NAFLD Therapeutics: How Will We Treat NASH 5-Years from Now?

Hong Kong Association for the Study of Liver Disease, Hong Kong, November 2018

Prof Quentin M. Anstee PhD, FRCP
Professor of Experimental Hepatology & Honorary Consultant Hepatologist,
Institute of Cellular Medicine,
Newcastle University, UK.

Disclosure Slide

Research Grant Funding
Abbvie, Allergan/Tobira, AstraZenica, GlaxoSmithKline, Novartis Pharma AG, Pfizer Ltd., Vertex.

Active Research Collaborations (including research supported through the EU IMI2 LITMUS Consortium*)

Consultancy

Speaker
Abbott Laboratories, Allergan/Tobira, BMS, Clinical Care Options, Falk, Genfit SA, Gilead, Integritas.

This lecture contains discussion of off-label/investigative use of commercial products, medical devices, biologic or pharmaceutical agents. The lecture is for academic purposes only and does not constitute any form of medical advice regarding use of these compounds in routine clinical practice or any form of financial advice/recommendation regarding the companies or the products discussed.
NAFLD Natural History

Steatohepatitis (NASH) is the biological driver of disease progression and fibrogenesis. The presence of advanced stage of fibrosis (F3-4) is the strongest predictor of long-term mortality.

Mortality Increases with Fibrosis Stage in NAFLD

Systematic review and meta-analysis of 5 studies, 1,495 NAFLD patients with 17,452 patient-years follow-up.

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>All-Cause Mortality</th>
<th>Liver-Related Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mortality Rate (per 1,000 PY)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Stage 0</td>
<td>15.2</td>
<td>17.1</td>
</tr>
<tr>
<td>Stage 1</td>
<td>27.9</td>
<td>27.9</td>
</tr>
<tr>
<td>Stage 2</td>
<td>45.8</td>
<td>45.8</td>
</tr>
</tbody>
</table>

Cardiovascular Disease 38%  
Non-Liver Malignancy 19%  
Liver Disease 8%  
Hepatocellular Carcinoma 1%  
Liver Transplantation 1%  
Infections 9%  
Other 18% / Unknown 8%  

Dulai et al., Hepatology 2017, Angulo et al., Gastroenterology 2015
1. **Target Obesity**
   - Lifestyle: Diet and Physical exercise
   - Bariatric Surgery

2. **Target the Metabolic Syndrome** — reduce CVD risk whilst selecting medication with additional ‘liver directed’ benefits
   - Insulin resistance/Type 2 diabetes mellitus
   - Hypertension
   - Dyslipidaemia

3. **Target the liver disease** — ameliorate steatohepatitis and prevent progression to fibrosis and cirrhosis

4. **Minimise down-stream complications such as HCC**

---

**Lifestyle Changes: Current Evidence**

- Weight reduction through diet and exercise should be recommended because *if sustained* it improves:
  - Cardiovascular risk profile [Hallsworth 2011 & 2015]
  - Steatohepatitis (7-9% weight loss) [Promrit 2010; Vilar-Gomez 2015]
  - Fibrosis (>10% weight loss) [Vilar-Gomez 2015]

- NAFLD patients lack confidence to exercise and may not be ready to make and sustain the necessary lifestyle changes [Frith, 2010; Centis, 2013]
Bariatric Surgery

Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients
Guillaume Lassele1,2, Robert Calazio1,2, David Boub1, Marie Pitectre1, Hélène Verkindt,1
Julien Labrousse,1 Morisot Reverdy,1 Emmanuelle Lebeurier,1 Blandine Dériany,1
Alexandre Louvet,1 Monique Romon,1 Alain Dharmel,1 François Pietteau,1,2 and
Philippe Metthum1,2
N = 82 cases with confirmed NASH and f/u Biopsy at 1-Year

Targeting the Liver Disease -

PHARMACOLOGICAL THERAPY FOR NAFLD...

Currently there are no licenced pharmacological treatments specifically for NAFLD
### Targeting Insulin Resistance & Oxidative Stress with Currently Available Agents

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Multiple</td>
<td>Multiple Studies</td>
<td>Investigator Led</td>
<td>Various</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>PPARγ agonist</td>
<td>PIVENS* Multiple Studies</td>
<td>Investigator Led</td>
<td>Reduction in NAS ≥2 without fibrosis worsening</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 analogue</td>
<td>LEAN* (NCT01237119)</td>
<td>Novo Nordisc† / IL</td>
<td>Resolution of NASH without fibrosis worsening</td>
</tr>
</tbody>
</table>

### Currently Available Pharmacological Compounds

#### Targeting Insulin Resistance

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Multiple</td>
<td>Multiple Studies</td>
<td>Investigator Led</td>
<td>Various</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>PPARγ agonist</td>
<td>PIVENS* Multiple Studies</td>
<td>Investigator Led</td>
<td>Reduction in NAS ≥2 without fibrosis worsening</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>GLP-1 analogue</td>
<td>LEAN* (NCT01237119)</td>
<td>Novo Nordisc† / IL</td>
<td>Resolution of NASH without fibrosis worsening</td>
</tr>
</tbody>
</table>

#### Targeting Oxidative Stress

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>Anti-oxidant</td>
<td>PIVENS* TONIC*</td>
<td>Investigator Led</td>
<td>Improvement in NAS ≥2 without fibrosis worsening</td>
</tr>
</tbody>
</table>

* Note Disclosures  *Phase IIb
Pioglitazone & Vitamin E for NASH: The Phase 2b PIVENS Study

- Both agents improved steatosis & inflammation scores
- Only Vitamin E reduced ballooning
- Neither Vitamin E or Pioglitazone reduced fibrosis

247 non-diabetic adults with biopsy proven NASH

Primary Endpoint = 2-point NAS reduction (inc. reduced ballooning) with no worsening of fibrosis

- Placebo (N = 83)
- Pioglitazone 30mg/day (N = 80)
- Vitamin E 800 IU/day (N = 84)

Inclusion: NAS ≥ 4, F ≤ 3

96 Weeks

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

P = 0.001*
OR 3.14

P = 0.04
OR 2.13

* Significance: P < 0.025

Pioglitazone for NASH: Further evidence

- 101 pre-diabetic/diabetic adults with biopsy proven NASH

Primary Endpoint = 2-point NAS reduction (inc. reduced ballooning) with no worsening of fibrosis

- Placebo (N = 51)
- Pioglitazone 45 mg/day (N = 50) + 500 kcal/day deficient diet

Inclusion: "Confirmed NASH" ?NAS ≥ 3, F ≤ 3

78 Weeks

P < 0.001

Cusi et al, Ann Int Med 2016

Pioglitazone produced a significantly higher resolution of NASH but no improvement in fibrosis.
Safety & Tolerability Issues

**Vitamin E**
- Increased all cause mortality risk at >400 IU/day
  - Miller, 2005; Bjelakovic, 2007
- Increased haemorrhagic stroke risk (although reduced embolic stroke risk)
  - Schwartz, 2010
- Increased Prostate carcinoma risk
  - Lippman, 2009; Klein, 2011

**Pioglitazone**
- Oedema and Weight gain
  - Basu, 2006; Sanyal, 2010
- Increased risk of Osteoporosis
  - Schwartz, 2006
- Increased Bladder Cancer risk (HR 1.63) in some, but not all studies
  - Toccori, 2016; Lewis, 2015

Use of these agents should be personalised for selected patients with histologically confirmed NASH after careful consideration of risk/benefit ratio.

---

**Liraglutide for NASH: The Phase 2b LEAN Study**

- **45 diabetic and non-diabetic adults with biopsy proven NASH**
- **Primary Endpoint** = resolution of NASH (loss of ballooning) with no worsening of fibrosis

<table>
<thead>
<tr>
<th>Inclusion: &quot;Definite NASH&quot;</th>
<th>NAS ≥3, F ≤3</th>
</tr>
</thead>
</table>

**Liraglutide 1.8mg/day (N = 23)**

**Placebo (N = 22)**

**48 Weeks**

- **Liraglutide improved NASH with no worsening of fibrosis.**
  - Unclear if effects were entirely independent of weight loss.
  - Unusually rapid disease progression observed in Placebo arm.

Armstrong et al, Lancet 2015
45 year old with type 2 diabetes and NASH with stage 3 fibrosis comes in to discuss therapeutic options...

- **Treat Metabolic Syndrome**
  - Hypertension
  - Dyslipidaemia*
  - T2DM

- **Control Obesity**
- **Reduce CVD Risk**
- **Reduce HCC Risk**

- **Targeting NASH**
  - Metformin
  - Simvastatin

- **Lifestyle Change**
  - Diet
  - Exercise
  - Bariatric Sx

- **Potential effects for “HCC Chemoprevention”**
  - Vitamin E
  - Pioglitazone
  - (Liraglutide)

- **“Liver Directed” Rx**

* NAFLD does not increase Statin DILI risk

**Pharmacotherapy: What’s on the Horizon...?**
Targeting Pathophysiological Processes

- **Normal Liver**
- **Steatosis**
- **Steatohepatitis**
- **Cirrhosis**

**Targets related to Insulin Resistance and/or Lipid Metabolism**
- PPARα/δ: Elafibranor, IVA337
- PPARα/γ: SAR465561
- THR-β: MGL-3196, OCA, GS-9674, LIN-315, LMB-763
- TGR5: INT-767, INT-777
- ASBT: Voxxiibat
- FGF19: INK-020, INK-012

**Targets related to Lipotoxicity & Oxidative Stress**
- PPARα/δ: Elafibranor, IVA337
- SREBP-1c: MPP-410, MPP-411
- LXR: Lovastatin, Simvastatin
- LOXL2: Simtuzumab
- Galectin: GR-MD-02

**Targets related to Inflammation and Immune activation**
- CCR2/5: Cenicriviroc
- AOC3: BI 1467335
- TLR4: JKB-121
- Anti-LPS: IMM-124E
- ASK1: Caspase-8, Emrinscan

**Targets related to Cell Death (Apoptosis and Necrosis)**
- Caspases: Emirican

**Targets related to Fibrogenesis & Collagen Turnover**
- THR-β: MGL-3196
- mTOT: MSDC-0602K
- FXR: OCA, GS-9674, LJN-452, LMB-763
- FXR: OCA, GS-9674, LJN-452, LMB-763

**Pathophysiology & Therapeutic Targets**

- Elafibranor (PPAR α/δ)
- Obeticholic Acid (FXR)
- Selonsirtib (ASK1)
- Cenicriviroc (CCR2/CCRS)

**Modified from Perruzo & Dufour, Liver International 2017**
### Compounds Currently in Phase 3 Clinical Trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic Acid</td>
<td>FXR agonist (bile acid derived)</td>
<td>REGENERATE</td>
<td>Intercept†</td>
<td>Co-primary endpoints: (i) Improvement in Fibrosis by ≥1-stage without worsening of NASH; (ii) Resolution of NASH without worsening of Fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NCT02548351)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elafibranor</td>
<td>PPAR α/δ agonist</td>
<td>RESOLVE-IT</td>
<td>Genfit†</td>
<td>Resolution of NASH (no ballooning, no/minimal lobular inflammation) without worsening of fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NCT02704403)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cenicriviroc</td>
<td>CCR2/CCR5 antagonist</td>
<td>AURORA</td>
<td>Allergan†</td>
<td>Improvement in Fibrosis by ≥1-stage without worsening of NASH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NCT03028740)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selonsertib</td>
<td>ASK1 inhibitor</td>
<td>STELLAR-3</td>
<td>Gilead†</td>
<td>Improvement in Fibrosis by ≥1-stage without worsening of NASH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NCT03053050)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>STELLAR-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NCT03053063)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Supporting Phase 2 Trial Publications:

† Note Disclosures

Sources: ClinicalTrials.gov and the UK NIHR Innovation Observatory

### Pathophysiology & Therapeutic Targets

- **FXR Agonists**
- **Bile Acids**
- **Inflammation**
- **Oxidative stress**
- **Apoptosis**
- **Fibrosis**
- **NASH**
- **Cirrhosis**
- **HCC**
- **Acetate**
- **Vasoconstriction**
- **Liver Transplant**

Modified from Persipa & Dallier, Liver International 2017
Enterohepatic Bile Acid Circulation & FXR/FGF19 Agonists

- BAs are secreted into the bile and reabsorbed in the terminal ileum.
- **Hepatic FXR activation** by BAs:
  - ↓ BA synthesis (CYP7A1),
  - ↓ Lipogenesis (SREB1c/ChREBP),
  - ↓ Gluconeogenesis,
  - ↑ Insulin sensitivity.

- **Ileal FXR activation** ↑FGF-15/19 production that acts via FGFR4:
  - ↓ BA synthesis (CYP7A1)
  - ↑ Hepatic glycogen storage
  - ↑ FA oxidation.

- Intestinal TGR5 activation by BAs promote GLP-1 release that promotes insulin release from pancreatic β-cells.
- **Muscle and adipose tissue TGR5 activation** increases thermogenesis and energy expenditure.

Exploitable drug targets:
- FXR agonists (OCA, GS-9674, LJN-452, LMB-763)
- TGR5 agonist (INT-767, INT-777)
- ASBT inhibitors (SHP-626)
- FGF-19 agonists (NMG-282)
Relevance of FXR Agonists in NAFLD Therapy

↑ Insulin Sensitivity  
↓ Gluconeogenesis  
↓ Bile acid synthesis  
↓ Lipogenesis  
↑ Fatty Acid oxidation

Obeticholic Acid (OCA) for NASH: The Phase 2b FLINT Study

283 diabetic and non-diabetic adults with biopsy proven NASH

Primary Endpoint = improvement of NAS ≥ 2 points with no worsening of fibrosis

Trial terminated early by DSMB due to clear effect  
Apparent beneficial effects for NASH & Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Reduced NAS</th>
<th>Reduced Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic Acid</td>
<td>45% (50/110)</td>
<td>35% (36/102)</td>
</tr>
<tr>
<td>Placebo</td>
<td>21% (23/109)</td>
<td>19% (19/98)</td>
</tr>
</tbody>
</table>

P = 0.0002
Obeticholic Acid (OCA) for NASH: The Phase 2b FLINT Study

![Graph showing changes in cholesterol, HDL, LDL, and triglycerides with Obeticholic Acid vs Placebo](image)

**Total Cholesterol**
- **Obeticholic Acid** vs **Placebo**: $P = 0.0009$

**HDL**
- **Obeticholic Acid** vs **Placebo**: $P = 0.01$

**LDL**
- **Obeticholic Acid** vs **Placebo**: $P < 0.0001$

**Triglycerides**
- **Obeticholic Acid** vs **Placebo**: $P = 0.88$

FXR-Related Targets Currently in Phase 2/3 Trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic Acid (INT-747, Ocaliva)</td>
<td>FXR agonist (bile acid derived)</td>
<td>FLINT (NCT01265498)</td>
<td>Intercept†</td>
<td>Co-primary endpoints: (i) Improvement in Fibrosis by ≥1-stage without worsening of NASH; (ii) Resolution of NASH without worsening of Fibrosis</td>
</tr>
<tr>
<td>GS-9674 (Pr-104)</td>
<td>FXR agonist (bile acid)</td>
<td>GS-US-402-1852 (NCT02548351)</td>
<td>Gilead†</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>LMB-763</td>
<td>FXR agonist (synthetic)</td>
<td>CLMB763X2201 (NCT02913105)</td>
<td>Novartis†</td>
<td>Change in Transaminase levels at 12 weeks.</td>
</tr>
<tr>
<td>Tropifexor</td>
<td>FXR agonist (synthetic)</td>
<td>FLIGHT-FXR (NCT02855164)</td>
<td>Novartis†</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>NGM-282</td>
<td>FGF-19 agonist</td>
<td>15-0105 (NCT02431116)</td>
<td>NGMBio†</td>
<td>Change in hepatic fat by MRI at 12 weeks.</td>
</tr>
<tr>
<td>Volixibat (SHP-626)</td>
<td>ASBT inhibitor</td>
<td>SHP626-201 (NCT02787304)</td>
<td>Shire</td>
<td>Improvement in NAS ≥2 without fibrosis worsening at 48 weeks.</td>
</tr>
</tbody>
</table>

*Note Disclosures*  *Phase III*
FGF19 Agonist (MGM-282) for NASH

- A 12-week Phase 2 randomized, placebo-controlled trial of MGM282 (3 mg and 6 mg) in biopsy-confirmed NASH revealed significant improvements in liver fibrosis.
- Subjects enrolled with biopsy-confirmed NASH in this open-label trial.
- Primary endpoint was the absolute change in FIB-4 at W12.
- Other fibrosis markers (APRI, AST/ALT) showed a significant reduction in the treatment group.
- Exploratory endpoint of change in liver histology at W12 was also observed.
- Revascularisation was started at W2 if LDL-C levels of 30 mg/dL were observed.

Decrease Across All NASH Histological Parameters with NGM282 at W12

Harrison et al, AASLD 2018
NGM-282 1mg for 12 weeks

- Mean change from Baseline in fibrosis stage = -0.1
- One subject had a 2-stage improvement in fibrosis: F2 → F0

NGM-282 3mg for 12 weeks

- Mean change from Baseline in fibrosis stage = -0.5
- Three subjects had a 2-stage improvement in fibrosis: all F3 → F1

Harrison et al, AASLD 2018

**LDL-C levels drop below baseline with rosvastatin**

- Decreased C4 and increased LDL-C levels reflect potent CYP7A1 inhibition
- Lipid particle change primarily driven by increase in large LDL particles
- Significant reductions in serum triglycerides (1 mg: -25%; 3 mg: -34% at week 12)

Harrison et al, AASLD 2018
PPARs as Therapeutic Targets for NAFLD

Metabolically active tissues (especially Liver)
- Fatty acid β-oxidation
- Hepatic Steatosis
- Gluconeogenesis
- Inflammatory genes controlled by NF-κB

Adipose tissue
- Insulin Sensitivity
- Hepatic Steatosis
- Inflammation
- Stellate cell activation
- Adipose FA Uptake
- Body weight
- Oedema
- Bone strength

Targets: PPAR γ (Glitazones), PPAR α/δ (Elafibranor), PPAR α/γ (Saroglitazar) and PPAR α/δ/γ (IVA337)

PPAR Related Targets Currently in Phase 2/3 Trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>PPAR γ agonist</td>
<td>PIVENS (NCT00063622)</td>
<td>Investigator Led</td>
<td>Reduction in NAS ≥2 without fibrosis worsening</td>
</tr>
<tr>
<td>Elafibranor</td>
<td>PPAR α/δ agonist</td>
<td>GOLDEN-505 (NCT01694849)</td>
<td>Genfit†</td>
<td>Resolution of NASH (no ballooning, no/minimal lobular inflammation) without worsening of fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RESOLVE-IT* (NCT02704403)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA-337</td>
<td>PPAR α/δ/γ agonist</td>
<td>NATIVE (NCT03008070)</td>
<td>Inventiva†</td>
<td>Percentage change from baseline in serum ALT and AST levels at week 16</td>
</tr>
<tr>
<td>Saroglitazar</td>
<td>PPAR α/γ agonist</td>
<td>EVIDENCES II (NCT03061721)</td>
<td>Zydus</td>
<td></td>
</tr>
</tbody>
</table>

*Phase III
† Note Disclosures
Elafibranor (ELA) for NASH: The Phase 2b GOLDEN-505 Study

274 diabetic and non-diabetic adults with biopsy proven NASH

Per Protocol Primary Endpoint = resolution of NASH (score 0 for >1 NAS component [S, B, I]) with no worsening of fibrosis

Results of Per Protocol Endpoint

Placebo Elafibranor 80mg Elafibranor 120mg

Elafibranor (ELA) for NASH: The Phase 2b GOLDEN-505 Study

274 diabetic and non-diabetic adults with biopsy proven NASH

Post Hoc Modified Primary Endpoint = resolution of NASH (loss of ballooning and 0-1 for inflammation) with no worsening of fibrosis

Results of Post Hoc Modified Endpoint

Placebo Elafibranor 80mg Elafibranor 120mg

Baseline Histology [N] | Placebo | ELA 120mg | OR | P-Value
--- | --- | --- | --- | ---
NAS ≥ 3 [N = 274] | 12% | 19% | 2.31 | 0.045
NAS ≥ 4 [N = 234] | 9% | 19% | 3.52 | 0.013

Ratziu et al, Gastroenterology, 2016
Pathophysiology & Therapeutic Targets

Lipid Metabolism, Lipotoxicity & Oxidative Stress in NAFLD

**Exploitable drug targets:**
- KHKi (PF-06835919)
- ACCi (GS-0976, PF-05221304)
- SCD1i (Aramchol)
- DGAT2i (PF-06865571)

**Diagram:**
- Hepatocyte free fatty acid flux
- Mitochondrial β-Oxidation
- Peroxisomal β-Oxidation
- Microsomal ω-Oxidation
- Mitochondrial Dysfunction
- Apoptosis & Necrosis
- NASH
### Other Compounds with Targets Related to Lipid Metabolism

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Trial Name</th>
<th>Company</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aramchol</td>
<td>SCD1</td>
<td>Aramchol_005 (NCT02279524)</td>
<td>Galmed†</td>
<td>Percentage change in the liver triglycerides concentration measured by NMRS.</td>
</tr>
<tr>
<td>BMS-986036</td>
<td>FGF21</td>
<td>NCT02413372</td>
<td>BMS†</td>
<td>Change in hepatic fat fraction (%) by MRI. Safety</td>
</tr>
<tr>
<td>PF-05221304</td>
<td>ACC inhibitor</td>
<td>C1171002 (NCT03248882)</td>
<td>Pfizer†</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>PF-06835919</td>
<td>KHK inhibitor</td>
<td></td>
<td>Pfizer†</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>PF-06865571</td>
<td>DGAT2 inhibitor</td>
<td></td>
<td>Pfizer†</td>
<td>Safety and tolerability</td>
</tr>
</tbody>
</table>

† Note Disclosures

ARREST: A one year global phase 2b randomized placebo-controlled trial

NASH resolution without worsening of fibrosis

Results: Fibrosis improvement and progression to cirrhosis

Ratziu et al, AASLD 2018
Acetyl CoA Carboxylase (ACC) Inhibition (GS-0976)

Open-Label Phase IIa Study

12-weeks treatment with GS-0976 led to significant reductions in de novo lipogenesis, MRI-PDFF and MRE-Liver Stiffness relative to Baseline levels.

Preliminary efficacy and safety of acetyl-CoA carboxylase (ACC) inhibitor GS-0976 in patients with compensated cirrhosis due to NASH

- Inhibition of hepatic de novo lipogenesis
- Decreases in liver fat by MRI-PDFF
- No effect of GS-0976 on MRE-stiffness

Changes from baseline to Week 12

<table>
<thead>
<tr>
<th>Substance</th>
<th>Median relative % change from BL to Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>−28.8 (−34.6, −14.8), p=0.004</td>
</tr>
<tr>
<td>AST</td>
<td>−12.3 (−22.6, −2.3)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>−8.3 (−25.0, 8.3)</td>
</tr>
<tr>
<td>GGT</td>
<td>−8.3 (−20.0, 13.2)</td>
</tr>
<tr>
<td>ELF</td>
<td>−3.0 (−6.2, 3.1)</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>−1.7 (−9.7, 16.1)</td>
</tr>
<tr>
<td>PiIIIPN</td>
<td>−9.2 (−40.5, 18.8)</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>−19.1 (−35.0, 41.2)</td>
</tr>
</tbody>
</table>

Adverse events and laboratory abnormalities

- In this 12-week, proof-of-concept study in patients with compensated NASH cirrhosis, GS-0976 was safe and associated with significant reductions in hepatic DNL, MRI-PDFF, and serum ALT

Thyroid Hormone Receptor (THRβ) Agonist (MGL-3196)

- Epidemiological studies link NAFLD with high rates of clinical and subclinical hypothyroidism.
- Evidence that NAFLD patients exhibit decreased thyroid hormone response gene expression in the liver.
- Patients with hypothyroidism exhibit:
  - Increased TG and Cholesterol levels.
  - Insulin resistance
- THRβ agonists potentially have beneficial effects including:
  - Decreased TG, LDL-Cholesterol, non-LDL-Cholesterol, Apolipoprotein B
  - Decrease PCSK9, so increased reverse cholesterol metabolism

MGL-3196, a selective thyroid hormone receptor-beta agonist significantly decreases hepatic fat in NASH patients at 12 weeks, the primary endpoint in a 36-week serial liver biopsy study

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)

Key Inclusion/exclusion:
- NASH: NAS ≥4 + F1–3
- MRI-PDFF: ≥10% liver fat

Baseline | Placebo (n=41) | MGL-3196 (n=84)
--- | --- | ---
NAS, mean (SD) | 4.8 (1.1) | 4.9 (1.0)
Fib n (%) D–1 | 21 (51.2) | 48 (57.1)
Fib n (%) 2–3 | 20 (48.8) | 36 (42.8)
Diabetic, n (%) | 13 (31.7) | 35 (41.7)
MRI-PDFF, mean (SD) | 19.8 (6.7) | 20.7 (7.0)

All baseline demographics comparable between groups

N=125

2:1 randomization Placebo

MGL-3196 80 mg/day (Possible dose adjustment +20 mg at Week 4)

MRI-PDFF: Liver biopsy Pharmacokinetic assessment MRI-PDFF Liver biopsy

Primary endpoint: relative ↓ MRI-PDFF fat Secondary: # achieving ≥30% ↓ MRI-PDFF fat, NASH/Fibrosis biomarkers and lipids, LMS

NASH Liver Biopsy Endpoints at Week 36

2-Point NAS Reduction with at least a 1-pt reduction in ballooning or inflammation (% of liver biopsies)

- Placebo
- MGL-3196 (all)
- MGL-3196 (high exp)
- MGL-3196, MRI responder

NASH Resolution ballooning=0, inflammation =0.3 with at least 2-point reduction in NAS (% of liver biopsies)

- Placebo
- MGL-3196 (all)
- MGL-3196 (high exp)
- MGL-3196, MRI responder

Change in Fibrosis Score on Liver Biopsy at Week 36

SHG Score

- Second Harmonic Generation (SHG) microscopy provides automated fully quantitative assessment of fibrosis on liver biopsy slides based on unique architectural features of collagen
- SHG score was generated and aligned with the pathologist baseline score (baseline, r=0.76), (left panel), blinded to treatment code
- Using SHG, MGL-3196 treated compared with placebo showed a statistically significant ≥1-pt reduction in fibrosis score at Week 36. Based on pathology score, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo

Harrison et al, AASLD 2018
Gut Microbiome

Oxidative Stress

Pathophysiology & Therapeutic Targets

Selonsirtib (ASK1)

Cenicriviroc (CCR2/CCR5)

Fibrosis

Inflammation

Apoptosis

Activated Stellate Cell

Activated Liver Cell

Cenicriviroc (CVC) is a CCR2/CCR5 Antagonist

Chemokine receptors type 2 (CCR2) and type 5 (CCR5) are expressed on cells that promote inflammation & fibrogenesis.

CCR2/CCR5 blockade potentially interferes with inflammatory signaling by Kupffer cells & Monocyte/Macrophage recruitment

CCR2/5 blockade potentially disrupts signaling that activates stellate cells
Ceniciviroc (CVC) for NASH: The Phase 2b CENTAUR Study

289 diabetic and non-diabetic adults with biopsy proven NASH

Primary Endpoint = improvement of NAS ≥ 2 points (with ≥1 point reduction in Inflammation or Ballooning) and no worsening of fibrosis

Key Secondary Endpoint = improvement in Fibrosis by ≥ 1 point with no worsening of steatohepatitis

• Year 1: No clear benefit for histological NASH but significant anti-fibrotic effect
• Year 2 data indicates the anti-fibrotic effect was maintained but without a statistically significant additive effect

Friedman et al, Hepatology 2017
ASK1 Inhibition in NASH (Selonsertib)

- Apoptosis signal-regulating kinase 1 (ASK1), aka MAP3K5.
- ASK1 pathway is activated in NASH and correlates with fibrosis stage.
- In rodent models, ASK1 inhibition improves steatosis, inflammation and fibrosis.
- Selonsertib (SEL, formerly GS-4997) is a selective, potent, small molecule inhibitor of ASK1.

Selonsertib (SEL) for NASH: Phase 2a GS-US-384-1497 Study

Adult patients with biopsy proven NASH + Fibrosis

Primary Endpoint ≥ 1 stage improvement of fibrosis

Results of Change in Fibrosis by ≥ 1 Stage

No Placebo Arm
(Simtuzumab: “no effect on histology or pharmacokinetics”)
Combination Therapy

Combination Therapy #1: Tropifexor (Novartis) + Cenicriviroc (Allergan)

Modified from Perrazo & Dufour, Liver International 2017
TANDEM Study

A 48-week, Phase 2b, multicenter, randomized, double-blind study

Combination Therapy #2: FXR ± ASK1i ± ACCi (Gilead)

Modified from Perrazo & Dufour, Liver International 2017
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

**Inclusion:**
- Clinical diagnosis of NAFLD
- MRI-PDFF ≥10% and MRE ≥2.88 kPa, or biopsy consistent with NASH and F2–F3
- Noncirrhotic (FibroTest™ <0.75, historical imaging and liver biopsy)

**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**
  - 7.1%
- **ACC**
  - −15.6%
- **FXR**
  - −32.0%
- **SEL + ACC**
  - −42.7%
- **SEL + FXR**
  - −32.0%
- **SEL + ACC + FXR**
  - −42.7%

**Median relative (%) change between baseline and Week 12**

- **MRE-stiffness**
  - ≥30% relative reduction
  - 10% (1/10)
  - 70% (7/10)
  - 0% (0/10)
  - 50% (10/20)
  - 15% (3/20)

**12-week therapy with SEL + ACC or FXR was safe and well tolerated**
- Combination regimens demonstrated beneficial effects on:
  - Hepatic DNL and steatosis
  - Liver biochemistry
  - Markers of fibrosis, including reduced lumican synthesis in SEL + ACC arm

- Phase 2, 48-week study with histological assessment ongoing to better characterize efficacy and safety of combinations vs monotherapies in advanced fibrosis due to NASH

Lawitz E, et al. EASL 2018, Paris. #PS-105
In the absence of regulator approved drug therapy, at present the treatment of NAFLD/NASH should focus on:

- **Weight loss** via calorific restriction diets (and exercise), or bariatric surgery
- **Reducing CVD risk-profile** (statins “safe”)
- Consider use of agents with trial evidence of a beneficial effect on NASH:
  - Pioglitazone, or possibly Liraglutide, in patients with T2DM.
  - Vitamin E may be used in selected non-diabetic patients.
  - Individualised decision making balancing known risks vs. benefits required for all.

- **NAFLD clinical practice guidelines published by AASLD (2017) and EASL-EASD-EASO (2016).**
- The drug-development pipeline for NAFLD/NASH is burgeoning. A number of promising compounds to treat NAFLD are entering Phase 2/3 clinical trials.
- Results of clinical trials must be awaited before any firm recommendations can be made in terms of efficacy or side-effect profiles for these new agents.
Acknowledgements

Prof Chris Day, Prof Ann Daly, Dr Olivier Govare, Dr Jeremy Palmer, Dr Marie Boyle, Dr Tim Hardy, Dr Yang-Lin Liu, Ms Emma Scott.

Prof Helen Reeves, Prof Fiona Oakley, Prof Derek Mann, Prof Jelena Mann, Dr Dina Tiniakos, Dr Stuart McPherson, Dr Kate Hallsworth, Ms Laura Haigh.

quentin.anstee@newcastle.ac.uk