What We Have Learned About Fatty Liver Disease

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Advances in Treatments
DMR results in improved hepatic and glycemic metabolic parameters in patients with T2D/NAFLD

Hypothesis:
Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive, endoscopic mucosal ablative procedure that may provide potential benefit in T2D with concomitant NAFLD/NASH.

Methods:
Double-blind, sham-controlled, prospective, multicenter in patients randomized 1:1 with sub-optimally controlled T2D (HbA1c of 7.5-10%, BMI ≥24 to ≤40kg/m²)

Main Findings:
DMR demonstrates superiority over sham in both MRI-PDFF and HbA1c lowering in patients with T2D (see Table).

Conclusions:
Single, non-pharmacological, DMR procedure safely provides disease-modifying benefits with metabolic improvements in liver fat content and glycemic control through 24 weeks to patients with T2D/NAFLD.

Table. Key Hepatic and Glycemic Study Findings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DMR (N=29)</th>
<th>Sham (N=36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute change in liver MRI-PDFF from baseline at 12 weeks, %Δ</td>
<td>-5.4</td>
<td>-2.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Relative change in liver MRI-PDFF from baseline at 12 weeks, %Δ</td>
<td>n=20</td>
<td>n=27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight change from baseline at 24 weeks, kg</td>
<td>n=38</td>
<td>n=34</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Liver MRI-PDFF at 12 weeks, n (%)/Reduction &gt;50%</td>
<td>16 (53)</td>
<td>6 (22)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Glycemic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c change from baseline at 24 weeks, % (mITT)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1c change from baseline at 24 weeks, % (PP)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Reduction in HbA1c, n (%):</td>
<td></td>
</tr>
<tr>
<td>-5% at 24 weeks</td>
<td>21 (60)</td>
</tr>
<tr>
<td>&lt;3% at 24 weeks</td>
<td>18 (51)</td>
</tr>
<tr>
<td>&lt;1% at 24 weeks</td>
<td>10 (29)</td>
</tr>
<tr>
<td>FPG change from baseline at 12 weeks, mg/dL: Mean</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with baseline FPG &lt;100 mg/dL</td>
<td>n=19</td>
</tr>
<tr>
<td>HbA1c, mean % change at 12 weeks</td>
<td>n=21</td>
</tr>
<tr>
<td>FPG, mean mg/dL change at 12 weeks</td>
<td>n=19</td>
</tr>
<tr>
<td>HOMA-IR change from baseline at 24 weeks</td>
<td>n=33</td>
</tr>
</tbody>
</table>

*Results data are presented, unless otherwise noted.*

Bergman JIGHM, et al., Abstract LO2
Tropifexor, a highly potent FXR agonist, produces robust and dose-dependent reductions in hepatic fat and serum alanine aminotransferase in patients with fibrotic NASH after 12 weeks of therapy: FLIGHT-FXR Part C interim results

**Aim:**
To assess the safety, tolerability, and efficacy of several doses of tropifexor (TXR) in patients with NASH (FLIGHT-FXR study)

**Methods:**
This is a phase 2 randomized, double-blind, placebo-controlled, 3-part study.

- Parts A & B (12 weeks each): results for doses up to 90 μg TXR were previously presented.
- Part C (48 weeks) evaluates the effects of 140 and 200 μg doses of TXR on biomarkers and histology in patients with biopsy-proven NASH and fibrosis stages 2-3.

**Main Findings:** Part C interim results (W12) are summarized in the table.

**Safety and tolerability:**
- The frequency of SAEs was low and comparable across groups.
- Among patients with pruritus, the majority in both TXR groups and all in the placebo group experienced events with mild (Grade 1) severity. Treatment discontinuation rates due to pruritus were low (TXR 140 μg: n=1 [2%]; TXR 200 μg: n=3 [6%]; placebo: 0%).
- Despite a dose-related increase in low-density lipoprotein-cholesterol, treatment discontinuation or dose reduction due to lipid abnormalities was not observed.

**Conclusions:**
Higher doses of TXR showed dose-dependent decreases in ALT, HFF, and body weight with good safety and manageable tolerability after 12 weeks of treatment.

Sanyal A, et al., Abstract LO4

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Placebo (N=51)</th>
<th>TXR 140 μg (N=50)</th>
<th>TXR 200 μg (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td></td>
<td></td>
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<tr>
<td>-8.9 (4.19) n=49</td>
<td>-20.1 (4.57) n=41; P=0.058</td>
<td>-23.6 (4.48) n=39; P=0.013</td>
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<tr>
<td><strong>Relative change in HFF (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10.26 (4.21) n=51</td>
<td>-16.99 (4.64) n=49; P=0.209</td>
<td>-31.37 (4.30) n=51; P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>GGT (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-2.5 (3.55) n=49</td>
<td>-39.2 (3.70) n=44; P&lt;0.001</td>
<td>-40.9 (3.62) n=46; P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.14 (0.36) n=50</td>
<td>-2.46 (0.38) n=46; P=0.010</td>
<td>-3.20 (0.37) n=46; P&lt;0.001</td>
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</tr>
</tbody>
</table>

*Measured as magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Data are presented as LS mean change (SE) with 2-sided P values reported for statistical significance. ALT, alanine aminotransferase; ANCOVA, analysis of covariance; FAS, full analysis set; GGT, gamma glutamyl transferase; HFF, hepatic fat fraction; LS, least square; SE, standard error; TXR, tropifexor.
Saroglitazar, a novel dual PPAR α/γ agonist, for NAFLD/NASH: a phase-2 RCT (EVIDENCES IV study)

Hypothesis:
Saroglitazar (Saro) is a novel dual regulator of lipid and glucose homeostasis with >1000 fold selectivity for PPARα over PPARγ.

Methods:
A phase-2 RCT to test Saro safety and effects on ALT and liver fat content in 106 patients with NAFLD or NASH with elevated ALT ≥50 U/L and BMI ≥25 kg/m²

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>Saro 4 mg (n=27)</th>
<th>Saro 2 mg (n=23)</th>
<th>Saro 1 mg (n=26)</th>
<th>Placebo (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage change in ALT (U/L)</td>
<td>-44.39</td>
<td>-33.16</td>
<td>-27.31</td>
<td>4.16</td>
</tr>
<tr>
<td>*p value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Absolute change in liver fat content (%) by MR-PDFF</td>
<td>-4.21</td>
<td>-0.42</td>
<td>0.53</td>
<td>-0.31</td>
</tr>
<tr>
<td>*p value</td>
<td>0.01</td>
<td>0.94</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>% change in weight (kg)</td>
<td>1.88</td>
<td>1.73</td>
<td>2.39</td>
<td>0.28</td>
</tr>
<tr>
<td>*p value</td>
<td>0.99</td>
<td>0.54</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

* p value derived from comparison each Saro dose vs placebo

Conclusions:
Saroglitazar Magnesium 4 mg significantly improved serum ALT, hepatic steatosis, insulin resistance, and dyslipidemia in patients with NAFLD/NASH.

Gawrieh S, et al., Abstract LO10
Emricasan (oral pan-caspase inhibitor) did not improve fibrosis or steatohepatitis in patients with NASH and F1-F3 fibrosis

**Objective:**
Assess whether emricasan improves fibrosis by at least 1 stage without worsening of steatohepatitis

**Methods:**
- Double-blind, placebo-controlled, randomized trial of emricasan 5 mg vs 50 mg vs placebo (1:1:1) for 72 weeks
- Patients with NASH on biopsy with NAFLD activity score ≥4 and fibrosis stage 1 (20%), 2, or 3

**Conclusions:**
Despite evidence of target engagement, the primary endpoint of fibrosis improvement was not met, and similar findings were observed with NASH resolution, inflammation, and ballooning.

Harrison SA, et al., Abstract 61
Positive Results From REGENERATE: A Phase 3 International, Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH


Obeticholic acid (OCA), a potent and selective FXR agonist, improved liver histology in a Phase 2 trial (FLINT) of patients with NASH.
REGENERATE Study Design

The interim analysis was conducted after 931 randomized patients with stage 2 or 3 liver fibrosis had or would have reached their actual/planned Month 18 visit (ITT population).

EOS analysis of clinical outcomes to confirm clinical benefit.

EOS, end of study; ITT, intent to treat; PBO, placebo; QD, once a day.


Study success was defined as achievement of one of these two primary endpoints:

- Fibrosis Improvement by ≥1 Stage with No Worsening of NASH
- OR
- NASH Resolution with No Worsening of Fibrosis
Study Eligibility Criteria

**KEY INCLUSION CRITERIA**

- Biopsy-confirmed NASH
- Fibrosis stage 2 or 3 (NASH CRN)
  - Exploratory cohort with fibrosis stage 1 and concomitant risk factors\(^a\)
- NAFLD activity score (NAS) ≥4

**KEY EXCLUSION CRITERIA**

- Evidence of other chronic liver disease
- Histologic presence of cirrhosis
- Total bilirubin >1.5 mg/dL
- ALT ≥10 × ULN
- HbA1c >9.5%
- Significant alcohol consumption\(^b\)

All biopsies were read centrally and at Month 18 biopsy slides were pair-read ensuring that pathologists were blinded to both treatment assignment and biopsy sequence.

\(^a\)Risk factors included type 2 diabetes, obesity (BMI ≥30 kg/m\(^2\)) or ALT >1.5 × ULN.

\(^b\)Defined as >2 units/day for females and >4 units/day for males for >3 months within 1 year before screening.

BMI, body mass index; CRN, clinical research network; HbA1c, glycated hemoglobin; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; ULN, upper limit of normal.
NASH Resolution with No Worsening of Fibrosis
Additional Primary Endpoint: ITT Population, N=931

Primary endpoint definition:
(i) overall pathologist assessment of “no steatohepatitis”; and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline.

Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis.

Resolution of Definite NASH with No Worsening of Fibrosis

**Overall Pathologist Assessment: ITT Population***

Post-hoc analysis with endpoint defined as: (i) overall pathologist assessment of "no steatohepatitis"; and (ii) no increase in fibrosis stage from baseline. P values are nominal.


*Medical Education Purposes Only*
Improvement in NAS ≥2 with No Worsening of Fibrosis and NAS Parameters ≥1: Per Protocol Population

P values are nominal.
Per protocol population (N=668).
Changes in Liver Biochemistry Over Time

**Per Protocol Population**

**ALT (U/L)**

**AST (U/L)**

**GGT (U/L)**

**ALP (U/L)**

Per protocol population (N=668).
SE, standard error.
REGENERATE Is the First Successful Phase 3 Study in Patients With NASH: Summary and Conclusion

- OCA 25 mg met the primary fibrosis endpoint at the Month 18 interim analysis
- The anti-fibrotic effect was dose dependent and consistent across endpoints and key subgroups
- Although the primary NASH resolution endpoint was not met, OCA ameliorated steatohepatitis based on pathologist overall assessment and improvement in key disease activity parameters
- OCA rapidly and sustainably improved ALT, AST and GGT
- AEs were mostly mild to moderate; the most common were consistent with the known profile of OCA
- The study is ongoing to confirm benefit on clinically important outcomes

Obeticholic Acid Treatment in Patients with Non-alcoholic Steatohepatitis: A Secondary Analysis of the REGENERATE Study Across Fibrosis Stages

Arun J. Sanyal, Vlad Ratziu, Rohit Loomba, Mary Rinella, Quentin M. Anstee, Zachary Goodman, Pierre Bedossa, Mandana Khalili, Jerome Boursier, Laura Stinton, Giulio Marchesini, Michael Allison, Jacob George, Perttu Arkkila, Luna Zaru, Leigh MacConell, Reshma Shringarpure, Zobair M. Younossi on behalf of the REGENERATE Study Investigators
Fibrosis Improvement by ≥1 Stage with No Worsening of NASH

Primary Endpoint: Expanded ITT Population

- The results in the Expanded ITT Population are similar to those observed in the Primary ITT analysis of patients with fibrosis stage 2 or 3.

Expanded ITT Population, N=1,218.

Primary endpoint definition: Fibrosis improvement by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis).

This primary endpoint was met in the Primary ITT Population.

P values are nominal.
NASH Resolution with No Worsening of Fibrosis

Additional Primary Endpoint: Expanded ITT Population

Expanded ITT Population, N=1,218.

Primary endpoint definition: (i) overall pathologist diagnostic assessment of “no steatohepatitis,” and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1, and (iii) no increase in fibrosis stage from baseline.

Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 interim analysis. P values are nominal.
Changes From Baseline in ALT and AST Over Time

**Expanded ITT Population**

Mean* (SE) Change from Baseline in ALT (U/L)

- Placebo (n=407)
- OCA 10mg (n=407)
- OCA 25mg (n=404)

Expanded ITT Population, N=1,218.

*Least square mean
SE, standard error.
Safety and Tolerability

Safety Population, N=1,968

Overall safety profile

- Pruritus was the most frequent AE (19% placebo, 28% OCA 10 mg, 51% OCA 25 mg)
- Frequency of SAEs was similar across groups (11-14%)
- Three deaths, unrelated to treatment, occurred on study (placebo, n=2; OCA 25 mg, n=1)

Hepatobiliary

- Gallstone-related AEs occurred at a rate of <1%, 1% and 3% in placebo, OCA 10 mg and OCA 25 mg patients, respectively
- Pancreatitis, a more serious and potentially gallstone-related event, was rare and evenly distributed across treatment groups (incidence <1%)
- Hepatic SAEs were rare (<1% in all treatment groups). While more occurred in the OCA 25 mg group, all cases were associated with confounding severe intercurrent illness and/or concomitant medications

Safety Population defined as all randomized patients with fibrosis stage 1, 2, or 3 who received at least 1 dose of study treatment.
AEs, adverse events; SAEs, serious adverse events
Safety and Tolerability

Safety Population

Lipids and Cardiovascular

• In patients receiving OCA, low-density lipoprotein cholesterol (LDLc) increased by month 1 and decreased thereafter, approaching baseline by month 18

• Statin therapy was initiated in 10% of placebo patients and 24% of each OCA treatment arm. Among OCA patients who initiated statins, LDLc increases reversed and fell to below baseline levels by month 6

• Incidence of cardiovascular AEs and SAEs was similar across the treatment groups (AEs: 5% placebo, 7% OCA 10 mg, and 6% OCA 25 mg; SAEs 2% placebo, 1% OCA 10 mg, 2% OCA 25 mg)

Glycemic Parameters

• In patients with type 2 diabetes, OCA treatment was associated with an early transient increase in glucose and HbA1c with return to levels similar to placebo by month 6

• No clinically meaningful changes were noted in non-diabetic patients

Safety Population, N=1,968.
HbA1c, hemoglobin A1c; LDLc, low density lipoprotein-cholesterol
Secondary Analysis of the REGENERATE Data in the Expanded ITT Population

Summary and Conclusion

- After 18 months of treatment, OCA improved liver fibrosis in the Expanded ITT Population, demonstrating consistent efficacy with the primary study results.

- Treatment with OCA also improved steatohepatitis and liver biochemistry in patients with NASH and fibrosis stage 1 to 3.

- AEs were mostly mild to moderate; the most common were consistent with the known profile of OCA.

- The REGENERATE month 18 interim analysis results are based on surrogate endpoints considered reasonably likely to predict clinical benefit.
  - Longer term OCA treatment effect on clinical outcomes has not yet been demonstrated.

- The study is ongoing through outcomes to characterize OCA’s clinical benefit.
Factors associated with mortality in lean, overweight and obese non-alcoholic fatty liver disease (NAFLD)

Aim:
To assess the prevalence and mortality of NAFLD subjects according to their body mass index (BMI) and presence of cardio-metabolic risk factors

Methods:
- NAFLD subjects from NHANES (1988-1994) with clinical and mortality data
- NAFLD was defined as hepatic steatosis by ultrasonography in the absence of other causes of chronic liver disease.

Conclusions:
- Presence of advanced liver fibrosis, CKD and risks for CVD, increases risk of mortality in lean, overweight, and obese NAFLD.
- Presence of any metabolic abnormality increases this risk only in the overweight and obese NAFLD.

Golabi P, et al., Abstract 32
NAFLD Simulator: an interactive, open-access tool for long-term risks of NAFLD and NASH

Aim:
To develop an open-access, interactive tool for patients and providers that helps them understand the risk of long-term adverse outcomes associated with NAFLD/NASH

Methods:
• Funded by the AASLD Innovation Fund, NAFLD Simulator allows users to enter patient demographics and current NAFLD stage, and predicts long-term (eg, 10-year) mortality (liver and non-liver) and cumulative risk of hepatocellular carcinoma and decompensated cirrhosis.
• The simulator uses a clinical valid mathematical model that simulates the natural history of NAFLD/NASH.
• Model-predicted patient survival was independently validated with a large observational study.

Conclusions:
NAFLD Simulator provides an innovative and educational platform to disseminate the long-term risk associated with NAFLD and NASH to patients and providers.

Chhatwal J, et al., Abstract 236
Machine learning models accurately interpret liver histology in patients with NASH

Hypothesis:
A machine learning approach (PathAl) could be utilized to train models to accurately interpret NASH histology.

Methods:
The PathAl research platform was used to train and test a deep learning model to interpret liver histology from 834 liver biopsies from a phase 3 trial of selonsertib (STELLAR-4).

Main Findings:
Machine learning predictions in the test set were highly correlated with pathologist readings for the NASH CRN (rs=0.83) and Ishak staging systems (rs=0.86; Figure) and for the components of the NAFLD Activity Score.

Conclusions:
Machine learning models showed high concordance with pathologist interpretations of the histological features of NASH.

Pokkalla H, et al., Abstract 187
Ultrasound-based CAP to detect longitudinal changes in liver fat when effect size is large – phase 2a Study

Objective:
Assess Controlled Attenuation Parameter (CAP) and MRI-Proton Density Fat Fraction (PDFF) in parallel – in a dose-ranging study of PF-05221304, a dual Acetyl-CoA carboxylase inhibitor

Methods:
- Serial MRI-PDFF and Fibroscan® assessments were obtained at Screening (for eligibility), Baseline, and Weeks 4, 12, and 16.
- A Mixed-Model-Repeated-Measures (MMRM) model was applied to analyze the 5 arms (placebo and four active doses) with output presented as least-square means (80% confidence intervals).
- Study population: 276 (90% of total randomized) adults with NAFLD and liver fat ≥8% at screen (on MRI-PDFF).

Conclusions:
CAP can be utilized to detect longitudinal changes in liver fat especially when magnitude of reduction in liver fat is large.

Tuthill TA, et al., Abstract 259