EASL CONGRESS
Milan, Italy 5–8 June 2024

Model simulations predict that the dual GLP-1/glucagon receptor agonism of pemvidutide will produce greater reductions in MASH NAS, liver fat, and fibrosis than GLP-1R mono-agonists.

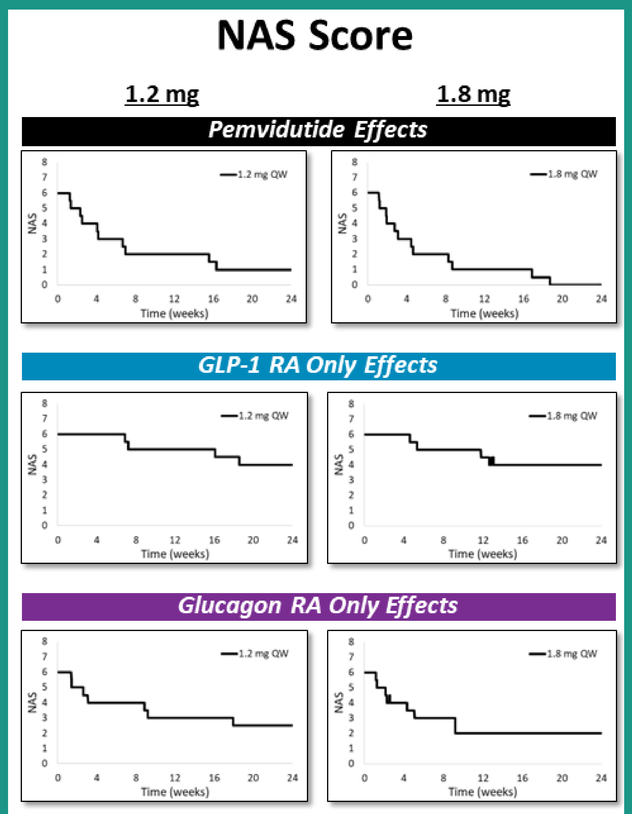

Figure 1. Simulated effects of 1.2 mg or 1.8 mg pemvidutide and the relative contributions of GLP-1 receptor agonism and GCGR agonism on NAS score over 24 weeks.

Contact information

Sarah Browne: sbrowne@altimmune.com

Acknowledgments

We would like to recognize Dr. Stephen Harrison for his contribution to this work and his tireless dedication to advancing needed treatments for metabolic liver disease.

Pemvidutide, a glucagon-like peptide 1/glucagon dual receptor agonist, improves metabolic dysfunction-associated steatohepatitis activity and fibrosis in a clinical quantitative systems pharmacology model

altimmune

S. Harrison[1], J. Suschak[2], M. McDaniel[3], Z. Kenz[3], S. Tomah[2], J. Kasper[2], M.S. Roberts[2], S. Siler[3], M.S. Harris[2], S. Browne[2]

[1] Pinnacle Clinical Research, San Antonio, TX, USA; [2] Altimmune, Inc, Gaithersburg, MD, USA ; [3] Simulations Plus, Inc, Lancaster, CA, USA

Introduction

Elevated liver fat content (LFC) is the primary pathophysiologic driver of metabolic dysfunction-associated steatohepatitis (MASH). In prior clinical trials, pemvidutide, a balanced (1:1) dual glucagon-like peptide 1 (GLP-1)/glucagon receptor (GCGR) agonist, achieved significant reductions in LFC and improvements in two non-invasive markers of MASH inflammation: alanine aminotransferase (ALT) levels and corrected T1 magnetic resonance imaging.

Aim

Employ NAFLDsym, a mechanistic quantitative systems pharmacology (QSP) model, to predict the effects of pemvidutide and the relative contributions of GLP-1 and GCGR receptor agonism on LFC, nonalcoholic fatty liver disease activity score (NAS), fibrosis, and weight loss in a simulated cohort of MASH subjects.

Methods

The QSP modeling of pemvidutide was coupled to simulated pemvidutide pharmacokinetic profiles using a 1-compartment model. Clinical trial data of pemvidutide from subjects with metabolic dysfunction-associated steatotic liver disease (MASLD) and/or overweight/obesity were used to calibrate the quantitative effects of pemvidutide 1.2 mg and 1.8 mg once weekly dosing over 24 weeks.

Table 1. Baseline characteristics of the simulated cohort and pemvidutide treated subjects.

Measure	MASH SimCohort	Pemvidutide MASLD Phase 1		Pemvidutide Obesity Phase 2	
		1.2 mg	1.8 mg	1.2 mg	1.8 mg
n	100	23	23	40	40
Body Weight, kg (SD)	105.7 (22.1)	102.4 (14.6)	98.9 (19.7)	100.0 (20.4)	102.1 (17.7)
LFC, % (SD)	25.0 (8.1)	21.6 (7.3)	21.8 (8.0)	NA	NA
ALT, U/L (SD)	48.5 (9.2)	32.4 (13.8)	36.4 (15.6)	24.8 (13.1)	23.7 (13.3)
NAS, (SD)	4.7 (1.3)	NA	NA	NA	NA
Fibrosis Stage, (SD)	2.2 (0.9)	NA	NA	NA	NA

Results

- A strong correlation was observed between clinically reported and QSP predicted effects of pemvidutide on weight loss and LFC at 24 and 12 weeks, respectively.
- At 24 weeks, the QSP model predicted pemvidutide 1.8 mg to result in complete resolution of NAS and a 1-point median improvement in MASH fibrosis.
- Adding GCGR agonism to GLP-1R agonism lead to further reductions in LFC from 21% to 62% and resulted in a 4-point greater decrease in median NAS.
- GLP-1 receptor agonism alone was predicted to have no effect on fibrosis within the 24-week timeframe.

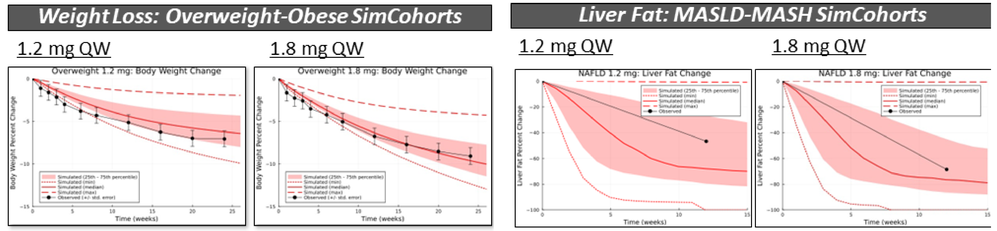

Figure 2. Correlations between simulated effects of 1.2 mg or 1.8 mg pemvidutide on weight loss or changes in LFC with observed changes from subjects treated with 1.2 mg or 1.8 mg pemvidutide for obesity for 24 weeks or MASLD for 12 weeks.

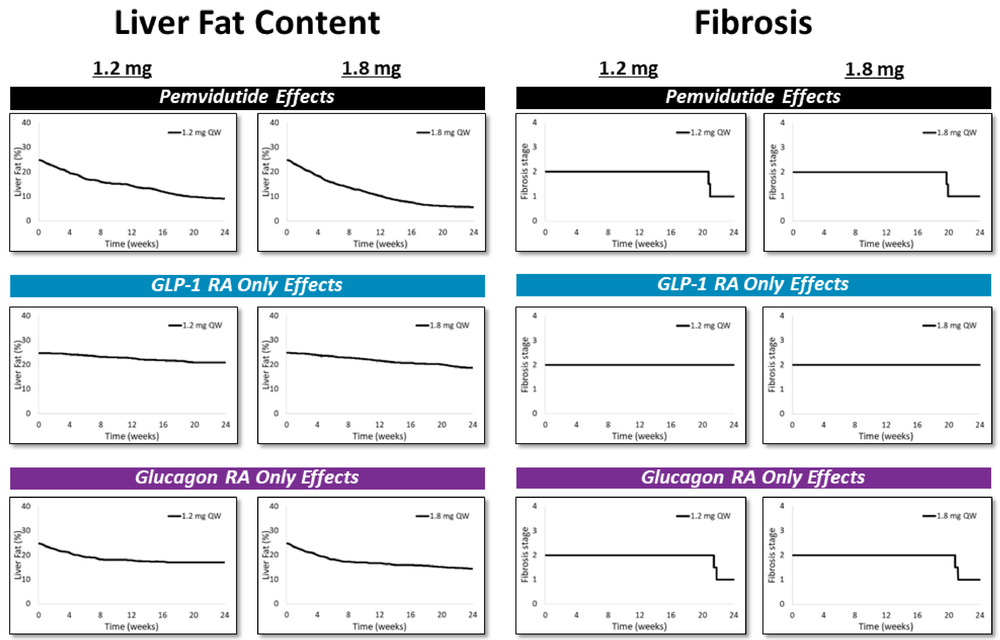

Figure 3. Simulated effects of 1.2 mg or 1.8 mg pemvidutide and the relative contributions of GLP-1 receptor agonism and GCGR agonism on LFC and fibrosis over 24 weeks.

Conclusions

The QSP model predicted the additive effects of GLP-1 and GCGR agonism in pemvidutide would have additive effects on reducing MASH LFC, NAS, and fibrosis and suggested that pemvidutide will have successful outcomes on MASH resolution and fibrosis improvement endpoints in an ongoing 24-week MASH clinical trial.