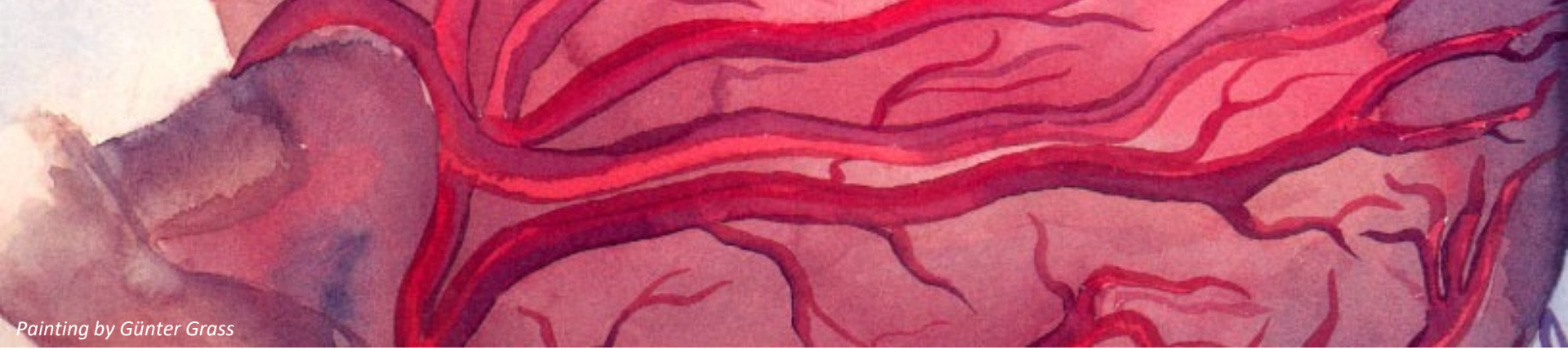

Efficacy and Safety of Aficamten in Obstructive Hypertrophic Cardiomyopathy Patients Eligible for Septal Reduction Therapy: A FOREST-HCM Analysis

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Speaker Disclosures

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- Board Member: Informatics for Life, Deutsche Gesellschaft für Kardiologie, ESC Myocardial Disease WG

Background

- Septal reduction therapy (SRT) has been used to successfully reduce left ventricular outflow tract (LVOT) gradients and improve symptoms and is guideline-recommended first-line therapy for severely symptomatic oHCM patients refractory to medical therapy.[1]
- At experienced centers, the safety and efficacy of both alcohol septal ablation and surgical myectomy are well established.[2]
- Nevertheless, some risk of procedural morbidity and mortality remain at even the most experienced centers, and increase as procedural volumes decline.[2]
- Post-procedural disease-related morbidity also remains, likely due to the inability of SRT to treat the underlying cardiomyopathy.[3]

- We evaluated the potential for aficamten, a next-in-class cardiac myosin inhibitor, to reduce the indication for SRT over extended follow up in FOREST-HCM.

[1] Ommen et al, Circulation 2024:149(23);e1239-e1311.
[2] Altibi et al, J Am Heart Assoc. 2023:12(10);e030194.
[3] Maurizi et al, Circulation, 2024:150(17);1377-1390.
LVOT, left ventricular outflow tract; oHCM, obstructive hypertrophic cardiomyopathy; SRT, septal reduction therapy

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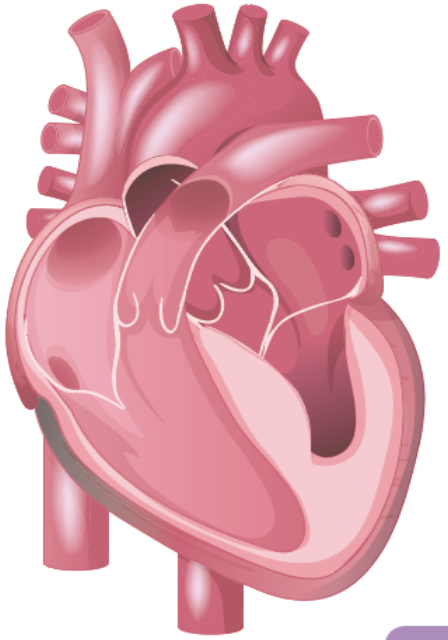
Background: Milestones in the treatment of HCM



1869 First report of HCM

1964 First myectomy

1994 First alcohol septal ablation

2019 Pioneer-HCM

2020 Explorer-HCM, MAVERICK-HCM

2021 TEMPO Trial

2023 SEQUOIA-HCM, REDWOOD-HCM

2024 Valor-HCM

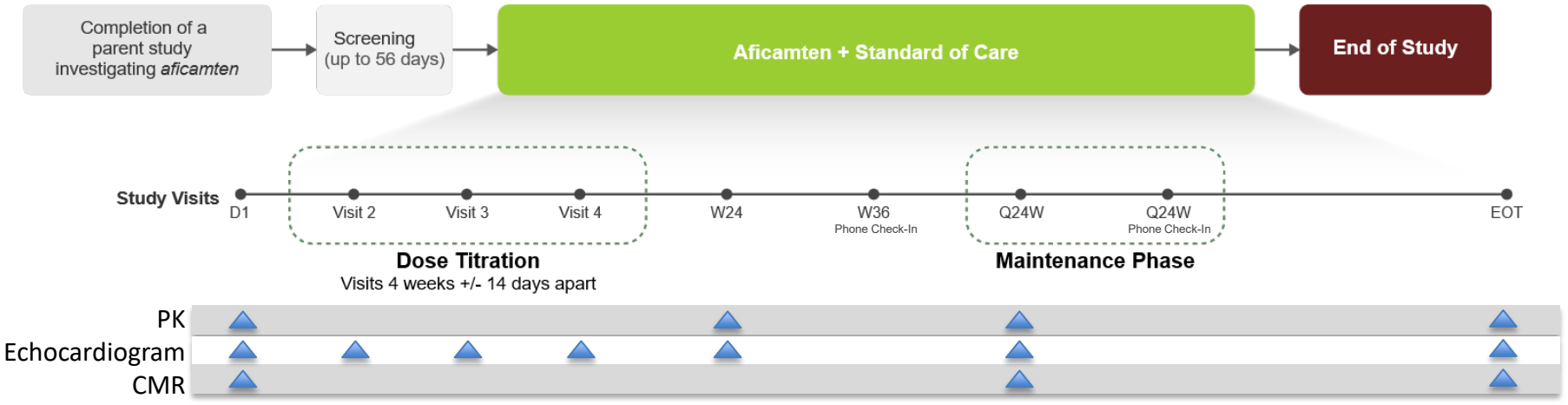
2025 CIRRUS-HCM, MAPLE-HCM, Odyssey-HCM

Long Term FOREST-HCM, MAVA-LTE

Ongoing ACACIA-HCM, CEDAR-HCM, Scout-HCM

Sedaghat-Hamedani et al, Rev Cardiovasc Med. 2026:27(1):47341

Background: FOREST-HCM study design



Guideline-eligibility for SRT was defined as patients treated according to standard of care (SoC), and according to the recent ACC/AHA and ESC consensus documents

SRT Eligible
Severe symptoms: NYHA Class III and peak
LVOT gradient ≥50 mmHg

CMR, cardiovascular magnetic resonance; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; PK, pharmacokinetics; SRT, septal reduction therapy

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Results: Baseline characteristics

- Data reported as N (%) for categorical and mean (SD) or median (IQR) for continuous data, as appropriate.

	SRT Eligible (N=105)	Not SRT Eligible (N=212)
Age, years	61.9 (12.8)	60 (12.7)
Male sex	**46 (43.8%)**	**130 (61.3%)**
Race		
White	97 (92.4%)	201 (94.8%)
Black	3 (2.9%)	2 (0.9%)
Asian	3 (2.9%)	6 (2.8%)
NYHA		
Class I	0 (0%)	11 (5.2%)
Class II	0 (0%)	**184 (86.8%)**
Class III	**105 (100%)**	**17 (8%)[a]**
Background Therapy		
Beta Blocker	57 (54.3%)	142 (67%)
Calcium channel blocker	33 (31.4%)	30 (14.2%)
Disopyramide	17 (16.2%)	28 (13.2%)
2 or more background HCM meds	17 (16.2%)	33 (15.6%)
LVEF	69.4 (5.5)	67.8 (5.9)
KCCQ-CSS	**58 (19.1)**	**76.9 (16.5)**
Resting LVOT Gradient, mmHg	**63 (39.3)**	**52.5 (35.2)**
Valsalva LVOT Gradient, mmHg	**109.7 (42.1)**	**86.2 (40.3)**
NT-proBNP, pg/mL	814 (387, 1714)	764.5 (328.5, 1528)
Troponin, ng/L	11.9 (5.5, 28.4)	10.7 (6.1, 18.8)

[a] Patients with NYHA class III symptoms were deemed not SRT eligible if LVOT gradient was not ≥50 mmHg

IQR, interquartile range; Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SRT, septal reduction therapy

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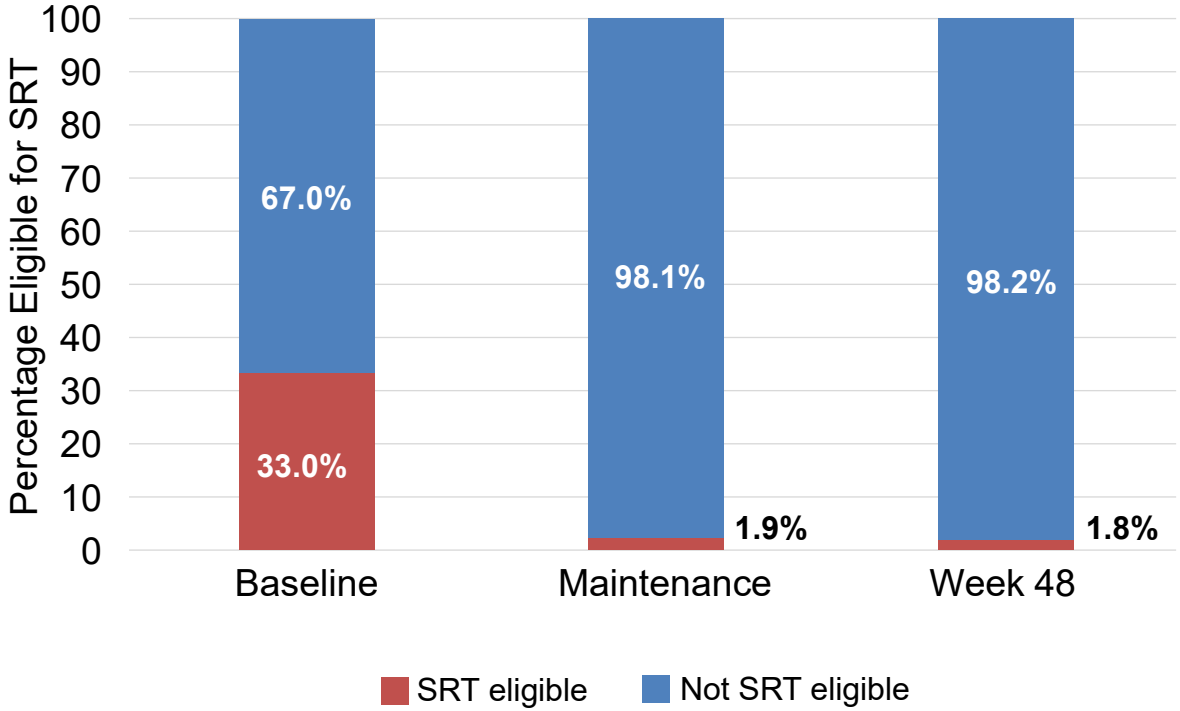
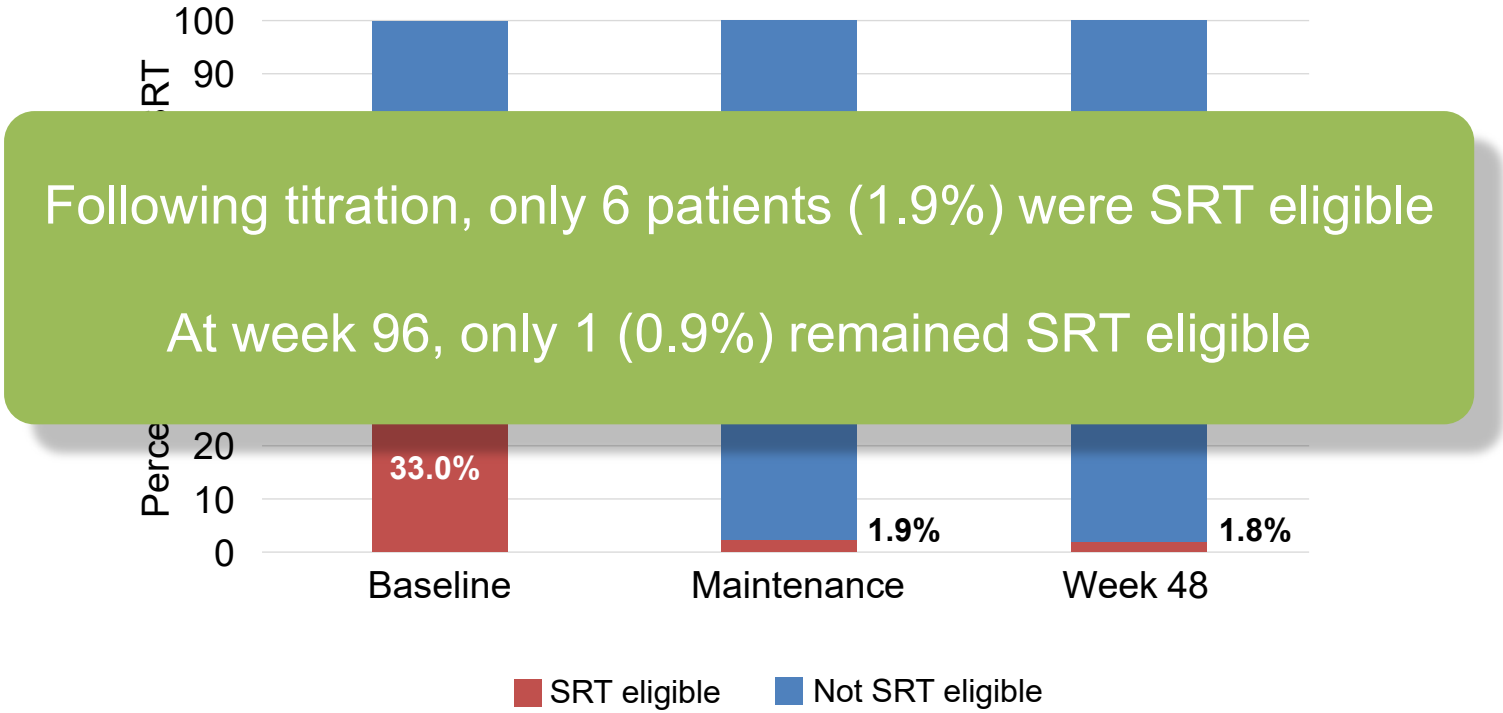
Results: Eligibility for SRT over time



SRT, septal reduction therapy

Results: Eligibility for SRT over time



Following titration, only 6 patients (1.9%) were SRT eligible

At week 96, only 1 (0.9%) remained SRT eligible

SRT, septal reduction therapy

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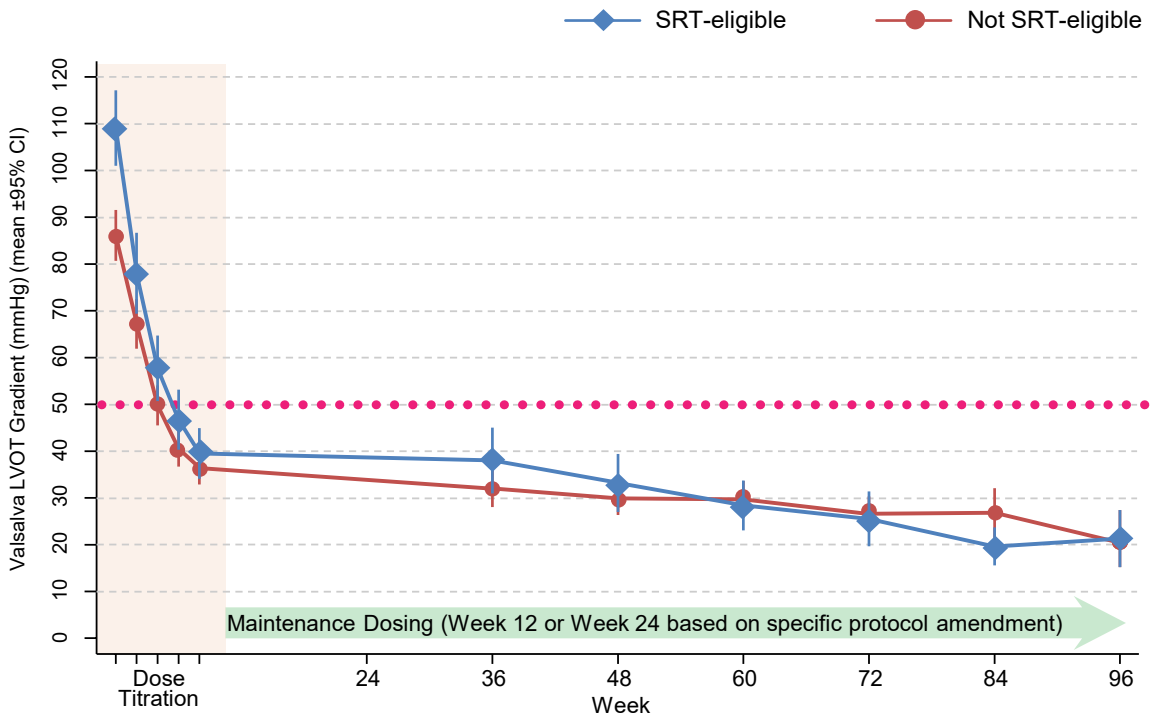
Results: Valsalva LVOT gradient over time

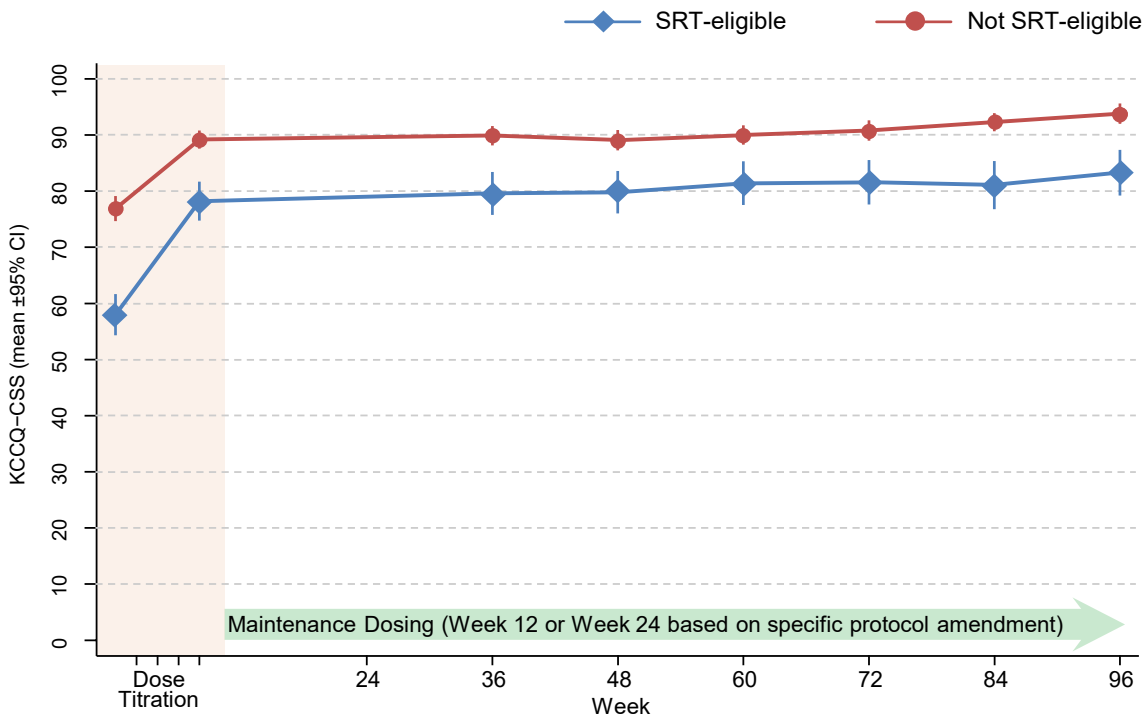


SRT eligible, N	104	96	95	82	80	53	45
Not SRT-eligible, N	211	185	182	169	158	100	62

Baseline 109.1 mmHg ± 8.1 mmHg vs Maintenance 39.5 mmHg ± 5.5 mmHg; p<0.0001 for SRT eligible group

LVOT, left ventricular outflow tract; SRT, septal reduction therapy

Results: KCCQ-CSS over time



SRT eligible, N	104	97	94	80	67	51	45
Not SRT-eligible, N	211	184	182	166	140	92	61

Baseline 58.0 ± 3.7 vs Maintenance 78.2 ± 3.5; p<0.001 for SRT eligible group

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; SRT, septal reduction therapy

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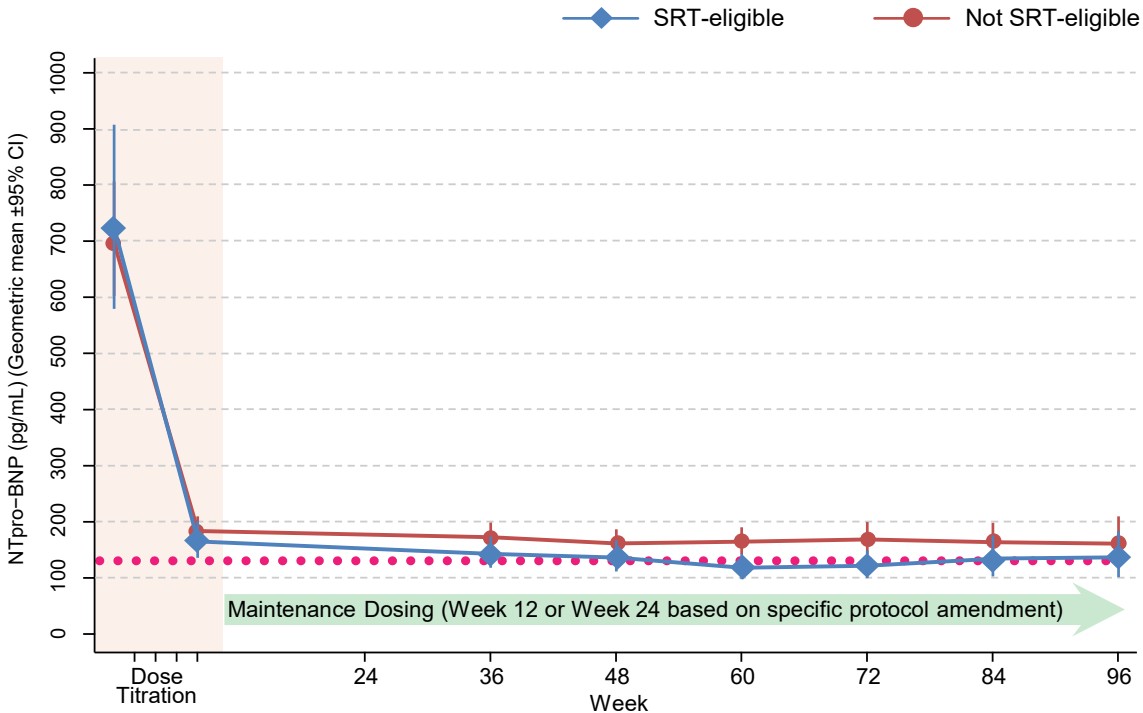
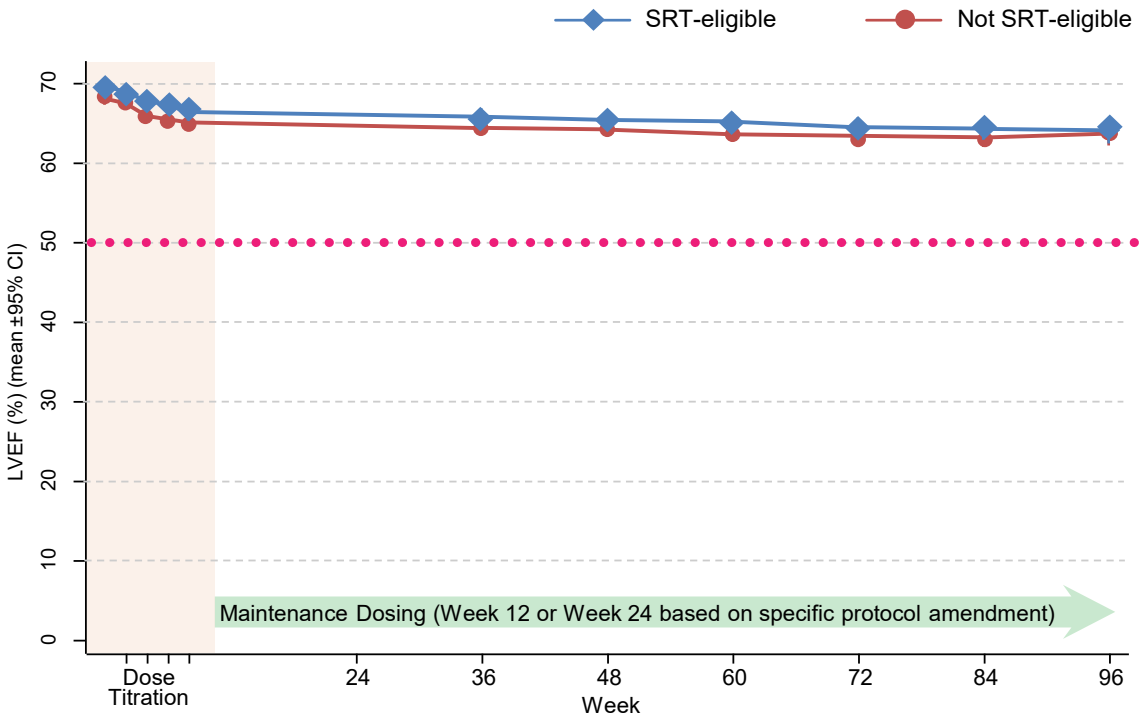
Results: NT-proBNP over time



Baseline 725 pg/mL [579, 907] vs Maintenance 165 pg/mL [136, 201]; p<0.001 for SRT eligible group

NT-proBNP, N-terminal pro-B-type natriuretic peptide; SRT, septal reduction therapy

Results: LVEF over time



SRT eligible, N	104	97	96	82	80	53	45
Not SRT-eligible, N	211	185	182	169	158	100	62

Baseline 69.5% ± 1.1% vs Maintenance 66.2% ± 1.1%; p<0.001 for SRT eligible group

LVEF, left ventricular ejection fraction; SRT, septal reduction therapy

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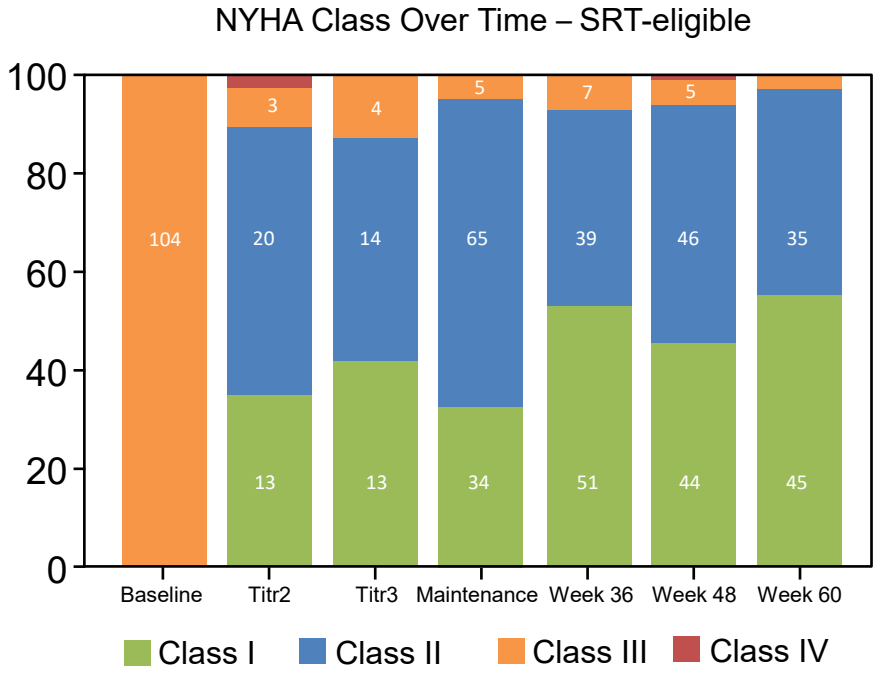
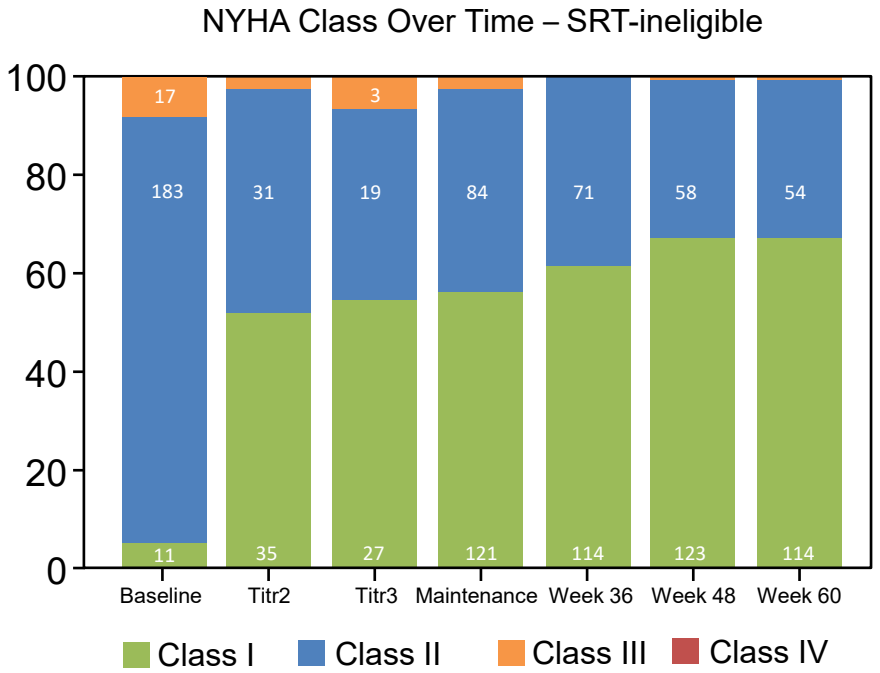
Results: NYHA over time



97.6% of SRT eligible patients improved by ≥1 NYHA class by week 60



66.3% of SRT ineligible patients improved by ≥1 NYHA class by week 60

Numbers in each graph represent n.
NYHA, New York Heart Association; SRT, septal reduction therapy; Titr, titration

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Safety

- No occurrences of LVEF <40%
- 2 SRT-eligible patients (at baseline) had transient decline in LVEF <50%
  - Exposure-adjusted incidence rate of 1.0 per 100 patient-years
- Most frequent cardiac TEAEs:

Preferred Term	SRT Eligible (N=105) n (%), m	SRT Ineligible (N=212) n (%), m	Overall (N=317) n (%), m
Palpitations	9 (8.6), 10	14 (6.6), 14	23 (7.3), 24
New onset atrial fibrillation	2 (1.9), 2	9 (4.2), 9	11 (3.5), 11
Angina pectoris	6 (5.7), 6	6 (2.8), 6	12 (3.8), 12
Sinus bradycardia	3 (2.9), 3	2 (0.9), 2	5 (1.6), 5
Tachycardia	2 (1.9), 2	3 (1.4), 3	5 (1.6), 5
Ventricular tachycardia	1 (1.0), 1	4 (1.9), 6	5 (1.6), 7

LVEF, left ventricular ejection fraction; SRT, septal reduction therapy; TEAE, treatment emergent adverse event

Conclusions

- Aficamten eliminates SRT eligibility in nearly all oHCM patients with durable efficacy over extended follow up.
- Improvements in clinically important assessments begin early in titration and remain stable over extended follow up and are similar between SRT eligible and non-eligible patients.
- SRT eligible patients treated with aficamten demonstrate a similar and favorable safety profile compared with non-SRT eligible patients.
- Aficamten treatment may provide an alternative to SRT in some patients and a trial of aficamten may be considered before SRT referral.

oHCM, obstructive hypertrophic cardiomyopathy; SRT, septal reduction therapy

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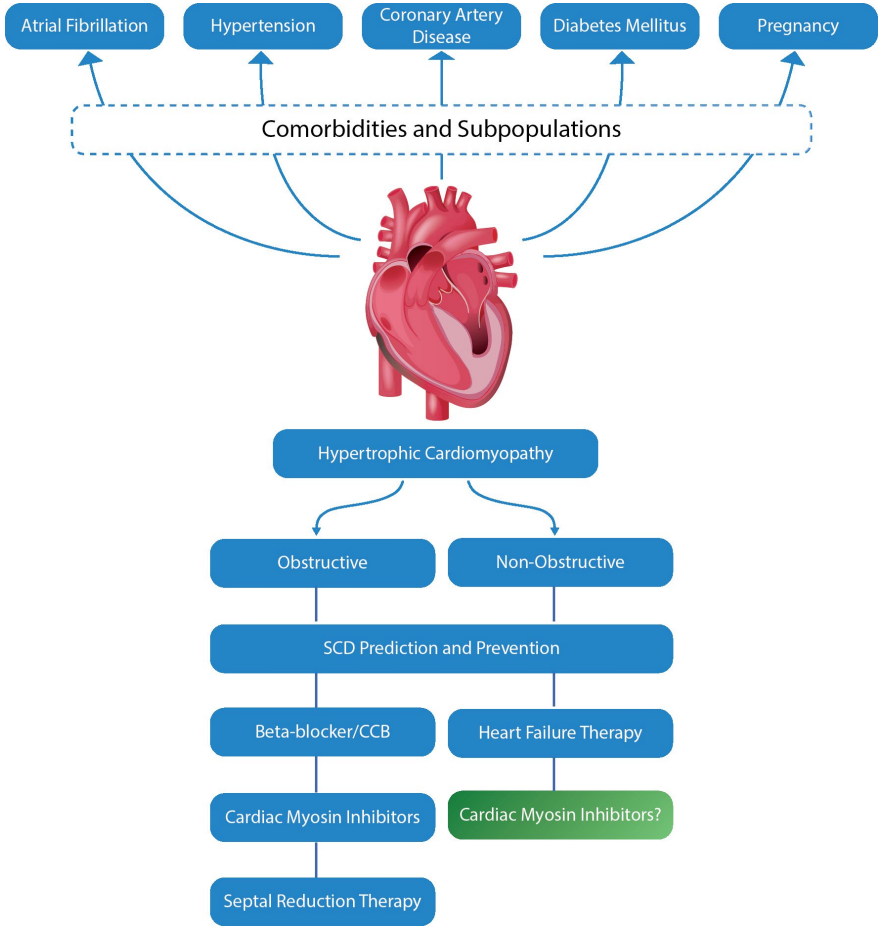
Conclusions

- Proposed approach to myosin inhibitor initiation in the treatment of oHCM



Adapted from Meder et al, Eur J Heart Fail. 2026, doi: 10.1093/ejhf/xuaf008

CCB, calcium channel blockers; oHCM, obstructive hypertrophic cardiomyopathy; SCD, sudden cardiac death

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- Investigators and study site staff
- Steering Committee members

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