HFSA 2022

ANNUAL SCIENTIFIC MEETING

WHERE **HEART FAILURE TEAMS** GATHER

Gaylord National Harbor, Washington, DC

September 30 – October 3, 2022

HFSA

HEART FAILURE SOCIETY OF AMERICA

Improvement in KCCQ Scores in Patients with Obstructive Hypertrophic Cardiomyopathy Treated with *Aficamten* in the REDWOOD-HCM OLE Study

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REDWOOD
HCM OLE

Disclosures

REDWOOD HCM OLE

- Site PI for Clinical Trials:
  - Bristol Myers Squibb: MAVA-LTE, VALOR-HCM
  - Cytokinetics: REDWOOD-HCM, REDWOOD-OLE, SEQUOIA-HCM
  - Novartis: ENTRESTO-HCM
- Steering Committee Member for Research Studies:
  - Bristol Myers Squibb: ODYSSEY-HCM, DISCOVER-HCM
  - Cytokinetics: REDWOOD-OLE, SEQUOIA-HCM
- Consulting Honoraria
  - Bristol Myers Squibb, Cytokinetics

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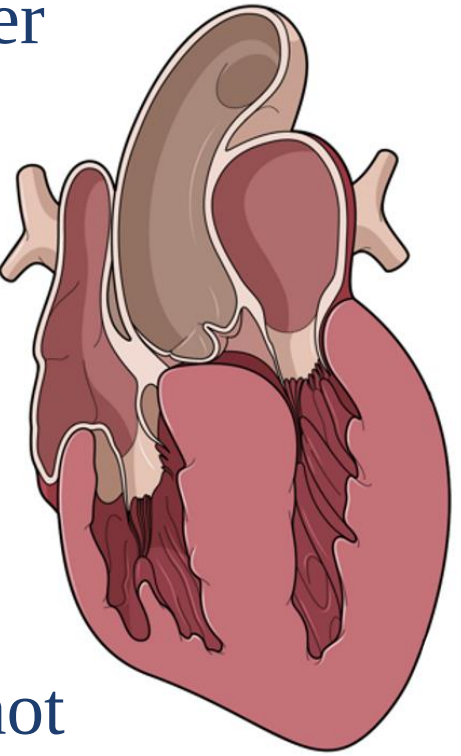
Background

REDWOOD HCM OLE

- Hypertrophic cardiomyopathy (HCM) is a myocardial disorder defined by unexplained left ventricular hypertrophy, fibrosis, hypercontractility, and abnormal relaxation
- Principal treatment goals for patients with obstructive hypertrophic cardiomyopathy (oHCM) are:
  - **Improve patients' health status (ie, symptoms, physical and social function, and quality of life) and functional capacity.**
  - **Improve hemodynamics**
- Standard of care pharmacological therapies for oHCM have not reliably been shown to improve patients' health status[1,2]



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1) Ommen SR *et al. Circulation* 2020;142:e558-e631. 2) Elliot PM *et al. Eur Heart J* 2014;35:2733-79.

Background

REDWOOD HCM OLE

- REDWOOD-HCM demonstrated that 10 weeks of treatment with the cardiac myosin inhibitor, *aficamten*, resulted in improvements in hemodynamics and cardiac biomarkers

- Patients who successfully completed REDWOOD-HCM were offered participation in the open label extension study (REDWOOD-HCM OLE)

- In REDWOOD-OLE, we aimed to assess the effect of *aficamten* treatment on patients' health status

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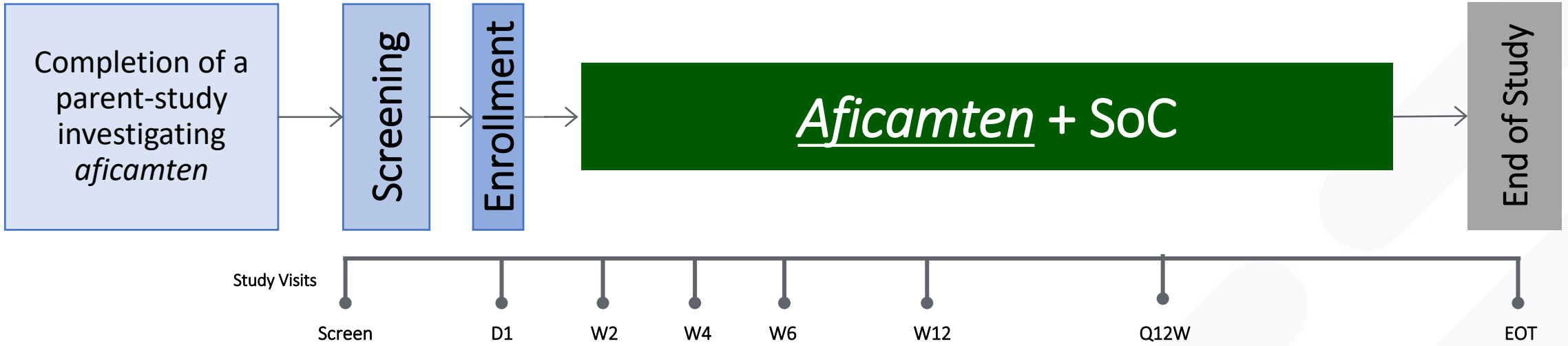
Study Design

REDWOOD HCM OLE



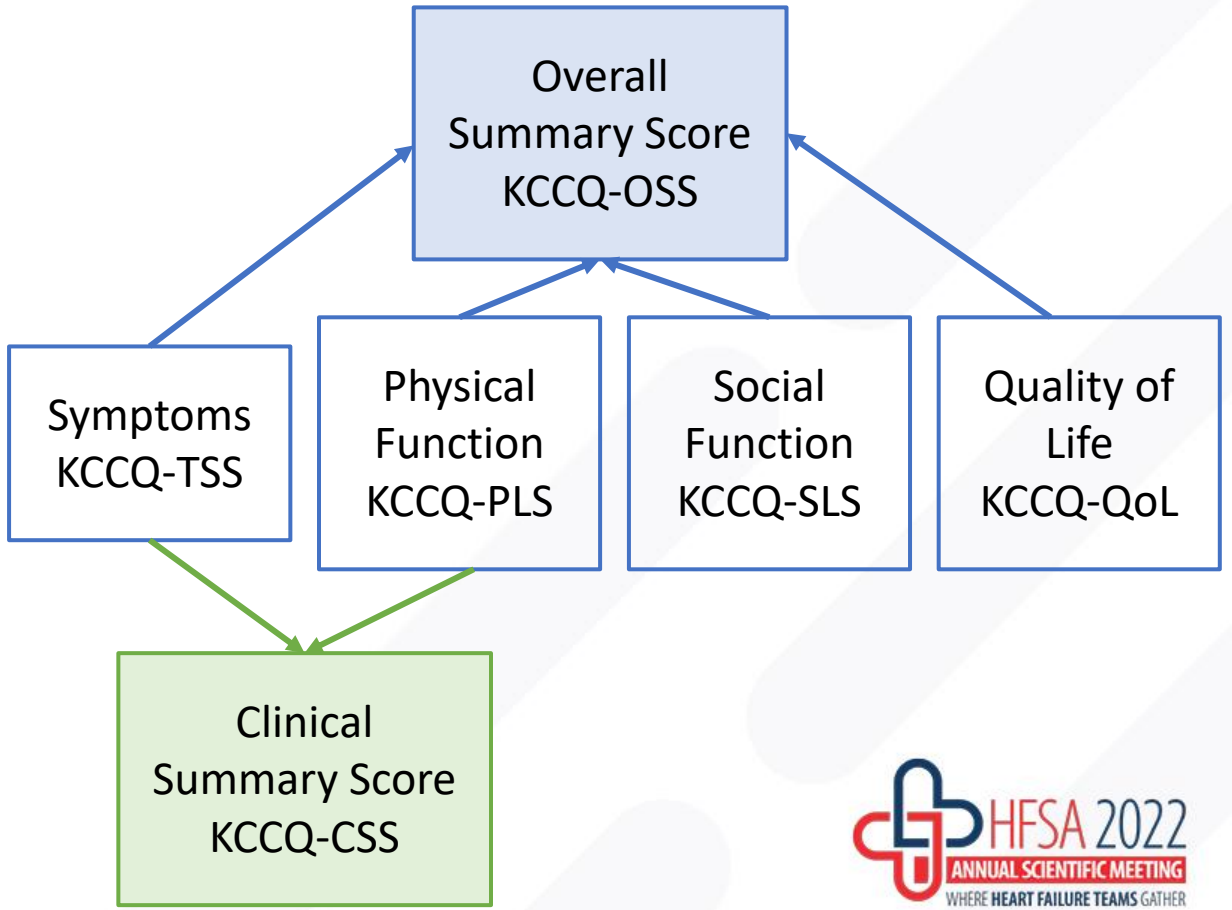
▲ KCCQ every 12 Weeks
▲ Truncated Echo
▲ CMR at Weeks 48, 144 and 240

Doses available for Investigator Driven Titration

5 mg | 10 mg | 15 mg | 20 mg

Methods

- Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item cardiomyopathy-specific questionnaire
- Range 0 – 100
  - Higher scores indicate fewer symptoms, better function/QoL
- Minimum clinically important difference from baseline = 5 points
- 5-, 10- and 20-point changes represent small, moderate-large, and large-very large changes[3]
- We report changes in KCCQ scores from baseline to 12 and 24 weeks of treatment with *aficamten*

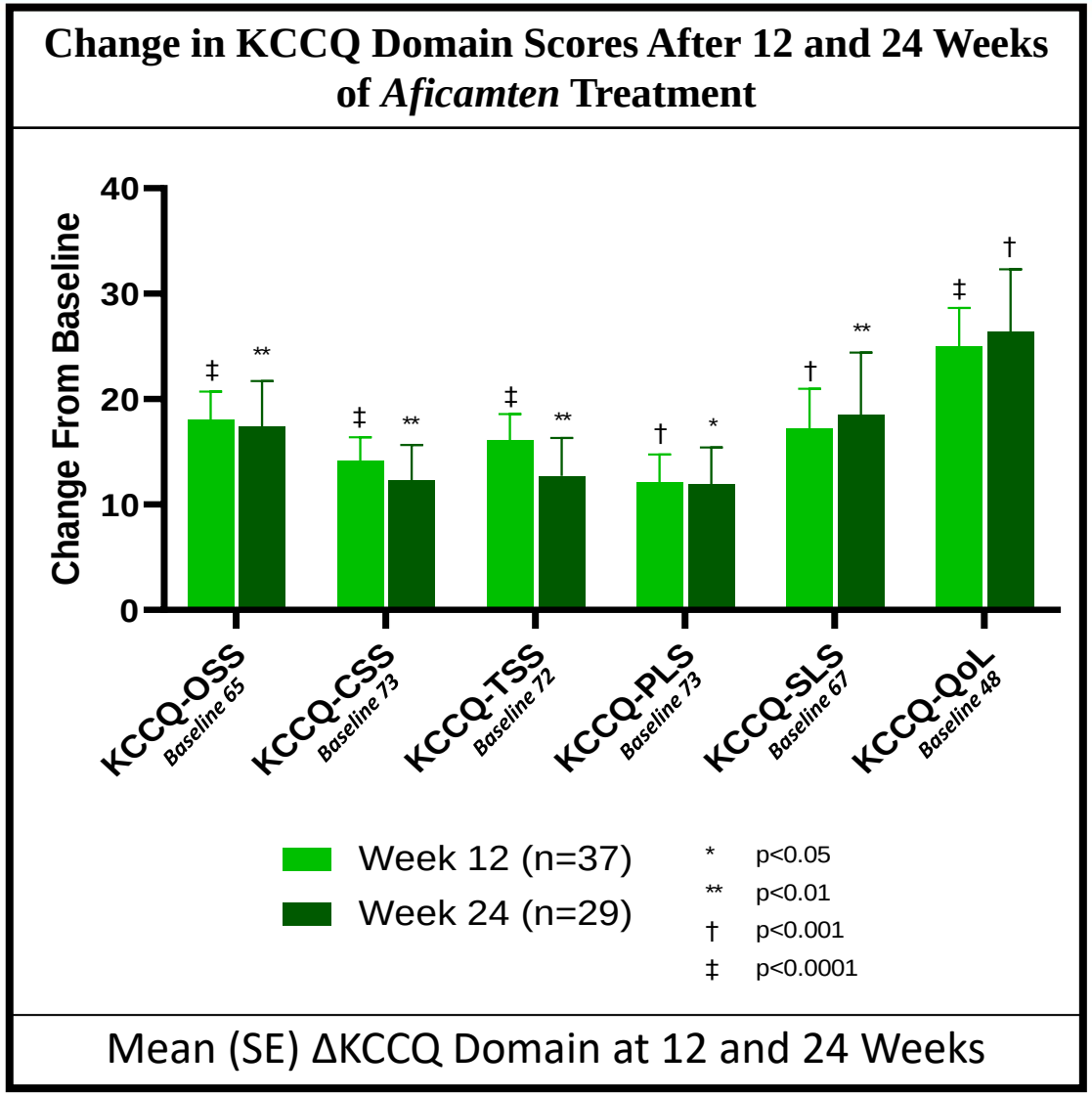


[3] Spertus JS *et al. Am Heart J* 2005; 150:707-15.

Results – Baseline Characteristics

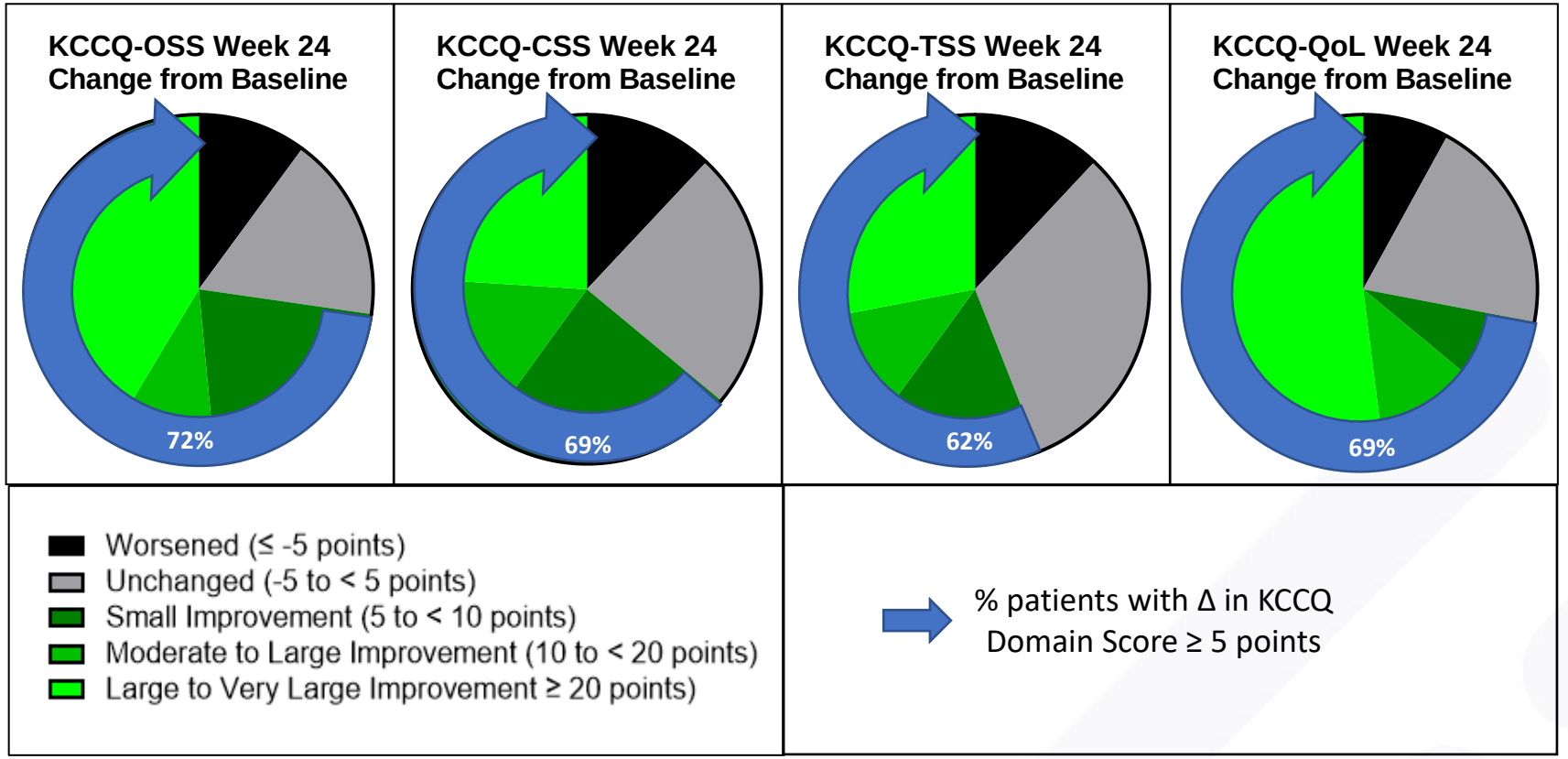
Baseline Characteristics	N = 42
Age (Years), Mean (SD) [Range]	59.2 (12.7) [23 - 82]
Female, n (%)	25 (59.5%)
BMI (kg/m2), Mean (SD) [Range]	29.7 (6.4) [22- 51]
NYHA Class, n (%)	
Class II	22 (52.4%)
Class III	**20 (47.6%)**
Positive family history of HCM, n (%)	10 (23.8%)
Background HCM Therapy, n (%)	
Beta Blocker	33 (78.6%)
Calcium Channel Blocker	7 (16.7%)
Disopyramide	**8 (19.0%)**
LVEF* at Screening (%), Mean (SD) [Range]	69.4 (4.1) [60-78]
LVOT-G*, Rest at Screening (mmHg), Mean (SD) [Range]	46.7 (26.3) [9-95]
LVOT-G*, Valsalva at Screening (mmHg), Mean (SD) [Range]	79.2 (30.2) [15-150]
NT-proBNP (pg/mL), Geometric Mean (%CV) [Range]	**642.6** (165.5) [70-8333]
Cardiac Troponin I (ng/L), Geometric Mean (%CV) [Range]	**15.2** (297.8) [3.4 – 2017.1]
Duration on Treatment in Weeks, Mean (SD) [Range]	**33.5** (14.1) [3-57]

Results – Health Status

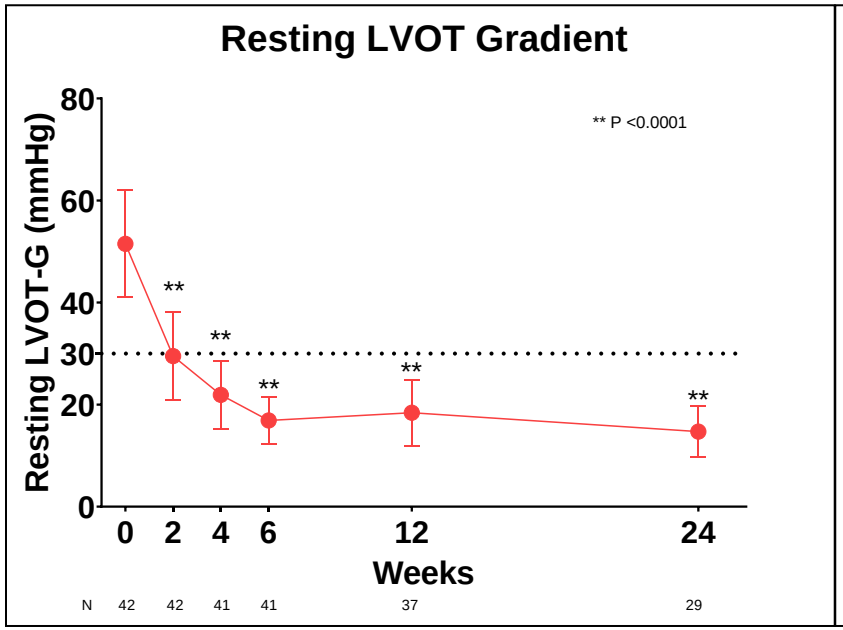


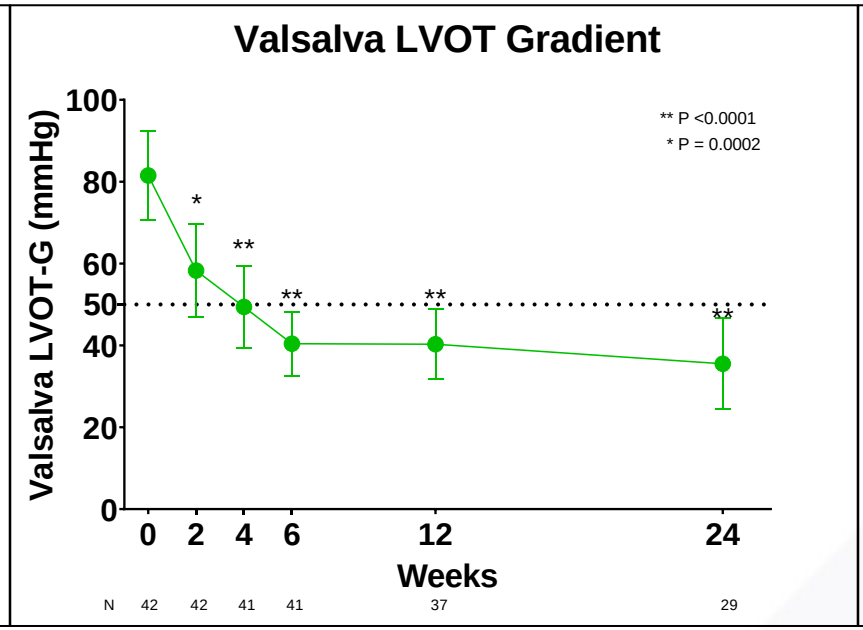
Substantial and significant positive impact on patient reported health status was noted across **ALL** KCCQ domains after 3 months of treatment and sustained for at least 6 months

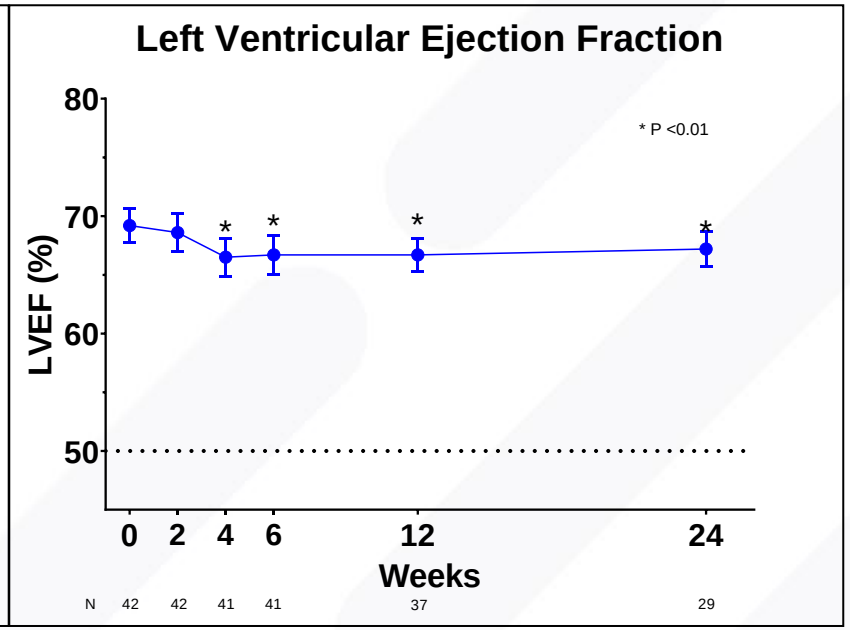
Results – Categorical Changes



Results – Hemodynamic Effect







Data presented as mean ± 95% Confidence Interval

Echocardiographic data from site reads

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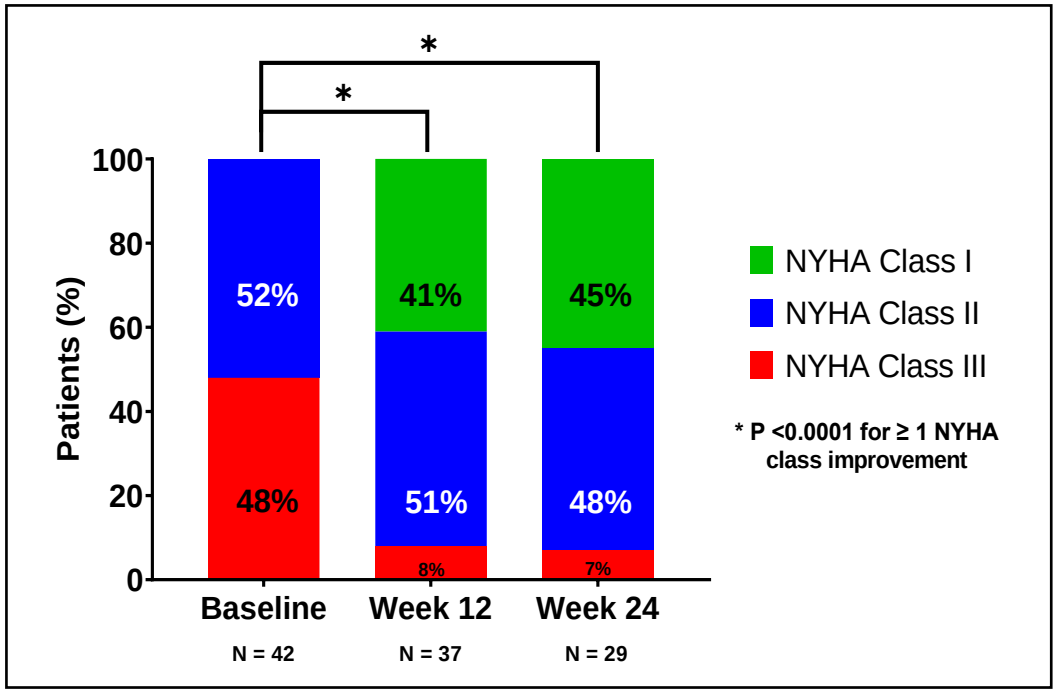
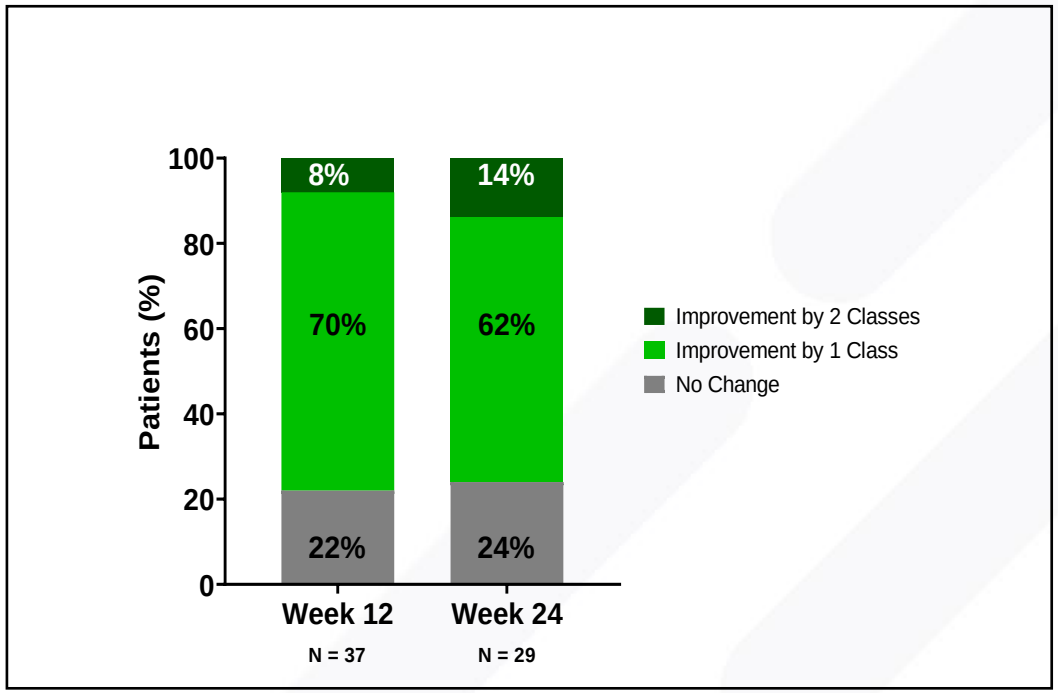
Results – Functional Status





No patients had a worsening of NYHA class from baseline

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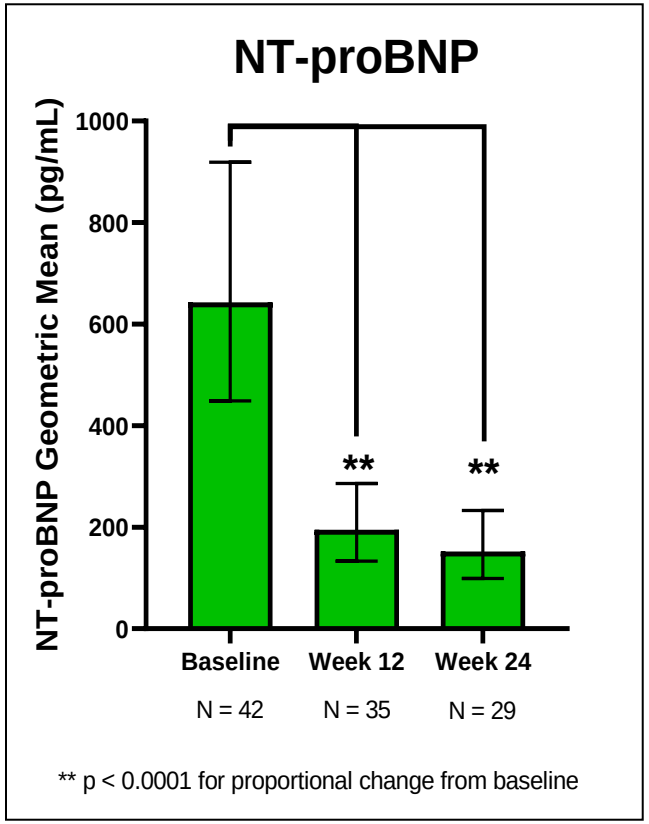
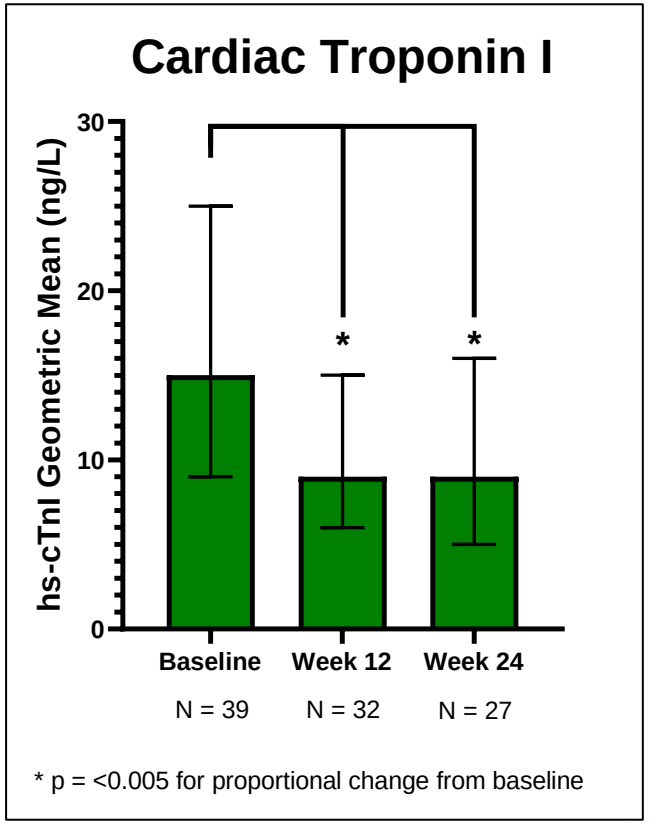
Results – Biomarkers





Data presented as geometric mean ± 95% Confidence Interval

70% reduction, relative to baseline, in NT-proBNP at Week 12 and Week 24

30% reduction, relative to baseline, in hs-Troponin I at Week 12 and Week 24

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Safety

Treatment Emergent Adverse Events (TEAE)	N=42
Patients with ≥1 TEAE	32 (76.2)
Patients with at ≥1 TESAE	2 (4.8)
Patients with ≥1 Related TEAE	10 (23.8)
Patients with ≥1 Severe TEAE	3 (7.1)
Early Termination	0
Deaths	0
Dosing	
Dose Reduction	2 (4.8)
Drug Interruption	1 (2.4)
Drug Withdrawal	0

Temporary dose reduction and/or treatment interruption

- 2 patients underwent temporary dose reduction/interruption
  - 1 patient with LVEF of 47% while experiencing a recurrence of known alcohol triggered atrial fibrillation → now on amiodarone for rhythm control (dose reduction and subsequently treatment interruption)
  - 1 patient with suspected QTc prolongation by the investigator (core lab calculated QTc confirmed no prolongation).
- Both patients are now receiving *aficamten* and are currently NYHA class 1

Conclusions

REDWOOD HCM OLE

- Treatment with *aficamten* resulted in marked and sustained improvements in all KCCQ domain scores for up to 6 months in this phase 2 open-label study
- Treatment benefits are observed early
- Health status benefits of *aficamten* treatment are paralleled by improvements in LVOT obstruction, left ventricular filling pressure and myocardial injury
- Future studies (SEQUOIA-HCM, NCT05186818; phase 3 RCT) will further shed light onto the effect of *aficamten* on health status

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I would like to thank:

All participants and their families.

ALL REDWOOD-HCM investigators, study coordinators, core laboratories, and Cytokinetics.

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Backup

Study Design

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Dose Titration allowed at any visit, but must be followed with an additional visit 2 weeks after a dose adjustment

Biplane LVEF		Post-Valsalva LVOT-G	Action
<50%			Reduce Dose
≥50% - 55%			No Dose Change
≥55%	and	<30 mmHg	No Dose Change
≥55%	and	≥30 mmHg	Increase Dose

Doses available for Investigator Driven Titration

5mg 10mg 15mg 20mg

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Safety

	N=42
Patients with ≥1 TEAE	32 (76.2)
Patients with at ≥1 TESAE	2 (4.8)
Patients with ≥1 Related TEAE	10 (23.8)
Patients with ≥1 Severe TEAE	3 (7.1)
Early Termination	0
Deaths	0
Dosing	
Dose Reduction	2 (4.8)
Drug Interruption	1 (2.4)
Drug Withdrawal	0

Temporary dose reduction and treatment interruption

- 45 y/o man with NYHA class II oHCM and a history of alcohol triggered atrial fibrillation and associated low LVEF prior to study participation.
- Patient developed recurrent symptomatic atrial fibrillation with associated LVEF of 47% (baseline LVEF = 60%) while receiving 15mg *aficamten*.
- *Aficamten* dose was decreased and then held for approximately 6 weeks d/t persistent atrial fibrillation. Sinus rhythm was restored after amiodarone started.
- LVEF increased to 60%, LVOT-G (resting 35 mmHg and Valsalva 71 mmHg) and *aficamten* was restarted and up-titrated to 10mg (LVEF 56%, resting and Valsalva LVOT-G 6 and 18 mmHg respectively). Currently the patient is NYHA class I.

Temporary dose reduction

- 68 y/o woman with NYHA class II oHCM had dose reduced when the PI was concerned about possible QTc > 500ms. Dose reduction from 10 mg to 5 mg for 1 week.
- QTc was evaluated by the core lab and found to be within limits for the patient and <500 ms.
- The dose was escalated back to 10 mg, and subsequently to 15 and 20 mg. QTc has remained stable, and the patient is currently NYHA class I

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KCCQ-OSS Worsening at Week 24

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	BASELINE						WEEK 24						
	KCCQ-OSS	NYHA Class	Resting LVOT-G	Valsalva LVOT-G	LVEF	NT-proBNP	KCCQ-OSS	NYHA Class	Resting LVOT-G	Valsalva LVOT-G	LVEF	NT-proBNP	Adverse Event
64 y/o male (001001-001)	71	3	46	69	66	554	58	2	6	16	58	62	None at Week 24
70 y/o female (001001-003)	67	2	42	65	70	1018	25	2	12	15	67	344	GI Blood loss anemia (Hb 14 → 11 g/dl)
71 y/o female (001001-012)	89	2	21	52	68	298	83	1	13	13	69	250	None at W24

- 3 patients reporting worsening KCCQ-OSS at Week 24 compared to baseline
- No patients were noted to have low LVEF
- All patients demonstrated:
  - Complete hemodynamic response (Resting LVOT-G < 30 mmHg and Valsalva LVOT-G < 50 mmHg)
  - Stable or improved NYHA class
  - Reduction in NT-proBNP

→ Worsening
→ Stable
→ Improvement

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Kansas City Cardiomyopathy Questionnaire (KCCQ) Domains
KCCQ-OSS = Overall Symptom Score
KCCQ-CSS = Clinical Summary Score
KCCQ-TSS = Total Symptom Score
KCCQ-PLS = Physical Limitation Score
KCCQ-SLS = Social Limitation Score
KCCQ-QoL = Quality of Life Score