Histologic improvement and sustained benefit across hepatic and metabolic biomarkers with pegozafermin therapy: Results from a 48-week multi-center, randomized, double-blind, placebo-controlled Phase 2b trial (ENLIVEN)

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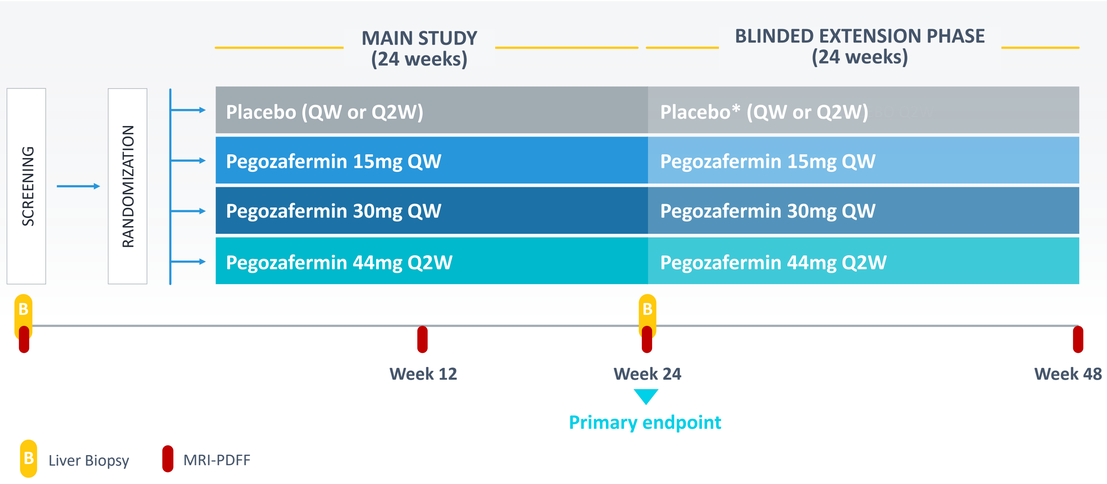
BACKGROUND

- FGF21 is an endogenous hormone regulating carbohydrate, lipid and energy metabolism. Pegozafermin (PGZ) is an FGF21 analog engineered to balance efficacy and long dosing interval. It is currently being investigated in Phase 3 trials for both MASH and severe hypertriglyceridemia.
- The Phase 2b ENLIVEN trial evaluated the efficacy and safety of PGZ given weekly (QW) or every two-weeks (Q2W) versus placebo in MASH patients with biopsy proven F2/F3 fibrosis. The primary histology endpoints were assessed at week 24, followed by a 24-week blinded extension phase, for a total of 48 weeks.

METHODS

ENLIVEN Trial Design



PRIMARY ANALYSIS POPULATION

- F2-F3 MASH; NAS ≥4

PRIMARY ENDPOINTS

- ≥1-stage fibrosis improvement with no worsening of MASH[1]
- MASH resolution with no worsening of fibrosis[2]

1.Improvement in liver fibrosis by ≥1 stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).
2.Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis (FDA draft guidance).
*Some placebo patients were re-randomized in the extension phase to receive pegozafermin.
NAS, NAFLD Activity Score; MRI-PDFF, Magnetic resonance imaging-estimated proton density fat fraction; QW: Every week; Q2W: Every 2 weeks.
Loomba et al, *N Engl J Med* 2023;389:998.

RESULTS

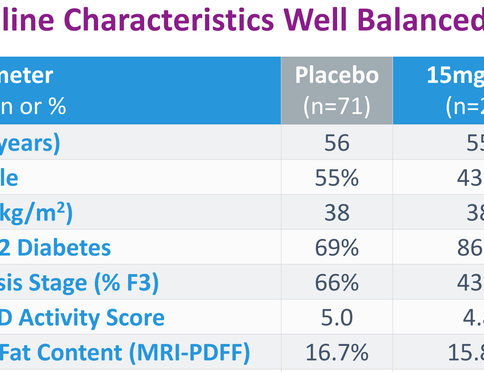
Baseline Characteristics Well Balanced Across Dose Groups

Parameter Mean or %	Placebo (n=71)	15mg QW (n=21)	30mg QW (n=73)	44mg Q2W (n=57)	Total (n=222)
Age (years)	56	55	55	55	**56**
Female	55%	43%	69%	65%	**61%**
BMI (kg/m^2)	38	38	35	36	**37**
Type 2 Diabetes	69%	86%	62%	61%	**66%**
Fibrosis Stage (% F3)	66%	43%	64%	53%	**60%**
NAFLD Activity Score	5.0	4.8	5.3	5.2	**5.1**
Liver Fat Content (MRI-PDFF)	16.7%	15.8%	16.7%	15.8%	**16.4%**
Liver Stiffness (VCTE, kPa)	14.1	11.2	12.5	13.2	**13.0**
PRO-C3 (ng/mL)	50	62	54	52	**53**
ALT (U/L)	50	61	60	56	**56**
AST (U/L)	41	48	47	42	**44**
HbA1c, overall population (%)	6.6	7.0	6.6	6.7	**6.7**
Triglycerides (mg/dL)	170	186	175	165	**172**

Source: Randomized Analysis Set.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; PRO-C3, N-terminal type III collagen propeptide; VCTE, Vibration-controlled transient elastography.
Loomba et al, *N Engl J Med* 2023;389:998.

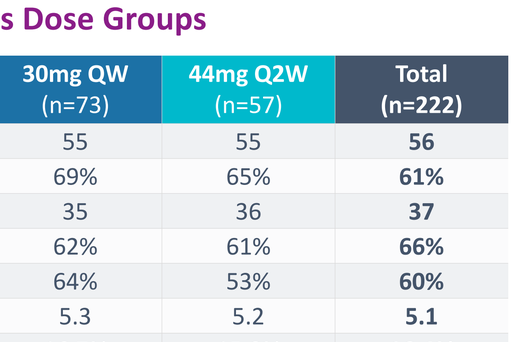
Primary Endpoints: PGZ Demonstrated Statistical Significance on Fibrosis Improvement and MASH Resolution at 30mg QW and 44mg Q2W Dose

Fibrosis Improvement Without Worsening of MASH at Week 24



Relative Risk*	1.0	2.9	3.5	3.6

MASH Resolution Without Worsening of Fibrosis at Week 24



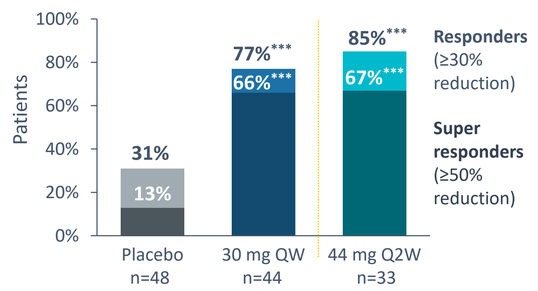
Relative Risk*	1.0	18.8	11.8	13.5

*Relative risk presented is calculated by dividing the drug response by placebo response. Relative risk calculated using statistical methods show similar results.
Source: Full Analysis Set; multiple imputation analysis via Cochran-Mantel-Haenszel (CMH) test stratified by type 2 diabetes mellitus (T2DM) status (yes vs. no) and fibrosis stage (F2 vs. F3).
Loomba et al, *N Engl J Med* 2023;389:998

RESULTS

PGZ Demonstrated Robust Liver Fat Reduction With High Responder Rates by MRI-PDFF at Week 24

Patients Achieving ≥30% and ≥50% Reduction in Hepatic Fat Fraction Versus Baseline[1]



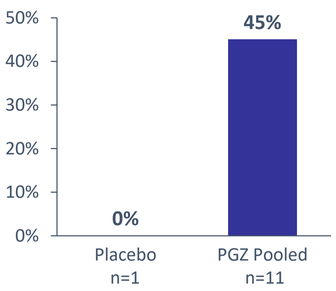
Parameter	Placebo (n=61)	30mg QW (n=66)	44mg Q2W (n=51)
MRI-PDFF	-15%	-50%	-55%
PRO-C3	6%	-18%	-17%
ELF	0.2	-0.3	-0.3

Results for the 15mg QW dose: -33%

1. Analysis via mixed model repeated measure (MMRM).
2. Analysis via Cochran-Mantel-Haenszel (CMH) test stratified by T2DM status (yes vs. no) and fibrosis stage (F2 vs. F3).
***p<0.001 versus placebo.
Loomba et al, *N Engl J Med* 2023;389:998.

Fibrosis Improvement Without Worsening of MASH in 45% of Patients with F4 Fibrosis at Baseline at Week 24

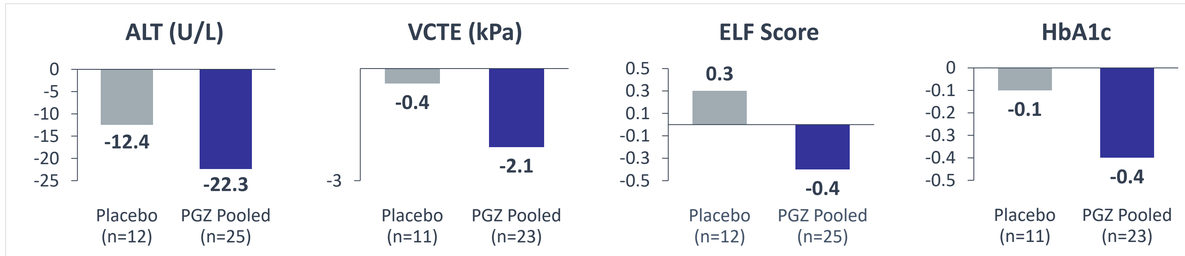
Fibrosis Improvement ≥1 Stage Without Worsening of MASH at Week 24



Parameter	Mean Change from Baseline on PGZ (n=12)
MRI-PDFF	-33%
ALT	-53%
AST	-31%
ELF	-0.4 units

Improvement in liver fibrosis by ≥1 stage and no worsening of steatohepatitis as defined as no increase in NAS for ballooning, inflammation, or steatosis. Post-Hoc Analysis.
Loomba et al, *N Engl J Med* 2023;389:998.
Presented AASLD 2024.

In Patients on Background GLP-1 Therapy, Greater Reductions Observed on Key Markers when PGZ is Added Versus Placebo

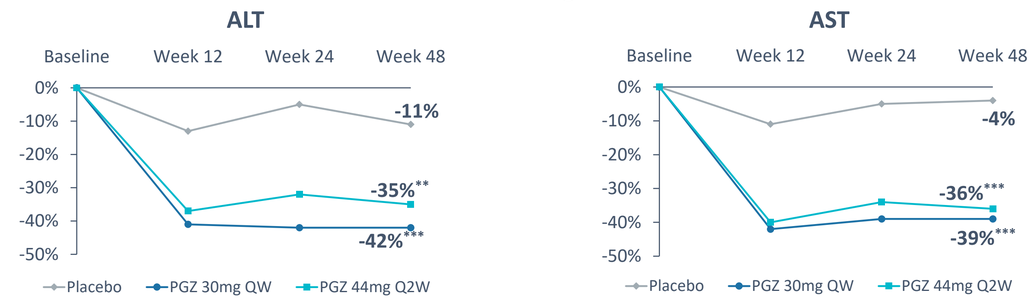


Source: Full Analysis Set. ELF and ALT reported as LS mean change from baseline; VCTE and HbA1c reported as median change (absolute) from baseline; MRI-PDFF reported as median percent change from baseline. Post-hoc analysis. Pooled data include 30mg QW and 44mg Q2W.

- Acceptable tolerability with nausea as most common AE. No treatment-related discontinuations.

PGZ Demonstrated Significant Sustained Improvements in Markers of Liver Injury/Inflammation (ALT and AST) over 48 Weeks

LS Mean Percent Change from Baseline



>85% of ALT responders^ maintained benefit from week 24 to week 48 on both PGZ doses

**p<0.01, ***p<0.001 versus placebo. Analysis via mixed model with repeated measure (MMRM). Baseline values based on Randomized Analysis set for total patients; results based on Full Analysis Set. ^ALT responder defined as ≥17 U/L reduction from baseline. Presented at EASL 2024.

PGZ Was Well Tolerated Across All Patients In ENLIVEN Most TEAEs were Grade 1 and Grade 2

Drug-related TEAEs in ≥10% of Patients Through 48 Weeks

Preferred Term	Placebo (n=50)	15mg QW (n=21)	30mg QW (n=72)	44mg Q2W (n=57)
Diarrhea	3%	24%	17%	9%
Nausea	1%	14%	21%	18%
Injection site erythema	4%	14%	14%	5%
Injection site rash	2%	0	10%	4%
Increased appetite	2%	10%	13%	5%

- At week 48, no statistically significant or clinically meaningful changes were observed in blood pressure, bone biomarkers or DXA with PGZ 30mg QW or 44mg Q2W relative to placebo.

Related discontinuations: Diarrhea [15mg QW] ; Diarrhea [30mg QW]; Nausea [30mg QW]; Diarrhea [30mg QW]; ISR erythema [30mg QW]; Pancreatitis [44mg Q2W]; Nausea [44mg Q2W]. Detailed safety and tolerability presented in Loomba et al, NEJM 2023; 48-week data presented at EASL 2024.Source: Safety Analysis Set. AE table cutoff ≥10% of patients for placebo, 30mg QW and 44mg Q2W doses. Bone biomarkers were CTX and P1NP.

CONCLUSIONS

- Treatment with PGZ in MASH patients with F2/F3 fibrosis led to highly significant fibrosis regression and MASH resolution at 24 weeks.
- PGZ treatment demonstrated significant improvements across various non-invasive tests (NIT) at 24 weeks with sustained effects up to 48 weeks.
- Week 48 data continue to support a favorable safety and tolerability profile.
- The ENLIGHTEN MASH program comprises both cirrhotic and noncirrhotic phase 3 studies and is currently underway to confirm these results.