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Plasma lipidomic profiling of subjects with overweight or obesity following treatment with the glucagon-like peptide 1/glucagon dual receptor agonist pemvidutide: an investigation of lipid signatures associated with metabolic dysfunction-associated steatohepatitis

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Pemvidutide significantly decreased serum lipids including inflammatory lipid sub-species at Week 12.

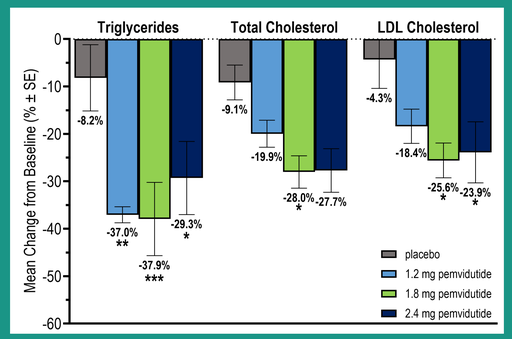

Figure 1. Pemvidutide treatment yielded significant decreases in serum lipids in subjects with overweight/obesity at Week 12. Relative change in serum lipids. *p*-values: **p*<0.05, ***p*<0.005, ****p*<0.001, vs. placebo

Lipid Class	Common name	Individual notation	PBO (n=10)	Pemvidutide 1.2mg (n=6)	Pemvidutide 1.8mg (n=9)	Pemvidutide 2.4mg (n=9)
Glycerophospholipids	Lyso-PI	LPI(18:1)		*		**
		LPI(18:1)		*	*	**
		LPI(18:2)		*		**
		LPI(18:2)		*		**
	Lyso-PC	PC(18:3/0:0)			***	
		PC(0:0/14:0)		**	***	***
	Lyso-PE	PE(16:1/0:0)			***	***
		PE(20:3/0:0)			***	**
		PE(0:0/16:1)		**	***	
		PE(0:0/18:2)			***	**
		PE(0:0/20:3)		**	***	**
Sphingolipids	Ceramides	Cer(d18:1/24:0)		**	**	***
		Cer(d18:1/23:0)	**	**	**	**
	CMH	CMH(d18:1/24:0)		**	***	***
	Sphingomyelin	SM(d18:1/12:0)			**	***
Sterols	Steroid sulfates	Andros-S			**	***
Glycoproteins	Acetyls	GlycA	*	*	*	*
		GlycB				*
		GlycF	*	*	*	*
		H/W Glyc-A				*
		H/W Glyc-B				*
Bile Acids	Glyco-conjugated	GDCA				**
	Tauro-conjugated	TCA				
		TDCA				*
		TCDCA				*

Figure 2. Pemvidutide treatment improved MASH-associated lipotoxic species in subjects with overweight/obesity at Week 12. Changes in phospholipid sub-species, sterols, inflammatory glycoproteins, and bile acids. The color code represents the $\log_2$(robust fold-change). Wilcoxon signed rank test p-values: **p*<0.05, ***p*<0.01, ****p*<0.001, vs. baseline.

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Introduction

- Approximately 70% of people with either obesity or MASH have dysregulated serum lipid profiles, with high levels of lipids and toxic lipid species associated with increased cardiovascular risk,
- Dyslipidemia can result in increased hepatic and systemic inflammation, exacerbating comorbidities such as cardiovascular disease and insulin resistance
- Pemvidutide is a balanced glucagon-like peptide 1 (GLP-1)/glucagon dual receptor agonist in clinical 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 and 68.5% relative liver fat reduction in a 12-week clinical trial of subjects with MASLD

Aim

- To analyze the change in lipidomic profile of subjects with overweight/obesity (NCT04561245) or overweight/obesity and MASLD (NCT05006885) following pemvidutide treatment

Methods

- Subjects with overweight/obesity or overweight/obesity and MASLD were treated with pemvidutide (1.2 mg, 1.8 mg, 2.4 mg) or placebo administered subcutaneously weekly for 12 weeks
- Plasma samples from study completers were analyzed by ultra-high performance liquid chromatography–mass spectrometry (UHPLC-MS) or nuclear magnetic resonance (NMR) at baseline, Week 6, and Week 12

Results

- Pemvidutide achieved significant reductions from baseline across multiple glycero- and phospholipid sub-species associated with MASH, including triglycerides, lysophosphatidylinositols (Lyso-PI) and lysophosphatidylethanolamines (Lyso-PE)
- Pemvidutide treatment resulted in significant reductions in atherosclerotic sphingolipids including ceramides
- Pemvidutide improved bile acid dysregulation, yielding reductions in glycol- and tauro-conjugated bile acids

Conclusions

- Pemvidutide administered weekly resulted in significant improvements in plasma lipidomic profiles, including reductions in triglycerides and MASH-associated glycero- and phospholipid species at 12 weeks of treatment
- Decreases in cardio-inflammatory Lyso-PI and Lyso-PC sub-species may reduce cardiovascular disease
- Lyso-PE decreases may reduce fat accumulation in MASH patient livers (Yamamoto et al. 2022)
- Elevated glycol- and tauro-conjugated bile acids are associated with fibrosis and increased MASLD activity, suggesting that pemvidutide improves these histological factors (Kalhan et al. 2011)
- These findings support pemvidutide's potential benefit on MASH-associated co-morbidities, including atherosclerosis and metabolic syndrome
- These data support the evaluation of pemvidutide in an ongoing biopsy-confirmed, 24-week Phase 2b MASH trial (IMPACT: NCT05989711)

References

- Yamamoto, Y et al. *Nutrients* 2022 PMC8839386
- Kalhan, S et al. *Metabolism* 2011 PMC2950914

Subjects with Obesity

A.

Lipid Class	Common name	Individual notation	PBO (n=10)	Pemvidutide 1.2mg (n=6)	Pemvidutide 1.8mg (n=9)	Pemvidutide 2.4mg (n=9)
Glycerophospholipids	Lyso-PI	LPI(18:1)				**
		LPI(18:1)				**
		LPI(18:2)				**
		LPI(18:2)			**	
	Lyso-PC	PC(18:3/0:0)			***	***
		PC(0:0/14:0)			**	***
	Lyso-PE	PE(16:1/0:0)		**	**	***
		PE(20:3/0:0)				***
		PE(0:0/16:1)			**	
		PE(0:0/18:2)			**	**
		PE(0:0/20:3)			**	**
Sphingolipids	Ceramides	Cer(d18:1/24:0)		**	**	**
		Cer(d18:1/23:0)		**	**	***
	CMH	CMH(d18:1/24:0)		**	***	***
	Sphingomyelin	SM(d18:1/12:0)			**	***
Sterols	Steroid sulfates	Andros-S			**	***
Glycoproteins	Acetyls	GlycA			*	**
		GlycB				*
		GlycF			*	*
		H/W Glyc-A				**
		H/W Glyc-B				*
Bile Acids	Glyco-conjugated	GDCA				**
	Tauro-conjugated	TCA				*
		TDCA				**
		TCDCA				**

B.

Lipid Class	Individual notation	PBO (n=10)	Pemvidutide 1.2mg (n=6)	Pemvidutide 1.8mg (n=9)	Pemvidutide 2.4mg (n=9)
Triacylglycerols	TG(44:1)		**	***	***
	TG(44:2)			***	***
	TG(45:1)				***
	TG(46:0)		**	**	***
	TG(46:1)		**	***	***
	TG(46:2)		**	***	***
	TG(46:3)		**	***	***
	TG(46:3)		**	***	***
	TG(47:0)		**	**	**
	TG(47:1)		**	***	***
	TG(47:2)		**	**	***
	TG(48:0)		**		
	TG(48:1)		**	***	***
	TG(48:2)		**	***	***
	TG(48:3)		**	***	***
	TG(49:1)		**	***	**
	TG(49:2)		**	***	***
	TG(49:3)		**	***	***
	TG(50:0)				
	TG(50:1)		**		
	TG(50:2)		**	**	**
	TG(50:3)		**	**	**
	TG(50:4)		**	**	**
	TG(51:1)		**	**	
	TG(51:2)		**	**	**
	TG(51:3)		**	**	**
	TG(52:1)		**		
	TG(53:1)		**		
	TG(53:2)		**		*
	TG(53:3)		**		**
	TG(54:0)				
	TG(54:1)				

Figure 3. Pemvidutide treatment improved MASH-associated lipids in subjects with overweight/obesity at Week 6. (A) Changes in phospholipid sub-species, sterols, inflammatory glycoproteins, and bile acids. (B) Changes in triglyceride sub-species. The color code represents the $\log_2$(robust fold-change from baseline). Wilcoxon signed rank test *p*-values: **p*<0.05, ***p*<0.01, ****p*<0.001, vs. baseline.

Subjects with MASLD

A.

Lipid Class	Common name	Individual notation	PBO (n=13)	Pemvidutide 1.2mg (n=15)	Pemvidutide 1.8mg (n=6)	Pemvidutide 2.4mg (n=7)
Glycerophospholipids	Lyso-PI	LPI(16:0)			**	
		LPI(18:1)			**	
		LPI(18:1)				
		LPI(18:2)	**	**	***	
		LPI(18:2)				**
		LPI(20:3)			**	**
	Lyso-PC	PC(18:3/0:0)			***	
		PC(0:0/14:0)				
		PC(14:0/0:0)			***	**
	Lyso-PE	PE(20:3/0:0)			***	**
		PE(0:0/16:1)		***	**	**
		PE(0:0/18:2)		**	***	**
		PE(0:0/20:3)		**	***	**
Sphingolipids	Ceramides	Cer(d18:1/21:0)			***	**
		Cer(d18:1/22:0)			***	**
		Cer(d18:1/24:0)			***	
		Cer(d18:1/23:0)			**	**
	CMH	CMH(d18:1/23:0)			**	
		CMH(d18:1/24:0)		**	***	**
	Sphingomyelin	SM(d18:0/22:0)			***	
		SM(d18:1/12:0)		**	**	
		SM(d18:1/23:0)			***	
		SM(d18:1/25:0)			**	
Sterols	Steroid sulfates	Andros-S		**	***	
Bile Acids	Glyco-conjugated	GDCA			**	
	Tauro-conjugated	TCA			**	
		TDCA				
		TCDCA			**	

B.

Lipid Class	Individual notation	PBO (n=13)	Pemvidutide 1.2mg (n=15)	Pemvidutide 1.8mg (n=6)	Pemvidutide 2.4mg (n=7)
Triacylglycerols	TG(44:1)			**	**
	TG(44:2)			**	**
	TG(45:1)			**	**
	TG(46:0)			**	**
	TG(46:1)			**	**
	TG(46:2)			**	**
	TG(46:3)			**	**
	TG(46:3)			***	**
	TG(47:0)			**	**
	TG(47:1)			**	**
	TG(47:2)			**	**
	TG(48:0)			**	**
	TG(48:1)			**	**
	TG(48:2)			**	**
	TG(48:3)			***	**
	TG(49:1)			**	**
	TG(49:2)			**	**
	TG(49:3)			***	**
	TG(50:0)			**	**
	TG(50:1)			***	**
	TG(50:2)			***	**
	TG(50:3)			***	**
	TG(50:4)			**	**
	TG(51:1)			**	**
	TG(51:2)			**	**
	TG(51:3)			**	**
	TG(52:1)			**	**
	TG(53:1)			**	
	TG(53:2)			**	
	TG(53:3)			**	
	TG(54:0)			**	
	TG(54:1)			**	**

Figure 4. Pemvidutide treatment improved MASH-associated lipids in subjects with MASLD at Week 6. (A) Changes in phospholipid sub-species, sterols, and bile acids. (B) Changes in triglyceride sub-species. The color code represents the $\log_2$(robust fold-change from baseline). Wilcoxon signed rank test *p*-values: ***p*<0.01, ****p*<0.001, vs. baseline.