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EFFICACY AND SAFETY OF PEMVIDUTIDE IN THE TREATMENT OF ADULTS WITH ALCOHOL USE DISORDER: RESULTS FROM RECLAIM, A 24-WEEK PHASE 2 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

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INTRODUCTION

- Alcohol use disorder (AUD) is a substantial public health burden, affecting 28.1 million adults in the U.S., with excessive alcohol use accounting for nearly 178,000 deaths annually[1,2]
- Excessive alcohol consumption can lead to alcohol-associated liver disease (ALD), one of the leading indication for liver transplantation in the U.S.[3]
- In 2019, <2% of patients with AUD were prescribed any of the three FDA-approved medications for treating AUD[4]
- Pemvidutide is a balanced 1:1 glucagon/glucagon-like peptide-1 (GLP-1) dual receptor agonist with direct liver (glucagon) effects that result in liver fat reduction, leading to reductions in inflammation and fibrosis, and metabolic (GLP-1) effects such as appetite suppression, decreased alcohol cravings and consumption, and weight loss[5]

AIM

- This study assessed the safety and efficacy of pemvidutide in reducing heavy drinking among adult patients with AUD

METHOD

- RECLAIM (NCT06987513) was a Phase 2, multi-center, randomized, double-blind, placebo-controlled trial in treatment-seeking patients with moderate-to-severe AUD per DSM-5, and BMI ≥25 kg/m2
  - Inclusion also required self-reported past-28-day alcohol consumption (via Timeline Follow-back [TLFB]) of at least 28 (men) or 21 (women) drinks/week with at least 3 heavy drinking days (HDDs)/week (≥5 drinks/day for men; ≥4 for women)
- Patients were randomized 1:1 to receive 1 mL subcutaneous pemvidutide or placebo injections weekly for 24 weeks
  - Pemvidutide was administered weekly at 1.2 mg for 4 weeks, 1.8 mg for 4 weeks, and 2.4 mg for 16 weeks
- All patients viewed a monthly computer-based video (Take Control)[6] on alcohol misuse
- The primary endpoint was change from baseline in heavy drinking days (HDDs)/week measured using the TLFB method
- Secondary endpoints included two FDA-qualified measures of alcohol use evaluated via TLFB (proportion of patients with a ≥2-level reduction in World Health Organization Risk Drinking Level [WHO-RDL] or zero HDDs), percent days abstinent (PDA) via TLFB, drinks per drinking day (DDD) via TLFB, serum levels of phosphatidylethanol (PEth, an alcohol biomarker) and body weight
- Exploratory endpoints included the change in percentage of HDDs (PHDDs) and 24-week absolute change in fibrosis-4 index (FIB-4)
- Safety endpoints that included treatment-emergent adverse events (AEs) were assessed

RESULTS

- Of the 100 eligible patients, 50 were randomly assigned to receive pemvidutide and 50 to receive placebo
- 45 patients (90.0%) in the pemvidutide group and 46 (92%) in the placebo group completed the trial, while 40 (80.0%) and 39 (78.0%), respectively, completed treatment
- All-cause discontinuation occurred in 10 patients receiving pemvidutide (20.0%) and 11 (22.0%) receiving placebo

Demographic and baseline clinical characteristics were similar across groups

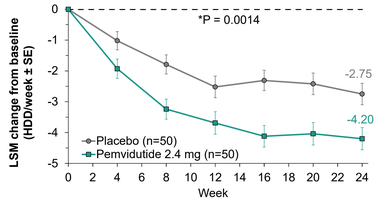
Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Placebo (N=50)	Pemvidutide 2.4 mg (N=50)
Age, years (SD)	50.0 (10.0)	50.8 (11.9)
Female sex, n (%)	26 (52)	26 (52)
Body weight, kg (SD)	96.0 (21.4)	92.0 (19.1)
BMI, kg/m² (SD)	32.5 (6.6)	32.3 (5.8)
AUD by DSM-5, n (%)		
Moderate (4–5 symptoms)	12 (24)	13 (26)
Severe (>5 symptoms)	38 (76)	37 (74)
Heavy Drinking Days/week (SD)	5.6 (1.5)	5.9 (1.3)
WHO Risk Drinking Level, n (%)		
Moderate	2 (4)	1 (2)
High	15 (30)	15 (30)
Very high	33 (66)	34 (68)
Percent Days Abstinent (SD)	12.2 (15.2)	8.2 (13.4)
Drinks per Drinking Day (SD)	9.9 (6.7)	8.5 (5.2)
Total alcohol consumption, g/28 days (SD)	3310.2 (2166.2)	3047.8 (2049.5)
PEth, ng/mL (SD)	374.6 (307.9)	406.2 (356.9)
FIB-4 (SD)	1.1 (0.6)	1.1 (0.4)
FIB-4 ≥ 1.3[a], n (%)	15 (30)	10 (20)

[a] Suggestive of intermediate-to-high risk of significant fibrosis (cut-off value reported by Angulo et al. 2013[7]).

Pemvidutide met the trial's primary endpoint at week 24 (reduction in HDDs/week)

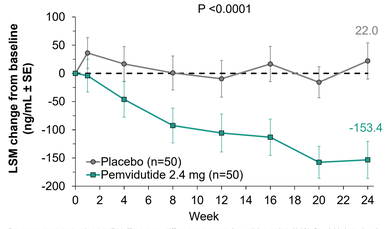
Figure 1. Change in Heavy Drinking Days (HDDs)/Week (Primary Endpoint)



Evaluated using TLFB method and data was analyzed using MMRM. *Multiplicity was addressed with a hierarchical fixed-sequence testing procedure (primary endpoint followed by WHO-RDL). Treatment difference at Week 24: -1.45 HDDs/week [95% CI, -2.32 to -0.58].

Self-reported drinking outcomes were corroborated by reductions in objective PEth concentrations in the pemvidutide group

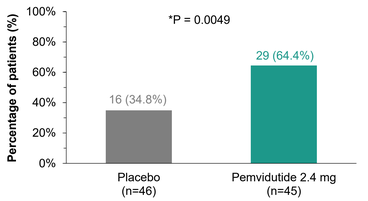
Figure 4. Change in Serum Phosphatidylethanol (PEth) Levels



Data was analyzed using MMRM. Treatment difference at week 24: -175.4 ng/mL [95% CI, -259.6 to -91.1].

In the pemvidutide group, nearly 2/3 of patients achieved a ≥2-level WHO-RDL reduction vs. ~1/3 on placebo

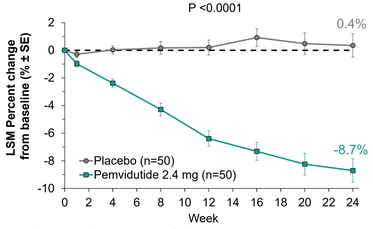
Figure 2. Proportion of Patients Achieving a ≥2-level WHO-RDL Reduction at Week 24



≥2-level WHO-RDL is recognized as an FDA Registrational Endpoint. Evaluated using TLFB method and data was analyzed using the CMH test. Denominator for the proportion is the number of subjects who have non-missing outcome data. *Multiplicity was addressed with a hierarchical fixed-sequence testing procedure (primary endpoint followed by WHO-RDL). Treatment difference at week 24: OR = 3.3 [95% CI, 1.4 to 7.7].

Patients on pemvidutide had a greater reduction in percent body weight at 24 weeks than those on placebo

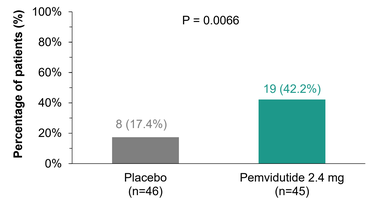
Figure 5. Percent **C**hange in Body Weight



Data was analyzed using MMRM. Treatment difference at week 24: -9.1% (-11.4 to -6.7).

In the pemvidutide group, more than double the proportion of patients achieved zero HDDs compared to placebo

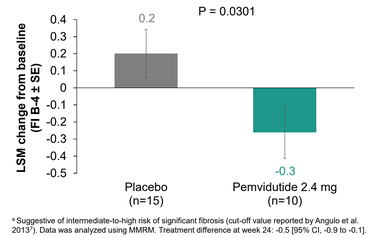
Figure 3. Proportion of Patients Achieving Zero Heavy Drinking Days (HDDs) at Week 24



Zero HDDs is a recognized as an FDA Registrational Endpoint. Evaluated using TLFB method and data was analyzed using the CMH test. Denominator for the proportion is the number of subjects who have non-missing outcome data. Treatment difference at week 24: OR = 3.8 [95% CI, 1.4 to 10.4].

Among patients with baseline FIB-4 ≥1.3, those on pemvidutide had a greater reduction in FIB-4 score than placebo at 24 weeks

Figure 6. Change in FIB-4 Score At Week 24 Among Patients with Baseline FIB-4 ≥1.3[a] (n=25)



[a] Suggestive of intermediate-to-high risk of significant fibrosis (cut-off value reported by Angulo et al. 2013[7]). Data was analyzed using MMRM. Treatment difference at week 24: -0.5 [95% CI, -0.9 to -0.1].

Table 2. Additional Endpoints of Alcohol Intake

Endpoint	Placebo (N=50)	Pemvidutide 2.4 mg (N=50)	Treatment difference
HDDs/week, sensitivity analysis[a]	-2.77 (-3.48 to -2.05)	-4.00 (-4.74 to -3.27)	-1.24 (-2.15 to -0.33)
Percentage of HDDs[b]	-39.4 (-49.2 to -29.5)	-60.0 (-70.3 to -49.8)	-20.7 (-33.2 to -8.2)
Drinks per Drinking Day[c]	-3.8 (-5.1 to -2.5)	-4.9 (-6.2 to -3.6)	-1.1 (-2.8 to 0.6)
Percent Days Abstinent[d]	20.5 (10.5 to 30.6)	38.9 (28.6 to 49.2)	18.4 (5.0 to 31.8)

Data are presented as LSM change from baseline (95% CI). [a] Sensitivity analysis for HDDs/week used an alternative handling of intercurrent events (ICEs) in which all TLFB observations following an ICE-1 (treatment discontinuation), ICE-2 (initiation of non-study AUD treatment), or ICE-4 (use of prohibited substances/ medications that may affect alcohol consumption outcomes) were considered missing. ICE-3 (death) did not occur. P = 0.008. [b] Represents the percentage of HDDs (percentage points) from weeks 21-24 via TLFB, P = 0.0014. [c] Subjects who were completely abstinent were assigned with a 0 value. P = 0.203. [d] P = 0.0075.

Table 3. Adverse Events

Event, n (%)	Placebo (N=50)	Pemvidutide 2.4 mg (N=50)
Serious adverse events	1 (2.0)[a]	2 (4.0)[b]
Serious adverse events related to trial drug	0 (0.0)	1 (2.0)
Severe adverse events	3 (6.0)	6 (12.0)
Severe adverse events related to trial drug	0 (0.0)	3 (6.0)[c]
Adverse events of special interest related to trial drug	0 (0.0)	0 (0.0)
Study drug-related adverse events leading to treatment discontinuation	0 (0.0)	5 (10.0)[d]
Gastrointestinal disorders	17 (34.0)	31 (62.0)
Nausea	12 (24.0)	22 (44.0)
Constipation	3 (6.0)	13 (26.0)
Diarrhea	5 (10.0)	10 (20.0)
Vomiting	3 (6.0)	9 (18.0)
Upper abdominal pain	3 (6.0)	4 (8.0)
Dry mouth	0 (0.0)	5 (10.0)
Gastroesophageal reflux disease	2 (4.0)	3 (6.0)
Dyspepsia	0 (0.0)	4 (8.0)

Adverse events were predominantly mild or moderate. [a] Spinal stenosis; [b] 1 subject with hyponatremia possibly related to trial drug, 1 subject with breast cancer; [c] 1 subject with hyponatremia (same as serious AE), 1 subject with migraine, 1 subject with fatigue, night sweats, nausea and gastroesophageal reflux disease; [d] 2 vomiting, 1 constipation, 1 fatigue, 1 exacerbation of hemorrhoids.

CONCLUSIONS

- The RECLAIM trial met its primary endpoint, with pemvidutide demonstrating a significantly greater reduction in HDDs/week than placebo among patients with moderate-to-severe AUD
- Patients treated with pemvidutide showed consistent improvements in other measures of self-reported alcohol consumption, body weight, and hepatic fibrosis risk (FIB-4)
- Pemvidutide-associated declines in HDDs/week were corroborated by objective measures of PEth concentration
- Given the well-documented hepatic burden of chronic alcohol use, the previously demonstrated glucagon-mediated hepatic lipid clearance by pemvidutide may offer an additional therapeutic benefit over GLP-1 receptor agonism alone
- These findings in a multi-site, placebo-controlled randomized trial may represent an important step forward in developing new potential treatments for AUD
- **Future Directions:** The significant effects by pemvidutide on both alcohol consumption and the potential for liver damage, together with its generally favorable safety profile, support further evaluation of pemvidutide in a Phase 3 trial for AUD

REFERENCES

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Abbreviations: AEs, Adverse events; ALD, Alcohol-associated liver disease; AUD, Alcohol use disorder; BMI, Body mass index; CI: Confidence interval; CMH, Cochran-Mantel-Haenszel; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, FIB-4, Fibrosis-4 index; Fifth Edition; GLP-1, glucagon-like peptide-1; HDDs, Heavy drinking days; LSM: Least-squares mean; MMRM: Mixed model for repeated measures; PEth, Phosphatidylethanol; PHDDs, Percentage of HDDs; SD: Standard deviation; SE: Standard error; TLFB, Timeline Follow-back; WHO: World Health Organization; WHO-RDL, World Health Organization-Risk Drinking Level