EMERGING THERAPIES FOR NAFLD

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We already have a very effective treatment

Probability of reaching NASH resolution, fibrosis regression and steatosis improvement according to weight loss percentage

52 weeks of lifestyle intervention

<table>
<thead>
<tr>
<th>% Weight loss (WL)</th>
<th>5%</th>
<th>7%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH-resolution</td>
<td>10%</td>
<td>26%</td>
<td>64%</td>
</tr>
<tr>
<td>FIBROSIS-regression</td>
<td>45%</td>
<td>38%</td>
<td>81%</td>
</tr>
<tr>
<td>STEATOSIS improvement</td>
<td>35%</td>
<td>65%</td>
<td>76%</td>
</tr>
<tr>
<td>% Patients achieving WL</td>
<td>70%</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Fig. 3. Probability of reaching NASH resolution, fibrosis regression (at least one stage) and steatosis improvement in patients with NASH under lifestyle intervention according to percentage of weight loss (modified from Vilar-Gomez et al.\textsuperscript{12}).
New drugs for NASH in clinical trials
Mechanisms of action of pharmacological treatments for NAFLD and NASH
Significant end-points in NASH clinical trials

- Improvement of steatosis
- Resolution of NASH
- Improvement of fibrosis

Most clinical trials are using single treatment modality, but combination therapy of multiple drugs to treat NASH is now developing.
# Phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Obeticholic acid (OCA)</th>
<th>Elafibranor</th>
<th>Selonsertib</th>
<th>Cenicriviroc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>FXR agonist</td>
<td>PPAR α/δ agonist</td>
<td>ASK1 Inhibitor – inhibiting apoptosis</td>
<td>CCR2/5 antagonist</td>
</tr>
<tr>
<td><strong>TRIAL</strong></td>
<td>REGENERATE</td>
<td>RESOLVE-IT</td>
<td>STELLAR 3</td>
<td>AURORA</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>NASH with F1 to F3</td>
<td>NASH with F1 to F3</td>
<td>NASH with F1-F3 NASH with compensated cirrhosis</td>
<td>NASH with F2 and F3</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td><strong>Fibrosis improvement without NASH worsening; NASH resolution without fibrosis worsening; liver death</strong></td>
<td>NASH resolution without fibrosis worsening; liver death</td>
<td><strong>Fibrosis improvement without NASH worsening as well as improvements in a number of secondary endpoints</strong></td>
<td><strong>Fibrosis improvement without NASH worsening; composite of progression to cirrhosis, liver-related outcomes, and all-cause mortality</strong></td>
</tr>
</tbody>
</table>

Adapted from clinicaloptions.com
Obeticholic acid – is a FXR agonist

The farnesoid X receptor (FXR) is a nuclear receptor that acts as a master regulator of bile acid metabolism and signaling.

- Triglyceride, fatty acid, and cholesterol synthesis
- Fatty acid oxidation
- Lipolysis

FXR binding site

Inflammation & fibrosis
- Exerts anti-inflammatory and anti-fibrotic effects in the liver, intestine and kidney

Lipid metabolism
- Downregulates hepatic fatty acid biosynthesis and VLDL formation

Carbohydrate metabolism
- Regulates insulin signaling and sensitivity, and hepatic gluconeogenesis

Insulin secretion
- Insulin sensitivity
- Glucose uptake
- Adipogenesis
- Lipid storage

Bile acid reabsorption
- FGF15/19 production

OCA-induced FXR activation

Adorini L, DDT 2012 – Neuschwander-Tetri BA, Lancet,
FLINT – OCA phase 2b study

- Improvement in aminotransferases
- Improvement of several histological parameters, including fibrosis
- Pruritus
- LDL–C increased

Phase 3 studies:
REGENERATE -2500 patients F1 to F3
REVERSE – 500 cirrhotic

Neuschwander-Tetri BA, Lancet, 2015
Elafibranor, First-in-class, has Pluripotent Activities: PPARα and δ Regulate Multiple Pathways Essential in NASH

**FIBROSIS**
- ↓ Fibrogenesis (TGFβ1, αSMA, Col1α1)
- ↓ Oxidative stress (CAT, SOD)
- ↓ Inflammation (MCP-1, IL-6, TNFα)

**LIVER DYSFUNCTION**
- ↓ steatosis (↑ lipid utilization)
- ↓ Oxidative stress (CAT, SOD)
- ↓ ALT, GGT, ALP
- ↑ Hepatic hemodynamics

**LIPID METABOLISM**
- ↑ Triglyceride clearance (APOC3)
- ↓ VLDL-APOB & ↓ LDL-APOB
- ↓ sd-LDL cholesterol level
- ↑ HDL cholesterol level (APOA1/A2)
- ↑ NEFA utilization (ACOX, CPT1, EHHADH)
- ↓ NEFA level (lipolysis, β-oxidation)

**INFLAMMATION**
- ↓ Atherogenic lipid profile
- ↓ Endothelial dysf. (ET-1, RGS5, Nox)
- ↓ Vessel Ox stress (CAT, GPx1, HO1)
- ↓ Vessel inflam (ICAM1, MCP1)

**GLUCOSE HOMEOSTASIS**
- ↑ Insulin sensitivity (Fgf21)
- ↓ Hepatic glucose output (PEPCK, FAS, ACC, PDG, G6PDH)
- ↓ insulin

**PPARα/δ**

**CVD RISK**
- ↓ NF-κB, ↓ TLRs
- ↓ TNFα, IL-1β
- ↓ IL-6, CRP, SAA, HG, fibrinogen
- ↓ Kupffer cell activation (BCL6)
Elafibranor showed significant better reversal of NASH, in a post-hoc analysis. Favourable results in cardiometabolic profile.

### Intention to treat analysis

<table>
<thead>
<tr>
<th>52 weeks treatment</th>
<th>Placebo (N=92)</th>
<th>Elafibranor 80 mg (n=93)</th>
<th>Elafibranor 120 mg (n=89)</th>
<th>P 120 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of NASH without fibrosis worsening</td>
<td>17%</td>
<td>23%</td>
<td>21%</td>
<td>0.28</td>
</tr>
</tbody>
</table>

### Post hoc analysis in NAS≥4

<table>
<thead>
<tr>
<th>52 weeks treatment</th>
<th>Placebo (N=76)</th>
<th>Elafibranor 80 mg (n=83)</th>
<th>Elafibranor 120 mg (n=75)</th>
<th>P 120 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of NASH without fibrosis worsening</td>
<td>11%</td>
<td>20%</td>
<td>20%</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Ratziu et al, Gastro, 2016
RESOLVE-IT: Elafibranor 120 mg vs placebo

- Phase 3 clinical trial on-going – 2000 patients
- NAS≥4, F1 to F3
- 20 countries in Europe, North and South America, Asia, Africa and Australia
- Expected results from an interim analysis

Genfit newsletter (June 2018):
- Elafibranor administration prevented liver tumour development in NAFLD/NASH animal models of disease
  - Elafibranor showed direct cytostatic properties on a large selection of human tumour cell-lines
Selonsertib - ASK1 inhibitor – inhibiting apoptosis showed to be effective in improving fibrosis

Loomba et al, Hepatology, 2017
Selonsertib - ASK1 inhibitor – inhibiting apoptosis **Stellar-3 and Stellar-4**

- **Stellar-3**: 808 patients with NASH with bridging fibrosis
- **Stellar-4**: 883 patients with NASH compensated cirrhosis
- 48-week trial of selonsertib in subjects with stage 3 and 4 NASH;
- Primary endpoint - 1-point decrease in fibrosis stage without worsening of NASH ballooning or inflammation.
- The study’s 5-year outcome is:
  - Reduction in progression to cirrhosis (STELLAR-3)
  - Reduction of hepatic decompensation, hepatocellular carcinoma, transplantation, or death (STELLAR-3 and 4)
Cenicriviroc – CCR2/CCR5 inhibitor

Phase 2b CENTAUR Study (2 yrs)

289 patients with biopsy proven NASH F1-F3

- N=145
- N=72
- N=72

213 patients with Y2 LB

Improvement in fibrosis by ≥1 stage AND no worsening of NASH (Response from Baseline to Year 2)

- Improvement rate: 17% (n=54) vs 15% (n=99)

Improvement in fibrosis by ≥2 stages AND no worsening of NASH (Response from Baseline to Year 2)

- Improvement rate: 3% (n=34) vs 11% (n=65)

Ratziu, ILC 2018
AURORA - CCR2/CCR5 inhibitor

- Phase 3 study-2000 patients
- NASH with F2 and F3
- The primary outcome is improvement of fibrosis without worsening NASH
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Study Population[1]</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saroglitazar</td>
<td>PPAR α/ɣ agonist</td>
<td>NAFLD (fibrosis stage 0-3), ALT &gt; 1.5 ULN</td>
<td>EVIDENCES II[2]</td>
<td>Change in ALT</td>
</tr>
<tr>
<td>IVA337</td>
<td>PPAR α/δ/ɣ agonist</td>
<td>NASH, SAF fibrosis score &lt; 4</td>
<td>NATIVE[3]</td>
<td>Improvement of SAF activity score</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 analogue</td>
<td>NASH (fibrosis stage 1-4), compensated cirrhosis</td>
<td>LEAN[4,5]</td>
<td>Liver histological improvement</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>GLP-1 analogue</td>
<td>NASH (fibrosis stage 2-3)</td>
<td>NN9931-4296[6]</td>
<td>NASH resolution without worsening of fibrosis</td>
</tr>
<tr>
<td>JKB-121</td>
<td>TLR-4 antagonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>Pro00062677[7]</td>
<td>Safety and tolerability; change in ALT, hepatic fat; TTR</td>
</tr>
<tr>
<td>NGM282</td>
<td>FGF19 agonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>15-0105[8]</td>
<td>Change in hepatic fat</td>
</tr>
<tr>
<td>BMS-986036</td>
<td>Pegylated FGF21</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>MB130-045[9]</td>
<td>Safety and tolerability; change in hepatic fat</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>THR-β agonist</td>
<td>NASH (fibrosis stage 1-3)</td>
<td>MGL-3196-05[10]</td>
<td>Change in hepatic fat</td>
</tr>
<tr>
<td>Volixibat</td>
<td>ASBT inhibitor</td>
<td>NASH (fibrosis stage 0-3)</td>
<td>SHP626-201[11]</td>
<td>Improvement in NAS without fibrosis worsening</td>
</tr>
</tbody>
</table>
Liraglutide – GLP-1 agonist - LEAN Study

- Incretin mimetic that acts as an agonist of glucagon-like peptide-1 receptor, used on Type 2 diabetes
- Significant histological improvement of

(Double-blinded, randomised, placebo-controlled phase 2 trial)

Non-tumorogenic variant of FGF19 that modulates bile acid synthesis affecting metabolic pathways

Significantly higher reduction in liver fat in the treated arm
MGL-3196 – THRβagonist

**MGL-3196, significantly decreases hepatic fat in NASH patients at 12 weeks, decreasing also LDL-C and aminotransferases**

Harrison et al, , ILC 2018
## Phase II

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Mechanism of Action</th>
<th>Study Population[1]</th>
<th>Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>LJN452</td>
<td>FXR agonist</td>
<td>NASH (fibrosis stage 0-3), elevated ALT or PDFF &gt; 10%, obesity, T2DM</td>
<td>FLIGHT-FXR[2]</td>
<td>Adverse event profile; change in transaminases</td>
</tr>
<tr>
<td>LMB763</td>
<td>FXR agonist</td>
<td>NASH (fibrosis stage 0-3), elevated ALT or PDFF &gt; 10%, obesity, T2DM</td>
<td>CLMB763X2201[3]</td>
<td>Adverse event profile and safety; change in transaminases</td>
</tr>
<tr>
<td>GS-9674 + GS-0976</td>
<td>FXR agonist + ACC inhibitor</td>
<td>NASH (fibrosis stage 2-3) or MRE &gt; 2.88 kPa, PDFF ≥ 10% or MRE &gt; 4.67 kPa, not compensated</td>
<td>GS-US-384-3914[5]</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>GS-0976</td>
<td>ACC inhibitor</td>
<td>NAFLD or NASH without cirrhosis</td>
<td>GS-US-426-3989[6]</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>PF-05221304</td>
<td>ACC inhibitor</td>
<td>NASH (fibrosis stage 1-3), MRE ≥ 2.5 kPa, PDFF ≥ 8%</td>
<td>C1171002[7]</td>
<td>Dose-response effect on liver fat</td>
</tr>
</tbody>
</table>
Novel synthetic activated carbons derived from phenolic resin
Powerful, non-selective adsorptive capacity
Bimodal porosity remove cytokines TNF-α, IL-6, IL-8 and IL-1β from human plasma in extracorporeal circuits
   - Micropores (<2nm)
   - Mesopores (2-50nm)
Rapid adsorption kinetics targeting key larger bioactive molecules such as endotoxin and cytokines

Oral nanoporous carbon therapy shows considerable promise as a safe oral non-absorbable interventional strategy to diminish disease pathogenesis in NAFLD

Clinical trial is about to start in patients with non-cirrhotic NASH in Europe
Improvement with pharmacological agents

A. Improvement in hepatic steatosis

![Graph showing percentage of patients with improvement in hepatic steatosis across different treatments with p-values indicated.]

B. Resolution of NASH

![Graph showing percentage of patients with resolution of NASH across different treatments with p-values indicated.]

C. Improvement in fibrosis

![Graph showing percentage of patients with improvement in fibrosis across different treatments with p-values indicated.]

Konerman et al, J Hepatol,
Take home messages

- A large number of promising phase 2 and 3 clinical trials are on-going, and results are expected

- Major issues with these clinical trials:
  - Difficulties in identifying patients
  - Stratifying risk, to identify the patients that really benefit from drug treatment
  - The majority of trials still use multiple liver biopsies, but hopefully that will change and reliable non-invasive methods will be identified
Take home messages

- Even if very effective drugs will be confirmed, it will be difficult to define treatment time, since it will tend to recur if the risk factors remain.
- Political measures to revert the epidemics of obesity are really needed.
Thank you