Health Status Benefits of Mavacamten in Patients with Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results from the Explorer-HCM Randomized Clinical Trial

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On behalf of the EXPLORER-HCM investigators

AMERICAN COLLEGE of CARDIOLOGY

Disclosures

- Presenting author
  - Consultant for Abbott, Amgen, Bayer, Janssen Pharmaceuticals, Merck & Co., MyoKardia Inc., Novartis, UnitedHealthcare
  - Grant Support from Abbott Vascular
  - Copyright to the SAQ, KCCQ and PAQ
  - Member, Board of Directors Blue Cross Blue Shield of Kansas City

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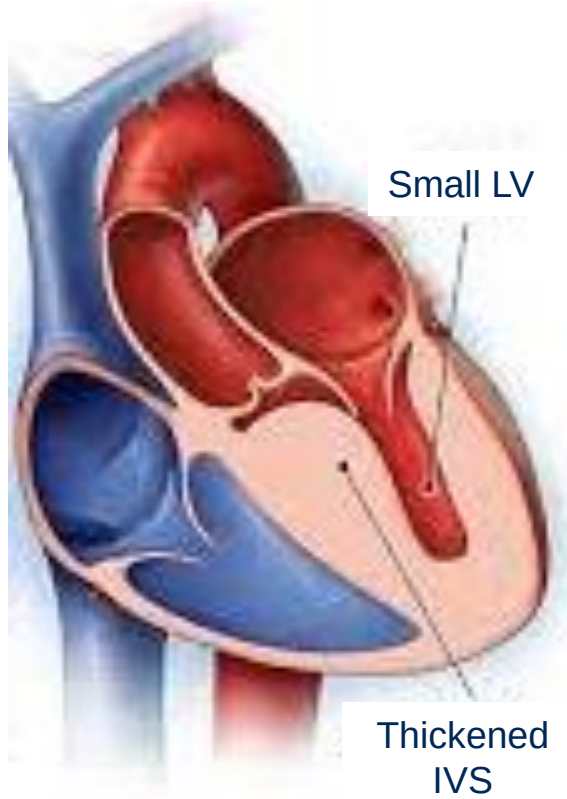
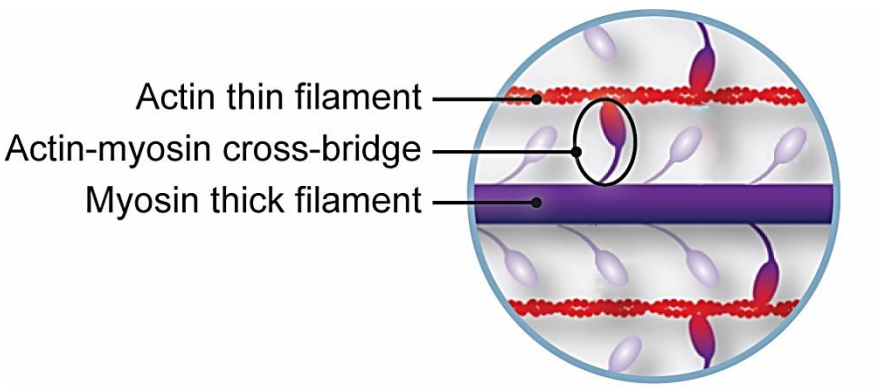
Background

- Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder
  - Unexplained left ventricular (LV) hypertrophy
  - Often caused by pathogenic variants in sarcomeric genes
- A primary treatment goal is to improve symptoms and function
  - Current therapies include beta-blockers, verapamil, disopyramide
  - Invasive options are considered for refractory symptoms
- Mavacamten decreases contractile function & improves peak VO_2,[1] but its impact on patients' health status –symptoms, function and quality of life – is incompletely understood



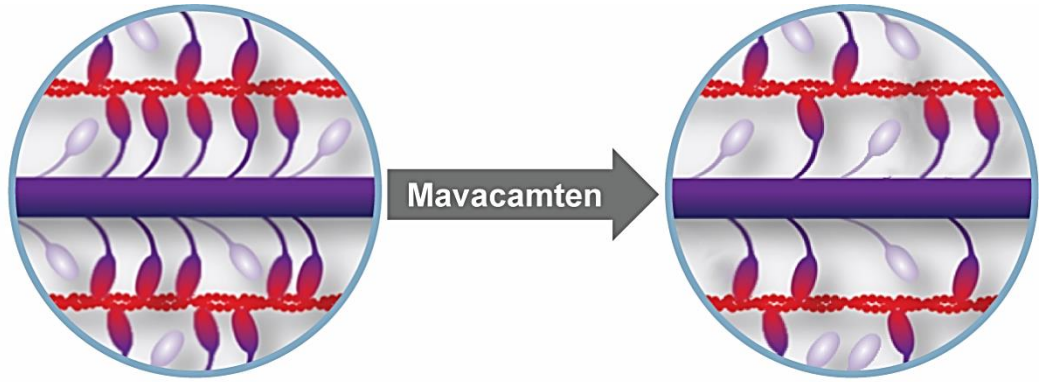
1. Olivotto I *et al. Lancet*. 2020;12(396):759–69

Mavacamten: Mechanism of Action



Normal Sarcomere

Normal contractility
Effective relaxation



HCM Sarcomere

HCM Pathophysiology
Hypercontractility
Impaired relaxation
Altered myocardial energetics

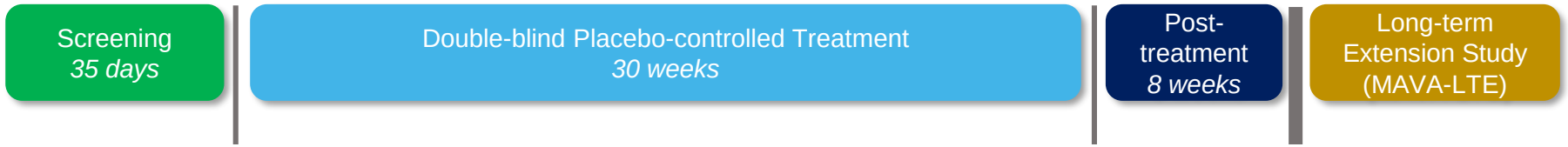
HCM Sarcomere with Mavacamten

Attenuated hypercontractility
Improved compliance
Improved energetics

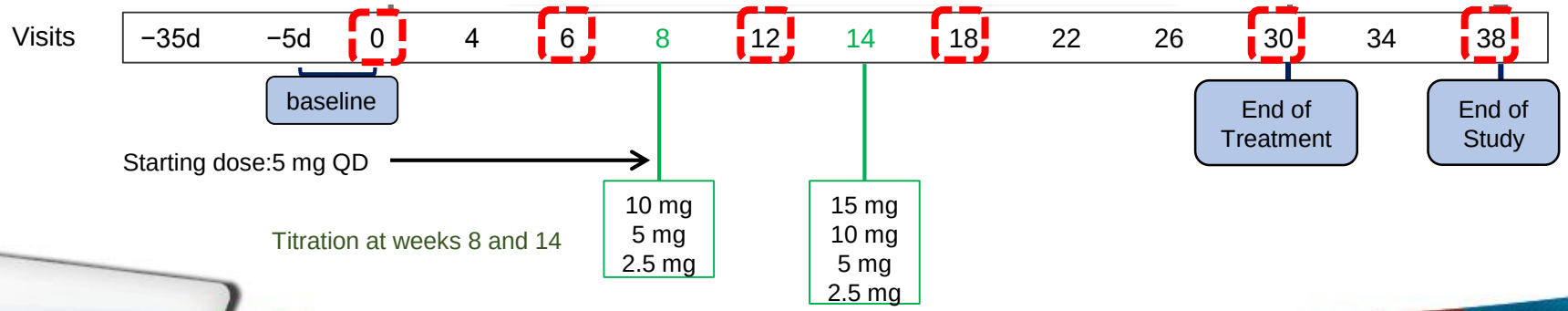
Mavacamten is a targeted inhibitor of cardiac myosin that reduces the number of myosin-actin cross-bridges and decreases contractility

EXPLORER-HCM Study Design
Pivotal Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial in Patients with Obstructive HCM[1]

Patients with LVOT gradient ≥50 mmHg and New York Heart Association (NYHA) class II-III symptoms were randomized 1:1 to receive once-daily oral mavacamten (starting dose of 5 mg with a 2-step dose titration) or placebo for 30 weeks



Quality of Life Assessed with the Kansas City Cardiomyopathy Questionnaire



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1. Ho CY *et al. Circ Heart Fail*. 2020;13(6):e006853

Quantifying Patients' Health Status

- Kansas City Cardiomyopathy Questionnaire
  - 23-item disease-specific questionnaire quantifying
    - Symptoms
    - Physical Function
    - Social Function
    - Quality of Life

    Clinical Summary Score

    Overall Summary Score
  - Range = 0-100, with higher scores indicating fewer symptoms, better function/QoL
  - 5-, 10- and 20-point changes = small, mod-large and large-very large changes[1–3]
  - Cognitive interviews confirmed relevance and understandability of the KCCQ to patients with oHCM
  - Extensive analyses of missing data suggested no biases

1. SpertusJS *et al. Am Heart J* 2005; 150:707-15 . 2. Pokharel Y *et al. JAMA Cardiol* 2017;2(12):1315–1321. 3. Kosiborod M *et al. Circulation* 2007;115(15):1975–81

Methods

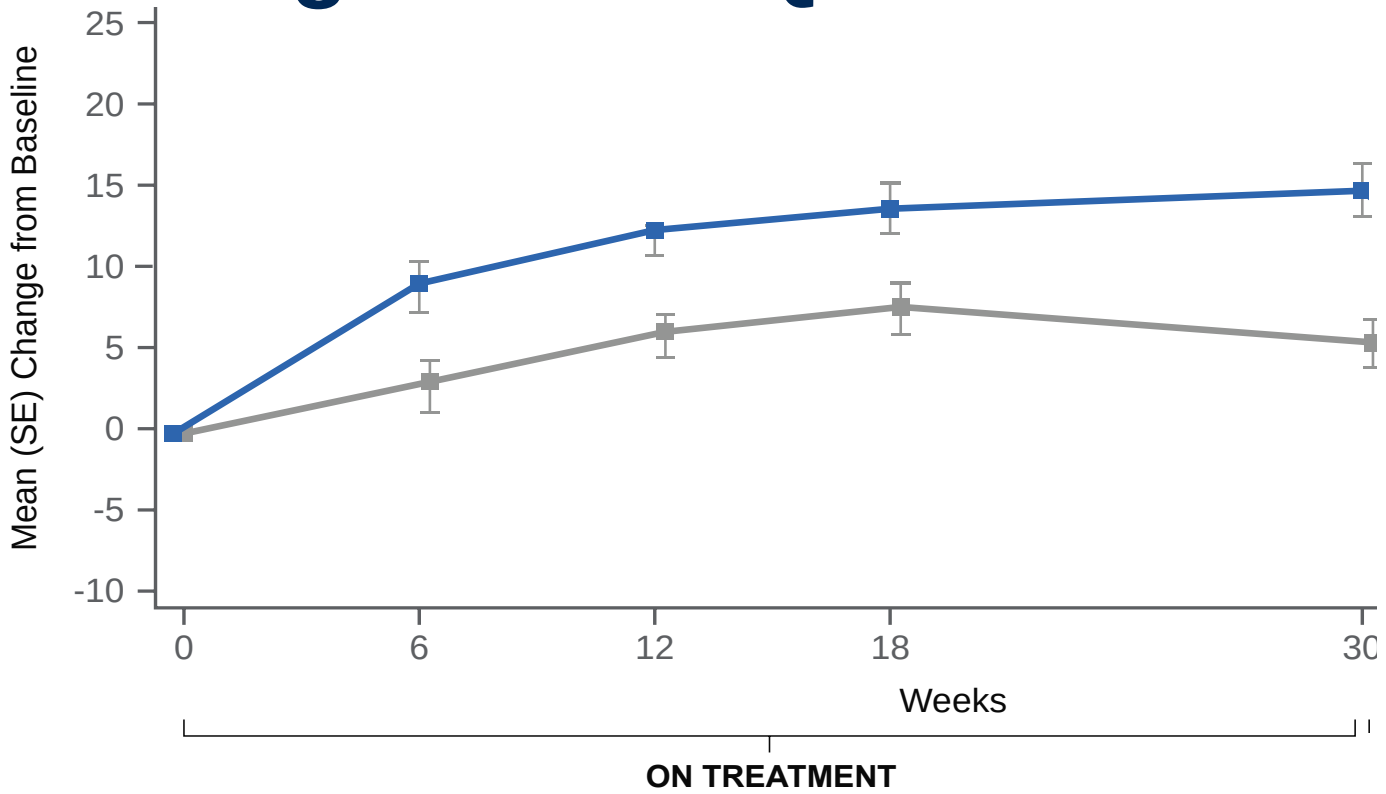
- Changes from baseline KCCQ scores plotted (means±SE) over time
- Comparisons performed using mixed model repeated measures analyses with primary outcome the differences at 30 weeks
  - Fixed effects: treatment, baseline KCCQ and variables used in stratification
    - NYHA Class, beta blocker use, planned ergometer type
  - Interaction between Treatment and Time
- Responder analyses to inform the observed mean differences
  - Worsened (≤-5 points)
  - Unchanged (-5 to <5 points)
  - Small Improvement (5 to <10 points)
  - Moderate to Large Improvement (10 to <20 points)
  - Large to Very Large Improvement (≥20 points)

Demographics and Baseline Characteristics

	Mavacamten (N=98)	Placebo (N=96)
Age, years	57.8 ± 12.7	58.2 ± 11.6
Male, n (%)	56 (57.1)	62 (64.6)
Beta-blocker users, n (%)	79 (80.6)	69 (71.9)
Calcium channel blocker users, n (%)	16 (16.3)	15 (15.6)
pVO2, mL/kg/min	19.3 ± 5.1	19.9 ± 5.1
NYHA class, n (%)		
Class II	70 (71.4)	71 (74.0)
Class III	28 (28.6)	25 (26.0)
KCCQ Overall Summary score	67.2 ± 17.2	65.7 ± 19.6
KCCQ Clinical Summary score	70.9 ± 16.3	70.3 ± 19.0

Data are mean ± standard deviation.

Mean change in KCCQ-Overall Summary Score

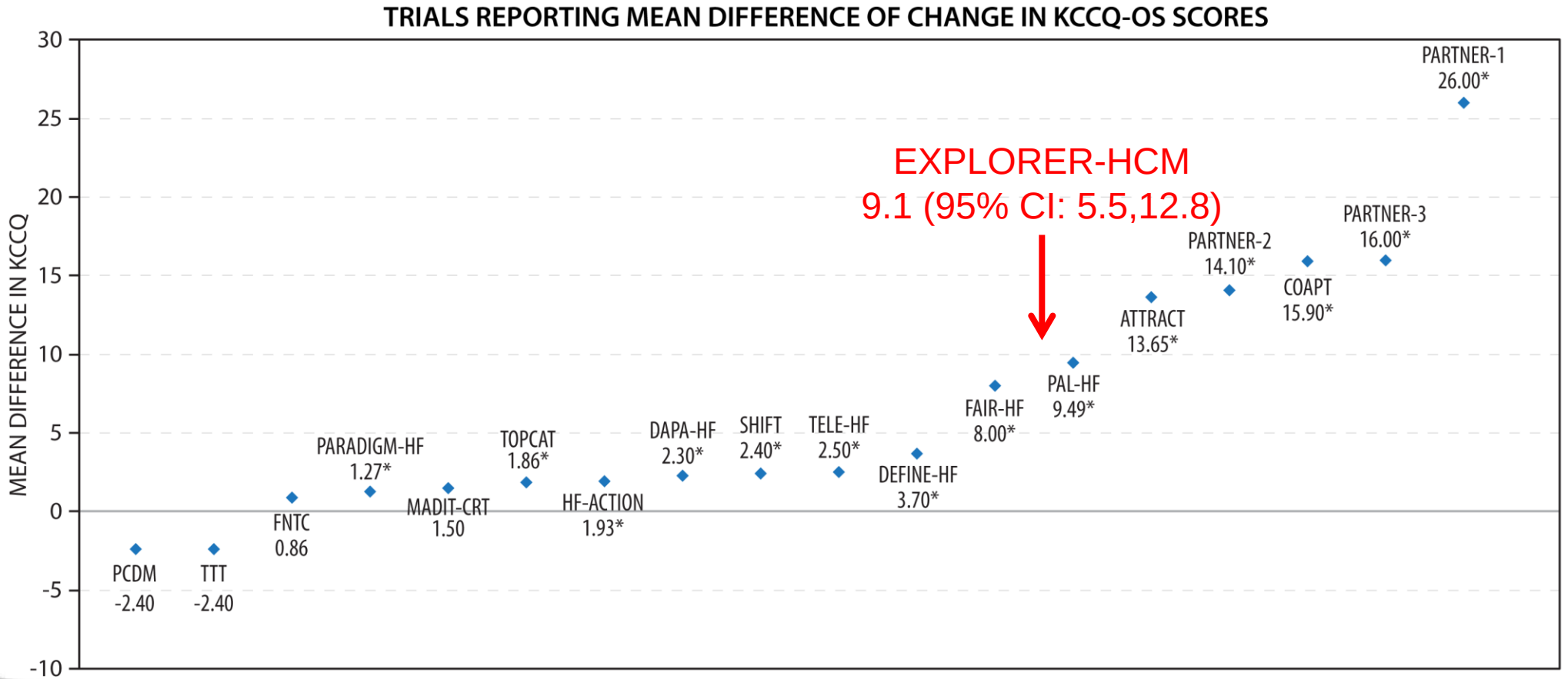


Difference in KCCQ-OS = +9.1 (95% CI: 5.5,12.8)

Number of Subjects with Non-Missing Data per W eek

Mavacamten	98	89	90	90	92
Placebo	96	82	91	93	88

Amongst Largest Mean KCCQ-OS Differences of any Medication



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Responder Analyses to Support Interpretation[1]

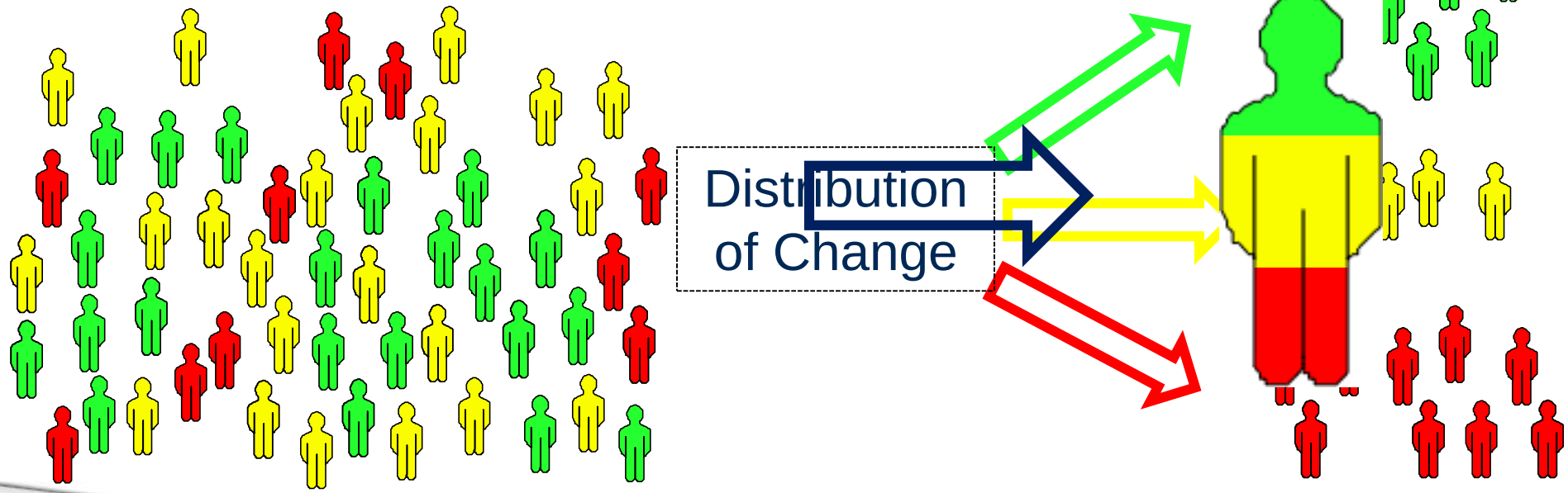
= Marked Improvement

= Minimal Change

= Marked Deterioration

Outcomes from a Study

Mean Treatment Difference



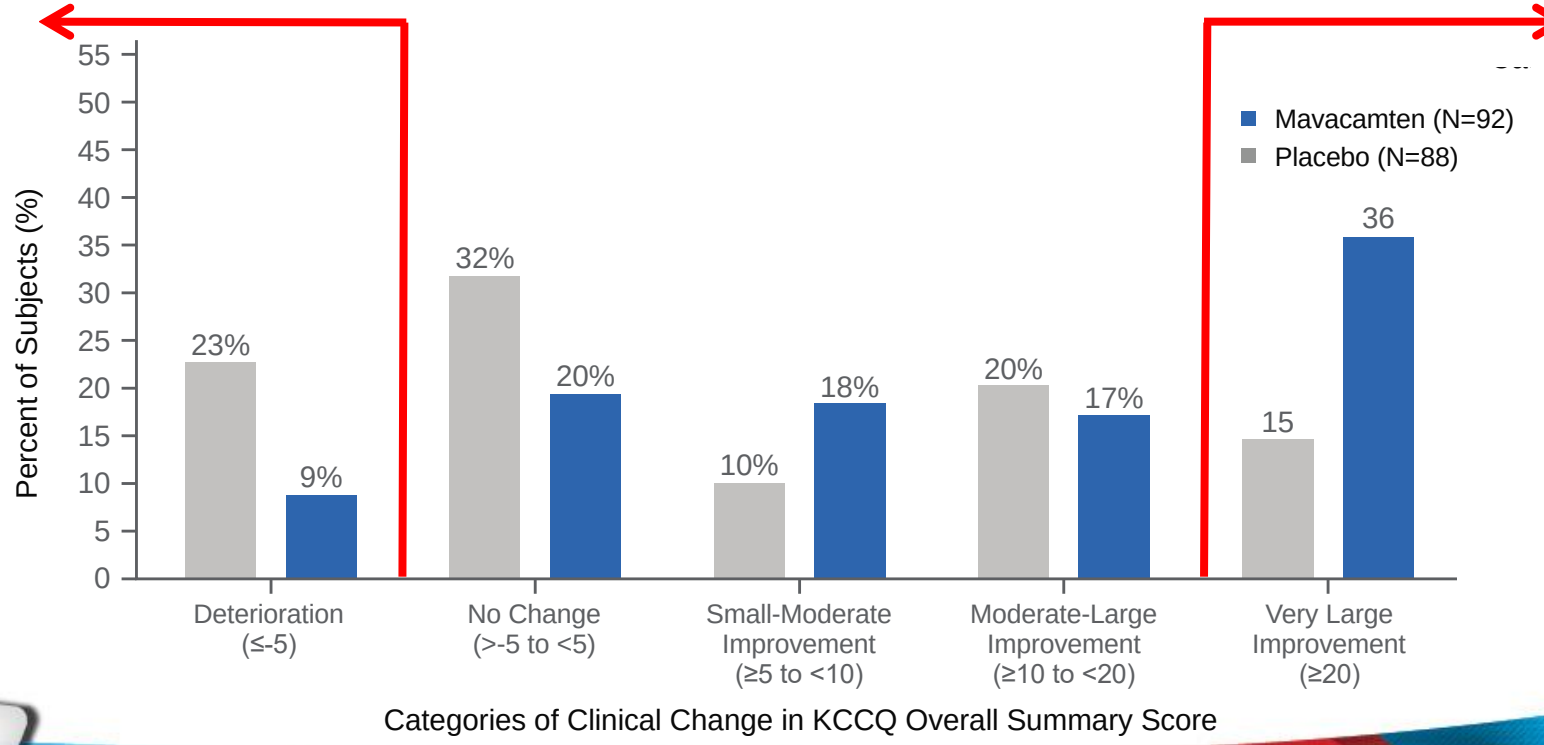
Spertus et al. J Am Coll Cardiol. 2020;76(20):2379–90.

Percentage of Participants Who Changed by Clinically Important Amounts at 30 Weeks

- A greater proportion of patients taking mavacamten achieved a very large clinically meaningful improvement in the KCCQ (≥20-point) compared to placebo
- A greater proportion of patients in the placebo arm had no change or deterioration in their health status at Week 30

23% vs.9%
NNT = ~7

36% vs.15%
NNT = ~5



Limitations

- 28% of patients missing either baseline or follow-up KCCQ data
  - Extensive analyses suggest no observable biases
- EXPLORER-HCM included patients with hemodynamically significant oHCM
  - Whether comparable benefits would be observed in other patient HCM populations requires additional study
- Longer term studies are needed to understand longer-term outcomes

Conclusions

- Mavacamten is associated with substantial health status improvements in patients with symptomatic oHCM
  - NNT for a large-to-very large improvement = ~5
- Benefits are observed early after treatment
- Benefits regress with treatment withdrawal
- Illuminating the benefits to patients can inform discussions on the use of mavacamten for oHCM

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Fellow co-authors:

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Especially, the patients and their families

Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

John A Spertus, Jennifer T Fine, Perry Elliott, Carolyn Y Ho, Iacopo Olivotto, Sara Saberi, Wanying Li, Chantal Dolan, Matthew Reaney, Amy J Sehnert, Daniel Jacoby

Summary

Background Improving symptoms is a primary treatment goal in patients with obstructive hypertrophic cardiomyopathy. Currently available pharmacological options for hypertrophic cardiomyopathy are not disease-specific and are often inadequate or poorly tolerated. We aimed to assess the effect of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status—ie, symptoms, physical and social function, and quality of life.

Methods We did a health status analysis of EXPLORER-HCM, a phase 3, double-blind, randomised, placebo-controlled trial. The study took place at 68 clinical cardiovascular centres in 13 countries. Adult patients (≥18 years) with symptomatic obstructive hypertrophic cardiomyopathy (gradient ≥50 mm Hg and New York Heart Association class II–III) were randomly assigned (1:1) to mavacamten or placebo for 30 weeks, followed by an 8-week washout period. Both patients and staff were masked to study treatment. The primary outcome for this secondary analysis was the Kansas City Cardiomyopathy Questionnaire (KCCQ), a well validated disease-specific measure of patients' health status. It was administered at baseline and weeks 6, 12, 18, 30 (end of treatment), and 38 (end of study). Changes from baseline to week 30 in KCCQ overall summary (OS) score and all subscales were analysed using mixed model repeated measures. This study is registered with ClinicalTrials.gov, NCT03470545.

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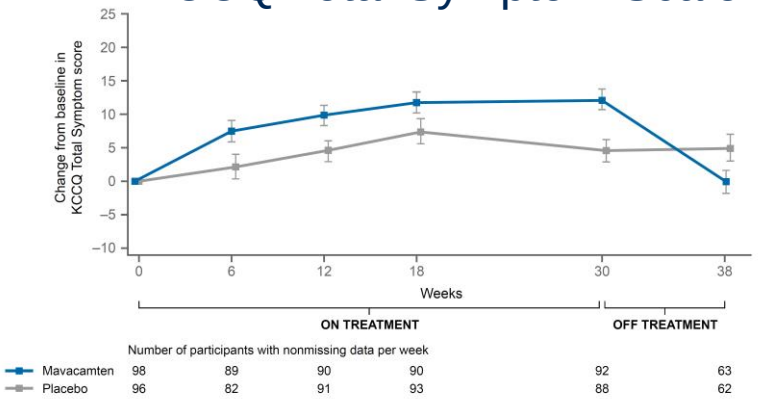
Backup Slides/Alternatives

Change from baseline overtime in KCCQ scales

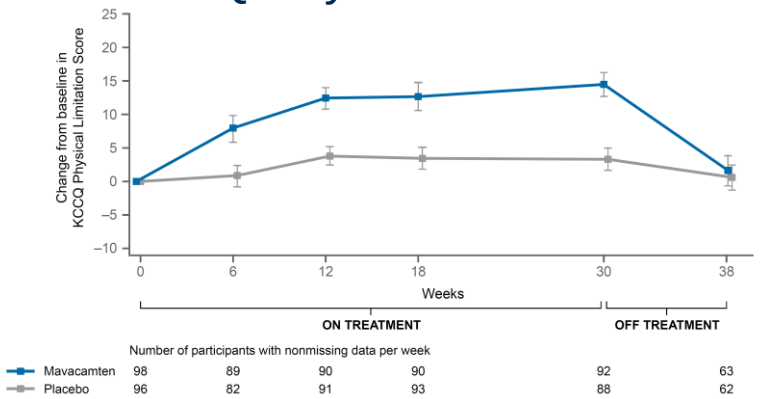
A

KCCQ Total Symptom Scale



B

KCCQ Physical Limitation Scale



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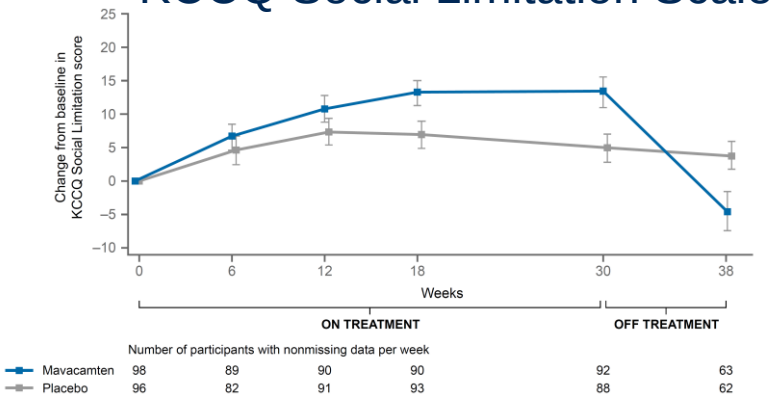
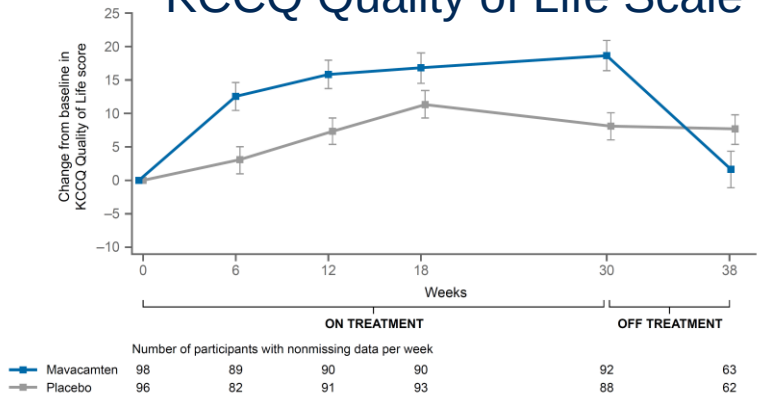
KCCQ Social Limitation Scale



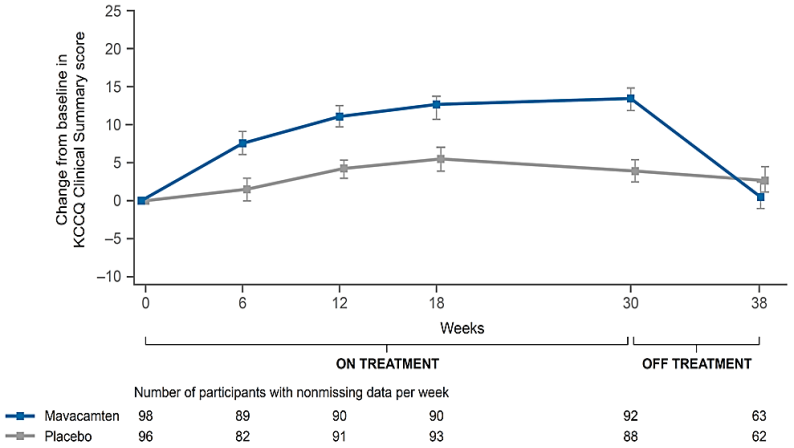
D

KCCQ Quality of Life Scale



E

KCCQ Clinical Summary Scale



Responder Analyses for KCCQ scales from baseline to Week 30