Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

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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 key baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Obeticholic acid (n = 141)</th>
<th>Placebo (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>52 ± 11*</td>
<td>51 ± 12</td>
</tr>
<tr>
<td><strong>% Female</strong></td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td><strong>% Hispanic</strong></td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>35 ± 7</td>
<td>34 ± 6</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>53%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>62%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Hyperlipidemia</strong></td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Vitamin E use</strong></td>
<td>21%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>ALT (U/L)</strong></td>
<td>83 ± 49</td>
<td>82 ± 51</td>
</tr>
<tr>
<td><strong>NAFLD activity score</strong></td>
<td>5.3 ± 1.3</td>
<td>5.1 ± 1.3</td>
</tr>
<tr>
<td><strong>Fibrosis stage</strong></td>
<td>1.9 ± 1.1</td>
<td>1.8 ± 1.0</td>
</tr>
</tbody>
</table>

(*± SD)

CONSORT diagram

345 patients assessed for eligibility
62 ineligible
283 randomized

141 obeticholic acid
  8 missing biopsies (imputed as no improvement)
  Protocol modified to eliminate last 64 biopsies (31 obeticholic acid, 33 placebo)
  102 with baseline and wk 72 biopsies
  110 included in final analysis

142 placebo
  11 missing biopsies (imputed as no improvement)
  98 with baseline and wk 72 biopsies
  109 included in final analysis

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 NAS components

**Steatosis**
- Placebo: 38%
- OCA: 61%
- $p = 0.001$

**Inflammation**
- Placebo: 35%
- OCA: 53%
- $p = 0.006$

**Ballooning**
- Placebo: 31%
- OCA: 46%
- $p = 0.03$

Improvement in fibrosis and NASH resolution

Fibrosis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>OCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of subjects improved</td>
<td>19%</td>
<td>35%</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td></td>
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</table>

NASH resolution

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>OCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of subjects improved</td>
<td>13%</td>
<td>22%</td>
</tr>
<tr>
<td>p (NS)</td>
<td>0.08</td>
<td></td>
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</table>

Change in score

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>OCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.1</td>
<td>-0.2</td>
<td></td>
</tr>
</tbody>
</table>

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

\[
P < 0.0001
\]

FLINT summary

• Obeticholic acid improved histological features of NASH including fibrosis
• Obeticholic acid treatment was associated with pruritus that was severe in 3%
• Elevated total and LDL cholesterol and decreased HDL cholesterol warrant further scrutiny in future trials