A Novel Controlled Metabolic Accelerator for the Treatment of Obesity-Related HFpEF: The HuMAIN-HFpEF Trial

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Presenter disclosures

- Ambarish Pandey reports the following:
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  - Consultant: outside of the present study as an advisor/consultant for Axon Therapies, Bayer, Cytokinetics, Edward Lifesciences, Emmi Solutions, Lilly USA, Medtronic, Merck, Novo Nordisk, Rivus, Roche Diagnostics, Sarfez Pharmaceuticals, Science 37, Semler Scientific, and Tricog Health
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Background

- Obesity-related HFpEF is common (80% of all HFpEF) and associated with worse hemodynamics, symptoms, quality-of-life, and a high risk of adverse outcomes[1-5]
- Among patients with obesity-related HFpEF, the GLP-1 agonist semaglutide significantly reduces body weight, and improves quality-of-life and exercise capacity at 52 weeks[6-8]
- However, skeletal muscle loss accounts for 30-40% of the weight loss achieved with semaglutide
- Loss of skeletal muscle may be detrimental in patients with HFpEF who have sarcopenic obesity with reduced skeletal muscle mass and significant skeletal muscle dysfunction.[9-12]
- Novel weight loss therapies that selectively reduce adipose tissue while preserving skeletal muscle mass could be an important addition to the treatment options for obesity-related HFpEF

HFpEF, heart failure with preserved ejection fraction; GLP-1, glucagon-iike peptide

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Background

- Mitochondrial uncoupling agents, also termed controlled metabolic accelerators (CMA), promote weight loss by increasing mitochondrial energy utilization, potentially resulting in a preferential loss of adipose tissue with sparing of skeletal muscle[13]
- HU6 is a first-in-class CMA that is metabolized in the liver to produce the controlled metabolite 2,4-dinitrophenol, an activator of the ADP/ATP carrier, causing controlled mitochondrial uncoupling[14]
- In a recent phase II trial, HU6 led to a significant, dose-dependent reduction in fat mass with preservation of the skeletal mass among patients with metabolic dysfunction associated steatosis liver disease, a metabolic disorder similar to obesity-related HFpEF[15,16]
- However, the efficacy and safety of HU6 in patients with obesity-related HFpEF is unknown.

CMA, controlled metabolic accelerator; HFpEF, heart failure with preserved ejection fraction.

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Study objective

To evaluate the efficacy and safety of HU6 in reducing body weight, improving exercise capacity and body composition among patients with obesity-related HFpEF

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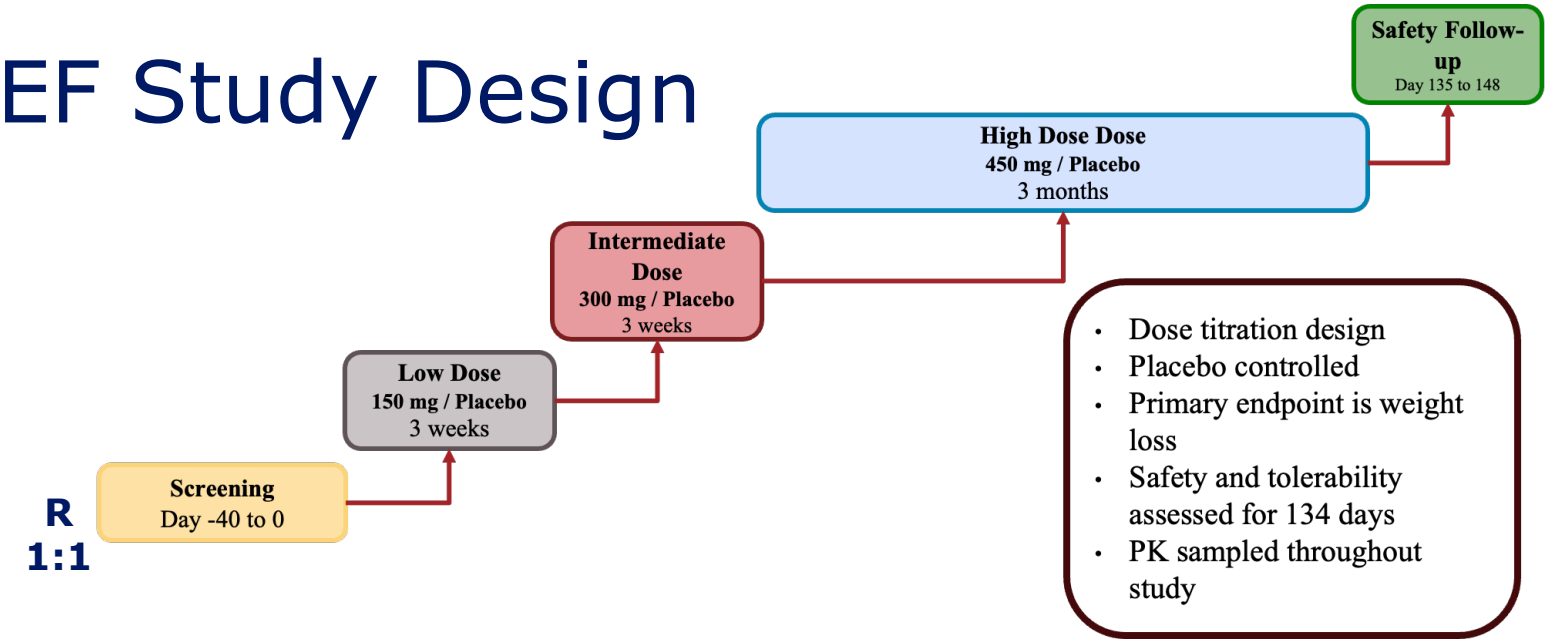
HuMain-HFpEF Study Design

N=66



Outcomes

- Primary efficacy endpoint: change in body weight
- Key secondary efficacy: change in peak VO_2
- Exploratory: body composition, KCCQ, 6MWD, hs-CRP, NT-proBNP

Key inclusion criteria

- Adults aged ≥30 years; BMI ≥30 kg/m^2; LVEF ≥50%; NYHA functional class II–III; KCCQ-OSS ≤80 points; reduced baseline peak exercise oxygen uptake (VO_2 ≤20 mL/kg/min for females or ≤22 mL/kg/min for males), ambulatory, and able to perform a 6-minute walk test and upright maximal exercise testing.
- Diagnosis of chronic HFpEF based on one of the following:
  - Documented hospitalization, emergency room, or urgent care visit with HFpEF as primary cause
  - Echocardiographic abnormalities
  - Elevated filling pressures at rest or exercise
  - Elevated natriuretic peptides

6MWD, 6-minute walk distance; BMI, body mass index; CRP, C-reactive protein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; R, randomization; VO2 – peak exercise oxygen uptake

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Statistical Analysis

- A sample size of 50 evaluable participants with 25 participants in each arm (HU6 and placebo) was determined to provide >95% power to detect a difference of 2.7 kg for the change from baseline in body weight. Enrollment of 62 participants was planned to ensure 50 evaluable participants.
- The intent-to-treat analysis was performed to assess treatment group differences using a mixed model for repeated measures adjusting for covariates.
- Least squares means (LSMs) were reported for between-group comparisons from this model.

LSM, least squares mean

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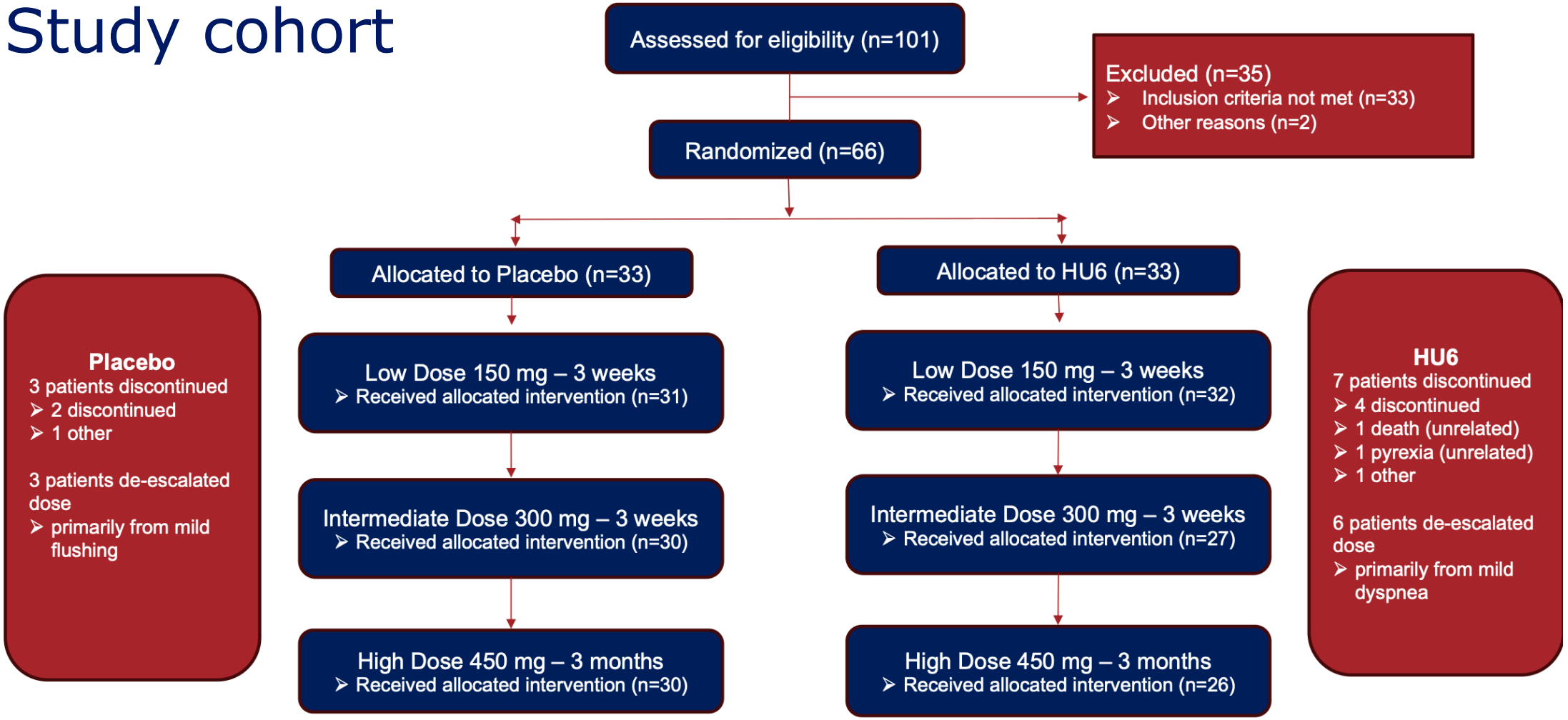
Study cohort



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Baseline characteristics

Characteristic	HU6 (N=33)	Placebo (N=33)
Age, years	63.8 ± 11.9	65.1 ± 12.3
Female Sex, n(%)	17 (51.5)	21 (63.6)
Body Mass Index, kg/m^2	38.8 ± 5.1	40.0 ± 8.2
Atrial fibrillation, (%)	7 (21.2)	7 (21.2)
Diabetes, n(%)	14 (42.5)	8 (24.2)
Glycated hemoglobin,	6.1 ± 0.8	6.0 ± 0.8
C-Reactive Protein (mg/L)	6.3 ± 7.5	5.4 ± 5.4
NT-proBNP (ng/L)	359 ± 748	265 ± 384
SGLT2i, n (%)	16 (49)	10 (31)
Loop diuretic, n (%)	21 (64)	24 (75)
MRA, n (%)	14 (42)	14 (44)
6-minute walk distance, m	346 ± 120	341 ± 98
Peak VO_2, ml/kg/min	13.6 ± 4.2	13.3 ± 3.2
KCCQ-OSS, points	62.9 ± 19.3	59.6 ± 18.6

Abbreviations: KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal-pro hormone BNP; SGLT2i = sodium-glucose cotransporter 2 inhibitors; VO_2 = volume of oxygen consumption Values are mean ± standard deviation or n (%)

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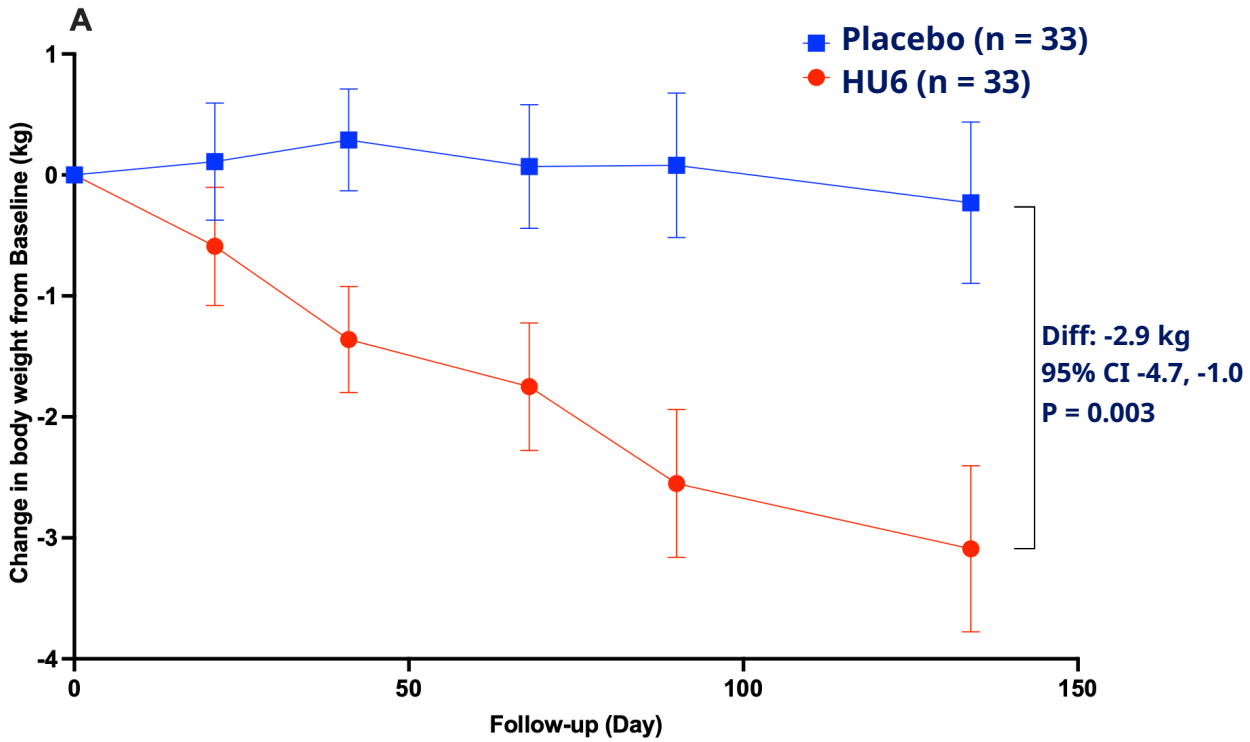
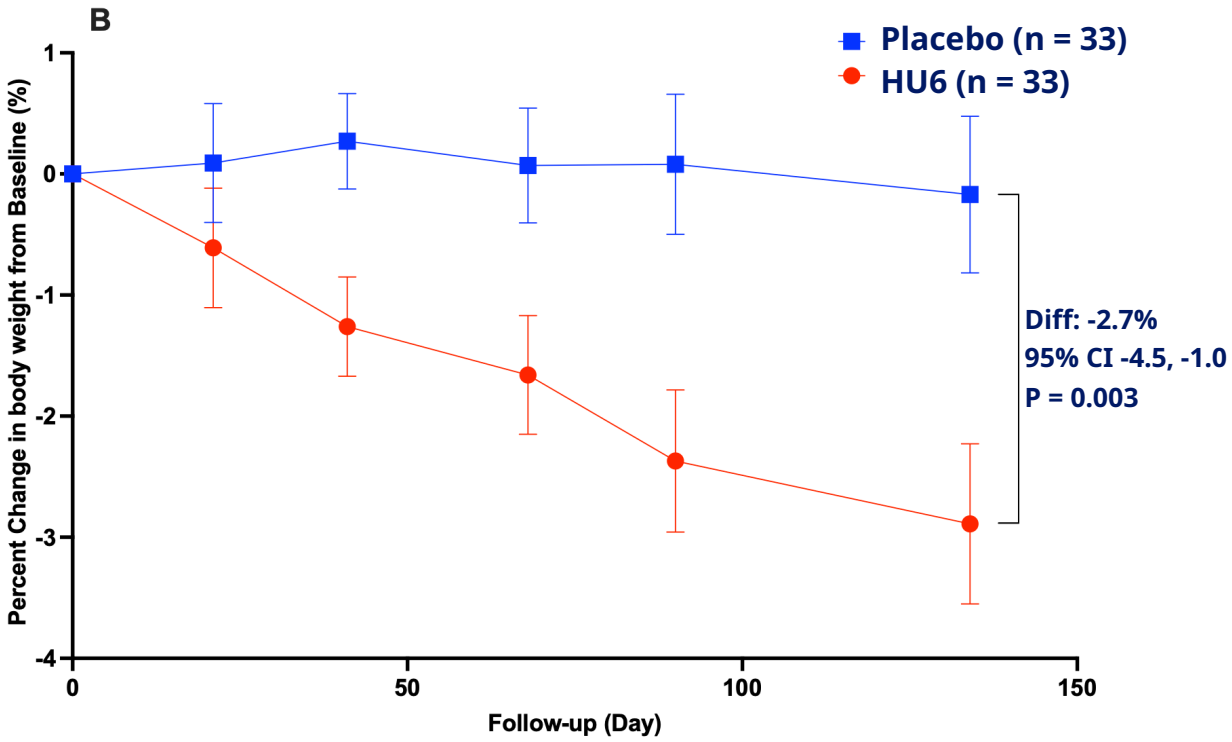
Effect of HU6 on body weight

Change in body weight (Kg)



Percent change in body weight (%)



Kg, kilogram

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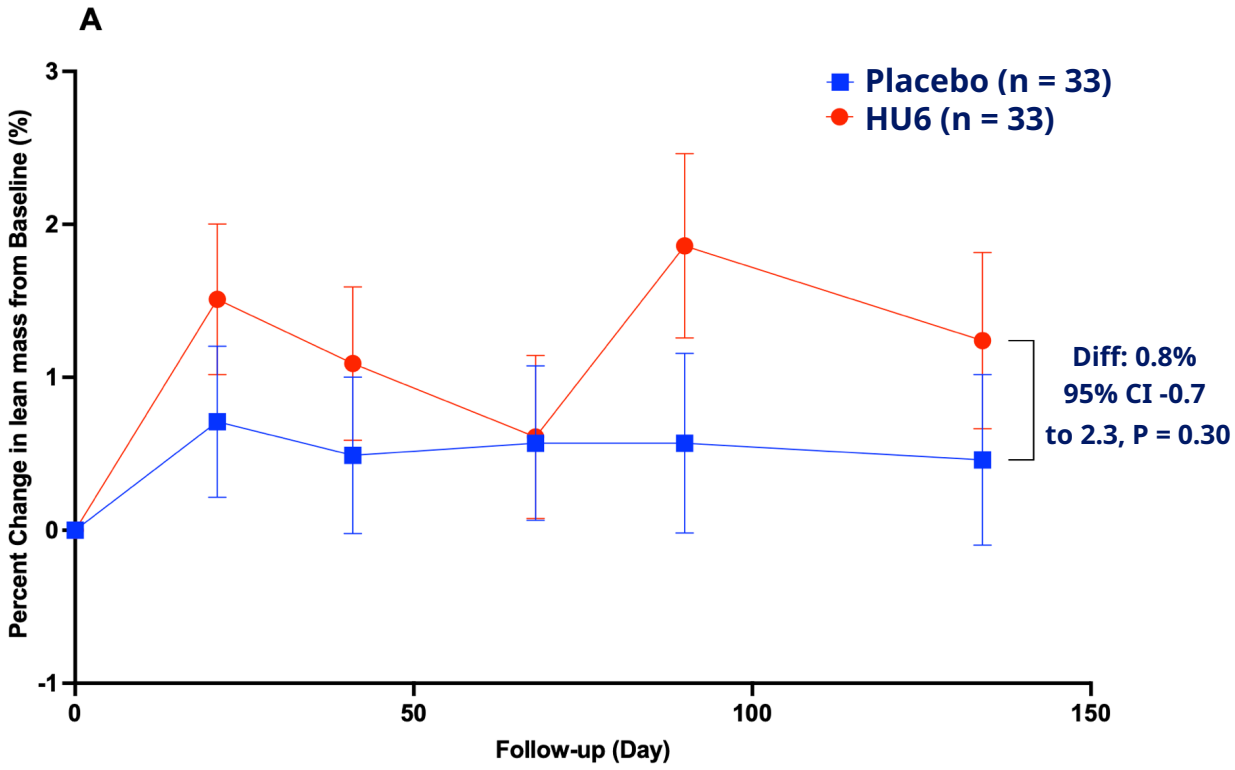
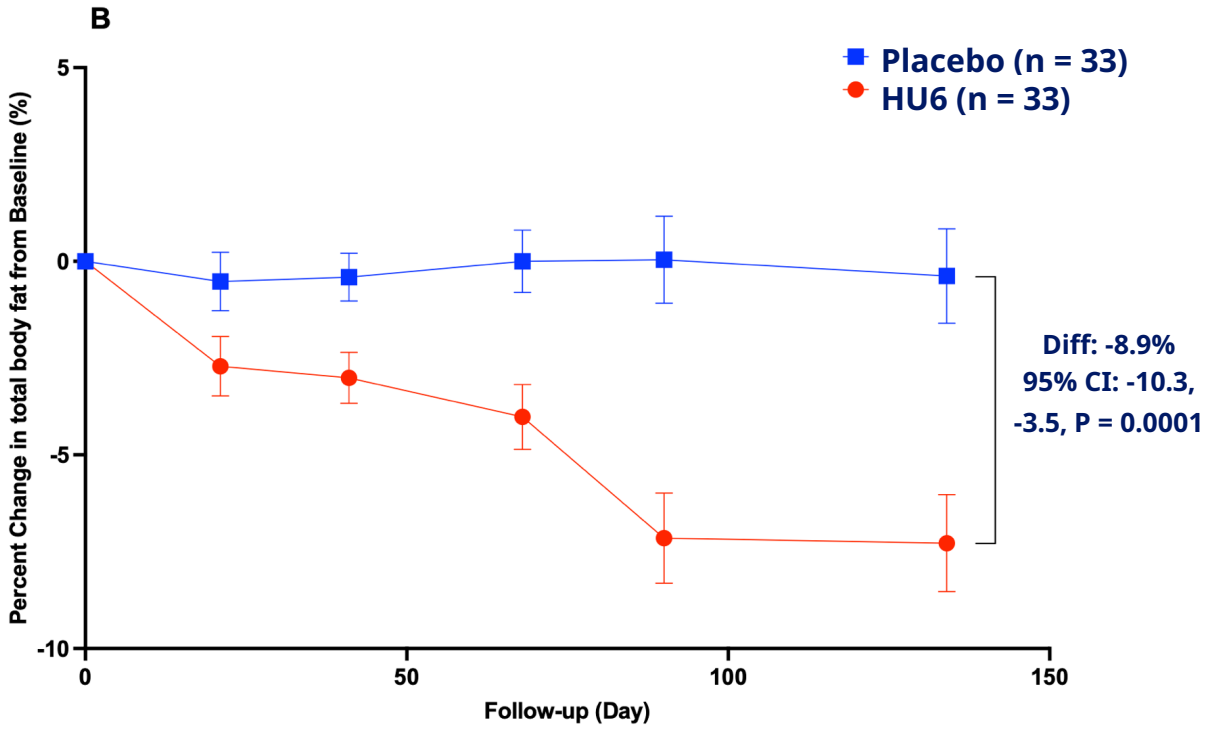
Effect of HU6 on body composition

Percent change in lean mass (%)



Percent change in fat mass (%)



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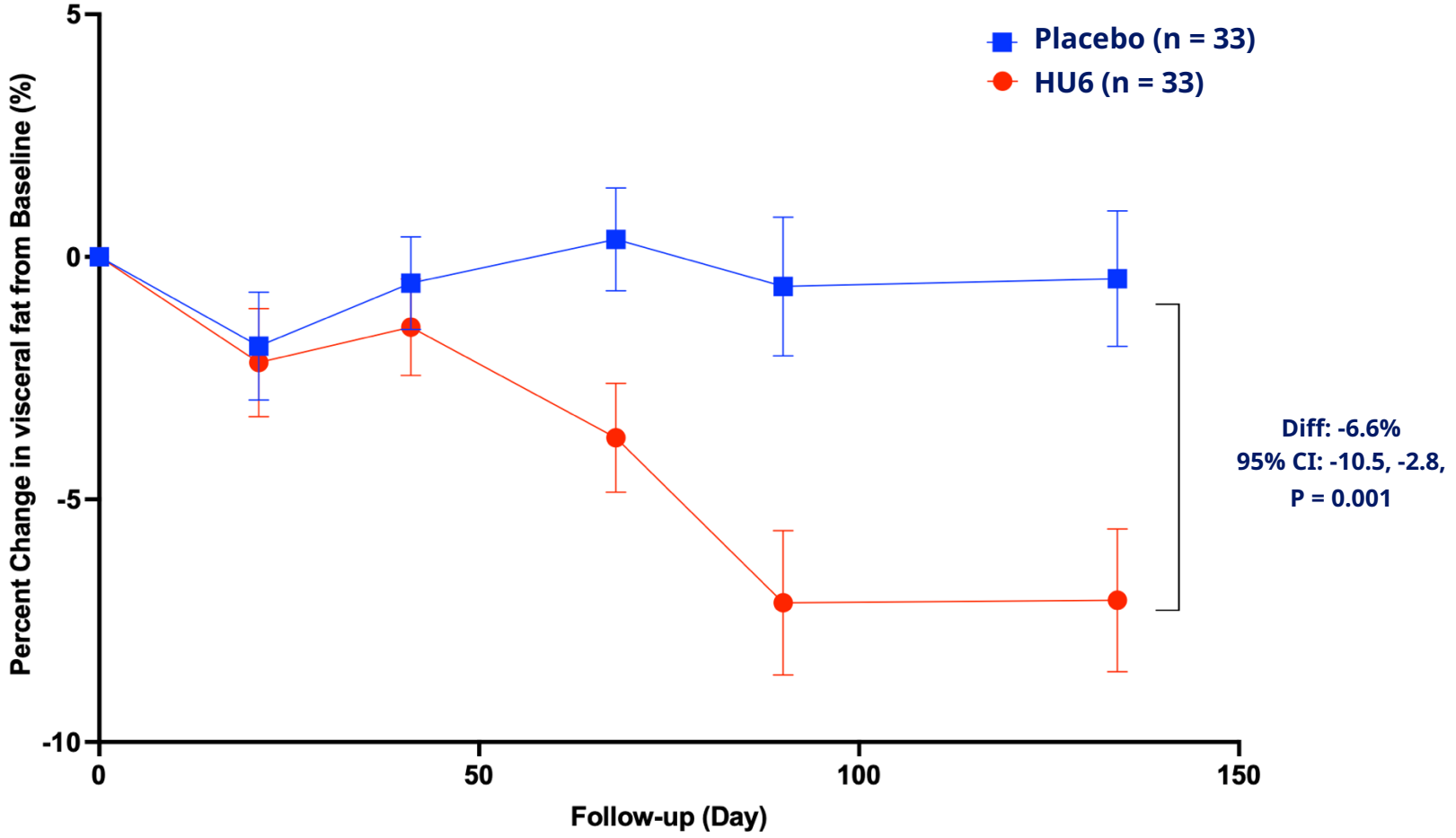
Effect of HU6 on percent visceral fat



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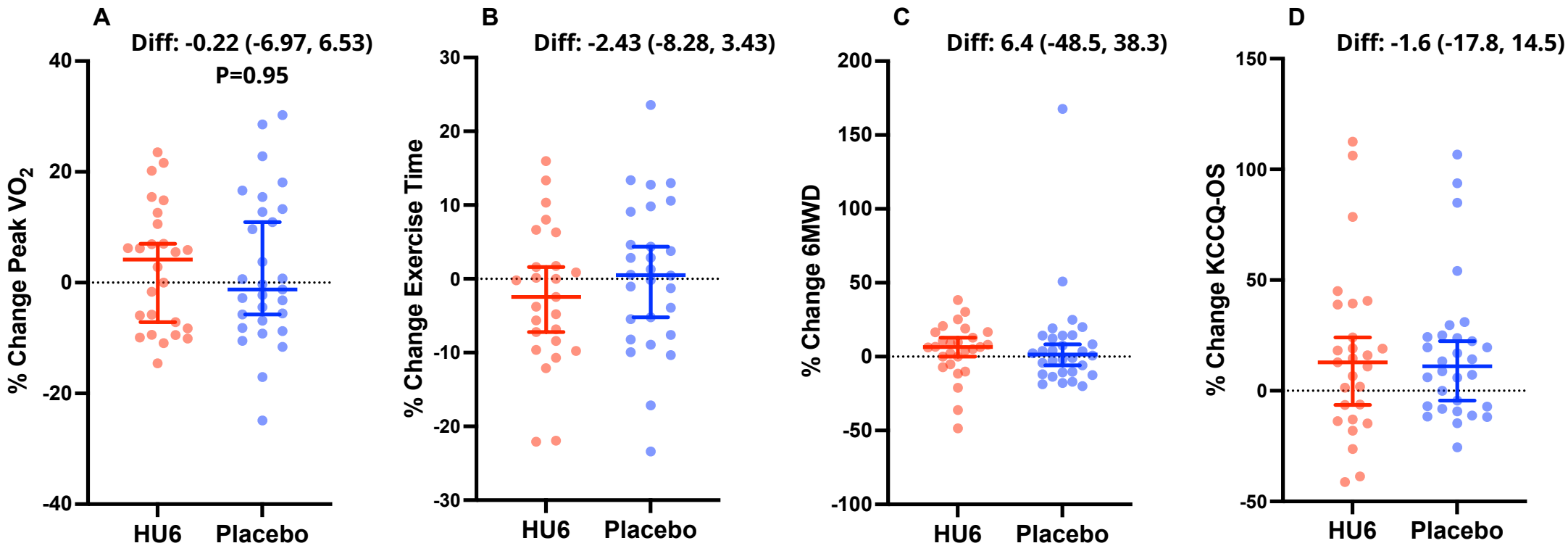
Effect of HU6 on exercise capacity and QOL



6MWD, 6-minute walk distance; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; VO2 – peak exercise oxygen uptake

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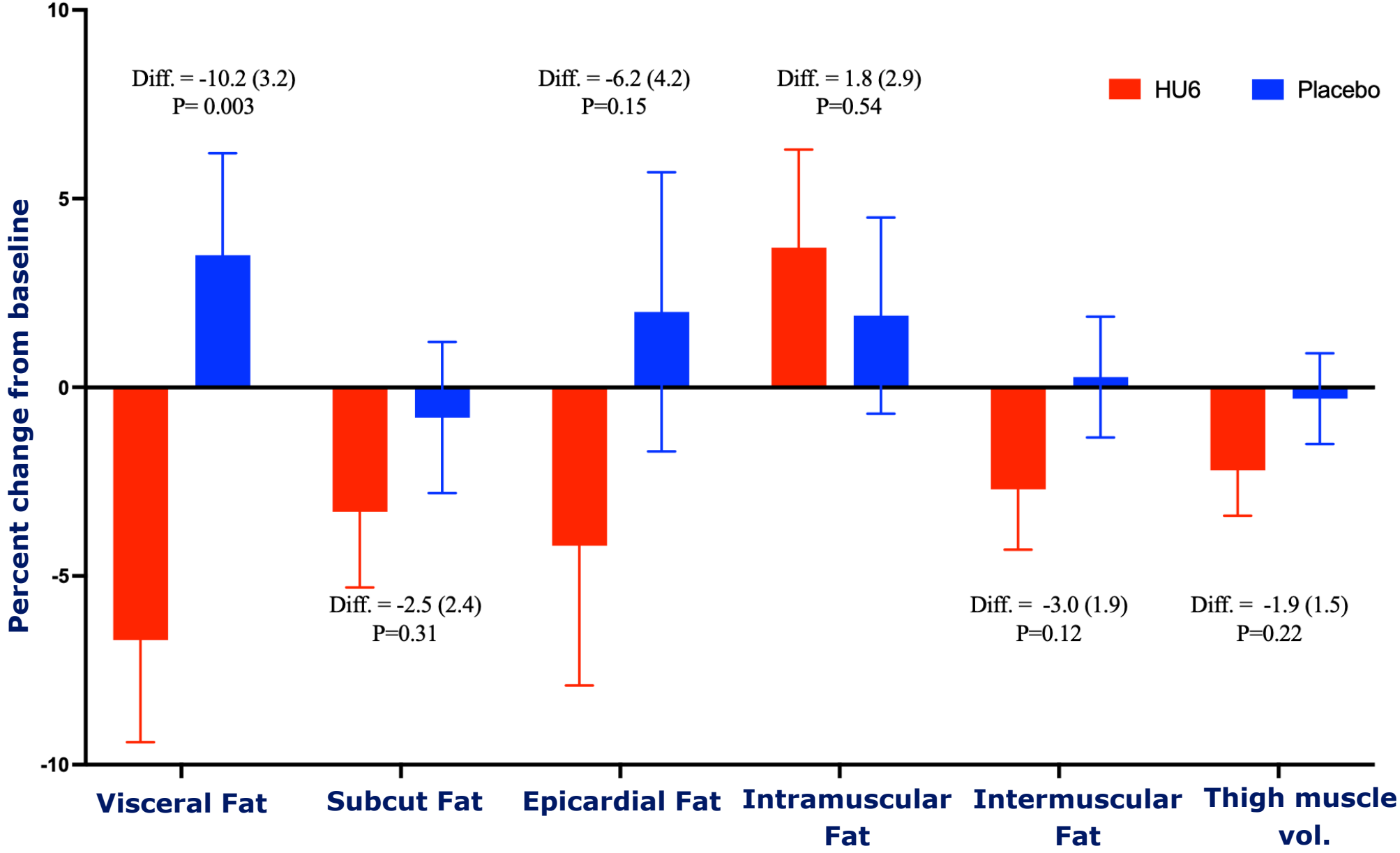
Effect of HU6 on body composition (MRI, n = 44)



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Effect of HU6 on cardiac structure and function

Echo parameters	HU6 LSM [95% CI]	Placebo LSM [95% CI]	HU6 vs. Placebo LSM [95% CI]
LV ejection fraction, %	**1.40 (-0.45, 3.25)**	**-2.36 (-3.95, -0.76)**	**3.76 (1.67, 5.84)**
LV mass, g	6.7 (-5.9, 19.3)	8.0 (-3.6, 19.6)	-1.3 (-16.0, 13.4)
RWT	0.009 (-0.02, 0.04)	0.0008 (-0.03, 0.03)	0.008 (-0.03, 0.05)
LV EDV, ml	-3.25 (-10.28, 3.77)	1.91 (-4.64, 8.46)	-5.17 (-13.35, 3.01)
LV ESV, ml	**-2.38 (-5.93, 1.16)**	**3.25 (-0.03, 6.54)**	**-5.64 (-9.80, -1.47)**
Stroke Volume, ml	-2.30 (-10.08, 5.47)	-2.53 (-9.87, 4.80)	0.23 (-8.91, 9.37)
LA volume, ml/m^2	1.20 (-1.29, 3.69)	1.87 (-0.42, 4.15)	-0.67 (-3.45, 2.12)
Average E/e' ratio	-0.89 (-1.91, 0.14)	-0.31 (-1.23, 0.61)	-0.58 (-1.75, 0.60)
TAPSE, cm	-0.03 (-0.18, 0.13)	-0.10 (-0.25, 0.04)	0.08 (-0.10, 0.25)
RV S' velocity, cm/s	**1.52 (0.27, 2.78)**	**-0.58 (-1.78, 0.62)**	**2.10 (0.67, 3.54)**
LV Global strain (A4C), %	0.38 (-0.57, 1.33)	-0.14 (-0.98,0.71)	0.52 (-0.55, 1.58)

LA – left atrial, LV – left ventricular, TAPSE - tricuspid annular plane systolic excursion, RV – right ventricular, EDV – end-diastolic volume, ESV – end-systolic volume, RWT – relative wall thickness

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Effect of HU6 on biomarkers

Biomarker	Within Group Change from Baseline to 19 weeks		Between Group Difference
	HU6	Placebo	HU6 vs. Placebo
	LSM (95% CI)	LSM (95% CI)	LSM (95% CI)
C-reactive protein, mg/L	1.2 (-8.1, 10.4)	4.1 (-4.3, 12.6)	-3.0 (-15.3, 9.4)
NT-proBNP, ng/L	36.9 (-279.3, 353.2)	-38.6 (-330.5, 253.4)	75.5 (-339.2, 490.2)
Troponin, ng/L	-84.9 (-168.8, -1.0)	-35.9 (-109.9, 38.1)	-49.1 (-151.2, 53.2)

LS means (LSM), confidence intervals (CIs), and p-values are from a mixed model for repeated measures with change from baseline as the dependent variable and treatment group, chronic controlled atrial fibrillation stratification group (presence/absence), HbA1c stratification group (normal range [<5.7%] versus ≥5.7% to ≤10%), time point, and treatment group by time point interaction as fixed effects, subject as a random effect, and baseline value as a covariate. Only patients with non-missing baseline and Visit 14 (End of Treatment) are included. Abbreviations: NT-proBNP – N-terminal pro-B-type natriuretic peptide

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Adverse Events

On-treatment adverse events	HU6 (N=33)	Placebo (N=32)	Total (N=65)
At least 1 AE	25 (75.8)	20 (62.5)	45 (69.2)
On-treatment AE	12 (36.4)	5 (15.6)	17 (26.2)
Serious AE	4 (12.1)	1 (3.1)	5 (7.7)
AE leading to discontinuation	2 (6.1)	0	2 (3.1)
AE leading to death	1 (3.0)	0	1 (1.5)
AE by maximum severity			
Mild	16 (48.5)	13 (40.6)	29 (44.6)
Moderate	6 (18.2)	6 (18.8)	12 (18.5)
Severe	3 (9.1)	1 (3.1)	4 (6.2)
AEs occurring in >4%			
Diarrhea	6 (18.2)	2 (6.3)	8 (12.3)
Covid-19	5 (15.2)	1 (3.1)	6 (9.2)
Headache	2 (6.1)	3 (9.4)	5 (7.7)
Dyspnea	4 (12.1)	0	4 (6.2)
Arthralgia	0	3 (9.4)	3 (4.6)
Back pain	1 (3.0	2 (6.3)	3 (4.6)
Cellulitis	1 (3.0)	2 (6.3)	3 (4.6)
Constipation	3 (9.1)	0	3 (4.6)
Fatigue	2 (6.1)	1 (3.1)	3 (4.6)
Flushing	1 (3.0)	2 (6.3)	3 (4.6)
Influenza	1 (3.0)	2 (6.3)	3 (4.6)
Joint swelling	3 (9.1)	0	3 (4.6)
Pain in extremity	2 (6.1)	1 (3.1)	3 (4.6)

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Conclusions

- Among patients with chronic, stable obesity-related HFpEF, HU6, a novel CMA, appeared to be safe, was well tolerated, and was associated with significant reductions in body weight.
- The weight loss effect of HU6 was associated with favorable changes in body composition with significant decreases in overall fat mass, visceral adiposity, and preservation of lean body mass.
- There were no significant changes in exercise capacity, 6MWD, QoL, and biomarkers with HU6 over the short treatment period.
- Future larger trials with longer-term follow-up are needed to evaluate whether HU6 can improve functional status and clinical outcomes in the growing population of patients with this disorder.

HF, heart failure; HFpEF, heart failure with preserved ejection fraction; SAE, serious adverse event.

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