**ACTIVITY OF SELADELPAR (MBX-8025), A POTENT AND SELECTIVE PPAR-δ AGONIST, ON BIOCHEMICAL MARKERS OF CHOLESTASIS**

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### Introduction

Seladelpar (MBX-8025) is a highly selective and potent agonist of human peroxisome proliferator-activated receptor delta (PPAR-δ)\(^1\). The safety and efficacy of seladelpar was evaluated at doses of 50, 100 and 200 mg per day in healthy volunteers, obese subjects with mixed dyslipidemia\(^2\)\(^3\) and subjects with homozygous familial hypercholesterolemia (HoFH)\(^4\).

Seladelpar was safe and well-tolerated in all three studies. In addition to reductions in LDL-C, we report here consistent treatment-related decreases in biochemical markers of cholestasis as well as effects on biomarkers of bile acid metabolism.

### Methods

#### Study Designs

**Multiple Ascending Dose (MAD) Study**
- Single center, double-blind, randomized, placebo-controlled study
- Healthy male subjects
- Placebo, seladelpar 50 mg, 100 mg or 200 mg (n=9/group)
- Once daily for 3 weeks

**Dyslipidemia Study**
- Multicenter double-blind, randomized, placebo-controlled parallel group study
- Non-diabetic obese subjects with hyperlipidemia
- Placebo, seladelpar 50 mg, 100 mg and/or atorvastatin 20 mg (n=28-32/group)
- Once daily for 8 weeks

**Homogygous Familial Hypercholesterolemia (HoFH) Study**
- Multicenter, open label, single-arm, dose-escalating design with 3 consecutive treatment periods
- Subjects with confirmed mutations in the LDL receptor gene
- Subjects receiving (n=7) or not receiving apheresis (n=9)
- 50 mg (4 wk) → 100 mg (4 wk) → 200 mg (4 wk)

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Study Subjects</th>
<th>N</th>
<th>Duration</th>
<th>Treatment</th>
<th>Placebo</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
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<tbody>
<tr>
<td>Healthy</td>
<td>36</td>
<td>3 weeks</td>
<td>Placebo</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>31</td>
<td>28</td>
<td>32</td>
<td>12</td>
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<td></td>
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<tr>
<td>Dyslipidemia</td>
<td>181</td>
<td>8 weeks</td>
<td>Placebo</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>18</td>
<td>17</td>
<td>15</td>
<td>7</td>
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<tr>
<td>HoFH</td>
<td>12</td>
<td>3 doses</td>
<td>Seladelpar</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>2</td>
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#### Results

**Biochemical Markers of Cholestasis and Lipids**

#### Mean % Change in ALP and GGT

<table>
<thead>
<tr>
<th>% Change in ALP</th>
<th>Healthy</th>
<th>Dyslipidemia</th>
<th>HoFH</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>6 (15)</td>
<td>-4 (9)</td>
<td>NA</td>
</tr>
<tr>
<td>MBX-8025 50 mg</td>
<td>-23 (8)</td>
<td>-64 (21)</td>
<td>-23 (13)</td>
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<tr>
<td>MBX-8025 100 mg</td>
<td>-39 (9)</td>
<td>-63 (20)</td>
<td>-29 (11)</td>
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<tr>
<td>MBX-8025 200 mg</td>
<td>-26 (9)</td>
<td>-40 (13)</td>
<td>NA</td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td>NA</td>
<td>7 (13)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% Change in GGT</th>
<th>Healthy</th>
<th>Dyslipidemia</th>
<th>HoFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>39 (61)</td>
<td>-4 (21)</td>
<td>NA</td>
</tr>
<tr>
<td>MBX-8025 50 mg</td>
<td>-26 (16)</td>
<td>-26 (25)</td>
<td>-22 (16)</td>
</tr>
<tr>
<td>MBX-8025 100 mg</td>
<td>-24 (14)</td>
<td>-28 (23)</td>
<td>-28 (16)</td>
</tr>
<tr>
<td>MBX-8025 200 mg</td>
<td>-20 (13)</td>
<td>-34 (15)</td>
<td>NA</td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td>NA</td>
<td>3 (22)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Mean (SD)

#### Changes in ALP and GGT

- **Dyslipidemia Study**
- Placebo, MBX-8025 50, 100, 200 mg

- **HoFH Study**
- Placebo, MBX-8025 50, 100, 200 mg and/or atorvastatin

#### Bile Acid Synthesis

- **Dyslipidemia Study**
- Placebo, MBX-8025 50, 100, 200 mg

- **HoFH Study**
- Placebo, MBX-8025 50, 100, 200 mg and/or atorvastatin

### Conclusions

- In all three studies, seladelpar was associated with a rapid and consistent decrease in ALP
- ALP changes were reversible upon seladelpar discontinuation
- ALP decreases were associated with a concomitant decreases in GGT
- Decrease in total bilirubin (TBIL) were also observed in healthy men and HoFH patients
- Decreases in markers of bile acid synthesis were seen in healthy volunteers
- A recent study\(^5\) in primary biliary cholangitis (NCT02609048) confirmed that these effects were observed in patients with cholestasis and were also associated with a decrease in biomarkers of bile acid synthesis

### References