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

Ambarish Pandey; Gregory Lewis; Barry Borlaug; Sanjiv Shah; Andrew Sauer; Sheldon Litwin; Kavita Sharma; Diane Jorkasky; Elizabeth Tarka; Shaharyar Khan; and Dalane Kitzman

[1]Department of Internal Medicine, Divisions of Cardiology and Geriatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA

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Presenter disclosures

- Ambarish Pandey reports the following:
  - Research support: American Heart Association, Applied Therapeutics, Gilead Sciences, National Institute of Health, Roche, and Ultromics
  - 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 and associated with worse symptoms, poor 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, concerns have been raised about loss of muscle mass with GLP-1RA in older patients with HFpEF who have sarcopenic obesity and significant skeletal muscle dysfunction[9-12]
- There is a need for novel weight loss therapies that selectively reduce adipose tissue while preserving skeletal muscle mass for management of older patients with obesity-related HFpEF

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

1. Borlaug BA et al. Cardiovasc Res 2023;118(18):3434-3450. 2. Obokata M et al. Circulation 2017;136(1):6-19. 3. Morgen CS et al. Mayo Clin Proc 2023;98(10):1458-1468. 4. Kitzman DW et al. JACC Heart Fail 2018;6(12):1008-1010 5. Haass M, Circ Heart Fail 2011;4(3):324-31. 6. Butler J et al. Lancet 2024;403:1635–1648 7. Kosiborod MN, N Engl J Med 2024;390(15):1394-1407. 8. Kosiborod MN N Engl J Med 2023;389(12):1069-1084. 9. Houston DK et al. J Nutr Gerontol Geriatr 2019;38(1):83-99. 10. Wilding JPH et al.. N Engl J Med 2021;384(11):989-1002. 11. Jensen SBK et al. JAMA Netw Open 2024;7(6):e2416775. 12. Kitzman DW et al. JAMA 2016;315(1):36-46.

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Background

- Mitochondrial uncoupling agents or 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, a first-in-class CMA, has recently been shown to significantly reduce fat mass with preservation of the skeletal mass among patients with metabolic dysfunction associated steatotic liver disease, a metabolic disorder similar to obesity-related HFpEF[14,15]
- 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.

13. Pravednikova AE et al. Mol Med 2020;26(1):51. 14. Capone F et al. Circulation 2023;147(6):451-453. 15. Noureddin M et al. Lancet Gastroenterol Hepatol 2023;8(12):1094-1105.

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Study objective

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

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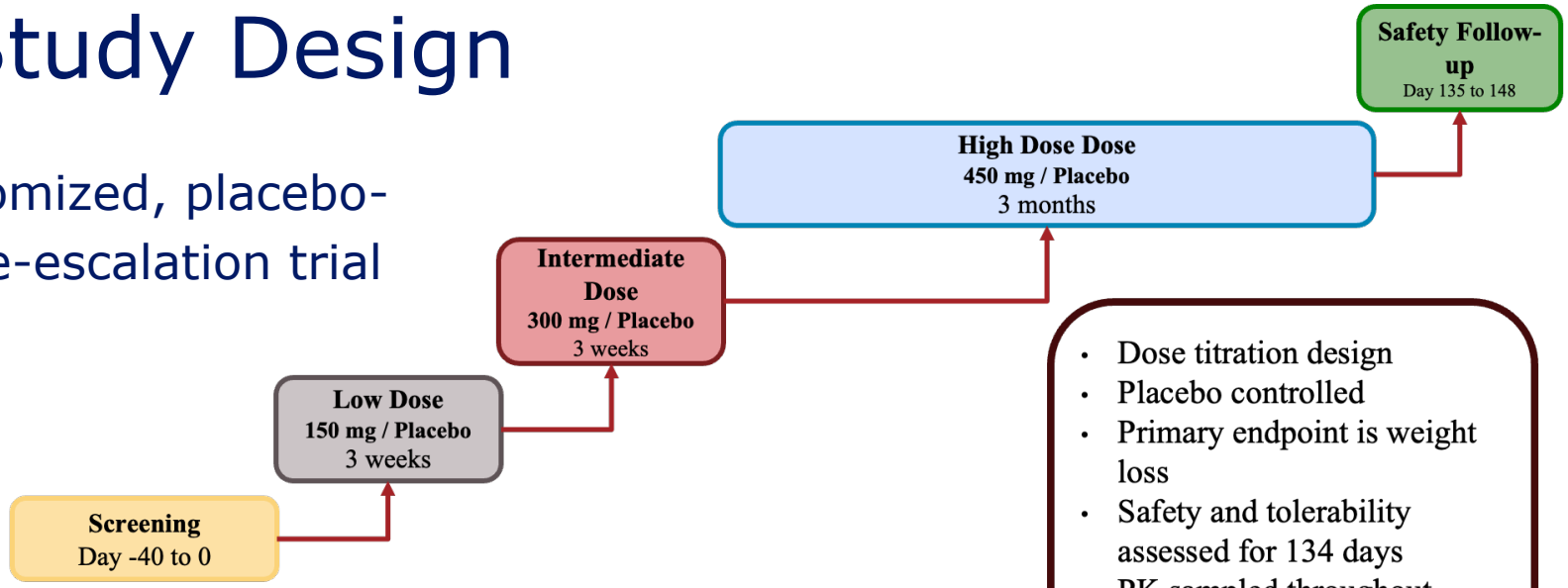
HuMain-HFpEF Study Design

Multi-center, phase 2a, randomized, placebo-controlled, double-blind, dose-escalation trial

N=66

1:1 Randomization (Placebo vs. HU6)



Key inclusion criteria

- Adults aged ≥30 years; BMI ≥30 kg/m^2; LVEF ≥50%; NYHA functional class II–III; KCCQ-OSS ≤80 points; low peak exercise oxygen uptake, and ambulatory
- 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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Outcomes

- *Primary endpoint*: Change in body weight from baseline to week 19
- *Key secondary endpoint*: Change in peak exercise oxygen uptake (VO_{2peak}) assessed by maximal cardiopulmonary exercise stress test
- *Other secondary endpoints*:
  - Changes in body composition using InBody Scale (InBody BWA, PA)
  - Changes in six-minute walk distance and quality of life (KCCQ)
  - Changes in cardiac structure and function by echocardiography
  - Changes in biomarkers of inflammation, NT-ProBNP, and hs-TnT

LSM, least squares mean

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Statistical Analysis

- The intent-to-treat analysis was performed to assess treatment group differences using a linear mixed model for repeated measures adjusting for covariates
- Treatment effect was reported as the difference in least squares means (LSMs) for between-group comparisons from this model

LSM, least squares mean

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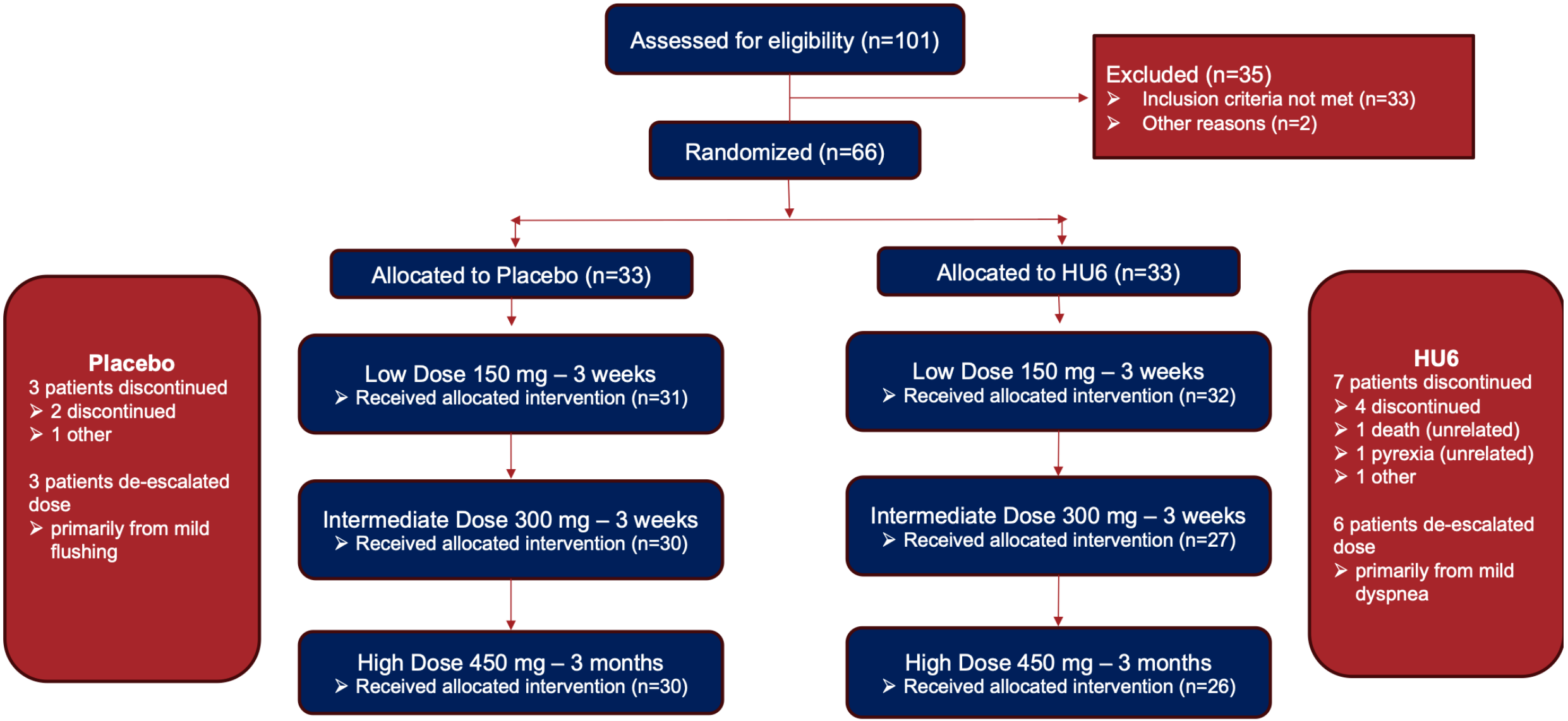
Study cohort



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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, (%)	51.5	63.6
Body Mass Index, kg/m^2	38.8 ± 5.1	40.0 ± 8.2
Body Weight , kg	110 ± 17	111 ± 27
Atrial fibrillation, (%)	21.2	21.2
Diabetes, n(%)	42.5	24.2
C-Reactive Protein (mg/L)	6.3 ± 7.5	5.4 ± 5.4
NT-proBNP (ng/L)	359 ± 748	265 ± 384
SGLT2i, (%)	49	31
Loop diuretic, (%)	64	75
MRA, (%)	42	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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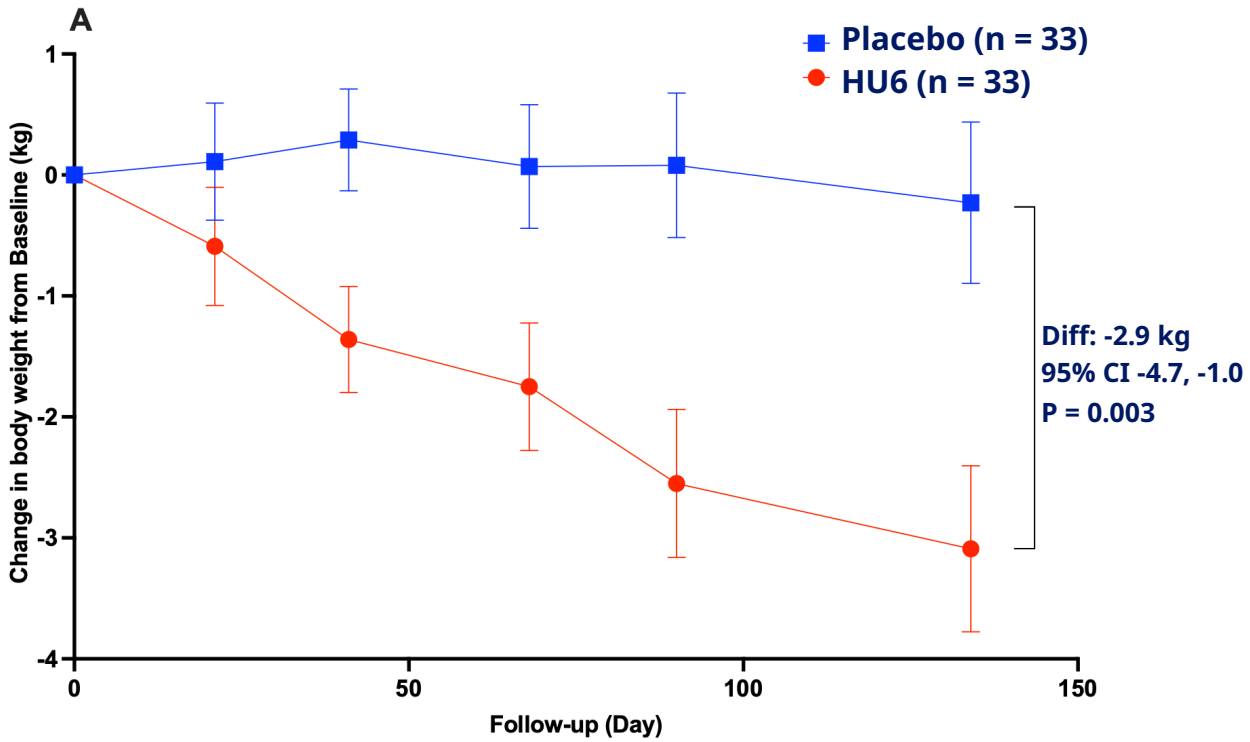
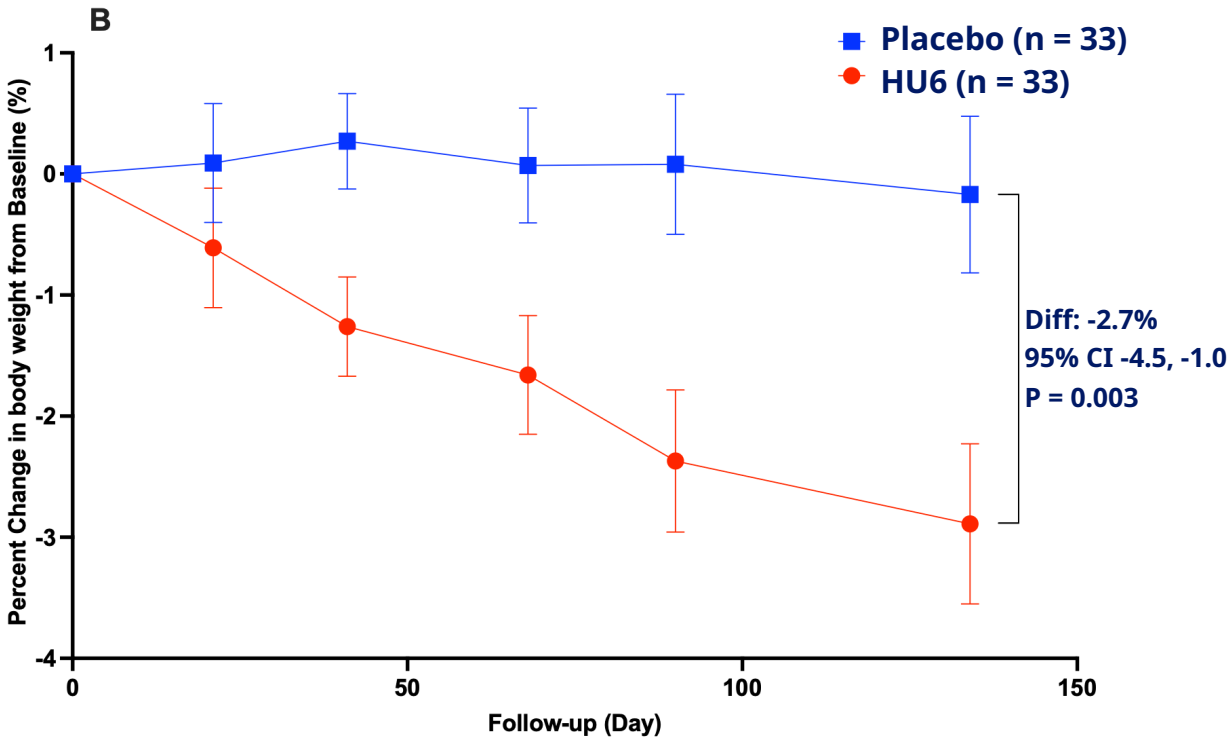
Effect of HU6 on body weight

Change in body weight (Kg)



Percent change in body weight (%)



Kg, kilogram

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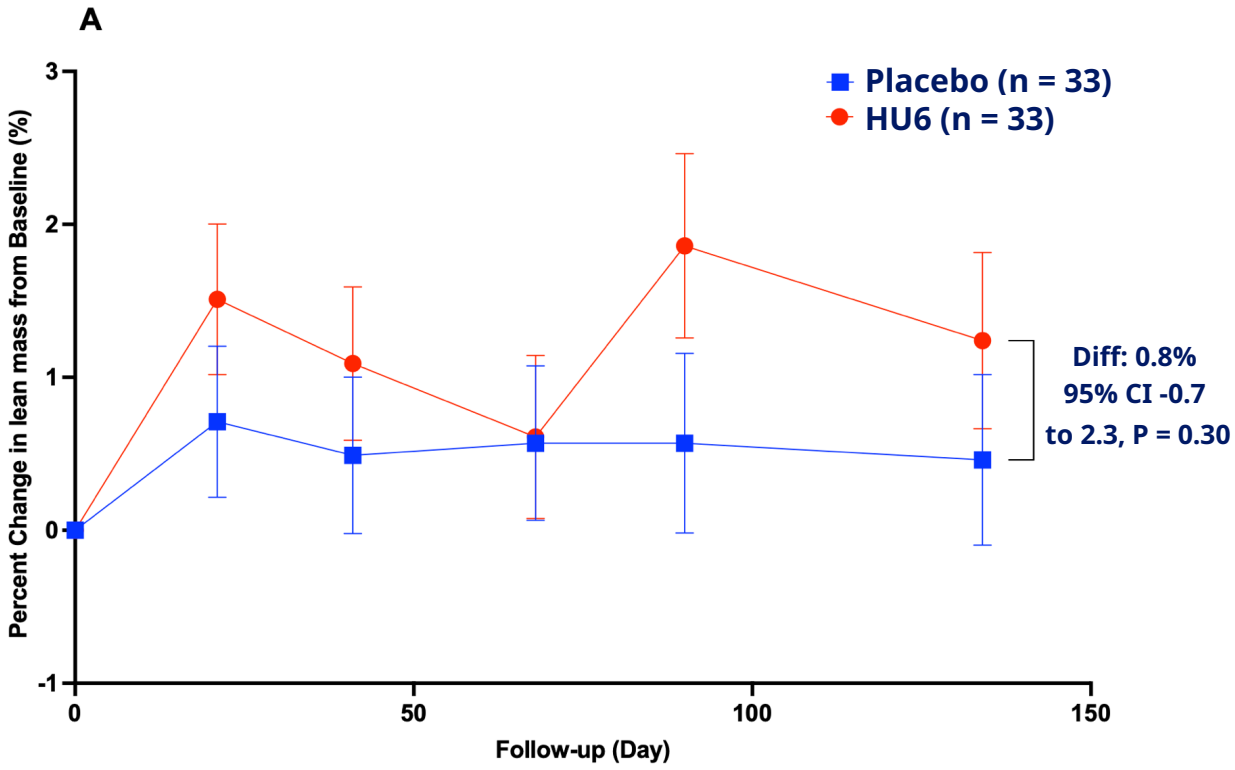
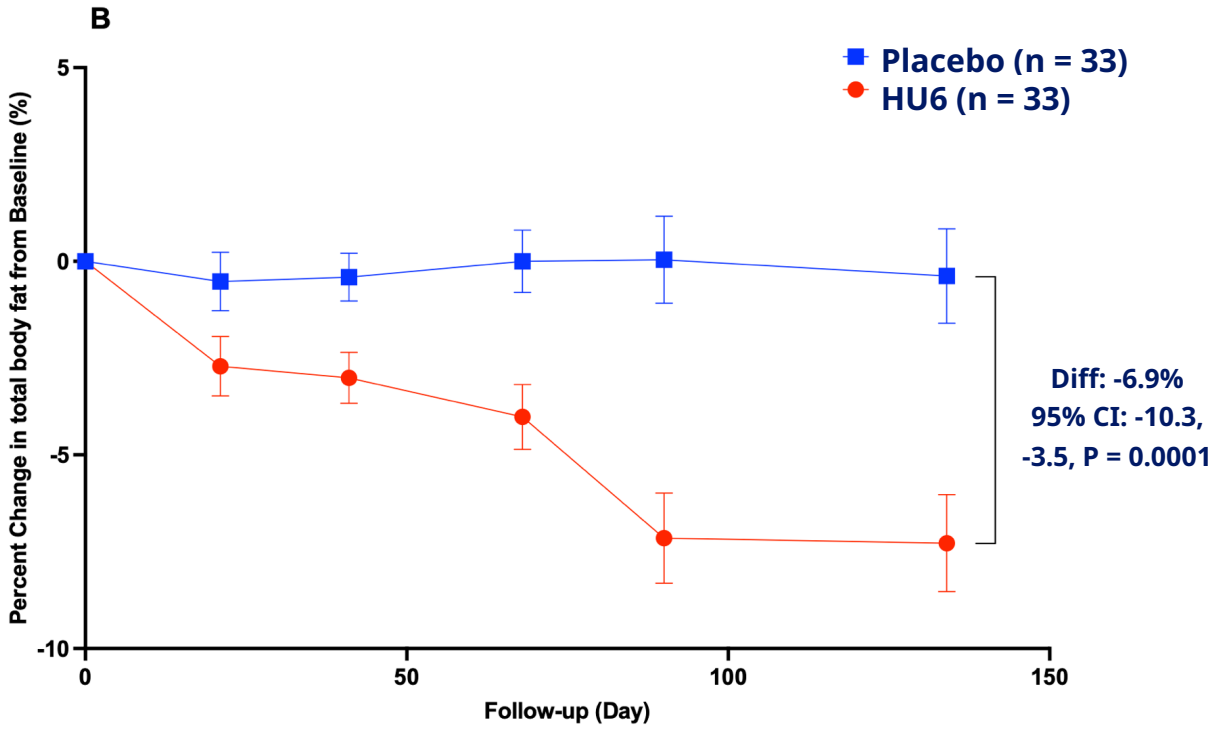
Effect of HU6 on body composition (InBody Scale)

Percent change in lean mass (%)



Percent change in fat mass (%)



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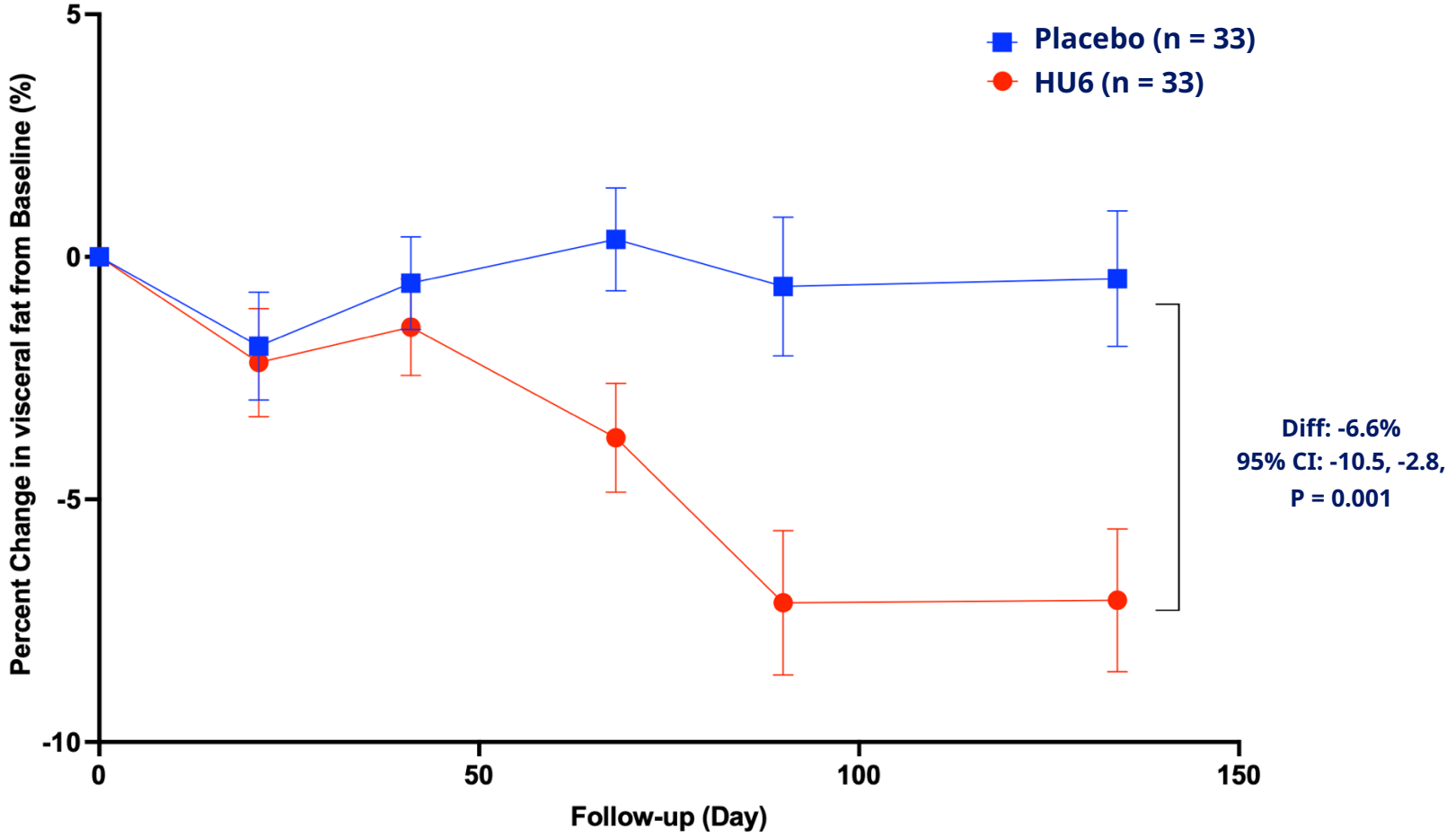
Effect of HU6 on percent visceral fat (InBody Scale)



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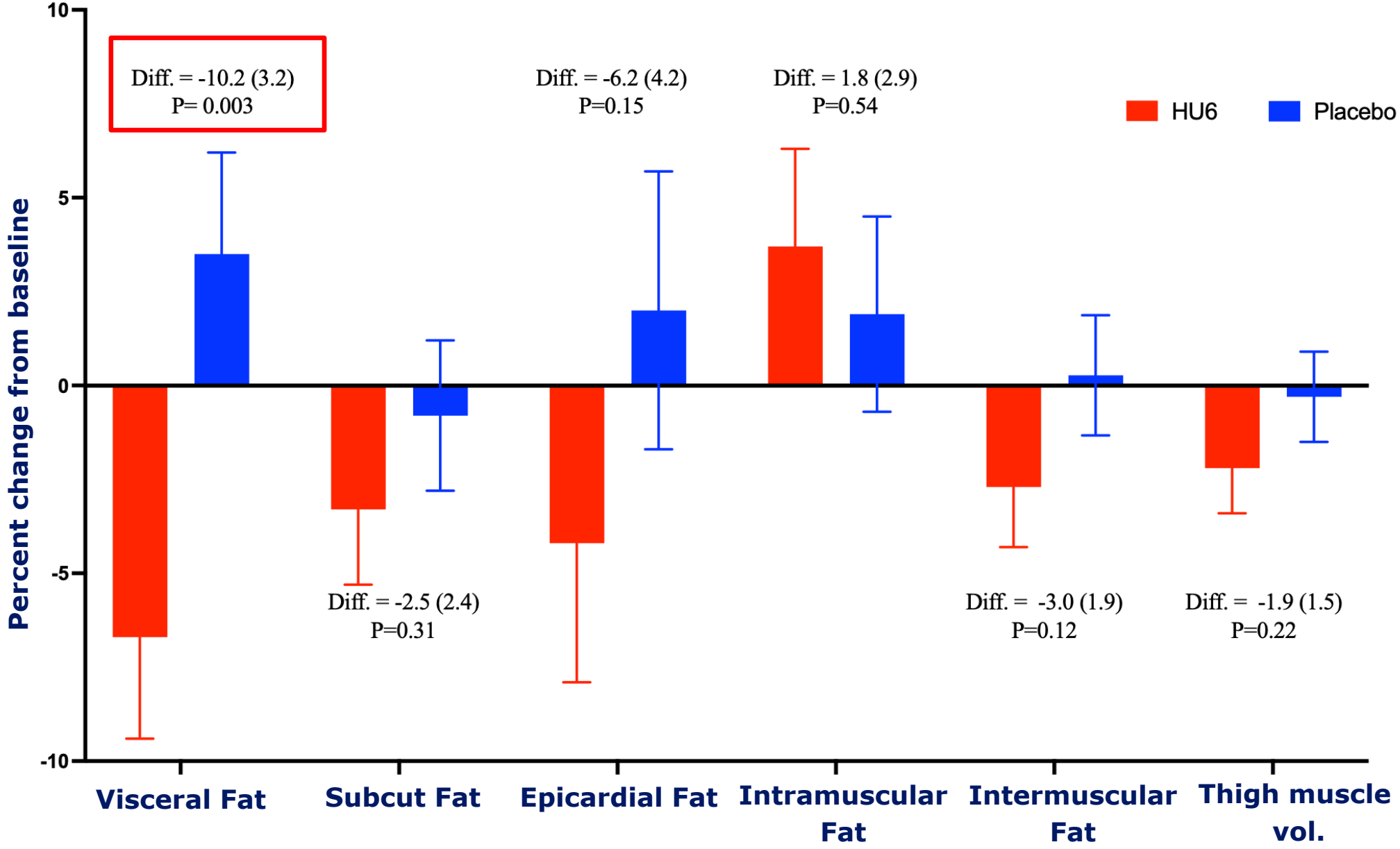
Effect of HU6 on body composition (MRI, n = 44)



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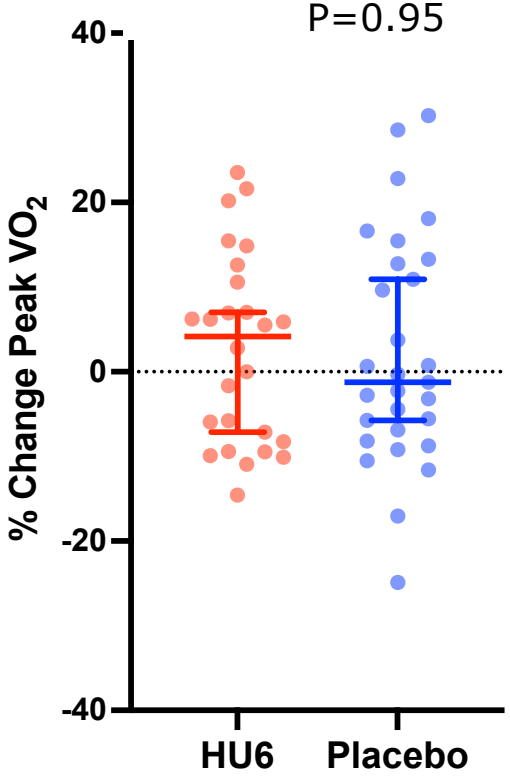
Effect of HU6 on exercise capacity and QOL

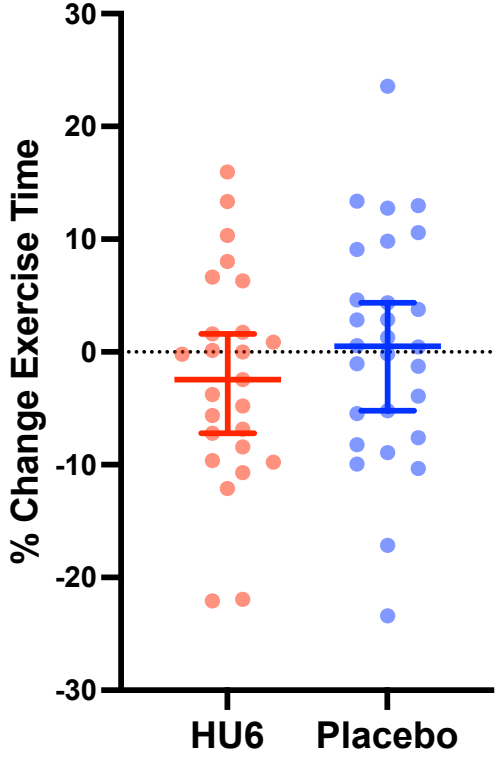
Peak VO_2

Diff: -0.22 (-6.97, 6.53)
P=0.95



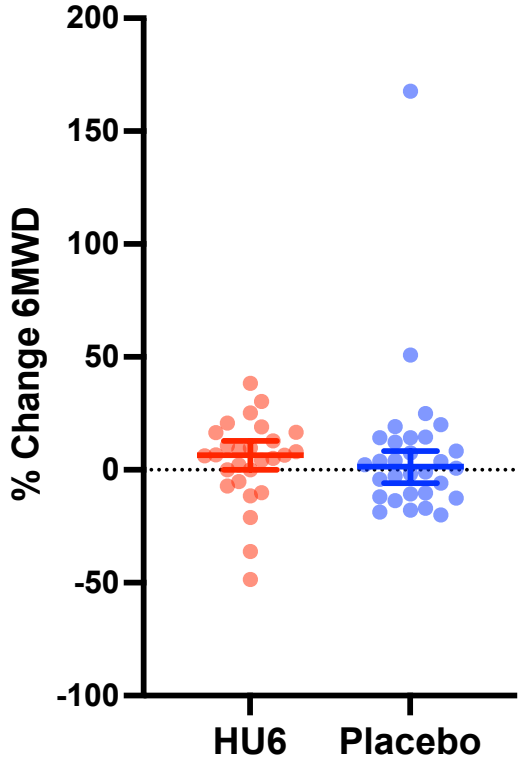
Exercise Time

Diff: -2.43 (-8.28, 3.43)



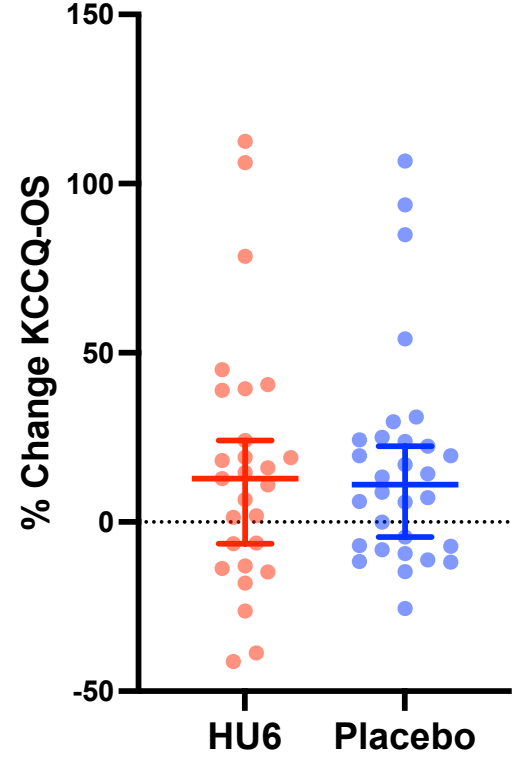
6MWD

Diff: 6.4 (-48.5, 38.3)



KCCQ

Diff: -1.6 (-17.8, 14.5)



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

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Effect on echocardiographic outcomes and biomarkers

Outcome	HU6 LSM [95% CI]	Placebo LSM [95% CI]	HU6 vs. Placebo LSM [95% CI]
Echocardiographic Parameters			
LV EF, %	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)
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)
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)
Biomarkers			
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)
C-reactive protein, mg/L	1.2 (-8.1, 10.4)	4.1 (-4.3, 12.6)	-3.0 (-15.3, 9.4)

LV – left ventricular, EF: Ejection fraction, TAPSE - tricuspid annular plane systolic excursion, RV – right ventricular, EDV – end-diastolic volume, ESV – end-systolic volume

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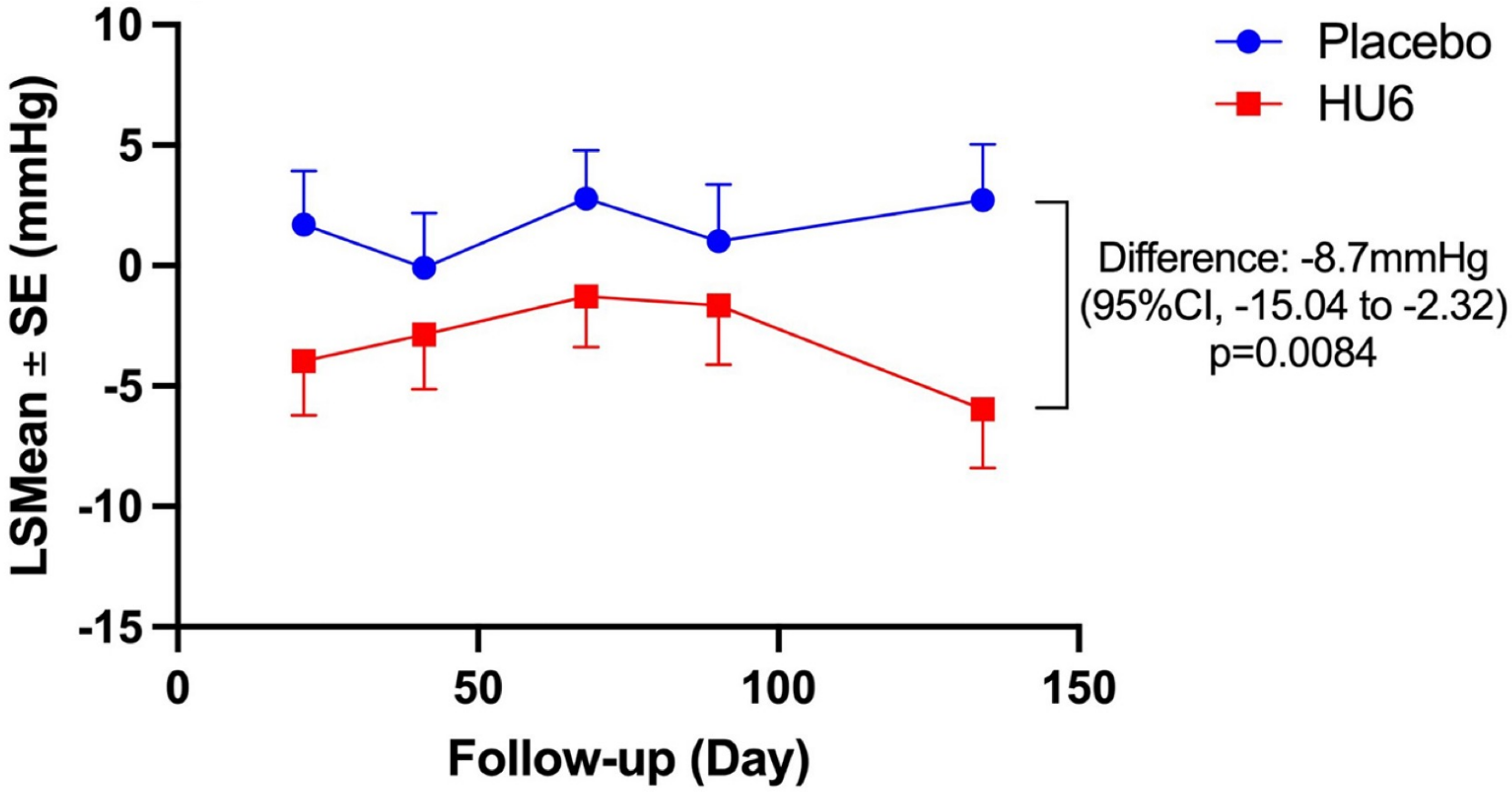
Effect of HU6 on change in systolic blood pressure



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Adverse Events

On-treatment adverse events (%)	HU6 (N=33)	Placebo (N=32)
Serious AE	12.1	3.1
AE leading to discontinuation	6.1	0
AE leading to death	3.0	0
AE by maximum severity		
Mild	48.5	40.6
Moderate	18.2	18.8
Severe	9.1	3.1
AEs occurring in >4%		
Diarrhea	18.2	6.3
Covid-19	15.2	3.1
Headache	6.1	9.4
Dyspnea	12.1	0
Arthralgia	0	9.4
Back pain	3.0	6.3
Cellulitis	3.0	6.3
Constipation	9.1	0
Fatigue	6.1	3.1
Flushing	3.0	6.3
Influenza	3.0	6.3
Joint swelling	9.1	0
Pain in extremity	6.1	3.1

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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 cardiac 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 obesity related HFpEF

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

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