DRUGS IN DEVELOPMENT FOR THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS

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Conflicts of Interest

• President, Sanyal Biotechnologies
• Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
• Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear, NovoNordisk
• Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Cirius, Boehringer Ingelhiem
• Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius
• ALL OPINIONS EXPRESSED ARE MY PERSONAL OPINIONS AND ONLY DATA IN THE PUBLIC DOMAIN WILL BE PRESENTED
Clinical outcomes vary based on stage of NASH

**Causes of death:**
- Cardiovascular
- Cancer
- Rare HCC

**Causes of death:**
- Cardiovascular
- Liver-related
- HCC

NAS → CIRRHOSIS → DEATH
CIRRHOSIS

Metabolism (steatosis)

Cell stress apoptosis

Inflammation

Fibrogenic remodeling

PPARs

CIRRHOSIS
Mitochondrial target of thiazolidinediones (mTOT)

Effects on pathways that impact NASH and Diabetes

- **Liver** (direct and indirect effects on multiple cell types)
  - Reduced lipid storage, increased fat oxidation
  - Improved insulin sensitivity
  - Decreased glucose production

- **Hepatocytes**
  - Reduced inflammation
  - Reduced stimuli for scarring

- **Stellate cells**
  - Reduced inflammation

- **Macrophages**
  - Reduced inflammation

- **Muscle**
  - Decreased fat content
  - Increased insulin sensitivity

- **Fat**
  - Decreased inflammation, increased adiponectin
  - Increased insulin sensitivity

- **Pancreas**
  - Preservation of b-cell phenotype

Improvement of NASH by PPARδ/α activation

Metabolic Syndrome

Visceral and liver fat & inflammation

Macrophages

Hepatocytes

PPARδ – PPARα

Inflammatory Cytokines

Metabolic Control

FA and lipoprotein metabolism

Tailleux, Wouters & Staels BBA 2012;1821:809-18
### Primary outcome (based on FDA definition)

**Efficacy on NAS≥4 at various stage of fibrosis**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Placebo</th>
<th>Elafibranor 80mg</th>
<th>Elafibranor 120mg</th>
<th>OR* [CI 95%]</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NAS≥4 (F0-F1-F2-F3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS, N=234</td>
<td>9%</td>
<td>13%</td>
<td>19%</td>
<td>3.52 [1.32, 9.40]</td>
<td>0.013</td>
</tr>
<tr>
<td>EES, N=202</td>
<td>11%</td>
<td>15%</td>
<td>21%</td>
<td>3.26 [1.17, 9.02]</td>
<td>0.024</td>
</tr>
<tr>
<td>NAS≥4 (F1-F2-F3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS, N=204</td>
<td>11%</td>
<td>15%</td>
<td>20%</td>
<td>3.75 [1.39, 10.12]</td>
<td>0.009</td>
</tr>
<tr>
<td>EES, N=176</td>
<td>13%</td>
<td>17%</td>
<td>22%</td>
<td>3.22 [1.15, 8.99]</td>
<td>0.026</td>
</tr>
<tr>
<td>NAS≥4 (F2, F3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS, N=118</td>
<td>7%</td>
<td>10%</td>
<td>13%</td>
<td>18.46 [4.80, 70.96]</td>
<td>0.0001</td>
</tr>
<tr>
<td>EES, N=99</td>
<td>9%</td>
<td>12%</td>
<td>15%</td>
<td>10.59 [2.52, 44.50]</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* comparison Elafibranor-120 mg vs Placebo

The 120 mg dose was effective in subpopulations of patients with any fibrosis (F1-F3), as well as in those with moderate or advanced fibrosis (F2-F3)
Obeticholic Acid - 6α-Ethyl Chenodeoxycholic Acid - INT-747

Semi-Synthetic Derivative of Chenodeoxycholic Acid

**CDCA**
chenodeoxycholic acid

**INT-747**
6α-ethyl chenodeoxycholic acid

<table>
<thead>
<tr>
<th>FXR EC&lt;sub&gt;50&lt;/sub&gt; (agonism)</th>
<th>8.66 μM</th>
<th>0.099 μM</th>
</tr>
</thead>
</table>

~ 100x↑ FXR agonism

Pelliciari R. J.Méd.Chem 2002
Effect of OCA on steatohepatitis

% of Patients w/ Improvement

1: Data from Tetri et al. *The Lancet*. Published online November 7, 2014.
2: All p-values compared to placebo. P-value calculated with the Cochran-Mantel-Haenszel test, stratified by clinic and diabetes status.
FXR agonists can raise LDL-cholesterol

Min et al, Cell Metabolism, 2012
LJN 452: first human experience

• **Rationale:** to de-risk the FXR pathway
• Single ascending dose and Multiple ascending dose
• Safe, well tolerated and transient dose-dependent increase in FGF-19, a marker of intestinal FXR engagement noted without LDL-C rise

Abstract # 32: Badman et al, Novartis Institutes for Biomedical Research, AASLD
FGF-19 for the treatment of NASH
NGM282 improves fibrosis and NASH-related histology in 12 weeks in patients with biopsy-confirmed NASH, which is preceded by significant decreases in hepatic steatosis, liver transaminases and fibrosis markers at 6 weeks.

Histological response at W12

“Early Histologic Responders” =
- Δ NAS ≥ 2 (with Inflammation or Ballooning)
- Δ Fibrosis ≥ 1
- Resolution of NASH

“Early Histologic Responders” defined as subjects with:
- Reduction in NAS ≥ 2, with ≥1 point in inflammation or ballooning
- Reduction in fibrosis ≥ 1, with no worsening of NASH
- Resolution of NASH (inflammation = 0-1 and ballooning = 0)

Fatty acid-bile acid conjugate (Aramchol) Phase IIa Trial

Mechanism of action: SCD1 inhibition

- Results: Liver fat change by NMRS *

* Magnetic resonance spectroscopy (MRS) is generally considered the clinical gold-standard noninvasive technique for in vivo fat and metabolite quantification. It is routinely used for measuring liver fat. (Houchun H. et al. Obesity 2010;18(4):841–7.)

CIRRHOSIS

Metabolism (steatosis)

Cell stress apoptosis

Inflammation

Fibrogenic remodeling

PPARs
FXR
GLP-1
FABAC
FGF21
Fibroblast Growth Factor 21 (FGF21)

- Non-mitogenic hormone
- Important regulator of energy metabolism
- FGF21 has a short half-life (1-2 hours)

FGF21 may have direct and indirect beneficial effects on non-alcoholic steatohepatitis (NASH) and NASH-related hepatic fibrosis

<table>
<thead>
<tr>
<th>Beneficial metabolic effects</th>
<th>Anti-fibrotic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Insulin sensitivity</td>
<td>↓ Pro-C3 (biomarker of fibrosis)</td>
</tr>
<tr>
<td>↓ Lipogenesis &amp; improvement in lipids</td>
<td></td>
</tr>
</tbody>
</table>

Adiponectin

↑ Adiponectin

Reduces steatosis, inflammation, and fibrosis

FGF, fibroblast growth factor; HDL, high density lipoprotein; LDL, low density lipoprotein.

Kharitonenkov A and Larsen P, Trends Endocrinol Metab. 2011;22(3):81-86;

Charles E. et al. Hepatology 2016;64(Suppl):17A.
Absolute Improvement in Hepatic Fat Fraction (MRI-PDFF) at Week 16

BMS-986036 QD and QW treatment compared with placebo significantly reduced hepatic fat fraction

*Inferential statistical analyses were conducted using a MMRM and not adjusted for multiple comparisons; †1 patient in each group completed treatment but did not have adequate MRI-PDFF scans at baseline and Week 16.
Thyroxine beta receptor agonists

Mechanism of action: The importance of liver THR-β in NASH

In humans THR-β agonism:
- ↓ Lowers LDL-cholesterol
- ↓ Lowers triglycerides
- ↓ Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

MGL-3196 improved hepatic steatosis

Relative change in MRI-PDFF (%)

Placebo
MGL-3196
High
Low
MGL-3196

P=0.02**
P<0.0001
P<0.0001
P<0.0001

n=38
n=78
n=44
n=34

*P<0.02

ALT

Placebo
MGL-3196
High

n=29
n=47
n=29

**NS

P=0.002
P<0.0001

-7.7
-13.5
-21

AST

Placebo
MGL-3196
High

n=38
n=78
n=44

NS

P=0.001
P=0.0002

-1.6
-7.4
-9.2

## Histological response to a thyroxine-beta receptor agonist

### MGL-3196 MRI-PDFF Responders\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>MGL-3196</th>
<th>MGL-3196 MRI-PDFF Responders(^1)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with baseline and end-of study liver biopsies(^2)</td>
<td>73</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>(\geq 2) point decrease in NAS</td>
<td>56% (p=0.02)</td>
<td>70% (p=0.001)</td>
<td>32%</td>
</tr>
<tr>
<td>NASH Resolution</td>
<td>27% (6.0%) (p=0.02)</td>
<td>39% (p=0.001)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)MGL-3196 MRI-PDFF responders = MGL-3196 treated patients with \(\geq 30\%\) relative fat reduction on Week 12 MRI-PDFF

\(^2\)does not include one end-of-study liver biopsy that was inadequate

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Madrigal Press Release 2018
Liraglutide improved NASH in a multicenter, double-blinded, randomised, placebo-controlled phase II trial

Primary endpoint: NASH resolution with no worsening of fibrosis

Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (n=23)</th>
<th>Placebo (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleiner fibrosis</td>
<td>-0.2 (0.8)</td>
<td>0.2 (1.0)</td>
</tr>
<tr>
<td>Improvement, n</td>
<td>6 (26.1)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>*p&lt;0.05 vs placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening, n (%)</td>
<td>2 (8.7)*</td>
<td>8 (36.4)</td>
</tr>
</tbody>
</table>

More diarrhea with liraglutide

- Liraglutide, a long-acting GLP-1 agonist dosed once daily SC, with overall benefits in T2DM
- Results replicated here; patients showed significant histological resolution of NASH
- Long-term and larger studies with liraglutide or other GLP-1 agonists in NASH are warranted

Armstrong MJ, et al. EASL 2015, Vienna. #G01
5 year effect of bariatric surgery for NASH

Evolution of NASH*  

- Baseline: 100% (3 severe, 2 moderate, 1 mild, No NASH)
- 1 year: 70% (3 severe, 2 moderate, 1 mild, No NASH)
- 5 years: 40% (3 severe, 2 moderate, 1 mild, No NASH)

*p<0.001   ns

*Paired biopsies

So where do we stand with therapeutics?

Konerman et al, J Hepatology 2018
Key Investigational Agents for NASH: Change in Absolute Liver Fat Content

1. Selonsertib (SEL) +/- Simtuzumab (SIM) open label pooled study data; simtuzumab data used as proxy for placebo data
2. Placebo-subtracted data; secondary analysis of OCA FLINT trial
3. Absolute changes in LFC for GS-0976 and GS-4997 calculated from baseline values and relative median change values
4. Ph2 expansion study (open label, ongoing): 0.3mg (n=19); 1mg (n=20); 3mg (n=16)
5. Absolute change in LFC for MGL-3196 calculated from baseline value (across entire study) and relative median change from baseline; data from ongoing blinded study where “High MGL-3196” was a pre-specified group of patients with relatively higher drug levels as measured by sex hormone binding globulin (marker of MGL-3196 hepatic level and activity) and “All MGL-3196” include low and high levels as measured by sex hormone binding globulin

Sources: BMS-986036 (EASL 2017); GS-0976 (AASLD 2017); GS-4997 (Loomba et al, Hepatology 2017); OCA (AASLD 2017); MGL-3196 (Press release Dec. 6, 2017 and transcript of webcast)

*Statistically significant
CIRRHOSIS

Metabolism (steatosis)

Cell stress apoptosis

inflammation

Fibrogenic remodeling

PPARs
FXR
GLP-1
FABAC
FGF21, TBR, ACC inhibitors

Vitamin E
ASK1

CCR2-CCR5 (Cencriviroc blocks this target)
CENTAUR: FINAL RESULTS

**Study design:** Randomized, double-blind, placebo-controlled study with 3 serial biopsies (Screening, Year 1 & 2)
- Adults with NASH (NAS ≥4; F1-3) in Arm A received Cenicriviroc (150 mg once daily) for 2 years; Arm B received Placebo in Year 1 and switched to Cenicriviroc in Year 2; and Arm C received Placebo for 2 years

**Results:**

- **Durability of antifibrotic response (Response from Year 1 to Year 2)**
  - **n=10**
    - Maintained ≥1-stage improvement: 30%
    - No change: 60%
  - **n=30**
    - Worsened

- **Improvement in fibrosis by ≥2 stages AND no worsening of NASH (Response from Baseline to Year 2)**
  - **n=34**
    - Placebo (Arm C): 3%
    - Cenicriviroc (Arm A): 11%
  - **n=65**
    - p=0.13

Ratziu et al, EASL 2018
CIRRHOSIS

Metabolism (steatosis)

Cell stress
apoptosis

Inflammation

Fibrogenic
remodeling

Vitamin E
ASK1

CCR2-CCR5 (Cencriviroc blocks this target)

Anti-fibrotics

PPARs
FXR
GLP-1
FABAC
FGF21

CIRRHOSIS
HVPG Primary Endpoint: Total Patient Population

1. Trend toward benefit with drug, but not statistically significant
2. Drug effect was significantly dependent on dose*varices in total group

<table>
<thead>
<tr>
<th>Mean Change</th>
<th>Placebo</th>
<th>GR-MD-02 2 mg/kg</th>
<th>GR-MD-02 8 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>From Baseline to Week 54</td>
<td>0.3</td>
<td>-0.37</td>
<td>-0.42</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.45</td>
<td>p=0.14</td>
<td>p=0.09</td>
</tr>
</tbody>
</table>

(Absolute Change)
(PCT Change)

Overall mean baseline HVPG=12.22 mmHg
(No significant difference between groups at baseline-ANOVA)

Mean ± SEM

1ITT with LOCF, ANCOVA with LSD

Harrison et al, EASL 2018
Rational approach to therapeutics for NASH

Disease stage

Disease activity (NAS)

Mainly anti-fibrotic

Targets:
- Metabolic
- Inflammation
- Fibrosis

Lifestyle
Metabolic targets

Mainly metabolic + Inflammatory
Proof of concept study of an apoptosis-signal regulating kinase (ASK1) inhibitor (selonsertib) in combination with an acetyl-CoA carboxylase inhibitor (GS-0976) or a farnesoid X receptor agonist (GS-9674) in NASH

Lawitz E, et al. EASL 2018, Paris. #PS-105

- Significant reductions in MRI-PDFF in patients treated with ACC
- Reductions in MRE-stiffness and TIMP-1 in patients treated with ACC monotherapy

MRI-PDFF responses

- SEL
- ACC
- FXR

≥30% relative reduction

<table>
<thead>
<tr>
<th>Percentage</th>
<th>SEL</th>
<th>ACC</th>
<th>FXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>7.1%</td>
<td>-15.6%*</td>
<td>-9.4%</td>
</tr>
<tr>
<td>70%</td>
<td>-42.7%*</td>
<td>-32.0%*</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>15%</td>
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</table>
Many drugs are in development- they will need to demonstrate histological improvement in the short term and clinically meaningful benefit in the long-term

Courtesy - Dr. David Kleiner