Nonalcoholic Fatty Liver Disease

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NAFLD, NAFL and NASH Defined

- NAFLD: Steatosis in >5% of hepatocytes
- NASH requires specific pathologic criteria: ballooning, inflammation
- Exclusion of secondary causes and AFLD (<20 grams i.e. 2 drinks per day)
- Risk factors are components of metabolic syndrome

The Global Prevalence of NAFLD and NASH

Prevalence of NASH in general population is between 1.5–6.5%
Prevalence of NASH among T2DM is 37.3% (24.7-50.0%)

Worldwide prevalence of NAFLD is 25%
Worldwide prevalence of NAFLD among people with T2DM is 55.5%

Global Prevalence of NAFLD: The Most Common of All Liver Diseases

Histologic Features of NASH

- Steatotic hepatocytes
- Ballooning of hepatocyte with Mallory-Denk body
- Perisinusoidal/pericentral fibrosis ("chicken wire fence" appearance)
Lobular Inflammation with Neutrophils in NASH
NAFLD Activity Score (NAS)

Steatosis (0-3)
+ Lobular inflammation (0-3)
+ Hepatocellular ballooning (0-2)

NAS score = (0-8)
NASH CRN fibrosis = (0-4)

- NAS ≥ 4 is generally agreed to distinguish simple steatosis from steatohepatitis
- Reduction in NAS ≥ 2 has been a primary endpoint in clinical trials

Stages of Fibrosis: NASH CRN

- **Score 0** – none
- **Score 1** – perisinusoidal or periportal
  - 1a – mild, zone 3, perisinusoidal
  - 1b – moderate, zone 3, perisinusoidal
  - 1c – portal/periportal
- **Score 2** – perisinusoidal and portal/periportal
- **Score 3** – bridging fibrosis
- **Score 4** – cirrhosis
Relationship Between Fatty Liver, NAFLD, NAFL, and NASH

Spontaneous Fibrosis Regression: An Important Consideration For Clinical Trials

### Longitudinal studies of NAFLD and NASH using Paired Biopsies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>Fibrosis Progressed (N)</th>
<th>Fibrosis Regressed (N)</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>712</td>
<td></td>
<td>37%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

### Changes in fibrosis stage among placebo treated patients in randomized trials

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Treatment time (weeks)</th>
<th>Fibrosis Progressed (N)</th>
<th>Fibrosis Regressed (N)</th>
<th>Mean Fibrosis Change</th>
<th>Mean NAS Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary</td>
<td>689</td>
<td></td>
<td>61/256 (24%)</td>
<td>112/477 (23%)</td>
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</tr>
</tbody>
</table>

Pathophysiology of NASH

Extrahepatic Manifestations of NAFLD

# Comorbid Conditions Associated With Nonalcoholic Steatohepatitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Estimated prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General US population</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>25.1</td>
</tr>
<tr>
<td>Obesity</td>
<td>39.8</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18.4</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>34.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29.0</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>14.0</td>
</tr>
</tbody>
</table>

High Prevalence of NAFLD in Diabetes

Cardiovascular Risk Factors That Coexist With NASH

Hyperinsulinemia
Type 2 diabetes
Atherogenesis
Myocardial dysfunction

Cardiovascular disease

Insulin clearance
Insulin resistance
Glucose production
Cytokines (systemic inflammation)
TB/HDL-C
ApoB

Heart disease:
- ATP generation
- Lipotoxicity
- Ischemia
- Diastolic dysfunction

Prevalence of Clinically Manifest Cardiovascular Disease in Patients With Type 2 DM

### Table 1. Principal Prospective Studies of the Association between Nonalcoholic Fatty Liver Disease and the Incidence of Major Cardiovascular Events.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Study Population</th>
<th>Age</th>
<th>Length of Follow-up (years)</th>
<th>Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamaguchi et al.</td>
<td>Community-based cohort of 1637 healthy subjects in Japan</td>
<td>22–83</td>
<td>5</td>
<td>Nonfatal coronary heart disease, ischemic stroke, and cerebral hemorrhage events</td>
<td>Increased risk of nonfatal CVD events associated with NAFLD independently of age, sex, BMI, smoking status, alcohol consumption, blood pressure, LDL cholesterol, triglycerides, and HDL cholesterol</td>
</tr>
<tr>
<td>Targher et al.</td>
<td>Nested case-control study in an outpatient cohort of patients with type 2 diabetes in Italy; 248 patients and 496 control subjects matched for age and sex, who did not have CVD or viral hepatitis at baseline</td>
<td>40–79</td>
<td>5</td>
<td>Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures</td>
<td>Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use (lipid-lowering, hypoglycemic, antihypertensive, and antiplatelet drugs), alcohol consumption, duration of diabetes, and levels of blood pressure, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT activity</td>
</tr>
<tr>
<td>Targher et al.</td>
<td>Valpolicella Heart Diabetes Study: outpatient cohort of 2103 patients with type 2 diabetes in Italy who did not have CVD or viral hepatitis at baseline</td>
<td>40–79</td>
<td>6.5</td>
<td>Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures</td>
<td>Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use, alcohol consumption, blood pressure, diabetes duration, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT</td>
</tr>
<tr>
<td>Haring et al.</td>
<td>Study of Health in Pomerania: population-based study of 4160 men and women in Germany who did not have viral hepatitis or cirrhosis at baseline</td>
<td>20–79</td>
<td>7.3</td>
<td>Death from any cause and death from CVD</td>
<td>Increased risk of death from any cause and death from CVD among men with NAFLD, independent of age, sex, waist circumference, alcohol consumption, physical activity, educational level, civil status (living alone vs. living with a spouse or partner), blood pressure, status with respect to diabetes, and Groll functional comorbidity index</td>
</tr>
</tbody>
</table>

Gut Dysbiosis is Playing an Increasingly Prominent Role in NAFLD Research

Dysbiosis
- Increased intestinal permeability
- Mediators of gut microbiota
  - Trimethylamine
  - Lipopolysaccharide
  - Altered short-chain fatty acids, primary and secondary bile acids and/or incretins

Alterations in hepatic structure and function
- Inflammation or fibrosis
- Lipids (sphingolipids)
- Synthesis and secretion of lipoprotein
- Synthesis of bile acids and cholesterol
- Acylcarnitines and branched-chain amino acids

Risk factors
- LDL cholesterol
- VLDL particles
- Bile acids
- Lipidome
- Redox biomarkers
- NO or oxidative stress
- Sulfur metabolism (aminothiols, H₂S)
- Oxidized lipids
- Pro-inflammatory cytokines

Increased risk of CVD and CKD

Cardiovascular and renal diseases
- Structural and functional changes
  - Increased arterial stiffness
  - Increased blood pressure
- Abdominal obesity
- Insulin resistance
- The metabolic syndrome

Once NAFLD is Diagnosed, What Can We Further Assess Noninvasively?

- steatosis vs steatohepatitis
  - NO
  - (though we are still trying)
- liver fibrosis
  - YES!
Interpretation of FIB-4 and NFS for the Diagnosis of Advanced Fibrosis (Stages 3-4)

FIB-4: Fibrosis-4 score; NFS: NAFLD Fibrosis Score

Biomarker Panels to Assess for Advanced Liver Fibrosis

**Parameters and biomarkers**

<table>
<thead>
<tr>
<th>Non-invasive biomarker detection methods</th>
<th>Cutoffs for advanced fibrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAFLD fibrosis score</strong>&lt;sup&gt;50&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Age, BMI, IFG and diabetes, AST-to-ALT ratio, platelets, and albumin</td>
<td>≤1.455</td>
</tr>
<tr>
<td></td>
<td>&gt;0.676</td>
</tr>
<tr>
<td><strong>FIB-4 index</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Age, AST, ALT, and platelet</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td></td>
<td>&gt;2.67</td>
</tr>
<tr>
<td><strong>Enhanced liver fibrosis test</strong>&lt;sup&gt;54&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Age, hyaluronic acid, aminoterminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1</td>
<td>≥9.8</td>
</tr>
<tr>
<td><strong>FibroTest</strong>&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, γ-glutamyltransferase, α2-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex</td>
<td>&gt;0.30</td>
</tr>
<tr>
<td></td>
<td>≥0.70</td>
</tr>
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FIB-4 Score

FIB-4 < 1.3 has 90% NPV for F3-4; FIB-4 > 2.67 has 80% PPV for F3-4

- Age-adjusted lower cutoff in patients > 65 years preserves high NPV

Imaging Techniques Used to Assess Fibrosis in NAFLD

Elastography

- **Vibration-controlled transient elastography (FibroScan®)**
  - Accurate in detecting advanced fibrosis
  - Estimates hepatic fat
  - Predicts risk of decompensation and complications
  - Correlates well with portal pressure
  - Most reliable in ruling out advanced disease
  - Most widely used

- **Shear wave elastography (SWE)**
  - Uses acoustic radiation force impulse (ARFI) technology
  - Point quantification: SWE or 2-D supersonic shear imaging (SSI) SWE

- **MR elastography**
  - Most accurate of the imaging modalities
  - Costly, no point-of-care access

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Fibroscan (Transient Elastography)
Meta-Analysis of Noninvasive Modalities to Detect Fibrosis in NAFLD

- 64 articles, n=13,046
- Summary of AUROC values:

<table>
<thead>
<tr>
<th>APRI</th>
<th>BARD</th>
<th>FIB-4</th>
<th>NFS</th>
<th>Fibroscan M probe</th>
<th>Fibroscan XL probe</th>
<th>Shear wave elastography</th>
<th>MRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77</td>
<td>0.76</td>
<td>0.84</td>
<td>0.84</td>
<td>0.88</td>
<td>0.85</td>
<td>0.95</td>
<td>0.96</td>
</tr>
</tbody>
</table>

- NFS and FIB-4 offer the best diagnostic performance for detecting advanced fibrosis among noninvasive serum indices
- MRE and SWE had the highest diagnostic accuracy for staging fibrosis in NASH

Utility of MR Elastography in Identification of Candidates for Pharmacologic Treatment of NASH Related Fibrosis: A Prospective Cohort Study

Combination of MRE and FIB-4 for ruling in ≥stage 2 fibrosis

UCSD-NAFLD cohort (N=238)
- MRE ≥3.3kPa
  - PPV: 86.9
- +
- FIB-4 ≥1.6
  - PPV: 61.5
- MRE ≥3.3kPa + FIB-4 ≥1.6
  - PPV: 97.1

Japan-NAFLD cohort (N=222)
- MRE ≥3.3kPa + FIB-4 ≥1.6
  - PPV: 91.0

Jung J, et al. EASL dILC2020. #AS097
A Simplified Algorithm for Evaluation of NAFLD

Abnormal plasma transaminases or history of fatty liver

Exclude alcohol and other causes of hepatic steatosis

Incidental finding of fatty liver on imaging (US, CT, MRI)

Confirm NAFLD on imaging (US, CAP or MRI)

Steatosis?

NAFLD

• T2DM +/- metabolic syndrome
• Confirm ↑ plasma ALT/AST
• Diagnostic panels (FIB-4, NFS) and/or plasma biomarkers*
• Liver US or transient elastography

What is the risk of NASH-fibrosis?

Low risk

Periodic Re-evaluation

High or indeterminate risk?

Liver biopsy

NAFL

NASH ruled out

Referral to specialist

NASH

Patients with type 1 or type 2 diabetes mellitus should routinely (approximately every 2 years) undergo diagnostic procedures for NAFLD. Serum levels of transaminases are not reliable indicators for the screening and diagnosis of NAFLD. Liver ultrasonography is the preferred first-line imaging method for the diagnosis of NAFLD.

Pragmatic Algorithm for the Management of Suspected NAFLD in Patients With Established Diabetes Mellitus

Overall Mortality Stratified on Fibrosis Stage Compared to Matched Controls

- 646 patients
- Retrospective case controlled study
- Median f/u 20 years

“We suggest a deeper emphasis on reducing fibrosis stage as an endpoint for future clinical trials in NASH”

Fibrosis Progression in Nonalcoholic Fatty Liver versus Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies

- 11 cohort studies including 411 patients with biopsy-proven NAFLD
  - 150 NAFL, 261 NASH
- Annual fibrosis progression rate:
  - Stage 0 fibrosis with NAFL at baseline: 0.07 (1 stage of progression over 14.3 years)
  - NASH at baseline: 0.14 (1 stage of progression over 7.1 years)
- **Hypertension** was a significant risk factor for progression

Patients with NAFL need to be followed!

“Patients with cirrhosis suspected because of NAFLD should be considered for HCC screening according to the AASLD practice guidelines. Current evidence does not support routine screening and surveillance for HCC in patients with noncirrhotic NASH.”

Management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities.

Weight loss: “… the key to improvement in the histopathological features of NASH”¹

- Caloric intake ↓ ≥30% or ~750 to 1,000 kcal/d improved IR and hepatic steatosis
  - Mediterranean diet shown to have benefit in reducing all-cause mortality, CV diseases, cancer, obesity and type 2 DM
  - WL 3% to 5% can improve steatosis, but 6% to 10% needed to improve NASH/fibrosis
- Exercise alone may reduce steatosis, but effect on other histologic features unknown
  - Recent study: Association of exercise and changes in NAFLD on ultrasound over 5 year period
  - Improved liver enzymes, insulin resistance
- No heavy alcohol consumption (insufficient data)

Current Management of NASH

• Weight loss: “… the key to improvement in the histopathological features of NASH”¹

• Optimize cardiovascular risk factors
  – NASH has been associated with increased incident cardiovascular disease (CVD) risk in a meta-analysis²
  – NAFLD has been associated with increased risk of CVD and CVD events in meta-analyses²,³
  – “Confirming the presence of NASH and the degree of fibrosis should prompt more aggressive CVD risk reduction”⁴

Weight Loss Pyramid

- Steatosis
  - Weight Loss ≥ 10%\(^1\)
- Ballooning/Inflammation
  - Weight Loss ≥ 7%\(^1\)
  - Weight Loss ≥ 5%\(^{1,2,3}\)
- NASH Resolution
  - Weight Loss ≥ 3%\(^{1,2,3,4}\)
- Fibrosis

Physiologic Effects of Exercise

- Increased peripheral insulin sensitivity → Decreased de novo lipogenesis
- Decreased visceral fat → Decreased lipid supply to liver
- Decreased VLDL clearance increased → Decreased lipid storage

# Off-Label Pharmacologic Treatment of NAFLD and NASH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E (antioxidant)</td>
<td>Inflammation, oxidative stress</td>
</tr>
<tr>
<td>Pioglitazone (thiazolidinedione)</td>
<td>PPARγ receptor</td>
</tr>
<tr>
<td>Liraglutide (incretin mimetic)</td>
<td>GLP-1 receptor</td>
</tr>
</tbody>
</table>

Vitamin E or Pioglitazone for NASH: PIVENS Trial

- N=247
- Vitamin E 800 IU/d vs pioglitazone 30 mg/d vs placebo
- Primary end point: NAS improvement by >2 points + no increase in fibrosis

Vitamin E in Patients with Advanced Fibrosis

- 236 patients with NASH and bridging fibrosis or cirrhosis
  - 90 patients took vitamin E 800 IU/day for >2 y
  - 90 patients did not take vitamin E
- In propensity matched subset: 71% cirrhosis, 67% diabetic
- Median follow-up 5.6 y
- Adjusted 10-y cumulative probability of HCC, vascular events and non-hepatic cancers were not different between vitamin E-exposed patients and controls

*Adjusted for fibrosis severity, age, gender, BMI, comorbidities, LDL cholesterol, LFTs, length of f/u on vitamin E

Vitamin E in Patients with Advanced Fibrosis

Adjusted transplant-free survival (%)

- Vitamin E: 78%
- No vitamin E: 49%

Hepatic Decompensation (%)

- Vitamin E: 37%
- No vitamin E: 69%

Long-Term Effect of Pioglitazone in NASH

~50% response rate vs. placebo

Pioglitazone + Vitamin E Versus Vitamin E in Patients with NASH and T2DM

<table>
<thead>
<tr>
<th>Treatment Vs PBO</th>
<th>Primary Endpoint: 2-point reduction in the NAS</th>
<th>Secondary Endpoint: Resolution of NASH*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone + vitamin E</td>
<td>54% vs 19%, <em>P = .003</em></td>
<td>43% vs 12%, <em>P = .005</em></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>31% vs 19%, <em>P = .26</em></td>
<td>33% vs 12%, <em>P = .04</em></td>
</tr>
</tbody>
</table>

*Key finding:* vitamin E alone was not different from PBO in achieving improvement in the primary liver histological outcome, and was less effective than the combination of vitamin E and pioglitazone.

Liraglutide (GLP-1 RA) for NASH

- NASH resolution with no fibrosis worsening at 48 weeks in overweight patients with biopsy-confirmed NASH*

*Roughly one-third of patients had type 2 diabetes.

Pharmacologic Treatment of NASH: AASLD Practice Guidance 2018

- **Metformin**
  - Not recommended for treating NASH in adult patients

- **Vitamin E**
  - At 800 IU/day improves liver histology in nondiabetic adults with NASH
  - Risks and benefits should be discussed with each patient
  - Not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

- **Pioglitazone**
  - Improves liver histology with and without T2DM in adults with biopsy-proven NASH
  - Risks and benefits should be discussed with each patient

- **GLP-1RAs**
  - It is premature to consider GLP-1 agonists to specifically treat liver disease in patients with NAFLD or NASH

Bariatric Surgery in Patients With NASH

- Improvement in NAS, including steatosis, ballooning, inflammation
  - 85% resolution of NASH at 1 year\(^1\)
  - Most benefit occurs in first post-op year; similar at 5-year follow-up\(^2\)
- Stabilization or improvement of fibrosis\(^3\)
  - 34% of patients improved at 1 year\(^1\)
  - Fibrosis by Brunt and METAVIR scores significantly reduced at year 5 vs baseline (AASLD 2018)
- Perioperative mortality in cirrhosis\(^4\)
  - Decompensated >> compensated > no cirrhosis
- Efficacy re: fibrosis regression and safety in cirrhosis not clearly established

Laparoscopic Sleeve Gastrectomy: A Promising Treatment for NASH?

Improvement in NASH and fibrosis 12 months after laparoscopic sleeve gastrectomy (N=95)

Fig. 1
Improvement of NASH at 12-month follow-up after surgery

NAS score significantly decreased from $5.20 \pm 1.96$ at baseline to $2.63 \pm 1.55$ at 1-year follow-up ($P < 0.001$)

Salman MA et al, Obesity Surgery 2020 Jan;30(1):87-95
Intrahepatic Drug Targets in Phase 2 and 3 Clinical Trials for NASH

**NASH Resolution**
- Resolution of steatohepatitis on overall histopathologic reading and
- No worsening of liver fibrosis

**Fibrosis Improvement**
- Improvement ≥1 fibrosis stage and
- No worsening of steatohepatitis

FDA, US Food and Drug Administration.
OCA 25 mg met the primary endpoint of improvement in liver fibrosis with no worsening of NASH (p=0.0002* vs placebo)
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

REGENERATE: Phase 3 Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH
REGENERATE: Phase 3 Randomized, Placebo-Controlled Study Evaluating Obeticholic Acid Treatment for NASH

Normalization of transaminases in patients with elevated baseline levels*

<table>
<thead>
<tr>
<th></th>
<th>ALT normalization</th>
<th>AST normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=134)</td>
<td>37.3%</td>
<td>29.3%</td>
</tr>
<tr>
<td>OCA 10 mg (n=129)</td>
<td>55.0%</td>
<td>44.8%</td>
</tr>
<tr>
<td>OCA 25 mg (n=131)</td>
<td>65.6%</td>
<td>54.7%</td>
</tr>
</tbody>
</table>

Younossi Z, et al. EASL 2019, Vienna, Austria. #GS-06
Phase 2 Trial Investigating Semaglutide in the Treatment of NASH Meets Primary Endpoint

“Trend toward reduced fibrosis” (NS)
Phase 2 Trial of Semaglutide in the Treatment of NASH

Semaglutide showed resolution of NASH with no worsening of fibrosis versus placebo in the phase 2 trial[^1]

*Statistically significant at 72 weeks (p < 0.05 vs placebo
Analysis was for patients with F1, F2 or F3

Phase 2 Trial of Semaglutide in the Treatment of NASH

Semaglutide showed numerical benefits in improvement of fibrosis without worsening of NASH. Fewer patients on semaglutide had progression of fibrosis compared with placebo.

*Statistically significant at 72 weeks (p < 0.05 vs placebo)

MGL-3196 (THR-Beta Agonist) vs PBO: Reductions in hepatic fat (MRI-PDFF), liver enzymes, and improvement in NASH

- 36-week, multicenter, randomized, double-blind, placebo-controlled serial MRI-PDFF, paired liver biopsy study

In humans, thyroid hormone receptor-β (THR-β) agonism:
- ↓ lowers LDL-cholesterol
- ↓ Lowers triglycerides
- ↓ lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

- MGL-3196: liver-directed, orally active, highly selective THR-β agonist, may reduce NASH by increasing hepatic fat metabolism and normalizing liver function

Harrison S, et al. AASLD 2018, San Francisco, USA. #14
MGL-3196 (THR-Beta Agonist) vs PBO: Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, and Improvement in NASH

Inclusion/exclusion
- 2:1 MGL-3196 to PBO
- 125 patients enrolled in U.S.; 18 sites
- NASH on liver biopsy: NAS≥4 with F1–3
- ≥10% liver fat on MRI-PDFF
- Includes diabetics, statin therapy, representative NASH population

Comparator/arms
- 2:1 MGL-3196 to PBO
- 125 patients enrolled in U.S.; 18 sites

Harrison S, et al. AASLD 2018, San Francisco, USA. #14
MGL-3196 (THR-Beta Agonist) vs PBO: Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, and Improvement in NASH

Resmetirom (MGL-3196): Phase 2 Results

- Week 36 vs placebo, resmetirom vs placebo
- More patients achieved a 2-point NAS improvement (56% vs 32%; $P=.02$)
- More patients achieved NASH resolution (27% vs 6%; $P=.02$)
- Reduced liver fat (MRI PDFF; $P<.0001$)
- Increased incidence of mild transient diarrhea with resmetirom occurred early in therapy
Phase 2 Study of the FGF19 Analogue Aldafermin (NGM282) in Patients With NASH

Aldafermin is a synthetically engineered FGF19 analogue

- Inhibited bile acid synthesis, hepatic fibrosis, inflammation, and steatosis after 12 weeks

Key inclusion criteria included:
- Biopsy-confirmed NASH with NAS ≥4 (1 point in each component); stage 2/3 liver fibrosis (F2 or F3 by NASH CRN)
- Absolute LFC ≥8% by MRI-PDFF
- ALT ≥19 IU/L in females, ALT ≥30 IU/L in males

Primary endpoint:
Absolute change in PDFF at Week 24

Secondary endpoints:
Biomarkers, liver histology

Harrison S, et al. EASL dILC2020. #LBO01
Phase 2 Study of the FGF19 Analogue Aldafermin (NGM282) in Patients With NASH

LFC by MRI-PDFF

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 24</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>19</td>
<td>15</td>
<td>-13%</td>
</tr>
<tr>
<td>Aldafermin 1 mg</td>
<td>18</td>
<td><strong>10</strong></td>
<td><strong>-39%</strong></td>
</tr>
</tbody>
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**p=0.02 vs placebo

Relative change in ALT

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo (n=25)</th>
<th>Aldafermin 1 mg (n=52)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>% change in ALT from baseline; LS mean (SE)</td>
<td>% change in ALT from baseline; LS mean (SE)</td>
</tr>
<tr>
<td>2</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>4</td>
<td>*</td>
<td>*</td>
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<td>6</td>
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<td>*</td>
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<tr>
<td>8</td>
<td>*</td>
<td>*</td>
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<tr>
<td>12</td>
<td>*</td>
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*p<0.001 vs placebo

Harrison S, et al. EASL dILC2020. #LBO01
Phase 2 Study of the FGF19 Analogue Aldafermin (NGM282) in Patients With NASH

Fibrosis improvement ≥1 stage with no worsening of NASH

- Placebo (n=22): 18 patients (20%)
- 1 mg 12 wk (n=50): 38 patients (76%)

Fibrosis improvement ≥1 stage with no worsening of NASH²

- F3 patients: 1 mg 24 wk (n=23): 30 patients (65%)
- Placebo (n=1): 0 patients

F3 patients with ≥30% LFC reduction

- Placebo (n=22): 0 patients
- 1 mg 24 wk (n=13): 46 patients (35%)

*Liver histology population (n=50 aldafermin vs n=22 placebo)

²Defined by CRN criteria: All biopsies were read blinded to treatment assignment and patient information.

Improvement in liver fibrosis by ≥1 stage with no worsening of NASH (steatosis, lobular inflammation, or hepatocyte ballooning grade), not powered for statistical significance

Harrison S, et al. EASL dILC2020. #LBO01
Future Treatment for NASH

• Increasingly crowded field of agents with diverse mechanisms of action have entered the arena from preclinical to phase 3
• First successful attainment of a primary endpoint in a phase 3 trial of a NASH agent has been reported, but approval by FDA of obeticholic acid has been deferred pending more data
• As many questions as answers
  – Duration of therapy
  – Threshold to determine treatment candidacy, e.g. fibrosis level
  – **Combination therapy likely to be needed targeting >1 pathway**
• For now, can use vitamin E in selected cases and/or collaborate with patients’ internist or diabetologist on the use of pioglitazone or GLP-1 agonists
• Consider referring patients with moderate or severe fibrosis for clinical trials