Lessons learned from NASH clinical trials

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Evolution of NASH inclusion criteria and histological endpoints

- **2010**: NAS>4 if def NASH, >5 if not*
- **2014**: F1-3
- **2015**: NAS>4
- **2016**: Focus on F>2

**Initiation of Phase 3 non-cirrhotic trials**
- PIVENS
- FLINT
- GOLDEN 505
- REGENERATE
- RESOLVE-IT
- Stellar 3
- AURORA
Lessons learned in published placebo controlled Phase 2 studies

<table>
<thead>
<tr>
<th>PIVENS</th>
<th>FLINT</th>
<th>GOLDEN</th>
<th>NGM</th>
<th>Centaur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central pathology critical</td>
<td></td>
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<tr>
<td>First trial to show fibrosis can improve with metabolic MoA</td>
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<tr>
<td>Higher Placebo response: milder disease, looser endpoint</td>
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<tr>
<td>Steatosis and ALT can improve quickly and dramatically</td>
<td></td>
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<tr>
<td>Appealing MoA may have been offset by redundant pathways or limited target engagement</td>
<td></td>
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</tbody>
</table>

High screen fail rate...50%

Resolution of NASH strongly tracks with fibrosis improvement (Brunt, Hepatology 2019)

Fibrosis improves when NASH improves

Center effect
Endpoints in early stage disease: ALT and PDFF – is one enough?
Endpoints in early phase 2 development

**ALT**
- ↑ALT associated with ↑ mortality
- Every 10 U/L ↓ in ALT: OR 1.3 for histological improvement or resolution of NASH
- >17 U/L ALT ↓ predicted response in FLINT

**MRI PDFF**
- > 5% absolute reduction*
- > 30% relative reduction*
- Associates with histological improvement

* Targets for efficacy are based on limited data

Validity of ALT and MRI PDFF to assess efficacy is MoA dependent

(PIVENS, TONIC)
Steatosis as an endpoint

**Pros**
- Easy to measure
  - Good agreement on histology
  - Accurate non-invasive measurement
- Degree of steatosis associated with increased metabolic risk
- ?Link to fibrosis progression

**Cons**
- Improvement not linked to outcomes
- Steatosis lessens as disease progresses

1 Ajmera et al baseline PDFF and fibrosis progression. Gastroenterology 2018
### Association between significant improvements in liver fat, ALT and histology in NASH trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/MoA</th>
<th>Steatosis</th>
<th>ALT</th>
<th>GGT</th>
<th>NASH res</th>
<th>Fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt loss</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PIVENS</td>
<td>Pio/PPAR(\gamma)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>PIVENS</td>
<td>Vit E</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Trend, (p=0.05)</td>
<td>-</td>
</tr>
<tr>
<td>FLINT</td>
<td>OCA/FXR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Trend, (p=0.08)</td>
<td>+</td>
</tr>
<tr>
<td>LEAN</td>
<td>Liraglutide/GLP-1</td>
<td>-</td>
<td>+ (trend)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>REGENERATE</td>
<td>OCA/FXR</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+*</td>
<td>+</td>
</tr>
<tr>
<td>GOLDEN</td>
<td>Elafibranor/PPAR(\alpha,\delta)</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+ (NAS(\geq)4)</td>
<td></td>
</tr>
<tr>
<td>Madrigal</td>
<td>THR(\beta)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+**</td>
</tr>
<tr>
<td>NGM (no Pbo)</td>
<td>NGM282/FGF19</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ARREST</td>
<td>Aramchol/SCD-1 modulator</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*By gestalt diagnosis
** By Histoindex only
Seladelpar Phase 2b Study in NASH

*Discordance between PDFF response and ALT*

**PDFF Relative Change from Baseline**

- Placebo
- 10 mg
- 20 mg
- 50 mg

**Relative ALT (%)**

Cymabay Press release, June 11, 2019

† Average placebo PDFF relative change (Viking, MGL, Pegbelfermin, GS4997, Aramchol): -5.25%
Precedent for liver chemistry improvement independent of steatosis

Younossi et al. ILC, Vienna 2019
The impact of the placebo response and importance of placebo control
### Protocol defined vs. modified NASH resolution

<table>
<thead>
<tr>
<th>NAS</th>
<th>n</th>
<th>Placebo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined primary outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>92 (17)</td>
</tr>
<tr>
<td>NAS ≥4 (moderate and severe)</td>
<td>234</td>
<td>76 (11)</td>
</tr>
<tr>
<td>NAS 3 (mild)</td>
<td>40</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Modified definition of response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>274</td>
<td>92 (12)</td>
</tr>
<tr>
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<tr>
<td>NAS 3 (mild)</td>
<td>40</td>
<td>16 (25)</td>
</tr>
</tbody>
</table>

### Response according to baseline fibrosis

<table>
<thead>
<tr>
<th>Population</th>
<th>Selection, n</th>
<th>Placebo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All NAS ≥4</td>
<td>234&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76 (9)</td>
</tr>
<tr>
<td></td>
<td>202&lt;sup&gt;c&lt;/sup&gt;</td>
<td>63 (11)</td>
</tr>
<tr>
<td>NAS ≥4 with fibrosis (any stage)</td>
<td>204&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66 (11)</td>
</tr>
<tr>
<td></td>
<td>176&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55 (13)</td>
</tr>
<tr>
<td>NAS ≥4 with moderate/advanced fibrosis (F2, F3)</td>
<td>118&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41 (7)</td>
</tr>
<tr>
<td></td>
<td>99&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32 (9)</td>
</tr>
</tbody>
</table>

b - all patients; c - those with EOT biopsy

Expected placebo response depends on the endpoint

- **NASH resolution**
  - FLINT, PIVENS, GENFIT, LEAN, REGENERATE, MGL, ARREST
  - **12%** (6.4-21%)

- **NAS improvement >2, no worse fibrosis**
  - FLINT, PIVENS, EPA, CVC, MGL, REGENERATE
  - **28%** (19-40%)

- **Fibrosis improvement >1 stage**
  - FLINT, CVC, MGL, STELLAR 3, REGENERATE
  - **16%** (12-23%)

*varies based on F1 inclusion*
Factors influencing placebo response

- Disease activity at baseline ✓
- Endpoint ✓
- Weight loss ✓
- Surreptitious Vit E use (intentional or non-intentional) ✗
- Dietary macronutrients: e.g. Fructose, olive oil, coffee ✗
- Change in activity level, intensity of exercise ✗
- Alcohol intake ✗
The pitfalls of current histologic endpoints
Currently accepted endpoints for non-cirrhotic NASH

- **Resolution of NASH, no worsening of fibrosis**
- **Reduction in fibrosis, no worsening of NASH**

Resolution or improvement of NASH could reflect disease progression.

- Fibrosis linked to hard clinical outcomes
- Needs to not adversely impact metabolic or inflammatory activity
**NASH Resolution With No Worsening of Fibrosis by criteria**

**Primary endpoint definition:** (i) pathologist overall histopathologic assessment of “no fatty liver disease” or “fatty liver disease (simple or isolated steatosis) without steatohepatitis”; (ii) NAFLD Activity Score (NAS): hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline.

Younossi et al. ILC, Vienna 2019

**Gestalt: Resolution of Definite NASH With No Worsening of Fibrosis**

Endpoint defined as (i) resolution of definite NASH (i.e., absence of steatohepatitis) based on pathologist overall diagnostic assessment and (ii) no worsening of fibrosis stage from baseline. P values are nominal. ITT population (N=931).
Improvement by NAS ≥2 and individual components

NAS Improvement ≥2 with No Worsening of Fibrosis

≥1 Point Improvement in

Steatosis

Lobular Inflammation

Hepatocellular Ballooning

% Patients

Younossi et al. ILC, Vienna 2019

P values are nominal.
Per protocol population (N=668).
### Inter- and Intra-rater Agreement on Major Categories

<table>
<thead>
<tr>
<th></th>
<th>Inter (adult)</th>
<th>Inter (ped)</th>
<th>Intra (adult)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>0.79</td>
<td>0.64</td>
<td>0.83</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.84</td>
<td>0.62</td>
<td>0.85</td>
</tr>
<tr>
<td>Lob. Inf.</td>
<td>0.45</td>
<td>0.28</td>
<td>0.60</td>
</tr>
<tr>
<td>Ballooning</td>
<td>0.56</td>
<td>0.22</td>
<td>0.66</td>
</tr>
<tr>
<td>Mallory’s</td>
<td>0.58</td>
<td>0.69</td>
<td>0.64</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>0.61</td>
<td>0.33</td>
<td>0.66</td>
</tr>
</tbody>
</table>

(All values are grouped, weighted Kappa values)
NAFLD Activity Score Discriminates Among Steatohepatitis Diagnoses In Adults
Is this NASH Donald Trump?

**Criteria:** Blond hair - likely dyed and modified, orange skin, small hands and CANNOT be diplomatic
Is this Donald Trump?

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✗✗✗✗
Is this Donald Trump?

Gestalt: You know him when you see him
Fibrosis Improvement by ≥1 Stage with No Worsening of NASH (ITT, F2/3)

Primary endpoint definition:
- Improvement in fibrosis by ≥1 stage (NASH CRN)
- AND
- no worsening of lobular inflammation, hepatocellular ballooning or steatosis

Younossi et al. ILC, Vienna 2019
Week 36: MGL-3196 impact on Fibrosis

Using traditional staining, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo (F1-3, ≈ 50% F1)

Second Harmonic Generation (SHG) microscopy:
Automated quantification of fibrosis on liver biopsy that correlated with pathologist read (baseline, r=0.76).

Those with F2/3 had more marked response
Variability in collagen burden within fibrosis stage

Both are technically stage 3 fibrosis

Histology courtesy of Elizabeth Brunt
Liver Collagen Burden is not Linear Across Fibrosis Stages

Chen et al., Medicine 2016 Aug; 95(35): e4736

N=274
Liver Collagen Burden is not Linear Across Fibrosis Stages

CV and Hurst Index decrease with increasing burden of fibrosis
0.07 for cirrhosis, 0.29 for F0

Chen et al., Medicine 2016 Aug; 95(35): e4736
Limitations of current histologic endpoints

- Discrepancy between gestalt and quantitative assessment for NASH resolution
- Inter-observer variability (between local and central as well as between experts)
- Fibrosis stages may not accurately reflect the burden of fibrosis as a continuous measure
Studies evaluating efficacy in cirrhosis
Challenges in trials using endpoints to define clinically meaningful benefit

- Prolonged compensated phase
- More advanced patients (decompensated) may reach outcomes more quickly...but may be out of therapeutic efficacy window

*Sanyal et al, Hepatology 2006, 43:682-689*
SIM had no effect on portal pressure compared to placebo in patients with CSPHTN (HVPG ≥10mmHg)

Mean HVPG at entry was 12 mm, 68% had CSPH

Harrison, et al. *Hepatology*. 2019
Progression to cirrhosis
Bridging Fibrosis

- Median follow-up 24.9 months (range, 0.3–41.4)

- 47 patients (21.5%) progressed to cirrhosis
  - 89% (n=42) histologic progression
  - 11% (n=5) clinical events

Liver related clinical events in patients with cirrhosis

- Median follow-up 24.9 months (range, 0.3–41.4)

Results: Impact of Fibrosis on Clinical Events

Cirrhosis

<table>
<thead>
<tr>
<th>Hazard Ratio *</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishak stage 5 vs 6 (baseline)</td>
<td>1.25</td>
<td>0.68, 2.29</td>
</tr>
<tr>
<td>No improvement vs improvement</td>
<td>9.63</td>
<td>1.33, 69.81</td>
</tr>
<tr>
<td>Hepatic collagen (baseline), per 5%</td>
<td>1.39</td>
<td>1.15, 1.69</td>
</tr>
<tr>
<td>Change from baseline, per 5%</td>
<td>1.20</td>
<td>1.03, 1.39</td>
</tr>
<tr>
<td>ELF (baseline)</td>
<td>2.37</td>
<td>1.69, 3.31</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>1.54</td>
<td>1.10, 2.15</td>
</tr>
</tbody>
</table>

- Increased risk of clinical events with:
  - Higher baseline hepatic collagen content and ELF
  - Worsening of fibrosis (by Ishak stage, collagen content, ELF)

* Separate multivariate models run with baseline and change from baseline for each variable.
Subclassification of cirrhosis is important

**Emricasan:** ITT no reduction in portal pressure vs Pbo

**Galectin:** ITT no reduction in portal pressure vs Pbo

**Post hoc analysis cirrhosis no varices (post hoc)**

**Absolute change from baseline HVPG**

- **Emricasan 5mg v Pbo:**
  - Least squares mean difference: -2.16
  - 95% lower CL: -3.8
  - 95% upper CL: -0.52
- **Emricasan 25mg v Pbo:**
  - Least squares mean difference: -2.26
  - 95% lower CL: -3.84
  - 95% upper CL: -0.67
- **Emricasan 50mg v Pbo:**
  - Least squares mean difference: -2.02
  - 95% lower CL: -3.76
  - 95% upper CL: -0.29

Favors emricasan $\leftrightarrow$ Favors placebo

**Post hoc analysis HVPG $>16$**

- **Emricasan 5mg v Pbo:**
  - Mean HVPG: 10.6mmHg vs 12.22mmHg

Garcia-Tsao G, et al. EASL 2019, Vienna, Austria. #LB-01
Chalasani et al 2018
### New lessons learned from NASH trials

<table>
<thead>
<tr>
<th>Early phase trials</th>
<th>REGENERATE</th>
<th>MGL, others</th>
<th>SIMTUZUMAB</th>
<th>STELLAR 3/4, GAL, EMR, CVC</th>
</tr>
</thead>
</table>
| • Steatosis and ALT can predict histological response  
• Thus far, ALT has been more consistently predictive of histological improvement | • Success can be achieved in phase 3 trial of NASH  
• Histological endpoint of NASH resolution needs further refinement | • Better mechanisms to measure fibrosis improvement on a linear scale are needed | • Natural history of NASH in F3 and F4 patients  
• Increased collagen burden and ELF predictive | • More appraisal of evidence prior to phase 3.  
• Adaptation of stopping rules should be developed.  
• Cirrhosis populations |
Thank you for your attention