EFFECT OF PEMVIDUTIDE, A GLP-1/GLUCAGON DUAL RECEPTOR AGONIST, ON CARDIOINFLAMMATORY LIPIDS

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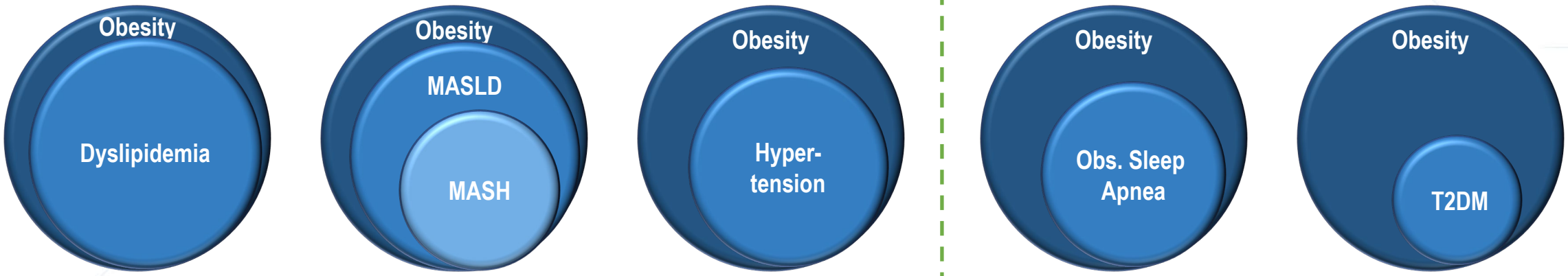
Disclosures

Employment: Altimmune, Inc.

Stock/Shareholding; Altimmune, Inc.

Patents/Other: Altimmune, Inc; U.S. Army

US PREVALENCE AND SIGNIFICANCE OF OBESITY COMORBIDITIES



66-70% Dyslipidemia[1,2]

58-75% MASLD[3,4,5]
15-36% MASH[3,4,6]

45-55% Hypertension[1,7]

41-45% Sleep Apnea[8,9]

19-23% T2DM[1,7]

Most significant comorbidities are dyslipidemia, MASLD/MASH, and hypertension

1) Bays, Harold, et. al. (2013) Obesity, adiposity, and dyslipidemia: A consensus statement from the National Lipid Association. Journal of Clinical Lipidology 7(4):304–383.
2) Lim Y, Boster J. Obesity and Comorbid Conditions. [Updated 2023 Feb 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; https://www.ncbi.nlm.nih.gov/books/NBK574535/
3) Quek, Jingxuan, et. al. (2023) Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population:. The Lancet Gastroenterology & Hepatology 8(1):20-30.
4) Vernon, G, et. al. (2011) Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 34:274–285.
5) Le, Michael, et. al. (2022) 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2022;20:2809–2817
6) Dufour, Jean-François, et. al. (2021) The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors–A targeted literature review. Endocrine and Metabolic Science 3.
7) Pantalone KM, et al. Prevalence and recognition of obesity and its associated comorbidities. BMJ Open 2017;7:e017583. doi:10.1136/ bmjopen-2017-017583
8) Romero-Corral, Abel, et. al. (2010) Interactions Between Obesity and Obstructive Sleep Apnea. Chest 137(3): 711-719.
9) Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. J Thorac Dis 2015;7(5):920-929.

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PEMVIDUTIDE MOA IS OPTIMIZED FOR OBESITY AND MASH

↑ Lipolysis
↑ Mobilization of Fat
↑ Energy Expenditure

Direct effects on Liver

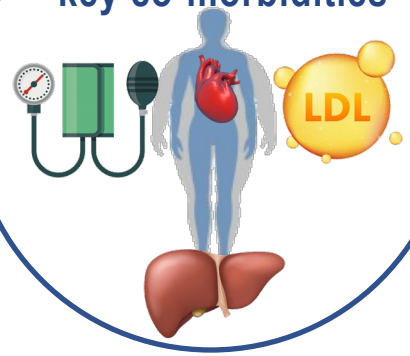
Glucagon

GLP-1

Direct effects on GI & Brain

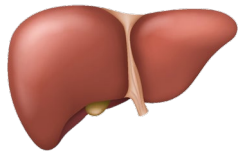
↓ Appetite
↓ Inflammation
↓ Gastric Emptying

Obesity & key co-morbidities



Phase 2b: MOMENTUM Trial

MASLD/MASH



Phase 2b: IMPACT Trial

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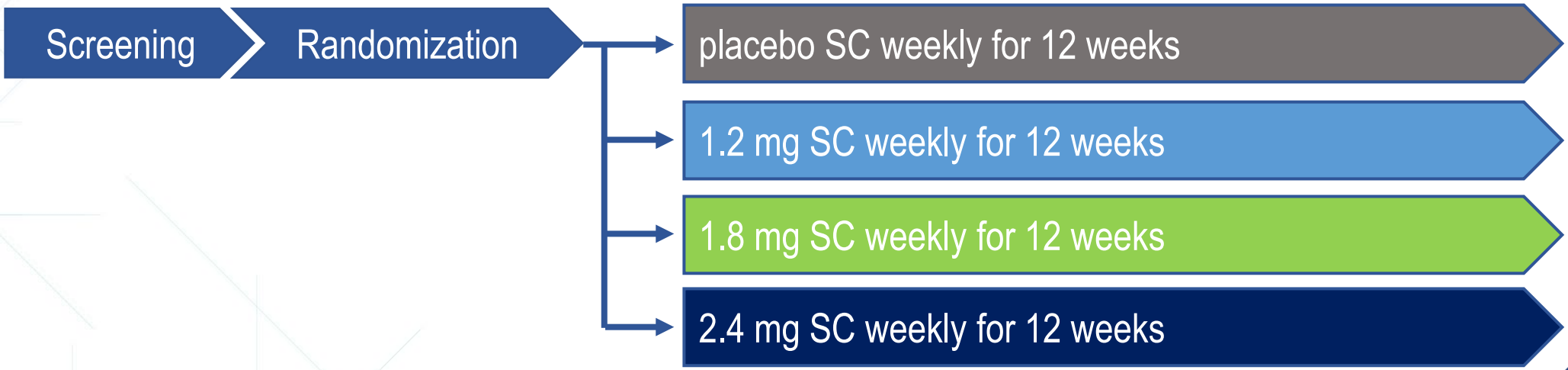
PEMVIDUTIDE PHASE 1 – TRIAL DESIGN

FIRST-IN-HUMAN

- 12-week, randomized, placebo-controlled study of pemvidutide in subjects with overweight or obesity but not T2DM
- 34 subjects randomized to pemvidutide or placebo, with placebos pooled across cohorts
- No caloric restriction or lifestyle intervention
- No dose titration



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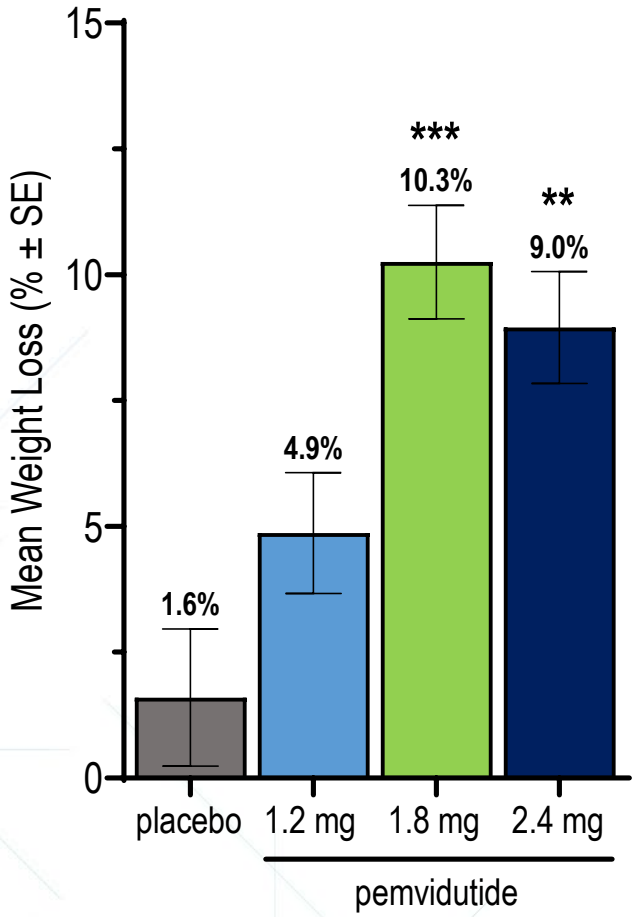
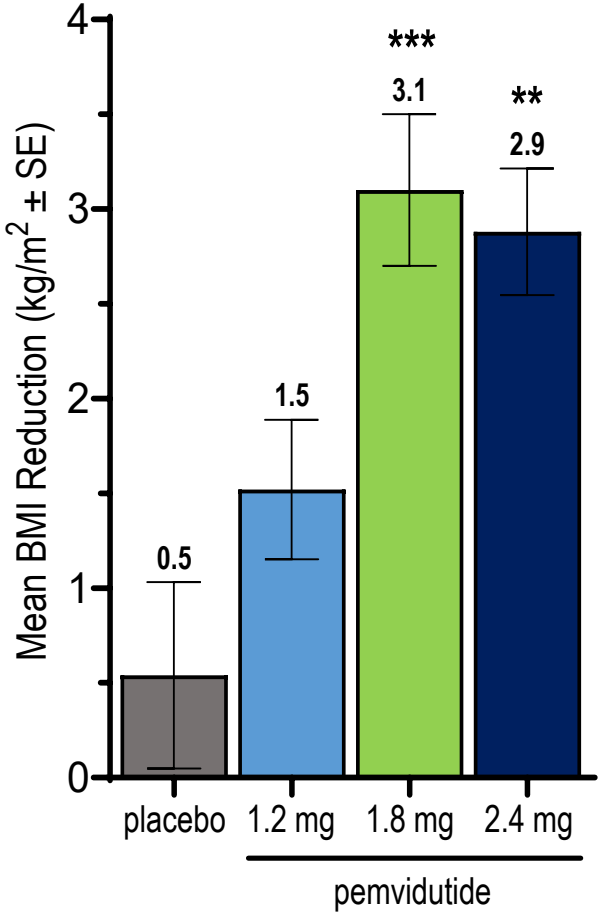
SUBSTANTIAL WEIGHT LOSS AT WEEK 12

UP TO 10.3% MEAN WEIGHT LOSS ACHIEVED WITH SIGNIFICANT DECREASES IN BMI





* p < 0.05
** p < 0.005
*** p < 0.001
vs. placebo
(ANOVA w/ Dunnett's)

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IMPROVEMENTS IN BLOOD PRESSURE ACROSS ALL DOSE GROUPS

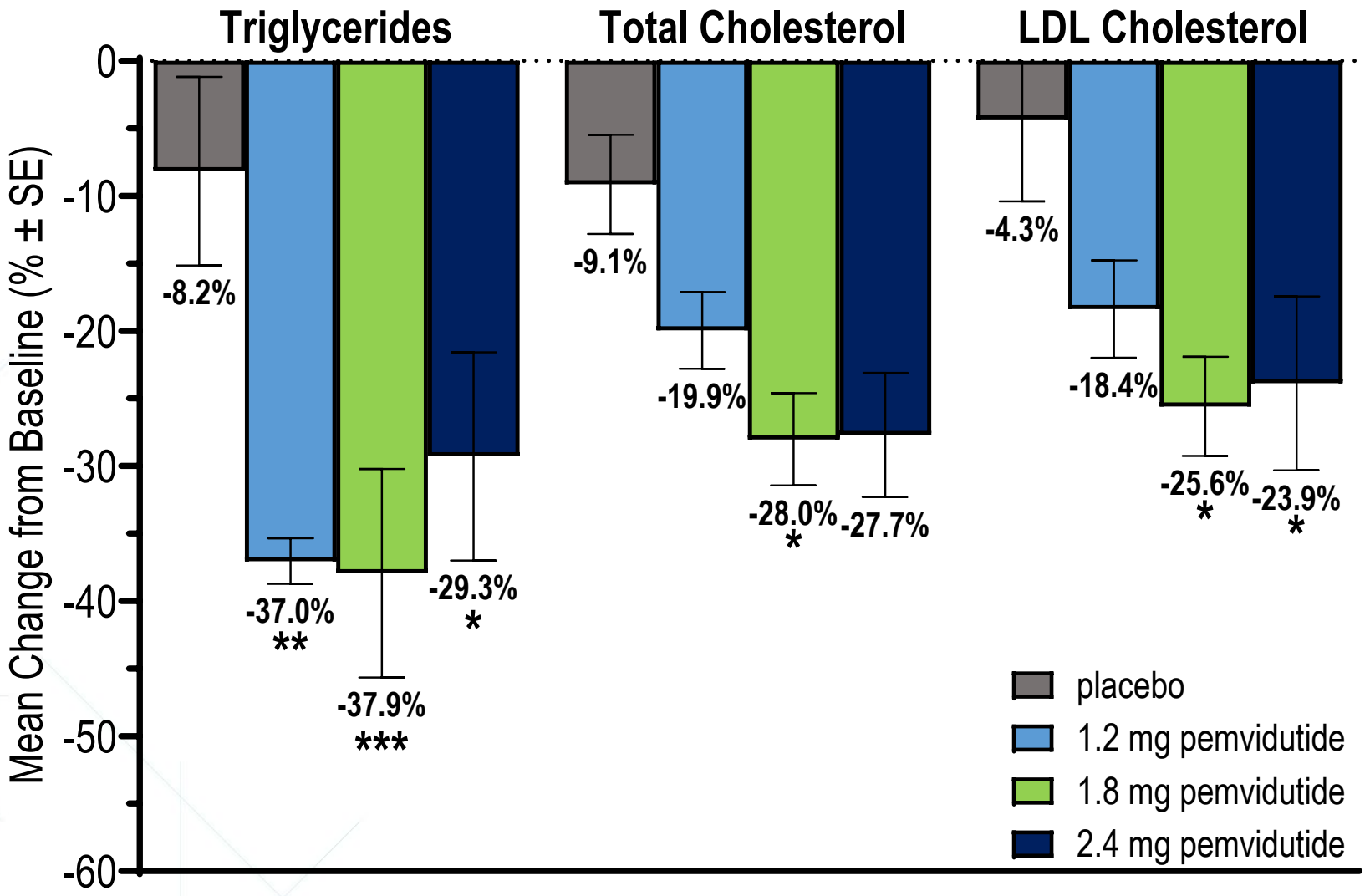
BIOMARKER OF CARDIOVASCULAR RISK

Characteristic		Treatment			
		placebo	1.2 mg pemvidutide	1.8 mg pemvidutide	2.4 mg pemvidutide
Change from Baseline, Weeks 1-12 [1]					
Systolic Blood Pressure	mm Hg (%)	-5.4 (-4.5%)	-10.2 (-8.2%)	-9.2 (-7.8%)	-12.7 (-10.4%)
Diastolic Blood Pressure	mm Hg (%)	-1.7 (-2.3%)	-5.2 (-6.7%)	-3.9 (-5.3%)	-7.2 (-9.4%)

[1] *means of weekly measurements, Weeks 1-12, compared to Baseline*

IMPROVEMENTS IN SERUM LIPIDS ACROSS ALL DOSE GROUPS

LIPIDS ASSOCIATED WITH CARDIOVASCULAR DISEASE



* p < 0.05
** p < 0.005
*** p < 0.001
vs. placebo
(ANOVA w/ Dunnett's)

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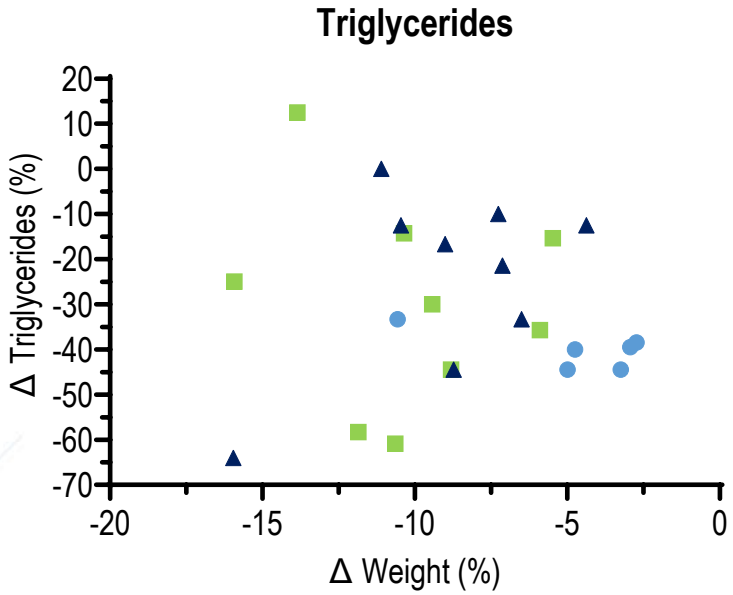
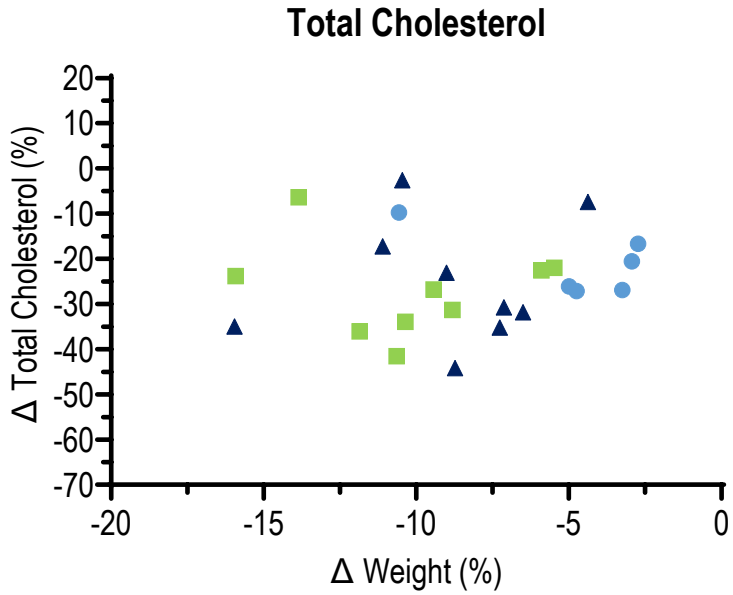
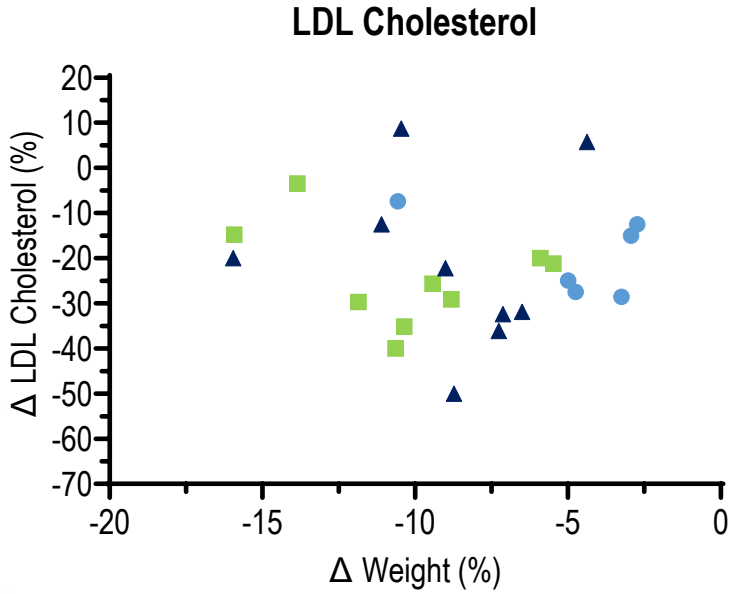
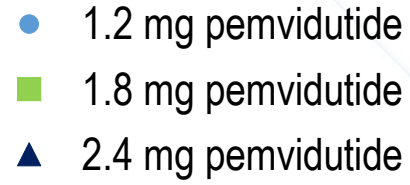
SERUM LIPID REDUCTIONS WERE INDEPENDENT OF WEIGHT LOSS

INDICATES THAT PEMVIDUTIDE HAD DIRECT EFFECTS ON SERUM LIPIDS









- **Regression p-values not statistically significant**

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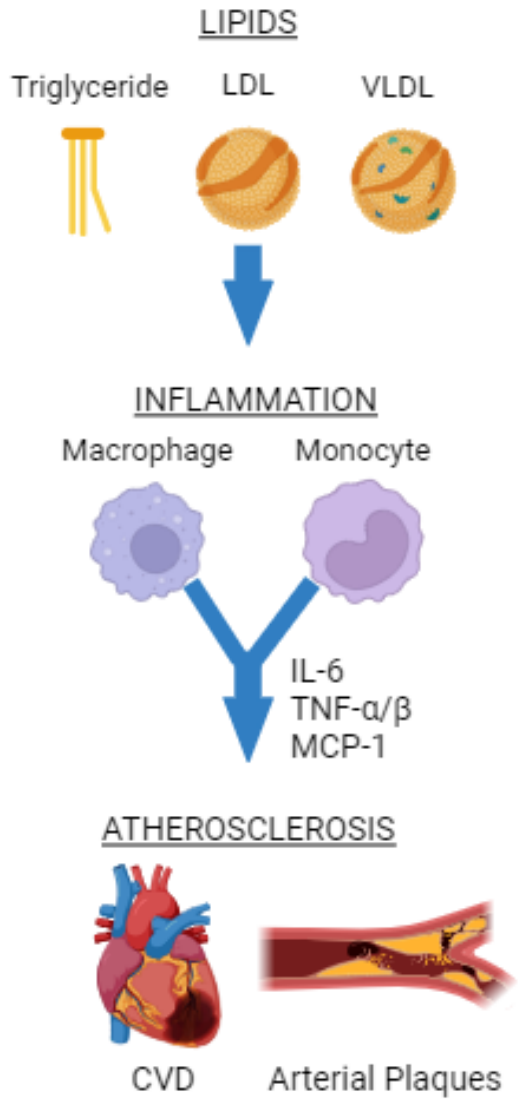
METABOLIC INFLAMMATION IS INVOLVED IN ALL PHASES OF ATHEROSCLEROSIS

DYSLIPIDEMIA PROMOTES CARDIOVASCULAR INFLAMMATION



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- **Atherosclerosis is multifactorial**
  - Lipid accumulation
  - Low-grade, chronic inflammation
  - Endothelial dysfunction and cell death
- **LDL are the major source of cholesterol and lipid accumulation in the arterial wall**
- **Atherosclerotic plaques are characterized by chronic inflammation**
- **Inflammatory cytokines exacerbate intracellular lipid accumulation and attract immune cells to inner arterial wall**
- **Interaction of immune cells with arterial endothelium enhances atherosclerotic lesions**

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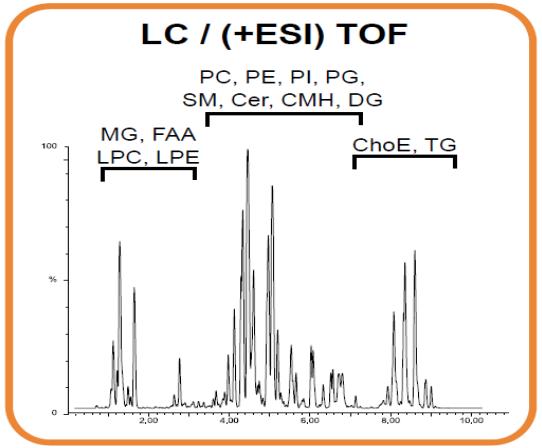
ANALYSIS OF CARDIOINFLAMMATORY LIPIDS AND GLYCOPROTEINS

USE METABOLOMICS TO INVESTIGATE PEMVIDUTIDE'S EFFECTS ON INFLAMMATORY LIPID SUBSPECIES AT WEEK 12

NMR

Parameter	CVR Association
Small, Dense LDL	+
Triglyceride Content	+
H/W GlycA	+
H/W GlycB	+

UHPLC-MS



Glycerophospholipids

PC, PE, PI, PG,
LPC, LPE, LPI, LPG

Glycerolipids

MAG
DAG
TAG

Sterols

CE
BA
ST

Fatty acyls

AC
NEFA
oxFA
FAA
NAE

Sphingolipids

Cer
SM
FSB
CMH

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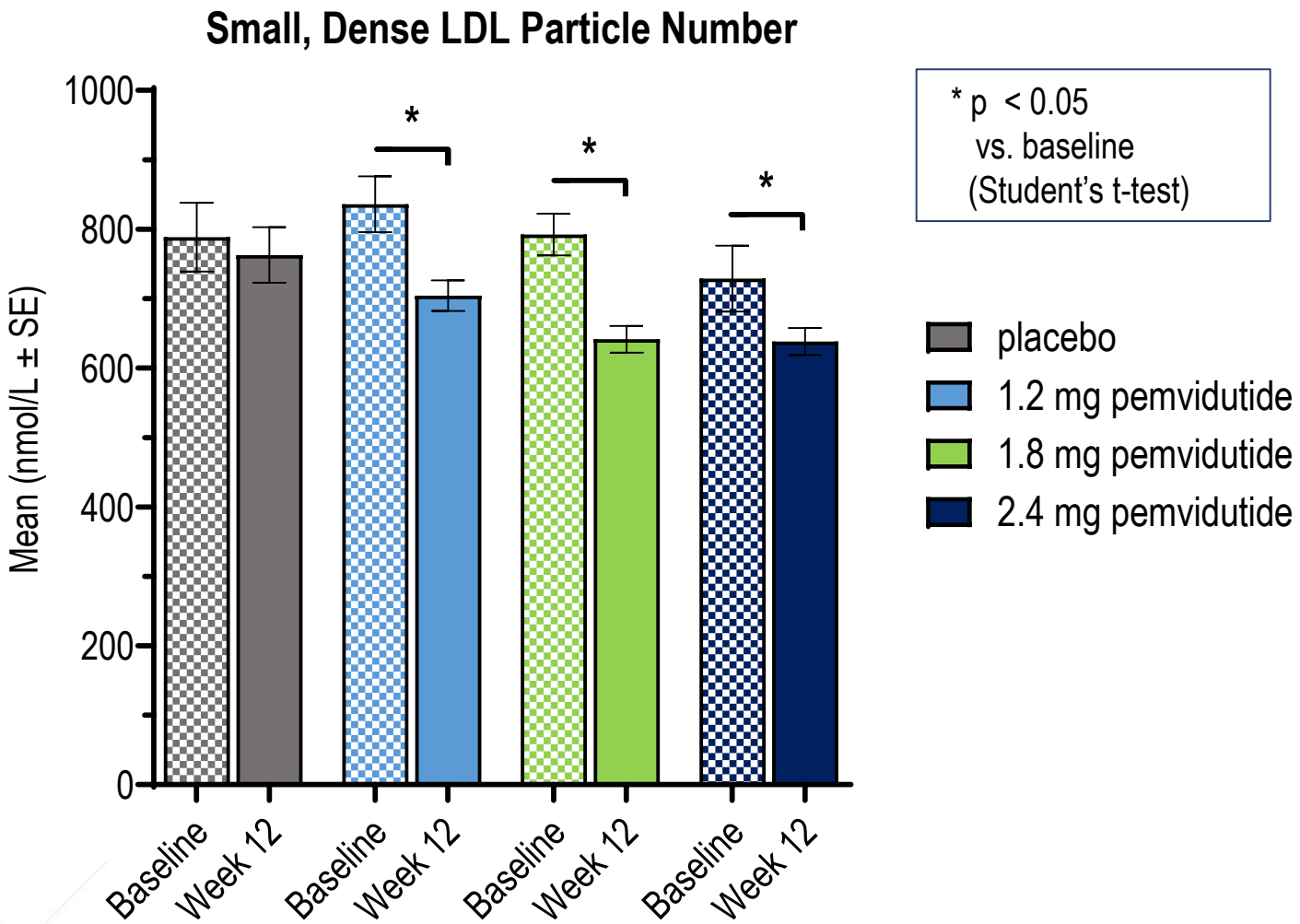
PEMVIDUTIDE DECREASES SMALL, DENSE LDL PARTICLE NUMBERS

ATHEROGENIC LDL SUBTYPE THAT MOST CONTRIBUTES TO ATHEROSCLEROTIC PLAQUES AND CARDIAC INFLAMMATION



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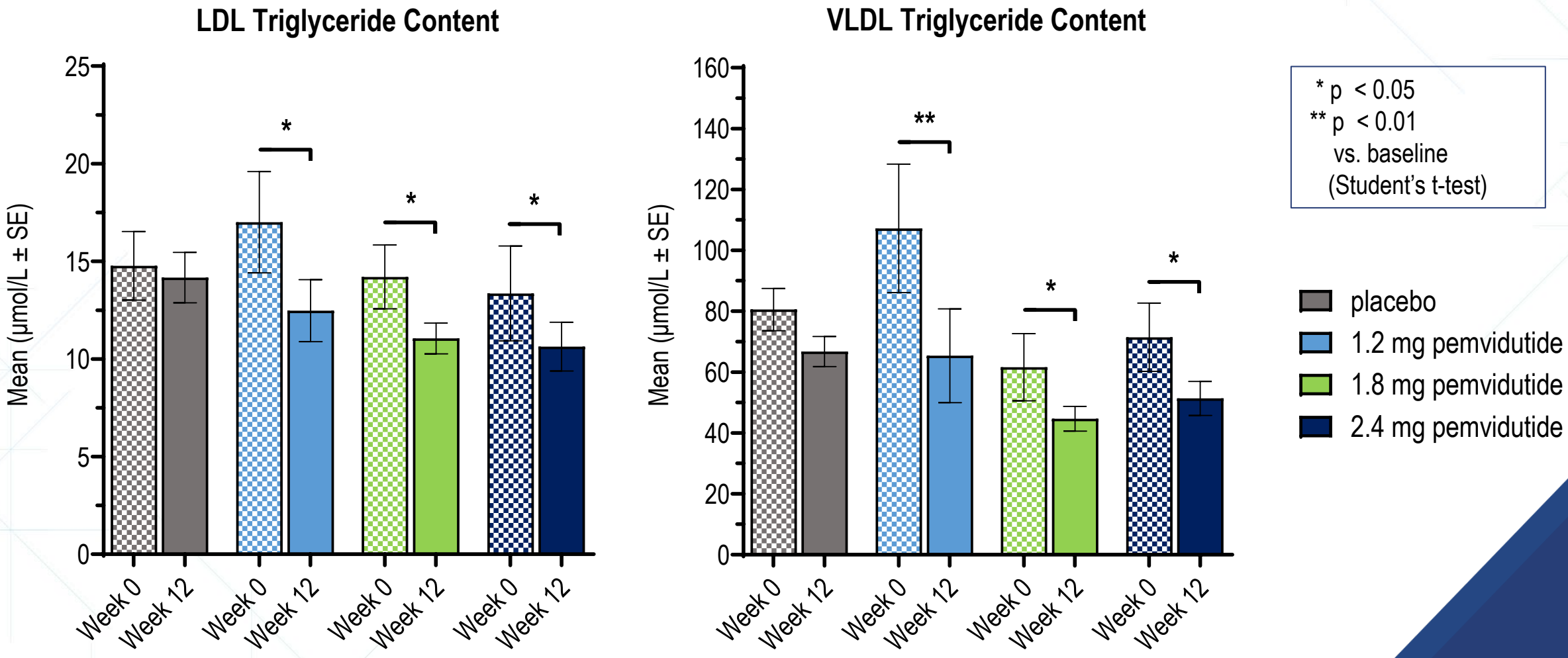
PEMVIDUTIDE DECREASES LIPOPROTEIN TRIGLYCERIDE CONTENT

TRIGLYCERIDE-RICH PARTICLES ARE ASSOCIATED WITH INCREASED INFLAMMATION AND PREMATURE ATHEROSCLEROSIS



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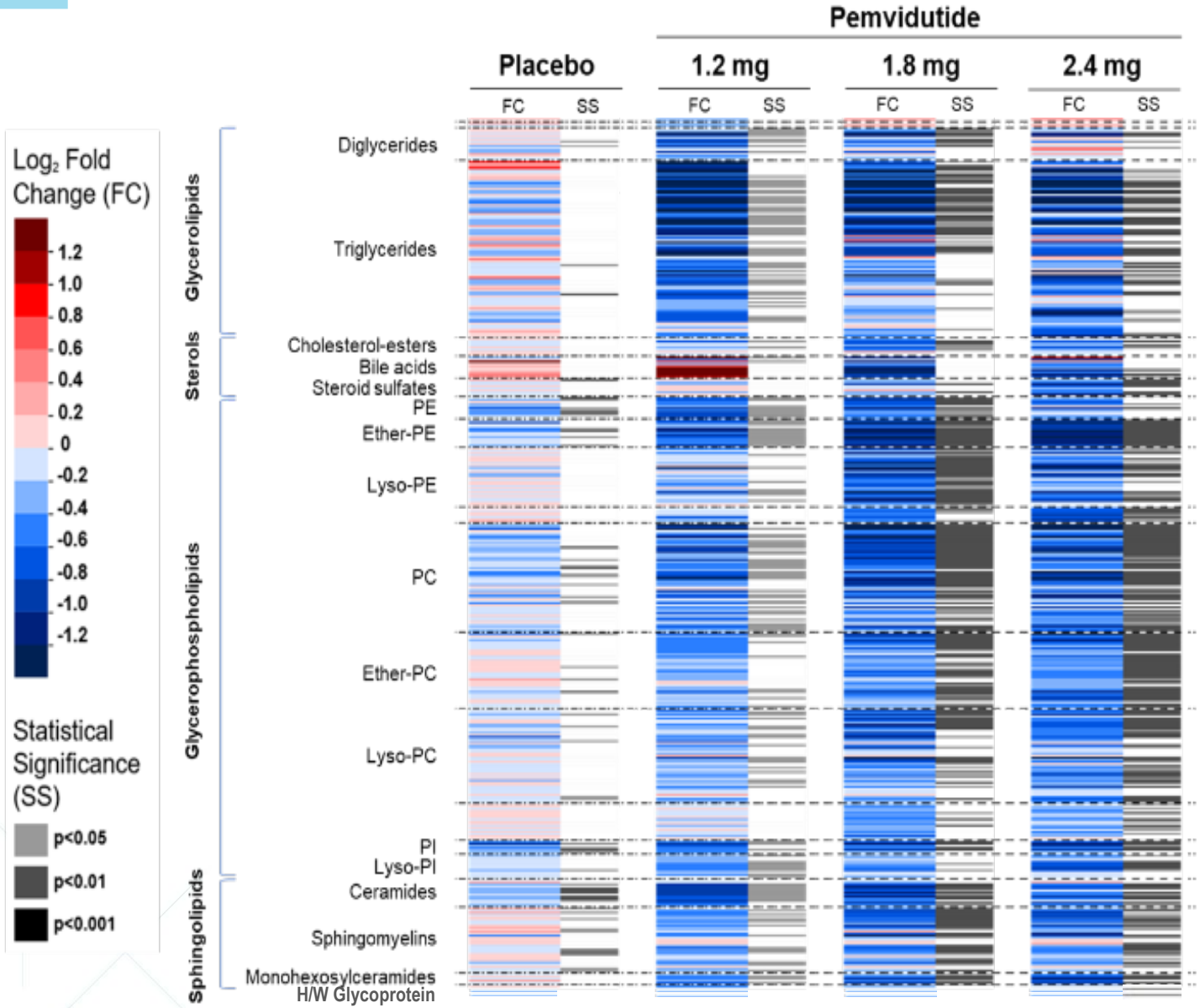
CHANGES IN LIPID AND GLYCOPROTEIN SUBSPECIES: BASELINE VS WEEK 12

PEMVIDUTIDE TREATMENT RESULTED IN SIGNIFICANT REDUCTIONS IN INFLAMMATORY LIPIDS AND GLYCOPROTEINS



Wilcoxon signed-rank test

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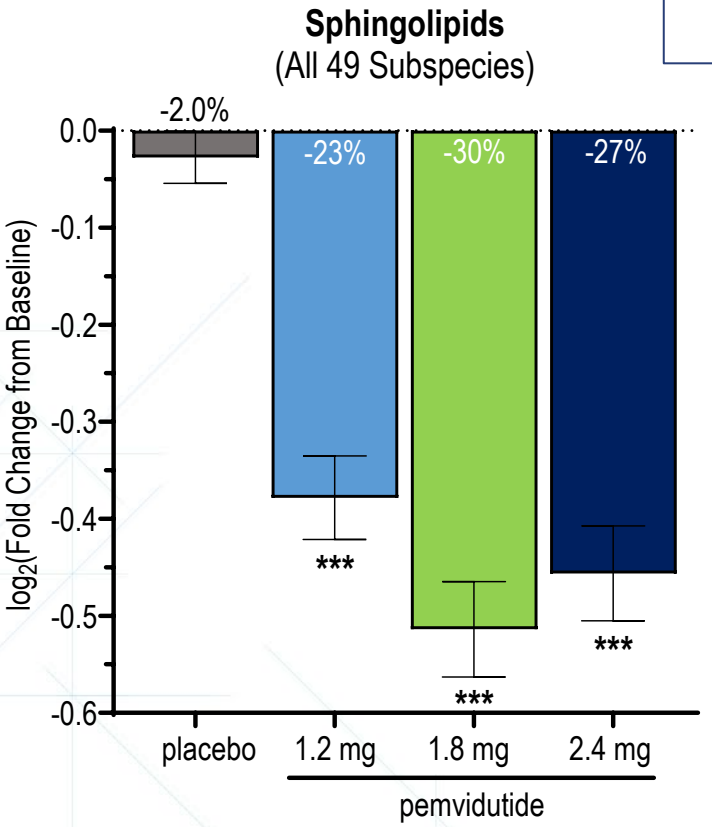
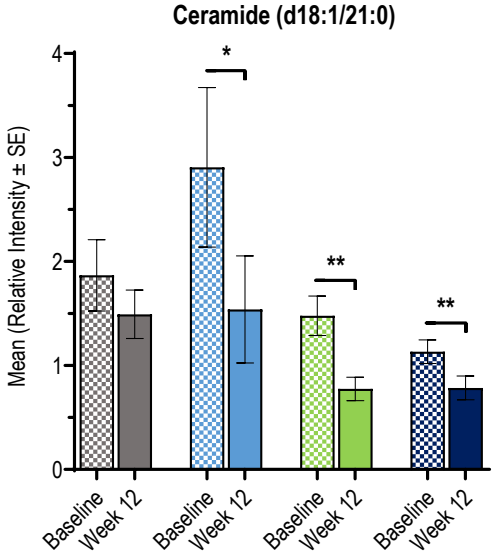
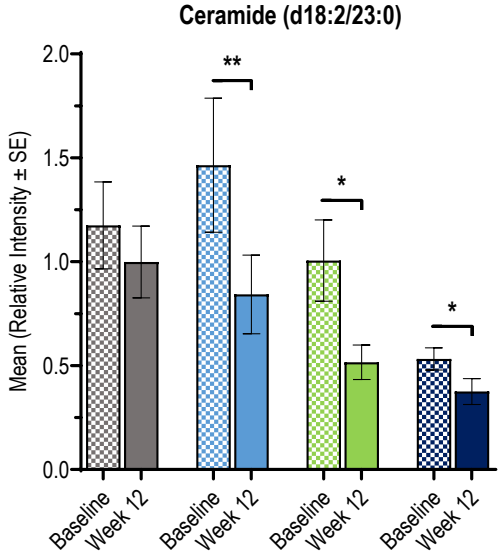
PEMVIDUTIDE DECREASES ATHEROSCLEROTIC SPHINGOLIPIDS

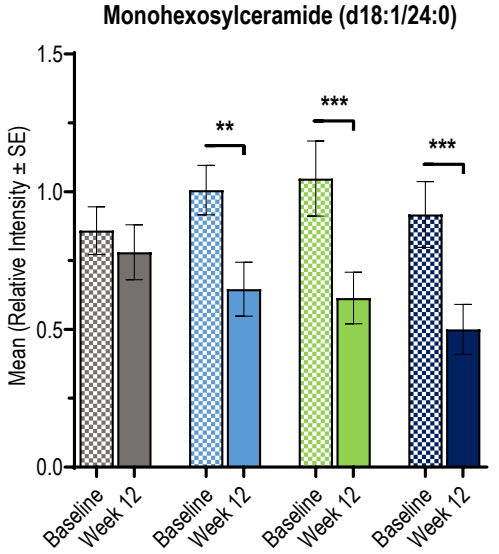
CORRELATES WITH CORONARY ARTERY SMOOTH MUSCLE INFLAMMATION AND ATHEROSCLEROTIC LESIONS

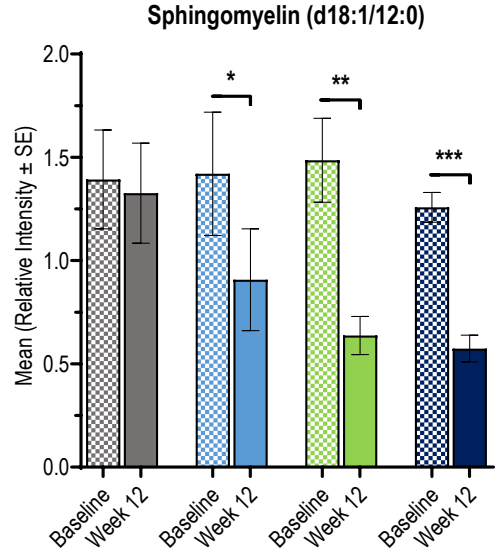
*** p < 0.001
vs. placebo
(ANCOVA)











* p < 0.05
** p < 0.01
*** p < 0.001
vs. baseline
(Student's t-test)

placebo
1.2 mg pemvidutide
1.8 mg pemvidutide
2.4 mg pemvidutide

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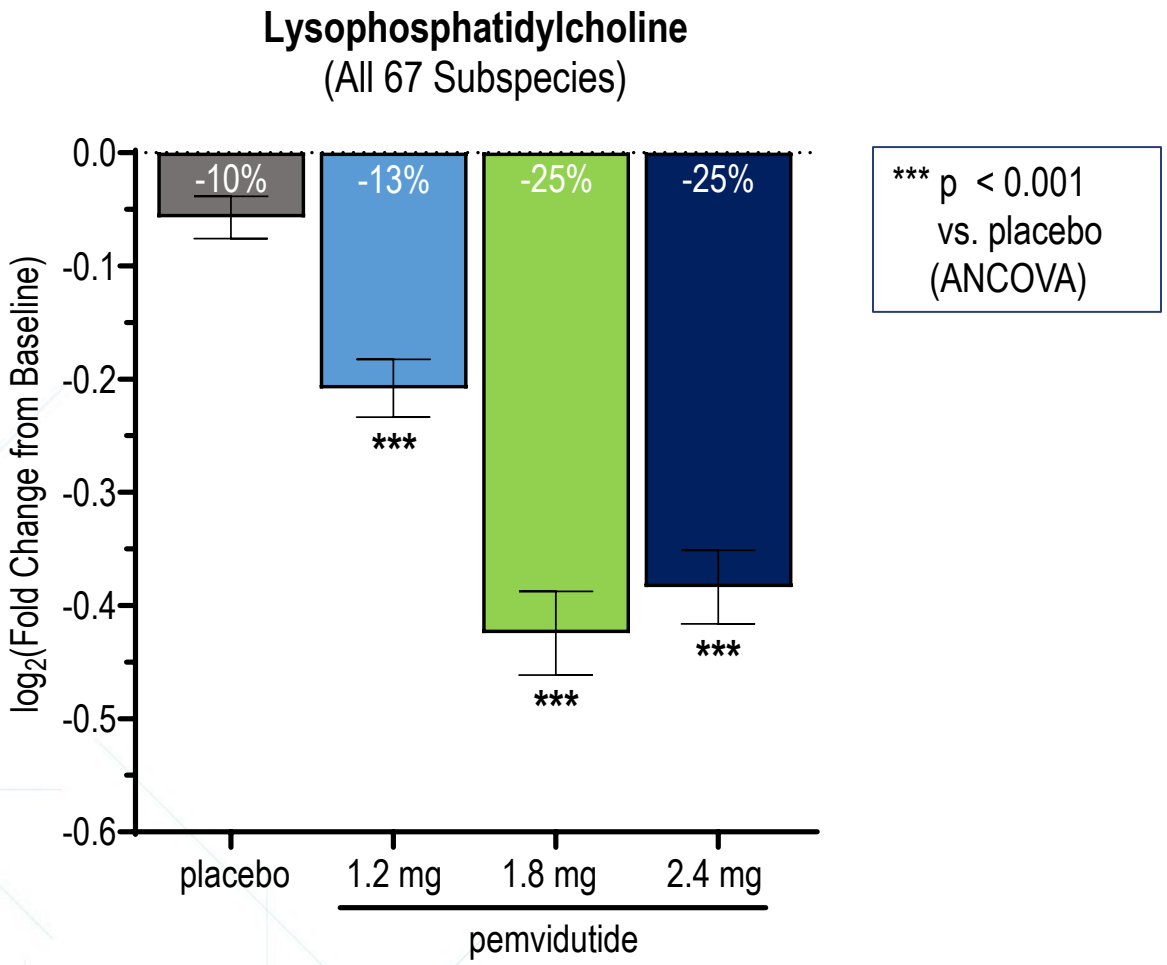
PEMVIDUTIDE DECREASES INFLAMMATORY LYSOPHOSPHATIDYLCHOLINES

DYSREGULATION CORRELATES WITH VASOCONSTRICTION



*** p < 0.001 vs. placebo (ANCOVA)

- **Elevated levels correlate with:**
  - Coronary artery inflammation
  - Carotid atheroma plaques
  - Insulin resistance
  - Diabetic retinopathy

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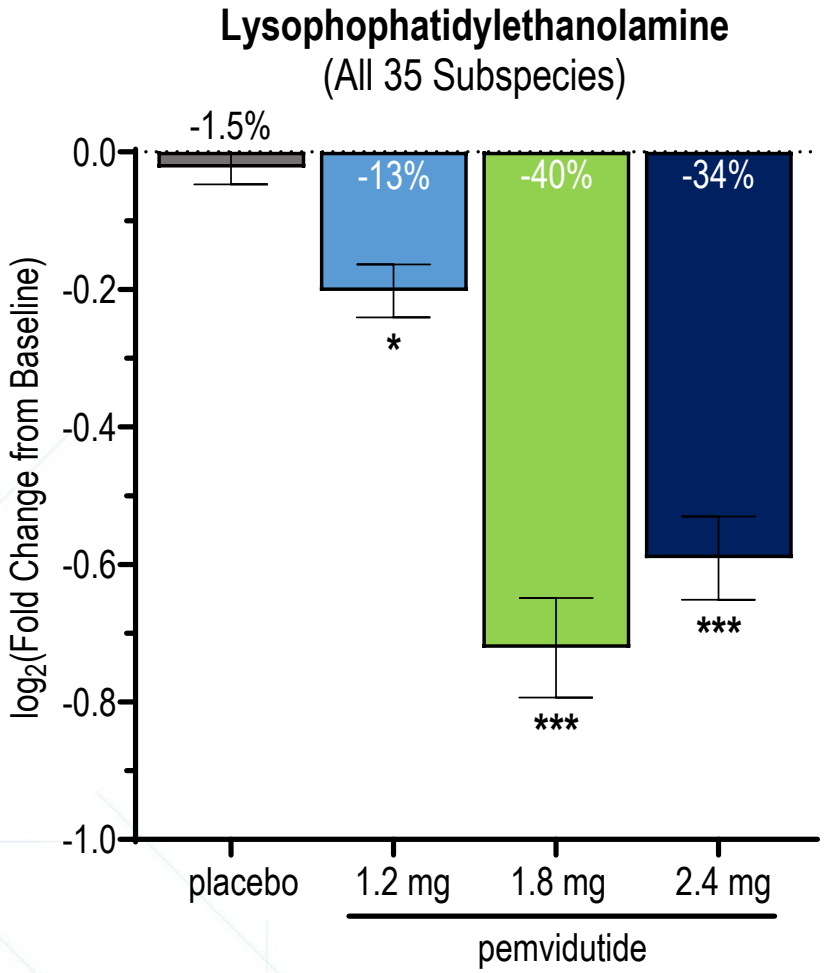
PEMVIDUTIDE DECREASES INFLAMMATORY LYSOPHOSPHATIDYLETHANOLAMINES

DYSREGULATION INCREASES RISK OF STROKE



* p < 0.05
*** p < 0.001
vs. placebo
(ANCOVA)

- Elevated levels in obese patients with recurrent cardiovascular disease
- Correlated with platelet hyperactivity and thrombo-inflammation
- Decreased by statin treatment
- MOMENTUM subjects on stable statin therapy had further decreases in serum lipids

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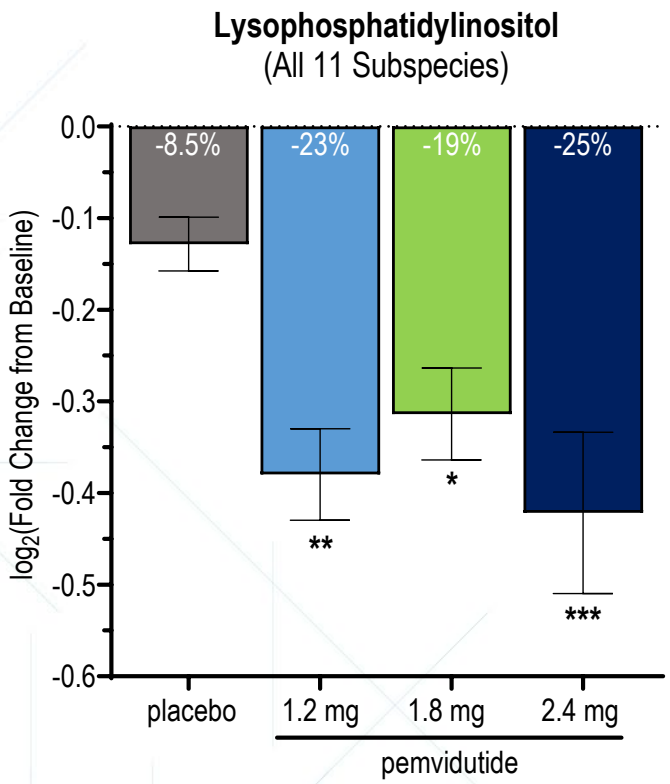
PEMVIDUTIDE DECREASES LYSOPHOSPHATIDYLINOSITOLS (LPI)

DYSREGULATION ASSOCIATED WITH HEPATIC LDL ACCUMULATION AND MASH SEVERITY

- LPI linked to reduced cholesterol efflux
- Pemvidutide increased reverse cholesterol transport (RCT) in preclinical studies
- Decreased LPI may contribute to the observed increase in RCT

Clinical



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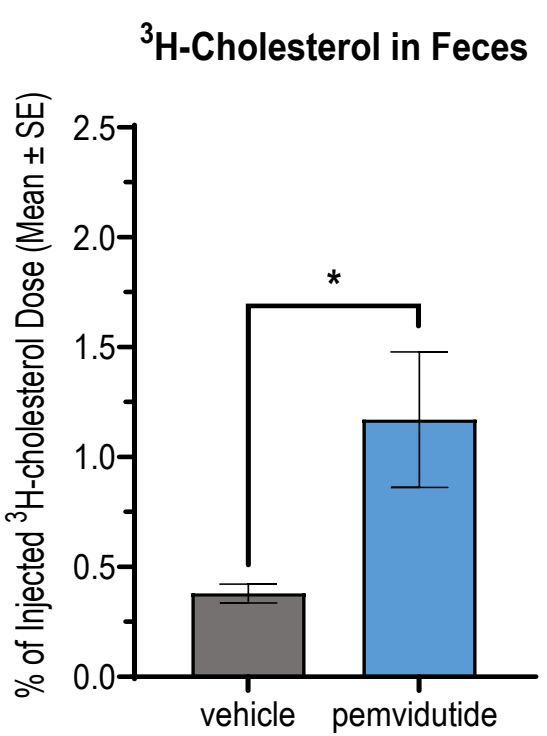
Preclinical



* p < 0.05
vs. placebo
(Student's t-test)

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SUMMARY

- **Significant reductions in body weight, BMI, and blood pressure**
- **Substantial and clinically meaningful reductions in triglycerides, total cholesterol, and LDL**
- **Significant reductions in cardioinflammatory lipids and lipid subspecies**
  - Significant reductions in small dense LDL, sphingolipids, and lysophospholipids
  - Significant reductions in glycoprotein biomarkers of systemic inflammation
- **Based on the above results, pemvidutide may have clinically meaningful effects on the risk of cardiovascular disease**

Thank you

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