Effect of pemvidutide (ALT-801), a GLP-1/glucagon dual receptor agonist, on pathogenic lipid mediators

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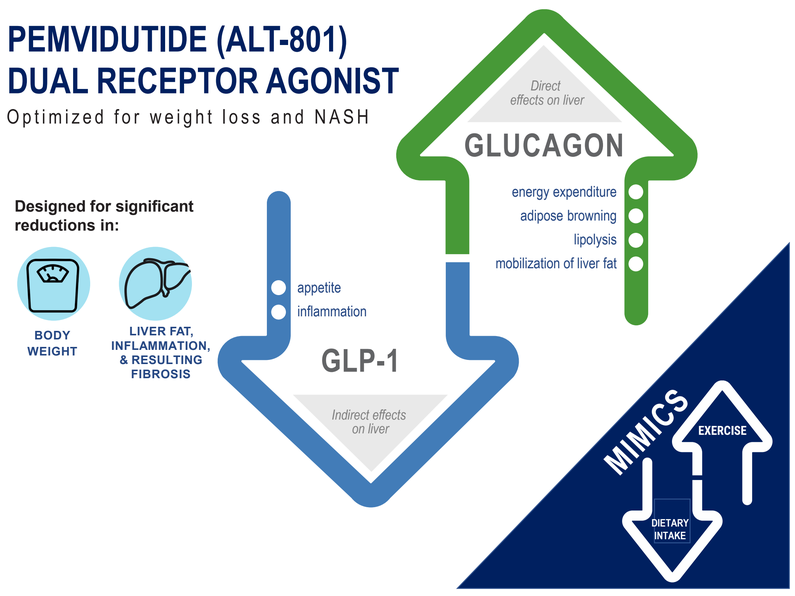
Background

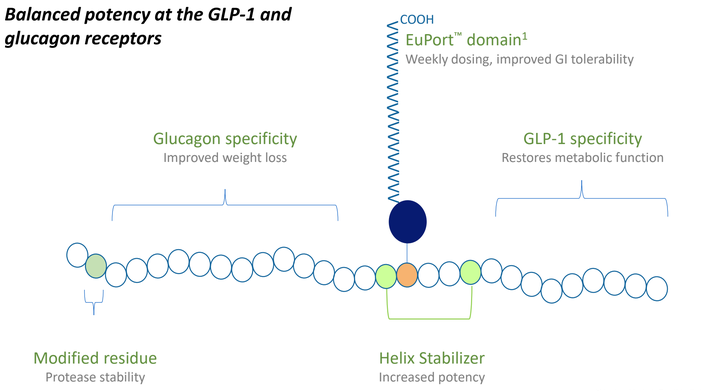
GLP-1 and glucagon receptor agonists may reduce CV risk

- The potential for CV risk reduction through incretin-based therapy is receiving increased attention
- Pemvidutide is a long-acting GLP-1/glucagon (1:1) dual receptor agonist under development for treatment of NASH and obesity. Pemvidutide combines the anorectic effects of GLP-1 receptor agonism (RA) with the increased energy expenditure and lipid-lowering effects of glucagon RA
- Plasma lipids serve multiple functions in biological systems such as energy storage, metabolic regulation, signaling, proliferation, and apoptosis
- The plasma lipidome can be analyzed using nuclear magnetic resonance (NMR) and ultra-high performance liquid chromatography mass spectrometry (UHPLC-MS)



Pemvidutide: Structure is key to differentiation

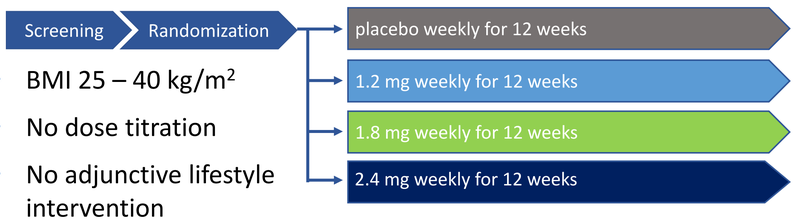
Balanced potency at the GLP-1 and glucagon receptors



[1]Nestor JJ et al, Peptide Science. 2021;113:e24221

Phase 1 Clinical Trial

- Thirty-four (34) subjects with overweight/obesity were randomized at 1 site in Australia (NCT0456124). Subjects were randomized 4:1 pemvidutide: placebo, with placebos pooled.



- BMI 25 – 40 kg/m^2
- No dose titration
- No adjunctive lifestyle intervention

Table 1. Key pharmacodynamic endpoints (change from baseline)

Endpoint		Treatment			
		1.2 mg (n=7)	1.8 mg (n=9)	2.4 mg (n=11)	pooled placebo (n=7)
Weight loss, %	mean (SEM)	-4.9 (1.4)	-10.3 (1.1)***	-9.0 (1.1)**	-1.6 (1.4)
BMI, %	mean (SEM)	-4.8 (1.22)	-10.4 (1.14)	-7.0 (1.12)	-0.8 (1.37)
Systolic BP, %	mean (SEM)	-10.2 (9.23)	-12.5 (8.04)	-17.4 (7.32)	-10.5 (12.45)
Diastolic BP, %	mean (SEM)	-4.7 (9.73)	-7.1 (3.02)	-6.0 (11.47)	-2.7 (13.54)
Total cholesterol, %	mean (SEM)	-20.0 (2.8)	-28.0 (3.4)*	-27.7 (4.6)	-9.1 (3.7)
LDL cholesterol, %	mean (SEM)	-18.4 (3.6)	-25.6 (3.7)*	-23.9 (6.4)*	-4.3 (6.1)
HDL cholesterol, %	mean (SEM)	-16.7 (1.9)	-30.3 (3.2)	-36.0 (3.8)	-19.2 (5.7)
Triglycerides, %	mean (SEM)	-37.0 (1.7)**	-37.9 (7.7)***	-29.2 (7.7)*	-8.2 (7.0)
Apoprotein B, %	mean (SEM)	-45.4 (4.8)	-23.4 (3.3)	-16.8 (10.9)	-9.9 (8.0)

* p < 0.05, ** p < 0.01, *** p < 0.001, vs. placebo

Aim

- To expand on this dataset, we used a high resolution lipidomics approach to investigate the effects of pemvidutide on lipids implicated in the pathogenesis of atherosclerosis and metabolic syndrome (MetS).
- We assessed pemvidutide-induced changes in the plasma lipoprotein and glycoprotein profiles of the three administered doses (1.2 mg, 1.8 mg and 2.4 mg) compared to placebo at the end of study (Day 84).

Methods

Nuclear magnetic resonance (NMR)

- Lipoprotein and glycoprotein profiling covering 33 lipoprotein related parameters was performed by ^{1}H-NMR on fasting plasma samples obtained at Day -1 (baseline), Day 43, and Day 84 from the 34 subjects who completed NCT0456124.

Ultra-high performance liquid chromatography mass spectrometry (UHPLC-MS)

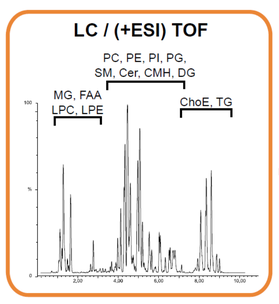
- Lipidomic profiling covering 600 lipid species was performed by ultra-high performance liquid chromatography–mass spectrometry on fasting plasma samples obtained at Day -1 (baseline), Day 43, and Day 84 from the 34 subjects who completed NCT0456124.

Metabolite extraction

- Add internal standard spiked extraction solvent.
- Collect metabolite extract.
- Dry and resuspend for UHPLC-MS analysis.

$CHCl_3$/ MeOH extract

UHPLC-MS analysis



Data processing

- LC/MS peak identification and integration.
- Intra- & interbatch normalization.
- Multivariate data analysis: principal component analysis.
- Univariate data analysis:
  - Analysis per group: Average and median group intensities, SD, SEM and Shapiro test (data normality).
  - Analysis between groups: Fold changes, *p*-values.

- Plasma fractionation was performed either using methanol to extract fatty acyls, bile acids, steroids, and lyso-glycerophospholipids, or using a chloroform/methanol mix to extract glycerolipids, cholesteryl esters, sphingolipids, and glycerophospholipids.
- Lipid classification followed the classification system proposed by Fahy et al. and the LIPID MAPS initiative (http://www.lipidmaps.org).

Results

Analysis of serum lipoprotein particles by 2D-NMR

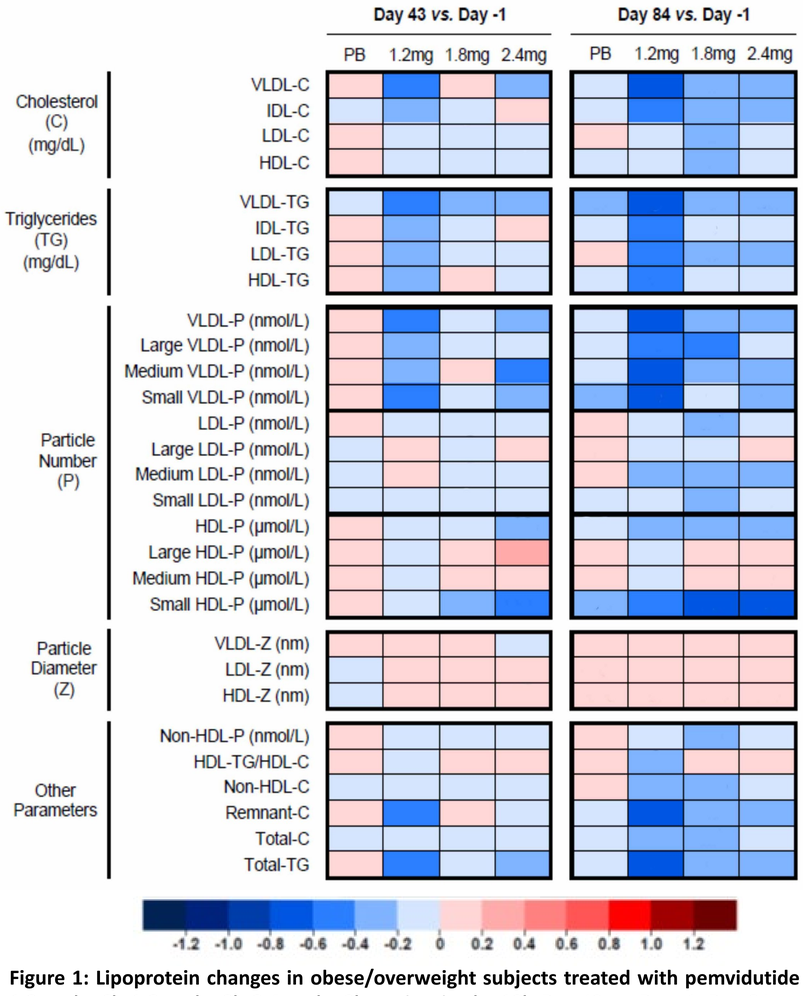


Figure 1: Lipoprotein changes in obese/overweight subjects treated with pemvidutide 1.2mg (n=6), 1.8mg (n=9), 2.4mg (n=9) or placebo (n=10). Day 43 vs. Day -1, Day 84 vs. Day -1. The color code represents the log2(robust fold-change) with blue colors denoting reduced lipoproteins (negative fold-changes) and red colors denoting increased lipoproteins (positive fold-changes).

Pemvidutide induces dose-dependent reductions across multiple bioactive lipid classes

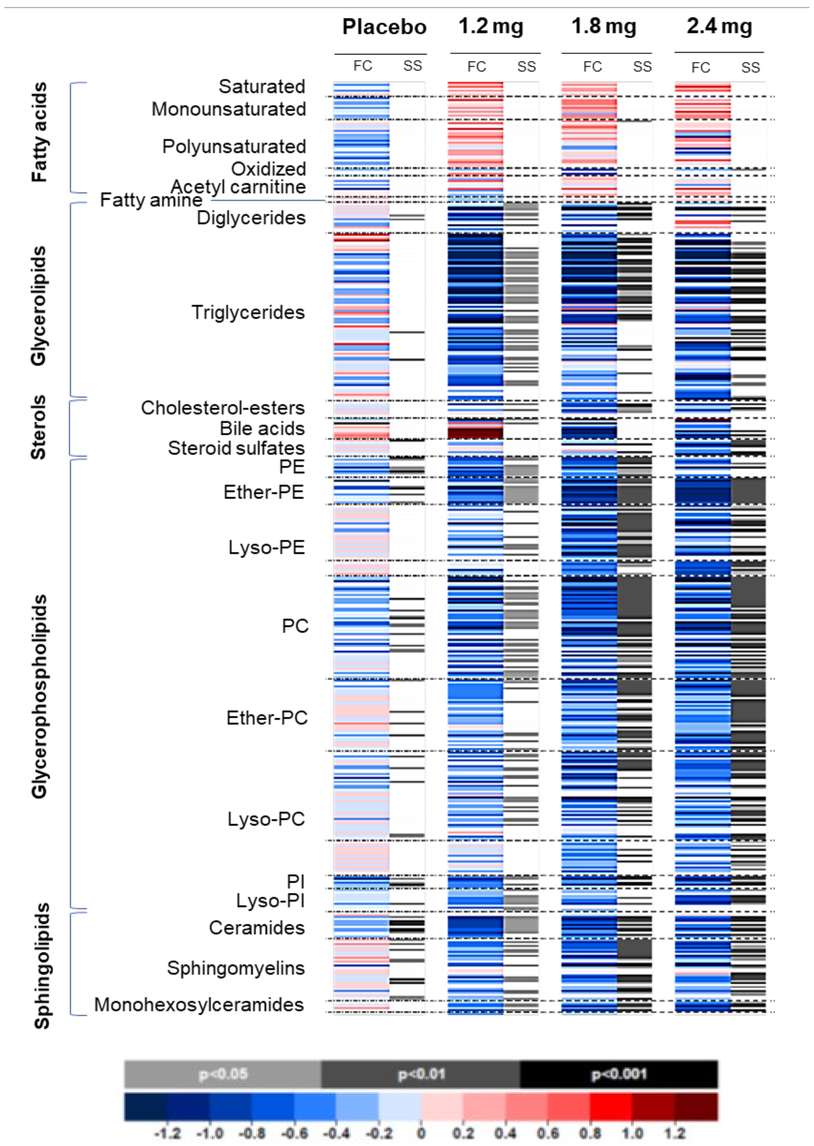


Figure 2: Lipidomic signatures in obese/overweight subjects treated with pemvidutide 1.2mg (n=6), 1.8mg (n=9), 2.4mg (n=9) or placebo (n=10) comparing changes at Day 84 vs Day -1. Results are presented as log2 pairwise fold change with blue colors denoting reduced metabolites (negative fold-changes) and red colors denoting increased metabolites (positive fold-changes). Grey/black bars indicate significant p-values of Wilcoxon test (light grey, p<0,05; dark grey, p<0.01; black, p<0.001). (definitions: PE = Phosphatidylethanolamine; PC = Phosphatidylcholine; PI = Phosphatidylinositol).

Figure 3: Volcano plots of changes in atherogenic lipid species following pemvidutide treatment. Y-axis is Log_{10} of the statistical changes based on Student's T test with horizontal dotted line corresponding to p value threshold of 0.01. X-axis represents the Log_2 fold-change with dotted lines corresponding to arbitrary change threshold of ±0.75.

Conclusions

- Pemvidutide treatment significantly reduced serum lipid levels, especially glycerolipids, glycerophospholipids and sphingolipids within 12 weeks of treatment.
- Pemvidutide caused generally consistent changes in lipoprotein particle subspecies as determined by 2D-NMR analysis
- Pemvidutide treatment significantly reduced pro-atherogenic lyso-PC levels, suggesting a potential for decreased oxidized LDL (Law et al 2019).
- Pemvidutide treatment significantly reduced atherosclerotic plaque forming ether-linked alkyl phosphatidylcholine (PC) and phosphatidyl-ethanolamine (PE) glycerophospholipids levels.
- Based on these findings, pemvidutide demonstrates promise as an agent for reducing CV risk.

References

- Fahy et al.. J. Lipid Res. 2005;46:839–861
- Law et al.. Int J Mol Sci. 2019;20(5):1149

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