Overview of the Clinical Trial Data on Non-alcoholic Steatohepatitis (NASH)

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• Consultant/Advisor:
  – Allergan, Arrowhead, Blade, Boehringer Ingleheim, BMS, Coherus, Consynance, Enanta, Gelesis, Gilead, Intercept, Lipocine, Madrigal, Medimmune, Merck, Metacrine, NGM, pH-Pharma, Prometheus
**NASH Pipeline in 2018 - Front Runners**

### Phase 1
- **Gilead GS-426-3897 (ACC1 Inhib)**
- **Gilead GS-402-1852 (FXR agonist)**
- **Taiwan JJKB-121 (TLR-4 antag)**
- **NuSirt NS-0200 (Met-Leu-sildenafil)**
- **Shire SHP-626 (ASBT inhib)**
- **BirdRock namacizumab (CNR1 mab)**
- **Pharmaxis PXS-S1 (LOX-2 sm mol)**

### Phase 2 a/b
- **Gilead GS-426-3897 (ACC1 Inhib)**
- **Gilead GS-402-1852 (FXR agonist)**
- **Taiwan JJKB-121 (TLR-4 antag)**
- **NuSirt NS-0200 (Met-Leu-sildenafil)**
- **Shire SHP-626 (ASBT inhib)**
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### Phase 3
- **Gilead – Selonsertib (ASK1 inhibitor)**
  - Phase 2 data *Published*
  - 2022+ Launch
- **Intercept OCA (FXR) PO**
  - Phase 2b data *published*
  - 2020+ Launch
- **Genfit GFT-505 (PPARα/δ)**
  - Phase 2b data *published*
  - 2022+ Launch
- **Tobira CVC (CCR2/5)**
  - Phase 2b interim data *published*
  - 2022+ Launch
- **Tobira CVC (CCR2/5)**
  - Phase 2b data in 2018
  - approved for T2DM
- **Novo Victoza (GLP-1)**
  - Phase 2b data published, approved for Diabetes
- **Madrigal - MGL 3196 (THR β-selective agonist)**
- **Galmed Aramchol (SCD1)**
- **Galectin GR-MD-02 (Galectin-3)**
  - Phase 2b data presented at EASL 2018

**Slide courtesy of Naga Chalasani (IU)**

*Represents earliest and most aggressive approval timelines.*
The lipotoxicity model of NASH and targets for therapy

Healthy eating habits, satiety or appetite modulators and bariatric surgery

Dietary fat
Chylomicron TG
Adipose tissue
TZDs
Circulating free FA

Dietary sugars
Exercise
Oxidative disposal (muscle and brown adipose tissue)
Fructose and glucose
Acetyl-CoA

Lipoprotein lipids
Liver free FA

Lipogenesis inhibitors
DNL

Mitochondrial β-oxidation
Steatosis
TG

Hypertriglyceridaemia

Hepatocyte injury
Inflammation

NASH
HCC
Fibrosis
Anti-fibrotics

Antioxidants
Anti-inflammatory agents
ER stress inhibitors

OSA or hypoxia
Probiotics and prebiotics
Gut microbiota products

Nature Reviews | Disease Primers

Brunt, E. M. et al. (2015) Nonalcoholic fatty liver disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.80
The lipotoxicity model of NASH and targets for therapy

- Liver free FA
- Lipotoxic lipids
- Mitochondrial β-oxidation
- Steatosis
- TG
- VLDL
- Hypertriglyceridaemia
- Hepatocyte injury
  - Inflammation
  - NASH
  - HCC
  - Fibrosis

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- Steatosis
- TG → VLDL
- Hypertriglyceridaemia

Lipotoxic lipids

Hepatocyte injury
- Inflammation

NASH
- HCC
- Fibrosis

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Targets of therapy

Healthy eating habits, satiety or appetite modulators and bariatric surgery

Dietary fat
- Chylomicron TG
  - Adipose tissue
    - TZDs
    - Circulating free FA
      - Liver free FA
        - Mitochondrial β-oxidation
          - Steatosis
            - TG
              - VLDL
                - Hypertriglyceridaemia
              - Lipotoxic lipids
                - Lipogenesis inhibitors
                - DNL

Exercise

Dietary sugars
- Oxidative disposal (muscle and brown adipose tissue)
- Fructose and glucose
  - Acetyl-CoA
    - Probiotics and prebiotics
      - Gut microbiota products

Hepatocyte injury
- Inflammation
  - Antioxidants
  - Anti-inflammatory agents
  - ER stress inhibitors
  - Anti-apoptotics
    - NASH
    - HCC
    - Fibrosis
    - Anti-fibrotics

Brunt, E. M. et al. (2015) Nonalcoholic fatty liver disease
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.80
Nature Reviews | Disease Primers
Drugs in Phase 3 trials

Elafibranor (PPARα/δ)  Obeticholic acid (FXR)  Cenicriviroc (CCR2/5)  Selonsertib (ASK-1 inhib)

Healthy eating habits, satiety or appetite modulators and bariatric surgery

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NASH  
HCC  
Fibrosis  
Anti-fibrotics

Antioxidants  
Anti-inflammatory agents  
ER stress inhibitors

NASH Ongoing Phase 3 trials

- Obeticholic acid: REGENERATE & REVERSE (Intercept)
- Elafibranor: RESOLVE-IT (Genfit)
- Selonsertib: STELLAR 3 & STELLAR 4 (Gilead)
- Cenicriviroc: AURORA (Allergan)

All are Phase3/4 adaptive design with histological end points for Subpart H conditional approval followed by clinical end points for full approval
Pioglitazone for NASH

• Pioglitazone 45 mg daily + diet x 18 months
  – N = 101
  – 1º endpoint: NAS improvement >= 2 and no worsening fibrosis
  – Diabetic subjects (n = 52) had a better response
  – Improvements maintained in a 18 month open label follow up study
    – Cusi et al, Ann Intern Med 2016;165:305-315
    – AASLD and EASL guidance: consider in non-cirrhotics with biopsy dx of NASH

Bril et al, Clin Gastroenterol Hepatol 2018;16:558-566
Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial


Partial funding for the trial, obeticholic acid, and placebo were provided by Intercept Pharmaceuticals under a Collaborative Research and Development Agreement with the NIDDK.
The FLINT trial

- Obeticholic acid (OCA), 25 mg orally daily vs placebo
- Inclusion: adults with NASH on biopsy, NAS ≥ 4;
  Exclusion: cirrhosis
- N = 283 patients randomized at 8 clinical centers
- 72 weeks of treatment
- Biopsy ≤ 3 mo. before treatment and after 72 weeks
- Primary endpoint
  - Improvement in NAFLD activity score ≥ 2 pts with no worsening of fibrosis

FLINT primary endpoint

- Improvement in NAFLD activity score* (NAS) ≥ 2 pts
  - * NAS = steatosis grade (0-3) + inflammation grade (0-3) + ballooning grade (0-2)
- No worsening of fibrosis
- Results:

Improvement in fibrosis and NASH resolution

**Fibrosis**

- Placebo: 19%
- OCA: 35%

**NASH resolution**

- Placebo: 13%
- OCA: 22%

*Change in score*

- Placebo: +0.1
- OCA: -0.2

*Statistical significance*

- Fibrosis: \( p = 0.004 \)
- NASH resolution: \( p = 0.08 \) (NS)

Enzymes and body weight

Serum lipids

Adverse events

• 6 severe adverse events in obeticholic acid group
  – 4 severe pruritus (1 stopped treatment)
  – 1 hypoglycemia
  – 1 possible cerebral ischemia (dysarthria and dizziness)

• Moderate or severe pruritus
  – 23% in obeticholic acid
  – 6% in placebo

Elafibranor, an Agonist of the Peroxisome Proliferator—Activated Receptor—α and —δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

Vlad Ratziu, Stephen A. Harrison, Sven Francque, Pierre Bedossa, Philippe Lehert, Lawrence Serfaty, Manuel Romero-Gomez, Jérôme Boursier, Manal Abdelmalek, Steve Caldwell, Joost Drenth, Quentin M. Anstee, Dean Hum, Remy Hanf, Alice Roudot, Sophie Megnien, Bart Staels, and Arun Sanyal on behalf of the GOLDEN-505 Investigator Study Group
Elafibranor—Phase IIb GOLDEN Trial

274 adult patients with histologic evidence of NASH; treatment with vitamin E, polyunsaturated fatty acids, or UDCA discontinued 3 months prior to biopsy; international RCT (Europe, United States)

Elafibranor 80 mg/day
Elafibranor 120 mg/day
Placebo

1 year

1° Endpoint
Resolution of NASH with no worsening of fibrosis

2° Endpoint
Change in NAS, fibrosis, liver enzymes, lipid parameters, metabolic markers, safety markers

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis; RCT, randomised controlled trial; UDCA, ursodeoxycholic acid.
GOLDEN 505 Primary Endpoint in ITT Population
Resolution of NASH Without Fibrosis Worsening

Protocol-defined (disappearance of steatosis or ballooning or lobular inflammation)

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate at Week 52 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17</td>
</tr>
<tr>
<td>ELF 80 mg</td>
<td>23</td>
</tr>
<tr>
<td>ELF 120 mg</td>
<td>21</td>
</tr>
</tbody>
</table>

Modified definition (no ballooning; lobular inflammation none or mild)

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate at Week 52 (%)</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>ELF 80 mg</td>
<td>13</td>
</tr>
<tr>
<td>ELF 120 mg</td>
<td>19</td>
</tr>
</tbody>
</table>

P = 0.28

P = 0.045


Slide courtesy of Naga Chalasani (IU)
GOLDEN 505 Primary Endpoint in Patients with NAS ≥4  Modified Definition

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 92)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>ELF 80 mg (n = 93)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>ELF 120 mg (n = 89)</td>
<td>19</td>
<td></td>
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</tbody>
</table>

P = .013

Abbreviations: ELF, elafibranor; NAS, nonalcoholic fatty liver disease activity score.
A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis With Fibrosis

Scott L. Friedman,1* Vlad Ratziu,2 Stephen A. Harrison,3 Manal F. Abdelmalek,4 Guruprasad P. Aithal,5 Juan Caballeria,6 Sven Francque,7 Geoffrey Farrell,8 Kris V. Kowdley,9 Antonio Craxi,10 Krzysztof Simon,11,12 Laurent Fischer,13 Liza Melchor-Khan,13 Jeffrey Vest,14 Brian L. Wiens,13 Pamela Vig,13 Star Seyedkazemi,13 Zachary Goodman,15 Vincent Wai-Sun Wong,16 Rohit Loomba,17,18 Frank Tacke,19 Arun Sanyal,20* and Eric Lefebvre13*

ILC 1368

Cenicriviroc treatment for adults with non-alcoholic steatohepatitis: Year 2 analysis of the Phase 2b CENTAUR study
Ratziu C, et al. ILC 2018

Slide courtesy of Naga Chalasani (IU)
Cenicriviroc (CVC) Targets Inflammation & Fibrogenesis

**NASH Disease Progression**

Metabolic-driven liver injury

→ Evokes inflammatory response

→ Drives fibrogenesis

**CVC Mechanism**

- Block inflammatory signaling
- Disrupt fibrogenic signaling
  - In activate stellate cells

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• Friedman, S. et al., Contemporary Clinical Trials, 47, March 2016
Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study

- First Phase 2b study in NASH to collect 3 serial biopsies over a 2-year duration
- Key eligibility criteria
  - Fibrosis stage 1-3 (NASH CRN), NASH diagnosis (NAS ≥4)
  - Enriched for T2DM, high BMI with at least 1 criteria of MetS, or bridging fibrosis and/or NAS ≥5
- Stratification factors: NAS (4 or ≥5) and fibrosis stage (≤2 or >2)
- Study conducted in the USA, EU, Australia, and Hong Kong
CVC demonstrated antifibrotic effect without impact on underlying steatohepatitis at Year 1 (ITT)

Arm A vs. Arms B+C

≥2-point improvement in NAS AND No worsening of fibrosis

- Arm A: 19%, Arm B+C: 16%
- p = 0.52

Complete resolution of NASH AND No worsening of fibrosis

- Arm A: 6%, Arm B+C: 8%
- p = 0.50

Improvement in fibrosis stage AND No worsening of NASH

- Arm A: 10%, Arm B+C: 20%
- p = 0.02

Proportion of participants, ITT (%)

n=144 n=145 n=144 n=145 n=144 n=145

Primary endpoint

Key secondary endpoints (surrogate composite endpoints)

CVC: cenicriviroc; ITT, intent-to-treat (missing data counted as failure);

Slide courtesy of Naga Chalasani (IU)
≥1-stage antifibrotic response with CVC following 2 years of treatment

Baseline to Year 2
Arm A vs. Arm C

<table>
<thead>
<tr>
<th>Improvement in fibrosis by ≥1 stage</th>
<th>Placebo (22%)</th>
<th>CVC (26%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=54</td>
<td>p=0.63</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Improvement in fibrosis by ≥1 stage AND no worsening of NASH</th>
<th>Placebo (17%)</th>
<th>CVC (15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=54</td>
<td>p=0.94</td>
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Post-randomization biopsy at Year 2

<table>
<thead>
<tr>
<th></th>
<th>Placebo n (%)</th>
<th>CVC n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>72</td>
<td>145</td>
</tr>
<tr>
<td>Evaluable</td>
<td>54 (75%)</td>
<td>99 (68.3%)</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>2 (2.8%)</td>
<td>4 (2.8%)</td>
</tr>
<tr>
<td>Missing*</td>
<td>16 (22.2%)</td>
<td>42 (29.0%)</td>
</tr>
</tbody>
</table>

Percentages based on randomized participants.

*Participants with missing post-Baseline biopsies were considered non-responders and excluded from the mITT analysis.

*Imbalance in missing liver biopsies at Year 2 predominantly affected Arm A.
≥2-stage antifibrotic response with CVC after 1 and 2 years of treatment

Arm A vs. Arm C (Subjects with Stage 2 or 3 Fibrosis)

Baseline to Year 1
- Placebo: 3% (n=38)
- CVC: 10% (n=82)
- p=0.15

Baseline to Year 2
- Placebo: 3% (n=34)
- CVC: 11% (n=65)
- p=0.13

Improvement in fibrosis by ≥2 stages AND no worsening of NASH

Slide courtesy of Naga Chalasani (IU)
The ASK1 Inhibitor Selonsertib in Patients With Nonalcoholic Steatohepatitis: A Randomized, Phase 2 Trial

GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtuzumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial


1University of California at San Diego, San Diego, CA; 2Texas Liver Institute, San Antonio, TX; 3The Liver Institute at Methodist Dallas, Dallas, TX; 4University of Calgary, Calgary, AB, Canada; 5University of Virginia, Charlottesville, VA; 6Gastroenterology Consultants of San Antonio, San Antonio, TX; 7Duke Clinical Research Institute, Durham, NC; 8Gilead Sciences, Inc., Foster City, CA; 9Inova Fairfax Hospital, Falls Church, VA; 10Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 11Intermountain Medical Center, Salt Lake City, UT
Study Design

Key inclusion criteria

- Biopsy-proven NASH with NAS ≥5 (≥1 point for steatosis, lobular inflammation, hepatocellular ballooning)
- F2–3 fibrosis

2:2:1:1:1 randomization (stratified by diabetes)

MRI-PDFF, magnetic resonance imaging-proton density fat fraction; MRE, magnetic resonance elastography; NAS, NAFLD Activity Score; SIM, simtuzumab.
Selonsertib & NASH

• After 24 weeks of treatment in patients with NASH and F2–3 fibrosis, selonsertib at 18 mg/day has beneficial effects on:
  – Fibrosis regression and progression
  – Liver stiffness by MRE
  – MRI-PDFF
  – ALT and GGT
  – CK-18

• selonsertib was safe and well-tolerated

• Phase 3 trials of selonsertib in patients with NASH and advanced fibrosis and cirrhosis have been initiated.
NGM282 FGF19 analogue phase 2 trial

**Primary endpoint:** 100% patients had decrease in absolute LFC ≥5%

**Mean decrease in relative LFC was 67%;** 100% patients had relative LFC ≥30%

- Rapid and significant reductions in: (C4), ALT and AST, fibrosis markers (PRO-C3), and LIF

**Conclusions**
- Unprecedented improvements in fibrosis and NASH-related histology, with earlier decreases in hepatic steatosis, liver transaminases and fibrosis markers

*NAS ≥4 (≥1 in each component), stage 1–3 fibrosis, absolute LFC ≥8% (MRI-PDFF)

†Defined as ≥1 stage fibrosis improvement, ≥2-point decrease in NAS or resolution of NASH

Harrison S, et al. ILC 2018, #5037 (GS-014)

Slide courtesy of Naga Chalasani (IU)
MGL-3196, a selective thyroid hormone receptor beta (THR-β) agonist: Phase 2 NASH study

**Background**
- MGL-3196 lowers LDL-C and TGs; and could reduce NASH by increased β-oxidation of liver lipids and improved mitochondrial function
- Safe and well tolerated in >300 dosed subjects (Phase 1)

**Methods**
- 125 patients with biopsy-proven NASH* and ≥10% liver fat on baseline MRI-PDFF randomized 2:1 to oral MGL-3196 qd or placebo for 36 weeks; blinded increase or decrease in dose possible based on exposure
- Serial liver biopsies performed

**Results (Week 12)**
- **Liver enzymes:** Decreases in ALT and AST in high-exposure MGL-3196 vs. PBO (p=0.04, 0.02, respectively)
- **Fibrosis biomarkers:** MGL-3196 significantly decreased ELF™ and Pro-C3 (up to 40% vs. PBO; p=0.009, 0.002, respectively) in patients with >ULN levels at baseline (reflective of more advanced fibrosis stage)
- **Safety**
  - Study still blinded; MGL-3196 shows very good tolerability: mostly mild–moderate AEs, balanced between all groups
  - Three SAEs, all unrelated to drug
  - No change in thyroid axis, heart rate or vital signs
  - Significant decreases in S/DBP for MGL-3196 vs. PBO

**Conclusions**
- MGL-3196 reduced NASH and liver fibrosis
- Histopathological assessment (36-week liver biopsy) will allow for correlations with baseline biopsy and multiple 12- and 36-week non-invasive imaging and biomarkers

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*NAS ≥4, F1–3
GR-MD-02, a Galectin-3 inhibitor, is better in patients with NASH cirrhosis without varices and mild portal hypertension (PH)

**Background:** Galectin-3 protein is implicated in the pathogenesis of NASH

**Methods:** 162 patients with NASH cirrhosis and PH, with no or small oesophageal varices (OVs), randomized 1:1:1 to 26 q2w IV infusions of GR-MD-02 2 mg/kg (GR2; n=54), 8 mg/kg (GR8; n=54), or PBO (n=54) over 52 weeks

**Results:**
- No significant differences in ΔHVPG (primary endpoint), fibrosis, or NAS between PBO and GR in total population, only improvement in hepatocyte ballooning vs PBO with GR2 (p=0.03); trend with GR8 (p=0.08)
- **Mild PH subgroup**a (n=53; 20 PBO, 17 GR2, 16 GR8): Significant difference in ΔHVPG between PBO and GR8 (p=0.036)
- **Safety:** GR-MD-02 well tolerated; similar rate of AEs and SAEs. More patients discontinued GR8 due to AEs (n=5; PBO and GR2, n=0)

**Conclusions**
- GR-MD-02 did not improve HVPG or liver fibrosis in total population, but significantly improved hepatocyte ballooning
- Significant and clinically relevant beneficial effects in patients with NASH cirrhosis with no OV and mild PH with GR2
- Significantly fewer GR2 patients developed new OVs at end-of-study
- These data warrant further investigating GR-MD-02 in NASH cirrhosis without varices

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*HVPG between ≥6 and <10 mmHg at baseline; ^HVPG decrease from baseline of both ≥2 mmHg and ≥20% Chalasani N, et al. ILC 2018, #5569 (LBO-001)
Summary

- Four drugs with different targets are in Phase 3 trials for NASH
  - Results expected in 1-2 years
- Many drugs in are Phase 2 trials with provocative results
- Future therapy may be combination therapy
- Ideally we will have personalized therapy
- Timeline: 2-5 years