Pegozafermin added to background GLP-1 therapy in patients with metabolic dysfunction-associated steatohepatitis with F2/F3 fibrosis: ENLIVEN 48-week extension data

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BACKGROUND

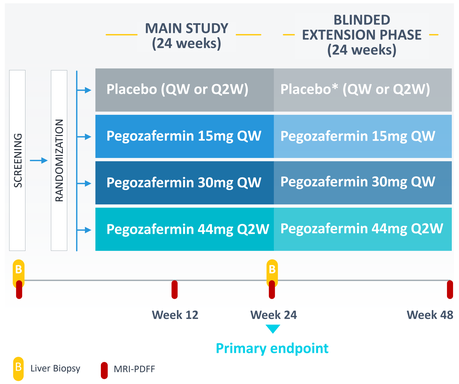
- Pegozafermin (PGZ), a long-acting fibroblast growth factor 21 (FGF21) analog, was evaluated in NASH patients with proven F2/F3 fibrosis (ENLIVEN trial) for efficacy/safety. This study demonstrated the benefit of PGZ in both hepatic and extra-hepatic parameters, including histologic improvements.
- Glucagon-like peptide-1 receptor agonists (GLP-1 therapy), approved for T2DM and obesity, decrease hepatic steatosis and inflammation and are currently being investigated as a treatment for MASH.
- We previously showed at 24 weeks PGZ on top of GLP-1 therapy (compared to GLP-1 therapy alone), improved markers of fibrosis and inflammation, and reduced liver fat and triglyceride levels.
- There were 41 patients on background GLP-1 therapy randomized to placebo or PGZ in the 48-week Safety Analysis Set (SAS); 36 in the Full Analysis Set (FAS).

OBJECTIVE

- To investigate the efficacy/safety of PGZ when added to existing background GLP-1 therapy over 48 weeks.

METHODS

ENLIVEN Trial Design



PRIMARY ANALYSIS POPULATION

- F2-F3 NASH; NAS ≥4

*Some placebo patients were re-randomized in the extension phase to receive PGZ.
NAS, NAFLD Activity Score; MRI-PDFF, Magnetic resonance imaging-estimated proton density fat fraction; QW: Every week; Q2W: Every 2 weeks

RESULTS

Baseline Characteristics of Subjects on Background GLP-1 Therapy Compared to Overall ENLIVEN Study Population

Parameter Mean or %	Total GLP-1 Therapy Use (n=41)	ENLIVEN Total Randomized (n=222)
Age (years)	55.0	55.6
Female	73.2%	60.8%
Weight (kg)	101.3	102.2
BMI (kg/m²)	36.5	36.6
BMI <30 kg/m²	17.1%	15.8%
BMI ≥30 and <35 kg/m²	14.6%	23.0%
BMI ≥35 kg/m²	68.3%	61.3%
Type 2 Diabetes	95.1%	66.2%
Hypertension	90.2%	73.9%
Liver Fat Content (MRI-PDFF)	15.8%	16.4%
Liver Stiffness (VCTE, kPa)	13.5	13.0
ELF Score >9.8	46.3%	50.0%
PRO-C3 (ng/mL)	41.5	52.8
ALT (U/L)	52.0	55.8
AST (U/L)	43.2	43.6
HbA1c, overall population	7.10	6.66
HbA1c, ≥6.5% subpopulation	80.5%	51.4%
Triglycerides (mg/dL)	168.7	171.9

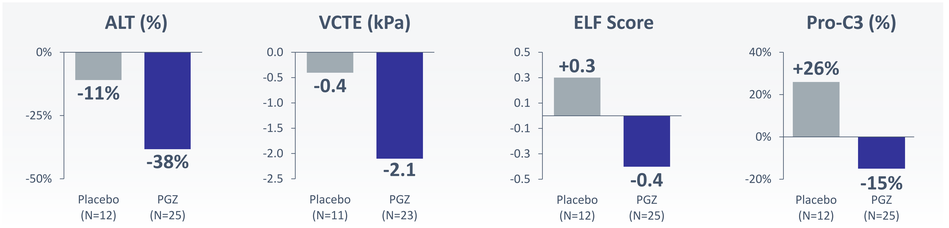
Randomized Analysis Set. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRI-PDFF, Magnetic resonance imaging-estimated proton density fat fraction; PRO-C3, N-terminal type III collagen propeptide; VCTE, Vibration-controlled transient elastography.

Overview of Concomitant GLP-1 Therapy

	Placebo (n=13)	PGZ Pooled (n=28)	Total GLP-1 Therapy (n=41)
Subjects on concomitant GLP-1 throughout the study	12	25	37
GLP-1 Category			
Semaglutide	8	13	21
Dulaglutide	6	10	16
Liraglutide	0	6	6
Exenitide	0	1	1

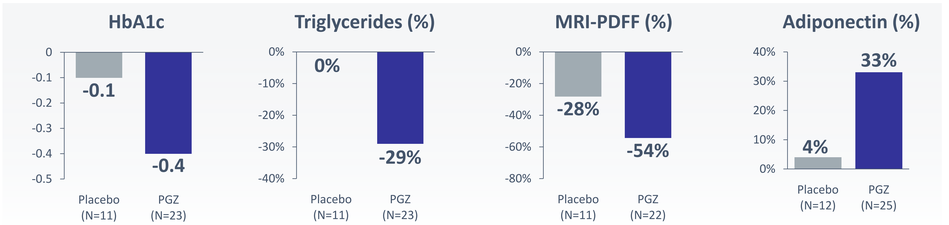
PGZ Pooled, 30mg QW+ 44mg Q2W

Greater Benefits on Fibrosis Markers Were Observed with PGZ vs. Placebo in Patients on Background GLP-1 Therapy at Week 24



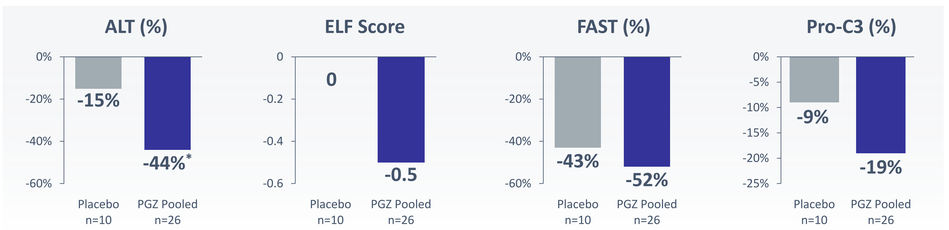
Source: Full Analysis Set. ELF, ALT and Pro-C3 reported as LS mean change from baseline; VCTE reported as median change (absolute) from baseline. Post-hoc analysis

Greater Benefits on Metabolic Markers Were Observed with PGZ vs. Placebo in Patients on Background GLP-1 Therapy at Week 24



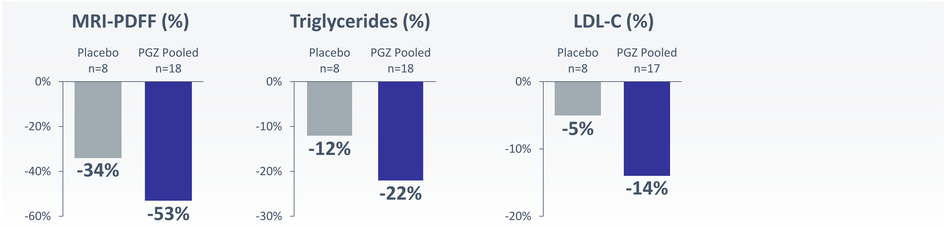
Source: Full Analysis Set. Adiponectin reported as LS mean change from baseline; HbA1c reported as median change (absolute) from baseline; MRI-PDFF and TG reported as median percent change from baseline. Post-hoc analysis

Sustained Benefits on Fibrosis Markers Were Observed with PGZ vs. Placebo in Patients on Background GLP-1 Therapy at Week 48



Source: Full Analysis Set. ELF, ALT, FAST and Pro-C3 reported as LS mean change from baseline.; *p<0.05 versus placebo. Post-hoc analysis.

Sustained Benefits on Metabolic Markers Were Observed with PGZ vs. Placebo in Patients on Background GLP-1 Therapy at Week 48



Source: Full Analysis Set. TG, and LDL-C and MRI-PDFF reported as median percent change from baseline. Post-hoc analysis

PGZ Treatment on Top of GLP-1 Therapy Leads to Additional Benefit in Liver fat, Inflammation and Fibrosis Markers

	Placebo (FAS) Week 48	PBO/GLP-1 Week 48	PGZ pooled/ GLP-1 Week 48
MRI-PDFF	-8%	-34%	-53%
ALT	-11%	-15%	-44%
Pro-C3	+5%	-9%	-19%
ELF score	+0.2	-0.0	-0.5

Week 48: Placebo (FAS) n=35
PBO/GLP-1: MRI-PDFF n= 8; ALT, Pro-C3 and ELF n=10
PGZ/GLP-1: MRI-PDFF n=18; ALT, Pro-C3 and ELF n=26

Long-term Treatment with PGZ on Top of GLP-1 Background Therapy Results in Sustained Improvements over a Wide Range of Liver NITs

	PGZ pooled Week 24	PGZ pooled Week 48
MRI-PDFF	-54%	-53%
ALT	-38%	-44%
Pro-C3	-15%	-19%
ELF score	-0.4	-0.5

Week 24: PGZ/GLP-1: MRI-PDFF n=22; ALT, Pro-C and ELF n=25
Week 48: PGZ/GLP-1: MRI-PDFF n=18; ALT, Pro-C3 and ELF n=26

Safety and Tolerability

- An acceptable safety and tolerability profile was retained when PGZ was added to background GLP-1 therapy. There with no treatment-related AE discontinuations.

CONCLUSIONS

- Patients on background GLP-1 therapy were more likely to be obese, have Type 2 diabetes, hypertension and HbA1c ≥ 6.5%.
- Addition of PGZ therapy to GLP-1 background therapy provided more extensive benefit versus GLP-1 therapy alone as measured by NITs for liver fat, inflammation and fibrosis.
- Benefits of PGZ treatment were sustained over the course of 48 weeks.
- PGZ, on top of GLP-1 therapy, continues to demonstrate a favorable safety and tolerability profile.