Mavacamten in sarcomeric HCM: a new approach

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Disclosures

EXPLORER-HCM

Study Investigators

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- MYK- 005-EXPLORER
- MYK-007-MAVA-LATE (LATE)
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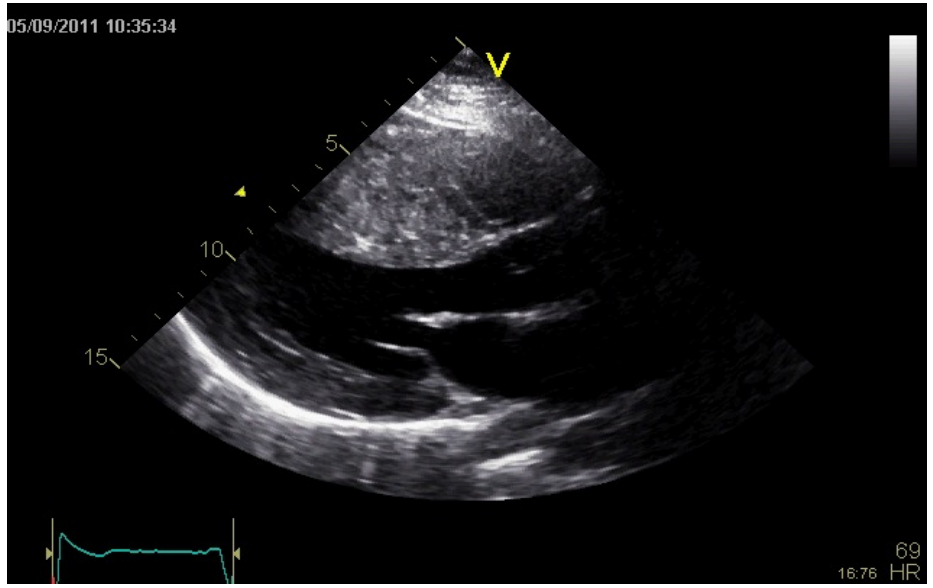
HCM

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder

- Unexplained left ventricular (LV) hypertrophy
- Often caused by pathogenic variants in sarcomeric genes

~ 1/3 non-obstructive HCM

~ 2/3 obstructive HCM



No targeted pharmacologic therapies

-Current medical therapies include beta-blockers, non-dihydropyridine CA, dysopiramide, :[1-2]

- Focus on symptomatic relief
- Obstruction/AF/ HF

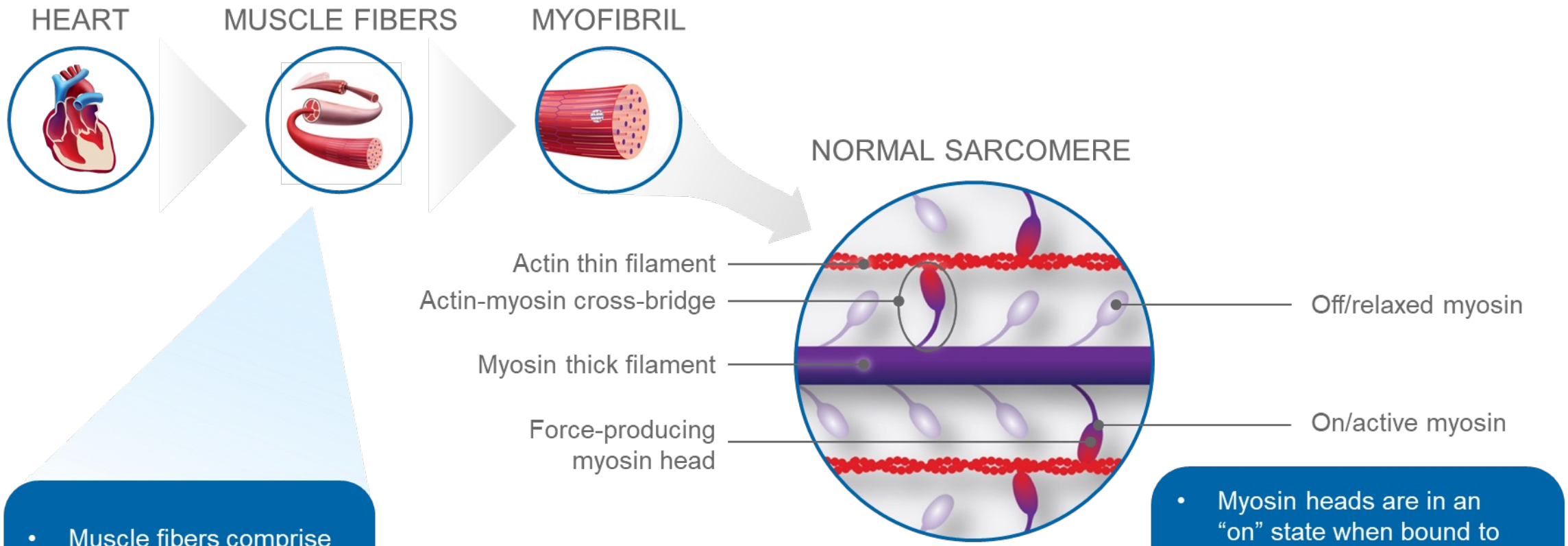
[1]Elliot PM. *Eur Heart J.* 2014;35(39): 2733-2779.
[2]Gersh BJ. *Circulation.* 2011;124(24):2761-2796.

HCM : new medical approaches

Targeted medical treatment that can modify the natural history of the disease an unmet need

- Modulation of myocardial energetics (perhexiline, trimetazidine)
- Inhibition of late- sodium channels (ranolazine and eleclazine)
- Reduction of fibrosis (spironolactone, valsartan, losartan)
- **Myosin inhibitors ?**

Normal myocardial contractility : the role of myosin heads



- Muscle fibers comprise myofibrils, which in turn are composed of bundles of sarcomeres

- Myosin heads are in an "on" state when bound to actin
- Active myosin heads produce the force with which sarcomeres contract

Libby P et al. Braunwald's Heart Disease. 11th ed. 2018.

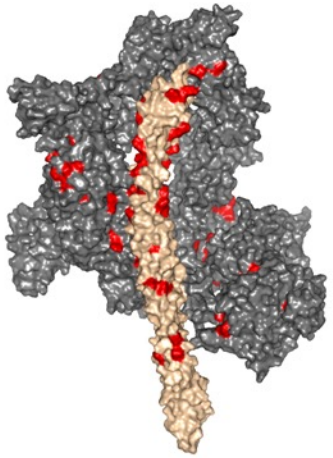
Myosin in sarcomeric HCM

In a healthy heart, 40-50% of myosins are in an "off" state

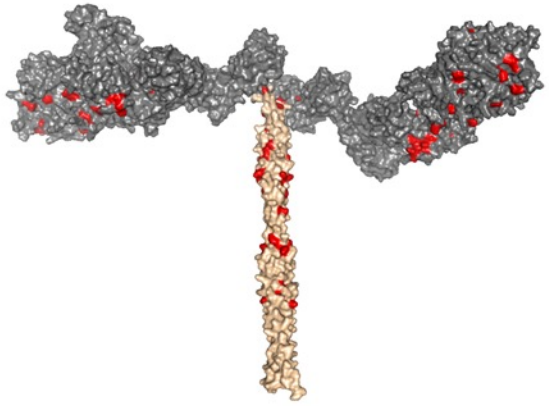
Normals: 50-60% myosins " "on"

In HCM, many mutations destabilize this state, and 15-20% of myosins are in an "off" state

HCM: 80-85% myosins "on"



"Off" state
No contraction

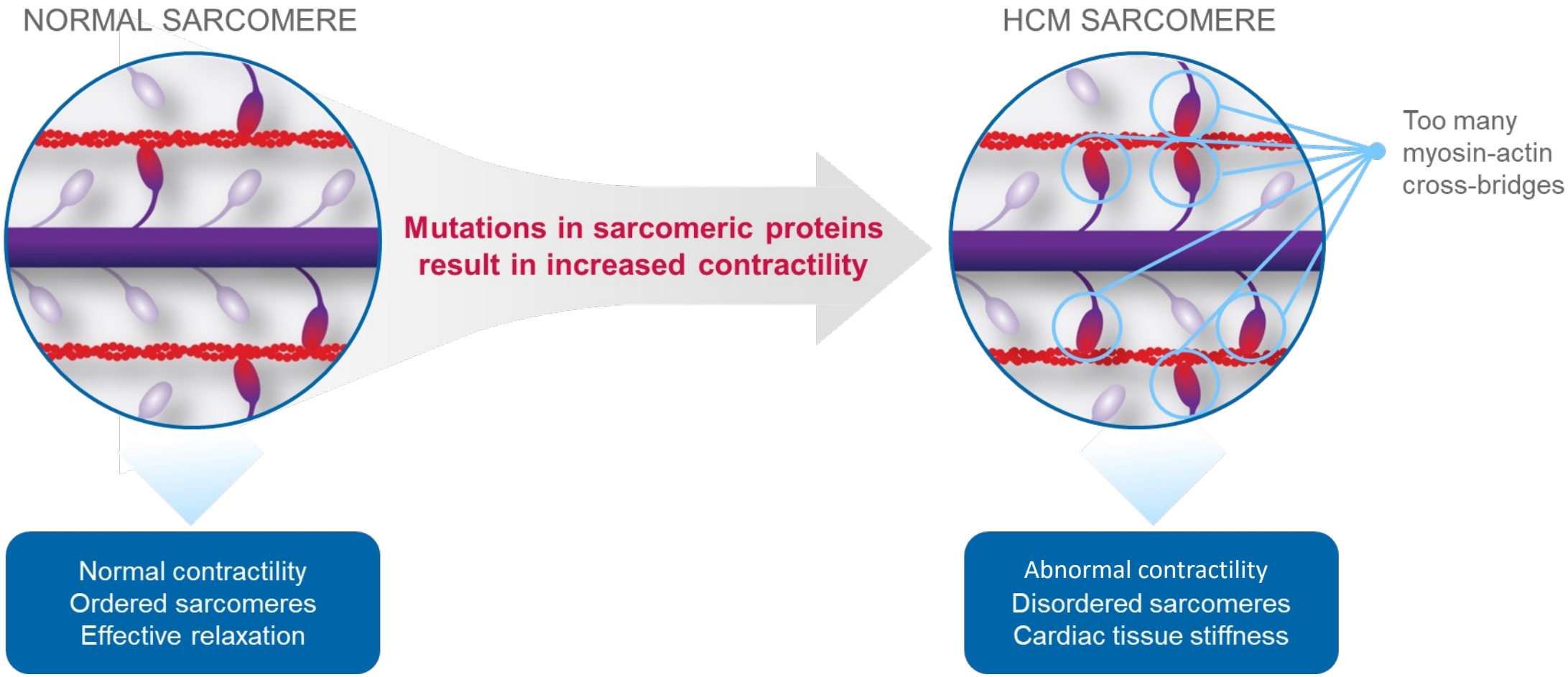


"On" state
Able to contract

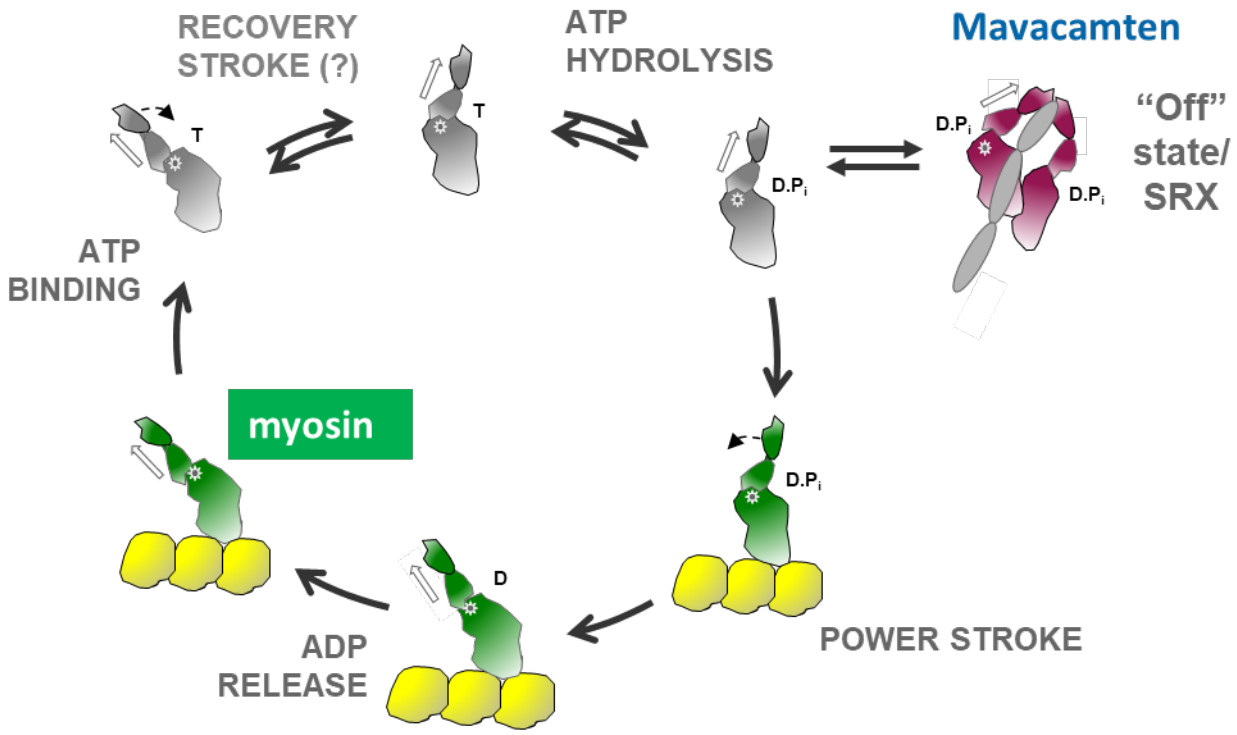
Too many myosins in the "on" state in HCM are thought to engage **too many cross-bridges** leading to **excess contractility** and **impaired relaxation**

Alamo L et al. eLife 6, e24634. 2017. Trivedi DV et al. Biophys Rev 110, 27-48. 2018.
Anderson RL et al. Proc Natl Acad Sci U S A 115:E8143-E8152. 2018.

HCM a sarcomeric disease



MYK-461, Mavacamten : a “targeted molecular approach” drug



- Sarcomere power output is the product of ensemble force generated by myosin heads and their velocity of movement along actin filaments
- In principle, either component of sarcomere power output could be a target for modulation, and agents that can reduce ensemble force generation can reduce power
- **Mavacamten was identified through a chemical screen for molecules that reduced the maximal actin-activated ATPase rate of myosin in bovine myofibrils**
- **Selective for cardiac myosin (nos skeletical muscle effects)**

Sarcomeric mutations destabilize the low energy super-relaxed state of cardiac myosin and promote excessive cross bridging with actin➔ High energy utilization, disordered relaxation,” hypercontractile” state

Metabolismo hepático, eliminação renal e fecal

SRX super relaxed state

Adapted from Trivedi DV et al. Annu Rev Biochem 2019.

Mavacamten and Myosin

Electron microscopy images of myosin

"On" state consumes energy

"Off" state energy-sparing

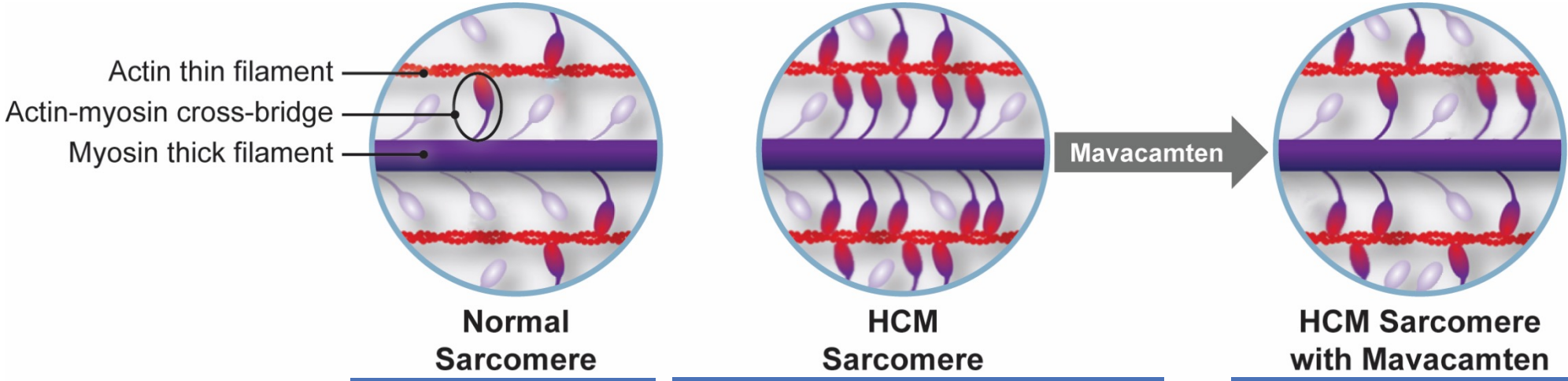
"myosin inhibitor"

Mavacamten is small molecule, selective allosteric inhibitor of cardiac myosin that brings cardiac myosin to natural state by reducing excessive contractility and improving left ventricular (LV) compliance:

- **Mavacamten reversibly binds to cardiac myosin to restore the population of myosin heads in the "off" state, thereby reducing the excess cross-bridges and normalizing ATP consumption**
- In addition, mavacamten can repopulate the "super-relaxed" state (SRX) of myosin, restoring cardiac reserve

Green EM et al. Science 351:617-621. 2016.
Anderson RL et al. Proc Natl Acad Sci U S A 115:E8143-E8152. 2018.

Mavacamten: Mechanism of Action



Normal Sarcomere

Normal contractility
Effective relaxation

HCM Sarcomere

HCM Pathophysiology
"Hypercontractility"
Impaired relaxation
Altered myocardial energetics

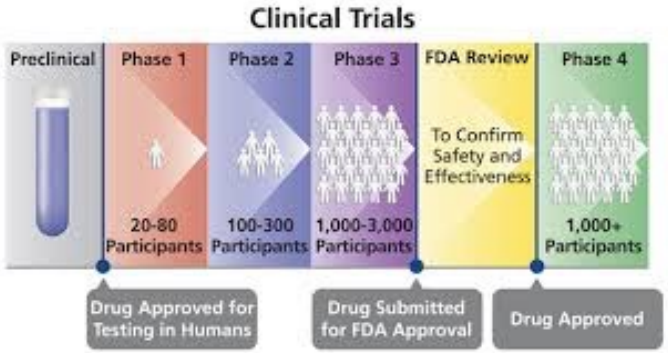
HCM Sarcomere with Mavacamten

Attenuated hypercontractility
?Improved relaxation
?Improved energetics

Mavacamten is a first-in-class, selective allosteric inhibitor of cardiac myosin

→ **Reduces the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM**

Mavacamten: clinical trials



Stage of Development	Phase 1	Phase 2	Phase 3	Phase 4
End Point	Safety	Efficacy	Efficacy	Efficacy
Specific End Point	Safety Profile	Cardiac Output	Reduction in Mortality Rate	Reduction in Mortality Rate
Types of Studies	Different Indications; Single or Multiple Dose	Placebo Controlled; Dose Escalation	Placebo Controlled; Long Term Follow Up	Comparative; New Indications

- ✓ **Preclinical**
- ✓ **Phase 1**-safety, tolerability, dosing strategy
- ✓ **Phase 2**- **Pioneer-HCM** open label, non-randomized target therapeutic range 350-700 ng/ml, 12 week, symptoms, gradient reduction, independent of betablockers, dose related reversible EF reduction (> 695 <1500 ng/ml,
  Pionneer-ole (open label extension)

Non-obstructive HCM → **MAVERICK-HCM Study**

- ✓ **Phase 3**

Obstructive HCM → **EXPLORER-HCM Study**

The MAVERICK-HCM Study
Safety and Efficacy of Mavacamten in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy

J Am Coll Cardiol. 2020 Jun 2;75(21):2649-2660. doi: 10.1016/j.jacc.2020.03.064.

Evaluation of Mavacamten in Symptomatic Patients With Nonobstructive Hypertrophic Cardiomyopathy

Carolyn Y Ho [1], Matthew E Mealiffe [2], Richard G Bach [3], Mondira Bhattacharya [2], Lubna Choudhury [4], Jay M Edelberg [2], Sheila M Hegde [5], Daniel Jacoby [6], Neal K Lakdawala [5], Steven J Lester [7], Yanfei Ma [2], Ali J Marian [8], Sherif F Nagueh [9], Anjali Owens [10], Florian Rader [11], Sara Saberi [12], Amy J Sehnert [2], Mark V Sherrid [13], Scott D Solomon [6], Andrew Wang [14], Omar Wever-Pinzon [15], Timothy C Wong [16], Stephen B Heitner [17]

MAVERICK-HCM:
Phase 2, placebo-controlled, dose-ranging study in non-obstructive HCM
16 weeks 40 HCM (19-21), 19 placebo

Primary objective: Safety and Tolerability

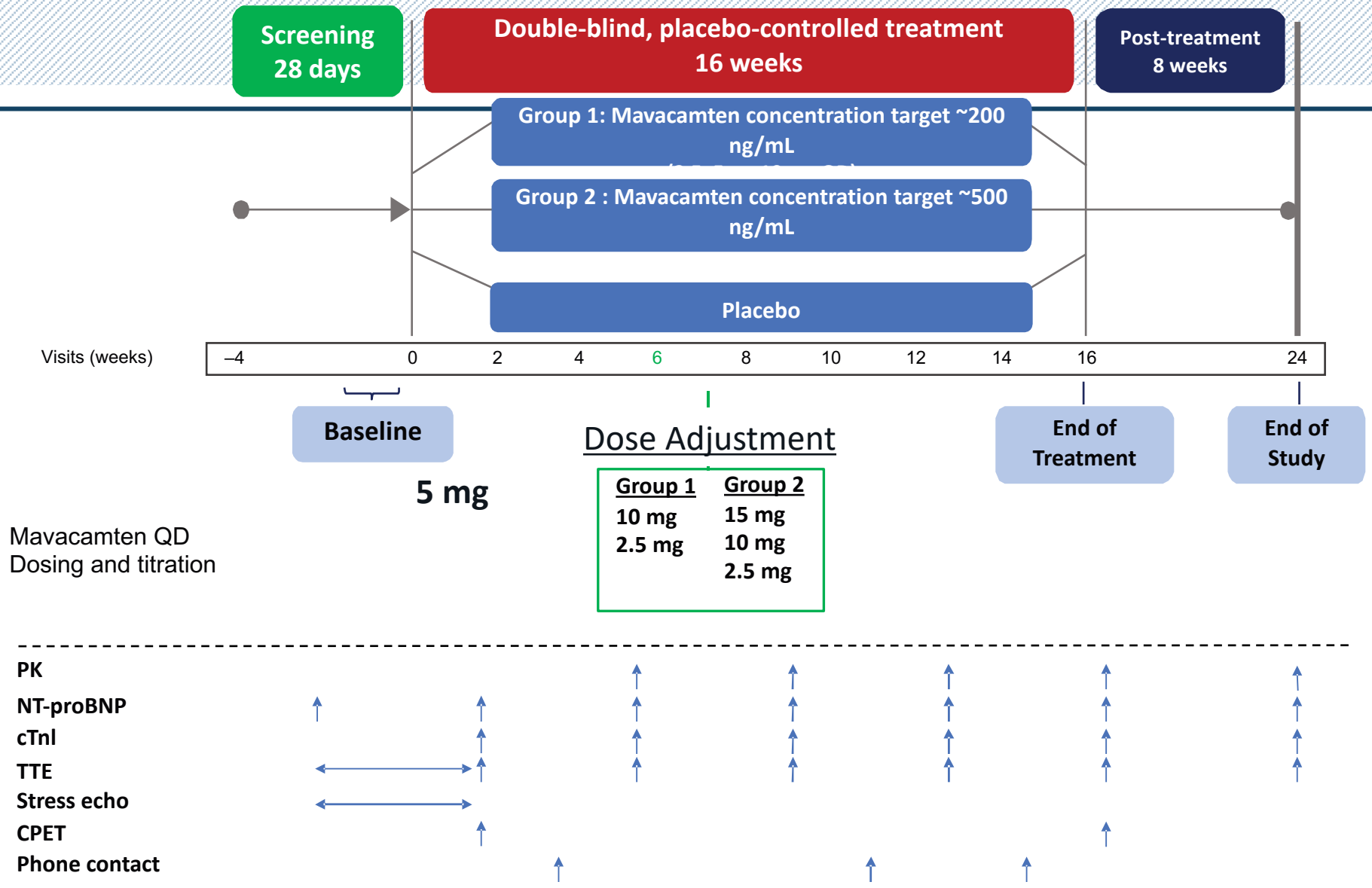
Key safety endpoint:

- Frequency and severity of treatment-emergent AEs (TEAEs), AEs of special interest, and SAEs

Exploratory Efficacy Objectives

- Change from baseline to Week 16 in:
  - N-terminal pro b-type natriuretic peptide (NT-proBNP)
  - Peak oxygen uptake (pVO_2) measured by cardiopulmonary exercise testing (CPET)
  - New York Heart Association (NYHA) Functional Class
  - Echocardiographic measures of LVEF and parameters of diastolic function (E/e')
  - Composite functional endpoint:
    1) ≥1.5 mL/kg/min increase in pVO_2 and ≥1 NYHA Class improvement; **OR**
    2) ≥ 3.0 mL/kg/min increase in pVO_2 with no worsening in NYHA Class

MAVERICK Study Design



Stopping Criteria: LVEF ≤45%, plasma drug concentration ≥1000 ng/mL, or Fridericia-corrected QT interval (QTcF) ≥500 ms

MAVERICK-HCM Summary

Mavacamten was **well tolerated** in most participants with non-obstructive HCM
No excess of serious adverse events
LVEF decreased 4 % (SD 8) in the pooled mavacamten group versus 2.3 % (SD 5) in placebo.

5 of 40 mavacamten participants (12.5%) had reversible reductions in LVEF<45% leading to protocol-driven treatment discontinuation.
LVEF recovered within 4-12 weeks.

Treatment with mavacamten resulted in **a dose-dependent reduction in serum levels of NT-proBNP and cTnI** suggesting physiological benefit.

Exploratory analyses suggest that patients with more severe disease expression (baseline elevated cTnI or E/e') may benefit more from mavacamten therapy

Biomarkers and clinical parameters will inform dosing strategies in future studies.
Results set the groundwork for future, larger scale studies in nHCM and potentially in HFpEF.

EXPLORER-HCM

The EXPLORER-HCM Study
Efficacy and Safety of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

The largest HCM randomized clinical trial

ESC 2020-Clinical Trials – Hot Lines presentations August 29th

Circulation: Heart Failure

METHODS PAPER

Study Design and Rationale of EXPLORER-HCM

Evaluation of Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy

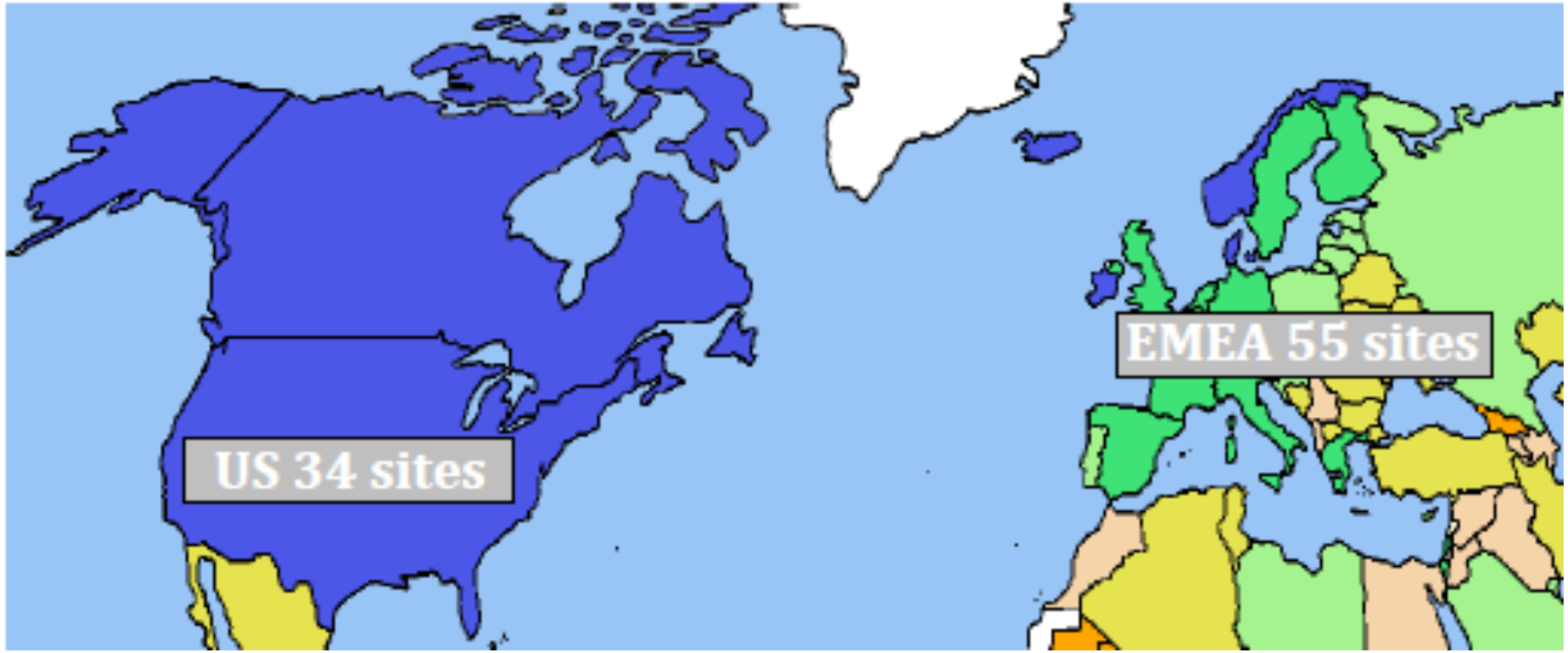
Carolyn Y. Ho, MD*; Iacopo Olivotto, MD*; Daniel Jacoby, MD; Steven J. Lester, MD; Matthew Roe, MD; Andrew Wang, MD; Cynthia Burstein Waldman, JD; David Zhang, PhD; Amy J. Sehnert, MD; Stephen B. Heitner, MD

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

*Iacopo Olivotto, Artur Oreziak, Roberto Barriales-Villa, Theodore P Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, Neal K Lakdawala, Matthew T Wheeler, Anjali Owens, Milos Kubanek, Wojciech Wojakowski, Morten K Jensen, Juan Gimeno-Blanes, Kia Afshar, Jonathan Myers, Sheila M Hegde, Scott D Solomon, Amy J Sehnert, David Zhang, Wanying Li, Mondira Bhattacharya, Jay M Edelberg, Cynthia Burstein Waldman, Steven J Lester, Andrew Wang, Carolyn Y Ho, Daniel Jacoby, on behalf of EXPLORER-HCM study investigators**

Lancet 2020

EXPLORER-HCM Study



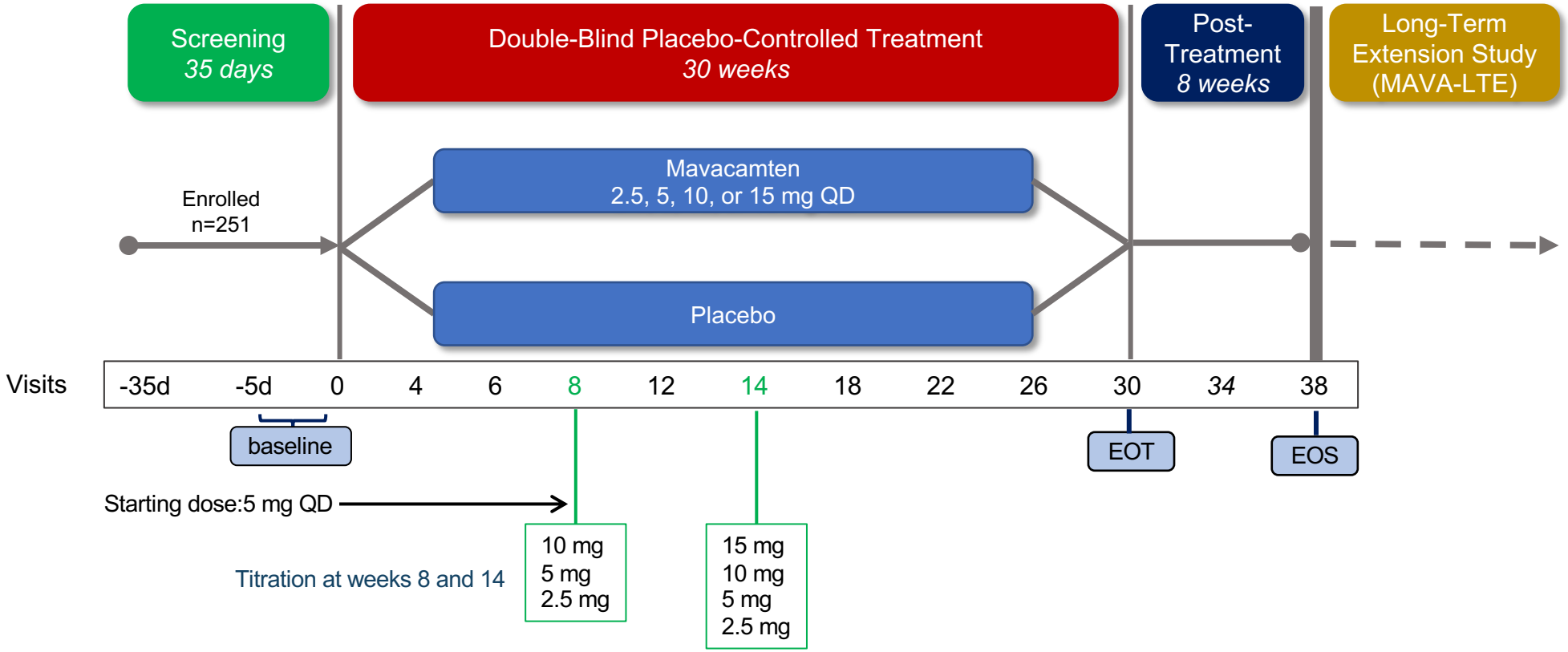
68 centers, 13 countries , 251 p (USA 43%, Europe 57%)
Portugal 7p 2,8 % (H Luz-3; HGO-4)
Real world HCM: age 58 (129, BB 75%
123 Mavacamten, 128 placebo, on top of BB, CA, 30 weeks

EXPLORER-HCM Study Design

EXPLORER-HCM

Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial in Patients With Obstructive HCM

HOCM with LVOT gradient ≥ 50 mmHg and NYHA class II (2/3)-III symptoms randomized 1:1 to receive once-daily oral mavacamten (starting dose of 5 mg, 2-step dose titration to achieve gradient without LV dysfunction with 350-700 ng/ml) or placebo for 30 weeks



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

EXPLORER-HCM Endpoints

EXPLORER-HCM

Primary composite functional endpoint

Change from baseline to Week 30		pVO_2		NYHA Classification
EITHER	**Composite 1**	≥1.5 mL/kg/min	***and***	Reduction of ≥1 class
OR	**Composite 2**	≥3.0 mL/kg/min	***and***	No worsening

Secondary endpoints included change from baseline to Week 30 in:

- Post-exercise LVOT gradient
- VO_2 max
- Proportion of patients with ≥1 NYHA class improvement
- Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS)
- HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore

Results-Primary Endpoint

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Difference (95% CI) P value
≥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	45 (36.6) *	22 (17.2)	19.4 (8.7, 30.1) 0.0005
BOTH ≥3.0 ml/kg/min increase in pVO_2 **AND** ≥1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.0, 21.0) 0.0005*

Secondary Endpoints

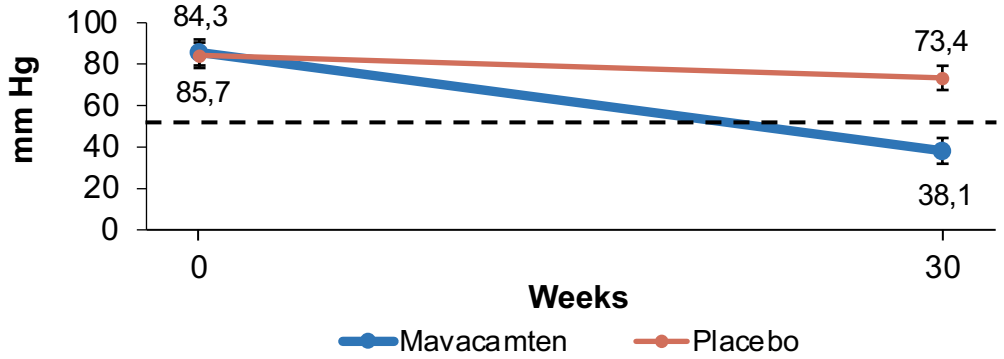
	Mavacamten	Placebo	Difference* (95% CI) P value
Post-exercise LVOT gradient, n†	117	122	
Change from baseline to week 30, mmHg, mean ± SD	–47 ± 40	–10 ± 30	–36 (–43.2, –28.1) <0.0001
pVO_2, n†	120	125	
Change from baseline to week 30, ml/kg/min, mean ± SD	1.40 ± 3.1	–0.05 ± 3.0	1.35 (0.58, 2.12) 0.0006
≥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
HCMSQ-SoB, n†	85	86	
Change from baseline to week 30, mean ± SD	–2.8 ± 2.7	–0.9 ± 2.4	–1.8 (–2.4 to –1.2) <0.0001

*Model estimated least-square mean differences were reported for continuous variables. †N = number analyzable for secondary end point based on N availability of both baseline and week 30 values.
HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore; Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS); LVOT, left ventricular outflow tract;

LVOT Gradients (rapid and sustained) and LVEF Over Ti

EXPLORER-HCM

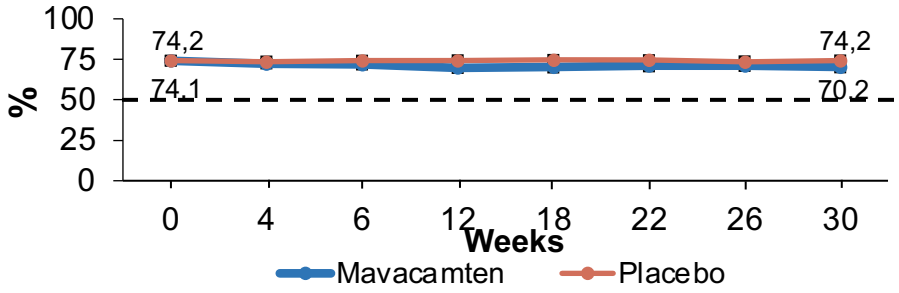
Mean (95% CI) post-exercise LVOT gradient



Number of patients at visit

Mavacamten	122		118
Placebo	127		123

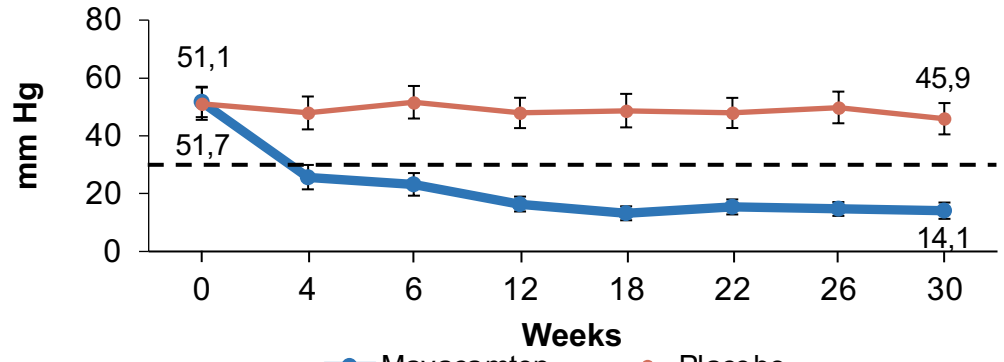
Mean (95% CI) LVEF



Number of patients at visit

Mavacamten	123	116	115	111	111	107	113	114
Placebo	128	115	117	120	119	121	121	119

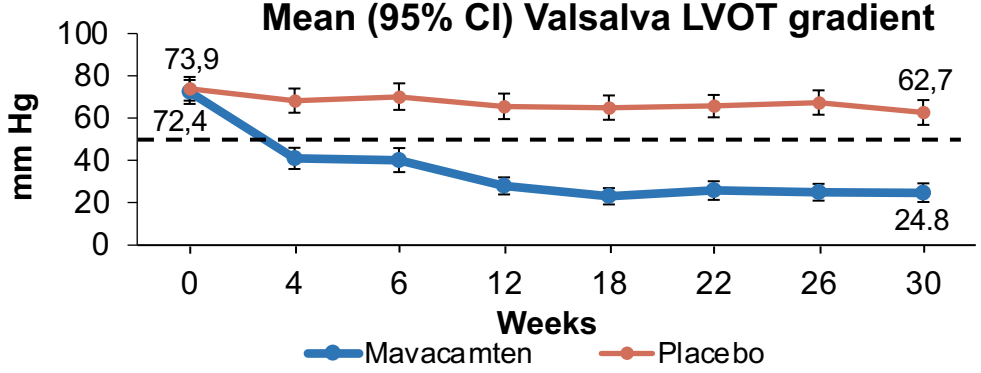
Mean (95% CI) resting LVOT gradient



Number of patients at visit

Mavacamten	123	119	119	118	116	118	120	117
Placebo	128	121	122	125	122	125	125	123

Mean (95% CI) Valsalva LVOT gradient



Number of patients at visit

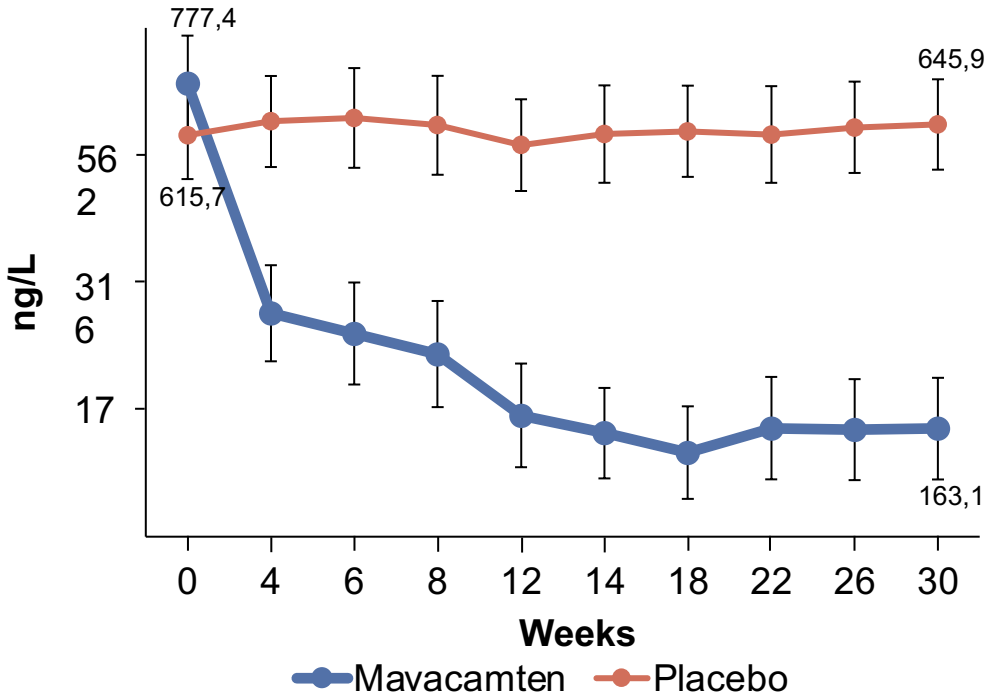
Mavacamten	123	117	118	118	116	118	120	117
Placebo	128	119	119	125	122	125	124	124

The dashed lines represent the threshold for guideline-based invasive intervention (post-exercise and Valsalva LVOT gradient >50 mm Hg), the threshold for guideline-based diagnosis of obstruction (resting LVOT gradient <30 mm Hg), or the protocol threshold for temporary discontinuation (LVEF <50%).

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

Cardiac Biomarkers over time (rapid and sustained)

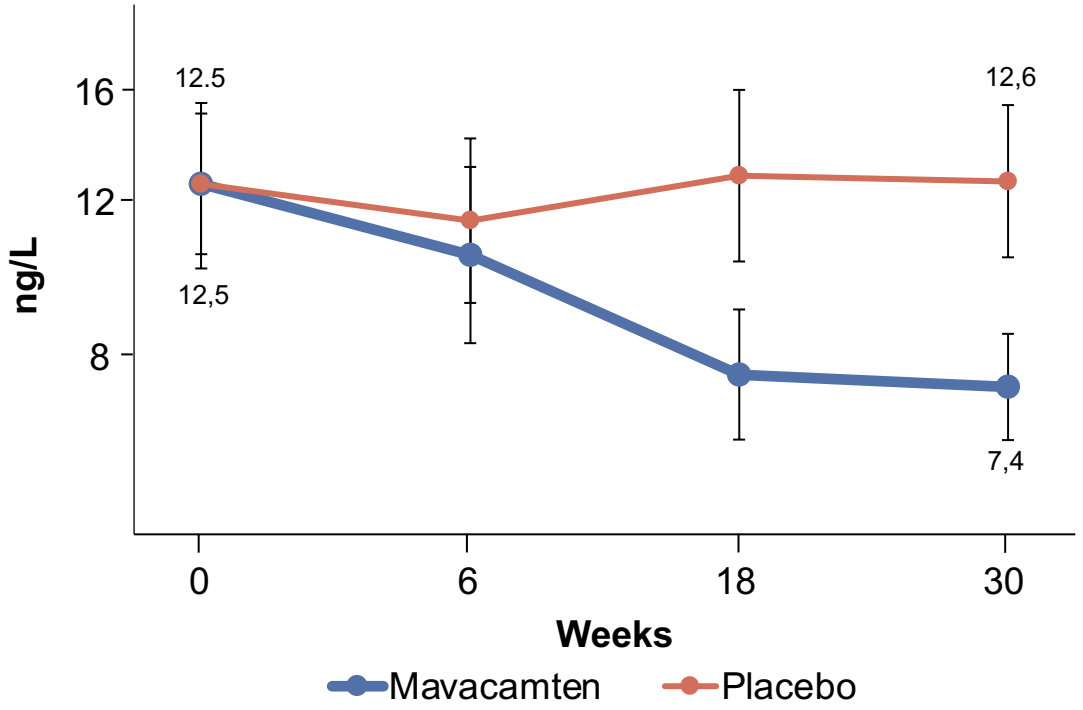
Geometric mean (95% CI) NT-proBNP



Number of patients at visit

Mavacamten	120	115	114	115	114	109	115	115	117	119
Placebo	126	118	112	119	116	117	124	121	120	123

Geometric mean (95% CI) hs-cTnI



Number of patients at visit

Mavacamten	120	86	102	115
Placebo	119	84	104	115

hs-cTnI, high-sensitivity cardiac troponin; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Summary of Safety through Week 30 (Treatment Period)

Adverse events Preferred term	Mavacamten (N = 123)	Placebo (N = 128)
Patients with ≥1 TEAEs, n (%)	108 (87.8)	101 (78.9)
Total number of SAEs	11	20
Patients with ≥1 SAE, n (%)	10 (8.1)	11 (8.6)
Atrial fibrillation	2 (1.6)	4 (3.1)
Syncope	2 (1.6)	1 (0.8)
Stress cardiomyopathy	2 (1.6)	0
Cardiac failure congestive	0	1 (0.8)
Sudden death	0	1 (0.8)

- **97% completion rate** through 30 weeks of treatment
- **Only 3 patients discontinued (due to AEs)**: 2 on mavacamten (AF, syncope), 1 on placebo (SCD)
- **➔No patients withdrew due to reduced LVEF or symptoms of heart failure**

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Protocol-Driven Temporary Discontinuations

- **Temporary discontinuation** for LVEF <50% occurred in 5 patients in the treatment period (3 on mavacamten, 2 on placebo)
- 4 additional patients on mavacamten had LVEF <50% at week 30 (end-of-treatment)
  - LVEF recovered to baseline in 3 patients by the end of the 8-week washout
  - The fourth patient experienced a procedural complication and severe LVEF drop following an ablation for atrial fibrillation during the washout period

All patients resumed treatment and completed the study

LVEF, left ventricular ejection fraction; QTcF, QT interval corrected using Fridericia's formula

EXPLORER HCM highlights

- Independent of genotype

- **37% of mavacamten treated patients achieved the primary endpoint** with statistical significance and clinically beneficial effects, representing a **doubling of response vs. 17% seen in placebo** (difference +19.4%; 95% CI, 8.7 to 30.1; p=0.0005). This primary endpoint was designed to specifically demonstrate benefit in both symptoms via NYHA Class and function based on pVO_2 by CPET.
- **65% of mavacamten patients improved by one NYHA class or more**, more than double the placebo rate (31%); p<0.0001.
- **Nearly 75% of patients reduced their LVOT gradient to <50 mmHg**, which is below guideline recommended criteria for invasive intervention (exploratory endpoint: 74% mavacamten vs 21% placebo).
- **27% of patients on mavacamten** (32 patients) **achieved NYHA Class I status (no symptoms) and regression of LVOT obstruction (ALL gradients <30 mmHg)** vs. <1% on placebo (1 patient). (exploratory endpoint)

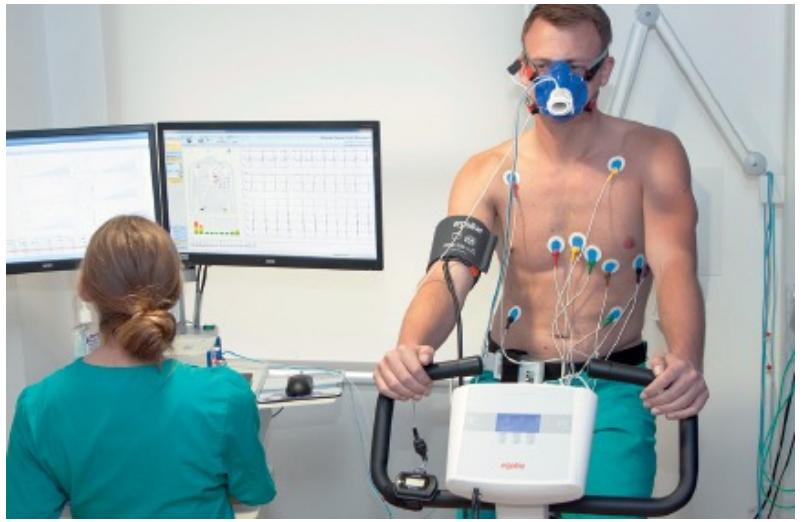
*Primary endpoint achieved mostly in patients without BB (>65), reflecting the negative effect of BB on CPET VO2max
More striking mavacamten effect because on BB?
VE/CO2:CPET parameter heart rate independent➔ Mavacamten >>>> placebo

EXPLORER HCM highlights

- **Reduction from baseline in NT-proBNP was 80% greater with mavacamten** than with placebo, and a **41% greater reduction in hs-cTnI** was seen with mavacamten as compared to placebo (exploratory endpoint).

The mean LVEF change in mavacamten was -4% compared to baseline (normalizing hypercontractility) and was expected based on mavacamten mechanism of action (placebo was essentially unchanged).

- **SCD** speculative: 2ndary to < LVOTO? Direct effect on the arrythmic milieu beyond gradient reduction (Maverick-Young non obstructive HMC with high TT and BNP? (Maverick)
  No differences in NSVT/SVT vs placebo



Conclusions

EXPLORER-HCM

EXPLORER-HCM trial demonstrated efficacy of mavacamten in obstructive HCM.
All primary & secondary endpoints met with high statistical significance ($p<0.0006$)

Mavacamten demonstrated clinically important effects on post-exercise LVOT gradients. Nearly 75% of patients saw a reduction below guideline-defined thresholds for invasive SRT and 56% showed complete relief of obstruction.

Mavacamten demonstrated marked improvements in NYHA class, exercise performance, and key aspects of health status, and were accompanied by reductions in serum NT-proBNP and troponin I levels.

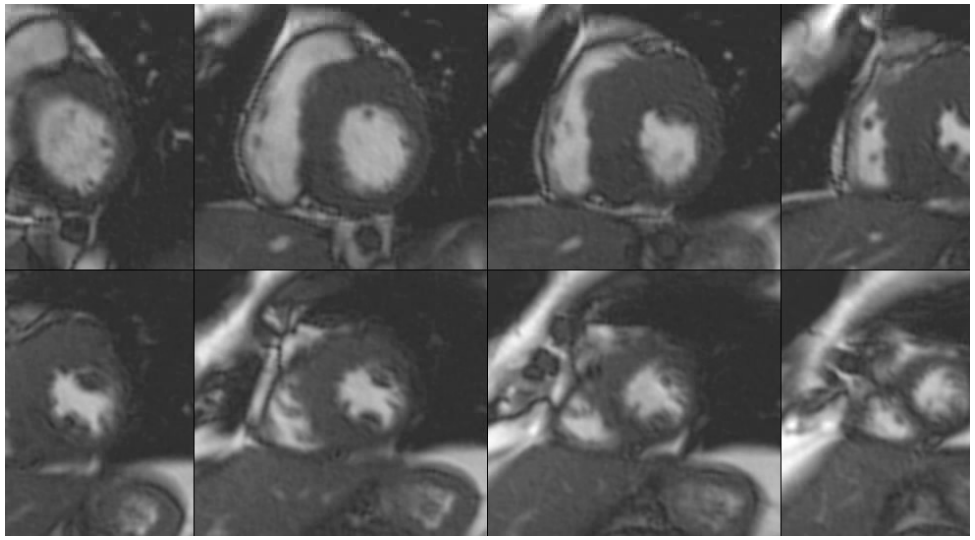
Mavacamten was well tolerated with a safety profile comparable to placebo.

EXPLORER CMR substudy

assessment of mass, structure and function

38 subjects from Explorer (17 mavacamten, 18 placebo)

CMR at Day 1 and Week 30 → Core lab Brigham and Women's Hospital

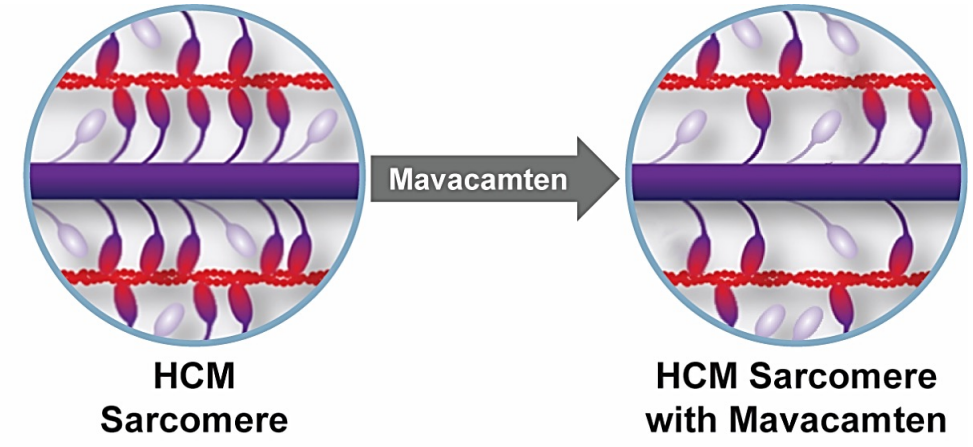


Primary CMR efficacy endpoint: change baseline to Week 30 in LV mass index

Exploratory CMR endpoints: fibrosis, LV wall thickness, LA volumes & function, LV function

Mavacamten : a personal view

- ✓Safe (no HR, BP effect, LVEF➔ dosage titration)
- ✓Effective (over BB and CA)
- ✓Portugal- 2 centers, 7 patients
- ✓Easy to “guess” Mavacamten or placebo
- ✓Needs:



-Long term AE/sAE ➔**MAVA-LTE (**active treatment), till 2025) long term adverse effects, possible withdrawal BB/CA

-> non-responders data

-- no NYHA IV, no dysopiramide, “old population”…

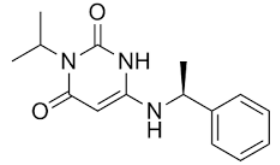
- Survival impact

- on top of BB/CA or alone? (synergistic effect or not?)

- Comparison ASA and myectomy➔**Valor-HCM** study (Mavacamten *vs* ASA) :US, Aug 20

Conclusions: mavacamten in the pipeline..

- To be registered as the first targeted therapy in obstructive HCM



- US: Mavacamten was granted ”breakthrough therapy” designation by the FDA (priority review), on track to regulatory submission in the first quarter of 2021

FDA

- Europe: discussions with the EMA and regulatory submission for marketing approval in the EU shortly thereafter

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