Effect of Pemvidutide, a GLP-1/Glucagon Dual Receptor Agonist, on Plasma Lipidomic Profiles in Subjects with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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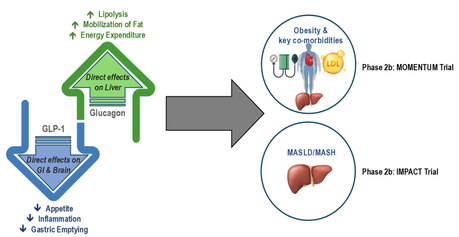
Background

MASLD and MASH ARE HEPATIC MANIFESTATIONS OF OBESITY

- Approximately 70% of people with either obesity or MASH have dysregulated serum lipid profiles
- Dyslipidemia can result in increased hepatic and systemic inflammation, exacerbating comorbidities such as cardiovascular disease and insulin resistance
- The primary morbidity associated with MASH is due to cardiovascular events as opposed to liver-specific events
- Pemvidutide is a long-acting GLP-1/glucagon dual receptor agonist under development for the treatment of MASH and obesity
- Pemvidutide achieved up to 15.6% weight loss in a 48-week clinical trial of subjects with obesity (NCT05295875)

Pemvidutide MOA is optimized for MASH and obesity



- 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 et al. 2012)

Aims

- To analyze the change in plasma lipidomic profile of subjects with overweight/obesity and MASLD following pemvidutide treatment.

Methods and Study Design

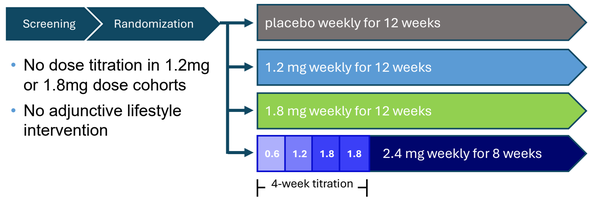
- Plasma samples from study completers were analyzed for changes in:
  - Lipoproteins by nuclear magnetic resonance (NMR)
  - MASH-associated phospholipids and sphingolipids by ultra-high performance liquid chromatography–mass spectrometry (UHPLC-MS)

Study Population – Key Eligibility Criteria

- Clinicaltrials.gov# NCT05006885 (Harrison et al. 2024)
- Men and women, ages 18-65 years
- BMI ≥ 28 kg/m^2
- MASLD, defined as liver fat content (LFC) by MRI-PDFF ≥ 10%
- Absence of significant fibrosis, defined as FibroScan® LSM < 10kPa
- Non-diabetes OR diabetes if:
  - Stable dose (≥ 3 months) metformin or SGLT-2 therapy AND
  - 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

Phase 1b MASLD Study Design

- Ninety-four subjects were randomized across 13 US sites to 1 of 4 treatment arms, stratified by the presence or absence of type 2 diabetes (T2D)



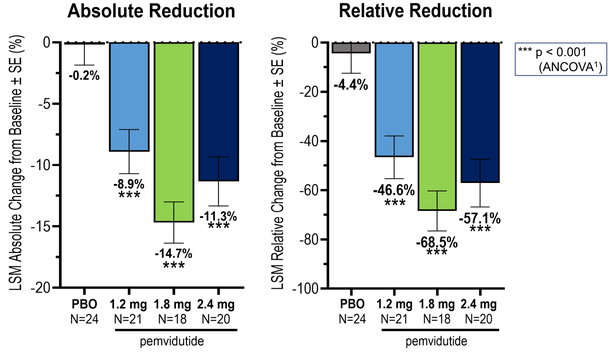
- No dose titration in 1.2mg or 1.8mg dose cohorts
- No adjunctive lifestyle intervention

Results

Baseline Characteristics of Study Participants

Characteristic		Treatment			
		PBO (N=24)	1.2 mg (N=23)	1.8 mg (N=23)	2.4 mg (N=24)
Age, years	mean (SD)	47.9 (14)	48.6 (11)	50.3 (9)	48.8 (8)
Gender	female, n (%)	14 (58.3%)	9 (39.1%)	12 (52.2%)	15 (62.5%)
Race	white, n (%)	21 (87.5%)	21 (91.3%)	20 (87.0%)	24 (100%)
	other, n (%)	3 (12.5%)	2 (8.7%)	3 (13.0%)	0 (0.0%)
Ethnicity	Hispanic, n (%)	14 (58.3%)	20 (87.0%)	19 (82.6%)	18 (75.0%)
	non-Hispanic, n (%)	10 (41.7%)	3 (13.0%)	4 (17.4%)	6 (25.0%)
BMI, kg/m^2	mean (SD)	36.9 (4.7)	36.3 (5.6)	35.4 (3.9)	35.3 (5.0)
Body weight, kg	mean (SD)	105.1 (20.8)	102.4 (14.6)	98.9 (19.7)	98.2 (18.9)
Diabetes status	T2D, n (%)	6 (25.0%)	7 (30.4%)	7 (30.4%)	7 (33.3%)
Liver fat content (LFC), %	mean (SD)	23.8 (9.2)	21.6 (7.3)	21.8 (8.0)	20.2 (7.0)
ALT, IU/L	mean (SD)	39.5 (21.4)	32.4 (13.8)	36.4 (15.6)	37.8 (24.4)
Triglycerides, mg/dL	mean (SD)	169.3 (90.1)	224.9 (119.1)	192.2 (114.9)	220.0 (169.3)
Total cholesterol, mg/dL	mean (SD)	181.4 (39.0)	186.9 (44.8)	200.0 (35.2)	182.2 (39.7)
LDL cholesterol, mg/dL	mean (SD)	100.0 (38.2)	100.2 (34.3)	116.6 (33.6)	101.3 (33.0)

Reduction in Liver Fat Content by MRI-PDFF



[1]Analysis of Covariance; placebo vs. treatment at Week 12

Rapid Reduction in Atherogenic Lipoproteins

Changes in Particle Number by NMR

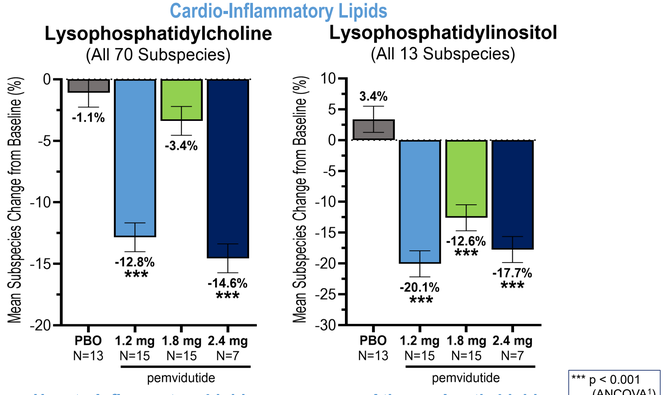
Lipoprotein Particle	PBO (N=12)	Pemvidutide 1.2mg (N=15)	Pemvidutide 1.8mg (N=15)	Pemvidutide 2.4mg (N=7)
VLDL-P		*	***	*
Large VLDL-P		*	**	**
Medium VLDL-P				
Small VLDL-P		*	***	**
LDL-P			**	
Large LDL-P				
Medium LDL-P			*	
Small LDL-P			**	*

Log$_2$ Fold Change (FC): 1.2, 1.0, 0.8, 0.6, 0.4, 0.2, 0, -0.2, -0.4, -0.6, -0.8, -1.0, -1.2

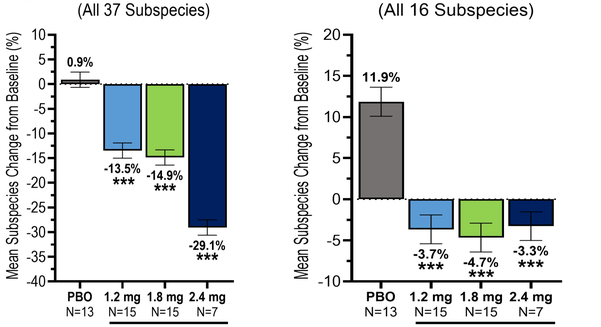
Significant changes in lipid particle numbers. The color code represents the log$_2$(robust fold-change from baseline to Week 6). Only showing threshold change ≥ 0.2. Wilcoxon signed rank test p-values: *p < 0.05, **p < 0.01, ***p < 0.001, vs. baseline.

Reduction in Plasma Lipotoxic Lipid Classes

Cardio-Inflammatory Lipids



Hepato-Inflammatory Lipids

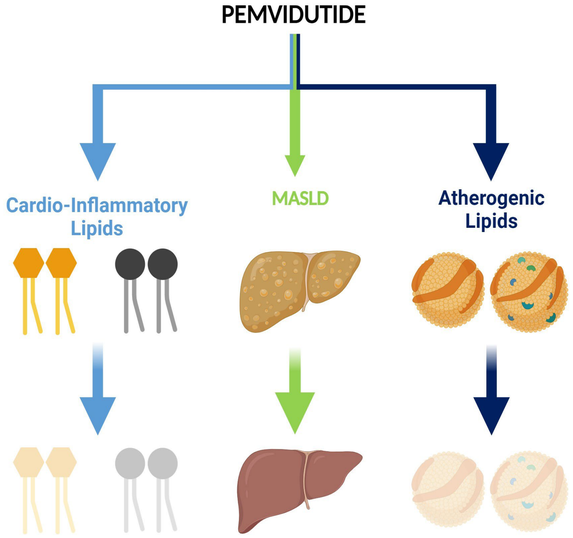


Atherosclerotic Lipids

[1]Analysis of Covariance; placebo vs. treatment at Week 12

Conclusions

- Pemvidutide administered weekly over 12 weeks resulted in:
  - Significant reductions in liver fat content within 12 weeks
  - Decreases in atherogenic small LDL-C
  - Decreases in MASH-associated phospholipid and sphingolipid species
  - Decreases in cardio-inflammatory lysophosphatidylcholines and lysophosphatidylinositols that may reduce cardiovascular disease (Aiyar et al. 2007; Xu et al. 2021)
  - Decreases in lysophosphatidylethanolamines that may reduce fat accumulation in MASH patient livers (Yamamoto et al. 2022)
  - Decreases in ceramides and monohexosylceramides that may decrease atherosclerotic lesions (Choi et al. 2021)
- These findings support pemvidutide's potential benefit on MASH-associated co-morbidities, including atherosclerosis, cardio-inflammation and metabolic syndrome
- Pemvidutide is being evaluated in an ongoing biopsy-confirmed, 24-week Phase 2b MASH trial (IMPACT: NCT05989711)



Reduced Systemic and Hepatic Lipotoxicity

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Conclusions diagram created with BioRender.com

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