Key Findings from the EXPLORER-HCM Study of Mavacamten in Obstructive Hypertrophic Cardiomyopathy: Insights From the Principal Investigator

Interviewee: Iacopo Olivotto

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Interview Summary

Hypertrophic cardiomyopathy (HCM) is a progressive myocardial disease that impacts function and quality of life. Patients with HCM may have shortness of breath (dyspnoea), effort intolerance, chest pain (angina), palpitations, and syncope,[1-3] and have increased risk of atrial fibrillation, stroke, heart failure (HF), and sudden cardiac arrest or death.[2-5] Community-based studies indicate the prevalence of HCM is 1 in 500, with many individuals remaining undiagnosed throughout life. HCM can affect people of any age, race, or sex.[1,5-7]

Obstructive HCM (oHCM) is characterised by unexplained left ventricular (LV) hypertrophy, which is associated with dynamic LV outflow tract (LVOT) obstruction, and is defined by the presence of either a resting or provoked LVOT peak gradient ≥30 mmHg.[8] Current pharmacological treatments for oHCM are nonspecific, cause side effects, or have limited efficacy in relieving symptoms;[1,2,8] hence, there is a significant unmet need for targeted treatment of this disease.

Mavacamten (MyoKardia, Brisbane, California, USA) is a first-in-class, targeted inhibitor of cardiac myosin that reduced LVOT obstruction, improved exercise capacity, and relieved symptoms of oHCM in the PIONEER-HCM Phase II study.[9,10] The EXPLORER-HCM Phase III was a pivotal, randomised, double-blind, placebo-controlled study,[11] conducted to investigate the efficacy and safety of mavacamten in treating symptomatic oHCM.[8,12]

For this article, EMJ conducted an interview on 9th September 2020 with the principal investigator of EXPLORER-HCM Dr Iacopo Olivotto, who has a wealth of experience and expertise in managing oHCM, to gain his perspectives on the study and its importance in the field.

TREATMENT OF OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY AND THE NEED FOR EXPLORER-HCM

Dynamic LVOT obstruction was recognised from the earliest clinical descriptions of HCM >60 years ago,[13,14] and is arguably the most visible and well-known pathophysiological component of this heterogeneous disease.[15] Dr Olivotto described how patients with oHCM have been treated to manage symptoms for >40 years with drugs developed for other cardiac conditions; however, these treatments act downstream and do not target the core molecular abnormalities of the disease. Furthermore, alcohol septal ablation or surgical removal of the obstruction is invasive, has inherent risk, requires expertise that is not widely available, and does not alter the long-term progression of myocardial dysfunction. Dr Olivotto reflected that there is much known about oHCM, including molecular mechanisms, genetics, risk, and natural history. From the time of diagnosis, there is a span of 20–30 years before the disease progresses to HF; therefore, this is an unexploited opportunity to interfere with the disease and halt disease progression.

EXPLORER-HCM was the first Phase III study to assess targeted, disease-specific treatment for oHCM, and comprised 251 mildly to moderately symptomatic patients (New York Heart Association [NYHA] functional Class II–III symptoms: 123 on mavacamten; 128 on placebo) at 68 centres in 13 countries.[8,12]

Dr Olivotto outlined: "oHCM is a neglected disease that affects millions of people worldwide and for which there is no licensed drug. We see the disease progressing and we have nothing to counter it. The need for EXPLORER-HCM reflects the need for a proper treatment for this disease. Interfering with the basic mechanism of disease is really what we need to do and EXPLORER-HCM is just the beginning."

OBJECTIVE AND KEY ENDPOINTS OF EXPLORER-HCM

EXPLORER-HCM was conducted to test a first-in-class, targeted strategy of myosin inhibition to improve LVOT obstruction and haemodynamic status, biomarker status, symptom burden, exercise capacity, and key aspects of quality of life.[8,12] The primary composite functional endpoint of EXPLORER-HCM was clinical response at Week 30 of treatment with mavacamten versus placebo compared to baseline, defined as either an increase in peak oxygen consumption (pVO_2) ≥1.5 mL/kg/min and reduction of ≥1 NYHA functional class, or an increase of ≥3.0 mL/kg/min in pVO_2 with no worsening of NYHA class.[8] Secondary endpoints included change in post-exercise LVOT gradient, NYHA class, pVO_2, and patient-reported outcomes assessed by the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). Safety endpoints included the incidence of major adverse cardiac events (death, stroke, acute myocardial infarction) and ventricular tachyarrhythmias. Exploratory endpoints were to characterise the effect of mavacamten on multiple aspects of oHCM pathophysiology.[8]

KEY FINDINGS FROM EXPLORER-HCM

All primary and secondary endpoints in EXPLORER-HCM achieved statistically and clinically significant differences compared to placebo ($p<0.001$ for all differences from placebo). The primary endpoint of EXPLORER-HCM was achieved by more than twice as many patients treated with mavacamten compared to placebo: 45/123 (37%) patients on mavacamten versus 22/128 (17%) on placebo, which was statistically significant (95% confidence interval [CI]: 8.7–30.1; $p=0.0005$).[12] Secondary endpoint results were as follows: patients on mavacamten compared to those on placebo had greater reductions in post-exercise LVOT gradient (36 mmHg; 95% CI: -43.2 to -28.1; $p<0.0001$); greater increase in pVO_2 (+1.4 mL/kg/min; 95% CI: 0.6–2.1; $p=0.0006$); and improved symptom scores (KCCQ-CSS: +9.1, 95% CI: 5.5–12.7; HCMSQ-SoB: -1.8, 95% CI: 2.4–1.2; $p<0.0001$).[10] Improvement of ≥1 NYHA class was reported in 80/123 (65%) and 40/128 (31%) patients in the mavacamten and placebo groups, respectively (+34%; 95% CI: 22.2–45.4; $p<0.0001$).[10]

Dr Olivotto noted: "To show such a benefit in mildly to moderately symptomatic patients is quite impressive." Safety and tolerability

of mavacamten were similar to placebo. Treatment-emergent adverse events were generally mild. One patient died (sudden death) in the placebo group.

EXPLORER-HCM Highlights the Benefits of Disease-Specific Treatment for Obstructive Hypertrophic Cardiomyopathy

Treatment with mavacamten in EXPLORER-HCM improved exercise capacity, LVOT obstruction, NYHA functional class, and health status in patients with oHCM.[12] In contrast to the broad intervention approach usually used in cardiology, the favourable results of this pivotal study highlight the benefits of disease-specific treatment for this condition.[12] Controlling obstruction and other structural aspects effectively in a noninvasive manner may postpone or avoid the need for surgery; this is currently being tested in a Phase III study, VALOR HCM.[16]

Dr Olivotto concluded: "EXPLORER-HCM shows that targeting aetiology with a precision medicine approach really pays off."

HOW DOES MAVACAMTEN DIFFER FROM CURRENT PHARMACOLOGICAL OPTIONS?

Dr Olivotto explained that established cardiac drugs, such as β-blockers, calcium antagonists, and anticoagulants, when used correctly, can be helpful in oHCM; however, rather than targeting the cause of disease, these therapies can help to manage symptoms, such as shortness of breath, palpitations, and chest pain, or complications, such as atrial fibrillation.

Dr Olivotto stated: "Mavacamten is a targeted drug that specifically inhibits cardiac myosin and is the closest possible treatment to gene therapy. It does not mend the gene, but it corrects the immediate consequences and pathophysiological cause of the disease. The beauty of this drug compared with other drugs available is the clean, precise action, with no effect on blood pressure and heart rate."

WHAT DOES THE TARGETED DRUG, MAVACAMTEN, MEAN FOR PATIENTS?

Dr Olivotto emphasised that the general well-being objectives of patients with chronic diseases sometimes differ greatly from those of physicians. Drug-related issues, such as poor digestion, prostate problems, and nocturnal palpitations, add up to a burden of disease that is hard to quantify in clinical practice and may be dismissed by physicians as not severe enough to be of concern or as not treatable.

Dr Olivotto highlighted: "Clearly, issues that are hard to quantify in clinical practice are core concerns for patients with chronic diseases such as oHCM. Patients wish to feel 100% well, rather than settling for 'just OK', and are looking for a drug that achieves this goal." Dr Olivotto's direct experience with mavacamten has been "quite rewarding" in this respect.

FUTURE PROSPECTS

The next steps for mavacamten in oHCM, outlined by Dr Olivotto, are to accrue long-term safety and efficacy data; establish the effects of the drug as monotherapy, which may be explored in an ongoing, long-term, safety extension study;[17] demonstrate the effects on natural history and outcome; and assess the impact on advanced disease.

Future research in other areas includes expanding understanding of how mavacamten works in nonobstructive disease and investigating whether this drug is useful in selected patients with HF with preserved ejection fraction, which accounts for approximately 50% of patients with HF,[18,19] for whom treatment is limited.[20]

Dr Olivotto concluded: "EXPLORER-HCM marks the first targeted drug for oHCM in Phase III and is the beginning of a new era. This study sets the stage for further studies looking at disease progression and early upstream treatment to prevent disease complications and change the natural history of the disease."

Biography

Dr Iacopo Olivotto

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Dr Iacopo Olivotto trained in Florence, Italy, and London, UK, and pursued a career firstly in emergency medicine and subsequently in cardiology at the Careggi University Hospital in Florence, Italy, where he currently serves as a staff physician. Dr Olivotto is the clinical co-ordinator of the Florence Referral Center for Cardiomyopathies.

Over the last two decades, Dr Olivotto's main clinical and research interests have included various aspects of cardiomyopathies, with special focus on HCM, ranging from clinical predictors of disease progression and outcome, arrhythmias, characterisation of the end-stage phase, medical and surgical management, imaging studies of coronary flow reserve with PET, functional and prognostic relevance of magnetic resonance studies, echocardiographic screening and early HCM diagnosis, studies of prehypertrophic phenotype, genetic studies addressing the prevalence and characterisation of HCM-causing mutations, genotype–phenotype correlations, family studies, developmental aspects of HCM, molecular studies of myofilament contractility, and correlation of *in vitro* findings with clinical and echocardiographic variables. These lines of research are being carried out in co-operation with a rapidly growing multidisciplinary team in Florence, as well as several distinguished institutions in Europe and the USA.

Dr Olivotto has been among the first in promoting randomised trials in cardiomyopathies based on translational approaches to the core pathophysiological mechanisms of disease. He has co-authored over 200 papers in peer-reviewed journals and serves as a reviewer for the main international cardiovascular journals. He is a founding member of the international Sarcomeric Human Cardiomyopathy Registry.

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