ASM 2024
HFSA ANNUAL SCIENTIFIC MEETING
Where Heart Failure Teams Gather

Monday Plenary Session: Late Breaking Clinical Research Session II
9:00 AM – 10:30 AM ET

Global Clinical Impact Of Aficamten In Obstructive Hypertrophic Cardiomyopathy: Results From SEQUOIA-HCM

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Introduction: In obstructive hypertrophic cardiomyopathy (oHCM), left ventricular outflow tract (LVOT) obstruction plays a critical role in generating limiting symptoms and other adverse outcomes. Aficamten, a novel cardiac myosin inhibitor, reduces LVOT gradient and enhances functional capacity in oHCM. However, a comprehensive analysis of aficamten's efficacy across key clinical outcomes has not been reported.

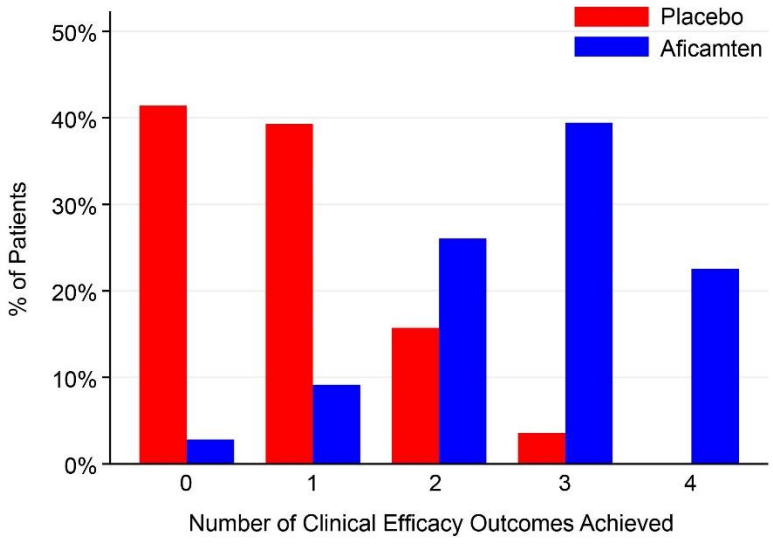
Hypothesis: In the pivotal phase 3 trial SEQUOIA-HCM (NCT05186818), aficamten's impact can be assessed across multiple clinically relevant outcome measures.

Methods: Patients with symptomatic oHCM were randomly assigned to receive either aficamten (n=142) or placebo (n=140) daily for 24 weeks. The four outcome measures assessed at 24 weeks and compared to baseline, were: 1) improvement in the burden of limiting symptoms with ≥1 change in NYHA class and/or ≥10-point increase in the Kansas City Cardiomyopathy Questionnaire-Clinical Summary score (KCCQ-CCS); 2) complete hemodynamic response (resting and Valsalva gradient of <30 mmHg and <50 mmHg, respectively); 3) ≥1.5 mL/kg/min change in peak oxygen consumption (pVO_2); 4) ≥50% reduction in serum NT-proBNP levels. Eligibility for septal reduction therapy (SRT) was also evaluated.

Results: At 24-weeks, 71% of patients receiving aficamten exhibited an improvement in limiting symptoms, 68% achieved a complete hemodynamic response, 47% showed enhanced exercise capacity, and 84% experienced a ≥50% decrease in NT-proBNP levels. These improvements were all significantly greater than those observed in the placebo group ($p \leq 0.002$). Improvement in ≥1 of these clinically relevant outcome measures occurred in 97% of patients treated with aficamten, including 23% who experienced improvements in all four measures (Figure), which was significantly greater than that observed with placebo (59% and 0%, respectively; $p<0.001$ for both comparisons). Furthermore, among patients initially eligible for SRT, 88% of those treated with aficamten no longer met criteria for SRT at week 24, compared to only 52% in the placebo group (p=0.002).

Conclusion: Treatment with aficamten was associated with broad clinical benefits in the vast majority of oHCM patients, including complete hemodynamic response with rest outflow gradient <30 mmHg, substantial alleviation of limiting symptoms, improvement in exercise capacity and significant decrease in NT-proBNP. These findings illuminate the clinical impact of aficamten in the treatment of symptomatic oHCM patients, including those eligible for SRT.

Figure: Proportion of Patients Achieving Clinical Response Categories



Myosin Inhibition In Heart Failure With Preserved Ejection Fraction: Primary Results Of The EMBARK HFpEF Trial

Author Block
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Background: Myosin inhibition is a proven therapy for obstructive hypertrophic cardiomyopathy (HCM) and has demonstrated promising early results in non-obstructive HCM. Patients with HFpEF and LVEF ≥60% have limited treatment options, as ARB, ARNI, and MRA are more effective in HF and LVEF <60%. LVEF ≥60-65% is also associated with increased mortality and adverse events; coronary microvascular dysfunction; and a small, stiff LV cavity that impairs diastolic filling. Myosin inhibition may be effective in these patients but has not yet been studied in HFpEF.
Methods: EMBARK-HFpEF (NCT04766892) was a phase 2a, open-label, single-arm, multicenter trial that investigated the effects of myosin inhibition with mavacamten in HFpEF. Inclusion criteria included age ≥50 years, LVEF ≥60%, and objective evidence of HF (one or more of: previous hospitalization for HF; elevated LV filling pressure; elevated historical NTproBNP or BNP; elevated E/e' ratio or LA enlargement with chronic loop diuretic use). At screening, (1) elevated NTproBNP; (2) LVEF ≥60%; and (3) LV wall thickness ≥12 mm or elevated LV mass index were required. Key exclusions were prior HCM or infiltrative cardiomyopathy; significant valve disease; and prior LVEF <45%. Participants were treated with mavacamten for 26 weeks, starting at 2.5 mg and titrated up to 5 mg at Week 14 based on LVEF and NTproBNP. Week 34 end-of-study labs were done 8 weeks after stopping mavacamten. Primary efficacy endpoints included changes in NTproBNP and troponin; safety endpoints included LVEF and adverse events.
Results: 30 participants were enrolled across 14 sites in US/Canada. The mean age was 75±8 years; 53% female; 10% Black; 23% Hispanic; and geometric mean NTproBNP 520 pg/ml, hsTnT 0.017 ng/ml, high-sensitivity troponin I (hsTnI) 8.35 pg/ml, and mean LVEF 67±5%. Comorbidities were common. Mavacamten reduced NTproBNP by 26% (95% CI -44%, -4%); hsTnT by 13% (95% CI -23%, -3%); and hsTnI by 20% (95 CI -32%, -6%). Biomarker values returned towards baseline after drug discontinuation (Table). NYHA class improved in 42% of patients (unchanged in the rest). Diastolic function parameters improved. Mean LVEF decreased by 3.2% (SD 4.9%) during treatment. Mavacamten was interrupted in 3 (10%) patients due to LVEF <50% (n=2) or >20% relative decrease from baseline (n=1, LVEF=58%); the lowest LVEF at interruption was 40%. LVEF recovered in all 3, and 1 patient restarted and

completed treatment. During the treatment-emergent period, there were no deaths, and 1 patient had worsening HF deemed unrelated to study drug.

Conclusions: In the first trial of myosin inhibition in HFpEF, mavacamten reduced NTproBNP and troponin without sustained LVEF reductions. These results support further investigation into myosin inhibition for HFpEF.

Endpoint	Visit	Change from baseline	95% CI
NTproBNP (pg/ml)	Week 12	-31.0%	-47.3%, -9.7%
	Week 26 (end of treatment)	**-26.5%**	**-43.9%, -3.6%**
	Week 34 (end of study)	-17.1%	-36.0%, +7.5%
Troponin-T (ng/ml)	Week 12	-6.7%	-22.0%, +11.5%
	Week 26 (end of treatment)	**-13.5%**	**-22.9%, -3.1%**
	Week 34 (end of study)	+2.3%	-9.7%, +16.0%
Troponin-I (pg/ml)	Week 12	-12.2%	-33.3%, +15.4%
	Week 26 (end of treatment)	**-20.2%**	**-32.3%, -5.8%**
	Week 34 (end of study)	+6.5%	-14.5%, +32.6%

Impact Of Pharmacological Therapy On Hemocompatibility Following Left Ventricular Assist Device Implantation: An Analysis From The ARIES-HM3 Trial

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Introduction: The ARIES-HM3 trial demonstrated that elimination of aspirin from the antithrombotic regimen of HeartMate 3 LVAD patients is safe and reduces risk of non-surgical bleeding (*JAMA. 2023;330(22):2171-2181*). The relationship of non-antithrombotic pharmacological therapy with hemocompatibility-related adverse events (HRAE) remain uncertain. Observational studies have suggested that drugs such as Renin-Angiotensin-Aldosterone system (RAAS) inhibitors, PDE-5 inhibitors, Digoxin and other heart failure-modifying therapy may influence bleeding and thrombosis related outcomes.
Objective: The purpose of this pre-specified secondary analysis is to investigate the impact and interaction of pharmacological therapy (with and without aspirin) on clinical outcomes following LVAD implantation.
Methods: The ARIES-HM3 study randomized 628 advanced HF patients implanted with a fully magnetically-levitated HM3 LVAD, 1:1 to an antithrombotic regimen of a Vitamin K Antagonist (target INR 2.0-3.0) with either aspirin or placebo. In a landmark analysis among 578 patients who contributed to the primary endpoint analysis and achieved at least 30 days of post-implant follow-up (the time point of medical therapy prescription and determination), we seek to examine the use and impact of background medical therapy (including anti-hypertensive medications, heart failure-specific therapy and other cardiovascular drugs) on the composite primary end point of survival free of major non-surgical HRAE including stroke, pump thrombosis, bleeding, and arterial peripheral thromboembolism at 12 months and the principal secondary endpoint of non-surgical bleeding. In this analysis, we shall also describe the interactions of pharmacological therapy with aspirin on primary and secondary endpoints.
Preliminary Findings: Table 1 summarizes the type and proportion of patients that received specific classes of drug therapy at 30-days post LVAD implantation, a finding generally equally distributed between placebo and aspirin groups. The comprehensive analysis for outcomes (including HRAE and individual components) will be completed by August 16th, 2024. We plan submission for a simultaneous publication of the results if accepted for presentation.
Conclusions: The findings from this large clinical trial-based analysis will serve to critically enhance our understanding of how pharmacological therapy may influence HRAE after LVAD implantation. Such findings will inform the risk-benefit considerations and serve to establish clinical guidelines for use of anti-hypertensive, heart failure-specific and other cardiovascular medications in advanced HF patients supported with durable LVADs.

Table 1: Proportion of patients receiving pharmacological therapy at 30-days post LVAD implantation.

	No. of Patients (%)		
Drug	Overall group (%) N=578	Placebo group (%) N=290	Aspirin group (%) N=288
RAAS inhibitor	**367 (63.5)**	**181 (62.4)**	**186 (64.6)**
ACE/ARB/ARNi	270 (46.7)	136 (46.9)	134 (46.5)
Aldosterone antagonist	243 (42.0)	121 (41.7)	122 (42.4)
Other HF Specific Therapy	**509 (88.1)**	**256 (88.3)**	**253 (87.9)**
Beta-blocker	206 (35.6)	98 (33.8)	108 (37.5)
Diuretic	445 (77.0)	224 (77.2)	221 (76.7)
SGLT2 inhibitor	8 (1.4)	4 (1.4)	4 (1.4)
Digoxin	118 (20.4)	59 (20.3)	59 (20.5)
Other Cardiovascular Drugs	**480 (83.0)**	**243 (83.8)**	**237 (82.3)**
Calcium channel blocker	43 (7.4)	28 (9.7)	15 (5.2)
Nitrate	23 (4.0)	9 (3.1)	14 (4.9)
Vasodilator	48 (8.3)	22 (7.6)	26 (9.0)
Statin	273 (47.2)	141 (48.6)	132 (45.8)
PDE5 inhibitor	104 (18.0)	52 (17.9)	52 (18.1)
Antiarrhythmic drug	281 (48.6)	147 (50.7)	134 (46.5)
Inotrope	27 (4.7)	17 (5.9)	10 (3.5)
Other medication	28 (4.8)	13 (4.5)	15 (5.2)

Atrial Secondary Mitral Regurgitation Outcomes Following Mitral Transcatheter Edge-to-Edge Repair With The MitraClip System

Author Block

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Introduction: Atrial secondary mitral regurgitation (ASMR) is a subgroup of SMR broadly defined by annular dilatation and/or left atrial (LA) enlargement and preserved left ventricular (LV) function. Most studies have evaluated heart failure SMR patients with reduced LV function, but little is known of the ASMR pathology or their prognosis following mitral transcatheter edge-to-edge repair (MTEER).
Aim: To evaluate the ASMR population and outcomes following MTEER from the global EXPANDed studies.
Methods: EXPANDed is a patient-level, pooled cohort of 2205 subjects from the global, post-market studies, EXPAND and EXPAND G4, that evaluate outcomes of subjects treated with the 3rd and 4th-generation MitraClip™ Systems. ASMR subjects were identified based on SMR etiology, history of atrial fibrillation, LV ejection fraction >50%, and presence of a coaptation depth <1 cm or LV end-diastolic dimension <4 cm. Baseline characteristics and outcomes through 1 year of ASMR subjects are reported. All echocardiographic measures were assessed by an independent echo core lab (ECL).
Results: Of the 967 SMR subjects treated with MTEER in EXPANDed, 112 (11.6%) were categorized as ASMR. At baseline, ASMR subjects were elderly (78.0 ± 7.9 years), majority female (53.6%), and symptomatic with a KCCQ-OS score of 49 ± 26 points and 78.6% NYHA III/IV. 47% had a HFH in the year prior to the procedure and 36% had renal failure. On average, ASMR subjects had small LV and large LA volumes relative to all SMR subjects (LVEDV 116.0 ± 43.1 ml ASMR, 169.9 ± 75.2 ml All SMR; LA volume 118.0 ± 79.1 ml ASMR, 104.0 ± 58.8 ml All SMR). Following MTEER, there was significant 1-year MR reduction to <=1+ in 95.9% of ASMR subjects (94.3% all SMR) and zero SLDA events. At 1 year, there was a 16% LVEDV reduction (11% reduction all SMR) with no significant LVESV change; significant improvements in quality of life (+16 pt KCCQ-OS improvement, +20 pt all SMR) and functional capacity (NYHA I/II: 80.3% 1 yr; 77.9% 1 yr all SMR) were observed. Kaplan-Meier 1-year estimates of all-cause mortality and HFH rates were 11.8% and 24.8%, respectively (15.7%, 23.0% all SMR), with a 48% reduction in 1-year HFH rates after MTEER (60% reduction all SMR). Additional outcomes of

ASMR subjects will be presented.

Conclusions: This study represents the largest report of ECL-assessed outcomes in ASMR subjects treated with MTEER. One-year outcomes show that ASMR subjects in EXPANDed were safely treated with the MitraClip System and experienced significant MR and LVEDV reduction, quality of life improvements, a low all-cause mortality rate, and reduced HFH rates, comparable to all SMR patients. These results suggest MTEER is associated with clinical benefit in ASMR. Future studies are needed to understand long-term ASMR progression.

A Novel Controlled Metabolic Accelerator For The Treatment Of Obesity-related Heart Failure With Preserved Ejection Fraction: HuMAIN-HFpEF Trial

Author Block

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Background: Excess body fat plays a pivotal role in the pathogenesis of Heart failure with preserved ejection fraction (HFpEF). HU6 is a first-in-class controlled metabolic accelerator (CMA) that activates the adenine nucleotide translocase channel, causing controlled mitochondrial uncoupling and increased metabolism. In previous studies, oral HU6 was well tolerated, produced fat-specific weight loss, and reduced biomarkers of inflammation. The primary objectives of the Hepatic Uncoupler Mitochondrial Accelerator IN HFpEF trial (HuMAIN-HFpEF) are to evaluate the impact of HU6 on safety and tolerability, weight loss, and exercise capacity among patients with chronic stable obesity-related HFpEF.
Methods: This was a Phase 2a, randomized, parallel-group, placebo-controlled, double-blind within-participant dose escalation trial with three oral doses of HU6 (150, 300, and 450 mg) and placebo. The primary efficacy endpoint was a change in body weight from baseline to Day 134. The key secondary efficacy endpoint was a change in peak oxygen uptake (VO_2, mL/kg/min) from baseline to Day 134 measured by cardiopulmonary exercise testing. Additional important outcomes included safety, body fat, quality-of-life measures, exercise time, epicardial and visceral fat, and biomarkers of inflammation. Clinicaltrials.gov: NCT05284617.
Results: Of the 66 participants randomized to HU6 or placebo (56% women, 17% Black), 65 were dosed, and 57 completed the study. Baseline characteristics were consistent with a population with obesity-related HFpEF (**Table**). The mean BMI and % body fat were 39 kg/m^2 and 47%, respectively, and 68% of participants had Class II/III obesity. Elevated CRP levels ($\geq$2 mg/mL) were observed in 65%. Exercise capacity was severely depressed with a mean peak VO_2 (mL/kg/min) of 13.3 mL/kg/min [SD: 3.7]). Sodium-glucose cotransporter-2 inhibitors were used by 39%. Seven serious adverse events, including 1 death, occurred in four participants during the treatment phase; all were considered unrelated to therapy.
Conclusions: The HuMAIN-HFpEF Trial is investigating HU6 as a novel potential treatment for patients with obesity-related HFpEF. The database lock is anticipated to occur in early July 2024. The complete baseline characteristics and main trial results will be presented at the meeting.

Table: Baseline characteristics of the randomized population in the HuMAIN-HFpEF trial

Baseline Characteristics	Study Cohort (N = 61)
Age (years)	64.5 ± 12.0
Female, n (%)	38 (57.5%)
Race, n (%) White Black/African American Other	 53 (80.3%) 11 (16.7%) 2 (3.0%)
Latino or Hispanic, n (%)	10 (15.2%)
Height (cm)	167 ± 10
Weight (kg)	111 ± 22
Body mass index (kg/m^2)	39.4 ± 6.9
Percent body fat	47.0 ± 6.1
Fat mass (kg)	52.4 ± 13.9
Glycated hemoglobin, %	6.1 ± 0.8
Glycated hemoglobin <5.7%, n (%)	24 (36.4%)
Glycated hemoglobin ≥5.7% to ≤10%, n (%)	42 (63.6%)
C-reactive protein (mg/L)*	3.7 (1.6 – 8.0)
Systolic blood pressure (mmHg)	124 ± 13
Diastolic blood pressure (mmHg)	74 ± 8
Heart rate (bpm)	70 ± 11
Estimated GFR (mL/min/1.73m^2)	79 ± 20
Chronic rate-controlled AF stratification group, n (%)	14 (21.2%)
KCCQ OSS*	62 (51 – 76)
KCCQ CSS*	65 (51 – 75)
NYHA Class, n (%) II III	 47 (71.2%) 19 (28.8%)
Peak VO_2 indexed by weight (mL/kg/min)	13.3 ± 3.7
Left ventricle ejection fraction (LVEF) (%)	60 ± 5
NT-proBNP (pg/mL)*	113 (59 – 281)
Average E/e' ratio	10.0 ± 3.0
CPET duration (min)	11.3 ± 3.3
Six-Minute Walk Distance (m)*	354 (256 – 419)
History of hypertension, n (%)	59 (89.4%)
History of atrial fibrillation, n (%)	11 (16.7%)
History of myocardial infarction, n (%)	2 (3.0%)
History of diabetes, n (%)	24 (36.3%)
SGLT2i, n (%)	26 (39.4%)
Diuretic, n (%)	57 (86.0%)
Beta-blocker, n (%)	38 (58.0%)

Data presented as counts (%) for categorical variables and mean (Standard deviation) for normally distributed continuous variables and median (25th , 75th percentile) for non-normally distributed continuous variable (*). Abbreviations: KCCQ: Kansas City Cardiomyopathy Questionnaire; NT-ProBNP: N-terminal pro brain natriuretic peptide; SGLT2i: Sodium glucose cotransporter-2 inhibitor; GFR: Glomerular Filtration Rate; CPET: Cardiopulmonary exercise time