A phase 2 proof of concept study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) who are inadequate responders to ursodeoxycholic acid (UDCA)

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- PFIZER: Grant support
- GSK: Consultancy
- NOVARTIS: Consultancy
- FALK: Speaker bureau

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Primary Biliary Cholangitis (PBC)

Disease pathophysiology

- Autoimmune disease of the liver affecting primarily women (90%)
- Characterized by portal inflammation, destruction of intrahepatic bile ducts and cholestasis
- Elevated liver function biomarkers
  - Alkaline phosphatases (ALP)
  - γ-glutamyl transpeptidase (GGT)
  - Total bilirubin
- Pruritus and fatigue are prominent symptoms
- Can progress to fibrosis, cirrhosis and liver failure

Incidence

- Affects 1 in 1,000 women over 40 (~300,000 patients in major markets)
- Qualifies as an orphan disease in US and EU
Ursodesoxycholic acid (UDCA), a natural bile acid, is first line therapy
  • However, up to 40-50% of patients do not respond adequately to treatment

Obeticholic acid (OCA), a synthetic bile acid, has been recently approved
  • Add-on therapy for patients who are inadequate responders to UDCA
  • Monotherapy for patients who are intolerant to UDCA
  • Up to 50% of patients inadequately respond to OCA add-on
  • Pruritus is a frequent side effect

Continuing unmet need for more potent and better tolerated treatments
### MBX-8025

<table>
<thead>
<tr>
<th>MBX-8025</th>
<th>Potent, selective PPAR-δ agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Administered orally, once daily</td>
</tr>
<tr>
<td></td>
<td>PRIME designation</td>
</tr>
</tbody>
</table>

### PPAR-δ receptor

- Distinct gene regulation from PPAR-α and –γ
- Uniquely expressed in hepatocytes, cholangiocytes, Kupffer and stellate cells
- Anti-inflammatory, modulator of bile acid metabolism

### Status

- Studied for lipid disorders: favorable effects on lipids and reductions in ALP & GGT
- Generally safe and well tolerated
- Now targeting indications with high unmet medical need
  - Primary biliary cholangitis (PBC)
  - Nonalcoholic steatohepatitis (NASH)

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PPAR-δ Mediated Pharmacological Actions
Multiple potential benefits in PBC

Bile Acids
- ↓ cholesterol synthesis
- ↓ bile acid synthesis

Fibrosis
- ↓ Connective Tissue Growth Factor (CTGF)
- ↓ stellate cell activation
- ↓ collagen deposition

Inflammation
- ↓ NFκB-dependent gene activation
- ↓ inflammatory cytokines
- ↓ hs-C-Reactive Protein (CRP)

Other Metabolic Effects
- ↓ LDL-C
- ↓ cholesterol absorption
- ↓ free fatty acids and increases insulin sensitivity
## MBX-8025 Phase 2 Proof-of-Concept Study in PBC

### Design
- Double-blind, placebo controlled, dose ranging 12-week study
- Targeting enrollment of ~75 subjects with PBC who had an inadequate response to UDCA after at least one year of treatment
- $\text{ALP} \geq 1.67$ upper limit of normal (ULN)
- Placebo or MBX-8025 (50 or 200 mg), UDCA continued
- >50 sites in North America and Europe

### Outcome parameters
- **Primary:** ALP
- **Secondary:** GGT, total bilirubin, incidence of pruritus and fatigue
- Multiple exploratory markers: e.g. $7\alpha$-hydroxy-4-cholestene-3-one (C4)

Study terminated early after 3 subjects developed grade 3 transaminase elevation and efficacy demonstrated proof-of-concept
- Safety and efficacy data for 26 subjects at time of study termination
- Additional data for 12 subjects available following termination visits
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Placebo</th>
<th>MBX-8025 50 mg</th>
<th>MBX-8025 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td></td>
<td>12</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td>56 (8)</td>
<td>54 (7)</td>
<td>55 (12)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td></td>
<td>11 (92)</td>
<td>12 (92)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>28 (6)</td>
<td>24 (5)</td>
<td>27 (4)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td></td>
<td>233 (73)</td>
<td>312 (95)</td>
<td>248 (89)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td></td>
<td>39 (25)</td>
<td>47 (31)</td>
<td>30 (15)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td></td>
<td>36 (13)</td>
<td>37 (18)</td>
<td>29 (10)</td>
</tr>
<tr>
<td>GGT, U/L</td>
<td></td>
<td>183 (123)</td>
<td>220 (152)</td>
<td>104 (41)</td>
</tr>
<tr>
<td>Total Bilirubin, mg/dL</td>
<td></td>
<td>0.70 (0.37)</td>
<td>0.73 (0.27)</td>
<td>0.63 (0.27)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td></td>
<td>4.2 (0.4)</td>
<td>4.3 (0.4)</td>
<td>4.2 (0.3)</td>
</tr>
<tr>
<td>Platelets, 10^3/μL</td>
<td></td>
<td>233 (87)</td>
<td>271 (86)</td>
<td>239 (77)</td>
</tr>
<tr>
<td>Total UDCA dose, mg/day</td>
<td></td>
<td><strong>1171 (258)</strong></td>
<td><strong>1004 (255)</strong></td>
<td><strong>975 (230)</strong></td>
</tr>
</tbody>
</table>
Safety Summary

- No Serious Adverse Events during the treatment period

- Transaminase elevations
  - Rapid onset (2 weeks), probably drug-related
  - Asymptomatic, no bilirubin elevation or eosinophilia, but decreased ALP and GGT
  - Fully and quickly (2-4 weeks) reversible on drug discontinuation
  - Dose dependent
  - MBX-8025 is > 90% cleared by the biliary system and might accumulate in the liver of PBC subjects due to impaired bile flow

<table>
<thead>
<tr>
<th>ALT elevation</th>
<th>Placebo</th>
<th>MBX-8025 50 mg</th>
<th>MBX-8025 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3*</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2 + 3*</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

- Other treatment discontinuation
  - One patient on 200 mg discontinued study drug for an AE of muscle pain/myopathy

*Grade 2: >3.0 - 5.0 x ULN; Grade 3: >5.0 - 20.0 x ULN*
Mean Changes in ALP
Patients treated for 12 weeks have their ALP normalized

![Graph showing changes in ALP over time for different treatment groups.]

- **Placebo (N = 12)**
- **MBX-8025 50 mg (N = 13)**
- **MBX-8025 200 mg (N = 10)**

*Error Bars are ±SEM*
Mean Changes in ALP (LOCF)

No dose difference

<table>
<thead>
<tr>
<th>ALP (%) LOCF, N = 35</th>
<th>N</th>
<th>Baseline (U/L)</th>
<th>Mean (%)</th>
<th>SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>233</td>
<td>-2</td>
<td>16</td>
</tr>
<tr>
<td>MBX-8025 50 mg</td>
<td>13</td>
<td>312</td>
<td>-53</td>
<td>14</td>
</tr>
<tr>
<td>MBX-8025 200 mg</td>
<td>10</td>
<td>248</td>
<td>-63</td>
<td>8</td>
</tr>
</tbody>
</table>
# Mean Percent Changes in Other Parameters of Interest (LOCF)

<table>
<thead>
<tr>
<th>% Change from Baseline</th>
<th>Placebo</th>
<th>50 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean</td>
<td>N</td>
<td>Mean</td>
</tr>
<tr>
<td>GGT</td>
<td>12</td>
<td>-1.8</td>
<td>13</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>12</td>
<td>-4.9</td>
<td>13</td>
</tr>
<tr>
<td>5' Nucleotidase</td>
<td>12</td>
<td>-1.6</td>
<td>13</td>
</tr>
<tr>
<td>LDL-C</td>
<td>12</td>
<td>-3.7</td>
<td>13</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>10</td>
<td>9.7</td>
<td>11</td>
</tr>
</tbody>
</table>
Median Percent Change in C4
A plasma marker of hepatic bile acid synthesis

7-α-hydroxy-4-cholesten-3-one (C4)

p-values vs. placebo by Wilcoxon test
No Indication of Pruritus as an Adverse Event (AE)

<table>
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<tr>
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<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Pruritus at Baseline(^1)</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus AE on Treatment</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Visual Analog Scale (VAS) ≥ 30
Comparison of ALP Changes (LOCF) with OCA Phase 2 Data

Adapted from Intercept Briefing Document for OCA, pg. 46
Conclusions

- MBX-8025 treatment markedly reduces biochemical markers of cholestasis
  - ALP, GGT, 5’-nucleotidase, total bilirubin
  - All subjects treated for 12 weeks achieved a normal ALP value
  - There was no statistical difference between the 50 and 200 mg doses

- The anti-cholestatic activity of MBX-8025 treatment is at least partly attributable to a marked suppression of bile acids synthesis

- No evidence that MBX-8025 induces pruritus

- MBX-8025 treatment was associated with a dose dependent elevation in transaminases
  - Signal not observed in prior clinical studies in other patient populations with normal hepatic function

- Based on the unprecedented efficacy and absence of dose response between the 50 and 200 mg groups, a study at lower doses of MBX-8025 is being initiated