A Pilot study of MBX-8025 in the Treatment of Homozygous Familial Hypercholesterolemia (HoFH)

Gaudet D.¹, Saheb S.², Bruckert E.², de Graaf J.³, Langslet G.⁴, Tardif J.-C.⁵, Bergheanu S.C.⁶, Steinberg A.⁷, Choi Y.-J.⁷, Martin R.⁷, McWherter C.⁷, Kastelein J.⁸, Boudes P.⁷

¹ ECOGENE-21 Clinical and Translational Research Center, and Lipidology Unit, CMGC, dept of Medicine, Université de Montréal, Chicoutimi, Québec, Canada
² Endocrinologie métabolisme et prévention cardiovasculaire, Institut E3M et IHU cardiométabolique (ICAN), Hôpital Pitié Salpêtrière, Paris, France
³ Radboud University Medical Center, Nijmegen, the Netherlands
⁴ Lipid Clinic, Oslo University Hospital, Oslo, Norway
⁵ Montreal Heart Institute, Montreal, Québec, Canada
⁶ InterEuropa Clinical Research, Rotterdam, the Netherlands
⁷ CymaBay Therapeutics, Newark, CA, USA
⁸ Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
Disclosures

• Employee of CymaBay Therapeutics, Inc., Newark, CA, USA
• Own options to buy shares of the company
Study Background

- MBX-8025 is a potent and selective PPAR-delta receptor agonist

- PPARs are nuclear receptors
- Ligand binding leads to activation or repression of PPAR-dependent genes
- PPAR-delta is more ubiquitous than PPAR-alpha and PPAR-gamma and acts on a different set of PPAR-dependent genes
  - Little overlap with PPAR-gamma dependent genes (glitazones)
  - Depending on experimental conditions, PPAR-delta/PPAR-alpha cross activation (fibrates-like)
- PPAR-delta is involved in cholesterol metabolism
  - Decrease the synthesis of cholesterol
  - Decrease the absorption of cholesterol
  - Potentially, increase cholesterol excretion through bile flow
- PPAR-delta mediates inflammation
  - Decrease NFκB-dependent genes (e.g. decrease mediators of inflammation)
Study Rationale

- MBX-8025 decreases LDL-C by 45% in the Watanabe Heritable Hyperlipidemic (WHHL) rabbit model of HoFH\(^1\)

- MBX-8025 decreases LDL-C in patients with mixed dyslipidemia\(^2\)
  - Doses 50 mg and 100 mg, oral once-daily
  - Decreases LDL-C > 30% with higher baseline levels
  - Suggestion of a dose-response

- Study LDL-C lowering effects of MBX-8025 in HoFH patients

---

\(^1\) LDL-R < 5% activity; Shiomi, et al. Atherosclerosis 2009
Phase 2 Pilot Study of MBX-8025 in Subjects with HoFH

Study objectives, design and patient profile

• **Study objectives**
  – Evaluate the potential of MBX-8025 to lower LDL-C in subjects with HoFH
  – Collect safety information
  – Investigate changes in other lipid parameters, including PCSK9 levels

• **Study design**
  – Open label study of 12 weeks duration
  – Dose escalation (50, 100 and 200 mg once daily) every 4 weeks
  – LDL-C measurement every 2 weeks

• **Patients**
  – 13 subjects with genetically confirmed HoFH (Canada, France, NL, Norway)
  – All subjects were on ezetimibe and maximum statin therapy
  – No subjects received lomitapide, mipomersen or a PCSK9 inhibitor
  – 8 subjects were on concomitant apheresis (2 weekly, 6 bi-weekly)
### Subjects Characteristics at Baseline

<table>
<thead>
<tr>
<th>HoFH subjects, mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Females:Males (n)</strong></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td><strong>LDL-C (range)</strong></td>
</tr>
<tr>
<td><strong>Total-C</strong></td>
</tr>
<tr>
<td><strong>HDL-C</strong></td>
</tr>
<tr>
<td><strong>TG</strong></td>
</tr>
<tr>
<td><strong>PCSK9¹</strong></td>
</tr>
</tbody>
</table>

¹ Normal range 177-460 ng/mL
## Individual Mutations and LDL-R Status

<table>
<thead>
<tr>
<th></th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>LDL-R status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S285L</td>
<td>13kd deletion</td>
<td>negative</td>
</tr>
<tr>
<td>2</td>
<td>D333G</td>
<td>D333G</td>
<td>defective</td>
</tr>
<tr>
<td>3</td>
<td>D283Y</td>
<td>T705Y</td>
<td>defective</td>
</tr>
<tr>
<td>4</td>
<td>D283Y</td>
<td>T705Y</td>
<td>defective</td>
</tr>
<tr>
<td>5</td>
<td>Q33X</td>
<td>Q33X</td>
<td>negative</td>
</tr>
<tr>
<td>6</td>
<td>A540T</td>
<td>A540T</td>
<td>defective</td>
</tr>
<tr>
<td>7</td>
<td>2548+5, G&gt;A</td>
<td>2548+5, G&gt;A</td>
<td>defective</td>
</tr>
<tr>
<td>8</td>
<td>c313+1, G&gt;A</td>
<td>c313+1, G&gt;A</td>
<td>defective</td>
</tr>
<tr>
<td>9</td>
<td>W66G</td>
<td>W66G</td>
<td>defective</td>
</tr>
<tr>
<td>10</td>
<td>W66G</td>
<td>W66G</td>
<td>defective</td>
</tr>
<tr>
<td>11</td>
<td>W66G</td>
<td>W66G</td>
<td>defective</td>
</tr>
<tr>
<td>12</td>
<td>W66G</td>
<td>10kb deletion</td>
<td>defective</td>
</tr>
<tr>
<td>13</td>
<td>W66G</td>
<td>W66G</td>
<td>defective</td>
</tr>
</tbody>
</table>
Responder Analysis for LDL-C

*Primary per protocol population*¹ (N=12)

<table>
<thead>
<tr>
<th>% Change in LDL-C</th>
<th>% Responder Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>-2.6 mg/dL</td>
</tr>
<tr>
<td>≥ 15</td>
<td>-10.9 mg/dL</td>
</tr>
<tr>
<td>≥ 20</td>
<td>-12.2 mg/dL</td>
</tr>
<tr>
<td>≥ 30</td>
<td>-12.6 mg/dL</td>
</tr>
</tbody>
</table>

¹ One patient was excluded for missing multiple apheresis sessions.
LDL-C % Change from Baseline

Percent Change from Baseline

Subject 1 2 3 4 5 6 7 8 9 10 11 12

Mean
Max
LDL-C and PCSK9 % Change from Baseline

Subject % Change from Baseline

PCSK9 LDL-C

Subject 1 2 3 4 5 6 7 8 9 10 11 12
PCSK9 Mean and Maximum % Change

% Change from Baseline

Subject  1  2  3  4  5  6  7  8  9  10  11  12
0  50  100  150  200

Mean
Max
Predictability of LDL-C responses

Factors explored

• Factors that do not seem to explain the variability of LDL-C responses
  – Genotype
  – LDL-R status, defective or negative
  – Apheresis: yes or no
  – Baseline LDL-C levels
  – HDL-C levels
  – Dose

• PCSK9 increase was ‘unexpected’
  – No evidence of dose-response
  – PCSK9 increase might have affected the LDL-C decrease in both ‘responders’ and ‘non-responders’
Tolerance and Safety

- **Two Serious Adverse Events**
  - AV fistula thrombosis and chest pain, unrelated to MBX-8025

- **Adverse Events of interest**
  - Two patients (brother and sister) with post-apheresis arthralgia
    No conclusive diagnosis. Possibly related to MBX-8025
  - One patient with chest pain, back pain, anemia and increased serum creatinine, all present in medical history. Possibly related to MBX-8025
  - No muscle-related adverse events (six patients with mild statin myopathy at baseline)

- **Laboratory abnormalities**
  - One mild elevation in liver transaminases, part of medical history, possibly due to statin toxicity and/or MBX-8025
  - Hemoglobin decreases observed in three patients with known chronic anemia associated with apheresis
Conclusions

• **Summary**
  - The LDL-C lowering effect of MBX-8025 is clinically significant for some patients
    • 7/12 have a ≥ 15% decrease corresponding to an absolute decrease -109 mg/dL (-2.8 mmol/L)
    - However, 5/12 patients showed little or no response
    - The increase in PCSK9 (40-60% overall) is intriguing and may have attenuated the LDL-C lowering effect
    - MBX-8025 was well tolerated and appears safe in HoFH

• **Next steps**
  - Analysis of additional lipid and inflammatory markers
  - Study in combination with PCSK9 inhibitor