HU6 Oral Investigational Therapy Reduces Liver Fat and Improves Adiposity Markers in Adults with MASH: Topline Results from a Phase 2 Randomized Placebo-Controlled Trial (M-ACCEL)

Late-Breaking Abstract Parallel Session 1

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Dr. Mazen Noureddin - Disclosures

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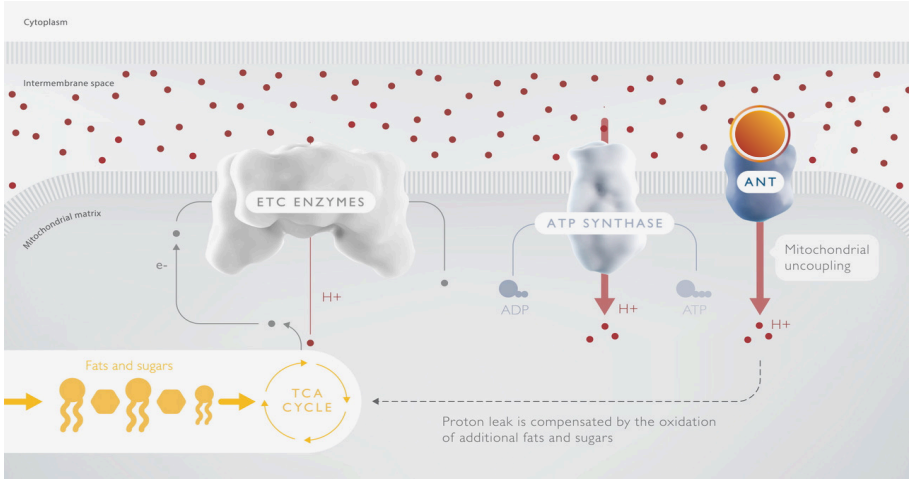
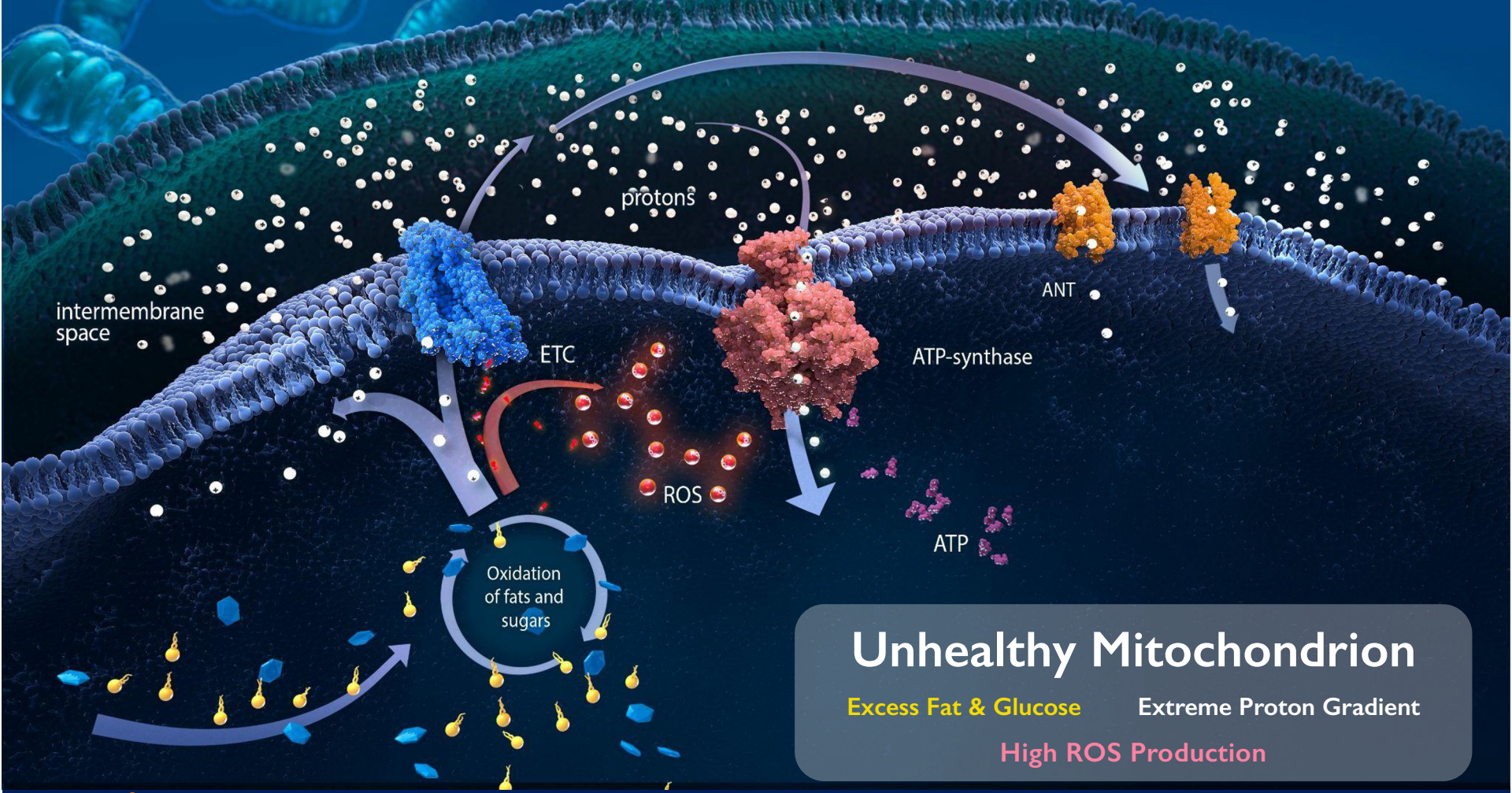
Background and Study Rationale

- HU6 is the lead investigational therapy within a new class of oral small molecule medicines - Controlled Metabolic Accelerators (CMAs)
- CMAs leverage the natural metabolic process of mitochondrial uncoupling to increase resting energy expenditure in a manner that is fat-selective, precision-controlled, and imperceptible to the patient
- Two prior Phase 2a studies have been completed to date with HU6 administered orally in subjects with MASLD[1] and obese-HFpEF, both of which met their primary endpoint
- This Phase 2a study (M-ACCEL) evaluated the efficacy of HU6 in reducing liver fat in adults with MASH



HU6 is an ANT-Activator
ANT - Adenine nucleotide translocase

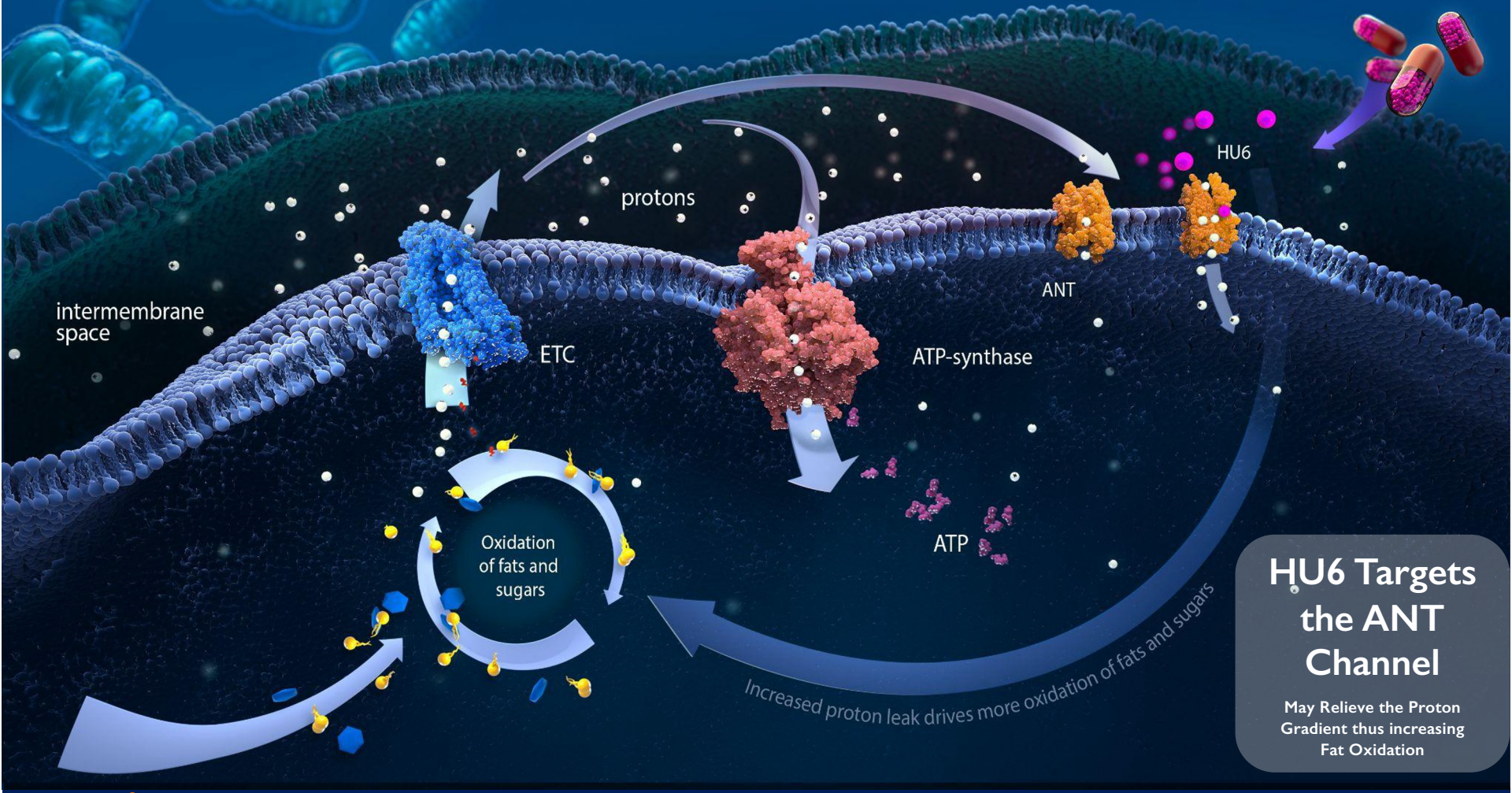
[1] The Lancet Gastroenterology & Hepatology 2023 Noureddin, et al.



Unhealthy Mitochondrion

Excess Fat & Glucose **Extreme Proton Gradient**

High ROS Production



HU6 Targets the ANT Channel

May Relieve the Proton Gradient thus increasing Fat Oxidation

Phase 2a M-ACCEL Study of HU6 in F2/F3 MASH

6-Month Study

Inclusion Criteria

- 271 patients included in safety analysis set*
- 228 patients included in pre-specified mITT**
- Age: ≥ 18 years
- BMI: ≥27.0 kg/m^2
- VCTE range: 7.0-15.0 kPa
- ≥ 8% LFC MRI-PDFF

Endpoints

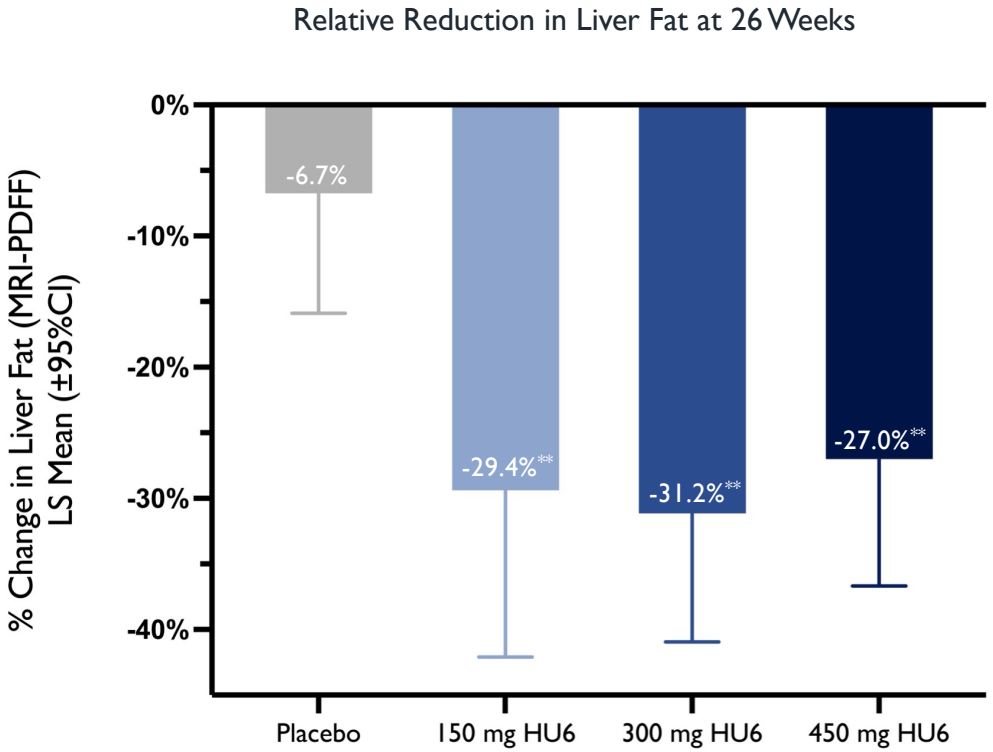
- Primary: Reduction in liver fat content by MRI-PDFF at last visit (6 months, ±2 weeks)
- Safety and tolerability assessed for 1 year from first dose

*Safety analysis set includes all randomized subjects.
**mITT was prespecified as the primary data for analysis and included all randomized patients with VCTE of 7.0 to 15.0 kPa, inclusive.

Baseline Characteristics

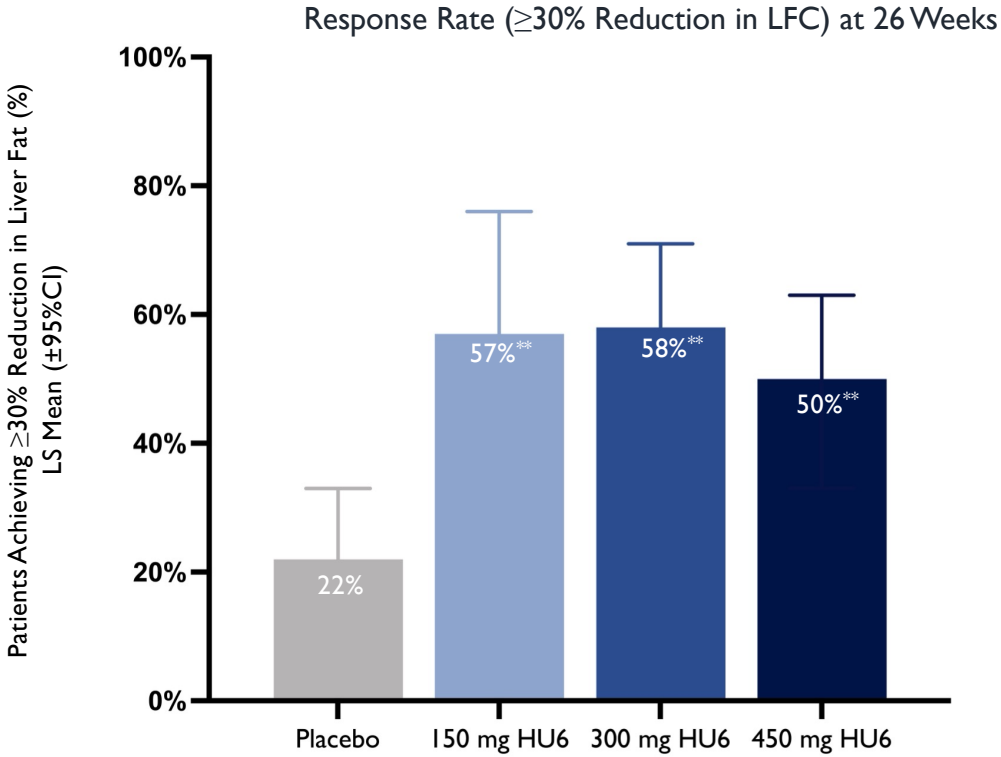
Measure	Placebo N=61	150 mg HU6 N=34	300 mg HU6 N=66	450 mg HU6 N=67
Age in Years, mean (s.d)	52.3 (10.4)	54.7 (12.5)	53.2 (13.0)	54.9 (11.1)
Gender Female, n (%)	28 (46%)	16 (47%)	27 (41%)	37 (55%)
BMI in kg/m^2, mean (s.d)	38.7 (5.6)	38.0 (5.9)	38.4 (6.0)	37.9 (6.4)
Diabetes Diagnosis at Baseline, n (%)	30 (49%)	24 (71%)	45 (68%)	50 (75%)
HbA1c in %, mean (s.d)	6.73 (1.4)	7.02 (1.3)	7.05 (1.3)	7.01 (1.1)
Liver Fat Content (MRI-PDFF) in %, mean (s.d)	17.1 (7.1)	17.4 (6.6)	17.7 (8.0)	17.6 (7.2)
Fibroscan VCTE in kPa, mean (s.d)	9.54 (2.5)	9.55 (1.8)	9.73 (2.1)	9.61 (2.2)

Primary Endpoint Met: Statistically Significant Reduction in Liver Fat at All Doses



**p<0.005 versus placebo

Majority of Patients Achieved ≥30% Liver Fat Reduction with HU6



≥30% relative decline in liver fat content (LFC) is highly correlated with histological improvements[1,2,3,4]

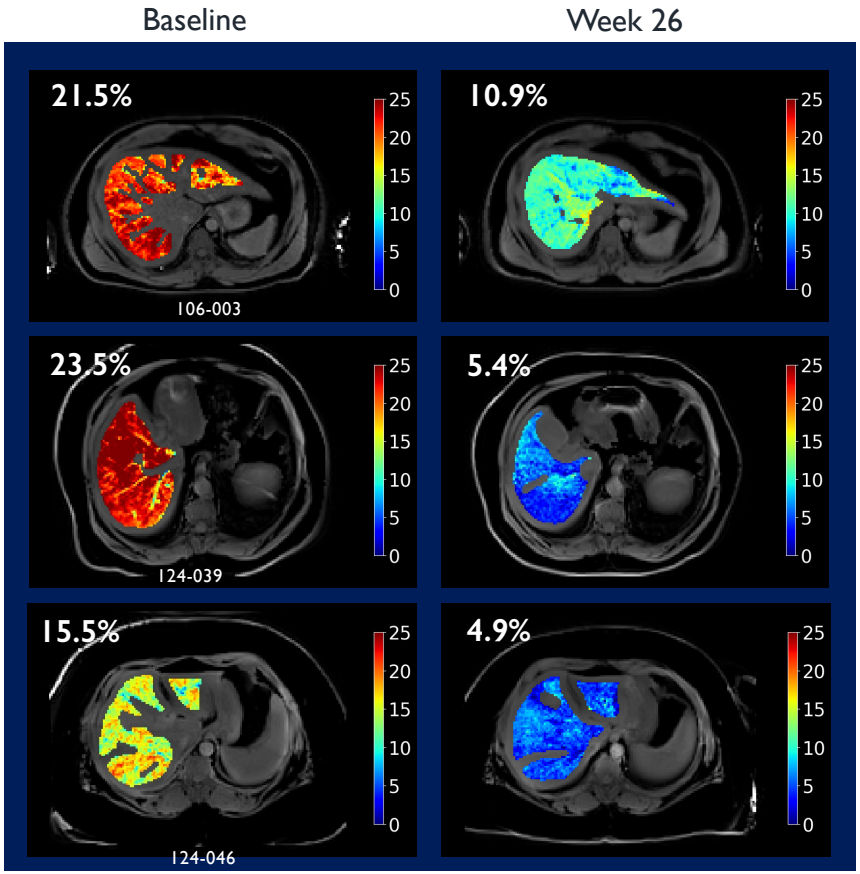
1. Alkhouri et al., 2024. 2. Brouwers et al., 2024. 3. Stine et al., 2021 4. Tamaki et al., 2022

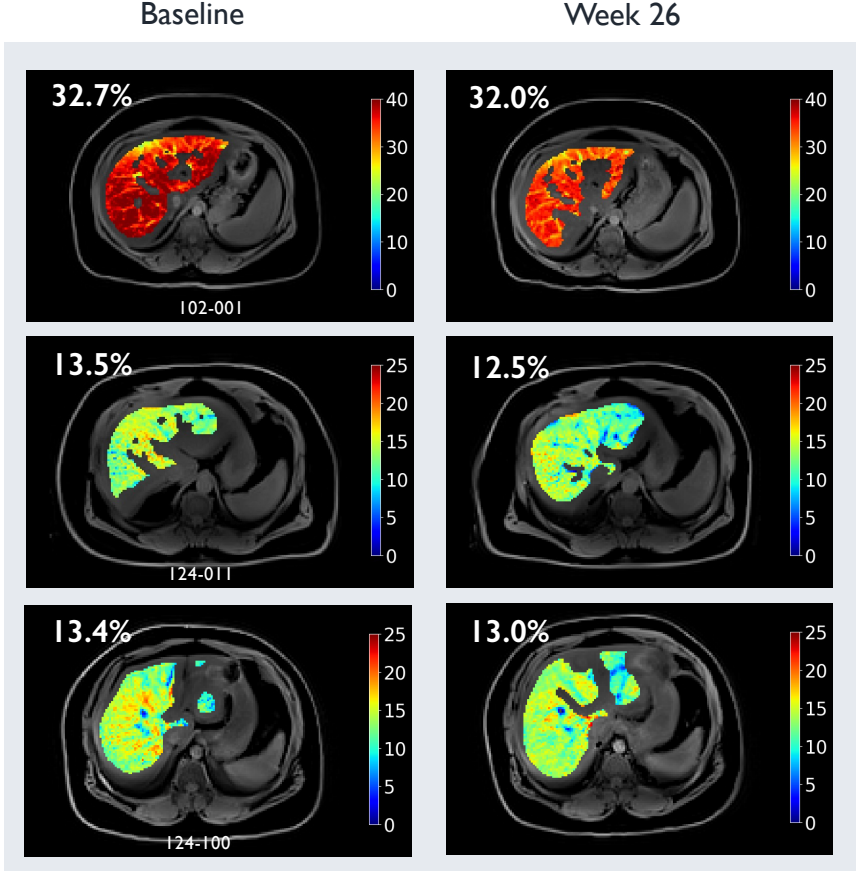
**p<0.005 versus placebo

450 mg HU6

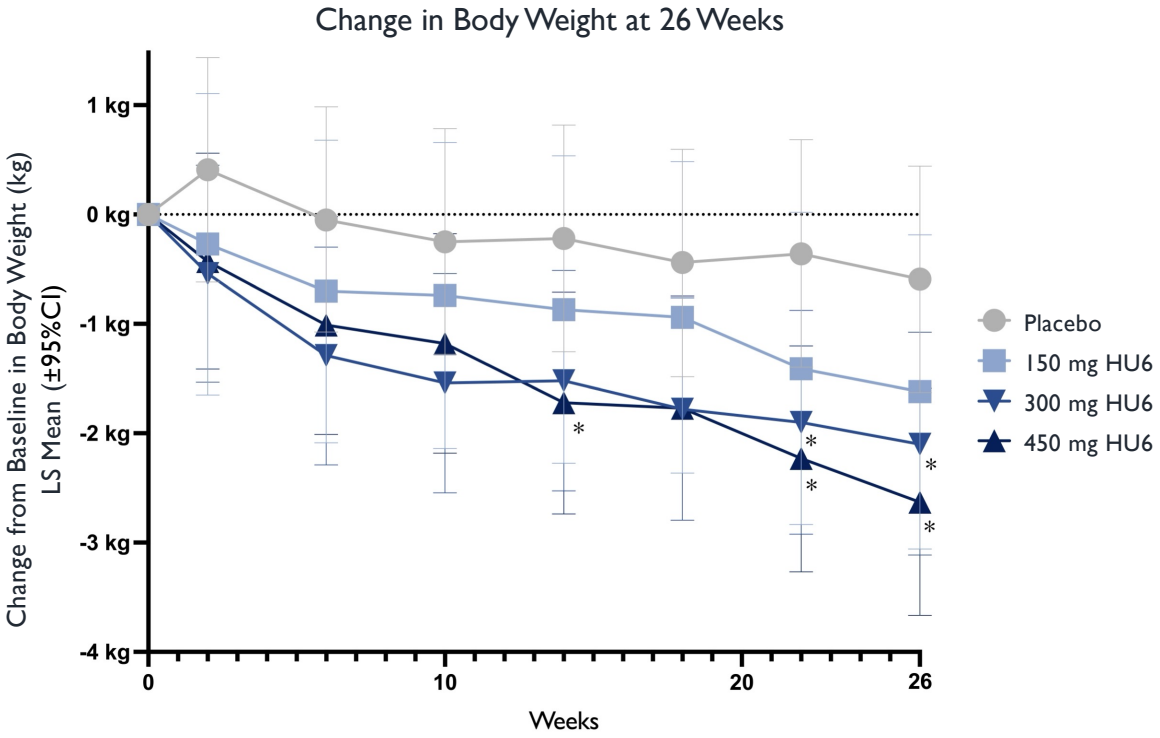
Liver Fat MRI-PDFF

Placebo





Reduction in Body Weight at 26 Weeks

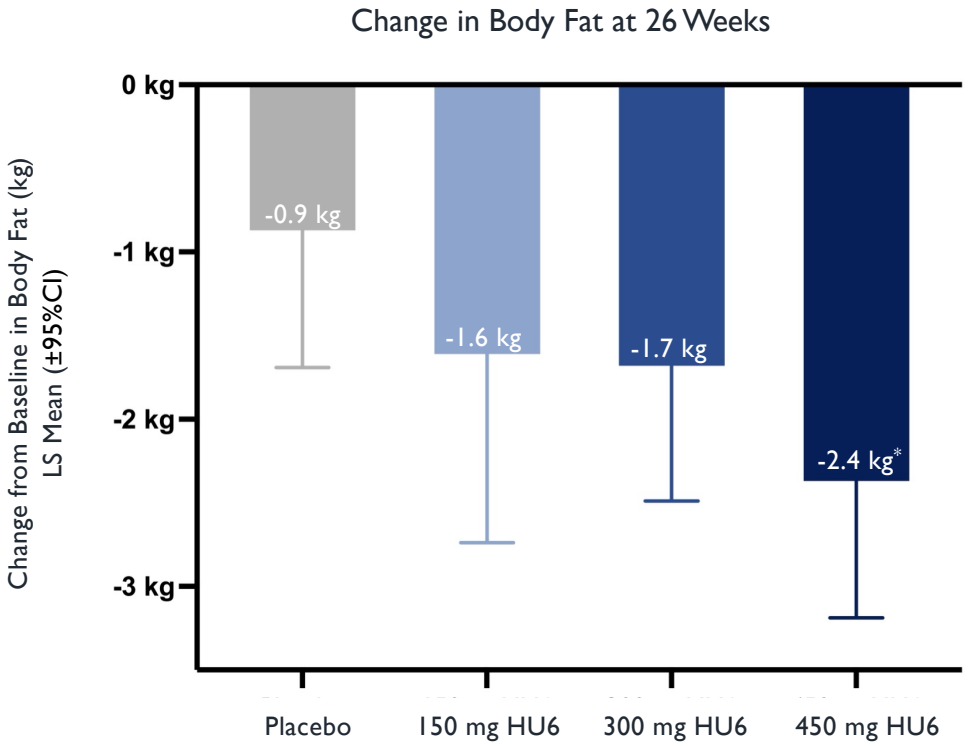


450 mg Dose (all p<0.05):

- **-2.6 kg** Weight loss from baseline
- **-2.4%** Change in Body Weight from baseline
- **-2.0 kg** Weight loss vs. placebo
- **-1.9%** Change in Body Weight vs. placebo

*p<0.05 vs placebo

Weight Loss is Fat-Selective with No Change in Skeletal Muscle Mass



450 mg Dose (all p<0.05):

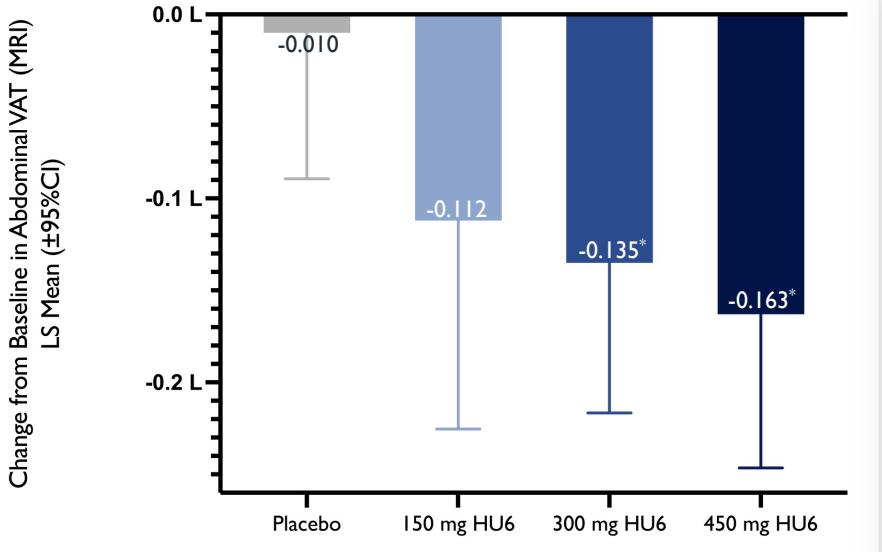
- **-2.4 kg** Fat loss from baseline
- Equates to a **4.6% reduction in total body fat**
- **-1.5 kg** Fat loss vs. placebo

Skeletal Muscle Mass unchanged at 6 months

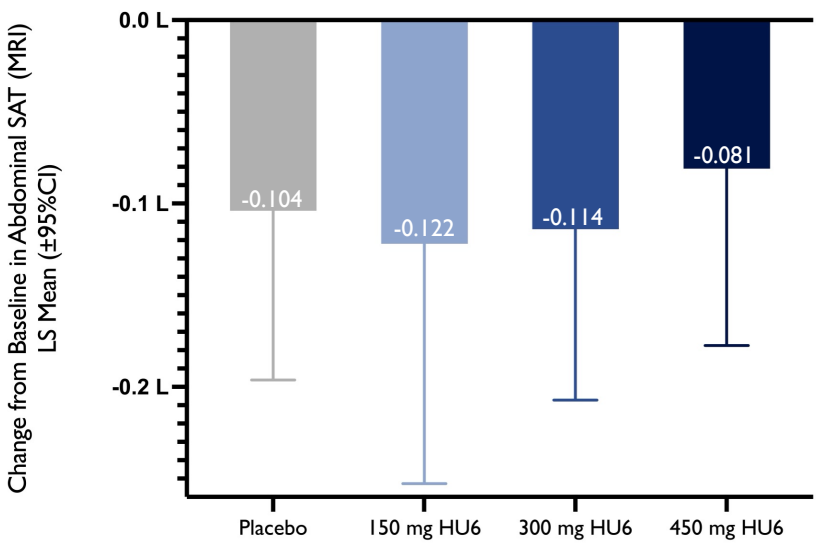
*p<0.05 versus placebo

Preferential Reduction in Abdominal Visceral Fat at 450 mg Dose

2:1 Reduction in Visceral: Subcutaneous Fat at 450 mg



Abdominal Visceral Adipose Tissue by MRI



Abdominal Subcutaneous Adipose Tissue by MRI

*p<0.05 versus placebo

Favorable Safety and Tolerability Profile

Summary AEs	Placebo N=77	150 mg HU6 N=40	300 mg HU6 N=76	450 mg HU6 N=78
Any TEAE	26 (34%)	15 (38%)	38 (50%)	30 (39%)
TE Serious Adverse Events	1 (1%)	0 (0%)	1 (1%)	3 (4%)
TEAE Leading to Treatment Discontinuation	0 (0%)	2 (5%)	2 (3%)	1 (1%)
Most Frequent TEAEs				
Gastrointestinal Disorders	12 (16%)	5 (13%)	11 (15%)	12 (15%)
Diarrhea	4 (5%)	0 (0%)	3 (4%)	5 (6%)
Nausea	2 (3%)	2 (5%)	4 (5%)	1 (1%)
Feces Soft	1 (1%)	1 (3%)	2 (3%)	3 (4%)
Abdominal Pain Upper	1 (1%)	1 (3%)	0 (0%)	2 (3%)

- HU6 was well tolerated
- ≤5% discontinuation rate due to TEAEs
- No individual AE occurred in ≥15% of subjects in any treatment group
- Most frequent class of AE was gastrointestinal disorders, with similar occurrence in placebo and each treatment group
- Flushing was infrequent, transient, and did not result in treatment discontinuation
- No metabolic fevers in M-ACCEL (or any other clinical trial of HU6 to date); highest temperature recorded in the clinic was 99.6F over 6-month study

Conclusion: HU6, a Novel Oral Controlled Metabolic Accelerator, Demonstrated Favorable Efficacy and Safety Profiles in MASH

- Primary endpoint met in Phase 2a M-ACCEL study with reduction in liver fat across all HU6 doses
- ≥30% liver fat reduction in majority of patients taking HU6
- Reductions in body weight and body fat with preservation of skeletal muscle mass
- ~2:1 selectivity for abdominal visceral vs subcutaneous fat reduction
- HU6 was generally safe and well tolerated, consistent with results of two prior Phase 2a studies; to date, ~450 patients have been treated with HU6
- Results confirm robust liver-centric effects of HU6 and support further development for MASH

Acknowledgements

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THANK YOU

Q&A

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