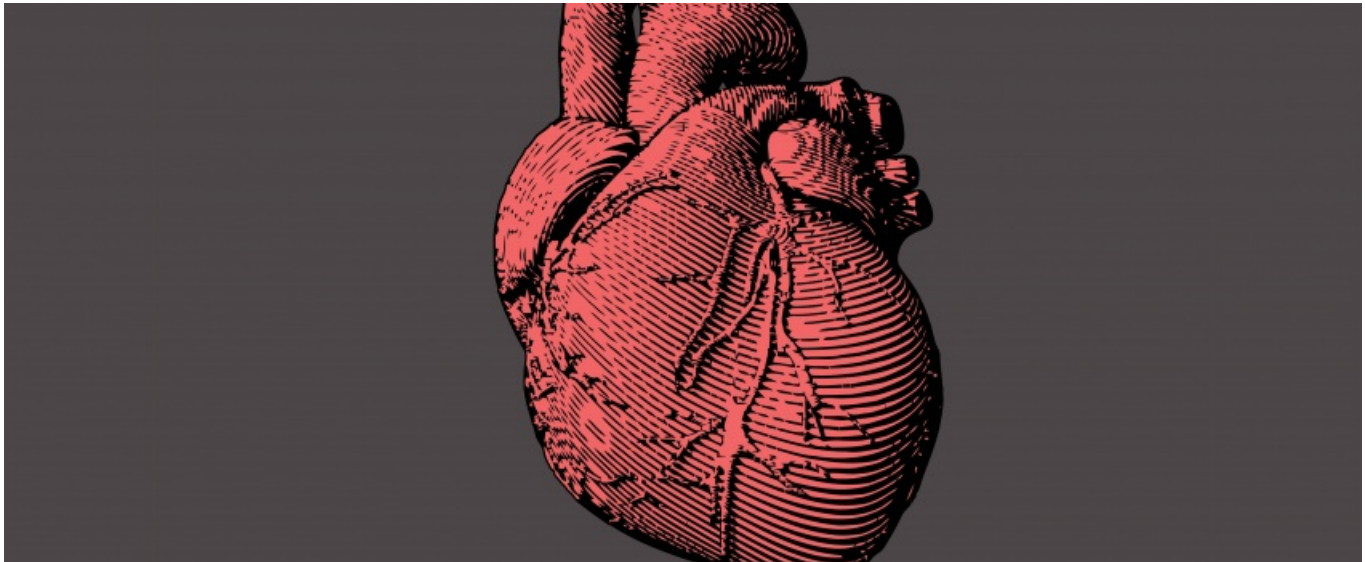


ESC 2020 - Myokardia odds-on for first approval in heart muscle disease



[Elizabeth Cairns](#)



Positive phase III data in hand, Myokardia heads to the FDA.

The pivotal Explorer-HCM trial of Myokardia's mavacamten was top-lined as a success in May, and now the magnitude of its benefit over placebo in patients with hypertrophic cardiomyopathy has been revealed. With twice as many responders in the treatment group as in the placebo arm Myokardia is well on track to submit an NDA at the beginning of next year.

The question for investors is whether the data are good enough not just for approval, but to hook a partner – or perhaps a buyer.

Hypertrophic cardiomyopathy is the most common genetic cardiovascular disease, affecting one in 500 people. Severe cases experience a progressive thickening of the heart muscles and consequent angina, heart failure, arrhythmia, syncope, or sudden cardiac death.

No therapies specifically for HCM exist; symptoms can be managed with generic drugs including beta blockers and blood thinners. Novartis's heart failure therapy Entresto is also used off-label. A cardiac myosin inhibitor, mavacamten could become the first therapy to treat the underlying cause of the disorder.

[Explorer-HCM](#) set mavacamten against placebo in 251 patients with symptomatic, obstructive HCM. Patients received an initial 5mg dose per day, with two opportunities, at week 12 and 28, to adjust the dose to between 2.5mg and 15mg based on drug plasma concentration measures of heart health.

Data presented at the virtual meeting of the European Society of Cardiology today showed that 37% of patients randomised to mavacamten responded, compared with 17% of the placebo recipients, a highly statistically significant finding.

Patients were deemed to have responded if they had met various measures of cardiac function, listed below.

All the secondary endpoints were met too, also with statistical significance.

Results

- Twice as many patients achieved the primary composite endpoint of clinical response in the mavacamten group vs the placebo group (37% vs. 17%)
- Mavacamten demonstrated significant improvement in all secondary endpoints compared with placebo:
 - ✓ Exercise capacity (pVO₂) improved
 - ✓ Symptoms assessed by physicians (NYHA class) improved
 - ✓ Obstruction of the LVOT gradient was reduced
 - ✓ Patient-reported outcome scores improved
- Mavacamten was well tolerated
 - ✓ Rates of treatment-emergent adverse events (87.8% vs 78.9%), serious adverse events (8.1% vs 8.6%), and serious cardiac adverse events (3.3% vs 3.1%) were comparable for patients treated with mavacamten and placebo

	Mavacamten (N = 123)	Placebo (N = 128)	Difference (95% CI)* P value
Primary endpoint			
EITHER ≥1.5 mL/kg/min increase in pVO ₂ with ≥1 NYHA class improvement OR ≥3.0 mL/kg/min increase in pVO ₂ with no worsening of NYHA class, n (%)	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1) 0.0005
Secondary endpoints†			
Post-exercise LVOT gradient, n	117	122	
Change from baseline to week 30, mm Hg, mean ± SD	-47 ± 40	-10 ± 30	-36 (-43.2, -28.1) <0.0001
pVO₂, n	120	125	
Change from baseline to week 30, mL/kg/min, mean ± SD	1.40 ± 3.1	-0.05 ± 3.0	1.35 (0.58, 2.12) 0.0006
≥1 NYHA class improvement, n	123	128	
Improvement from baseline to week 30, n (%)	80 (65.0)	40 (31.3)	34 (22.2, 45.4) <0.0001
KCCQ-CSS, n	92	88	
Change from baseline to week 30, mean ± SD	13.6 ± 14.4	4.2 ± 13.7	9.1 (5.5, 12.7) <0.0001
HCM5Q-SoB, n	85	86	
Change from baseline to week 30, mean ± SD	-2.8 ± 2.7	-0.9 ± 2.4	-1.8 (-2.4, -1.2) <0.0001

*Model estimated least-square mean differences were reported for continuous variables.
 †N = number analyzable for secondary end point based on availability of both baseline and week 30 values.
 HCM5Q-SoB, HCM 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; pVO₂, peak oxygen consumption.

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Source: Professor Iacopo Olivotto and the European Society of Cardiology.

Explorerer-HCM threw up no safety concerns either, with rates of treatment-emergent adverse events and serious cardiac adverse events being similar in the two arms – the rate of serious adverse events was numerically higher with placebo.

Presenting the data, Professor Iacopo Olivotto of Careggi University Hospital in Florence said the Explorerer-HCM results “provide evidence to support mavacamten as the first potential disease-specific, targeted treatment for obstructive HCM”.

Over to the FDA, then. Without approved therapies available for comparison it is tricky to predict mavacamten’s chances of regulatory success, and it is possible that a drug that only helps 37% of patients will not be considered good enough. But that possibility seems fairly remote. Mavacamten has breakthrough status, suggesting that the FDA is on board with the trial design, and HCM is a clear unmet need.

Mavacamten is the most advanced project in development for HCM by some way. There is an ongoing academic phase II trial, [SilicoFCM](#), comparing Entresto with lifestyle management; perhaps Novartis could glom onto the results of this to seek label expansion into HCM. But the pharma giant has said nothing about doing so, and in any case phase III trials would presumably be necessary.

Otherwise there is only Celltrion’s CT-G20, in a [24-patient phase I trial](#) versus placebo. Its primary outcome measure is the adverse event rate after 12 days of administration, and data could come in early 2021.

So if the FDA plays ball, Myokardia will have the HCM niche all to itself for some time. And with analysts forecasting blockbuster sales – \$1.9bn in 2026 according to sellside consensus compiled by *EvaluatePharma* – Myokardia might be able to attract a partner. The company is partnered with LianBio for China, but since Myokardia’s partnership with Sanofi ended in January 2019 rights in the US and Europe are up for grabs.

As for a buyer, the group’s stock [doubled in price when the top-line hit was revealed](#), and Myokardia now has a market cap in excess of \$5bn. The opportunity for a bigger player to bag a bargain might have passed.

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