Abstract: 228

Long-term safety and effectiveness of mavacamten in symptomatic obstructive hypertrophic cardiomyopathy (oHCM) patients (pts): update from PIONEER open-label extension (PIONEER-OLE) study

Authors:
A Wang¹, SB Heitner², D Jacoby³, S Lester⁴, L Fang⁵, G Balaratnam⁵, AJ Sehnert⁵, ¹Duke Health Center at Southpoint - Durham - United States of America, ²Oregon Health & Science University, Knight Cardiovascular Institute - Portland - United States of America, ³Yale University School of Medicine - New Haven - United States of America, ⁴Mayo Clinic Arizona - Phoenix - United States of America, ⁵MyoKardia, Inc. - South San Francisco - United States of America,

Topic(s):
Myocardial Disease: Pharmacotherapy

Citation:

Funding Acknowledgements:
MyoKardia

Background: In a phase 2 PIONEER-HCM study, pts with symptomatic, obstructive hypertrophic cardiomyopathy (oHCM) showed improvement in left ventricular outflow tract (LVOT) obstruction, exercise capacity, and symptoms after 12 wk of treatment with the novel myosin modulator, mavacamten (Mava).

Purpose: To examine the long-term safety and effectiveness of Mava in PIONEER-OLE study

Methods: PIONEER-OLE (NCT03496168) is an ongoing 2-y multicenter study for adults with symptomatic oHCM who completed PIONEER-HCM (NCT02842242). The starting dose of Mava is 5 mg/d with titration at wk 6 to an individualized therapeutic dose (5, 10, or 15 mg). Evaluations are at wk 4, 6, 8, 12 and every 12 wk thereafter to monitor LV ejection fraction (LVEF), LVOT gradient, New York Heart Association (NYHA) class, NT-proBNP, drug concentration, and safety.

Results: 13 pts (mean age, 57.8 y; 9 male; 12 on beta-blockers) were enrolled. Mean baseline LVOT obstruction and LVEF, and wk 12 changes from baseline, were similar to those in PIONEER-HCM (Table). Mava significantly reduced resting and provoked LVOT gradients and NT-proBNP at wk 12 and 24 compared with baseline (P<.004). Of 10 pts who reached wk 24, 8 reported improvement in NYHA class (1 improved Class III to II; 7 improved Class II to I), and 2 pts remained Class II. Mava has been well tolerated up to 40 wk; 31 adverse events (AEs; 22 mild, 5 moderate) were reported in 8 pts; 1 pt had 3 severe and 1 serious AE (cholangiocarcinoma); all AEs were unrelated to study drug.

Conclusion: Despite management with current therapies, pts enrolled in PIONEER-OLE with similar levels of obstruction and hypercontractility as in PIONEER-HCM. In this longest observation period, Mava significantly reduced obstruction (LVOT gradient) in pts with oHCM beyond standard HCM therapy, while maintaining normal LVEF and improving symptoms.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PIONEER-HCMa</th>
<th>PIONEER-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Wk 12</td>
</tr>
<tr>
<td></td>
<td>Mean±SD (n=13)</td>
<td>Mean±SD (n=13)</td>
</tr>
<tr>
<td>LVOT Rest</td>
<td>69.7±53.9</td>
<td>27.8±31.3</td>
</tr>
</tbody>
</table>

Data extraction date January 24, 2019 aCombined results shown for pts from PIONEER-HCM originally in cohort A (n=5) and cohort B (n=8) bBaseline in PIONEER-OLE occurred 6–18 months after completion of PIONEER-HCM cNumber of pts with data available for analysis, unless otherwise specified
Abstract:
Long-term safety and effectiveness of mavacamten in symptomatic obstructive hypertrophic cardiomyopathy (oHCM) patients (pts): update from PIONEER open-label extension (PIONEER-OLE) study

Authors: A Wang1, SB Heitner2, D Jacoby3, S Lester4, L Fang5, G Balaratnam5, AJ Sehnert5
1Duke Health Center at Southpoint - Durham - United States of America, 2Oregon Health & Science University, Knight Cardiovascular Institute - Portland - United States of America, 3Yale University School of Medicine - New Haven - United States of America, 4Mayo Clinic Arizona - Phoenix - United States of America, 5MyoKardia, Inc. - South San Francisco - United States of America

Topic(s): Myocardial Disease: Pharmacotherapy

Citation:

Funding Acknowledgements:

MyoKardia

Background: In a phase 2 PIONEER-HCM study, pts with symptomatic, obstructive hypertrophic cardiomyopathy (oHCM) showed improvement in left ventricular outflow tract (LVOT) obstruction, exercise capacity, and symptoms after 12 wk of treatment with the novel myosin modulator, mavacamten (Mava).

Purpose: To examine the long-term safety and effectiveness of Mava in PIONEER-OLE study

Methods: PIONEER-OLE (NCT03496168) is an ongoing 2-y multicenter study for adults with symptomatic oHCM who completed PIONEER-HCM (NCT02842242). The starting dose of Mava is 5 mg/d with titration at wk 6 to an individualized therapeutic dose (5, 10, or 15 mg). Evaluations are at wk 4, 6, 8, 12 and every 12 wk thereafter to monitor LV ejection fraction (LVEF), LVOT gradient, New York Heart Association (NYHA) class, NT-proBNP, drug concentration, and safety.

Results: 13 pts (mean age, 57.8 y; 9 male; 12 on beta-blockers) were enrolled. Mean baseline LVOT obstruction and LVEF, and wk 12 changes from baseline, were similar to those in PIONEER-HCM (Table). Mava significantly reduced resting and provoked LVOT gradients and NT-proBNP at wk 12 and 24 compared with baseline (P<.004). Of 10 pts who reached wk 24, 8 reported improvement in NYHA class (1 improved Class III to II; 7 improved Class II to I), and 2 pts remained Class II. Mava has been well tolerated up to 40 wk; 31 adverse events (AEs; 22 mild, 5 moderate) were reported in 8 pts; 1 pt had 3 severe and 1 serious AE (cholangiocarcinoma); all AEs were unrelated to study drug.

Conclusion: Despite management with current therapies, pts enrolled in PIONEER-OLE with similar levels of obstruction and hypercontractility as in PIONEER-HCM. In this longest observation period, Mava significantly reduced obstruction (LVOT gradient) in pts with oHCM beyond standard HCM therapy, while maintaining normal LVEF and improving symptoms.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Mean±SD (n=13)</th>
<th>Wk 12</th>
<th>Mean±SD (n=12)</th>
<th>Change at Wk 12±SD (n=12)</th>
<th>Wilcoxon Signed Rank P value</th>
<th>Wk 24</th>
<th>Mean±SD (n=10)</th>
<th>Change at Wk 24±SD (n=10)</th>
<th>Wilcoxon Signed Rank P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT Rest gradient, mmHg</td>
<td>93.7±55.6</td>
<td>36.8±37.5</td>
<td>89.9±30.7</td>
<td>23.6±20.0</td>
<td>66.4±35.3</td>
<td>.0020</td>
<td>21.1±11.5</td>
<td>-67.3±33.5</td>
<td>.0039</td>
<td></td>
</tr>
<tr>
<td>LVOT Valsalva gradient, mmHg</td>
<td>73.0±5.6</td>
<td>64.6±10.5</td>
<td>72.0±4.9</td>
<td>67.6±7.2</td>
<td>-4.4±5.5</td>
<td>.0269</td>
<td>68.2±6.5</td>
<td>-3.2±3.3</td>
<td>.0195</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>73.0±5.6</td>
<td>64.6±10.5</td>
<td>72.0±4.9</td>
<td>67.6±7.2</td>
<td>-4.4±5.5</td>
<td>.0269</td>
<td>68.2±6.5</td>
<td>-3.2±3.3</td>
<td>.0195</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>1601.3±2782</td>
<td>684±980</td>
<td>1836±2886</td>
<td>181±211</td>
<td>-1759±2789</td>
<td>.0005</td>
<td>170±225</td>
<td>-2128±3104</td>
<td>.0039</td>
<td></td>
</tr>
</tbody>
</table>

Data extraction date January 24, 2019 aCombined results shown for pts from PIONEER-HCM originally in cohort A (n=5) and cohort B (n=8) bBaseline in PIONEER-OLE occurred 6-18 months after completion of PIONEER-HCM cNumber of pts with data available for analysis, unless otherwise specified