2020 Third Annual National Conference

November 19-21, 2020

Red Rock Hotel – Las Vegas, NV
New and Developmental Agents for NASH
Disclosures

Christina Hanson, FNP-C
- Speakers Bureau: Intercept Pharmaceuticals, Clinical Area-NASH, PBC
- Speakers Bureau: Salix, Clinical Area-IBS, HE

April G. Morris, FNP
- Speakers Bureau: AbbVie, Clinical Area-HCV
- Speakers Bureau: Gilead Sciences, Clinical Area-HCV
- Speakers Bureau: Intercept Pharmaceuticals, Clinical Area-PBC

Ann Moore, FNP
- Speakers Bureau: AbbVie, Clinical Area-HCV
- Speakers Bureau: Gilead Sciences, Clinical Area-HCV
- Speakers Bureau: Intercept Pharmaceuticals, Clinical Area-PBC
Why Is Drug Development for NASH Important?
NAFLD Is Among the Most Important Causes of Liver Disease Worldwide

24% Current estimate of global NAFLD prevalence

33-59% NASH prevalence estimate among patients with NAFLD

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

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

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

Risk of severe liver disease compared to controls\(^1\)

Liver-related mortality rate ratio\(^{12}\)

<table>
<thead>
<tr>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
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</thead>
<tbody>
<tr>
<td>1.9</td>
<td>1.7</td>
<td>5.5</td>
<td>14.3</td>
<td>104.5</td>
</tr>
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</table>

95% confidence intervals
(0.90–4.10) (0.84–3.24) (3.10–9.70) (7.90–25.8) (57.2–191.1)

<table>
<thead>
<tr>
<th>REF</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
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</thead>
<tbody>
<tr>
<td>1.41</td>
<td>9.57</td>
<td>16.69</td>
<td>42.3</td>
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</tr>
</tbody>
</table>

95% confidence intervals
(0.17–11.95) (1.67–54.93) (2.92–95.36) (3.51–510.34)

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).

Cl, confidence interval; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PYF, patient years of follow-up.

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
- No worsening of liver fibrosis

**Fibrosis Improvement**
- Improvement $\geq 1$ fibrosis stage
- No worsening of steatohepatitis

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

Therapeutic Targets in NAFLD/NASH

1. Metabolic
   - BMS-896026
   - FGF-21
   - Adiponectin
   - TNFα
   - FFA
   - PPAR agonists e.g., elafibranor
   - MGL-3196
   - ACC inhibitor GS-0976
   - SREBP-1
   - SHP
   - FXR/TGR5
   - FXR agonists e.g., obeticholic acid
   - INT-767
   - NGM 282
   - Bile acids
   - Volixibat
   - Gut-liver axis

2. Cell death
   - Insulin resistance
   - Insulin/glucose
   - Insulin sensitizer
   - Mitochondrial dysfunction
   - ROS
   - ER stress
   - JNK
   - Apoptosis
   - Kupffer cells
   - Inflammatory monocytes
   - Lymphocytes
   - Extracellular matrix

3. Inflammation
   - CCR2/5 inhibitor cenicriviroc
   - Galecin-3 inhibitor GR-MD-02
   - TLR2/3 inhibitor selonsertib
   - FFA
   - UPR

4. Fibrosis
   - LOXL2?
   - e.g., simtuzumab
   - AOC3 inhibitor BI 1467335

# NASH Agents in Phase 3 Clinical Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target (mechanism)</th>
<th>Trial, patients and primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cenicriviroc</td>
<td>Inflammation/ immune activation (CCR2/5 antagonist)</td>
<td>AURORA (n=2000*, fibrosis stage 2–3)</td>
</tr>
<tr>
<td>Elafibranor</td>
<td>Lipotoxicity/ oxidative stress (PPARα/δ agonist)</td>
<td>RESOLVE-IT (n=2000*, fibrosis stage 1–3)</td>
</tr>
<tr>
<td>Obeticholic acid</td>
<td>Lipotoxicity/oxidative stress (FXR agonist)</td>
<td>REGENERATE (n=2065*, fibrosis stage 1–3)</td>
</tr>
<tr>
<td>Selonsertib</td>
<td>Apoptosis/necrosis (ASK1 inhibitor)</td>
<td>STELLAR-4 (n=883, compensated cirrhosis)</td>
</tr>
<tr>
<td>Resmetirom (MGL-3196)</td>
<td>Lipotoxicity (TRβ agonist)</td>
<td>STELLAR-3 (n=808, fibrosis stage 3)</td>
</tr>
<tr>
<td>Aramchol</td>
<td>Lipotoxicity (FABAC)</td>
<td>Phase 3 study (n=2000*, fibrosis stage 2–3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase 3 study (n=2000*, fibrosis stage 2–3)</td>
</tr>
</tbody>
</table>

### Target Mechanisms
- Resmetirom (MGL-3196): Lipotoxicity (TRβ agonist)
- Aramchol: Lipotoxicity (FABAC)
- Elafibranor: Lipotoxicity/oxidative stress (PPARα/δ agonist)
- Cenicriviroc: Inflammation/ immune activation (CCR2/5 antagonist)
- Obeticholic acid: Lipotoxicity/oxidative stress (FXR agonist)
- Selonsertib: Apoptosis/necrosis (ASK1 inhibitor)

### Estimated Readout
- **REGENERATE**: Feb 2019
- **STELLAR-4**: Feb 2019
- **STELLAR-3**: Apr 2019
- **RESOLVE-IT**: Q2 2020
- **REVERSE**: 2021
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*)

Metabolic Targets: Resmetirom
## Phase 3 NASH Clinical Trials, Ongoing: MAESTRO-NASH and MAESTRO-NAFLD-1

<table>
<thead>
<tr>
<th>Compound/Indication</th>
<th>Clinical Trial</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Resmetirom**      |                |              |         |         | Completed | - MRI-PDFF, biopsy: positive  
                      | (MGL-3196)     |              |         |         |          |   • 36 week with 36 week open-label extension  
                      | **Thyroid Hormone Receptor-beta (THR-B) Agonist** | **Phase 2** MGL-3196-05 | | | |  
| **Treatment of NASH** |                | Recruiting |        |        | Recruiting | - Treatment of NASH with Fibrosis Stage 2-3  
                  |                |              |         |        |          |   • Serial liver biopsy  
                  |                |              |         |        |          |   • 52 week phase 3;  
                  |                |              |         |        |          |   • 54 month Phase 4  
                  |                |              |         |        |          | **Harrison, Stephen. Resmetirom for the Treatment of NASH.**  

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.
Resmetirom Development Path Across the Spectrum of NAFLD/NASH

Resmetirom CV Benefits

- Fatty Liver
- LDL-C
- ApoB
- Triglycerides
- Lp(a)

Total US NAFLD: (NASH plus NAFL) 83 million (2015)

US patient Numbers

- 1.3 million
- 2.0 million
- 3.4 million
- 6.3 million
- 3.5 million

F0 F1 F1B F2 F3 F4

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.
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

36 WEEKS OF Main Study

- 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

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

Primary Endpoint:
Relative Change in Hepatic Fat Fraction Assessed by MRI-PDFF

Least squares mean difference from baseline (95% CI): -22.5% (-32.9 to -12.2), P < .0001
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**

**≥ 30% Fat Reduction (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Change (Relative)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>-9.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MGL-3196 MGL-3196</td>
<td>-36.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MGL-3196 Low MGL-3196</td>
<td>-42.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>MGL-3196 High MGL-3196</td>
<td>-22.5</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

**NASH Resolution at week 36 biopsy**

<table>
<thead>
<tr>
<th>Group</th>
<th>% of biopsies</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>60.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High MGL-3196</td>
<td>75.0</td>
<td>*p&lt;0.04</td>
</tr>
<tr>
<td>Low MGL-3196</td>
<td>41.2</td>
<td></td>
</tr>
</tbody>
</table>

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.
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

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.

Gut-Liver Axis/Bile Acids
Mechanisms of Late-Stage Investigational Agents for NASH: Obeticholic Acid

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.


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**
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
Inflammation/Fibrosis Targets
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)

Pioglitazone: PPAR-Gamma Agonist
What Is PXL-065?

Pio is a mixture of 2 stereoisomers with dramatically different properties:

- **S-Pio** (stabilized)
  - MPC inhibitor
  - PPARγ agonist
  - Undesired side effects:
    - Weight gain
    - Fluid retention

- **PXL065** (stabilized R-Pio)
  - MPC inhibitor
  - Very weak PPARγ agonist
  - Anti-inflammatory
  - NASH efficacy
SCREENING (up to 8 weeks)

-8 0 3 6 12 18 24 30 36 38

V1 V2 V3 V4 V5 V6 V7 V8 V9

SCREENING PERIOD IN WEEKS

DOUBLE BLIND TREATMENT (36 weeks)

PLACEBO QD – 30 patients
PXL065 7.5 mg QD – 30 patients
PXL065 15 mg QD – 30 patients
PXL065 22.5 mg QD – 30 patients

FOLLOW-UP (2 weeks)

END OF TREATMENT

END OF STUDY

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%**
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)\(^1\)

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**Primary Endpoint at Yr 1\(^1\)**
- ≥ 2 Point NAS Improvement and No Fibrosis Worsening
- Cenicriviroc 150 mg: 19 out of 145
- Placebo: 16 out of 144
- \(P = .52\)

**Secondary Endpoint at Yr 2\(^2\)**
- ≥ 2 Stage Fibrosis Improvement and No NASH Worsening
- Cenicriviroc 150 mg: 11 out of 65
- Placebo: 3 out of 34
- \(P = .13\)

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**Subset of Patients Achieving ≥1 Stage Fibrosis Improvement at Yr 1\(^2\)**
- Cenicriviroc 150 mg: 60 out of 30
- Placebo: 30 out of 10

*Subset achieving ≥ 1-stage improvement in fibrosis at Yr 1.
NASH Alliances: Race for the Cure

Gilead
- Monotherapies: Cilofexor (CIL), Firsofastat (FIR), Selonsertib (SEL) (failed in STELLAR trials), ATLAS combo trial ongoing: CIL + FIR, CIL + SEL, FIR + SEL

Novartis
- Monotherapies: Tropifexor (TRO), Nidufexor, Licoglifozin

Collaborations
- 24-wk safety SEMA dose-escalation study
- Combo toxicology & clinical DDI studies
- TANDEM P2b trial enrolling
- TRO + CEN

Novo-Nordisk
- Monotherapies: Liraglutide, Semaglutide (SEMA)

Pfizer
- Monotherapies: ACCi, DGAT2i, KHKi

Allergan
- Monotherapies: Cenicriviroc (CEN), AURORA Phase 3 enrolling
Proportion of Subjects with Resolution of NASH without Worsening of Fibrosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Route</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efruxifermin</td>
<td>16 Wks</td>
<td>Ph2a</td>
<td>50%</td>
</tr>
<tr>
<td>Lanifibranor</td>
<td>24 Wks</td>
<td>Ph2b</td>
<td>48%</td>
</tr>
<tr>
<td>Aldafermin</td>
<td>24 Wks</td>
<td>Ph2a</td>
<td>54%</td>
</tr>
<tr>
<td>Resmetirom</td>
<td>36 Wks</td>
<td>Ph2a</td>
<td>49%</td>
</tr>
<tr>
<td>Seladelpar</td>
<td>52 Wks</td>
<td>Ph2a</td>
<td>67%</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>72 Wks</td>
<td>Ph2b</td>
<td>47%</td>
</tr>
<tr>
<td>Ocaliva</td>
<td>78 Wks</td>
<td>Ph3</td>
<td>47%</td>
</tr>
</tbody>
</table>

* 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.

Fibrosis Improvement Landscape Monotherapies

Proportion of Subjects with ≥1 Stage Improvement in Fibrosis without Worsening of NAS$^1$

- **Efruxifermin**: 16 Wks (Ph2a) Weekly Injection
- **Lanifibranor**: 24 Wks (Ph2b) Daily Oral
- **Aldafermin**: 24 Wks (Ph2a) Daily Injection
- **Resmetirom**: 36 Wks (Ph2a) Daily Oral
- **Seladelpar**: 52 Wks (Ph2a) Daily Oral
- **Semaglutide**: 72 Wks (Ph2b) Daily Injection
- **Ocaliva**: 78 Wks (Ph3) Daily Oral

**Increasing dosing duration**
- **24 Wks**:
  - Efruxifermin: 62%, Lanifibranor: 46%, Aldafermin: 38%, Resmetirom: 29%, Seladelpar: 24%, Semaglutide: 34%, Ocaliva: 12%
  - Pbo (N=2), All EFX (N=40), 50mg (N=13)
- **78 Wks**:
  - Efruxifermin: 48%, Lanifibranor: 32%, Aldafermin: 29%, Resmetirom: 24%, Seladelpar: 20%, Semaglutide: 36%, Ocaliva: 18%
  - Pbo (N=62), 0.8mg (N=63), 1.2g (N=69), Pbo (N=22), 1mg (N=50), Pbo (N=34), All (N=79), Pbo (N=25), 20mg (N=42), 50mg (N=46), Pbo (N=80), 0.2mg (N=78), 0.4mg (N=82), Pbo (N=313), 0.4mg (N=312), 25mg (N=308)
### Phase 2 Combination Therapy Trials

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

- **POC study** (n=109, biopsy-proven NASH and fibrosis stage 2-3)
  - Safety and tolerability
  - 24 weeks treatment

- **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

- **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

- **NEXSCOT** (n=250, phenotypic NASH, ELF ≥8.5 and PDFF≥8%)
  - Safety and tolerability
  - ELF, MRI, PDFF, lipids
  - 12 weeks treatment

- **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.