SESSION 6 • ADVANCES IN NASH PHARMACOLOGY

Similarities and differences between classical FXR agonists versus non-steroidal agents

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Financial Disclosures

• Advisor
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  – Falk Foundation, Gilead, Intercept, MSD, Roche

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  – Falk Foundation, Gilead, Intercept, Roche

• Property rights
  – The Medical University of Graz has filed patents on medical use of norUDCA and I am listed as co-inventor

Unlabeled Use Disclosure

• All discussed bile acid signaling therapies of NASH are investigational only
Key Points – Bile Acid Signaling Pathways in NASH

• Bile acids as signaling molecules with hormonal functions
  – Bile acids = steroid hormones, ‘enterohepatic’ hormones
  – Signal during their enterohepatic circulation, pool cycles 4-6x/d
  – Central role in control of metabolism, inflammation and gut integrity / microbiota

• Defective bile acid (FXR-FGF19) signaling in NAFLD/NASH
  – Role of serum / fecal bile acids as prognostic signature ↔ severity of NASH / fibrosis
  – Bile acid toxicity could contribute to cellular injury and carcinogenesis

• Good rationale and opportunities for therapeutic modulation of bile acid signaling in NAFLD/NASH
  – FXR-FGF19 (gut-liver) axis; TGR5
  – norUDCA (independent of FXR / TGR5)

1: Nobili et al., Liver Int 2018; Jiao et al., Gut 2018
2: Lelouvier et al., Hepatology 2016; Puri et al., Hepatology 2018
3: Yoshimoto et al., Nature 2013

Reviewed in: Arab et al., Hepatology 2017
Arab, Arrese & Trauner, Annu Rev Pathol 2018
Bile Acid Signaling as Therapeutic Target

FXR = Farnesoid X Receptor
(Nuclear Bile Acid Receptor)

(Non-)Steroidal FXR-Ligands
• PBC, PSC, EHBA
• NAFLD/NASH
• Portal HT, IBS-D

FXR

FXR Ligands

• FGF19 (NGM282)
• NTCP Blockers (Myrcludex)

Cholesterol

Bile Acids

Bile

Enterohepatic Circulation

Microbiota

FGF-19

GLP-1

TGR5

NTCP Blockers

Bile Salt Export Pump

Cholehepatic Shunting

norUDCA

BSEP

Treatment of
Pruritus, cholestasis
Hyperchol., NASH

Trauner et al., *Hepatology* 2017; 65: 1393-1404
BAs as Key Regulators of TG & Glc Metabolism In NAFLD

Arab JP, Karpen SJ, Dawson PA, Arrese M, Trauner M. HEPATOLOGY 2017; 65: 350-362
Steroidal and Non-steroidal FXR Agonists

- OCA first-in-class steroidal FXR ligand (phase 3, approval in PBC)
- Non-steroidal FXR ligands - no BA structure (phase 2 – examples):
  - Different pharmacokinetics, efficacy & AE profile (pruritus, cholesterol)?
  - Efficacy signals in phase 2 studies
  - PX-104 (NASH), GS-9674 (Cilofexor – PBC, PSC, NASH)
  - LJN452 (Tropifexor – PBC, NASH), LMB763 (NASH)
  - EDP-305 (NASH, PBC), EYP001 (NASH), MET409 (NASH)

Also see: Trauner et al., Hepatology 2017
Bile Acid & FXR Signaling as Therapeutic Target

FXR = Farnesoid X Receptor
(Nuclear Bile Acid Receptor)

(FXR-Ligands)
- PBC, PSC, EHBA
- NAFLD/NASH
- Portal HT, IBS-D

Microbiota
- Formation of secondary BAs
- Bacterial 7α-dehydroxylation
- Deconjugation

Trauner et al. Hepatology 2017; 65:1393-1404
Evolutionary tree of FXR agonists reaching clinical stage
Table 1 Overview of clinical trials in NASH for nonsteroidal FXR agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Company</th>
<th>Highest developmental stage/clinical trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic acid (INT-747)</td>
<td>NASH</td>
<td>Intercept Pharmaceuticals</td>
<td>Phase III/NCT02548351</td>
</tr>
<tr>
<td>Obeticholic acid (INT-747)</td>
<td>NASH, compensated cirrhosis</td>
<td>Intercept Pharmaceuticals</td>
<td>Phase III/NCT03439254</td>
</tr>
<tr>
<td>Px-104</td>
<td>NAFLD</td>
<td>Phenex Pharmaceuticals</td>
<td>Phase Ia (discontinued)/NCT01999101</td>
</tr>
<tr>
<td>Tropifexor (LJN452)</td>
<td>NASH</td>
<td>Novartis</td>
<td>Phase Ia/NCT02855164</td>
</tr>
<tr>
<td>Tropifexor (LJN452)</td>
<td>NASH</td>
<td>Novartis</td>
<td>Phase II combination trial with cenicriviroc/ NCT03517540</td>
</tr>
<tr>
<td>Nidufexor (LMB763)</td>
<td>NASH</td>
<td>Novartis</td>
<td>Phase IIa/NCT02913105</td>
</tr>
<tr>
<td>Cirolfexor (GS-9674)</td>
<td>NASH</td>
<td>Gilead Sciences</td>
<td>Phase II/NCT02854605</td>
</tr>
<tr>
<td>EYP001</td>
<td>NASH</td>
<td>Enyo Pharma</td>
<td>Phase Ia/NCT03812029</td>
</tr>
<tr>
<td>MET409</td>
<td>NASH, IBD</td>
<td>Metacrine</td>
<td>Phase I: Homepage: “We are currently conducting a Phase 1 clinical trial of MET409 in healthy volunteers”</td>
</tr>
</tbody>
</table>

Table adapted from Gege et al., Handb Exp Pharmacol 2019.
Obeticholic acid (OCA) in NASH (FLINT Trial)

- OCA 25 mg vs PBO (72 w, n=283)
- Improved liver enzymes (but AP ↑)
- Improved liver histology features (incl. fibrosis); 1° endpoint neg.
- Weight reduction (~2kg)
- AE: pruritus less than in PBC
- Serum lipids: HDL-C ↓ / LDL-C ↑ (managed by statins)
- Insulin resistance (HOMA) ↑
- Long term benefits? (REGENERATE) NCT02548351

Younossi et al., ILC 2019 GS-06
METHODS

Slide courtesy Younossi Z, et al. ILC 2019; Presentation GS-06.

REFERENCES
Positive Results from REGENERATE: A Phase 3, International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid (OCA) Treatment for NASH

RESULTS

- OCA 25 mg met the primary endpoint of improvement in liver fibrosis with no worsening of NASH (p=0.0002* vs placebo)
- The antifibrotic effect of OCA was dose dependent and consistent across endpoints and key subgroups
- Although the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met, OCA improved NASH disease activity based on several key histologic parameters including NAFLD activity score, hepatocyte ballooning and lobular inflammation

*Statistically significant in accordance with the statistical analysis plan as agreed with the FDA. All other p values are nominal.

**Per protocol population with available fibrosis data at Month 18/EOT (n=656).
REGENERATE: Safety

- **Pruritus** incidence peaked within first 3 months before declining
- In OCA 25 mg arm, 9% discontinued due to pruritus, mostly protocol driven
- **Cardiovascular AE rates** ≤ 2% in all arms

- **LDL increased** and **HDL decreased** early with OCA; recovered with clinical management
- **Hepatic TEAE** rates similar across arms
  - Hepatic serious AEs in < 1%, numerically more cases in OCA 25 mg arm

<table>
<thead>
<tr>
<th>TEAEs Occurring in ≥ 10% of Patients in Any Arm, n (%)</th>
<th>OCA 10 mg (n = 653)</th>
<th>OCA 25 mg (n = 658)</th>
<th>Placebo (n = 657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>183 (28)</td>
<td>336 (51)</td>
<td>123 (19)</td>
</tr>
<tr>
<td>LDL increased</td>
<td>109 (17)</td>
<td>115 (17)</td>
<td>47 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>72 (11)</td>
<td>83 (13)</td>
<td>77 (12)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (12)</td>
<td>71 (11)</td>
<td>88 (13)</td>
</tr>
<tr>
<td>Constipation</td>
<td>65 (10)</td>
<td>70 (11)</td>
<td>36 (5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>65 (10)</td>
<td>67 (10)</td>
<td>62 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44 (7)</td>
<td>49 (7)</td>
<td>79 (12)</td>
</tr>
</tbody>
</table>
Steroidal and Non-steroidal FXR Agonists

- OCA first-in-class steroidal FXR ligand (FLINT, REGENERATE)
- Non-steroidal FXR ligands - no BA structure (phase 2 – examples):
  - Different pharmacokinetics, efficacy & AE profile (pruritus, cholesterol)?
  - Efficacy signals in phase 2 studies
  - PX-104, GS-9674 (Cilofexor*)
  - LJN452 (Tropifexor*), LMB763
  - EDP-305, EYP001, MET409, …

*Phase 2 Studies demonstrated reductions in liver enzymes and liver fat (MRI-PDFF)

Also see: Trauner et al., Hepatology 2017
Cilofexor (GS-9674) Reduces Liver Fat and Liver Enzymes in NASH (Phase II)

GS-9674 reduced liver fat by MRI-PDFF and liver biochemistry (AST, ALT, GGT)
- Improvements in markers of fibrosis (ELF, TIMP-1, PIII-NP, liver stiffness) in MRI-PDFF responders
- No significant changes in lipids or glycemic parameters

Slide courtesy R. Myers (Gilead)
Patel K, et al. AASLD 2018 (Poster #5418)
Cilofexor (GS-9674) Impact on Liver biochemistry

Median relative percent change at Week 24 (IQR)

GS-9674 100 mg  GS-9674 30 mg  Placebo

ALT
AST
GGT
ALP

Slide courtesy R. Myers (Gilead)
Patel K, et al. AASLD 2018 (Poster #5418)
Tropifexor (LJN-452) impact on hepatic fat & liver enzymes (FLIGHT FXR Study - Phase 2 b)

% with ≥5% drop in PDFF*

Drop in GGT

- Comparable rates of adverse events including pruritus for tropifexor and placebo
- Mild dose response increase of LDL and decrease of HDL, unchanged triglycerides
Alanine Aminotransferase (ALT) in all subjects

*Rapid decline and sustained effect with 90 µg*

![Graph showing the geometric mean percentage change from baseline (95%CI) for ALT (U/L) in all subjects under Placebo, TXR 60 µg, and TXR 90 µg over weeks 0 to 12.]

CI, confidence interval; TXR, tropifexor

Slide courtesy C. Brass (Novartis)
Sanyal A, et al. AASLD 2018 (#LB-23)
Fig. 9  Improvement of hepatic steatosis with FXR agonists. Results are from separate studies and do not represent a reflection of head-to-head direct comparison of listed agents on outcomes of interest. Trials for individual treatment agents employed different enrollment criteria and durations of therapy, and the primary endpoint definitions were not identical (TRX, tropifexor; GS, cilofexor)
Theoretical advantages of nonsteroidal FXR agonists still remain to be proven clinically (no class effect – judge compounds individually)

<table>
<thead>
<tr>
<th></th>
<th>Patients with moderate to severe pruritus (%)</th>
<th>HDL lowering to baseline</th>
<th>LDL increase to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCA 25 mg</td>
<td>23</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Placebo</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tropifexor 90 μg</td>
<td>8</td>
<td>Yes/mild</td>
<td>Yes</td>
</tr>
<tr>
<td>Tropifexor 60 μg</td>
<td>14</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cilofexor 100 mg</td>
<td>14</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Cilofexor 30 mg</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Placebo</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NAFLD = Hepatic Manifestation of Metabolic Syndrome

61-100% Obese
66-85% IR
18-33% IGT/T2DM

Traussnigg & Trauner, *Digestive Diseases* 2015; 33: 598-607
FXR agonists reduce portal hypertension by multiple mechanisms of action along the gut-liver axis

Similar effects & mechanisms with OCA:
Verbeke et al., Hepatology 2014; 59: 2286-98
Mookerjee et al., J Hepatol 2015; 62: 325-31
Verbeke et al., Am J Pathol 2015; 185: 409-19
Verbeke et al., Sci Rep 2016; &: 33453

Schwabl et al., J Hepatol 2017; 66: 724-733
• Bile acids as signaling molecules with hormonal functions
  – Central role in control of metabolism, inflammation and gut integrity / microbiota

• Defective bile acid signaling in NAFLD/NASH
  – Role of serum / fecal bile acids as pathogenetic and prognostic signature

• Multitude of opportunities for therapeutic modulation of bile acid signaling in NAFLD/NASH
  – FXR-FGF19 (gut-liver) axis: steroidal and non-steroidal FXR agonists
  – Most advanced human data exist for OCA (REGENERATE)
  – Theoretical advantage of non-steroidal FXR ligands still remains to be proven
  – norUDCA (independent of FXR / TGR5)
  – Future perspective: bile acid backbone of combination therapy (e.g. ATLAS, TANDEM)
Thank you for your attention!