

## EDITORIAL &amp; PRODUCTION

<b>Senior Vice President</b> Jeff Prescott, PharmD, RPh	<b>Assistant Editors</b> Jenna Geisinger Daniel Greaves
<b>Assistant Director, Content Services</b> Angelia Szwed	<b>Medical Writers</b> Amber Schilling, PharmD Valerie Sjoberg Samantha Stone, PhD
<b>Scientific Directors</b> Danielle Jamison, PharmD, MS Darria Zangari, PharmD, BCPS, BCGP	<b>Copy Chief</b> Jennifer Potash
<b>Senior Clinical Project Managers</b> Ida Delmendo Danielle Mroz, MA	<b>Copy Supervisors</b> Rachelle Laliberte Paul Silverman
<b>Clinical Project Managers</b> Lauren Burawski, MA Ted Pigeon	<b>Medical &amp; Scientific Quality Review Editor</b> Stacey Abels, PhD
<b>Project Managers</b> Lindsay Caporrino Lindsay McCay Jessica Toye	<b>Copy Editors</b> Cheney Baltz Georgina Carson Rebekah Harrison Kirsty Mackay
<b>Editor</b> Victoria Pelletier	<b>Creative Director, Publishing</b> Melissa Feinen
<b>Associate Editors</b> Hayley Fahey Jill Pastor Amanda Thomas	<b>Art Director</b> Julianne Costello

## SALES &amp; MARKETING

<b>Vice President</b> Gil Hernandez	<b>National Account Managers</b> Robert Foti Ryan O'Leary
<b>Senior National Account Managers</b> Ben Baruch Megan Halsch	<b>National Account Associate</b> Kevin George

## OPERATIONS &amp; FINANCE

<b>Circulation Director</b> Jon Severn circulation@mjhassoc.com	<b>Vice President, Finance</b> Leah Habitz, CPA
	<b>Controller</b> Katherine Wyckoff

## CORPORATE

<b>Chairman &amp; Founder</b> Mike Hennessy Sr	<b>Senior Vice President, Content</b> Silas Inman
<b>Vice Chairman</b> Jack Lepping	<b>Senior Vice President, I.T. &amp; Enterprise Systems</b> John Moricone
<b>President &amp; CEO</b> Mike Hennessy Jr	<b>Vice President, Human Resources and Administration</b> Shari Lundenberg
<b>Chief Financial Officer</b> Neil Glasser, CPA/CFE	<b>Vice President, Mergers &amp; Acquisitions</b> Chris Hennessy
<b>Chief Marketing Officer</b> Michael Baer	<b>Executive Creative Director, Creative Services</b> Jeff Brown
<b>Executive Vice President, Operations</b> Tom Tolvé	
<b>Executive Vice President, Global Medical Affairs &amp; Corporate Development</b> Joe Petroziello	



© 2020 Managed Care & Healthcare Communications, LLC

Opinions expressed by authors, contributors, and advertisers are their own and not necessarily those of Managed Care & Healthcare Communications, LLC, the editorial staff, or any member of the editorial advisory board. Managed Care & Healthcare Communications, LLC, is not responsible for accuracy of dosages given in articles printed herein. The appearance of advertisements in this publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality, or safety. Managed Care & Healthcare Communications, LLC, disclaims responsibility for any injury to persons or property resulting from any ideas or products referred to in the articles or advertisements.

This publication was sponsored by MyoKardia.

# Efficacy and Safety of Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results of the EXPLORER-HCM Study

This *AJMC*<sup>®</sup> Clinical Brief provides key information regarding the EXPLORER-HCM study (NCT03470545), the results of which were originally presented by Iacopo Olivetto, MD, at the European Society of Cardiology Congress 2020 – The Digital Experience, which was held from August 29 to September 1, 2020. The results of EXPLORER-HCM were simultaneously published in *The Lancet* (doi:10.1016/S0140-6736(20)31792-X). The authors of the publication in *The Lancet* are Olivetto I, Oreziak A, Barriales-Villa R, et al. Please consult the full publication in *The Lancet* for complete study information and author affiliations.

## BACKGROUND

Cardiomyopathies are defined by abnormalities of the ventricular myocardium that are both structural and functional but that are not explained by either flow-limiting coronary artery disease or abnormal loading conditions.<sup>1</sup> Hypertrophic cardiomyopathy (HCM) refers to cardiomyopathy characterized by increased left ventricular (LV) wall thickness that cannot be entirely accounted for by abnormal loading conditions.<sup>1</sup> The primary pathophysiologic features of HCM include hypercontractility, disordered relaxation and left ventricular compliance, and impaired cardiac energetics.<sup>2</sup> Patients with HCM may experience dynamic ventricular outflow tract (LVOT) obstruction, and obstructive HCM is defined as a peak LVOT gradient of 30 mm Hg or greater.<sup>2</sup> Patients with HCM may be highly symptomatic and have impaired functionality and reduced quality of life.<sup>3,4</sup> HCM can be progressive, with cardiac remodeling and worsening of cardiac function leading to complications such as atrial fibrillation (AF) or heart failure.<sup>1,3</sup> HCM may also lead to sudden cardiac arrest or death.<sup>3</sup>

$\beta$ -Blockers are currently recommended as first-line pharmacologic management in patients with symptomatic LVOT obstruction; however, their use is not particularly well studied in the disease.<sup>1,5</sup> Additionally, although  $\beta$ -blockers can be effective in reducing symptoms, many patients with HCM are unable to tolerate  $\beta$ -blocker therapy.<sup>5</sup> Alternatives to  $\beta$ -blockers include nondihydropyridine calcium channel blockers (such as verapamil and diltiazem) and the antiarrhythmic disopyramide, but all these agents must be used with caution. A decrease in blood pressure with verapamil or diltiazem treatment may cause increased outflow obstruction and consequent pulmonary edema, whereas disopyramide is associated with anticholinergic adverse events (AEs) and prolongation of the QTc interval.<sup>1,5</sup> Moreover, none of these pharmaceutical treatment options address the underlying molecular mechanisms of HCM.<sup>6</sup>

Invasive procedures, most prominently ventricular septal myectomy (Morrow procedure) and percutaneous alcohol septal ablation, are generally more effective than the available drug therapies. However, invasive procedures are reserved for patients with advanced disease (eg, New York Heart Association [NYHA] class III-IV) and are associated with risk of complications.<sup>1</sup> The need for surgeons and cardiologists experienced in these procedures to achieve optimal outcomes has also limited the availability of procedures.<sup>1,6</sup> Taken together, the limitations associated with current treatment options highlight the need for novel pharmacologic treatments to address obstructive HCM.<sup>2,6</sup>

Pathophysiological studies have shown that in HCM, dysfunction in the sarcomere results in an excess of actin-myosin cross-bridging. This, in turn, causes excessive energy consumption in addition to hypercontractility and impaired relaxation.<sup>2</sup> Some patients with HCM have genetic mutations that are considered pathogenic or likely pathogenic.<sup>3</sup> The classification and interpretation of genetic variants have evolved over time, and this is an area of ongoing research.<sup>7</sup> In published reports, the percentage of patients with HCM who have disease-causing mutations has ranged from approximately 30% to 45%.<sup>6,8</sup>

Mavacamten is the first agent in a new class of myosin inhibitors—small molecules that selectively target the underlying pathophysiology of HCM by reducing actin-myosin cross-bridge formation, thus improving excess contractility and utilization of myocardial energy.<sup>2</sup> The phase 3 EXPLORER-HCM study was designed to assess the efficacy and safety of mavacamten in patients with symptomatic obstructive HCM.<sup>2</sup>

## METHODS

EXPLORER-HCM was a pivotal phase 3, multicenter, randomized, double-blind study of the safety and efficacy of mavacamten in adults with a clinical diagnosis of obstructive HCM, peak LVOT gradient at least 50 mm Hg, and NYHA class II or III symptoms.<sup>2,6</sup> After a screening period of up to 35 days, 251 eligible patients were randomized 1:1 to receive oral mavacamten or placebo for 30 weeks, followed by an 8-week posttreatment period, and after that the option to enter a long-term extension study (MAVA-LTE; NCT03723655).<sup>2,6</sup> The starting dose of mavacamten was 5 mg once daily, with the option to adjust the dosage at weeks 8 and 14. During titration, dosing adjustments were guided by mavacamten plasma concentration and echocardiography results. Mavacamten doses of 2.5 mg, 5 mg, 10 mg, or 15 mg were given to reduce the LVOT gradient to less than 30 mm Hg and maintain a mavacamten plasma concentration level within the range of 350 to 700 ng/mL.<sup>2,6</sup> Based on the results of pharmacokinetic modeling, 15 mg/day was the highest dose.<sup>2</sup> Concomitant use of  $\beta$ -blockers or calcium channel blockers was allowed if they were initiated prior to participation in the study; use of disopyramide was not permitted.<sup>2</sup>

The primary end point consisted of 2 composite functional end points, and achieving either of these was considered a successful primary outcome. These were defined as changes from baseline of either: (1) an increase of at least 1.5 mL/kg/min in peak oxygen consumption ( $pV_{O_2}$ ), as determined by cardiopulmonary exercise testing in addition to a reduction of at least 1 NYHA functional class, or (2) an increase of at least 3.0 mL/kg/min in  $pV_{O_2}$  with no worsening in NYHA functional class.<sup>2</sup> Secondary end points consisted of changes from baseline at week 30 in postexercise LVOT gradient,  $pV_{O_2}$ , NYHA class, and scores on 2 patient-reported outcome (PRO) instruments: the Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score for health-related quality of life and the HCM Symptom Questionnaire Shortness of Breath subscore for HCM core symptoms.<sup>2</sup> The primary and secondary end points were designed in

collaboration with HCM experts, patients with HCM, and regulatory authorities to comprehensively evaluate outcomes.<sup>6</sup>

## RESULTS

### Efficacy

Baseline characteristics were similar between the 2 groups with regard to age, concomitant therapy, NYHA functional class,  $pV_{O_2}$ , and echocardiographic parameters.<sup>6</sup> The starting ejection fraction was 74% in both groups, and the postexercise LVOT gradient was 86 and 84 mm Hg in the mavacamten and placebo groups, respectively. History of AF was less common in the mavacamten group (10%) than in the placebo group (18%), whereas those in the mavacamten group had higher baseline levels of serum N-terminal pro B-type natriuretic peptide (NT-proBNP). Overall, 92% of patients were receiving background  $\beta$ -blockers or calcium channel blockers.<sup>6</sup>

The results for all primary and secondary end points—which assessed symptoms, exercise capacity and function, LVOT obstruction, and key aspects of quality of life—were highly significant, as shown in **Table 1**.<sup>6</sup> The proportion of patients achieving 1 of the 2 composite primary outcomes was more than double in the mavacamten group versus the placebo group (37% vs 17%;  $P = .0005$ ). The number of patients achieving both of the primary composite end points was 2.5-fold greater in the mavacamten group (20% vs 8%;  $P = .0005$ ).<sup>6</sup>

Improvements in the mavacamten group were significantly greater compared with the placebo group for all the secondary end points, including change at week 30 in postexercise LVOT gradient ( $-47$  vs  $-10$ ;  $P < .0001$ ) and change in  $pV_{O_2}$  (1.4 vs  $-0.1$ ;  $P = .0006$ ). Improvement of 1 or more NYHA class was more than twice as common in the mavacamten group (65% vs 31%;  $P < .0001$ ), and PROs also strongly favored the mavacamten group over the placebo group.<sup>6</sup>

The benefits of mavacamten treatment observed for the secondary end point of postexercise LVOT gradient were seen not just in the overall group but across a variety of patient subgroups, regardless of age, sex, body mass index, baseline left ventricular ejection fraction (LVEF),  $\beta$ -blocker use, baseline NT-proBNP level, and HCM genetic testing results.<sup>6</sup> Mavacamten also conferred improvements that occurred early and were sustained in resting and Valsalva LVOT gradients versus placebo (**Figure**).<sup>6</sup>

The EXPLORER-HCM trial also assessed several exploratory efficacy end points as shown in **Table 2**, including the number of patients who achieved a reduction of postexercise LVOT peak gradient to less than 50 mm Hg (ie, below the standard threshold for invasive septal reduction therapy), which was met by 74% versus 21% of the mavacamten and placebo patients, respectively.<sup>6</sup> Relief of LVOT obstruction (ie, postexercise gradient  $< 30$  mm Hg) was seen in more than half of all patients treated with mavacamten (57%) compared with 7% in the placebo group.<sup>6</sup> In addition, 32 of 117 patients (27%) treated with mavacamten became asymptomatic (defined as being NYHA class I) and were below the guideline-based definition of obstruction (all LVOT gradients  $< 30$  mm Hg) versus 1 of 126 patients with placebo ( $< 1\%$ ).<sup>6</sup>

Rapid and sustained decreases in cardiac biomarkers of myocardial wall stress and injury were also observed in patients treated

**Table 1.** Results of EXPLORER-HCM: Primary and Secondary End Points<sup>6,a</sup>

Primary end point <sup>b</sup>			
	Mavacamten group (n = 123)	Placebo group (n = 128)	Difference <sup>c</sup> (95% CI, P value)
Either $\geq 1.5$ mL/kg/min increase in $pVO_2$ with $\geq 1$ NYHA class improvement or $\geq 3.0$ mL/kg/min increase in $pVO_2$ with no worsening of NYHA class	45 (37%)	22 (17%)	19.4 (8.7-30.1, $P = .0005$ )
$\geq 1.5$ mL/kg/min increase in $pVO_2$ with $\geq 1$ NYHA class improvement	41 (33%)	18 (14%)	19.3 (9.0-29.6)
$\geq 3.0$ mL/kg/min increase in $pVO_2$ with no worsening of NYHA class	29 (24%)	14 (11%)	12.6 (3.4-21.9)
Both $\geq 3.0$ mL/kg/min increase in $pVO_2$ and $\geq 1$ NYHA class improvement	25 (20%)	10 (8%)	12.5 (4.0-21.0)
Secondary end points <sup>d</sup>			
	Mavacamten group	Placebo group	Difference <sup>c</sup> (95% CI, P value)
Postexercise LVOT gradient change from baseline to week 30, mm Hg	-47 (40), n = 117	-10 (30), n = 122	-35.6 (-43.2 to -28.1; $P < .0001$ )
$pVO_2$ change from baseline to week 30, mL/kg/min	1.4 (3.1), n = 120	-0.1 (3.0), n = 125	1.4 (0.6-2.1; $P = .0006$ )
$\geq 1$ NYHA class improvement from baseline to week 30 <sup>e</sup>	80 (65%)	40 (31%)	34% (22-45; $P < .0001$ )
Change from baseline to week 30 in KCCQ-CSS <sup>e</sup>	13.6 (14.4), n = 92	4.2 (13.7), n = 88	9.1 (5.5-12.7; $P < .0001$ )
Change from baseline to week 30 in HCMSQ-SoB <sup>e</sup>	-2.8 (2.7), n = 85	-0.9 (2.4), n = 86	-1.8 (-2.4 to -1.2, $P < .0001$ )

HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score; LVOT, left ventricular outflow tract; NYHA, New York Heart Association;  $pVO_2$ , peak oxygen consumption.

<sup>a</sup>Data are n (%) or mean (SD).

<sup>b</sup>Patients with a nonevaluable primary end point and an NYHA secondary end point were considered as nonresponders.

<sup>c</sup>Model-estimated least-square mean differences were reported for continuous variables.

<sup>d</sup>N was the number analyzable for secondary end points based on availability of both baseline and week 30 values.

<sup>e</sup>Because of the smaller numbers evaluable for patient-reported outcome end points, additional post hoc analyses compared the reasons for missing data.

Reprinted from *The Lancet*, 396(10253), Olivetto I, et al, Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial, P759-P769, Copyright 2000, with permission from Elsevier.

with mavacamten compared with placebo. At week 30, there was an 80% higher reduction in NT-proBNP in the mavacamten group than in the placebo group, whereas reduction in high-sensitive cardiac troponin I was 41% higher in the mavacamten group.<sup>6</sup>

### Safety

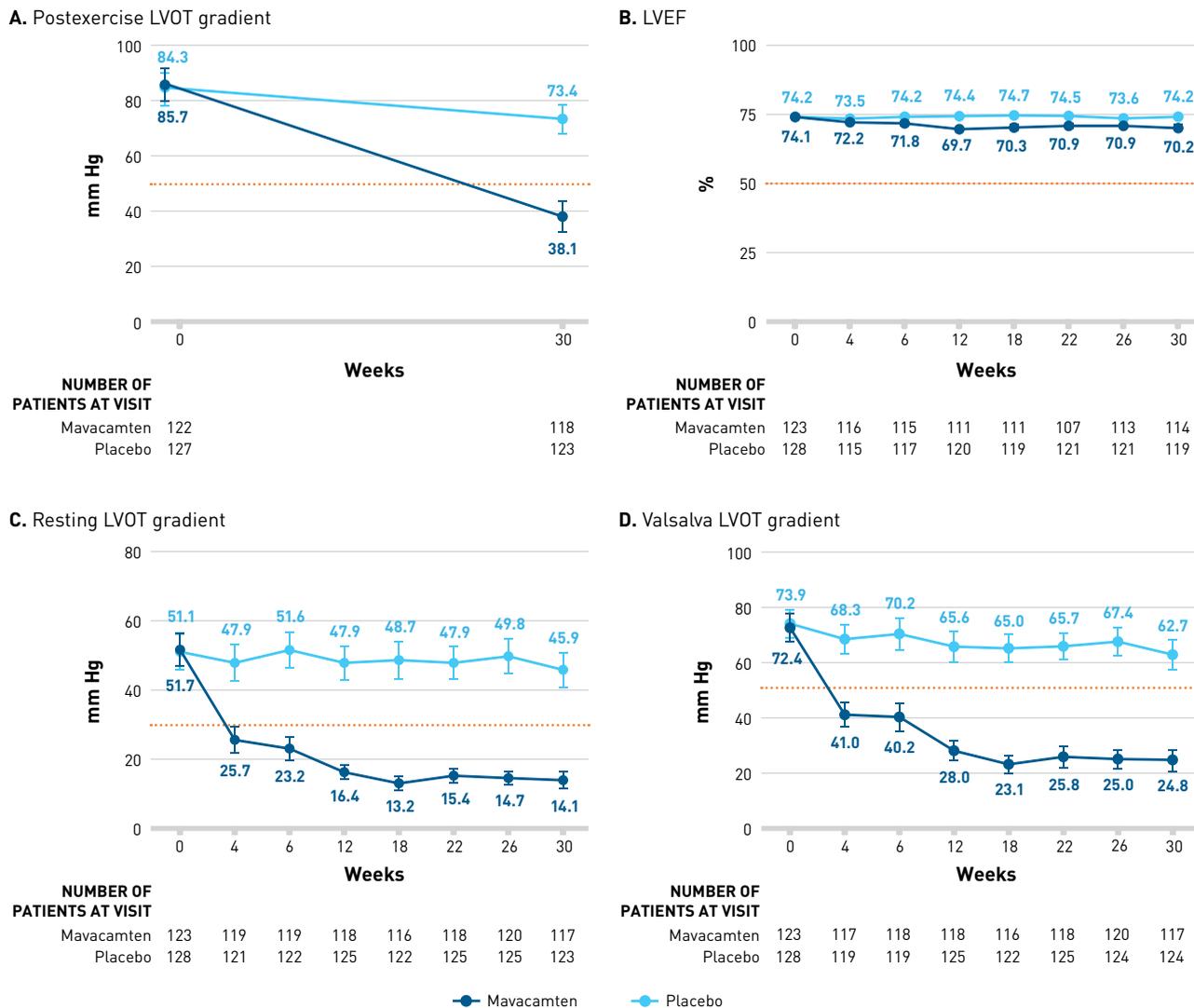
The rate of treatment completion was 97%.<sup>6</sup> Overall, 88% of patients in the mavacamten group and 79% in the placebo group experienced a treatment-emergent AE (TEAE), and most TEAEs were mild in severity.<sup>6</sup> Three patients discontinued treatment because of AEs, 2 of whom were in the mavacamten group.<sup>6</sup> Eleven serious AEs (SAEs) were reported in 10 patients in the mavacamten group compared with 20 SAEs reported in 11 patients in the placebo group. Serious cardiac AEs were reported in 4 patients receiving mavacamten (2 cases of AF and 2 of stress cardiomyopathy) and in 4 patients receiving placebo (3 cases of AF and 1 case of AF and congestive heart failure). One patient in the placebo group experienced sudden death.<sup>6</sup>

The change from baseline in systolic function (mean reduction in LVEF) observed in the mavacamten group was small, -3.9%, compared with -0.01% in the placebo group.<sup>6</sup> Five patients (3 and 2 in the mavacamten and placebo groups, respectively) were subject to temporary discontinuation for LVEF less than 50% based on prespecified criteria in the study protocol; LVEF normalized in all 5 patients, who resumed treatment and completed the study. At week 30, an additional 4 patients in the mavacamten group experienced LVEF less than 50%, 3 of whom recovered after the 8-week washout period. The fourth patient underwent ablation for AF during the washout period and experienced a complication related to the procedure. This patient had a severe drop in LVEF followed by partial recovery to an LVEF of 50%.<sup>6</sup>

### CONCLUSIONS

The results of the EXPLORER-HCM study showed that treatment with mavacamten met the efficacy and safety end points. In this

Figure. EXPLORER-HCM: LVOT Gradients and LVEF<sup>6</sup>



LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

Reprinted from *The Lancet*, 396(10253), Olivetto I, et al, Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial, P759-P769, Copyright 2000, with permission from Elsevier.

Table 2. EXPLORER-HCM: Key Exploratory Efficacy End Points<sup>6,a</sup>

	Mavacamten group	Placebo group	Difference (95% CI)
Postexercise LVOT peak gradient <50 mm Hg <sup>b</sup>	75/101 (74%)	22/106 (21%)	53.5 (42.0-65.0)
Postexercise LVOT peak gradient <30 mm Hg <sup>c</sup>	64/113 (57%)	8/114 (7%)	49.6 (39.3-59.9)
NYHA class I and all LVOT gradients <30 mm Hg	32/117 (27%)	1/126 (1%)	26.6 (18.3-34.8)

LVOT, left ventricular outflow tract; NYHA, New York Heart Association.

<sup>a</sup>Data are n/N (%), unless otherwise indicated.

<sup>b</sup>Threshold for guideline-based invasive intervention. Only patients with baseline postexercise LVOT peak gradient of at least 50 mm Hg were assessed.

<sup>c</sup>Threshold for guideline-based diagnosis of obstruction. Only patients with baseline postexercise LVOT peak gradient of at least 30 mm Hg were assessed.

Reprinted from *The Lancet*, 396(10253), Olivetto I, et al, Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial, P759-P769, Copyright 2000, with permission from Elsevier.

first positive randomized phase 3 trial in patients with obstructive HCM, mavacamten showed improvement across comprehensive measures that assessed symptoms, function, health status, and levels of biomarkers of myocardial wall stress and injury that are correlated with long-term outcomes in HCM. Treatment with mavacamten was largely well tolerated, and mavacamten demonstrated a safety profile similar to that of placebo. The long-term efficacy and safety of mavacamten are currently being evaluated in the MAVA-LTE study. The results of EXPLORER-HCM support the benefits of mavacamten for targeted, disease-specific pharmacotherapy for obstructive HCM.<sup>6</sup> •

## REFERENCES

1. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779. doi:10.1093/eurheartj/ehu284
2. Ho CY, Olivotto I, Jacoby D, et al. Study design and rationale of EXPLORER-HCM: Evaluation of Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy. *Circ Heart Fail*. 2020;13(6):e006853. doi:10.1161/CIRCHEARTFAILURE.120.006853
3. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med*. 2018;379(7):655-668. doi:10.1056/NEJMr1710575
4. Cox S, O'Donoghue AC, McKenna WJ, Steptoe A. Health related quality of life and psychological well-being in patients with hypertrophic cardiomyopathy. *Heart*. 1997;78(2):182-187. doi:10.1136/hrt.78.2.182
5. Gersh BJ, Maron BJ, Bonow RO, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(24):2761-2796. doi:10.1161/CIR.0b013e318223e230
6. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):P769-P769. doi:10.1016/S0140-6736(20)31792-X
7. Mazzarotto F, Girolami F, Boschi B, et al. Defining the diagnostic effectiveness of genes for inclusion in panels: the experience of two decades of genetic testing for hypertrophic cardiomyopathy at a single center. *Genet Med*. 2019;21(2):284-292. doi:10.1038/s41436-018-0046-0
8. Ho CY, Day SM, Ashley EA, et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHARe). *Circulation*. 2018;138(14):1387-1398. doi:10.1161/CIRCULATIONAHA.117.033200

## Ask the Investigator: Q&A With Iacopo Olivotto, MD

After presenting the results of the EXPLORER-HCM study (NCT03470545) at the European Society of Cardiology Congress 2020 – The Digital Experience, Iacopo Olivotto, MD, addressed questions from the audience.

**Is it time to admit that  $\beta$ -blockers do not work in most patients with obstructive hypertrophic cardiomyopathy? Do you believe that improvement in diastolic function played a part in the positive findings?**

**Iacopo Olivotto, MD:** In this trial,  $\beta$ -blockers seem to have created more problems than they solved. Patients on  $\beta$ -blockers had worse oxygen consumption findings, and that was expected. The long-term extension trial to gather more safety information is ongoing, and we are considering [whether] to allow physicians to withdraw  $\beta$ -blockers from patients [who] are doing well on mavacamten.

With regard to [the second part of the question], we definitely have very good animal data [in dogs] showing that mavacamten had an effect on diastolic parameters. And we do have the MAVERICK-HCM [NCT03442764] data showing promise in patients with nonobstructive HCM [hypertrophic cardiomyopathy], showing a very promising fall in troponin and NT-proBNP [N-terminal pro b-type natriuretic peptide].

[Regarding EXPLORER-HCM,] we are now looking very actively at the diastolic parameters in this particular subset of patients with obstructive HCM. When patients have obstructive HCM and you relieve the gradient, you have a number of benefits on diastolic function, which are directly mediated from gradient reduction. Distinguishing the direct effects of mavacamten

on the myocardium from those that are mediated by gradient reduction is not easy at this stage. We are hopeful and confident that we can show [benefit] in the very near future.

**Just to clarify, regarding the issue of maintenance of medications like  $\beta$ -blockers and verapamil—in this trial, these medications may have been maintained for safety reasons. Do you think that mavacamten has a future as a single therapy?**

**Olivotto:** Yes, I think so. I think that it is quite possible. Of course, in patients with HCM, it is also nice to have control of heart rate, because faster heart rates are not beneficial for these patients. So we know now that to some extent, wisely used  $\beta$ -blockers can be useful in patients, particularly when young and active. So I think that these are to some extent complementary. But if you are interested in treating obstruction per se, then a single [drug] approach with mavacamten is probably a very reasonable approach.

**One of the major risks in hypertrophic cardiomyopathy is sudden death. The EXPLORER-HCM trial was 30 weeks, so that's a little short to see any effect on sudden death. But what are your expectations regarding any effect on sudden death?**

**Olivotto:** It's an excellent question. Well, first of all, we know that obstruction is associated with doubling of risk of sudden death, so though we are talking about small absolute numbers, if you look at relative numbers, if you have obstructive HCM, you have double the chances of having sudden death compared with nonobstructive disease. So although it's never been proven that if you relieve obstruction you reduce the risk of sudden death, we have a long follow-up after myectomy in many patients showing very small rates of sudden death. So I would expect that just by reducing the gradient, you are somehow providing benefit.

We know that with sarcomere gene mutations, we have electrophysiological remodeling of cardiomyocytes. I would be hopeful, and again this has to be proven, that by acting on the remodeling caused by the downstream effects of these mutations, there may be favorable electrophysiological effects to be identified in these patients. If we just look at the small numbers [from EXPLORER-HCM], we don't have the power to see this. In terms of looking at ventricular arrhythmias, the rate of nonsustained VT [ventricular tachycardia] was the same in the 2 treatment arms.

**Do you believe mavacamten will reduce symptoms in patients with HCM with left ventricular outflow tract obstruction**

**in the long term, or should mavacamten be seen more as a bridge to myectomy?**

**Olivotto:** Actually, I think that the aim is the opposite. There is an ongoing study called VALOR-HCM [NCT04349072], which will hopefully demonstrate that if you use mavacamten, you may postpone or reduce the need for surgery. So, of course, the big question here is: What is the long-term safety [profile] of mavacamten, and [for] how long can we give it? Can we give it for decades, as many of these patients would require, in a safe manner? We know that the effects of mavacamten are very reversible in the short to mid-term. But hopefully this drug will allow much earlier and broader treatment. For patients with obstructive HCM, who are in [New York Heart Association] class II, for example, they are still not doing well, but they would not be referred to a surgeon. So they are basically left to live with their symptoms. Also, surgical expertise and interventional expertise for this disease are limited, and we know from real-world trials and registries that aside from a very few experienced centers, patients with HCM [don't have access to surgical] interventions. So having a drug that can [relieve symptoms] makes it sort of more democratic to treat obstruction worldwide. •



