Efficacy and Safety of Aficamten in Patients Guideline-Eligible for Septal Reduction Therapy in the FOREST-HCM Trial

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Background

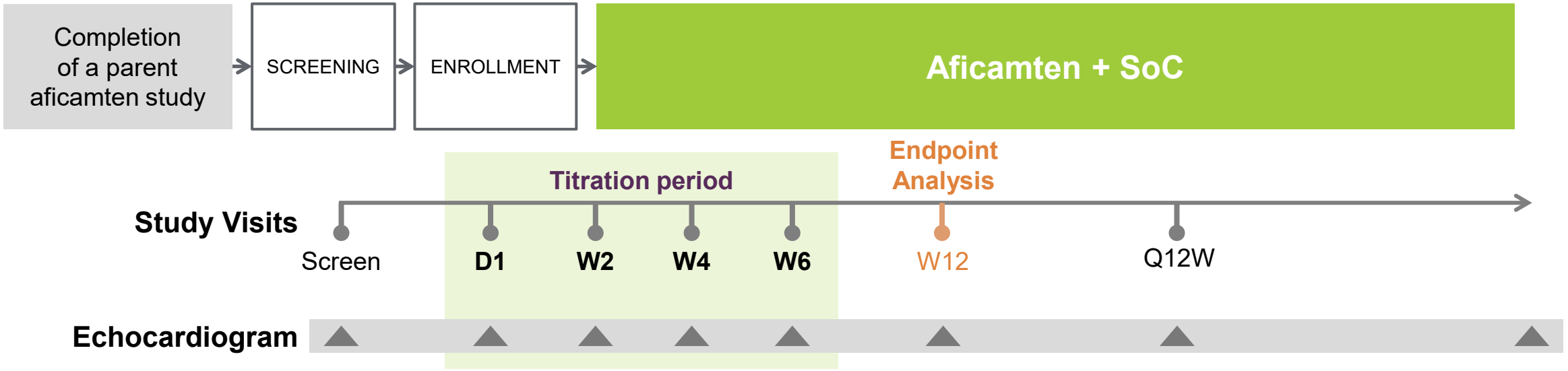
Guideline-eligibility for SRT was defined as patients treated according to standard of care (SoC), and according to the recent ACC/AHA and ESC consensus documents:

- **Severe symptoms (NYHA class ≥ III)**

  AND

- **LVOT gradient ≥ 50 mmHg**

FOREST-HCM (NCT04848506) intentionally allows for the integration of the treating physician's clinical impression (symptoms, imaging and biomarkers) into the dose adjustment algorithm in keeping with a possible real-world application. Up-titration of asymptomatic patients with residual obstruction was not mandated.

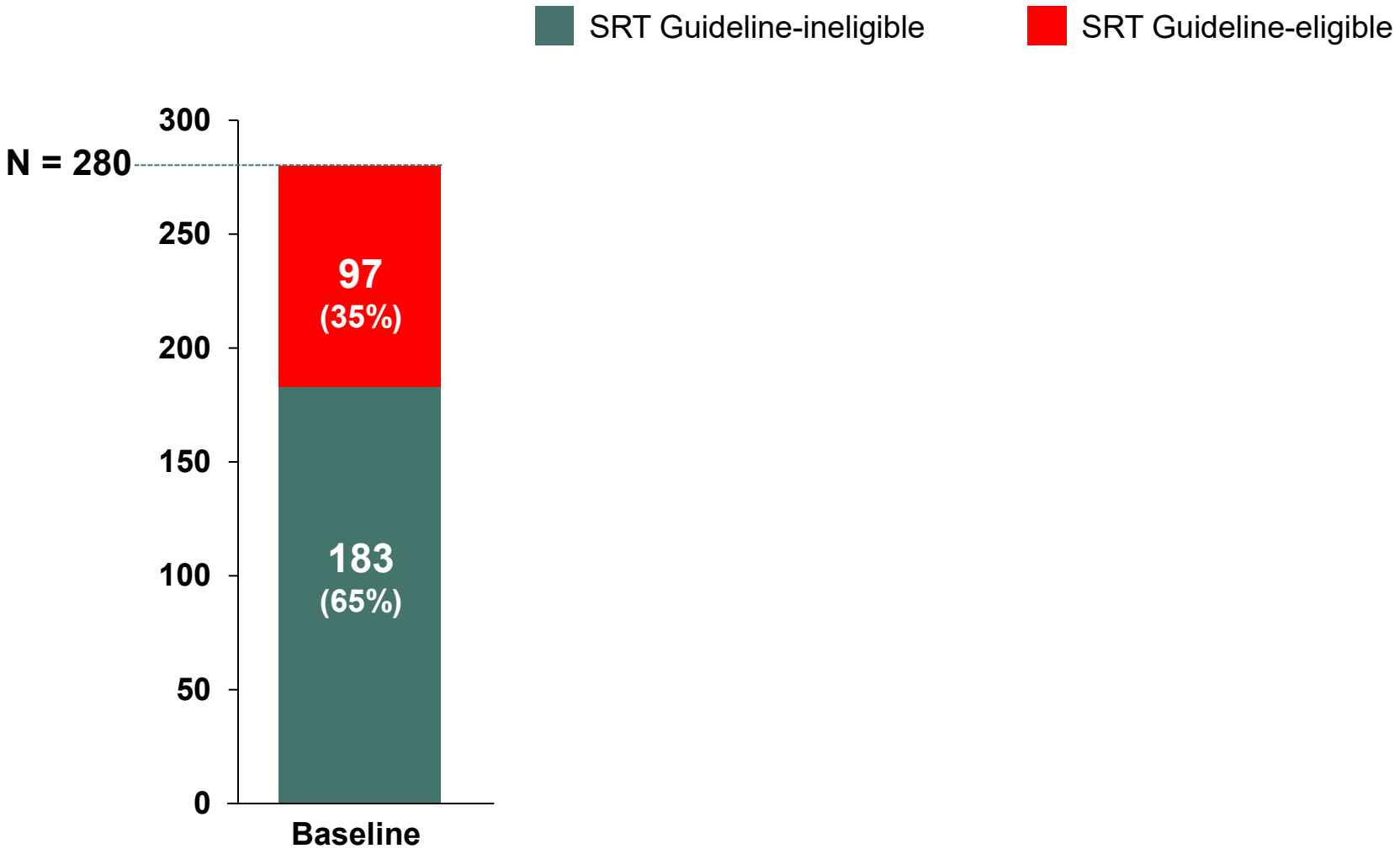


RESULTS: Baseline Characteristics

Characteristic	SRT eligible (N=97)	SRT ineligible (N=183)
Age (Years), Mean (SD)	62.7 (12.3)	60.2 (12.3)
Female, n (%)	56 (57.7)	68 (37.2)
NYHA Class, n (%)		
Class I	0	10 (5.5)
Class II	0	158 (86.3)
Class III	97 (100)	15 (8.2)
KCCQ-CSS, Mean (SD)	58 (19)	77 (17)
Beta Blocker, n (%)	54 (55.7)	129 (70.5)
Calcium Channel Blocker, n (%)	43 (44.3)	43 (23.5)
Disopyramide, n (%)	16 (16.5)	27 (14.8)
LVEF* (%), Mean (SD)	70 (6)	68 (6)
Rest LVOT-G* (mmHg), Mean (SD)	63 (40)	53 (36)
Valsalva LVOT-G* (mmHg), Mean (SD)	108 (42)	86 (41)
NT-proBNP (pg/mL), Median (IQR)	818 (392, 1843)	778 (332, 1581)

KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF, Left Ventricular Ejection Fraction; LVOT-G, Left Ventricular Outflow Tract Gradient; NT-proBNP, N-terminal Pro-B-type Natriuretic Peptide; NYHA, New York Heart Association; SD, Standard Deviation.
*site reported

RESULTS: Change from Baseline to Week 12 Guideline-Eligibility for SRT



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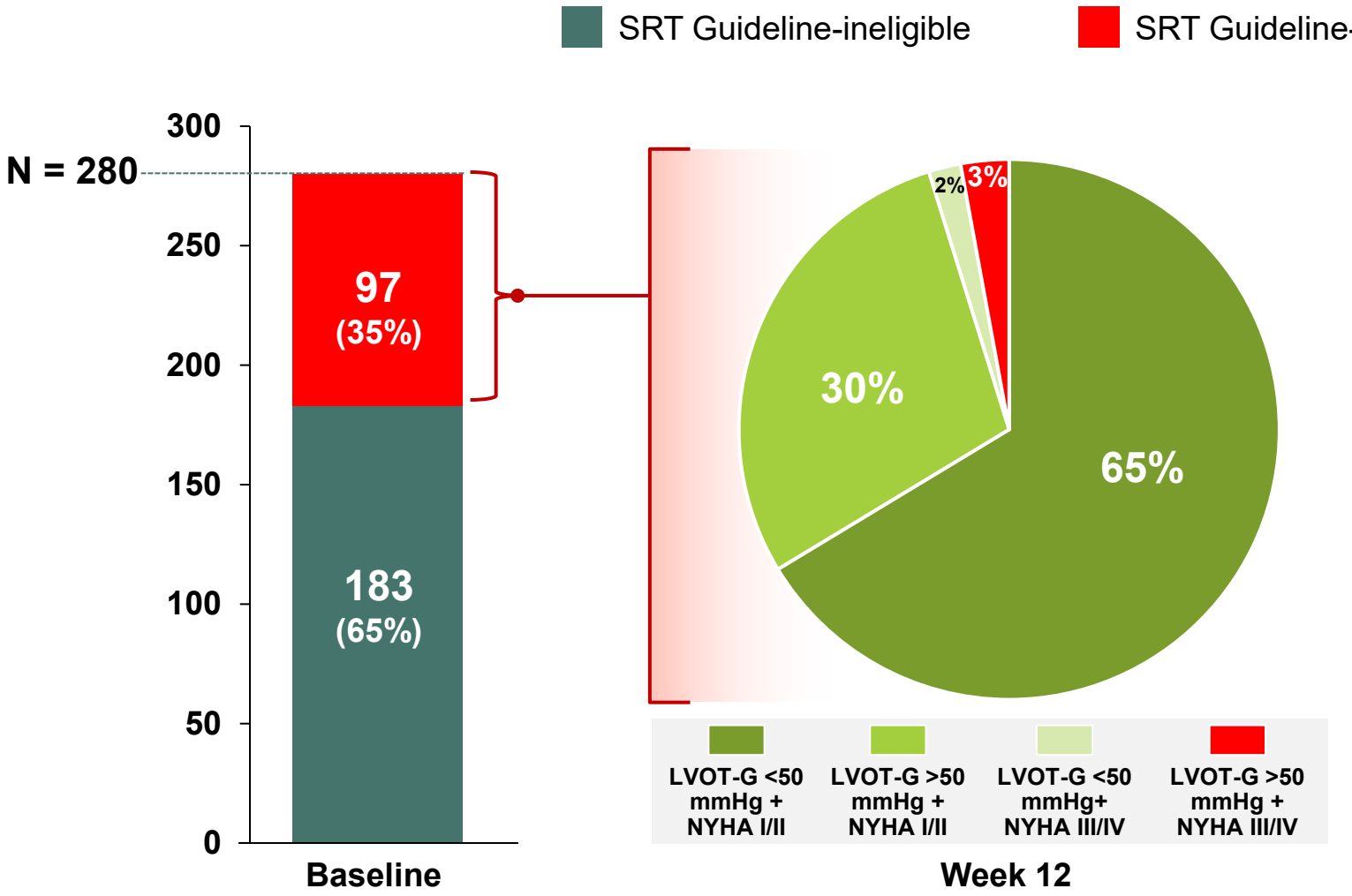

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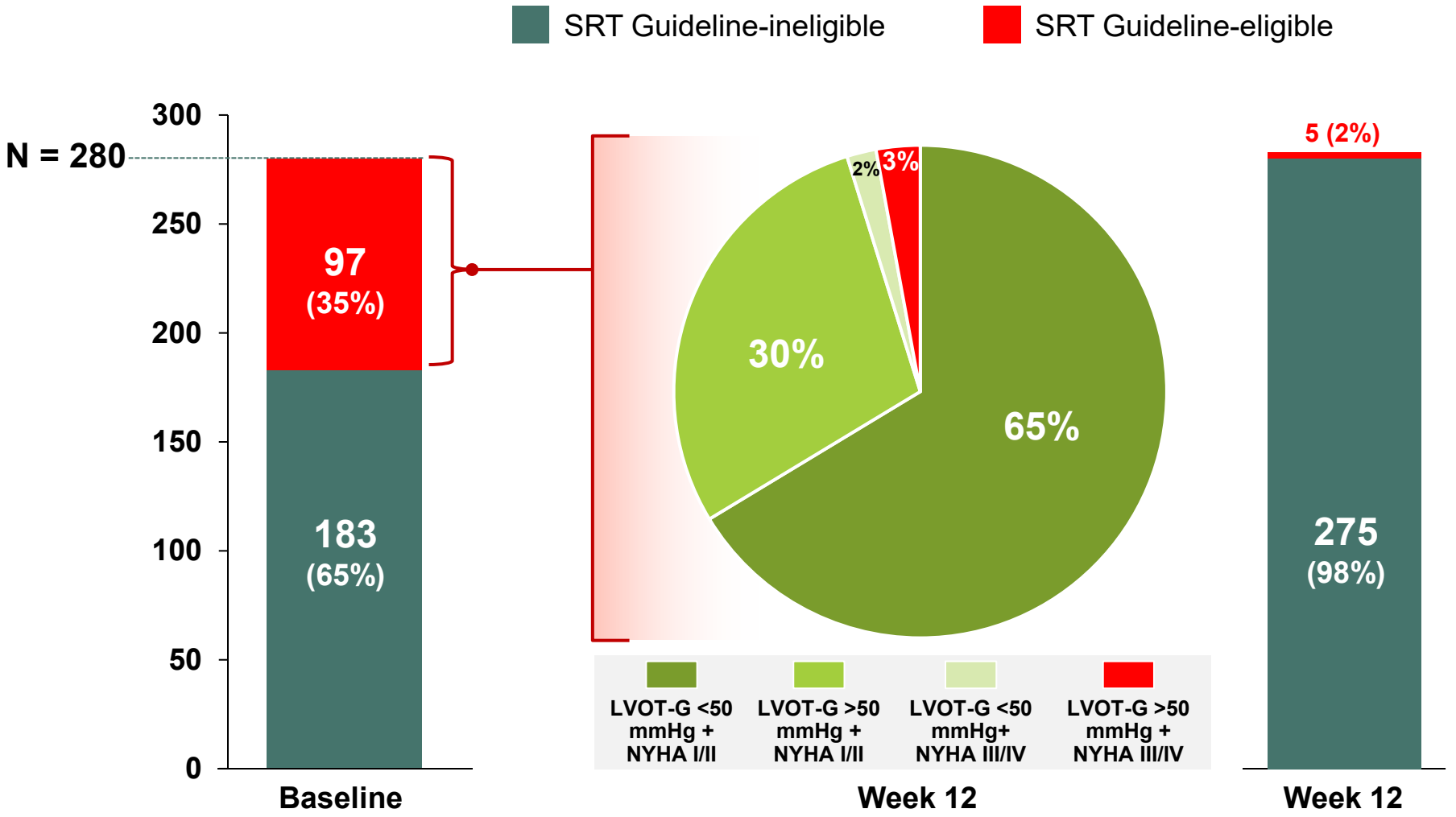


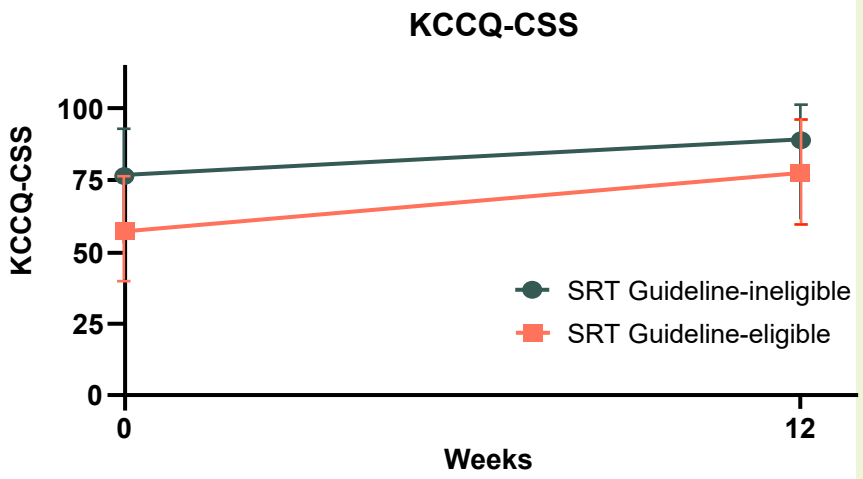
Of the 97 patients guideline-eligible for SRT at baseline

97%

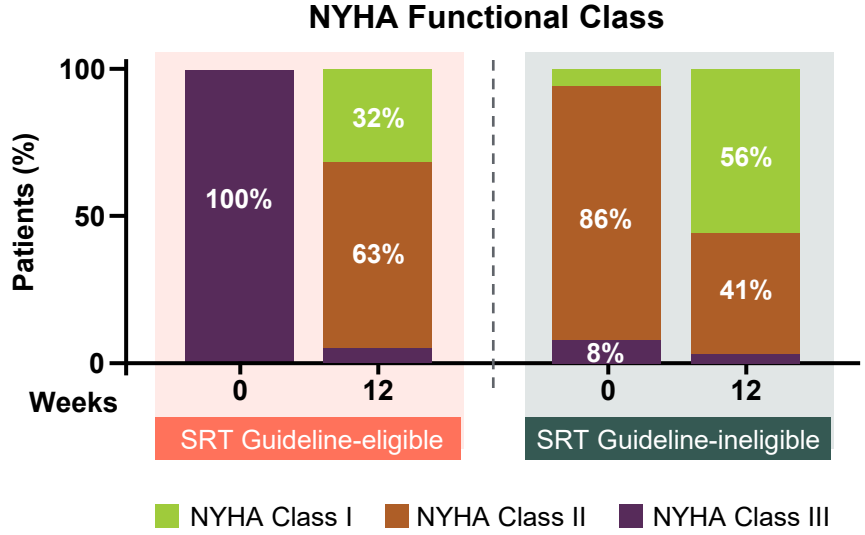
were guideline-**ineligible** for SRT by Week 12

Treatment effect was durable up to week 24

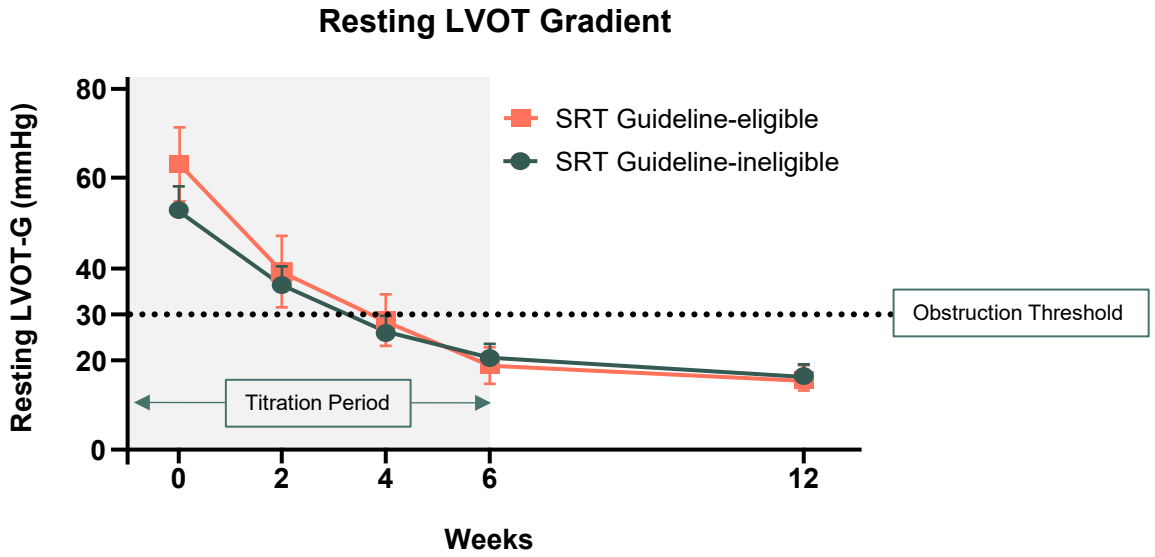
RESULTS: Symptoms, Patient-Reported Outcomes, and LVOT Gradients

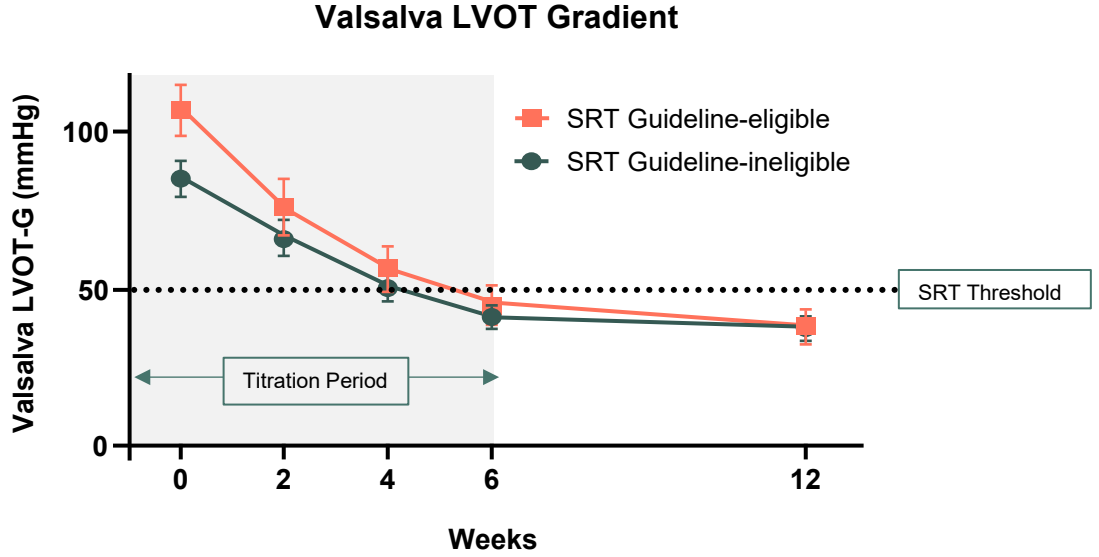


KCCQ-CSS proportional improvement: 35% vs 15% (SRT-eligible vs ineligible)

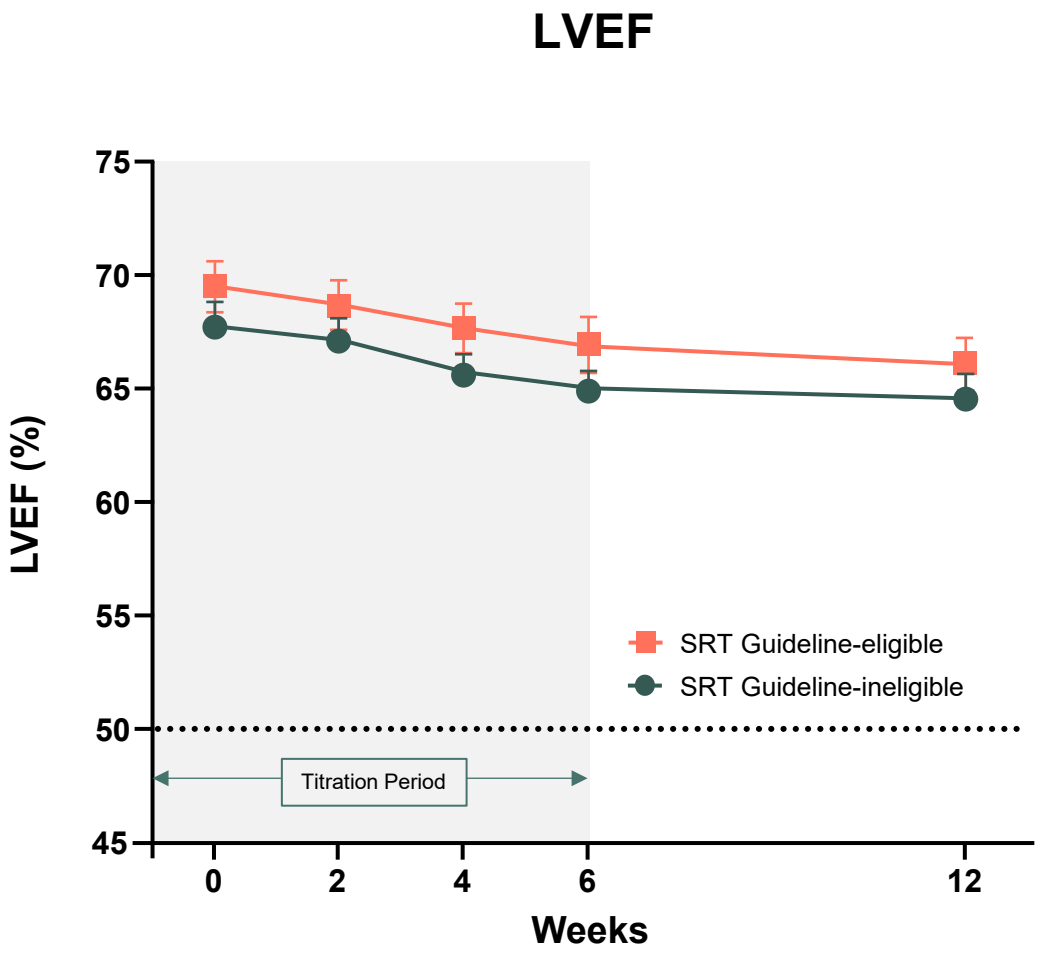


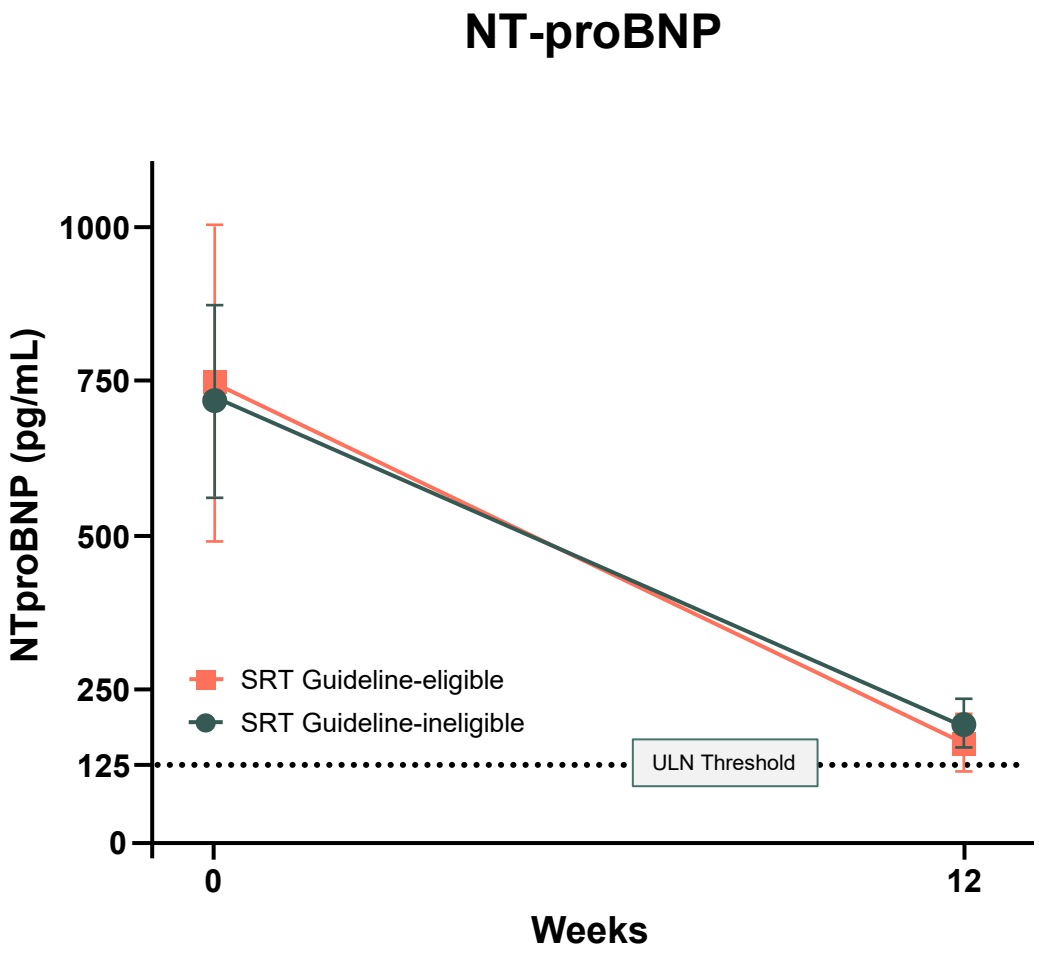
By week 12, 95% of SRT guideline-eligible and 55% of SRT guideline-ineligible patients achieved ≥ 1 NYHA class improvement





RESULTS: LVEF and NT-proBNP





Changes in LVEF were modest, stable after titration, and similar between groups. NT-proBNP improvement was marked and similar, independent of SRT eligibility.

ULN, upper limit of normal

Safety

	SRT Eligible (N=98) n (%)	SRT Ineligible (N=184) n (%)	Total (N=282) n (%)
Exposure (patient years)	23.2	43.4	66.6
Patients with ≥1 TESAE	1 (1.1)	8 (4.3)	9 (3.2)
Patients with TEAE Leading to Drug Withdrawal	0	0	0
LVEF^ < 50%	2 (2.0)	2 (1.1)	4 (1.4)
LVEF^ < 50% with Heart Failure*	0	0	0
Atrial Fibrillation or Flutter	2 (2.0)	5 (2.7)	7 (2.5)
New Onset	0	1 (0.5)	1 (0.4)
Recurrent	2 (2.0)	4 (2.2)	6 (2.1)

^ site read; *new onset or worsening heart failure
Note: The table summarizes events up to Week 12 of the study

Exposure adjusted incidence of LVEF < 50% and atrial fibrillation or flutter demonstrate low rates without important between group differences

Conclusions

Despite standard of care therapy,

a third of patients enrolled in FOREST-HCM were **guideline-eligible for SRT**

At 12 weeks:

- **Aficamten treatment rapidly improved the symptom and LVOT gradient criteria used to define guideline-eligibility in 97% of patients** who met these criteria at baseline
- **Regardless of baseline guideline-eligibility status,** patients treated with aficamten reported substantial improvements in health status, functional status, hemodynamic and biomarker measures
- **Aficamten was well tolerated,** and occurrences of LVEF <50% were low (<2% overall), none of which were associated with clinical heart failure