SUPPLEMENTARY APPENDIX

Valsartan in Early Stage Sarcomeric Hypertrophic Cardiomyopathy:

A Randomized Phase 2 Trial

Table of Contents

Table S1. Participating Sites, Investigators, Study Coordinators, and Core Laboratory Directors

Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA
Carolyn Y. Ho, MD, Neal K. Lakdawala, MD, Allison L. Cirino, MS

Site Coordinator(s): Lauren Conner, Stephanie Harris, Lia Kaynor, Kermshilse Picard

Department of Cardiology, Boston Children's Hospital, Boston, MA
Steven D. Colan, MD, Renee Margossian, MD

Site Coordinator: Jane Messere

University of Michigan, Ann Arbor, MI, USA
Sharlene M. Day, MD (currently at University of Pennsylvania); Mark Russell, MD
Site Coordinators: Maryann Concannon, Ben Johnson

Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
Anna Axelsson, MD, PhD, Henning Bundgaard, MD, PhD

Site Coordinators: Elsebet Eriksen, Jeanette Broberg

Cleveland Clinic Foundation, Cleveland OH, USA
Kenneth Zahka, MD, Harry M. Lever, MD

Site Coordinators: Rita Brienza RN, BSN, Andrea Rohr, BS

Laboratory of Genetics and Molecular Cardiology, Heart Institute, University of Sao Paulo Medical School, Brazil
Alexandre C. Pereira, MD, PhD, Jose E Krieger, MD, PhD, Luciana Sacilotto, MD, Edmundo Arteaga, MD, Murilo O Antunes, MD

Site Coordinator: Alexandra Vieira

Division of Pediatric Cardiology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Anne M. Murphy, MD

Site Coordinators: Yemissi Sanni, Olivia Koerner Swift, Haley Rue

Washington University School of Medicine, St. Louis, MO, USA
Charles Canter, MD (,Department of Pediatrics); Richard Bach, MD (Cardiovascular Division, Department of Medicine)

Site Coordinator: Teresa Roberson

Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
Matthew T. Wheeler, MD, PhD, Euan Ashley, MD, PhD

Site Coordinators: Austin E Bland, Jeffrey W Christle, Annika M Dries, Brianna M Tucker, Rebecca Fuhlbrigge, Aleksandra Pavlovic, Yael Shmargad, Dana Ben-Tzur

Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
Ivan Wilmot, MD
Site Coordinators: Paula Casson, Amy Pajk, Lauren Bueche

Vanderbilt University Medical Center, Nashville, TN, USA
Jason R. Becker, MD (currently at University of Pittsburgh Medical Center); Jonathan H. Soslow, MD
Site Coordinator: Susan M. Sommers, RN

Division of Cardiovascular Medicine Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
Anjali T. Owens, MD
Site Coordinators: Laura Fleszar, Jessica Kim

Children's Hospital of Philadelphia, Philadelphia, PA, USA
Joseph W. Rossano, MD, Kimberly Y. Lin, MD
Site Coordinator: Sydney Reilly

Toronto Hospital for Sick Children, Toronto, ON, Canada
Lee Benson, MD
Site Coordinator: Rita Nobile

University of Colorado Anschutz Medical Campus, Aurora, CO, USA
Luisa Mestroni, MD, Matthew Taylor, MD, PhD
Site Coordinators: Mercedes Zirbes , Jean Jirikowic

Department of Medicine, University of Chicago, Chicago, IL, USA
Amit R. Patel, MD
Site Coordinator: Tiffany Hart

Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA
Philip Thrush, MD, Elfriede Pahl, MD

Yale University School of Medicine, New Haven, CT, USA *(Virtual Site)*
E. Kevin Hall, MD

Feinberg School of Medicine, Bluhm Cardiovascular Institute, Northwestern University, Chicago, IL, USA *(Virtual Site)*
Lubna Choudhury, MD

Core Laboratory Directors

Echocardiography Core Laboratory
Steven D. Colan, MD, Renee Margossian, MD
Department of Cardiology, Boston Children's Hospital, Boston, MA , USA

Cardiac Magnetic Resonance Imaging Core Laboratory
Jose D. Vargas, MD, PhD
MedStar Heart and Vascular Institute, Washington, DC, USA

Cardiopulmonary Exercise Core Laboratory
Gregory D. Lewis, MD
Cardiac Unit, Massachusetts General Hospital, Boston, MA, USA

Clinical Events Committee

Chair:
Akshay S. Desai, MD, MPH
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Members:
Neal K. Lakdawala, MD
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA USA

Elizabeth D. Blume, MD
Department of Cardiology, Boston Children's Hospital, Boston, MA , USA

Executive Committee

Eugene Braunwald, MD
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA
Carolyn Y. Ho, MD
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Calum A. MacRae, MD, PhD
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

John J.V. McMurray, MD
British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

E. John Orav, MD
Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

Scott D. Solomon, MD
Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA

Table S2. Primary and Secondary Outcomes Excluding Participants Who Withdrew from the Trial Early

Outcome	**Including All 178 Patients** **Adjusted Change in Z-score***	**Excluding 11 Early Withdrawals** **Adjusted Change in Z-score***
Composite Z-Score	**P=0.001**	**P=0.001**
Valsartan	+0.136 [0.049, 0.223]	+0.135 [0.055, 0.216]
Placebo	-0.095 [-0.192, 0.002]	-0.109 [-0.190, -0.028]
Difference	0.231 [0.098, 0.364]	0.244 [0.127, 0.362]
Components of the Primary Outcome		
Maximum LV Wall Thickness[a]	**P=0.062**	**P=0.039**
Valsartan	0.16 [-0.69, +1.00]	0.13 [-0.69, +0.94]
Placebo	1.32 [+0.42, +2.21]	1.35 [+0.54, +2.17]
Difference	-1.16 [-2.37, +0.06]	-1.23 [-2.39, -0.06]
E' Velocity[b]	**P=0.017**	**P=0.003**
Valsartan	0.016 [-0.19, +0.22]	0.003 [-0.19, +0.19]
Placebo	-0.33 [-0.57, -0.10]	-0.37 [-0.56, -0.18]
Difference	0.35 [+0.06, +0.63]	0.37 [+0.12, +0.62]
S' Velocity[b]	**P=0.45**	**P=0.39**
Valsartan	-0.031 [-0.28, +0.21]	-0.05 [-0.30, +0.19]
Placebo	-0.165 [-0.43, +0.10]	-0.19 [-0.44, +0.05]
Difference	0.13 [-0.21, +0.48]	0.14 [-0.18, +0.46]
LV Mass[c]	**P=0.12**	**P=0.08**

Valsartan	-4.32 [-7.32, -1.32]	-4.68 [-7.65, -1.72]
Placebo	-1.11 [-4.04, +1.81]	-1.22 [-4.18, +1.74]
Difference	3.20 [-0.81, +7.22]	3.46 [-0.48, +7.40]
LA Volume[c]	**P=0.59**	**P=0.63**
Valsartan	2.47 [-0.31, +5.25]	2.12 [-0.55, +4.79]
Placebo	1.45 [-1.27, +4.17]	1.23 [-1.42, +3.89]
Difference	1.02 [-2.70, +4.74]	0.89 [-2.72, +4.50]
LV End Diastolic Volume[c]	**P=0.047**	**P=0.03**
Valsartan	4.51 [+1.41, +7.61]	4.17 [+1.36, +6.97]
Placebo	0.41 [-2.77, +3.59]	-0.13 [-2.93, +2.66]
Difference	4.10 [+0.06, +8.14]	4.30 [+0.53, +8.07]
LV End Systolic Volume[c]	**P=0.24**	**P=0.13**
Valsartan	3.69 [+1.77, +5.62]	3.65 [+1.86, +5.45]
Placebo	2.20 [+0.28, +4.13]	1.90 [+0.09, +3.71]
Difference	1.49 [-1.00, +3.97]	1.75 [-0.52, +4.03]
NTproBNP[d]	**P=0.025**	**P=0.033**
Valsartan	0.02 [-0.14, +0.18]	0.01 [-0.14, +0.16]
Placebo	0.27 [+0.11, +0.43]	0.25 [+0.10, +0.40]
Difference	-0.25 [-0.47, -0.03]	-0.24 [-0.46, -0.02]
Troponin T[d]	**P=0.37**	**P=0.25**
Valsartan	0.06 [-0.02, +0.14]	0.06 [-0.02, +0.14]
Placebo	0.11 [+0.02, +0.20]	0.12 [+0.03, +0.21]

Difference	-0.05 [-0.16, +0.06]	-0.06 [-0.17, +0.04]

Sensitivity analyses comparing results of the primary analysis mixed model linear regressions comparing changes in the outcome between treatment groups with and without participants who withdrew from the trial early.

*Adjusted for the baseline value of the outcome (normalized), NYHA class, sex, age, pubertal status, body mass index, race (white vs not white), genotype (thick vs thin filament variants), LV ejection fraction, systolic blood pressure, beta-blocker use, calcium channel blocker use. Two-sided p-values for secondary outcomes were not adjusted for multiple testing.

[a]Adjusted for body surface area; [b]Adjusted for age; [c]Indexed to body surface area; [d]Log-transformed, with change measured relative to baseline

Table S3. Primary Outcomes Using Original Eligibility Criteria, Omitting LV Volumes in the Composite Outcome, and Omitting Participants with Maximal LV Wall Thickness >20 mm.

	Adjusted Mean Change in Normalized Measure		Between-Group Differences*	Adjusted P-Value
Outcome and Subjects	**Placebo**	**Valsartan**		
Original Composite Z-Score	**n=90** -0.095 [-0.192, 0.002]	**n=88** +0.136 [+0.049, +0.223]	-0.231 [-0.364, -0.098]	0.001
Original Composite Z-score with original eligibility criteria (Age≤30; MLVWT≤20)*	**n=55** -0.118 [-0.247,0.012]	**n=49** +0.170 [+0.049, +0.290]	-0.287 [--0.468, -0.107]	0.002
Composite Z-Score, Omitting LVEDV and LVESV components	**n=90** -0.094 [-0.211, +0.022]	**n=88** +0.113 [+0.004,+0.221]	-0.207 [-0.366, -0.048]	0.011
Composite Z-Score, Omitting Patients with MLVWT>20 mm	**n=81** -0.107 [-0.210, -0.003]	**n=66** +0.161 [+0.059, +0.264]	-0.268 [-0.416, -0.119]	0.001

Sensitivity analyses comparing results of the primary analysis mixed model linear regressions comparing changes in the outcome between treatment groups with original eligibility criteria, omitting LV volume components of the primary composite outcome, and omitting participants with severe hypertrophy (maximal LV thickness >20 mm)
*Eligibility criteria were revised once early during trial enrollment, increasing the upper age limit from 30 to 45 years, and maximal left ventricular wall thickness from 20 to 25 mm. Sample size decreased from 178 to 104; the majority due to the change in the age limit. p-values are 2-sided.
MLVWT, maximal left ventricular wall thickness; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume.

Table S4. Proportion of Participants Showing Improvement for Primary and Secondary Outcomes

Outcome	Adjusted Improvement Rates*		Adjusted Odds Ratio 95% CI and p-value
	Placebo	Valsartan	
Improvement on any component†	91%	95%	2.05 [0.59, 7.07] p=0.37
Number of Components that Showed Improvement	3.8	4.7	1.5 [1.2, 1.9] p<0.001
Proportion with Improvement in Components of the Primary Outcome			
Maximum LV Wall Thickness[a]	34%	52%	2.09 [1.09, 4.01] p=0.03
E' Velocity[b]	31%	53%	2.59 [1.33, 5.05] p=0.005
S' Velocity[b]	35%	49%	1.79 [0.88, 3.67] p=0.11
LV Mass[c]	56%	69%	1.81 [0.90, 3.63] p=0.10
LA Volume[c]	49%	44%	0.82 [0.41, 1.63] p=0.57
LV End Diastolic Volume[c]	56%	70%	1.81 [0.80, 4.10] p=0.15
LV End Systolic Volume[c]	69%	66%	0.85 [0.41, 1.75] p=0.66
NTproBNP[d]	33%	47%	1.80 [0.89, 3.65] p=0.10
Troponin T[d]	10%	14%	1.43 [0.48, 4.31] p=0.52

Each subject was scored as a "success" or "failure" based on improvement in any individual metric at 24 months. Successes and failures were compared between treatment groups using Fisher's exact test, through a mixed effects logistic regression adjusting for correlations and *adjusted for the baseline value of the outcome (normalized), sex, age, pubertal status, body mass index, LV ejection fraction, systolic blood pressure and maximum left ventricular wall thickness. Two-sided p-values for secondary outcomes were not adjusted for multiple testing.

†Unadjusted and based on unimputed data; too few people had no successes to model. [a]Adjusted for body surface area; [b]Adjusted for age; [c]Indexed to body surface area;

[d]Log-transformed, with change measured relative to baseline

Table S5. Prespecified Subgroup Analyses

All Patients (n=178):

	Within-Group Changes in the Normalized Measures*		Between-Group Differences*	Adjusted* P-Value
	Placebo (n=90)	**Valsartan n=88)**		
Composite Z-Score	**-0.095 [-0.192, 0.002]**	**+0.136 [0.049, 0.223]**	**0.231 [0.098, 0.364]**	**0.001**
Maximum LV Wall Thickness[a]	1.32 [+0.42, +2.21]	0.16 [-0.69, +1.00]	-1.16 [-2.37, +0.06]	0.062
E' Velocity[b]	-0.33 [-0.57, -0.10]	0.016 [-0.19, +0.22]	0.35 [+0.06, +0.63]	0.017
LV End Diastolic Volume[c]	0.41 [-2.77, +3.59]	4.51 [+1.41, +7.61]	4.10 [+0.06, +8.14]	0.047
NTproBNP[d]	0.27 [+0.11, +0.43]	0.02 [-0.14, +0.18]	-0.25 [-0.47, -0.03]	0.025

*Adjusted for the baseline value of the outcome (normalized), sex, age, pubertal status, body mass index, LV ejection fraction, systolic blood pressure and maximum left ventricular wall thickness. Two-sided p-values for secondary outcomes were not adjusted for multiple testing.

†Unadjusted and based on unimputed data; too few people had no successes to model. [a]Adjusted for body surface area; [b]Adjusted for age; [c]Indexed to body surface area; [d]Log-transformed, with change measured relative to baseline

By Sex:

Male (n=109)	Within-Group Changes in the Normalized Measures*		Between-Group Differences*	Adjusted* P-Value
	Placebo (n=55)	**Valsartan (n=54)**		
Composite Z-Score	-0.106 [-0.237, 0.025]	+0.102 [-0.011, 0.215]	0.208 [0.021, 0.396]	0.030
Maximum LV Wall Thickness[a]	1.44 [+0.23, +2.65]	0.62 [-0.48, +1.70]	-0.83 [-2.47, +0.81]	0.32
E' Velocity[b]	-0.28 [-0.61, +0.05]	-0.10 [-0.38, +0.19]	0.19 [-0.24, +0.61]	0.39
LV End Diastolic Volume[c]	-0.59 [-4.53, +3.36]	4.02 [+0.12, +7.93]	4.61 [-0.76, +9.98]	0.09
NTproBNP[d]	0.26 [+0.01, +0.51]	-0.09 [-0.34, +0.15]	-0.36 [-0.66, -0.05]	0.02

Female (n=69)	Within-Group Changes in the Normalized Measures*		Between-Group Differences*	Adjusted* P-Value
	Placebo (n=35)	**Valsartan (n=34)**		
Composite Z-Score	-0.088 [-0.241, 0.064]	+0.198 [0.052, 0.345]	0.287 [0.066, 0.507]	0.011
Maximum LV Wall Thickness[a]	1.44 [-0.11, +3.00]	-0.85 [-2.37, +0.67]	-2.29 [-4.54, -0.05]	0.046

E' Velocity[b]	-0.42 [-0.79, -0.04]	0.29 [-0.07, +0.06]	0.70 [+0.16, +1.24]	0.01
LV End Diastolic Volume[c]	0.56 [-3.56, +4.69]	5.71 [+1.70, +9.72]	5.15 [-0.56, +10.86]	0.08
NTproBNP[d]	0.36 [+0.13, +0.59]	0.21 [-0.01, +0.43]	-0.15 [-0.49, +0.20]	0.41

By Baseline Age Group:

Ages ≤ 18 (n=77)	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=39)	**Valsartan (n=38)**		
Composite Z-Score	-0.148 [-0.302, 0.007]	+0.093 [0.043, 0.230]	0.241 [0.041, 0.441]	0.019
Maximum LV Wall Thickness[a]	1.43 [-0.06, +2.93]	0.67 [-0.74, +2.07]	-0.77 [-2.43, +0.90]	0.37
E' Velocity[b]	-0.39 [-0.85, +0.07]	-0.18 [-0.58, +0.21]]	0.20 [-0.36, +0.77]	0.48
LV End Diastolic Volume[c]	-1.03 [-6.24, +4.18]	5.69 [+1.24, +10.13]	6.72 [-0.30, +13.14]	0.04
NTproBNP[d]	0.21 [-0.01, +0.55]	0.04 [-0.22, +0.31]	-0.23 [-0.63, +0.17]	0.27
Ages > 18 (n=101)	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=51)	**Valsartan (n=50)**		
Composite Z-Score	-0.034 [-0.158, 0.089]	+0.154 [0.027, 0.281]	0.189 [0.014, 0.363]	0.034
Maximum LV Wall Thickness[a]	0.82 [-0.44, +2.08]	0.11 [-1.17, +1.40]	-0.71 [-2.42, +1.01]	0.42
E' Velocity[b]	-0.26 [-0.51, -0.02]	0.16 [-0.07, +0.40]]	0.43 [+0.12, +0.73]	0.01
LV End Diastolic Volume[c]	2.52 [-1.21, +6.25]	2.42 [-1.37, +6.20]	-0.10 [-5.19, +4.98]	0.97
NTproBNP[d]	0.25 [+0.06, +0.44]	0.01 [-0.19, +0.22]	-0.24 [-0.53, +0.06]	0.11

By Baseline Maximal Left Ventricular Wall Thickness:

BSA-adjusted Z-score ≤7.3 (n=89)	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=48)	**Valsartan (n=41)**		
Composite Z-Score	-0.143 [-0.289, 0.001]	+0.225 [0.083, 0.368]	0.368 [0.169, 0.567]	0.0003
Maximum LV Wall Thickness[a]	1.21 [+0.04, +2.38]	-0.43 [-1.62, +0.76]	-1.64 [-3.27, -0.01]	0.048

E' Velocity[b]	-0.55 [-0.91, -0.19]	-0.15 [-0.22, +0.52]	0.70 [+0.20, +1.20]	0.01
LV End Diastolic Volume[c]	-0.09 [-4.50, +4.31]	6.52 [+2.12, +10.91]	6.61 [+1.71, +11.51]	0.01
NTproBNP[d]	0.30 [+0.06, +0.53]	-0.01 [-0.27, +0.24]	-0.31 [-0.68, +0.06]	0.10

BSA-adjusted Z-score >7.3 (n=89)	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=42)	**Valsartan (n=47)**		
Composite Z-Score	-0.027 [-0.167, 0.112]	+0.039 [-0.081, 0.159]	0.069 [-0.115, 0.249]	0.471
Maximum LV Wall Thickness[a]	1.29 [-0.18, +2.77]	0.74 [-0.60, +2.08]	-0.55 [-2.57, +1.47]	0.59
E' Velocity[b]	-0.11 [-0.41, +0.19]	-0.04 [-0.29, +0.20]	0.07 [-0.30, +0.44]	0.71
LV End Diastolic Volume[c]	1.68 [-4.05, +7.41]	2.08 [-3.69, +7.85]	-0.40 [-6.68, +7.48]	0.91
NTproBNP[d]	0.23 [-0.01, +0.47]	0.07 [-0.15, +0.30]	-0.16 [-0.46, +0.15]	0.31

By Disease-Causing Gene:

***MYBPC3* (n=91)**	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=44)	**Valsartan (n=47)**		
Composite Z-Score	+0.005 [-0.140, 0.150]	+0.142 [0.018, 0.266]	0.137 [-0.052, 0.327]	0.155
Maximum LV Wall Thickness[a]	+0.50 [-0.85, +1.86]	+0.22 [-0.99, +1.44]	-0.28 [-2.01, +1.46]	0.75
E' Velocity[b]	-0.30 [-0.68, +0.07]	-0.05 [-0.34, +0.25]	0.26 [-0.21, +0.73]	0.28
LV End Diastolic Volume[c]	-1.18 [-6.39, +4.03]	+4.45 [+0.08, +8.82]	5.63 [--1.15, +12.41]	0.10
NTproBNP[d]	+0.19 [-0.05, +0.44]	+0.08 [-0.15, +0.31]	-0.11 [-0.46, +0.23]	0.53

***MYH7* (n=61)**	**Within-Group Changes in the Normalized Measures***		**Between-Group Differences***	**Adjusted* P-Value**
	Placebo (n=36)	**Valsartan (n=25)**		
Composite Z-Score	-0.127 [-0.316, 0.063]	+0.142 [-0.063, 0.346]	0.268 [-0.053, 0.483]	0.015
Maximum LV Wall Thickness[a]	1.65 [+0.12, +3.19]	-0.19 [-1.91, +1.54]	-1.84 [-3.86, +0.18]	0.07

E' Velocity[b]	-0.45 [-0.79, -0.11]	+0.03 [-0.35, +0.40]	0.48 [+0.06, +0.90]	0.02
LV End Diastolic Volume[c]	1.72 [-2.41, +5.85]	3.65 [-1.05, +8.36]	1.93 [-4.14, +8.01]	0.53
NTproBNP[d]	0.31 [+0.05, +0.57]	0.02 [-0.26, +0.31]	-0.29 [-0.63, +0.05]	0.10

Subgroup Interaction P-values

Subgroups	**Outcome**				
	Primary Composite	**Maximum LV Wall Thickness**	**E-Prime Velocity**	**LV End Diastolic Volume**	**NTproBNP**
Male vs Female	P=0.48	P=0.55	P=0.08	P=0.59	P=0.45
Age ≤ 18 vs Age > 18	P=0.81	P=0.68	P=0.89	P=0.048	P=0.68
Max LVWTz ≤ 7.3 vs Max LVWTz > 7.3	P=0.04	P=0.58	P=0.08	P=0.16	P=0.54
MYBPC3 vs MYH7	P=0.59	P=0.52	P=0.71	P=0.53	P=0.62

Prespecified subgroup analyses assessed the influence of sex, genotype (*MYH7* vs *MYBPC3* variants), and other baseline characteristics on treatment response. Multivariable analyses were performed using formal interaction terms in linear regression models for the primary composite z-score outcome.

Table S6. Adjusted changes in Blood Pressure, Serum Creatinine, and Serum Potassium

	Adjusted* Mean Change in Raw Measure		**Between-Group Differences***
	Placebo (n=90)	**Valsartan (n=88)**	
Systolic Blood Pressure, mmHg	+1.2 [-1.3, +3.7]	-2.1 [-4.6, +0.4]	-3.3 [-6.9, +0.2] P=0.07
Diastolic Blood Pressure, mmHg	+1.5 [-0.5, 3.5]	-2.6 [-4.6, -0.6]	-4.1 [-6.8, -1.3] P=0.004
Creatinine, mg/dL	+0.03 [-0.01, +0.07]	+0.02 [-0.02, +0.06]	-0.01 [-0.06, +0.04] P=0.65
Potassium, mmol/L	+0.02 [-0.06, +0.10]	+0.04 [-0.04, +0.11]	+0.01 [-0.09, +0.12] P=0.79

*Mean change at Year 2 compared with baseline, adjusted for the baseline value of the outcome, NYHA class, maximum LV wall thickness, sex, age, pubertal status, body mass index, race (white vs not white), Hispanic ethnicity, genotype (thick vs thin filament variants), LV ejection fraction, systolic blood pressure, beta-blocker use, calcium channel blocker use. Between group difference = valsartan-placebo. Missing data were imputed.

Table S7. Adverse Events

Placebo (n=90)	Valsartan (n=88)
All Adverse Events	
98 Adverse Events in 48 People	128 Adverse Events in 51 People
42 (47%) people with no AE	37 (42%) people with no AE
29% with 1 AE	17% with 1 AE
10% with 2 AE's	20% with 2 AE's
14% with 3 or more AE's	21% with 3 or more AE's
Relationship to HCM	
30 of 98 AE's related to HCM (31%)	30 of 128 AE's related to HCM (23%)
Relationship to Drug	
Not Related: 65 (66%)	Not Related: 70 (55%)
Possibly Related: 29 (30%)	Possibly Related: 56 (44%)
Probably Related: 4 (4%)	Probably Related: 1 (1%)
Definitely Related: 0 (0%)	Definitely Related: 1 (1%)
(Probably: New murmur, MVR / severity=1)	(Probably: Headache / severity=1)
(Probably: Hypotension / severity=1)	(Definitely: Postural hypotension / severity=1)
(Probably: Elevated creatinine / severity=1)	
(Probably: Creatinine clearance decrease / severity=1)	
Severity	
Mild: 65 (66%)	Mild: 98 (77%)

Moderate: 21 (21%)	Moderate: 24 (19%)
Severe: 11 (11%)	Severe: 5 (4%)
Life-Threatening: 1 (1%) (Syncope)	Life-Threatening: 0 (0%)
Death: 0 (0%)	Death: 1 (1%) (pedestrian accident)
Serious Adverse Events	
14 Serious Adverse Events in 10 People	8 Serious Adverse Events in 8 People
7 of 14 SAE's are related to HCM (50%)	4 of 8 SAE's are related to HCM (50%)
0 out of 14 related to Drug	1 out of 8 SAE's possibly related to Drug
#1: Cervical cancer / unrelated HCM/ severity=3 Hysterectomy / unrelated HCM/ severity=3	#1: Death (pedestrian accident) / unrelated HCM/ severity=5
#2: Hospitalization for Depression /unrelated HCM/ severity=2	#2: ICD placement / related HCM/ severity=3
#3: Viral syndrome / unrelated HCM/ severity=3	#3: Syncope / related HCM/ severity=2
#4: ICD placement / related HCM/ severity=2 ICD malfunction / unrelated HCM/ severity=1	#4: Palpitations / related HCM/ severity=2
#5: Syncope / related HCM/ severity=4 ICD placement / related HCM/ severity=3	#5: PVCs / unrelated HCM/ severity=1
#6: Syncope / unrelated HCM/ severity=2	#6: Sepsis / unrelated HCM/ severity=3
#7: Profound anemia / unrelated HCM/ severity=3	#7: Pregnancy / unrelated HCM/ severity=3
#8: ICD placement / related HCM/ severity=3	#8: Chest pain / unrelated HCM / possibly related to Drug / severity=1

#9: Inducible ventricular tachycardia /related HCM/ severity=3 ICD placement / related HCM/ severity=3	
#10: Chest pain admit /related HCM/ severity=3	

Table S8. Genetic Variants in VANISH Participants

Group	Gene	Variant (c.)	Variant (p.)	N
Placebo	ACTC	889G>T	Ala297Ser	1
Placebo	MYBPC3	2308 G>A	Asp770Asn	1
Placebo	MYBPC3	2454 G>A	Trp818Ter	1
Placebo	MYBPC3	2550 delC	Asn850LysfsX29	1
Placebo	MYBPC3	2864_2865delct	Pro955fs	1
Placebo	MYBPC3	3330+2T>C		2
Placebo	MYBPC3	3414dupC	Val1139ArgfsTer10	2
Placebo	MYBPC3	3662del T	Leu1221Argfs*19	1
Placebo	MYBPC3	772 G>A	Glu258Lys	5
Placebo	MYBPC3	1892delT	Phe631fs	3
Placebo	MYBPC3	1153_1168delGTGGAACTGGC	Val385Metfs	1
Placebo	MYBPC3	1310delT	Val437Glyfs	2
Placebo	MYBPC3	1504C>T	Arg502Trp	2
Placebo	MYBPC3	1509 C>G	Phe503Leu	1
Placebo	MYBPC3	1624G>C	Glu542Gln	1
Placebo	MYBPC3	1928-2A>G		2
Placebo	MYBPC3	2048G>A	Trp683X	1
Placebo	MYBPC3	2170C>T	Arg724Trp	1
Placebo	MYBPC3	2308 G>A	Asp770Asn	1
Placebo	MYBPC3	2490insT	Ser830fsX832	1
Placebo	MYBPC3	2670G>A	Trp890X	2
Placebo	MYBPC3	2774-2775delAG	Glu925fs1094X	1
Placebo	MYBPC3	2905+1G>A		1
Placebo	MYBPC3	3124_3125insAA	Thr1042LysfsX	2
Placebo	MYBPC3	3330+2T>G		3
Placebo	MYBPC3	3330+5 G>C		1
Placebo	MYBPC3	3697C>T	Gln1233X	1
Placebo	MYBPC3	821+1G>A		2
Placebo	MYH7	1012G>A	Val338Met	2
Placebo	MYH7	2191 C>T	Pro731Ser	3
Placebo	MYH7	2524 A>G	Ser842Gly	1
Placebo	MYH7	2555T>C	Met852Thr	1
Placebo	MYH7	5135G>A	Arg1712Gln	1
Placebo	MYH7	746 G>A	Arg249Gln	1
Placebo	MYH7	1477 A>G	Met493Val	1
Placebo	MYH7	1491 G>T	Glu497Asp	1
Placebo	MYH7	1505A>G	Lys502Arg	1
Placebo	MYH7	170 C>A	Ala57Asp	1

Placebo	MYH7	1816 G>A	Val606Met	3
Placebo	MYH7	1954A>G	Arg652Gly	1
Placebo	MYH7	1987C>T	Arg663Cys	1
Placebo	MYH7	1988G>A	Arg663His	5
Placebo	MYH7	2104A> G	Ile702Val	1
Placebo	MYH7	2156G>A	Arg719Gln	2
Placebo	MYH7	2167C>T	Arg723Cys	3
Placebo	MYH7	2389G>A	Ala797Thr	1
Placebo	MYH7	2544G>C	Glu848Asp	1
Placebo	MYH7	2609G>A	Arg870His	2
Placebo	MYH7	2788 G>A	Glu930Lys	1
Placebo	MYH7	968T>A	Ile323Asn	1
Placebo	MYH7	1750G>C	Gly584Arg	1
Placebo	MYL2	239C>A	Thr80Asn	1
Placebo	MYL3	170C>A	Ala57Asp	1
Placebo	MYL3	445A>G	Met149Val	1
Placebo	TNNI3	592 C>G	Leu198Val	2
Placebo	TNNT2	856 C>T	Arg286Cys	1
Placebo	TNNT2	274C>T	Arg92Trp	1
Placebo	TNNT2	821+1G>T		1
Placebo	TPM1	457 C>G	HIs153Asp	1
Valsartan	ACTC	301G>A	Glu101Lys	2
Valsartan	MYBPC3	1484G>A	Arg495Gln	1
Valsartan	MYBPC3	1624G>C	Glu542Gln	1
Valsartan	MYBPC3	1678delG	Asp560fs	1
Valsartan	MYBPC3	1790G>A	Arg597Gln	1
Valsartan	MYBPC3	1928-2A>G		4
Valsartan	MYBPC3	2429G>A	Arg810His	1
Valsartan	MYBPC3	671_673delTGC	Leu224del	1
Valsartan	MYBPC3	772 G>A	Glu258Lys	2
Valsartan	MYBPC3	3330+T>G		1
Valsartan	MYBPC3	1210C>T	Gln404X	1
Valsartan	MYBPC3	1090G>C	Ala364Pro	1
Valsartan	MYBPC3	1504C>T	Arg502Trp	1
Valsartan	MYBPC3	1509 C>G	Phe503Leu	1
Valsartan	MYBPC3	177_187del	Glu60fs	1
Valsartan	MYBPC3	1892delT	Phe631fs	1
Valsartan	MYBPC3	2308 G>A	Asp770Asn	3
Valsartan	MYBPC3	2373_2374insG	Trp792fs	1
Valsartan	MYBPC3	2374 T>C	Trp792Arg	2
Valsartan	MYBPC3	2454G>A	Trp818X	1

Valsartan	MYBPC3	2490dupT	His831Serfs	1
Valsartan	MYBPC3	2541C>G	Tyr847X	1
Valsartan	MYBPC3	2827C>T	Arg943X	1
Valsartan	MYBPC3	2864_2865delCT	Pro955Argfs	1
Valsartan	MYBPC3	3079delGinsAA	Asp10271Lysfs	1
Valsartan	MYBPC3	3192_3193insC	Lys1065fs	1
Valsartan	MYBPC3	3330+2T>G		4
Valsartan	MYBPC3	3491-14 _3491-8dCCTGTCA		1
Valsartan	MYBPC3	3624delC	Lys1209SerfsX	1
Valsartan	MYBPC3	3697 C>T	Gln1233X	1
Valsartan	MYBPC3	436dupA	Thr146AsnfsX	1
Valsartan	MYBPC3	459delC	Ile154LeufsX	2
Valsartan	MYBPC3	821+1G>A		1
Valsartan	MYBPC3	927-2A>G		3
Valsartan	MYBPC3	177-187 del	Glu60fs	1
Valsartan	MYH7	1012G>A	Val338Met	1
Valsartan	MYH7	1052A>C	Lys351Thr	1
Valsartan	MYH7	2191 C>T	Pro731Ser	1
Valsartan	MYH7	2201A>C	Gln734Pro	1
Valsartan	MYH7	2334C>G	Asp778Glu	1
Valsartan	MYH7	1208g>a	Arg403G1n	1
Valsartan	MYH7	1987 C>T	Arg663Cys	5
Valsartan	MYH7	2156G>A	Arg719Gln	3
Valsartan	MYH7	2221 G>T	Gly741Trp	2
Valsartan	MYH7	2681A>G	Glu849Gly	1
Valsartan	MYH7	2770G>A	Glu924Lys	2
Valsartan	MYH7	2788 G>A	Glu930Lys	1
Valsartan	MYH7	2788 G>C	Glu930Gln	1
Valsartan	MYH7	4135G>A	Ala1379Thr	1
Valsartan	MYH7	746G>A	Arg249Gln	2
Valsartan	MYL2	45_46delinsT	Asn16fs	1
Valsartan	MYL3	445A>G	Met149Val	1
Valsartan	TNNI3	431T>C	Leu144Pro	2
Valsartan	TNNI3	484C>T	Arg162Trp	1
Valsartan	TNNT2	236 T>A	lle79Asn	3
Valsartan	TNNT2	856C>T	Arg286Cys	1
Valsartan	TNNT2	487_489delGAG	Glu163del	1
Valsartan	TPM1	457C>G	His153Asp	2
Valsartan	TPM1	523G>A	Asp175Asn	1
Valsartan	TPM1	673A>G	Ile225Val	1

Table S9. Eligibility Criteria for the VANISH Trial

Inclusion Criteria	Exclusion Criteria
1. Age 8 to 45 years 2. LV wall thickness ≥12 mm and ≤25mm or z-score ≥3 and ≤18 as determined by rapid assessment by the echocardiographic core laboratory 3. NYHA functional class I or II 4. No resting or provoked LV obstruction (peak gradient ≤ 30 mm Hg)	1. Contraindication to angiotensin receptor blocker (ARB) administration 2. Medical conditions that may confound interpretation of biomarkers of collagen synthesis (fibrosis, inflammatory states, cancer, trauma or surgery within 6 months of enrollment) 3. Concomitant use of spironolactone, lithium, aliskiren, ARB, or angiotensin converting enzyme (ACE)-inhibitors. 4. Pregnant or breastfeeding women or women of childbearing potential with no effective contraceptive method 5. Uncontrolled systemic arterial hypertension (persistent systolic blood pressure >160 mmHg and/or diastolic blood pressure >90 mmHg in adults or equivalent in children [e.g., systolic blood pressure >99th or diastolic blood pressure >95th percentile for sex, age, and height centile based on the American Academy of Pediatrics normal values]) 6. Prior septal myectomy, alcohol septal ablation, or treatment for symptomatic heart failure 7. Known or suspected coronary artery disease or evidence of prior myocardial infarction based on symptoms or cardiac imaging 8. More than mild valvular heart disease, clinically relevant congenital heart disease, or left ventricular ejection fraction (LVEF) <55% 9. Secondary prevention implantable cardioverter-defibrillator (ICD) or history of appropriate ICD therapy

Table S10. Primary Model Details*

Effect	valsartan	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept		-0.6761	0.5566	16	-1.21	0.2421	0.05	-1.8559	0.5038
comp2b		-0.01954	0.08653	24	-0.23	0.8233	0.05	-0.1981	0.1591
nyha		-0.1634	0.1127	24	-1.45	0.1599	0.05	-0.3960	0.06912
mlvwtb_z		-0.00103	0.01001	24	-0.10	0.9192	0.05	-0.02168	0.01963
ageb		0.003106	0.004065	24	0.76	0.4523	0.05	-0.00528	0.01150
PUBERTY		-0.01133	0.08913	24	-0.13	0.8999	0.05	-0.1953	0.1726
bmib		0.002641	0.006086	24	0.43	0.6682	0.05	-0.00992	0.01520
RACE_W		0.4089	0.1860	24	2.20	0.0377	0.05	0.02514	0.7927
HISPANIC		0.01751	0.07988	24	0.22	0.8283	0.05	-0.1473	0.1824
gene_thick		0.2896	0.09142	24	3.17	0.0042	0.05	0.1009	0.4783
LVEF		-0.00808	0.004792	24	-1.69	0.1048	0.05	-0.01797	0.001813
systolic_bpb		0.005744	0.002832	24	2.03	0.0538	0.05	-0.00010	0.01159
betablocker		-0.08584	0.07944	24	-1.08	0.2906	0.05	-0.2498	0.07812
calciumblocker		-0.01349	0.1831	24	-0.07	0.9419	0.05	-0.3914	0.3645
GENDER		0.08973	0.05899	24	1.52	0.1413	0.05	-0.03203	0.2115
valsartan	0	-0.2617	0.05735	24	-4.56	0.0001	0.05	-0.3800	-0.1433
valsartan	1	0	.	.	.	.	.	.	.

*This table shows the details of the mixed model linear regression model from the first imputed dataset.