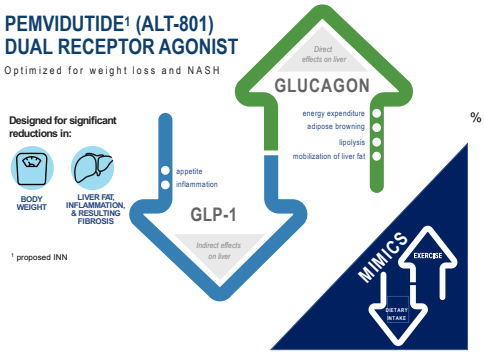
A placebo-controlled, double-blind, first-in-human study of pemvidutide (ALT-801), a novel GLP-1/glucagon dual receptor agonist for the treatment of NASH and obesity

M. Scott Harris[1], John Nestor[2], Joyce James[3], Sarah K. Browne[1], Jacques D. Payne[1], Staci M. Steele[1], Robert Casper[1], Anvar Suyundikov[1], Vyjayanthi Krishnan[1], M. Scot Roberts[1], Stephen A. Harrison[4] , Altimmune, Inc, Gaithersburg, MD, USA; [2] Spitfire Pharma, South San Francisco, CA, USA; [3] Corvid, Oakland, CA, USA; [4] Pinnacle Research, San Antonio, TX, USA

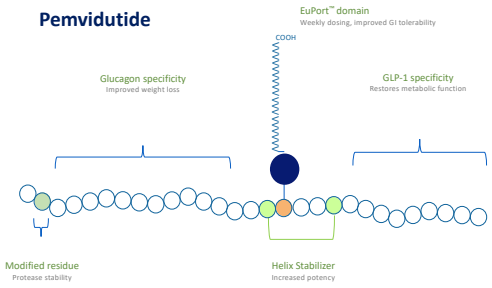
Background

NASH and NAFLD
HEPATIC MANIFESTATIONS OF OBESITY

- The treatment of obesity is the cornerstone of the treatment of NASH and NASH-associated morbidity, including cardiovascular disease and extrahepatic malignancy
- Drugs in development for NASH should target the weight loss achieved by bariatric surgery
- 10% or greater body weight loss blunts NASH progression and reverses NASH fibrosis
- Dual GLP-1:glucagon agonists combine the reduced caloric intake effects of GLP-1 receptor agonists with the increased energy expenditure and lipometabolic effects of glucagon receptor agonists on the liver



Structure is Key to Differentiation



- The proprietary EuPort™ domain has been shown to prolong serum half-life (t1/2) and slow bloodstream entry, which could improve tolerability
- The 1:1 ratio of GLP-1 and glucagon agonism within pemvidutide has been hypothesized to provide brisk and robust weight loss while maintaining glucose control (Day 2012; Peptide Sci 9:443-50)
- Optimized pharmacokinetics (PK) using Euport technology combined with balanced agonism— pemvidutide is designed with goal of enhanced efficacy and tolerability without use of titration

Aims

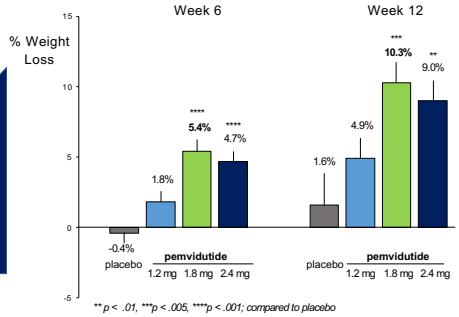
- The aims of the current study were 1) to assess the safety and PK of pemvidutide in the absence of dose titration; and 2) to evaluate its effects on weight loss and liver fat content (LFC), both important attributes in the treatment of NASH

Methods

- This was a placebo-controlled, double-blind, first-in-human trial comprised of single ascending dose (SAD) cohorts of 0.4, 1.2, 2.4, 3.6 and 4.8 mg and multiple ascending dose (MAD) cohorts of 1.2, 1.8, and 2.4 mg administered weekly by subcutaneous (SC) injection for 12 weeks, **without use of dose titration**
- Overweight and obese but otherwise healthy subjects (BMI 25-40 kg/m^2) were randomized 3:1 and 4:1 in SAD and MAD cohorts to pemvidutide or placebo, respectively, with placebos pooled for analyses
- The primary endpoint of the study was safety and tolerability. Secondary endpoints included change in body weight and PK
- Change in LFC by MRI-PDFF was evaluated in exploratory analyses of subjects >5% by MRI-PDFF at baseline

Results

Weight Loss at Week 12



***p < .01, ***p < .005, ****p < .001; compared to placebo*

- By Week 12, subjects receiving pemvidutide achieved mean weight losses of 4.9%, 10.3%, and 9.0% at the 1.2 mg, 1.8 mg, and 2.4 mg doses, respectively

PK

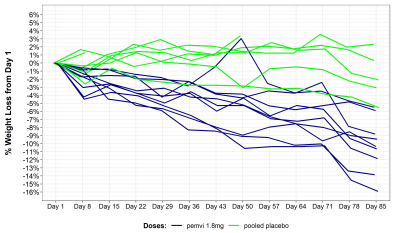
- Time to peak drug concentration (Cmax) was slow at 70 hrs, while t1/2 was extended at 110 hours, compatible with weekly dosing

Safety

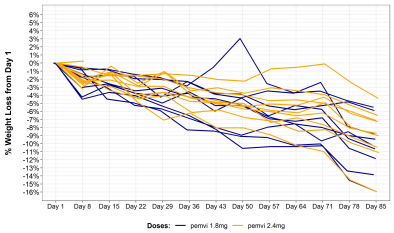
Characteristic		Treatment			
		1.2 mg	1.8 mg	2.4 mg	Pooled placebo
AEs leading to discontinuation	n (%)	0 (%)	0 (%)	0 (%)	0 (%)
Serious or severe AEs	n (%)	0 (%)	0 (%)	0 (%)	0 (%)
Nausea					
Mild	n (%)	1 (14.3%)	5 (55.6%)	5 (45.5%)	1 (14.3%)
Moderate	n (%)	1 (14.3%)	1 (11.1%)	5 (45.5%)	0 (0.0%)
Vomiting					
Mild	n (%)	1 (14.3%)	1 (11.1%)	5 (45.5%)	1 (14.3%)
Moderate	n (%)	0 (0.0%)	1 (11.1%)	3 (27.3%)	0 (0.0%)
Diarrhea					
Mild	n (%)	0 (0.0%)	0 (0.0%)	2 (18.2%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Constipation					
Mild	n (%)	0 (0.0%)	1 (11.1%)	2 (18.2%)	0 (0.0%)
Moderate	n (%)	0 (0.0%)	1 (11.1%)	1 (9.1%)	0 (0.0%)
Hyperglycemia	n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

- No study discontinuations due to adverse events (AEs)
- Nausea was the most frequently reported adverse event (AE), with most being mild in severity
- No subjects experienced diarrhea at 1.2 mg and 1.8 mg
- No changes in glucose control, HbA1c or mean heart rate
- No severe or serious AEs
- One subject receiving pemvidutide 1.8 mg and 1 subject receiving placebo experienced 3-5x elevations of ALT without other significant findings

Weight Loss Trends

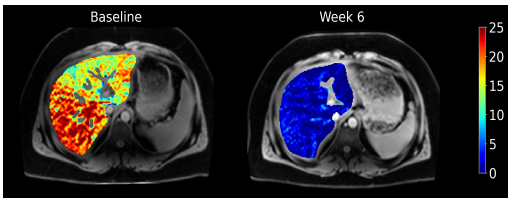


- 100% of subjects achieved 5% weight loss and 55% of subjects achieved 10% weight loss by Week 12
- Weight loss occurred rapidly and consistently across study weeks



- Trend lines of individual subject plots at 1.8 mg and 2.4 mg were similar. The absence of plateau suggested that sustained effects, potentially exceeding 20% weight loss, will be observed over longer dosing durations

Liver Fat Content (LFC) by MRI-PDFF at Week 6



- Subjects with baseline LFC as high as 19.5% (see above) achieved reductions of LFC to undetectable levels

Treatment Group	Weight Loss (%) at Week 6	MRI-PDFF					
		Baseline	Week 6	Absolute Δ at Week 6 (%)		Relative Δ at Week 6 (%)	
				Individual	Mean	Individual	Mean
Placebo	0.5	5.2	3.7	1.5	1.5	28.8	28.8
ALT-801 1.2 mg	1.0	19.1	14.0	5.10	6.50	26.7	48.2
	5.1	11.2	3.4	7.80		69.6	
ALT-801 1.8 mg	4.4	12.4	< LOD	11.65	11.65	94.0	94.0
ALT-801 2.4 mg	3.7	17.0	< LOD	16.25	11.50	95.6	91.9
	4.9	5.5	< LOD	4.75		86.4	
	3.1	7.0	< LOD	6.25		89.3	
	4.7	19.5	< LOD	18.75		96.2	

- All subjects receiving pemvidutide 1.8 or 2.4 mg achieved undetectable levels of liver fat by MRI-PDFF, **a greater than 90% reduction**, at Week 6 (LOD, limit of detection = 1.5%; for absolute and relative Δ, values < LOD are set at 0.75%)

Conclusions

- **Double-digit weight loss** in 12 weeks and decreases in LFC to levels below the limit of detection, *without the need for dose titration*, suggest pemvidutide could be a promising new agent for treatment of NASH and its co-morbidities
- The reduction of liver fat to **undetectable levels** in 6 weeks could set a new standard for the magnitude and speed of liver fat reduction in NASH therapeutics

altimmune