Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1.

VALOR HCM Trial Leadership

Cleveland Clinic Coordinating Center for Clinical Research (C5Research): Steven E. Nissen MD (Executive Committee Chairman), Milind Y. Desai MD (Study Principal Investigator), Kathy Wolski MPH (Lead Statistician), Christina Sewell BSN (Lead Project Manager), Ellen McErlean MSN (Manager, Project and Site Management), Tammy Gamble (Project Specialist)

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C5Research Stats: Kathy Wolski MPH (Lead Statistician), Qiuqing Wang (statistician), Craig Balog (statistical programming support).

Medpace Contract Research Organization: Dr. Richard Lee (Medical Monitor), James Creager (Clinical Trial Manager), Brian Knauf (Data Manager)

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Inclusion Criteria:

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines prior to initiation of any study-specific procedure
2. At least 18 years old at screening
3. Body weight > 45 kg at screening
4. Adequate acoustic windows to enable accurate TTE (refer to the central echocardiography laboratory's manual of operations)
5. Diagnosed with oHCM (unexplained LV hypertrophy with non-dilated ventricular chambers in the absence of other cardiac [e.g. aortic stenosis, hypertension]) or systemic disease. Patient has maximal septal wall thickness ≥ 15 mm or ≥ 13 mm with family history of HCM consistent with current ACC/AHA 2011. Patient must meet ACC/AHA 2011 guideline recommendations for invasive SRT therapies as follows:
   - Clinical criteria: Despite maximally tolerated drug therapy, severe dyspnea or chest pain (NYHA Class III or IV), or for the purposes of the VALOR Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope.
   - Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy of ≥15mm (or ≥13mm with family history of HCM) (read by the core echocardiography laboratory)
   - Anatomic criteria: targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator
6. Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure
7. Subjects referred or considered for ASA must have an adequate first septal perforating branch of the left anterior descending (LAD) coronary artery amenable for the Interventionalist to perform the procedure
8. Documented oxygen saturation at rest ≥ 90% at screening
9. Documented LVEF ≥ 60% at screening according to core echocardiography laboratory reading
10. Female subjects not pregnant or lactating and, if sexually active, must either practice true abstinence or use 1 of the following highly effective birth control methods from screening through 4 months after the last dose of study drug:

- Estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Female surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to screening. Females are considered postmenopausal if they have had amenorrhea for ≥1 year after cessation of all exogenous hormonal treatments, and follicle stimulating hormone (FSH) levels are in the postmenopausal range.
- Male partners of female subjects must also use a contraceptive (eg, barrier, condom, or vasectomy) from screening through 4 months after the last dose of study drug.

Exclusion Criteria:

1. Previously participated in a clinical study with mavacamten (individuals who failed screening for a prior mavacamten study may participate)
2. Hypersensitivity to any of the components of the mavacamten formulation
3. Participated in a clinical trial in which the subject received any investigational drug (or currently using an investigational device) within 30 days prior to screening, or at least 5 times the respective elimination half-life (whichever is longer)
4. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
5. Planned invasive procedure during the first 32 weeks of the study
6. Papillary muscle or mitral valve in need of repair or any other intracardiac procedure planned (however, if need for mitral valve repair is discovered during SRT procedure, the subject will continue to be followed on study)
7. For individuals on beta blockers, calcium channel blockers, or disopyramide, any dose adjustment of these medications < 14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study
8. Any medical condition that precludes upright exercise stress testing
9. Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present at screening per the investigator's evaluation of the subject's electrocardiogram (ECG)
10. Persistent or permanent atrial fibrillation and subject not on anticoagulation for ≥ 4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months prior to screening
11. Previously treated with invasive septal reduction (surgical myectomy or percutaneous ASA). However, if the subject has a history of a suboptimal or a failed alcohol septal ablation and there is no evidence on site read prescreening echocardiogram of an ASA, the subject may be included after consultation with the MyoKardia or CRO medical monitor.
12. Planned implantable ICD placement or pulse generator change during the first 32 weeks of the study.

13. ECG abnormality considered by the investigator to pose a risk to subject safety (eg, second degree atrioventricular block type II).
14. Acute or serious comorbid condition (e.g. major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study
    a. Pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
    b. History of malignant disease within 10 years prior to screening:
        - Subjects who have been successfully treated for non-metastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ may be included in the study
        - Subjects with other malignancies who are cancer-free for more than 10 years prior to screening may be included in the study
15. History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to subject safety or interfere with study evaluations, procedures, or completion
16. Safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the central laboratory reference range) at screening as assessed by the central laboratory; however, a subject with safety laboratory parameters outside the normal limits may be included if all the following criteria are met:
    a. Safety laboratory parameters outside normal limits are considered by the investigator to be clinically not significant
    b. If an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be $< 3 \times$ the upper limit of the laboratory reference range
    c. Body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2
17. Has known moderate or severe aortic valve stenosis or moderate to severe aortic stenosis determined at screening (as read by the echocardiography core laboratory)
18. Positive serologic test at screening for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of hepatitis B s-antibody positive, which is a marker of immunity
19. Known active infection with Covid-19 (PCR+) within 90 days of screening. If subject had a PCR+ test within 6 months of screening, they must have a negative Covid-19 test at screening.
20. Prior treatment with cardiotoxic agents, such as doxorubicin or similar
21. Unable to comply with the study requirements, including the number of required visits to the study site
22. First-degree relative of personnel directly affiliated with the study at the study site, any study vendor, or the study sponsor

eTable 1: Key Baseline Patient Characteristics, Separated by Sex

Characteristic	Mavacamten exposure			
	Placebo crossover group 40 Weeks		Original Mavacamten group 56 Weeks	
	Men (N=25)	Women (N=27)	Men (N=29)	Women (N=27)
Age – years, mean (SD)	59.3 (8.2)	62.3 (12.1)	56.4 (14.7)	63.4 (13.0)
Duration of obstructive hypertrophic cardiomyopathy disease – years, mean (SD)	8.5 (9.6)	5.3 (4.5)	9.2 (12.4)	5.7 (3.9)
Medical History – no. (%)				
Family history of hypertrophic cardiomyopathy	7 (28.0)	8 (29.6)	12 (41.4)	5 (18.5)
Atrial fibrillation	4 (16.0)	3 (11.1)	11 (37.9)	0 (0.0)
Hypertension	15 (60.0)	17 (63.0)	16 (55.2)	20 (74.1)
Syncope or pre-syncope	14 (56.0)	14 (51.9)	18 (62.1)	11 (40.7)
Internal cardioverter defibrillator	4 (16.0)	6 (22.2)	7 (24.1)	2 (7.4)
New York Heart Association functional class – no. (%)				
Class II with exertional syncope	2 (8.0)	0 (0.0)	3 (10.3)	1 (3.7)
Class III or higher	23 (92.0)	27 (100.0)	26 (89.7)	26 (96.3)
Type of septal reduction therapy recommended – no. (%)				
Alcohol septal ablation	3 (12.0)	2 (7.4)	3 (10.3)	5 (18.5)
Myectomy	22 (88.0)	25 (92.6)	26 (89.7)	22 (81.5)
Background hypertrophic cardiomyopathy therapy – no. (%)				
Beta blocker monotherapy	14 (56.0)	10 (37.0)	15 (51.7)	11 (40.7)
Nondihydropyridine calcium channel blocker monotherapy	5 (20.0)	5 (18.5)	3 (10.3)	4 (14.8)
Beta blocker and calcium channel blocker	3 (12.0)	6 (22.2)	3 (10.3)	3 (11.1)
Beta blocker and disopyramide	2 (8.0)	2 (7.4)	5 (17.2)	6 (22.2)
Calcium channel blocker and disopyramide	0 (0.0)	2 (7.4)	1 (3.4)	0 (0.0)
Beta blocker, calcium channel blocker and disopyramide	1 (4.0)	0 (0.0)	0 (0.0)	2 (7.4)
Echocardiographic parameters, mean (SD)				
LVOT gradient – mmHg				
Resting	48.9 (30.5)	44.5 (28.2)	43.7 (26.9)	59.3 (34.2)
Valsalva	80.1 (30.2)	78.6 (30.1)	62.3 (23.7)	89.2 (31.9)
Post-exercise	92.6 (34.2)	73.9 (37.3)	79.6 (30.1)	85.7 (39.4)

LV ejection fraction, %	68.5 (2.2)	68.3 (2.6)	66.8 (3.7)	69.4 (3.6)
Left atrial volume index, mL/m^2	39.9 (15.6)	40.8 (15.4)	41.3 (20.5)	41.4 (11.3)
LV mass index, g/ m^2	128.6 (34.9)	112.1 (30.4)	119.0 (29.9)	119.4 (29.7)
Septal E/e'	18.3 (9.6)	17.9 (6.3)	16.9 (8.7)	22.4 (8.8)
KCCQ-23 CSS+-points, mean (SD)	71.4 (18.2)	64.0 (18.8)	70.5 (18.1)	68.5 (14.4)
Laboratory measurements, median (IQR)				
NT-proBNP, ng/L	786 (350, 1331)	664 (393, 1166)	530 (204, 1383)	1243 (481, 3141)
Cardiac troponin I, ng/L	15.3 (11.4, 24.6)	11.2 (4.5, 29.9)	17.4 (7.5, 36.6)	17.2 (6.4, 28.2)

eTable 2: Final Dosing Chart for the Study in Both Groups

Final Dosing	Patients initially treated with mavacamten N=56	Patients crossed over to mavacamten at Week 16 N=52
	Final dosing at Week 56	**Final dosing at Week 56**
2.5 mg	11 (19.6)	6 (11.5)
5 mg	17 (30.4)	14 (26.9)
10 mg	16 (28.6)	23 (44.2)
15 mg	12 (21.4)	9 (17.3)

eTable 3. Select End Points for 40 and 56 Weeks of Exposure to Mavacamten, Separated by Sex

	Mavacamten exposure			
	40 weeks		56 weeks	
	Men (N=25)	Women (N=27)	Men (N=29)	Women (N=27)
Primary endpoint	4 (16.0)	6 (22.2)	2 (6.9)	3 (11.1)
At least 1 class of NYHA improvement	20 (80.0)	17 (65.4)	25 (89.3)	26 (96.3)
At least 2 class of NYHA improvement	9 (36.0)	9 (34.6)	14 (50.0)	10 (37.0)
Change in KCCQ-23-CSS, mean (95% CI)	10.2 (4.4 to 16.1)	13.0 (5.1 to 20.9)	12.1 (5.0 to 19.2)	16.2 (11.3 to 21.1)
Change in resting LVOT gradient (mmHg)	-35.2 (-47.4 to -23.0)	-31.2 (-44.3 to -18.0)	-29.8 (-40.9 to -18.8)	-38.7 (-55.2 to -22.2)
Change in Valsalva LVOT gradient (mmHg)	-58.1 (-74.6 to -41.5)	-51.1 (-67.8 to -34.5)	-34.8 (-50.5 to -19.1)	-57.7 (-72.4 to -42.9)
Change in NT-proBNP – ng/L, median (95% CI) ‡	-442 (-815 to -175)	-423 (-659 to -154)	-196 (-413 to -109)	-723 (-1427 to -273)
Change in cardiac troponin I – ng/L, median (95% CI) ‡	-10 (-17.7 to -3.1)	-4.2 (-10.0 to -2.8)	-6.4 (-14.2 to 0.3)	-7.4 (-15.9 to -2.8)
Change in LV filling pressures (E/'e' ratio)	-5.7 (-9.9 to -1.6)	-1.7 (-3.3 to -0.06)	-3.4 (-5.7 to -1.1)	-5.0 (-7.3 to -2.7)
Change in left atrial volume index – ml/m^2	-3.4 (-6.2 to -0.6)	-7.0 (-10.7 to -3.2)	-4.8 (-9.7 to 0.09)	-6.2 (-9.6 to -2.8)

eTable 4: Data on Patients Proceeding to SRT

Subject	Original treatment arm	Age	Sex	Mavacamten dose before SRT	LV ejection fraction at end of treatment prior to SRT	SRT type	End of treatment	Valsalva LVOT gradient (mm Hg) at end of treatment (pre-SRT)	Valsalva LVOT gradient (mm Hg) 24 weeks post-SRT	NYHA Class at 24 weeks post-SRT	Notes
1	Placebo*	55	Male	0	70%	Myectomy	Week 8	75	13	I	No complications
2	Placebo*	45	Male	0	68%	ASA	Week 8	10	8	I	No complications
3	Placebo to mavacamten crossover	57	Male	5 mg	70%	ASA	Week 20	43	49	III	Underwent repeat ASA at 8 months after an unsuccessful first one with relief of LVOT gradient
4	Placebo to mavacamten crossover	36	Female	15 mg	72%	Myectomy	Week 32	53	24	I	Wound cellulitis
5	Placebo to mavacamten crossover	62	Female	10 mg	67%	Myectomy	Week 56	102	8	I	Post-operative hypotension, thrombocytopenia, pneumothorax, hallucinations
6	Mavacamten	22	Male	5 mg	68%	Myectomy	Week 28	73	18	I	No complications
7	Mavacamten	66	Female	15 mg	71%	Myectomy	Week 16	46	12	II	Postoperative respiratory failure and atrial fibrillation
8	Mavacamten	41	Female	5 mg	60%	Myectomy	Week 4	51	71	II	No complications

*these 2 patients underwent SRT before week 16 and were not included in subsequent analyses, as discussed in main body of the manuscript

eTable 5: Week 56 Data on Eligible Patients Who Did Not Choose to Undergo SRT

Subject	Treatment Arm	Age	Sex	Baseline Valsalva LVOT gradient (mmHg)	Mavacamten dose	NYHA Class	LVEF (%)	Valsalva LVOT gradient (mmHg)*	Post-exercise LVOT gradient (mmHg)
1	Placebo	41	Female	120.3	15 mg	III	73	100.6	N/A
2	Placebo	72	Female	75.6	2.5 mg	III	66	83.6	N/A
3**	Placebo	70	Male	101.9	0 mg**	III	58	130.1	N/A
4	Placebo	62	Male	56.3	15 mg	II	70	75.6	82.4
5	Mavacamten	66	Female	68.8	10 mg	II	63	24.6	57.3

*LVOT gradient values listed are the maximum LVOT values within Week 56 analysis window, which were used to determine the SRT Eligibility. Mavacamten dose and LVEF values are all reported from the same visit as the maximum LVOT gradient value.
**Subject continued to be followed on study after discontinuing study drug (same subject as described in narrative for '1 heart failure admission')

eTable 6: Dose Changes in Background HCM Therapy From Baseline Through Week 56

	Placebo-to-mavacamten N=52	Original mavacamten N=56	Total N=108
Beta blocker (n=83 at baseline)			
Increased dose	3 (5.8)	2 (3.6)	5 (4.6)
Decreased dose	3 (5.8)	10 (17.9)	13 (12.0)
Maintained dose	32 (61.5)	33 (58.9)	65 (60.2)
Calcium channel blocker (n=38 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	2 (3.8)	3 (5.4)	5 (4.6)
Maintained dose	19 (36.5)	13 (23.2)	32 (29.6)
Disopyramide (n=19 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	0	2 (3.6)	2 (1.9)
Maintained dose	7 (13.5)	9 (16.1)	16 (14.8)

eTable 7: Safety End Points and Adverse Events Through Week 56

Characteristic	Placebo-to-mavacamten (40 weeks exposure) N=52	Original mavacamten (56 weeks exposure) N=56	Total mavacamten N=108
Safety endpoints			
Permanent study drug discontinuation a) LV ejection fraction <30% b) Two consecutive LV ejection fraction measurements of < 50% despite dose reduction to 2.5 mg	2 (3.8) 1 (1.9)	0 0	3 (2.8)
One Temporary Interruption for LV ejection fraction (>30% to <50%)	2 (3.8)	7 (12.5)	9 (8.3)
Total with ANY LV ejection fraction (<50%)	5 (9.6)	7 (12.5)	12 (11.1)
Cardiac death	1 (1.9)*	0	
Heart failure hospitalization	1 (1.9)¥	0	
Serious treatment-emergent adverse events			
Patients with at least one serious treatment-emergent adverse event	6 (11.5)	4 (7.1)	10 (9.3)
Atrial fibrillation	0	3 (5.4)	3 (2.8)
Congestive heart failure	1 (1.9)	0	1 (0.9)
Ventricular arrhythmia	1 (1.9)	0	1 (0.9)
Severe gastroesophageal reflux	1 (1.9)	0	1 (0.9)
Drug administration site reaction	2 (3.8)	0	2 (1.9)
COVID-19	0	1 (1.8)	1 (0.9)
Clostridium difficile infection	0	1 (1.8)	1 (0.9)
Fall	1 (1.9)	0	1 (0.9)
Life-threatening syncope	1 (1.9)	0	1 (0.9)
Nephrolithiasis	1 (1.9)	0	1 (0.9)
Acute respiratory failure	0	1 (1.8)	1 (0.9)

Pulmonary embolism	0	1 (1.8)	1 (0.9)
Peripheral venous disease	1 (1.9)	0	1 (0.9)

* This patient had a site-reported LV ejection fraction of 30% and mavacamten was discontinued. Details in supplemental file.

¥ This patient was admitted for congestive heart failure with concomitant atrial fibrillation and had a core-lab reported LV ejection fraction < 30%. Mavacamten was permanently discontinued. Details in supplemental file.

eTable 8: Correlation Between Mean (± SD) Site-Read and Core-Lab Read Echocardiographic Measurements (Obtained Between Weeks 32-56)

	Core laboratory read echo	Site-read echo	Correlation, r	p-value
LV ejection fraction	64.8 ± 4.9	64.0 ± 6.1	0.46	<0.001
Valsalva LVOT gradient, mmHg	26.1 ± 26.6	24.3 ± 29.7	0.86	<0.001
Resting LVOT gradient, mmHg	15.2 ± 16.9	12.5 ± 17.7	0.90	<0.001

eAppendix 2.

Narrative about 1 death and permanent drug discontinuation

81-year-old patient with oHCM and a prior history of unsuccessful alcohol septal ablation was originally randomized to placebo. At Week 16, their LV ejection fraction was 73% with a Valsalva LVOT of 53.55 mmHg, and was classified as NYHA Class III. They chose to continue in the study and began 5 mg of mavacamten. Between weeks 16 and 28, the LV ejection fraction ranged from 65-72% and Valsalva LVOT gradient ranged from 12-53 mm Hg. At Week 28, their mavacamten was increased to 10 mg and at Week 32, their LVEF was 57% with a Valsalva LVOT gradient of 6.1 mmHg. They were maintained on 10 mg through Week 44 visit (LVEF of 60% on site-read echocardiogram). At Week 56, the site-read echocardiogram was remarkable for decreased LVEF of 30%, no systolic anterior motion of the mitral valve, LVOT gradient at rest and Valsalva of 0 mmHg and severe mitral regurgitation. Patient was deemed to be asymptomatic without signs of congestive heart failure. Mavacamten was permanently discontinued, and they were scheduled to return for a follow visit in 2 weeks. However, their baseline HCM medications (disopyramide and verapamil) were continued as directed by the treating cardiologist.

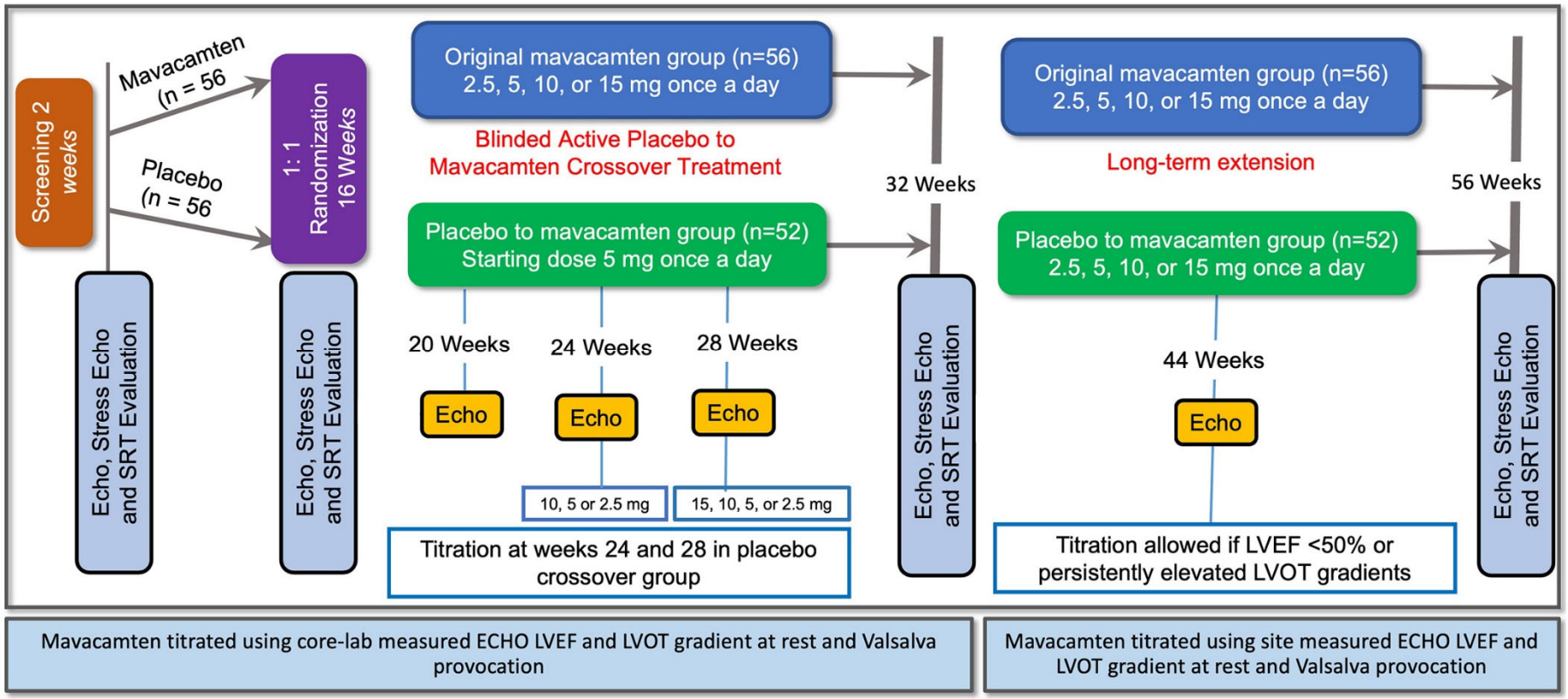
Subsequently, the patient was evaluated by a pulmonologist 3 days later and was found to have mild forced expiratory wheeze consistent with mild asthma. It was considered possibly secondary to mold exposure and they were started on a fluticasone inhaler. The patient died 4 days later in their sleep with cause of death determined to be sudden cardiac death. The autopsy report showed cardiomegaly with an enlarged left ventricle, dilated thoracic ascending aorta, and an area of upper septal scarring (deemed to be due to prior alcohol septal ablation). There was coronary artery sclerosis but narrowing <50%, firm lungs on exam with underlying pulmonary fibrosis. Pneumonia was found (reported difficulty in grossly differentiating lobar versus diffuse pneumonia due to fibrosis). There was no evidence of myocardial infarction and a dilated aortic root was seen with no dissection.

Narrative about 1 heart failure admission and permanent drug discontinuation

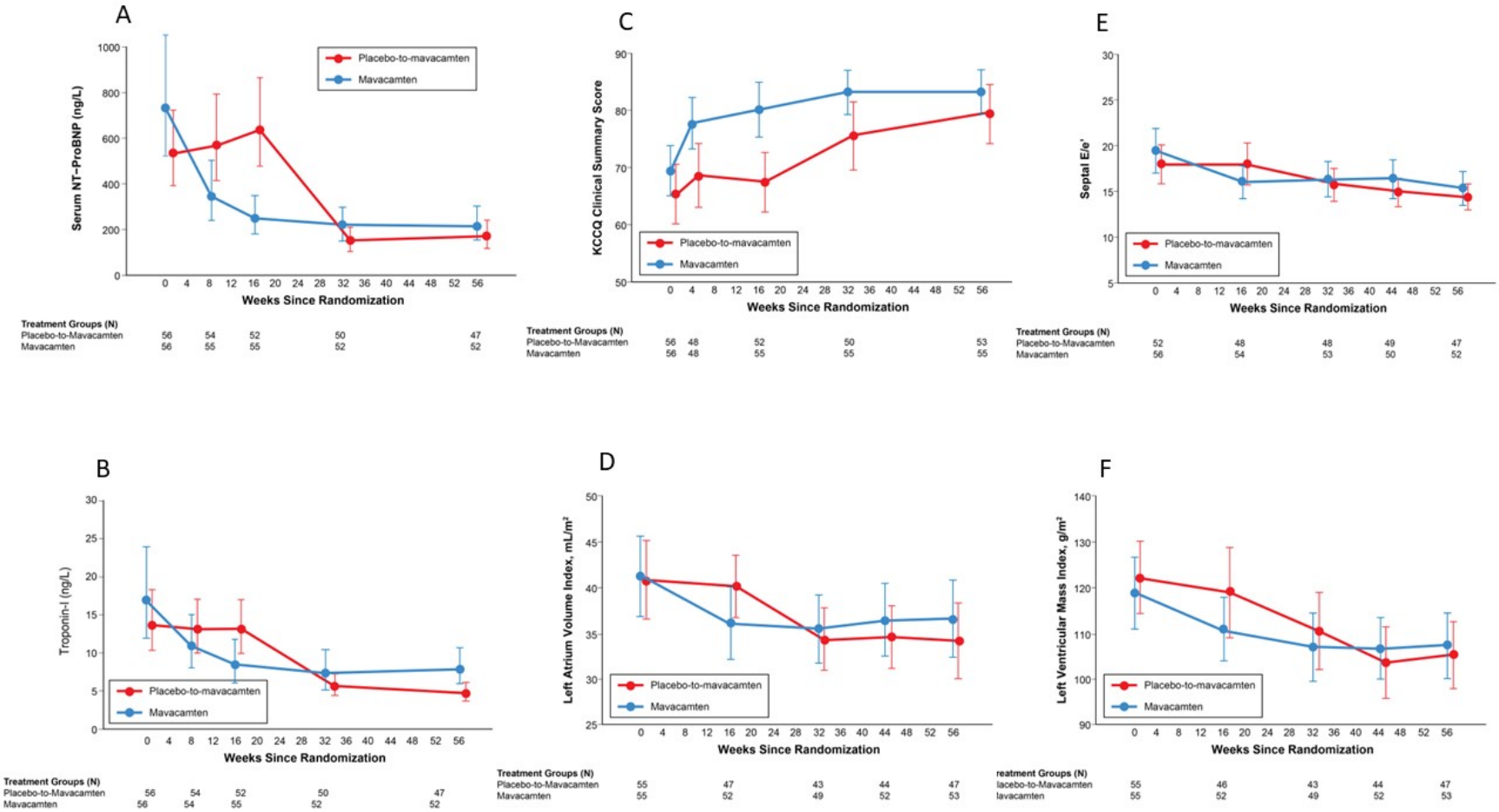
70-year-old patient with oHCM randomized to placebo. During the double-blind period, their LVEF ranged from 61-66% with a Valsalva LVOT of 84.77-106.48 mmHg. At Week 16, they chose to remain in the study and received 5 mg of mavacamten. At Week 24, their LVEF was 60% with a Valsalva LVOT of 60.75 mmHg. Their dose was increased to 10 mg. At Week 28, their LVEF was 55% with a Valsalva LVOT of 34.07 mmHg and the dose was increased to 15 mg. Soon after, the subject was diagnosed with new-onset atrial fibrillation, was started on apixaban 5 mg twice daily and referred to electrophysiology. Four weeks later, they underwent an outpatient direct current cardioversion and sinus rhythm was restored. No action was taken with regards to study medication.

Few days later, the subject began experiencing worsening symptoms and had irregular heart rate which was determined to be rapid atrial fibrillation and an LVEF that had decreased to 30%. Mavacamten was discontinued permanently followed by a second successful cardioversion the next day. Two weeks later, during the subject's end of treatment study visit, they were found to be in congestive heart failure and hospitalized for acute decompensated HF. They underwent a left heart catheterization which revealed no obstructive coronary artery disease. They were treated with appropriate guideline directed medical therapy and discharged. At week 56 follow-up and beyond, patient has remained in normal sinus rhythm and LV ejection fraction has normalized. In the longer-term, their LVOT gradient on Valsalva was > 50 mm Hg. However, they have chosen not to undergo SRT and have been managed on commercially approved HCM medical therapy.

eFigure 1: Dose Titration Scheme for VALOR-HCM Trial

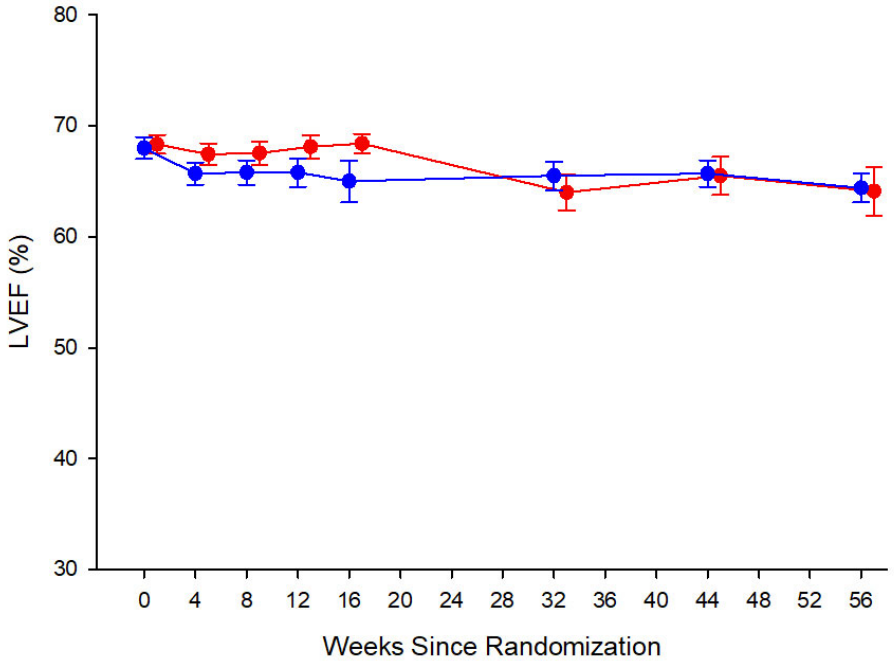


eFigure 2: Change in Biomarker and Echocardiographic Parameters From Baseline to Week 56 for the Original Mavacamten and the Placebo Cross-Over Groups



A: NT-Pro BNP, B: Troponin I C: KCCQ-CSS D: LV Mass Index E: Septal E/e' F: LA volume index
Plotted values for NT-proBNP and Troponin I represent means and 95% confidence intervals of back-transformed geometric means and corresponding confidence intervals. Plotted values for the rest represent means and standard errors.

eFigure 3: Left Ventricular Ejection Fraction at Various Time Points (Baseline to Week 56) in the Original Mavacamten and Placebo Cross-Over Groups



Plotted values represent means and standard errors.

eFigure 4: Correlation Between Site-Read and Core Laboratory Echocardiographic LVEF Measurements