Long-term effects of mavacamten treatment in obstructive hypertrophic cardiomyopathy (HCM): updated cumulative analysis of the EXPLORER cohort of MAVA-long-term extension (LTE) study up to 120 weeks


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Introduction: Mavacamten was efficacious and well tolerated in patients (pts) with obstructive HCM over a median follow-up of 62 weeks in a previous interim analysis of the ongoing MAVA-LTE study (NCT03723655) (data cut-off; August 31, 2021). Here, we report an updated cumulative analysis of the EXPLORER cohort of MAVA-LTE up to 120 weeks.

Methods: Pts who completed EXPLORER-HCM (NCT03470545) could enroll in MAVA-LTE. All pts initiated the study with mavacamten 5 mg/day per protocol; dose adjustments to 2.5, 10, or 15 mg were based on site-read Valsalva left ventricular outflow tract (LVOT) gradient and LV ejection fraction (LVEF).

Results: In total, 231 pts (median age, 61 years; 39% female) enrolled in the EXPLORER cohort of MAVA-LTE. Median time on study was 101 weeks at data cut-off (May 31, 2022) with variations due to differences in enrollment timing. At data cut-off, 215 pts remained on treatment (total adjusted exposure: 475 pt-years). Mavacamten dosing of pts who reached week 120 (n=80) was: 2.5 mg (27.5%); 5 mg (31.3%); 10 mg (26.3%); 15 mg (12.5%). Between weeks 48–120, 34 of 231 (14.7%) pts underwent dose adjustments. Mavacamten treatment showed sustained improvements in mean [SD] change from baseline to week 120 in LVOT gradients (resting, −35.3 [33.0] mmHg; Valsalva, −47.0 [37.3] mmHg), left atrial volume index (−8.5 [10.3] mL/m2) and E/e’ average (−3.9 [5.0]) (Table). At week 120, 83.5% of pts had a Valsalva LVOT gradient ≤30 mmHg. Mavacamten was associated with sustained reduction from baseline to week 120 in N-terminal pro B-type natriuretic peptide (NT-proBNP) level (Table); 75.9% of pts improved by ≥1 class New York Heart Association class (Figure). Mean (SD) LVEF decreased by 9.1% (7.1) from baseline to week 120 but remained in the normal range. Since the previous interim analysis (data cut-off: August 31, 2021), 1 additional transient reduction in LVEF <50% occurred resulting in temporary treatment interruption (a total of 13 pts [5.6%] experienced LVEF <50% from study initiation). The pt resumed treatment at a lower dose 4 weeks after the event. In total, 74 serious adverse events (SAE) were reported in 47 pts (20.3%), with 18 new SAEs and 13 additional pts (5.6%) with SAEs since the previous interim analysis, including 1 new SAE (atrial fibrillation) considered drug related. No new safety signals were identified. One additional death (leading to a total of 4) occurred, due to intracranial hemorrhage. Like the previous 3 deaths (due to acute myocardial infarction, cardiac arrest, and bacterial endocarditis) the event was considered unrelated to the study drug.

Conclusions: Long-term mavacamten treatment up to 120 weeks showed sustained improvements in LVOT obstruction, symptoms, and NT-proBNP levels in pts with symptomatic obstructive HCM consistent with the findings of the parent study. Mavacamten treatment continues to be well tolerated with no new safety signals observed.
### Table. Changes from baseline to weeks 48, 96, and 120 in MAVA-LTE (EXPLORER cohort)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n = 231)</th>
<th>At Week 48 (n = 219)</th>
<th>At Week 96 (n = 172)</th>
<th>At Week 120 (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT gradient, mmHg Resting</td>
<td>48.5 (31.9)</td>
<td>-35.0 (32.4)</td>
<td>-37.8 (32.9)</td>
<td>-35.3 (33.0)</td>
</tr>
<tr>
<td>Valsalva</td>
<td>69.2 (33.1)</td>
<td>-44.2 (36.0)</td>
<td>-51.8 (36.8)</td>
<td>-47.0 (37.3)</td>
</tr>
<tr>
<td>NT-proBNP, ng/l, median (IQR)</td>
<td>766 (-1086, -168)</td>
<td>-601 (-1148, -176)</td>
<td>-1104, -166</td>
<td>-458 (-76)</td>
</tr>
<tr>
<td>LVEF (resting), %</td>
<td>73.9 (5.9)</td>
<td>-7.3 (8.4)</td>
<td>-8.7 (8.5)</td>
<td>-0.7 (7.1)</td>
</tr>
<tr>
<td>LAVI (resting), ml/m²</td>
<td>38.3 (13.0)</td>
<td>-6.7 (8.8)</td>
<td>-6.4 (9.7)</td>
<td>-3.9 (10.3)</td>
</tr>
<tr>
<td>E/e’ average (resting)</td>
<td>17.5 (7.1)</td>
<td>-3.7 (5.3)</td>
<td>-4.0 (5.5)</td>
<td>-3.9 (5.2)</td>
</tr>
</tbody>
</table>

*Number of patients who reached the last point at the data cut-off (31 May 2022). *According to the American Society of Echocardiography/European Association of Cardiovascular Imaging 2015 guidelines, the normal LVEF range for males is 52–72% and for females is 54–74%.*

Data presented are mean (SD) unless otherwise stated.

- Patients had variable time off treatment after parent study due to the COVID-19 pandemic.
- Baseline is defined as last non-missing measurement prior to the first dose of mavacamten in MAVA-LTE.
- IQR, interquartile range; LTE, long-term extension; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; SD, standard deviation.

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### Figure. Change from baseline in NYHA functional class in MAVA-LTE (EXPLORER cohort)

- **6.1%** improved by 1 class
- **59.3%** improved by 2 classes
- **14%** remained the same
- **22.8%** worsened by 1 class

Counts for NYHA functional class assessments included Weeks 48, 108, and 120 as per the study protocol.

NYHA, New York Heart Association.