- **Comparator/Arms**
  - 2:1 Resmetirom to placebo
  - 125 patients enrolled in USA, 18 sites
  - Resmetirom or placebo, oral, once daily; dose 80mg (+/- 20mg dose adjustment possible at week 4)
- **Inclusion/Exclusion**
  - NASH on liver biopsy: NAS>/=4 with fibrosis stage 1-3
  - >/=10% liver fat on MRI-PDFF
  - Includes diabetics, statin therapy, representative NASH population
- **36 week extension study in 31 patients who completed the main 36 week study – all received 80 or 100mg of Resmetirom**

Harrison. *Lancet*. 2019 Nov 30;394 (10213):2012-2024. November 11, 2019.
https://doi.org/10.1016/S0140-6736(19)32517-6.

Resmetirom: Wk 12 Efficacy for Treatment of NASH (ITT Population)

- Randomized, double-blind, placebo-controlled phase II trial in patients with biopsy-confirmed NASH with hepatic fat fraction ≥ 10%

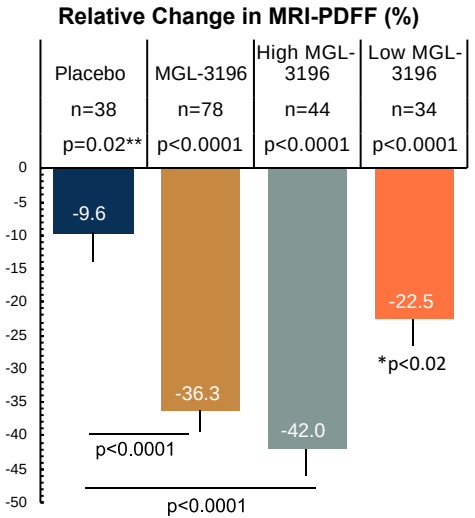


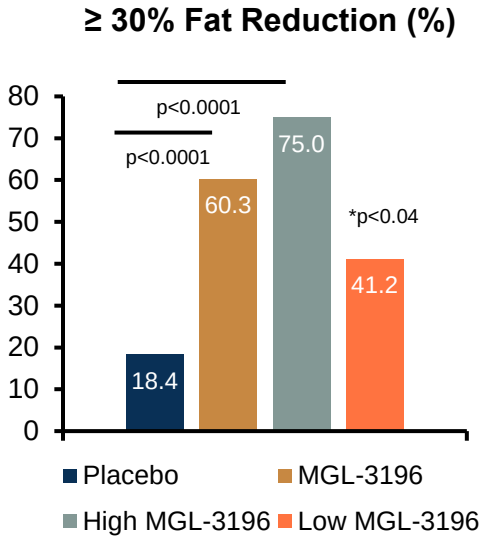
Slide credit: clinicaloptions.com.

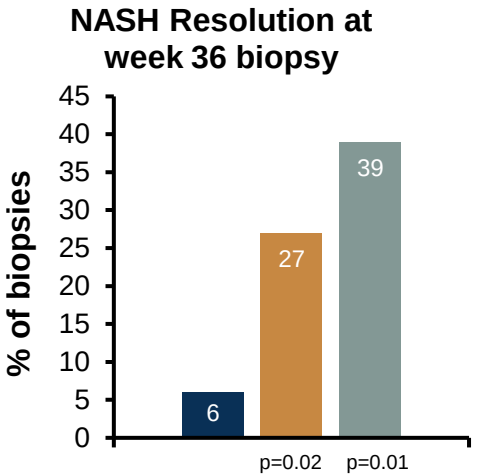
Harrison. *Lancet*. 2019 [Epub].

Resmetirom Significantly Decreases Hepatic Fat in NASH Patients at Week 12 MRI-PDFF, and Was Associated With NASH Resolution at Week 36 Biopsy

Fat Reduction at week 12 MRI-PDFF

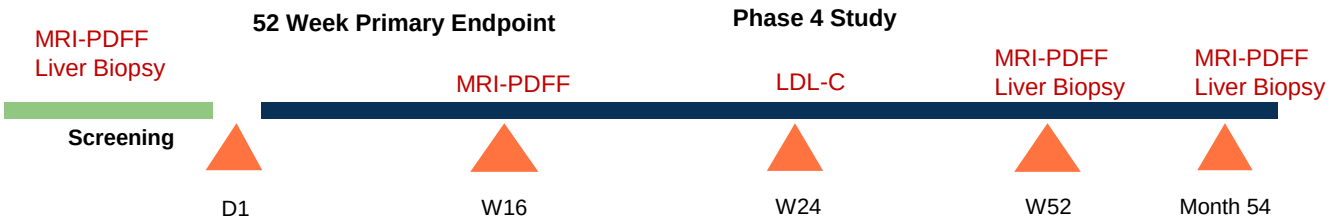






Harrison SA, et al. *J Hepatol.* 2019;70(suppl):e791-e792. Abstract SAT-347.

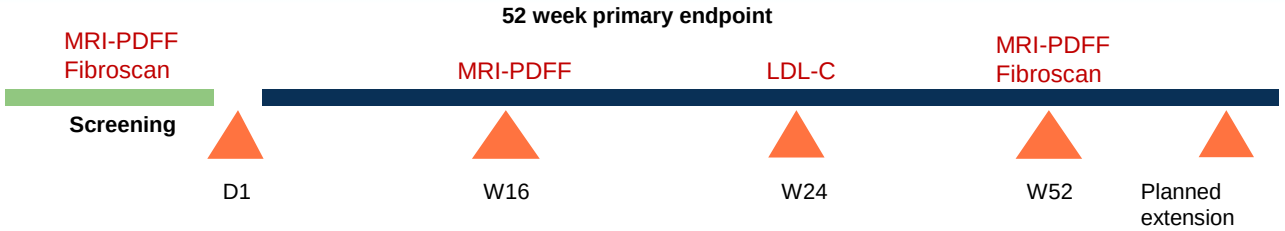
Phase 3/4 MAESTRO-NASH Study Design: Randomized, Double Blind, Placebo Controlled: Serial Liver Biopsy Study



- **Comparator/Arms**
  - 1:1:1 MGL-3196 80, 100mg, placebo
  - 900 F2/F3 patients enrolled in USA, Europe for primary Week 52 analysis, 200 F1 patients
  - Up to 2000 patients total enrollment for Phase 4 including first 900
  - >150 centers, world-wide
- Key **inclusion/exclusion**
  - Requires 3 metabolic risk factors (Metabolic Syndrome); Fibroscan kPa consistent with F2-F3 CAP >=280
  - NASH on liver biopsy; NAS>=4 with fibrosis stage 1A (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, and remainder F2
  - >= 8% liver fat on MRI-PDFF
- **Primary Endpoints**
  - Resolution of NASH at week 52 with at least 2 point reduction in NAS with no worsening of fibrosis
  - Phase 4: reduction in liver related events or progression to cirrhosis
  - Key secondary endpoints: Additional NASH biopsy endpoints, imaging MRI-PDFF, Fibrosis biomarkers
  - Composite liver-related outcome at 54 months (histologic evidence of cirrhosis on biopsy, MELD>=15, hepatic decompensation, liver transplant, all cause mortality)

Harrison, Stephen. Resmetirom for the Treatment of NASH. https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/.

Phase 3 MAESTRO-NAFLD-1 Trial (Presumed NASH) Study Design: Randomized, Double Blind, Placebo Controlled



- **Comparator/Arms**
  - 1:1:1:1 MGL-3196 80, 100mg, placebo, open label arm: NASH patients on 100mg Resmetirom to assess non-invasive measures of safety and efficacy and will include special safety populations with compensated cirrhosis and renal impairment)
  - 800 patients (Open label-100mg arm in up to 200 patients) excludes advanced patient F2/F3 NAS >=4 who qualify for MAESTRO-NASH
  - Up to 65 centers US
- Key **inclusion/exclusion**
  - Requires 3 metabolic risk factors (Metabolic syndrome)
  - Fibroscan kPa.>=F1, CAP>=280, except where eligible for MAESTRO-NASH
  - MRI-PDFF (>=8%)
- **Primary Endpoints**
  - Evaluate the tolerability and safety of Resmetirom 80mg or 100mg versus placebo measured by incidence of AE's
  - Key secondary endpoints: MRI-PDFF, Fibrosis biomarkers, LDL cholesterol, TG's, ApoB, PRO-C3

Harrison, Stephen. Resmetirom for the Treatment of NASH. https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/.

Safety

- AE’s, mostly mild, a few moderate balance between groups. Increase in Resmetirom treated relative to placebo in loose stools, typically a single episode, only at the beginning of therapy, GI AE’s no increased over placebo in Phase 1 or NASH extension study
- No lab abnormalities or other AE’s were increased in Resmetirom compared to placebo group
- No effects on thyroid axis hormones in the Main, Extension study or healthy volunteers; no change in thyroid status, symptoms or signs (total of 400 treated patients and subjects
- 7 SAE’s, distributed between placebo and drug treated, all single occurrences, non related

Harrison, S. Effects of Resmetirom (MGL3196 on Hepatic Fat, Lipids, Liver Enzymes and Markers of Liver Fibrosis in an Open Label 36 Week Extension Study in NASH Patients. https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/.

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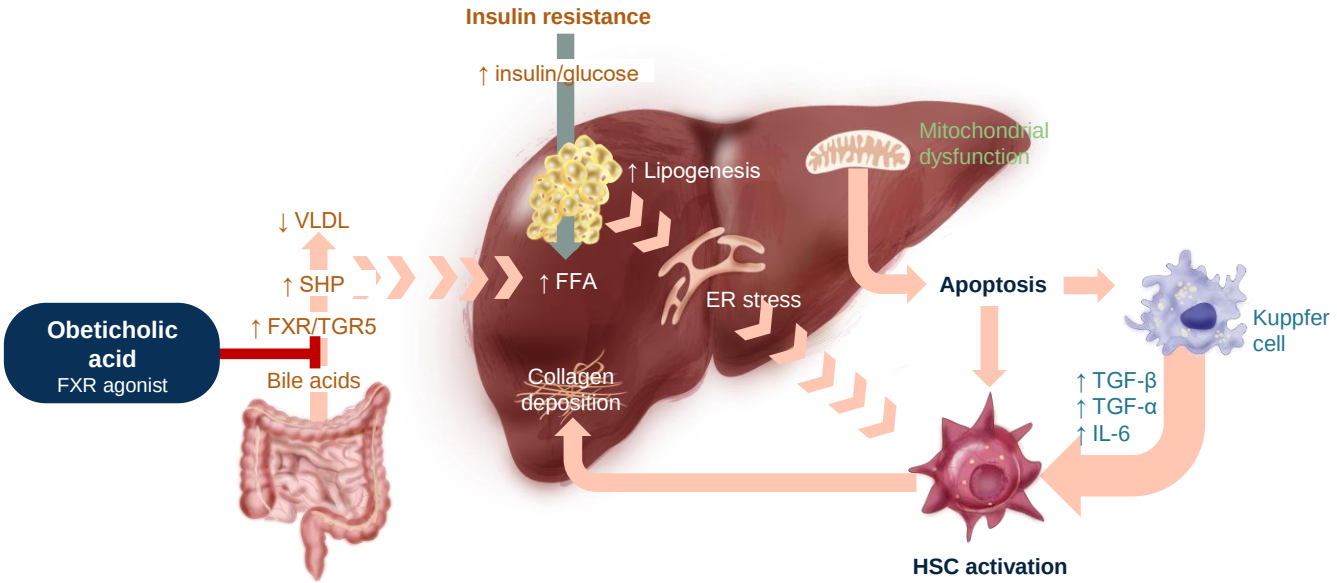
Gut-Liver Axis/Bile Acids

Mechanisms of Late-Stage Investigational Agents for NASH: Obeticholic Acid

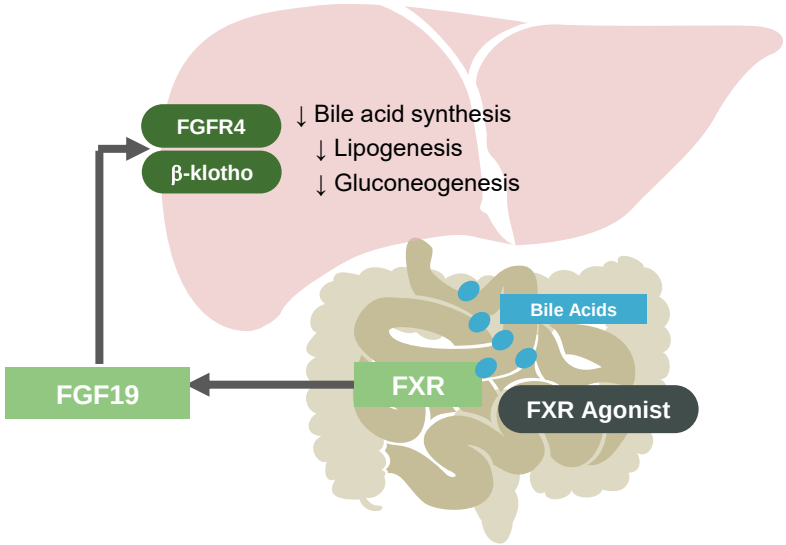


ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Adapted from Konerman MA, et al. *J Hepatol*. 2018;68:362-365.

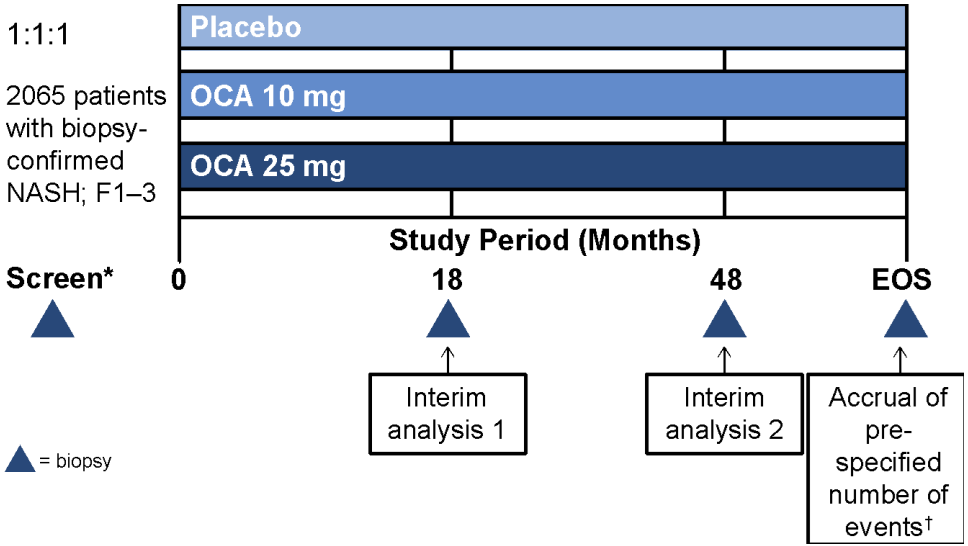
FXR Agonists

‡

- Bile acids (OCA) or non-bile acid (GS-9674)
- Highly selective for FXR
- Oral administration
- Induce FGF19
- OCA approved in PBC
- **Completed Phase 3 in patients with NASH



The REGENERATE Study

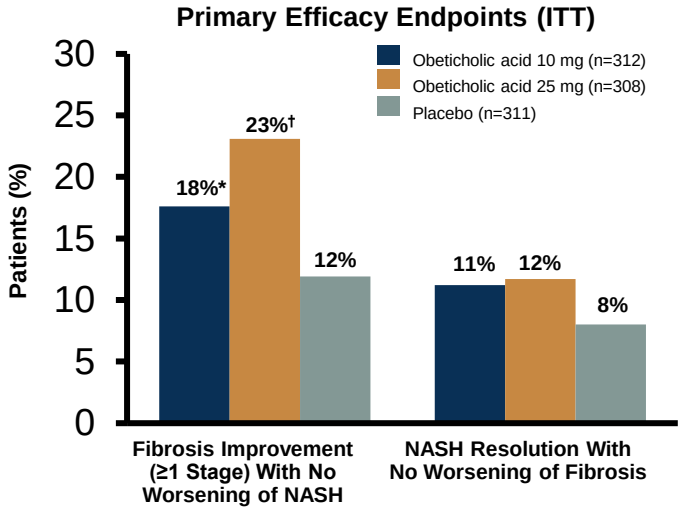


*NASH confirmed by biopsy ≤6 months before Day 1. †Placebo and OCA 25-mg groups only.
Abbreviations: EOS, end of study; OCA, obeticholic acid.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02548351.
Ratziu V, et al. Abstract THU-488. Presented at: EASL 2016; 13-17 April, 2016; Barcelona, Spain.

REGENERATE Study: 18-Month Interim Efficacy Analysis

- **Fibrosis improvement** (≥1 stage) and no worsening of NASH in patients (obeticholic acid versus placebo)
  - 10 mg: 18% versus 12% (*P*<0.05)
  - 25 mg: 23% versus 12% (*P*=0.0002) versus placebo

- **Pruritus: 50% in the OCA 25 mg arm**
- **Worsening lipid profile: Increase in LDL and decrease in HDL**
- **Cholecystitis**



FDA Review for Accelerated Approval of OCA

- June 2020
  - Denied accelerated approval
  - Why?
    - It was determined that histopathologic endpoint remains uncertain
    - Uncertain endpoint did not outweigh potential risks to support accelerated approval
  - FDA recommendation for Intercept:
    - Submit additional post-interim analysis efficacy and safety analysis data from REGENERATE study

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Inflammation/Fibrosis Targets

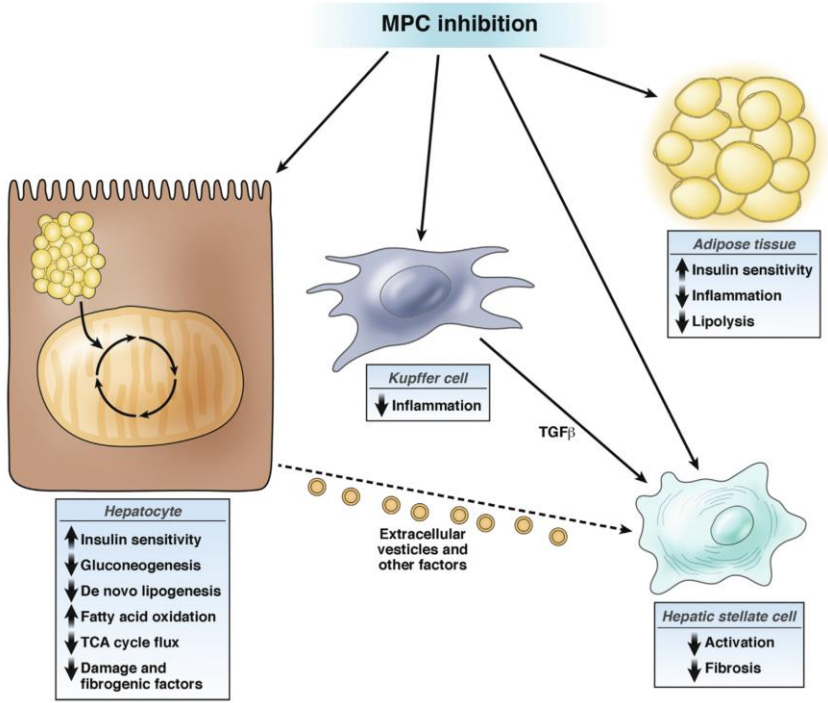
DESTINY: **D**euterium-stabilized R-pioglitazone (PXL065) **E**fficacy and **S**afety **T**rial **I**n **N**ASH

A Phase 2, **36-week**, randomized, double-blind, **placebo**-controlled, parallel group trial to assess the efficacy and safety of PXL065 versus placebo in **noncirrhotic**, biopsy-proven Nonalcoholic Steatohepatitis (NASH) patients

Mechanism of Action (MOA)

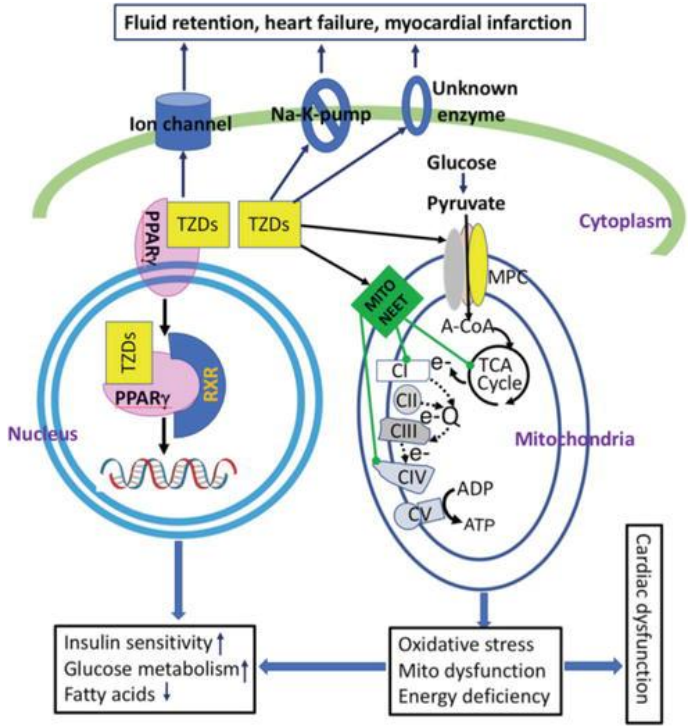
- There are three pathways for hepatic glucose production:
  1. Breakdown of glycogen (glycogenolysis)
  2. Gluconeogenesis from glycerol
  3. Gluconeogenesis from lactate/**pyruvate**/amino acids. (deranged in the diabetic liver)
- Pyruvate carboxylation to oxaloacetate is required for gluconeogenesis from pyruvate.
- Pyruvate carboxylase, is exclusively localized to the mitochondrial matrix → transport of pyruvate across the inner mitochondrial membrane through **MPC** is a prerequisite step in gluconeogenesis.

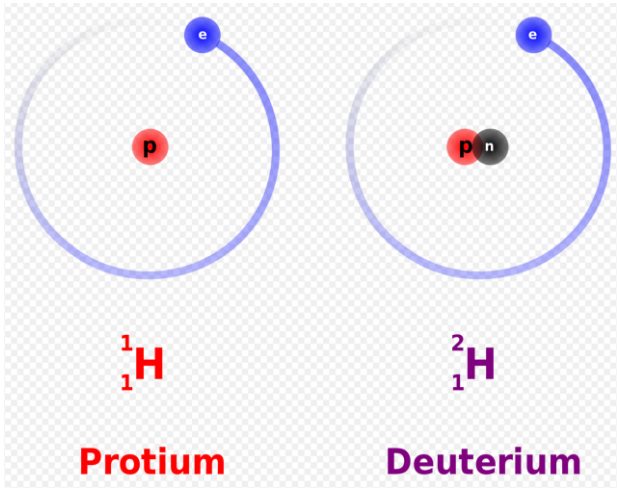
Mechanism of Action (MOA)



McCommis, et al. *Cell Mol Gastroenterol Hepatol*. 2019;7:275–284.

Pioglitazone: PPAR-Gamma Agonist



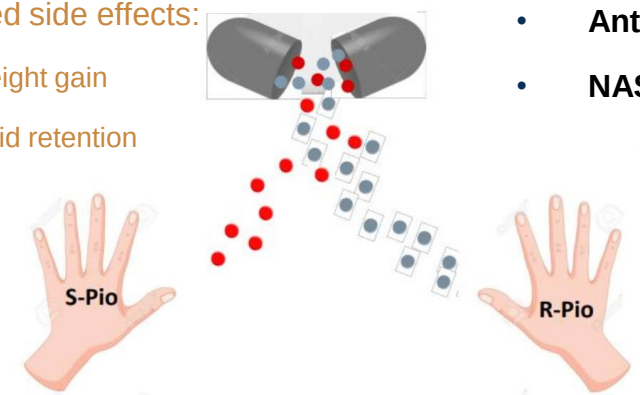


What Is PXL-065?

Pio is mixture of 2 stereoisomers with dramatically different properties

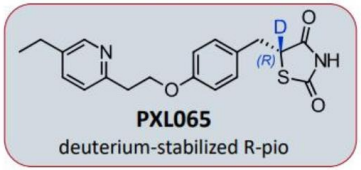
S-Pio (stabilized)

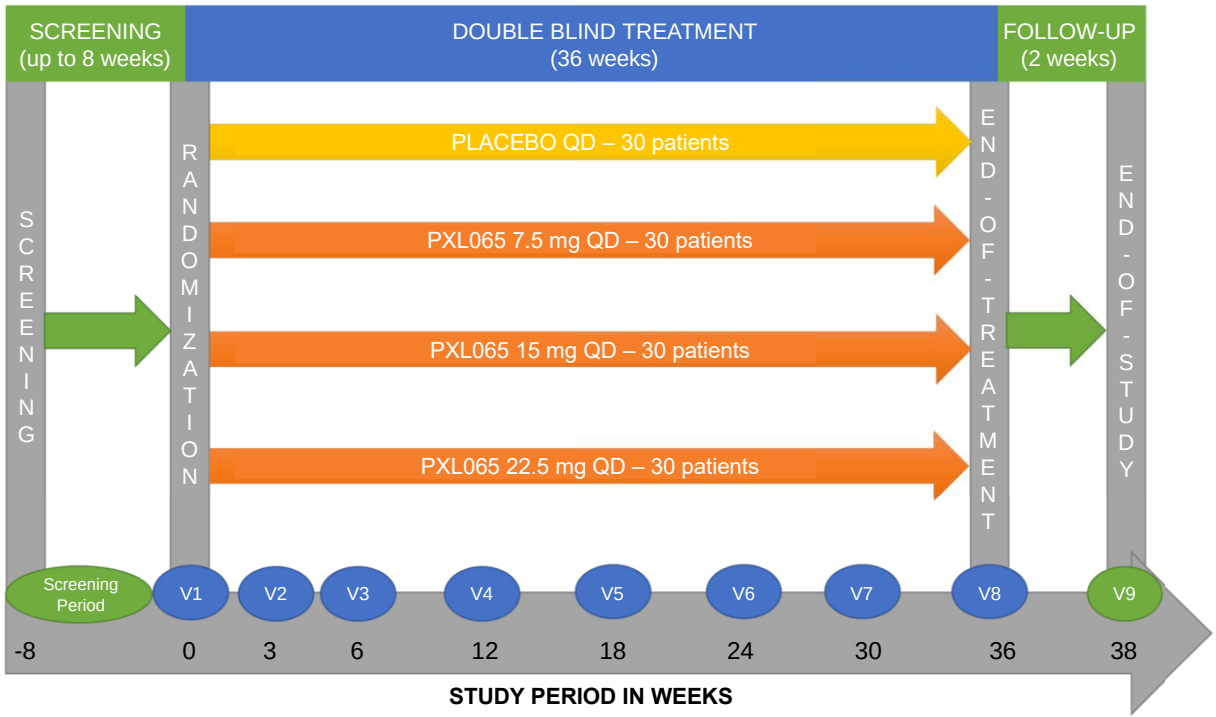
- MPC inhibitor
- PPAR**γ** agonist
- Undesired side effects:
  - Weight gain
  - Fluid retention



PXL065 (stabilized R-Pio)

- MPC inhibitor
- Very weak PPAR**γ** agonist
- **Anti-inflammatory**
- **NASH efficacy**




SCREENING
(up to 8 weeks)
DOUBLE BLIND TREATMENT
(36 weeks)
FOLLOW-UP
(2 weeks)
SCREENING
RANDOMIZATION
END-OF-TREATMENT
END-OF-STUDY
PLACEBO QD – 30 patients
PXL065 7.5 mg QD – 30 patients
PXL065 15 mg QD – 30 patients
PXL065 22.5 mg QD – 30 patients
Screening Period
V1
V2
V3
V4
V5
V6
V7
V8
V9
-8
0
3
6
12
18
24
30
36
38
STUDY PERIOD IN WEEKS

Primary Endpoints

- Primary endpoint
  - **Relative** change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT)
- Secondary endpoints:
  - **Absolute** change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT)
  - Response defined as an **absolute reduction in LFC ≥ 5%** from baseline to Week 36 (V8-EoT)
  - Response defined as a **relative reduction in LFC ≥ 30%** from baseline to Week 36 (V8-EoT)
  - Response defined as a **relative reduction in LFC ≥ 50%** from baseline to Week 36 (V8-EoT)
  - Response defined as a **LFC value at Week 36 (V8-EoT) that is normalized, i.e. ≤5%**

Cenicriviroc: A CCR 2/5 Antagonist That Targets Inflammation

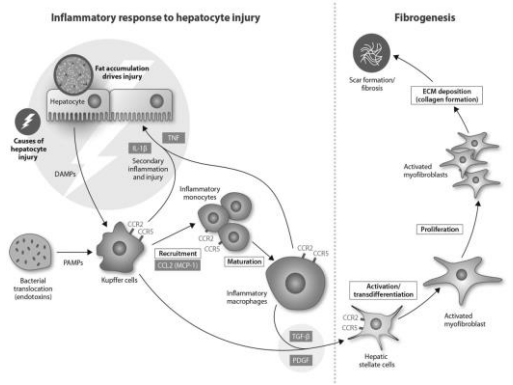
- Activation of CCR type 2/5 receptors
  - Promotes recruitment and migration of monocytes to the liver
    - Maturate into pro-inflammatory macrophages

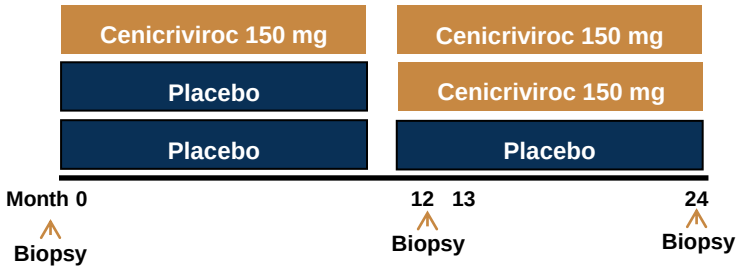
CENTARU: Phase 2b (n=289)

NASH (biopsy diagnosis)

- Biopsy diagnosis, NAS ≥4, fibrosis stage 1-3 (NASH-CRN)

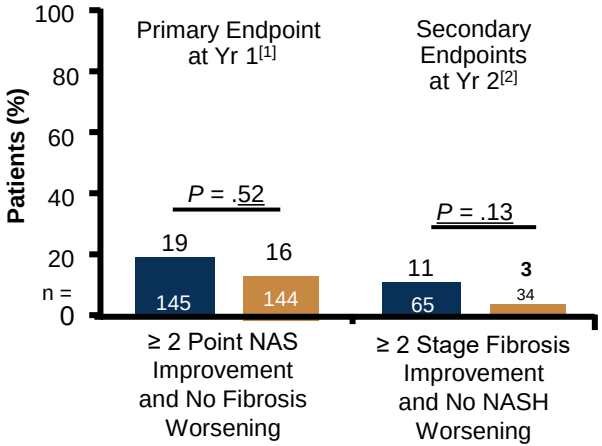
3 serial biopsies collected over the 2-year study period

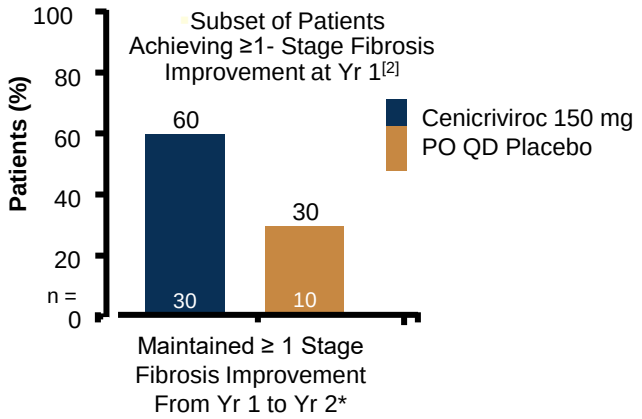




CENTAUR: Cenicriviroc vs Placebo in Patients With NASH at Year 1 and 2

- International, randomized, double-blind, phase IIb study in patients with NASH, NAS ≥ 4 and F1-F3 fibrosis (N = 289)[1]

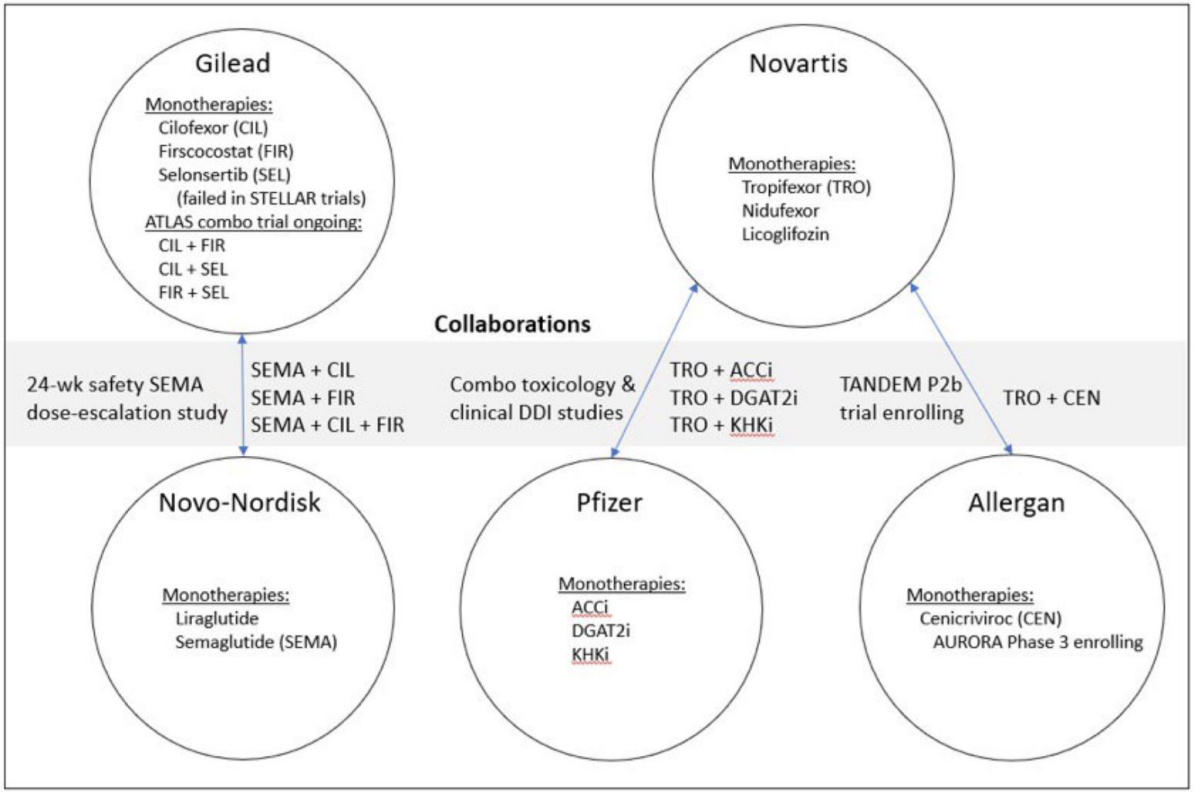




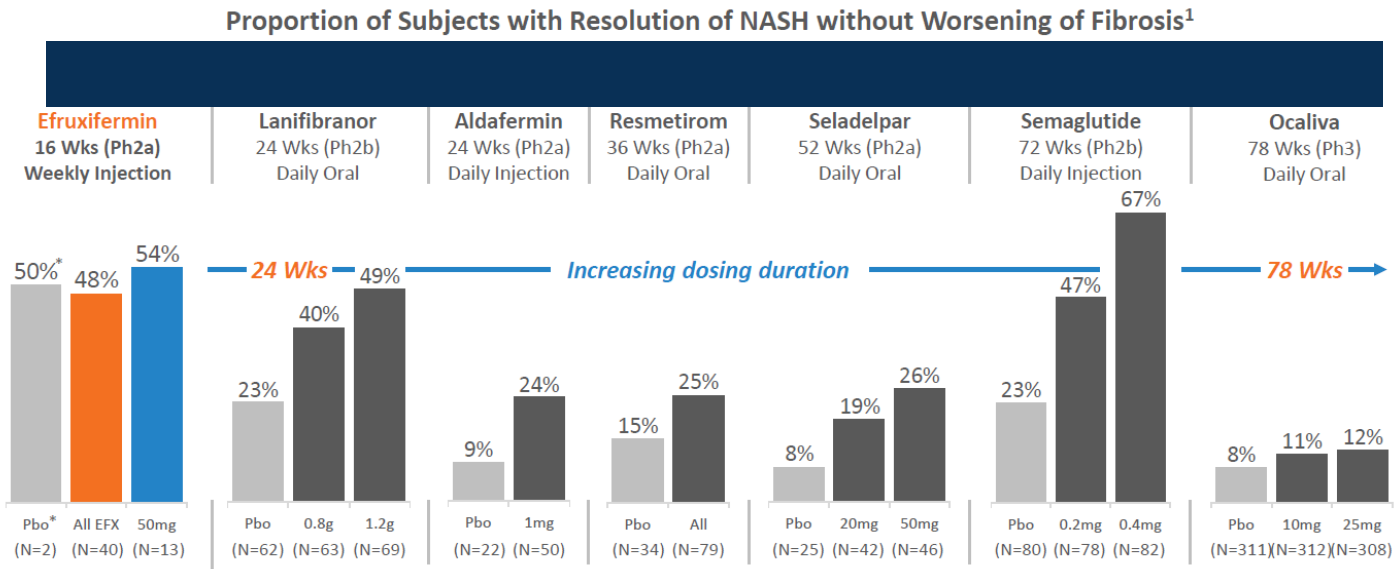
*Subset achieving ≥ 1-stage improvement in fibrosis at Yr 1.

1. Friedman. *Hepatology*. 2018;67:1754; 2. Ratziu. EASL 2018. Abstr GS-002.

NASH Alliances: Race for the Cure



NASH Resolution Landscape Monotherapies

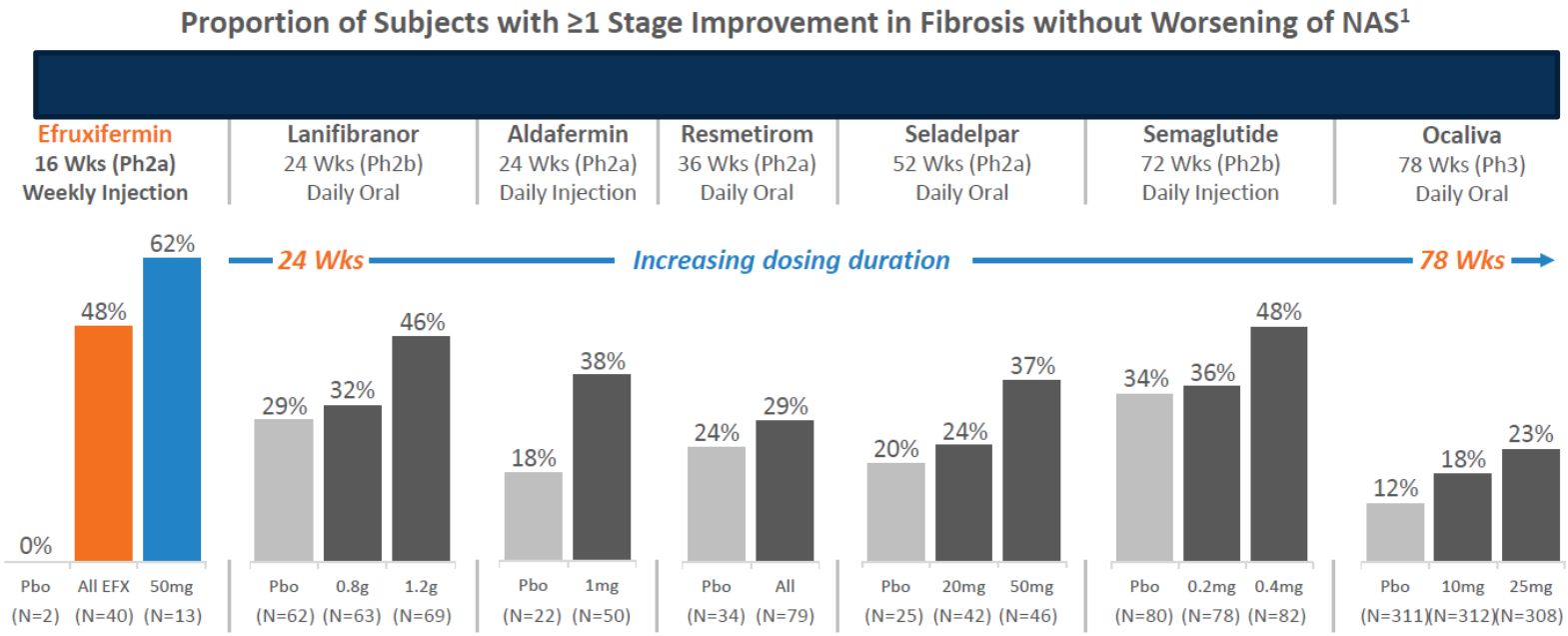


** A single placebo responder lost 25 pounds over 16 weeks (11% weight reduction)*

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted.

Inventiva (2020) June 16 Corporate Presentation; NGM Bio (2020) June 3 Corporate Presentation; Harrison, S et al. (2019) Lancet 394(10213):2012-24; CymaBay (2020) March 12 Press Release; Novo Nordisk (2020) June 19 R&D Investor Presentation; Younossi Z et al. (2019) Lancet 394(10215):2184-96. All trademarks are the property of their respective owners.

Fibrosis Improvement Landscape Monotherapies



Phase 2 Combination Therapy Trials

Agent	Target (mechanism)	Trial, patients and primary endpoint(s)
Semaglutide Firsocostat Cilofexor	GLP1 agonist ACC inhibitor FXR agonist	**POC study (n=109, biopsy-proven NASH and fibrosis stage 2–3)** • Safety and tolerability • 24 weeks treatment
Tropifexor Cenicriviroc	FXR agonist CCR2/5 antagonist	**TANDEM (n=200, NASH and fibrosis stage 2–3)** • Safety and tolerability • Fibrosis improvement ≥1 stage without NASH worsening or NASH resolution without fibrosis worsening • 48 weeks treatment
Tropifexor Licogliflozin	FXR agonist SGLT1 and 2 inhibitor	**ELIVATE (n=210, NASH and fibrosis stage 2–3)** • Fibrosis improvement ≥1 stage without NASH worsening or NASH resolution without fibrosis worsening • 48 weeks treatment
LYS006 Tropifexor	LTA4 hydrolase inhibitor FXR agonist	**NEXSCOT (n=250, phenotypic NASH, ELF ≥8.5 and PDFF≥8%)** • Safety and tolerability • ELF, MRI-PDFF, lipids • 12 weeks treatment
Selonsetrtib Firsocostat Cilofexor	ASK1 inhibitor ACC inhibitor FXR agonist	**ATLAS (n=395, NASH and fibrosis stage 3-4)** • Safety and tolerability • Fibrosis improvement ≥1 stage without NASH worsening • 48 weeks treatment

Closing Thoughts

- All aspects of NAFLD development and progression can be targeted.
- Combination therapy should be considered in patients with aggressive disease.
- NASH-specific therapies are coming soon and should change the attitude toward screening and treatment.