Effects of Pemvidutide, a GLP-1/Glucagon Receptor Dual Agonist on Liver Fat and Weight Loss: Results of a Phase 1b Multicenter, Randomized, Double-blind, Placebo-controlled Trial in Patients with Non-alcoholic Fatty Liver Disease

Stephen A. Harrison[1], John Suschak[2], M. Scot Roberts[2], Jay Yang[2], Liang He[2], Bertrand Georges[2], Lakisha Rodwell-Green[2], Randy Brown[2], Shaheen Tomah[2], M. Scott Harris[2], Sarah K. Browne[2]

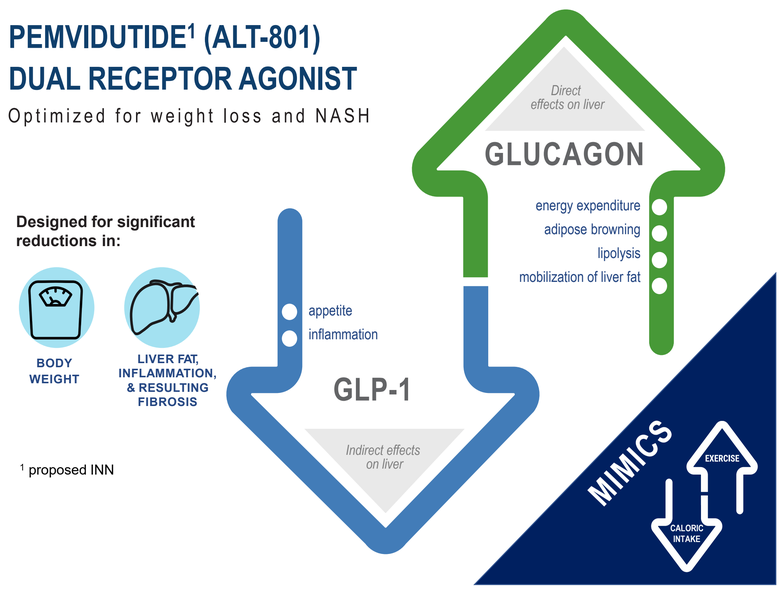
[1] Pinnacle Research, San Antonio, TX, USA; [2]Altimmune, Inc, Gaithersburg, MD, USA

Background

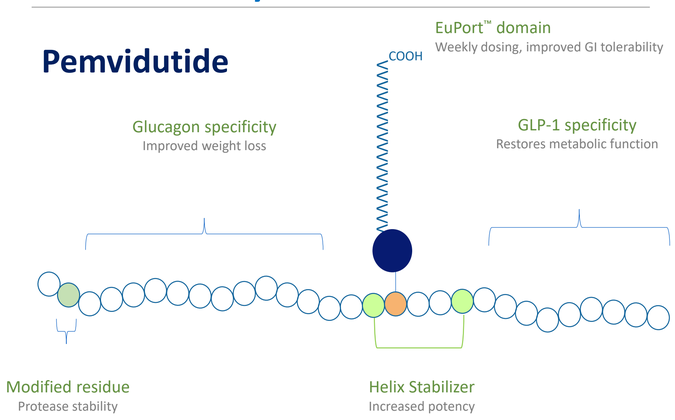
NASH and NAFLD

HEPATIC MANIFESTATIONS OF OBESITY

- Reductions in liver fat content, liver enzymes, and body weight are cornerstones of the treatment of NASH and NASH-associated morbidities, including cardiovascular disease and extrahepatic malignancy
- Pemvidutide is a long-acting GLP-1/glucagon dual receptor agonist under development for treatment of NASH and obesity
- Dual GLP-1:glucagon agonism combines the reduced caloric intake effects of GLP-1 receptor agonists with the increased energy expenditure and lipometabolic effects of glucagon receptor agonists



Structure is Key to Differentiation



- The 1:1 potency ratio of GLP-1 and glucagon agonism within pemvidutide is hypothesized to provide the optimal balance of efficacy and tolerability (Day 2012; Peptide Sci 9:443-50.)
- Proprietary EuPort™ domain prolongs serum half-life (t1/2) and slows bloodstream entry, which is thought to improve safety and tolerability

Aims

- To assess the safety, tolerability, and effects of pemvidutide on reduction of liver fat content, alanine aminotransferase (ALT), and body weight in patients with NAFLD

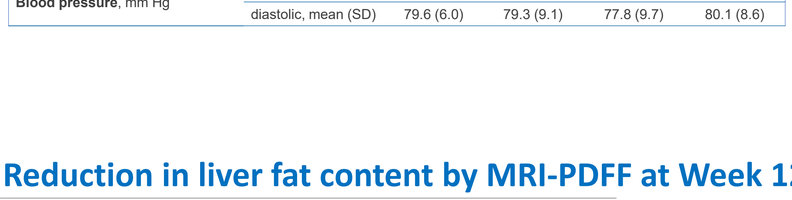
Methods

Study Population – Key Eligibility Criteria

- Men and women, ages 18-65 years
- BMI ≥ 28 kg/m^2
- NAFLD, 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%
- ALT and aspartate aminotransferase (AST) laboratory values ≤ 75 IU/L

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
- No adjunctive lifestyle intervention

Key Efficacy Endpoints

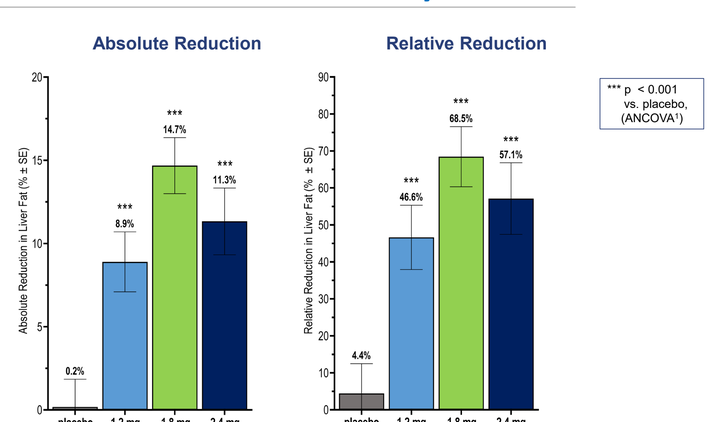
- Primary: Reduction in LFC by MRI-PDFF at Week 12
- Secondary: Percent (%) weight loss at Week 12

Results

Characteristics of Study Participants

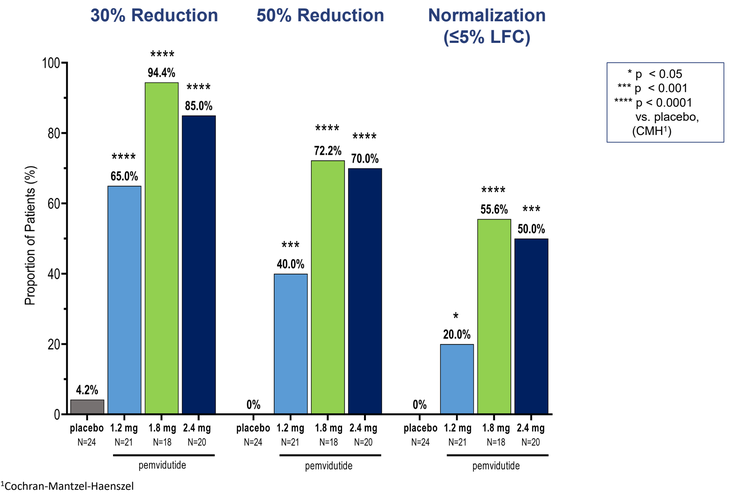
Characteristic		Treatment			
		Placebo (n = 24)	1.2 mg (n=23)	1.8 mg (n=23)	2.4 mg (n=24)
Age, years	mean (SD)	47.9 (14)	48.6 (11)	50.3 (9)	48.8 (8)
Gender	female, n (%)	14 (58.3%)	9 (39.1%)	12 (52.2%)	15 (62.5%)
Race	white, n (%)	21 (87.5%)	21 (91.3%)	20 (87.0%)	24 (100%)
	other, n (%)	3 (12.5%)	2 (8.7%)	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)
Iron-corrected T1 (cT1), ms	mean (SD)	943.4 (94.3)	916.7 (101.2)	894.7 (161.3)	927.6 (18.3)
Blood pressure, mm Hg	systolic, mean (SD)	122.8 (11.4)	129.0 (14.1)	123.2 (15.9)	125.9 (12.3)
	diastolic, mean (SD)	79.6 (6.0)	79.3 (9.1)	77.8 (9.7)	80.1 (8.6)

Reduction in liver fat content by MRI-PDFF at Week 12



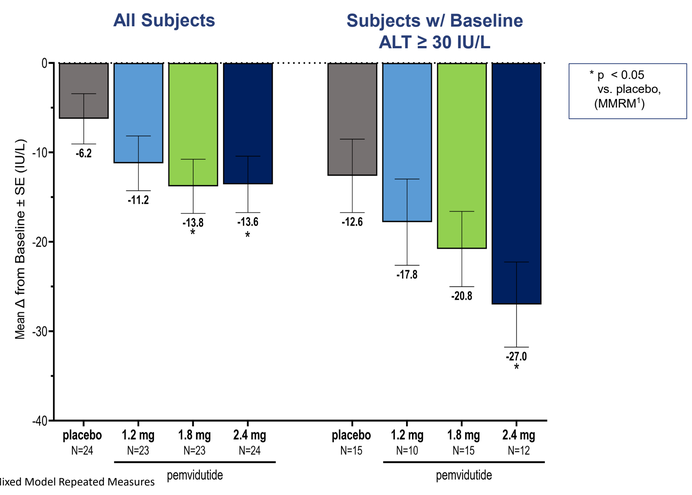
[1]Analysis of Covariance

PDFF Responder Analyses at Week 12



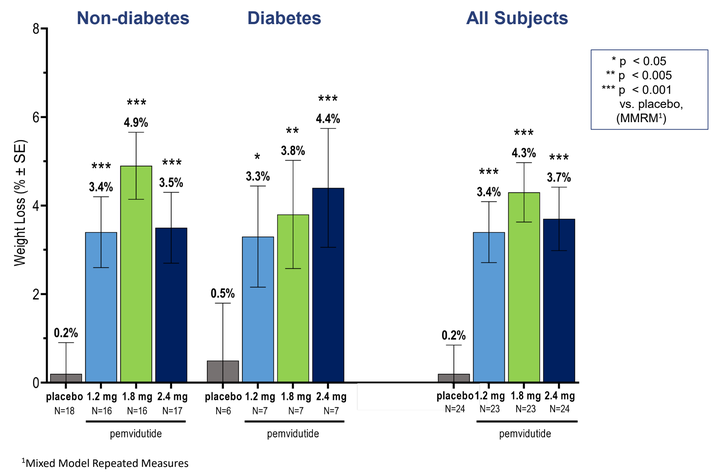
[1]Cochran-Mantzel-Haenszel

Reduction in ALT at Week 12



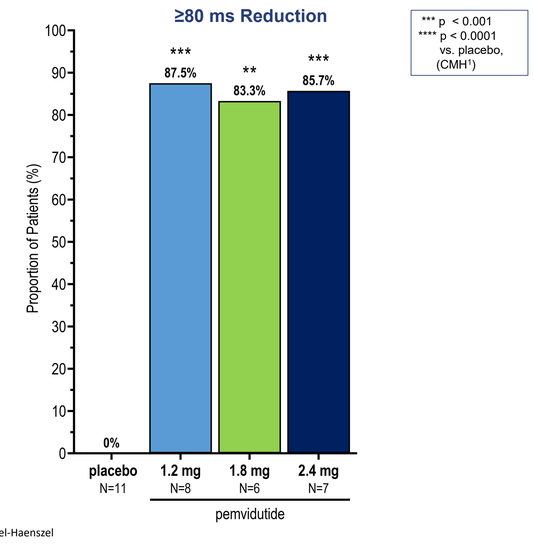
[1]Mixed Model Repeated Measures

Key Secondary Endpoint: Percent (%) Reduction in Body Weight at Week 12—Efficacy Estimand



[1]Mixed Model Repeated Measures

Iron-corrected T1 (cT1) Responder Analyses at Week 12



[1]Cochran-Mantzel-Haenszel

Safety

Characteristic		Treatment			
		Placebo (n = 24)	1.2 mg (n=23)	1.8 mg (n=23)	2.4 mg (n=24)
Severe AEs	n (%)	**0 (%)**	**0 (%)**	**0 (%)**	**0 (%)**
SAEs	n (%)	**0 (%)**	**0 (%)**	**0 (%)**	**0 (%)**
AEs leading to treatment discontinuation	n (%)	**0 (%)**	**0 (%)**	**1 (4.3%)**	**1 (4.2%)**
Nausea					
Mild	n (%)	3 (12.5%)	3 (13.0%)	6 (26.1%)	6 (25.0%)
Moderate	n (%)	0 (0.0%)	1 (4.3%)	6 (26.1%)	3 (12.5%)
Vomiting					
Mild	n (%)	0 (0.0%)	3 (13.0%)	2 (8.7%)	2 (8.3%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Diarrhea					
Mild	n (%)	4 (16.7%)	3 (13.0%)	5 (21.7%)	1 (4.2%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation					
Mild	n (%)	0 (0.0%)	3 (13.0%)	4 (17.4%)	1 (4.2%)
Moderate	n (%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)

No significant changes in liver enzymes, fasting glucose, HbA1c, or mean heart rate across all treatment groups

- Study medication was well tolerated even in the absence of dose titration
- Nausea was the most frequently reported adverse event (AE), with most being mild in severity
- No SAEs or severe AEs, with a low rate of AEs leading to discontinuation

Conclusions

- Robust relative liver fat (>68%) and serum ALT (27 IU/L) reductions with >83% of subjects achieving a reduction in cT1 of ≥80 ms at 12 weeks are predictive of NASH resolution and fibrosis improvement in a NASH clinical trial
- Significant placebo-adjusted relative body weight reduction of 4.7% in subjects without T2D with 1.8 mg dose
- No severe or serious AEs and low rates of AEs leading to treatment discontinuation
- Well-tolerated without the need for dose titration, consistent with prior experience
- No signals of hepatotoxicity and no evidence of loss of glycemic control

Disclosures
SH: Scientific advisor/consultant: Akero, Alentis, Altimmune, Arrowhead, Axcella, Cirius, Cymabay, Echosens, Fibronostics, Forest Labs, Galectin, Genfit, Gilead,Hepagene, Hepion, HistoIndex, Intercept, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novo Nordisk, PathAI, Poxel, Sagimet, Terns, Viking, 89 Bio. Stock options: Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, Metacrine, NGM Bio, Northsea. Grant/Research support: Akero, Axcella, BMS, Cirius, CiVi Biopharma, Conatus, Cymabay, Enyo, Galectin, Genentech, Genfit, Gilead, Hepion, Hightide, Intercept, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer, Sagimet, Viking. JS, MSR, JY, LH, BG, LRG, RB, ST, MSH, and SKB are employees of Altimmune.

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