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Week 48 Results From the Phase 2b ENLIVEN Extension Study Investigating Pegozafermin for the Treatment of Metabolic Dysfunction-Associated Steatohepatitis with Fibrosis

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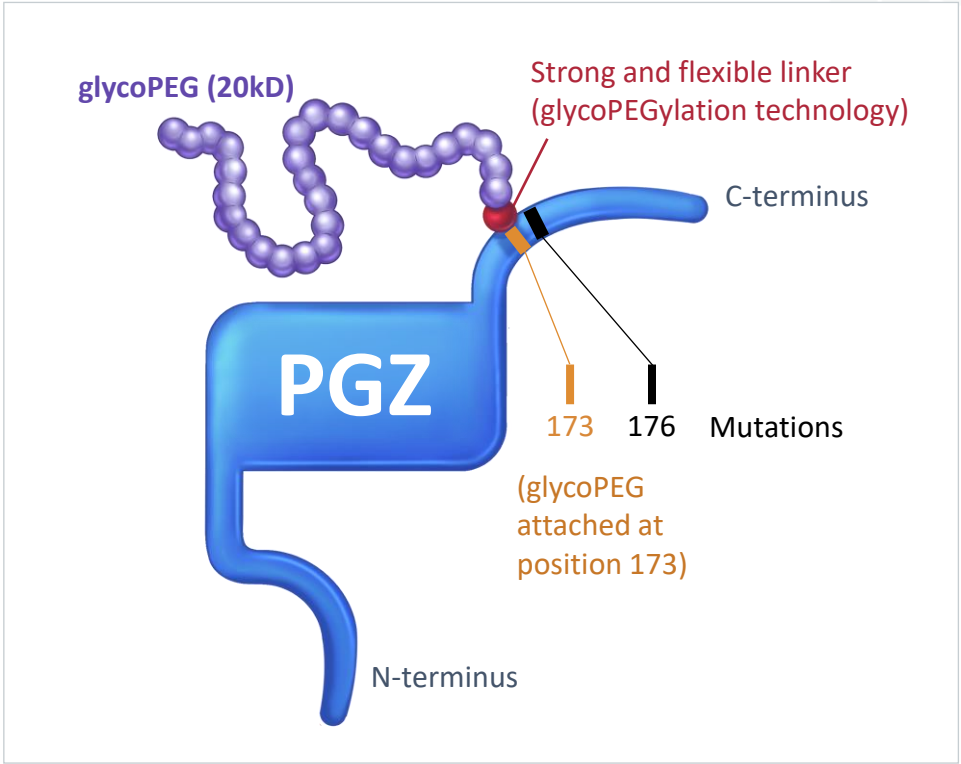
Pegozafermin is an FGF21 Analog Optimally Engineered to Balance Efficacy and Long Dosing Interval

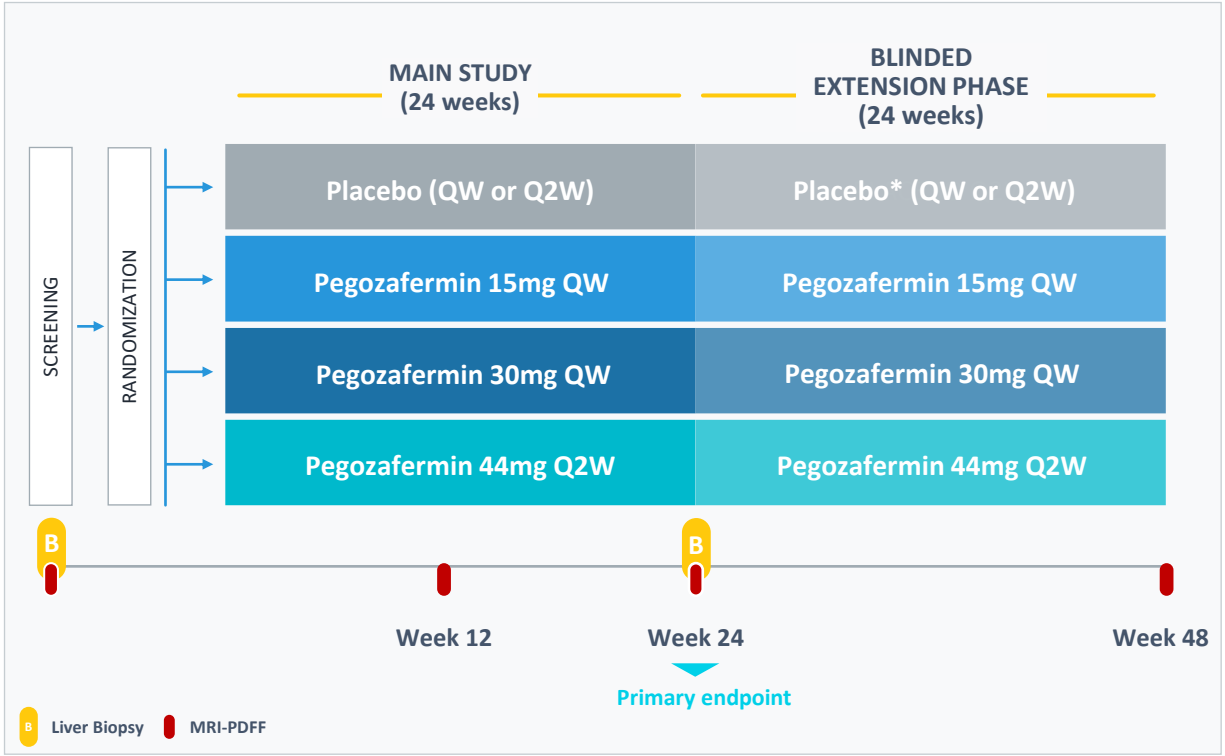
- The half-life of native FGF21 is 1-2 h; half-life of pegozafermin is 55 to 100 h[1,2]
- GlycoPEGylation prevents C-terminal degradation[3]
- Mutation at position 173 prevents cleavage of FGF21 structure by FAP[3,4]
- Low nanomolar potency against FGF receptors 1c, 2c, 3c, similar to native FGF21



FAP, fibroblast activation protein; FGF21, fibroblast growth factor 21; PEG, polyethylene glycol

1. Loomba R, et al. *Lancet Gastroenterol Hepatol.* 2023;8(2):120-132. 2. Loomba R, et al. Poster presented at the American Association for the Study of Liver Diseases (AASLD) Meeting, November 8-12, 2019 (Boston, MA). Accessed October 7, 2022. https://www.89bio.com/wp-content/uploads/2019/11/89Bio_SAD-poster_final.pdf 3. Tillman EJ, Rolph T. *Front Endocrinol.* 2020;11:601290. 4. Dunshee DR, et al. *J Biol Chem*. 2016;291(11):5986-5996.

ENLIVEN – Study Design for Phase 2b Trial



PRIMARY ANALYSIS POPULATION

- F2-F3 NASH; NAS ≥4

PRIMARY ENDPOINTS

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

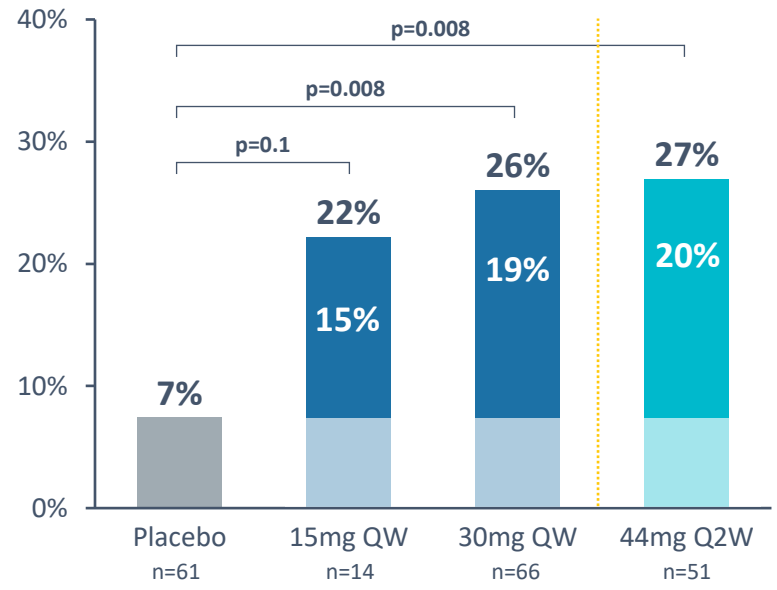
KEY SECONDARY EFFICACY ENDPOINTS

- ≥2-point change in NAS with no worsening of fibrosis
- Non-invasive liver markers (liver fat, liver injury, fibrosis markers)

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

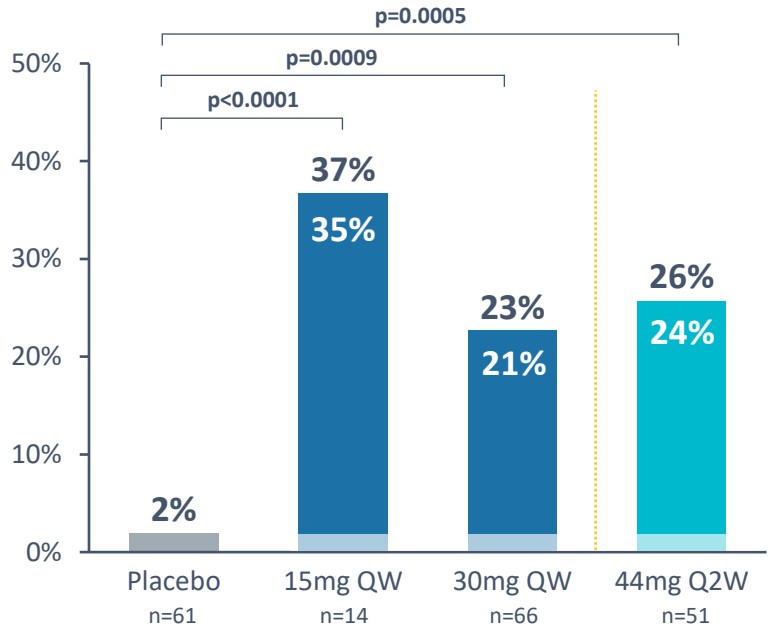
Primary Endpoints: Pegozafermin Demonstrated Statistical Significance on Fibrosis Improvement and MASH Resolution at 30mg QW and 44mg Q2W Dose

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



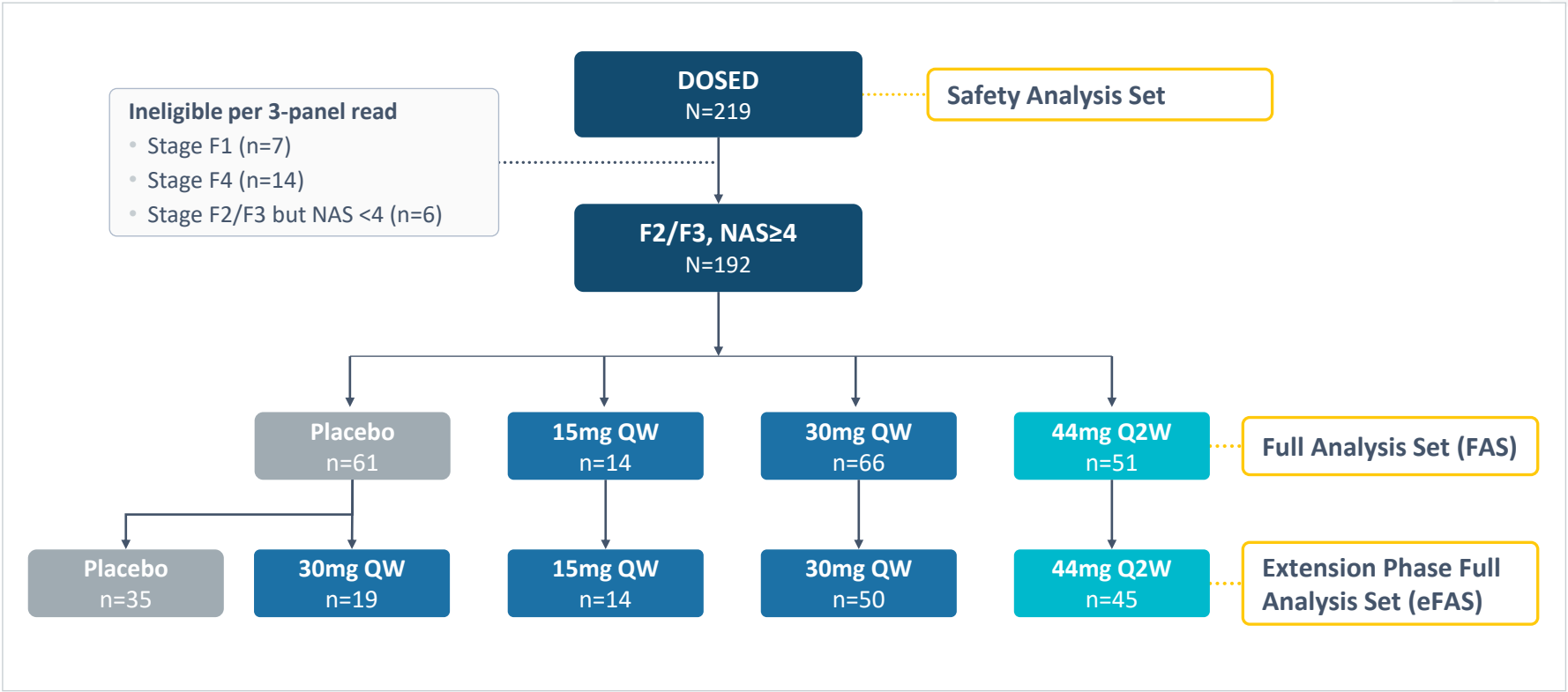
Relative Risk*	1.0	18.8	11.8	13.5

*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).

Objective

- To evaluate the safety and efficacy of PGZ treatment (30mg QW and 44mg Q2W) compared to placebo on non-invasive tests over the blinded 24-week extension phase of ENLIVEN (48-week data).

ENLIVEN Patient Disposition and Analysis Sets



Analysis Sets were prospectively defined
MRI-PDFF Analysis Set = all patients in FAS with baseline and at least one post-baseline MRI-PDFF assessment (n=181).

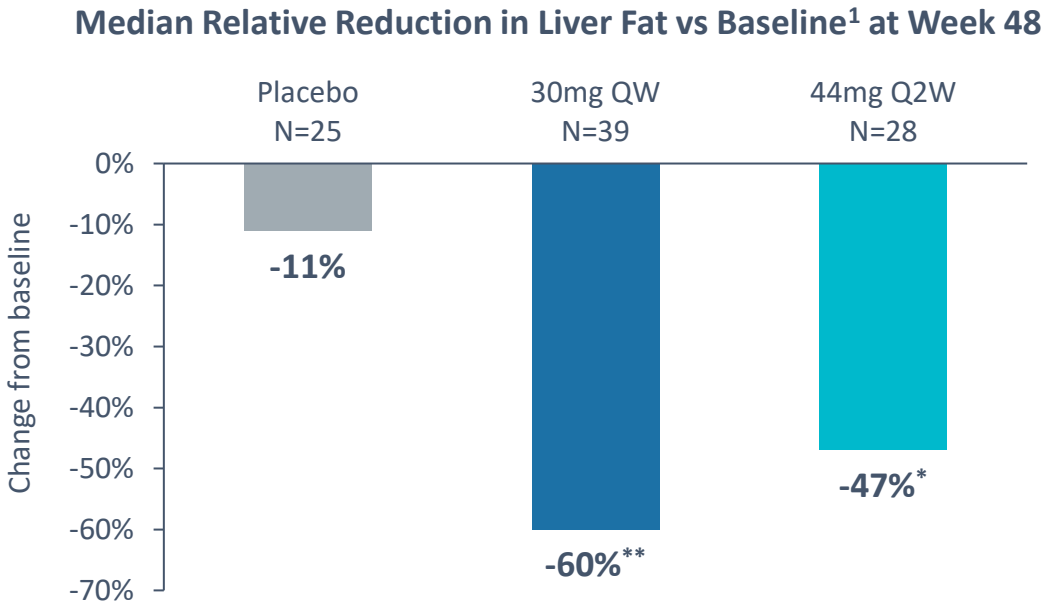
Baseline Characteristics Well Balanced Across Extension Phase Groups

Parameter Mean or %	Placebo (n=35)	15mg QW (n=14)	30mg QW (n=50)	44mg Q2W (n=45)	Placebo (Main) and 30mg QW(Extension) (n=19)	Total (n=163)
Age (years)	56	54	54	56	57	**55**
Female	63%	50%	66%	69%	58%	**64%**
BMI (kg/m^2)	38	39	36	36	38	**37**
Type 2 Diabetes	66%	86%	60%	62%	79%	**66%**
Fibrosis Stage (% F3)	69%	64%	68%	60%	68%	**66%**
NAFLD Activity Score	5.1	5.1	5.3	5.2	5.4	**5.2**
Liver Fat Content (MRI-PDFF)	16.7%	16.2%	16.5%	16.2%	16.7%	**16.5%**
Liver Stiffness (VCTE, kPa)	13.2	11.5	12.5	12.7	16.6	**13.1**
PRO-C3 (ng/mL)*	43	45	43	41	41	**43**
ALT (U/L)	46	60	63	56	49	**56**
AST (U/L)	40	52	49	41	41	**44**
HbA1c, overall population (%)	6.7	7.1	6.7	6.6	6.7	**6.7**
Triglycerides (mg/dL)	172	207	181	160	169	**174**

Baseline characteristics were consistent with baseline characteristics reported in randomized analysis set (n=222)

*PROC-C3 were analyzed on Cobas e801
Source: Full Analysis Set.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; PRO-C3, N-terminal type III collagen propeptide; VCTE, Vibration-controlled transient elastography.

Pegozafermin Maintained Robust Liver Fat Reduction Measured by MRI-PDFF at Week 48

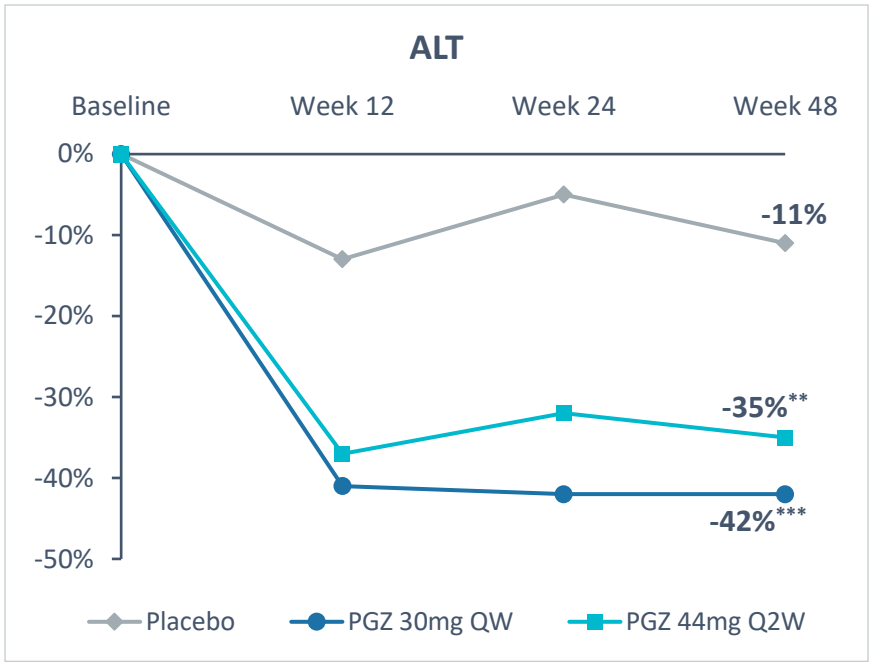


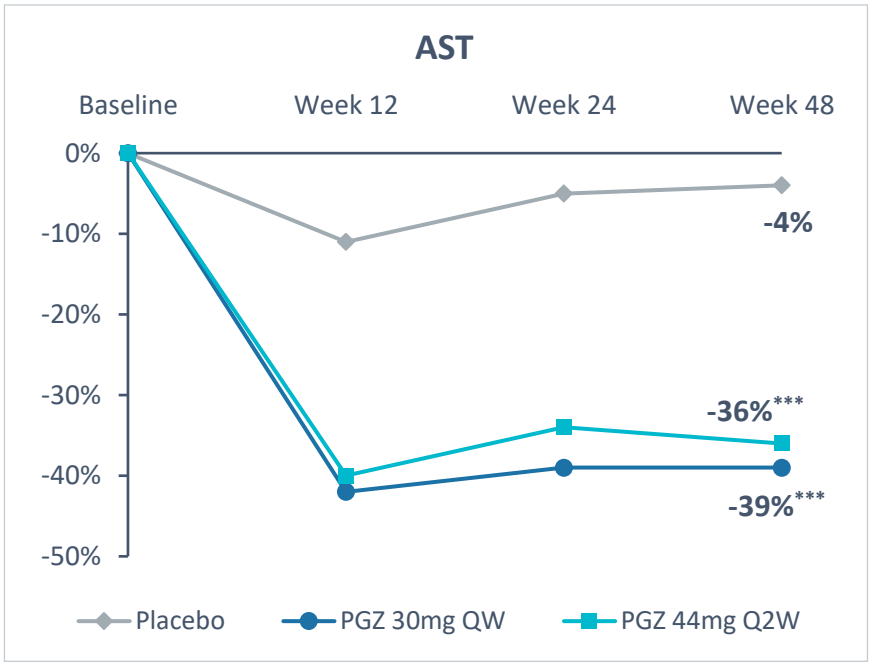
84% of super-responders^ on PGZ 30 mg QW at week 24 maintained benefit at week 48

[1]Analysis via non-parametric statistical method.
MRI-PDFF Analysis Set in patients with >10% liver fat at baseline.
^Super-responders defined as ≥50% reduction from baseline
*p<0.05, **p<0.01 versus placebo; super-responder defined as ≥50% relative reduction from baseline

Pegozafermin Retained Improvements in Markers of Liver Injury/Inflammation (ALT and AST) over 48 Weeks

Mean Percent Change from Baseline

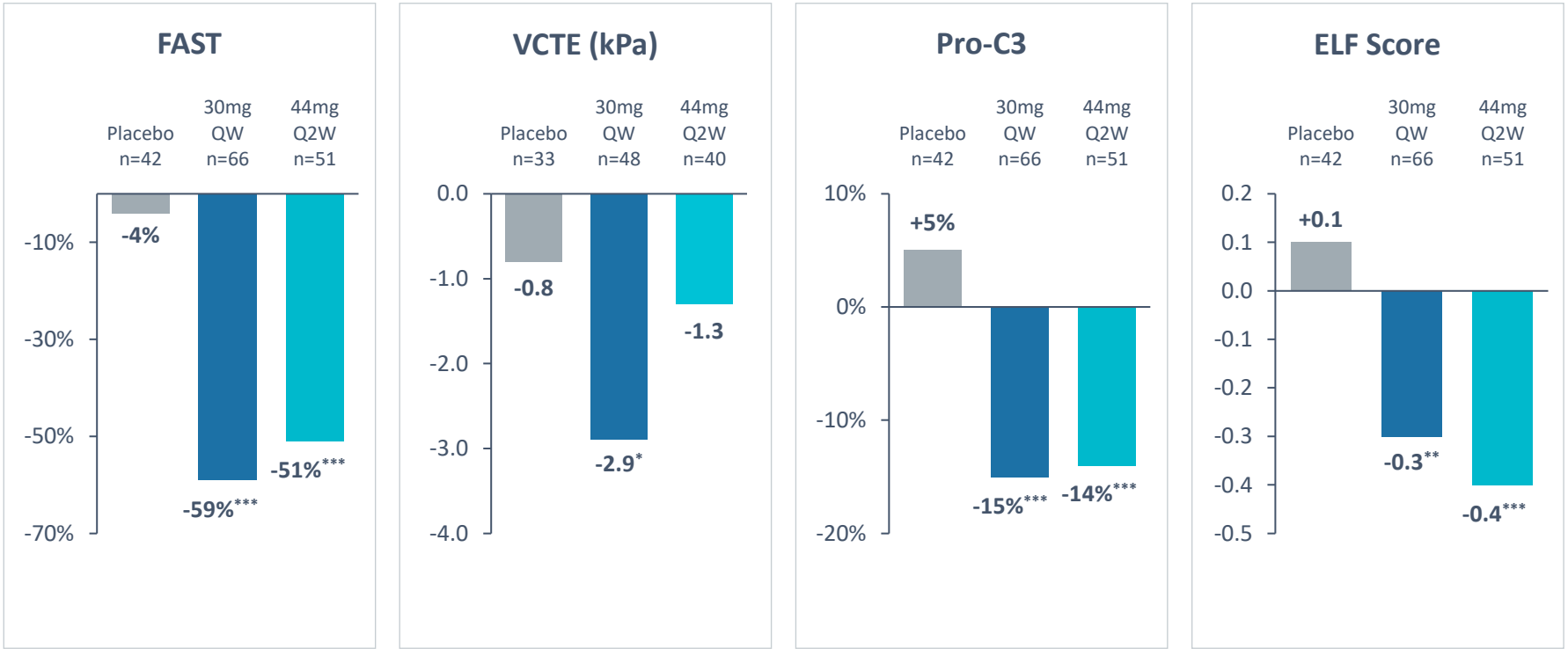




>85% of ALT responders ^ maintained benefit from week 24 to week 48 on both PGZ doses

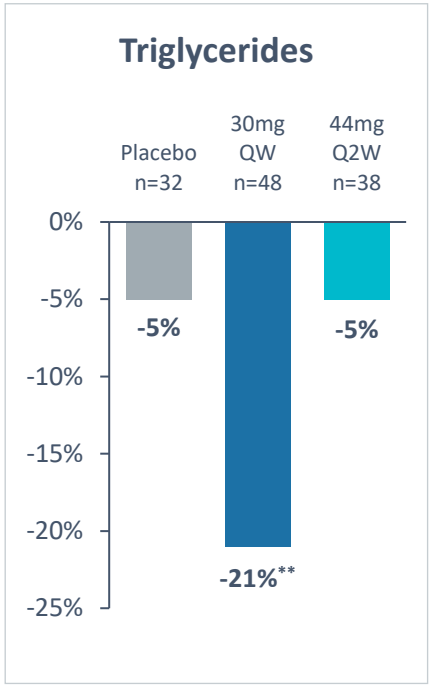
**p<0.01, ***p<0.001 versus placebo. Analysis via mixed model with repeated measure (MMRM). Baseline values based on Randomized Analysis set for total patients; results based on Full Analysis Set. ^ALT responder defined as ≥17 U/L reduction from baseline

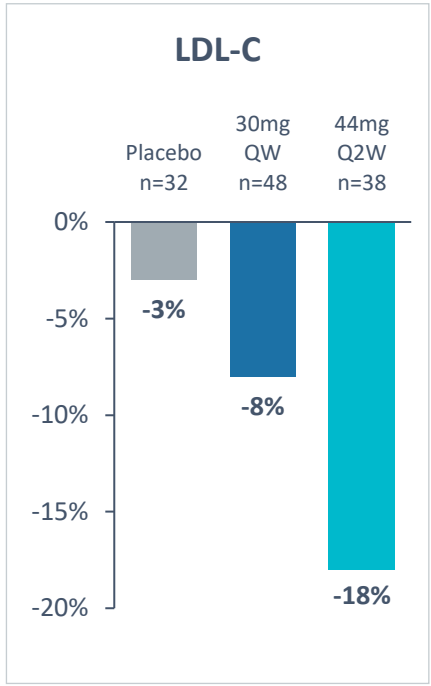
Pegozafermin Demonstrated Sustained Significant Reductions in NITs of Liver Inflammation and Fibrosis at Week 48

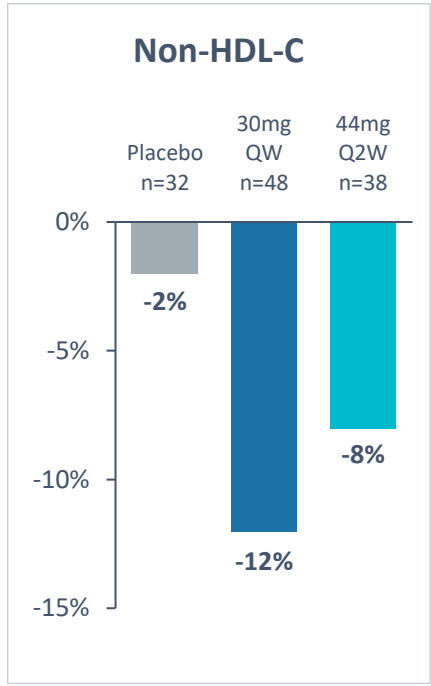


Analysis via MMRM for FAST, PRO-C3 and ELF score; via non-parametric statistical method for VCTE median relative reduction
Source: Full Analysis Set, VCTE results from patients with week 48 assessment.
*p<0.05, **p<0.01, ***p<0.001 versus placebo.

Pegozafermin Demonstrated Continued Benefit in Metabolic Endpoints Over 48 Weeks







Analysis via MMRM for HbA1c and non-parametric statistical method for Triglycerides, LDL-C and Non-HDL-C; **p<0.01 versus placebo.
Source: Full Analysis Set; Median change from baseline except for HbA1c; HbA1c in patients with T2DM and baseline >7.0% (n=53)

Long-term Treatment with Pegozafermin Results in Sustained Improvements over a Wide Range of Liver NITs

	Placebo Week 24 (n=42)	Placebo Week 48 (n=35)	30mg QW Week 24 (n=66)	30mg QW Week 48 (n=50)	44mg Q2W Week 24 (n=51)	44mg Q2W Week 48 (n=45)
MRI-PDFF	-6%	-11%	-56%	-60%	-60%	-47%
ALT	0%	-11%	-42%	-42%	-32%	-35%
AST	-2%	-4%	-39%	-39%	-34%	-36%
Pro-C3	+6%	+2%	-18%	-15%	-17%	-14%
FAST	-3%	-1%	-56%	-59%	-57%	-51%
VCTE (kPa)	-0.1	-0.8	-2.8	-2.9	-1.5	-1.3
ELF score	+0.2	+0.1	-0.3	-0.3	-0.3	-0.4

Full Analysis Set; preliminary data
LS mean change from baseline except for MRI and VCTE which are medians. VCTE n=139 at week 24; n=121 at week 48
MRI-PDFF in patients with >10% liver fat at baseline (n=108 at week 24; n=92 at week 48)

Reliable Treatment Effect Observed in Placebo Patients Re-randomized to Pegozafermin During the Extension Phase

Change from Baseline

Parameter	Main Study Placebo n=19	Extension Phase 30mg QW n=19
MRI-PDFF	-21%	-63%
ALT	-2%	-32%
AST	-2%	-31%
PRO-C3	+8%	-17%
FAST	-14%	-53%
VCTE (kPa)	-0.7	-2.4
ELF score	+0.1	-0.2

19 patients were re-randomized from placebo to 30mg QW at week 24 and continued through week 48

Mean change from baseline except for VCTE which is median
MRI-PDFF in patients with >10% liver fat at baseline (n=17); Full Analysis Set

Pegozafermin 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 30 mg QW or 44 mg Q2W relative to placebo.

	Placebo	15mg QW	30mg QW	44mg Q2W
Drug-related AEs leading to discontinuation	0	5%[a]	6%[b]	4%[c]
Drug-related Serious Adverse Event (SAE)	0	0	0	2%[c]

Related discontinuations: [a] Diarrhea [15 mg QW] ; [b] Diarrhea [30 mg QW]; Nausea [30 mg QW]; Diarrhea [30 mg QW]; ISR erythema [30 mg QW]; [c] Pancreatitis [44 mg Q2W]; Nausea [44 mg Q2W].

Detailed safety and tolerability presented in Loomba et al, NEJM 2023
Source: Safety Analysis Set. AE table cutoff ≥10% of patients for placebo, 30mg QW and 44mg Q2W doses. Bone biomarkers were CTX and P1NP.

Conclusion

- Pegozafermin treatment demonstrated significant improvements across various non-invasive tests (NIT) for hepatic steatosis, inflammation and fibrosis at 24 weeks; effects were sustained up to 48 weeks

- Re-randomization of placebo patients to PGZ 30mg QW confirmed reproducibility of the treatment effect seen at 24 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