Pemvidutide-Induced Liver Fat Reduction in Subjects with Metabolic Dysfunction-Associated Steatotic Liver Disease Correlates with Improvements in Non-Invasive Markers of Inflammation and Fibrosis: Results of a 24-Week Multicenter, Randomized, Double-blind, Placebo-controlled Trial

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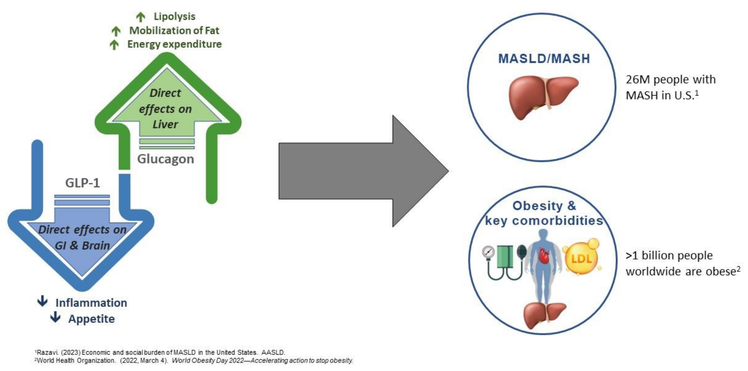
Background

MASLD and MASH

HEPATIC MANIFESTATIONS OF OBESITY

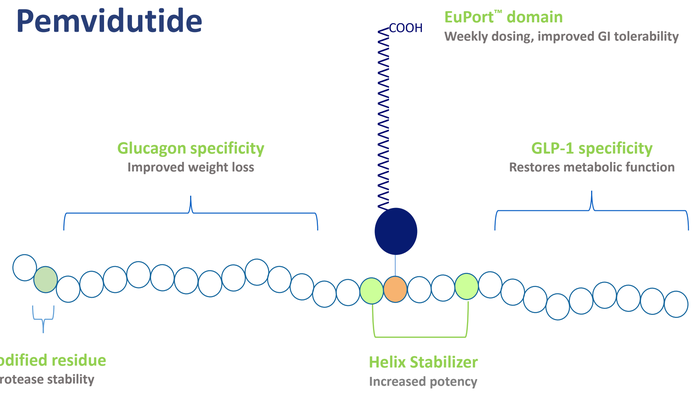
- Approximately 70% of individuals with obesity have metabolic dysfunction-associated steatotic liver disease (MASLD), a condition of excess liver fat
- 20-30% of MASLD subjects may advance to metabolic dysfunction-associated steatohepatitis (MASH), an inflammatory form of MASLD
- MASH-related inflammation may lead to fibrosis and progression to cirrhosis
- Reductions in liver fat content (LFC), liver enzymes, and body weight are cornerstones of the treatment of MASLD/MASH and their associated comorbidities
- Pemvidutide is a long-acting GLP-1/glucagon dual receptor agonist under development for the treatment of MASLD/MASH and obesity

PEMVIDUTIDE MOA IS OPTIMIZED FOR MASLD/MASH AND OBESITY



[1]Razavi. (2023) Economic and social burden of MASLD in the United States. AASLD.
[2]World Health Organization. (2022, March 4). *World Obesity Day 2022—Accelerating action to stop obesity.*

Structure is Key to Differentiation



- The 1:1 ratio of GLP-1 and glucagon agonism, as found in pemvidutide, was shown to provide the optimal balance of efficacy and safety (Day J, Pept Sci 2012)
- The proprietary EuPort™ domain extends the plasma half-life and likely accounts for the lower C_{max} and extended T_{max} of pemvidutide, slowing entry into the bloodstream

Aims

- Evaluate the correlation between changes in LFC and non-invasive markers of inflammation
- Evaluate the anti-fibrotic effects of pemvidutide in subjects with significant LFC and suspected fibrosis using serum-based biomarkers of fibrogenesis

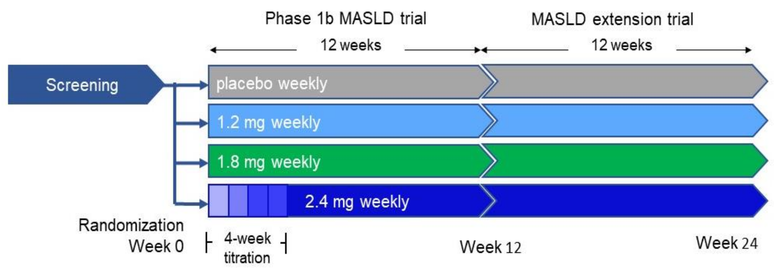
Methods

Study Population – Key Eligibility Criteria

- Clinicaltrials.gov# NCT05292911
- Men and women, ages 18-65 years
- BMI ≥28 kg/m^2
- MASLD: defined as LFC by MRI-PDFF ≥10%
- FibroScan® LSM <10kPa
- Non-diabetes OR diabetes if:
  - Stable dose (≥3 months) metformin or SGLT-2 therapy
  - No use of insulin, sulfonylureas, DPP-4, GLP-1 treatment
- HbA1c <9.5%
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) laboratory values ≤75 IU/L

Study Design

- Sixty-four subjects received study drug weekly for 24 weeks



Outcome Measures

- Correlation between reductions in LFC and markers of liver inflammation [corrected T1 (cT1), ALT]
- In subjects with suspected fibrosis, change in the serum fibrosis markers Enhanced Liver Fibrosis (ELF) and procollagen type III N-terminal peptide (PIIINP), and change in liver stiffness measurement (LSM)

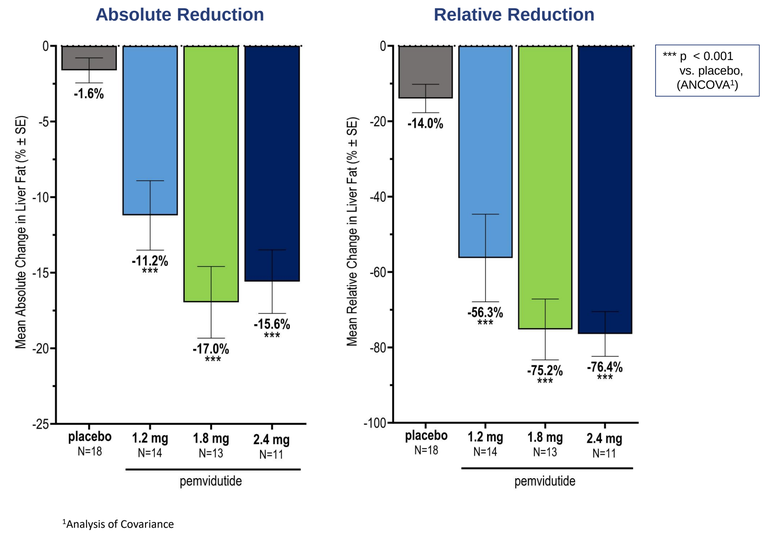
Results

Characteristics of Study Participants

Characteristic		Treatment			
		Placebo (n = 19)	1.2 mg (n=16)	1.8 mg (n=15)	2.4 mg (n=14)
Age, years	mean (SD)	49.0 (15)	48.6 (11)	49.9 (10)	48.4 (8)
Gender	female, n (%)	11 (57.9%)	7 (43.8%)	8 (53.3%)	8 (57.1%)
Race	white, n (%)	17 (89.5%)	14 (87.5%)	13 (86.7%)	14 (100%)
	other, n (%)	2 (10.5%)	2 (12.5%)	2 (13.3%)	0 (0.0%)
Ethnicity	Hispanic, n (%)	11 (57.9%)	15 (93.8%)	12 (80.0%)	9 (64.3%)
	not Hispanic, n (%)	8 (42.1%)	1 (6.3%)	3 (20.0%)	5 (35.7%)
BMI, kg/m^2	mean (SD)	37.1 (4.9)	36.7 (6.1)	36.0 (3.8)	37.0 (5.3)
Body weight, kg	mean (SD)	104.4 (21.2)	101.4 (16.3)	100.9 (13.2)	107.4 (17.2)
Diabetes status	T2D, n (%)	5 (26.3%)	3 (18.8%)	6 (40.0%)	3 (21.4%)
Liver fat content (LFC), %	mean (SD)	24.0 (9.6)	20.1 (7.7)	23.9 (7.4)	20.5 (6.5)
ALT, IU/L	mean (SD)	41.0 (21.3)	32.4 (14.2)	35.3 (13.0)	39.6 (26.6)
ELF	mean (SD)	8.9 (0.6)	8.6 (0.6)	8.7 (0.7)	9.0 (1.1)
PIIINP, µg/L	mean (SD)	8.7 (2.6)	7.7 (3.0)	8.0 (2.6)	8.9 (3.3)
LSM, kPa	mean (SD)	6.7 (0.9)	6.9 (2.0)	6.1 (1.3)	6.5 (1.8)
cT1[1], ms	mean (SD)	933.4 (114.7)	892.1 (96.3)	909.4 (162.0)	933.7 (21.9)

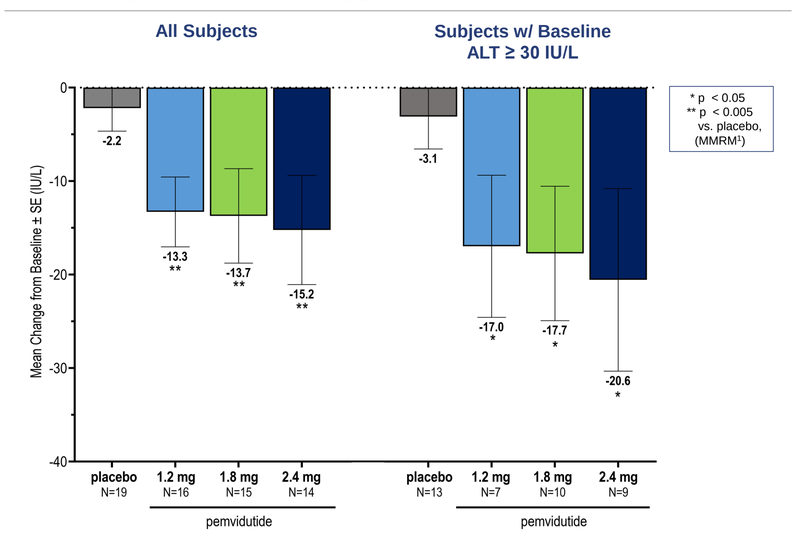
[1]A subset of study subjects were evaluated by cT1

Reduction in LFC by MRI-PDFF at Week 24



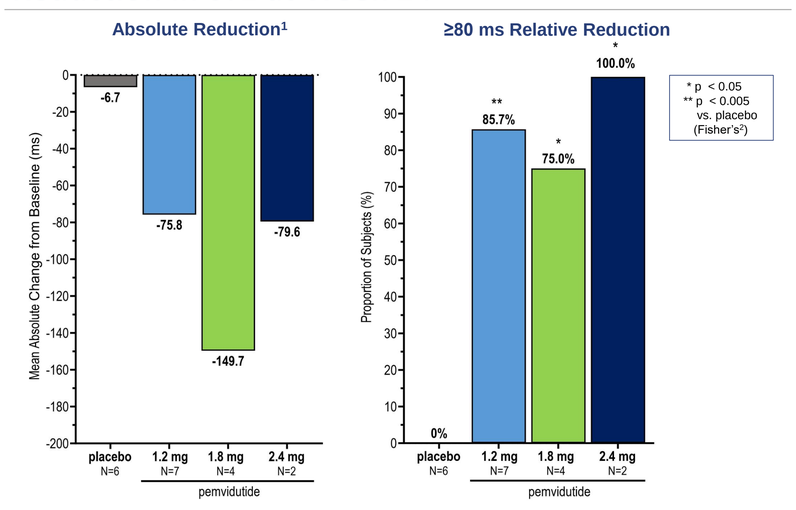
[1]Analysis of Covariance

Reduction in ALT at Week 24



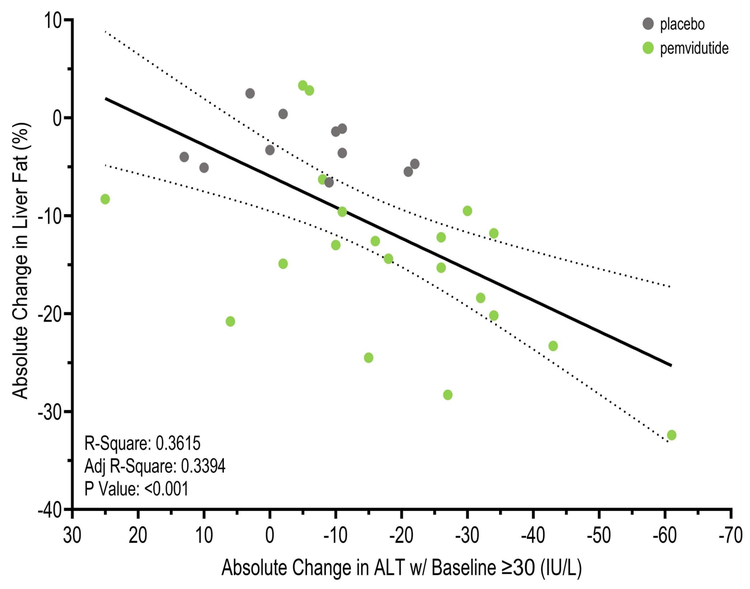
[1]Mixed Model Repeated Measures

Reduction in cT1 at Week 24

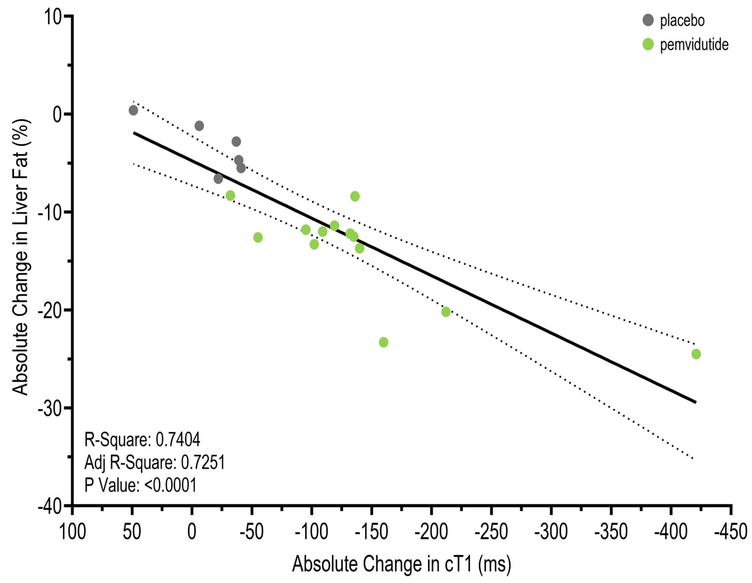


[1]Analysis of Covariance of cT1 median measurements
[2]Fisher's Exact Test

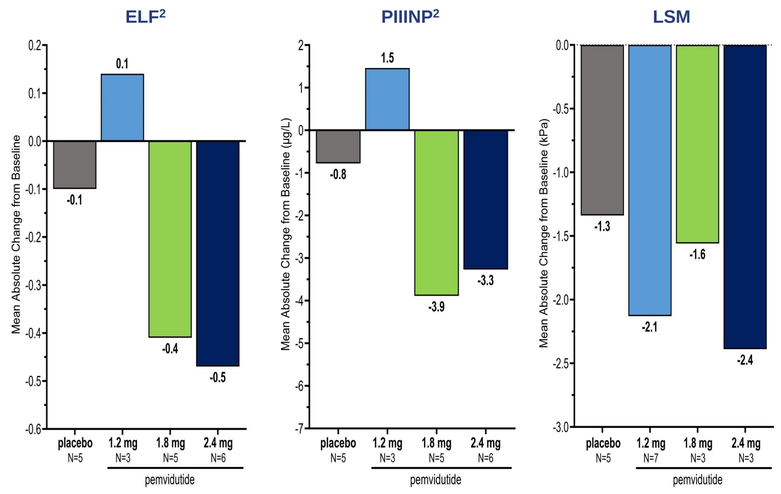
Reductions in LFC correlate with reductions in ALT



Reductions in LFC correlate with reductions in cT1



Pemvidutide reduces markers of liver fibrosis[1]



[1]Upper tertile baseline characteristics
- baseline ELF scores, mean (SD) : placebo = 9.6 (0.4); 1.2 mg = 9.3 (0.5); 1.8 mg = 9.4 (0.3); 2.4 mg = 9.7 (0.6)
- baseline PIIINP µg/L, mean (SD): placebo = 10.6 (2.0); 1.2 mg = 10.1 (2.7); 1.8 m g = 9.6 (3.4); 2.4 mg = 11.0 (2.2)
- baseline LSM kPa, mean (SD): placebo = 7.7 (0.3); 1.2 mg = 8.6 (0.9); 1.8 m g = 8.0 (0.5); 2.4 mg = 8.4 (1.0)

[2]Upper tertiles are from the same subject population

Conclusions

- Pemvidutide treatment resulted in reductions of up to 76.4% in relative LFC, 15.2 IU/L in serum ALT, and 149.7 ms in cT1 at 24 weeks
- Reductions in LFC correlated with improvements in non-invasive biomarkers of inflammation
- A reduction in ALT of ≥17 IU/L, which has been predictive of improvements in liver histology, was observed at all three doses of pemvidutide in subjects with baseline ALT of ≥30 IU/L (Loomba R, Gastro 2019)
- Up to 100% of subjects had an 80 ms relative reduction in cT1, which has been associated with a 2-point reduction in NAFLD activity score (Dennis A, Front Endocrinol 2021)
- In a subset of subjects with suspected fibrosis, reductions in serum-based biomarkers of fibrogenesis and liver stiffness were observed
- These observations suggest that pemvidutide may lead to significant reduction in hepatic inflammation and fibrosis in biopsy-driven MASH clinical trials

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