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GASTROINTESTINAL TOLERABILITY OF PEMVIDUTIDE WITHOUT DOSE TITRATION IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS FROM THE PHASE 2B IMPACT TRIAL

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INTRODUCTION

- MASLD affects 25–30% of individuals worldwide (occurring in up to 80% of individuals with obesity), with 20–30% advancing to MASH.[1-4] Mortality in non-cirrhotic MASH is primarily driven by cardiovascular and hepatic complications[1]
- Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist that comprises a EuPort™ side chain, which enables once-weekly dosing and may slow entry into the circulation, potentially contributing to improved tolerability[5,6]
- At Week 24, pemvidutide achieved MASH resolution without worsening fibrosis. By Week 48, it demonstrated dose-dependent reductions in NITs of inflammation and fibrosis, accompanied by significant weight loss[6,7]

AIMS

- IMPACT (NCT05989711), was a 48-week, phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed F2/F3 MASH[7]
- Primary histological endpoints (MASH resolution/fibrosis improvement) were measured at Week 24[7]
- Secondary endpoints included non-invasive tests (NITs) for liver fat content, inflammation, and fibrosis, along with weight loss, measured at Weeks 24 and 48[7]
- Here, we assessed the incidence, severity, and clinical impact of commonly reported GI AEs at Week 52, following the 4-week off-drug follow-up visit

METHODS

- Two hundred twelve patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg) administered without dose titration, or placebo for 48 weeks. Safety was monitored throughout the trial and data regarding the incidence of GI AEs of interest were analyzed
- Continuous safety data was summarized with descriptive statistics (arithmetic mean, SD, median, minimum, and maximum) by dose and treatment (pemvidutide or placebo)
- Categorical safety data was summarized with frequency counts and percentages by dose, treatment group, and day where applicable

RESULTS

- The mean age was 53 years, mean BMI was 39 kg/m^2, 58% were female, and 43% of patients had type 2 diabetes (**Table 1**)

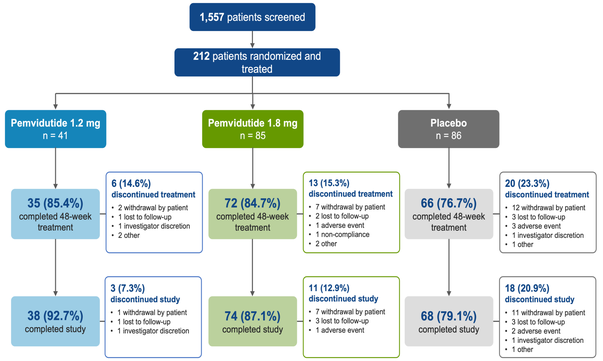
Table 1. Baseline Characteristics

Characteristic	1.2 mg Pemvidutide (N=41)	1.8 mg Pemvidutide (N=85)	Placebo (N=86)
Age, years	55.2 (13.0)	53.4 (12.4)	52.5 (12.2)
Sex, female	25 (61.0%)	50 (58.8%)	48 (55.8%)
BMI, kg/m^2	39.2 (8.4)	38.7 (6.9)	38.3 (8.4)
Type 2 Diabetes	18 (43.9%)	36 (42.4%)	36 (41.9%)
F3 Fibrosis	17 (41.5%)	39 (45.9%)	40 (46.5%)
ELF Score	10.0 (0.8)	9.9 (1.0)	9.7 (0.8)
LSM, kPa	12.3 (3.6)	12.8 (4.4)	12.5 (4.4)
LFC, %	20.0 (7.1)	19.0 (6.8)	19.6 (6.4)
ALT, IU/L	67.6 (54.6)	67.6 (43.0)	56.6 (32.7)

Data are presented as mean (SD) or n (%)

- See **Figure 1.** Most patients completed study treatment as planned, with treatment completion rates of 85.4%, 84.7%, and 76.7% in the pemvidutide 1.2 mg, pemvidutide 1.8 mg, and placebo groups, respectively
- Treatment discontinuations due to AEs were rare, occurring in 0.0% (n=0) and 1.2% (n=1), in the 1.2 mg and 1.8 mg groups, compared to 3.5% (n=3) in the placebo group **(Figure 1)**
- Overall TEAE rates were similar across treatment groups, with 82.9% of the 1.2 mg, 87.1% of the 1.8 mg, and 77.9% of placebo patients experiencing at least one TEAE

Figure 1. Study Disposition



Percentages are based on the number of randomized patients in each group (ITT population). Treatment completion and study completion are summarized separately. Some patients who discontinued treatment remained in the study and completed it. Data are based on an interim cut prior to lock.

- Gastrointestinal TEAEs were the most frequent adverse events overall (50.9%), occurring in 41.5% of 1.2 mg, 64.7% of 1.8 mg, and 41.9% of placebo patients
- Outside of GI events, the most common TEAEs overall occurred in Infections (46.2%; mostly UTIs and upper respiratory infections), General/Admin Site (24.1%; mostly fatigue and injection site reactions), Metabolism (22.6%), Musculoskeletal (18.4%), and Nervous System (17.0%; mostly headache) organ classes
- The most common GI AEs (reported by ≥5% of patients overall) followed a dose-dependent pattern, with GI AEs at the 1.2 mg dose roughly equivalent to placebo **(Table 2)**

Table 2. GI Adverse Events

Adverse Events n (%)	1.2 mg Pemvidutide (N=41)	1.8 mg Pemvidutide (N=85)	Placebo (N=86)
GI TEAE	17 (41.5)	55 (64.7)	36 (41.9)
Nausea	9 (22.0)	35 (41.2)	15 (17.4)
Diarrhea	5 (12.2)	19 (22.4)	7 (8.1)
Constipation	5 (12.2)	15 (17.6)	10 (11.6)
Vomiting	3 (7.3)	10 (11.8)	2 (2.3)

- Two patients (2.3%) discontinued treatment due to GI AEs in the placebo group and one patient (1.2%) in the 1.8 mg group
- No serious GI AEs related to study drug and no severe GI TEAEs were reported; all GI AEs were mild to moderate, as associated with this drug class
- The majority of GI AEs occurred within the first 4-8 weeks of treatment followed by marked diminution regardless of the cohort analyzed

CONCLUSIONS

- In patients with MASH, pemvidutide was generally well-tolerated with fewer treatment discontinuations due to AEs than placebo. Specifically, GI AEs were mild to moderate and followed a dose-dependent pattern
- Despite the IMPACT trial not employing a dose titration phase, the safety and tolerability profile was notable. Given these findings, the incorporation of a simple 1 or 2 step titration regimen to exploit the inherent tolerability of pemvidutide may further improve tolerability
- These overall safety and GI tolerability findings complement the positive effects on MASH, hepatic biomarker improvements, and clinically meaningful weight loss demonstrated across the Phase 2b IMPACT trial[6,7]

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Abbreviations: AE, Adverse Event; Cmax, Maximum Concentration; GI, Gastrointestinal; GLP-1, Glucagon-Like Peptide-1; ITT, Intention-to-Treat; LFC, Liver Fat Content; MASH, Metabolic Dysfunction-Associated Steatohepatitis; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; NCT, National Clinical Trial; NIT, Non-Invasive Tests; SD, Standard Deviation; Tmax, Time to Maximum Concentration

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