Future NASH Therapies

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Pathogenesis of NASH and Related Fibrosis

ACC, acetyl-CoA carboxylase; AOC, amine oxidase, copper containing; ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; DNL, de novo lipogenesis; ER, endoplasmic reticulum; FFA, free fatty acids; FGF, fibroblast growth factor; FXR, farnesoid X receptor; IL, interleukin; JNK, Jun N-terminal kinases; LPS, lipopolysaccharide; NLRP3, nucleotide-binding oligomerization domain and leucine rich repeat and pyrin domain containing protein 3; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SCD, stearoyl CoA desaturase; SGLT, sodium-glucose linked transporter; SHP, small heterodimer partner; SREBP, sterol regulatory element binding proteins; TGF, transforming growth factor; TGR5, G protein-coupled bile acid receptor 1; TLR, toll like receptor; TNF, tumor necrosis factor; TR, thyroid receptor; UPR, unfolded protein response VLDL, very low density lipoprotein.

NASH Landscape in 2019: Clinical Programs

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Goals of Any Treatment for NASH

- Improve metabolic abnormalities
- Decrease inflammation
- Prevent / arrest / reverse liver fibrosis
  - AASLD recommends pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes
- Improve systemic outcomes (eventually)
Sources of Excess Clinical Outcomes in NAFLD and Where Interventions Will Have Greatest Impact

- **NAFL**
- **NASH**
- **NASH with fibrosis**
- **NASH Cirrhosis**

Cardiovascular, CKD and all-cause cancer outcomes

Liver decompensation

Most closely tied to liver-related mortality

Closest to cirrhosis and most likely to benefit from prevention of progression
Goal for Treatment and Drug Development

Resolve NASH – strongest predictor of hepatic fibrosis
Improve fibrosis – strongest predictor of morbidity/mortality
Targets/Emerging Therapies for NASH

GOAL in 20 minutes:
Overview of leading targets for NASH
• PPARs
• GLP-1
• THR β
• Stearoyl-CoA Desaturase-1
• FGF 19 and FGF 21
• FXR
Focus on those targets with therapies in late-stage clinical trials with histologic endpoints
Peroxisome Proliferator-Activated Receptors

Pan-PPAR Lanifibranor: The NATIVE Trial

A 24-week, Phase 2b study of 247 participants with NASH

**Interventions:** Placebo vs pan-PPAR agonist lanifibranor 800 mg/day and 1,200 mg/day

**Safety:** Generally well tolerated. Mild weight gain comparable with PPARγ effects

**ITT Primary outcome:** ≥ 2 point improvement of the SAF activity score (ballooned hepatocytes and inflammation) and no worsening of fibrosis at 24 weeks

**ITT Secondary outcome:** Improvement of fibrosis by at least one stage and no worsening of NASH

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants meeting endpoint (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Lanifibranor 800 mg</td>
<td>28</td>
<td>0.53</td>
</tr>
<tr>
<td>Lanifibranor 1,200 mg</td>
<td>42</td>
<td>0.011</td>
</tr>
</tbody>
</table>

ITT, intention to treat; PPAR, peroxisome proliferator-activated receptors; SAF, steatosis, activity, and fibrosis. Francque SM et al., AASLD Liver Meeting, Abstract 12, 2020.
Metabolic Effects of GLP-1 Receptor Agonists

GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Semaglutide in NASH Trial

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

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GLP-1, glucagon-like peptide-1; NASH, non-alcoholic steatohepatitis; OD, once-daily.
Thyroid Hormone Receptor β Selective Agonists

- Good biological rational: More overt hypothyroidism in NASH\textsuperscript{1,2}

\[ \text{THR} \beta \]
(Liver, Brain)
Lipid metabolism
inflammation

\[ \text{THR} \alpha \]
Heart rate,
contractility

\[ \text{Phase 2} \quad \text{VK2809} \]
\[ \text{Phase 3} \quad \text{Resmetirom} \]

BA, bile acid; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; THR, thyroid hormone receptor.

Resmetirom (MGL-3196) for NASH

36-week phase 2 trial in 125 participants with NASH (NAS ≥4 with F1–3)\(^1\)

**Interventions:** 2:1 80 mg resmetirom *versus* placebo

**Primary outcome:** Change from BL in hepatic fat fraction at Week 12 and 36

**Safety:** Adverse events were mostly mild or moderate and were balanced between groups

ALT, alanine aminotransferase; ApoB, apolipoprotein B; BL, baseline; LDL-C, low-density lipoprotein cholesterol; NAS, non-alcoholic fatty liver disease activity score.

Stearyl-CoA Desaturase-1 (SCD-1) Inhibition

Aramchol: ARREST Results (Key Outcomes at Week 52)

52-week phase 2b trial in 247 participants with NASH, NAS ≥4 and liver fat 5.5%

**Interventions**: 2:2:1 Aramchol 400 mg QD versus 600 mg QD versus placebo

**Primary endpoint**: Change in liver fat at Week 52 (MRS)

**Safety**: Aramchol was generally well tolerated. No difference in adverse event rate vs placebo

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**≥5% absolute reduction from baseline**

- Placebo (n=41): 24.4%
- Aramchol 400 (n=90): 36.7%
- Aramchol 600 (n=83): 47%

Aramchol 600 versus placebo p=0.0279
Or 2.77 (95% CI: 1.12-6.89)

**NASH resolution without worsening of fibrosis**

- Placebo (n=40): 5%
- Aramchol 400 (n=80): 7.5%
- Aramchol 600 (n=78): 16.7%

Aramchol 600 versus placebo p=0.051
Or 4.74 (95% CI: 0.99-22.7)

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BL, baseline; CI, confidence interval; MRS, magnetic resonance spectroscopy; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; OR, odds ratio; QD, once daily.

Fibroblast Growth Factors (FGF) 19 and 21

**Phase 2**

**FGF-19 Agonist**
- Aldafermin (FGF-19)

**FGF-21 Agonists**
- Pegbelfermin (FGF-21)
- Bio89-100 (FGF-21)
- Efruxifermin (FGF-21)

Efruxifermin (FGF-21) for NASH

- NASH with NAS ≥ 4 and F1-3 fibrosis. Liver fat ≥ 10%.
- 80 subjects with 1:1:1:1 to 25 mg, 50 mg, 70 mg vs placebo
- Subjects achieving ≥ 30% reduction in MRI-PDFF had liver biopsy

Clinically meaningful reductions in glycemic control, lipoprotein levels
11 of 40 EFX patients (28%) had ≥ 2 points improvement in fibrosis
Farnesoid X Receptor (FXR) Agonists

FXR agonists are not approved for the treatment of NASH. FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; LPS, lipopolysaccharide; SREB-1, sterol regulatory element-binding protein-1; TG, triglyceride; TGFβ, transforming growth factor beta; VLDL, very-low-density lipoprotein. Adapted from Jansen et al. Nat Rev Gastroenterol Hepatol. 2014;11:55–67.
Phase 3 trial in 1,968 participants with NASH, NAS ≥4 and F2/F3

**Interventions**: 1:1:1 OCA 10 mg QD *versus* 25 mg QD *versus* placebo

**Primary outcomes**: Improvement in fibrosis with no worsening in NASH and NASH resolution with no worsening of fibrosis

**Primary efficacy endpoints (ITT population N=931)**

- Fibrosis improvement by ≥1 stage with no worsening of NASH
  - Placebo (n=311): 12%
  - Obeticholic acid 10 mg (n=312): 18%
  - Obeticholic acid 25 mg (n=308): 23%
  - *p* = 0.0002

- NASH resolution without worsening of fibrosis
  - Placebo (n=311): 8%
  - Obeticholic acid 10 mg (n=312): 11%
  - Obeticholic acid 25 mg (n=308): 12%
  - *p* = 0.18

Obeticholic acid is not approved for the treatment of NASH.

*Statistically significant in accordance with the statistical analysis plan as agreed with FDA. All other *p* values were nominal; ITT, intent-to-treat; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; QD, once daily.

Why Are Combination Therapies Needed in NASH?

- Efficacy of single drugs has been limited and disappointing
  - High profile failures include:
    - Simtuzumab
    - Selonsertib
    - Elafibranor
    - Cenicriviroc
    - Celgene
    - Obeticholic acid?
- Therefore, combinations may:
  - Enhance efficacy
  - Create synergistic activity and/or capture more patients if different mechanisms drive disease in different patients
Current Approach to Combinations

- Use two drugs with separate targets/mechanisms of action
- Choice of combinations based on strategic considerations more than experimental data

  - *e.g. A company has two assets ‘in-house’ or a strategic partner*
    - « Metabolic target » + « Anti-fibrotic target »
    - « Metabolic target » + « Anti-inflammatory target »
    - « Anti-inflammatory target » + « Anti-fibrotic target »
Conclusions

• Multiple treatments that interrupt the pathophysiological properties of NASH are in development
• There is no FDA-approved drug for NASH – only one drug (OCA) is under FDA NDA review
• The landscape of emerging therapies for NASH is robust
• Emerging therapies targeting metabolic risk demonstrate benefit against NASH which may translate into positive outcome on halting or delaying time to fibrosis progression
• Combination therapy using drugs with different mechanisms-of-action is likely the future of NASH treatment