PROOF OF EFFICACY FOR SELADELPAR, A SELECTIVE PPAR-δ AGONIST, IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS NON-RESPONSIVE TO URSODEOXYCHOLIC ACID: RESULTS OF AN INTERNATIONAL PHASE 2 RANDOMIZED CONTROLLED CLINICAL STUDY

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Introduction
Seladelpar (MBX-8025) is a potent, selective peroxisome proliferator-activated receptor-delta (PPAR-δ) agonist. In previous studies1-3 in the absence of cholestatic, seladelpar was well tolerated and caused a significant decrease in alkaline phosphatase (ALP) and other cholestatic markers. Patients with primary biliary cholangitis (PBC), a chronic cholestatic liver disease, who inadequately respond to first-line therapy with ursodeoxycholic acid (UDCA), have a higher risk of disease progression. In this study (NCT02650094, EudraCT 2015-002068-39), we evaluated the potential efficacy and safety of seladelpar in patients with PBC and an insufficient response to UDCA.

Methods
A double-blind, randomized, placebo-controlled phase 2 study
Planned 75 PBC patients with an inadequate response to UDCA
UDCA + 1.67x upper limit of normal (ULN)
Placebo, Seladelpar 50 or 200 mg/day, oral
Patients continued with current UDCA doses
The study was terminated early after observing futility of ALT (CTCAE grade 3) in 3 patients while also confirming proof-of-concept efficacy
LOCF imputation method was used for the analyses

Baseline Characteristics

<table>
<thead>
<tr>
<th>MBX8025-21528 Study</th>
<th>Placebo</th>
<th>Seladelpar 50 mg</th>
<th>Seladelpar 200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age, years</td>
<td>58 (8)</td>
<td>54 (7)</td>
<td>55 (12)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>11 (92)</td>
<td>12 (92)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 (5)</td>
<td>25 (5)</td>
<td>27 (4)</td>
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<td>PBC Duration, years</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>ALP, units</td>
<td>233 (72)</td>
<td>319 (95)</td>
<td>248 (59)</td>
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<tr>
<td>GGT, U/L</td>
<td>183 (123)</td>
<td>220 (152)</td>
<td>104 (41)</td>
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<tr>
<td>AST, U/L</td>
<td>36 (13)</td>
<td>39 (25)</td>
<td>39 (25)</td>
</tr>
<tr>
<td>ALT, mg/dL</td>
<td>146 (64)</td>
<td>137 (35)</td>
<td>118 (33)</td>
</tr>
<tr>
<td>FGF19, pg/mL</td>
<td>107 (95)</td>
<td>119 (65)</td>
<td>138 (119)</td>
</tr>
</tbody>
</table>

Results

Safety
No Serious Adverse Events on treatment
- ALT elevation in 2 patients on 200 mg and one on 50 mg (CTCAE grade 3): Rapid onset, dose-dependent, fully reversible on drug discontinuation
- One patient on 200 mg with a grade 3 ALT also had a reversible increase in serum creatinine
- One patient on 200 mg discontinued for an AE of muscle pain/myalgia

Conclusions
Seladelpar has overt anti-cholestatic activity that appears linked to a decreased bile acid synthesis, resulting from both a decrease in cholesterol absorption and synthesis and a down-regulation of cholesterol 7α-hydroxylase
There was no difference in activity between the 50 mg and 200 mg dose groups
Seladelpar was associated with reversible and dose-dependent increases in transaminases
Lower doses are being explored in an ongoing phase 2 study (NCT02650094, EudraCT 2015-002068-39)

References

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Graphs and tables included in the document.