Pegozafermin for the treatment of non-alcoholic steatohepatitis patients with F2/F3 fibrosis: A multi-center, randomized, double-blind, placebo-controlled Phase 2b trial

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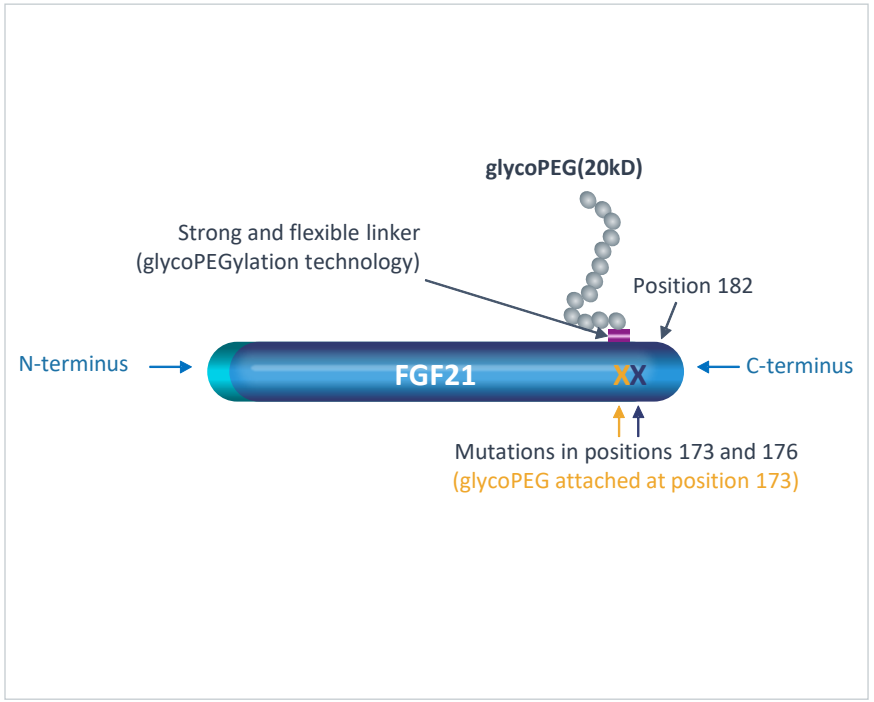
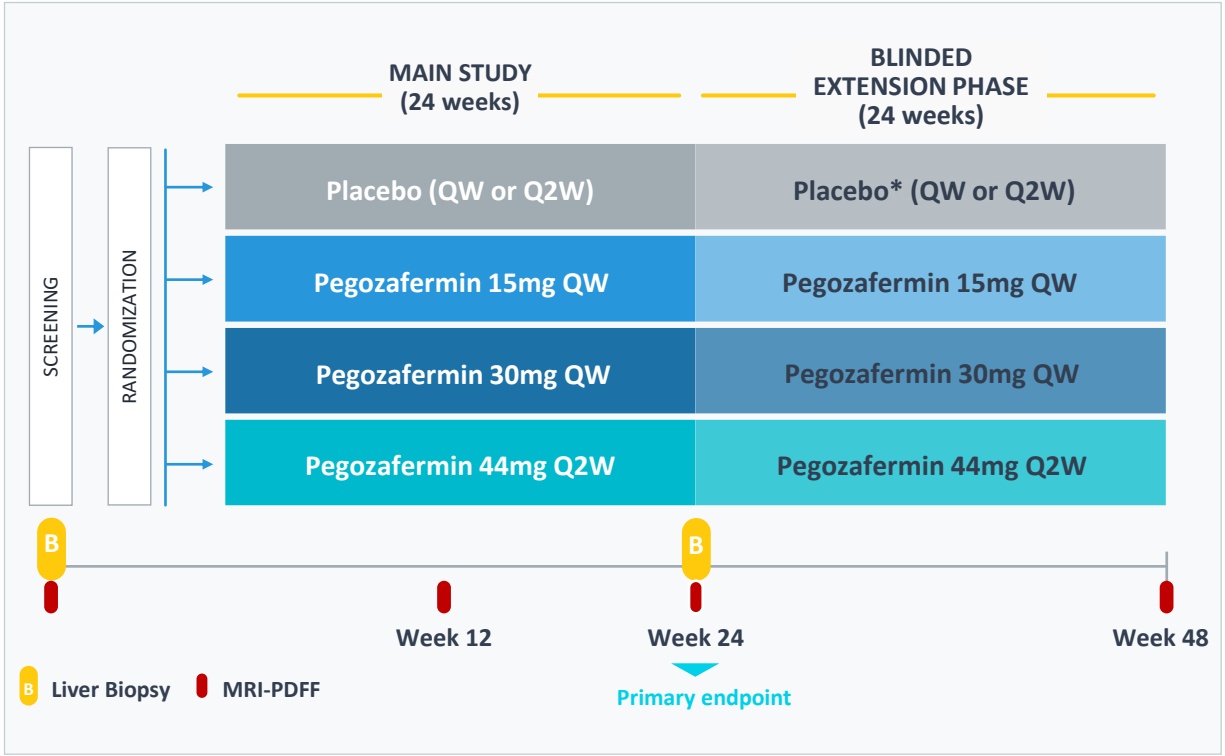
Pegozafermin is an FGF21 Analog Optimally Engineered to Balance Efficacy and Long Dosing Interval



- **Built using glycoPEGylation technology with site-specific mutations**
- **Low nanomolar potency against FGF receptors 1c, 2c, 3c, similar to native FGF21**

ENLIVEN – Study Design for Phase 2b Trial



PRIMARY ANALYSIS POPULATION

- F2-F3 NASH; NAS ≥4

PRIMARY ENDPOINTS

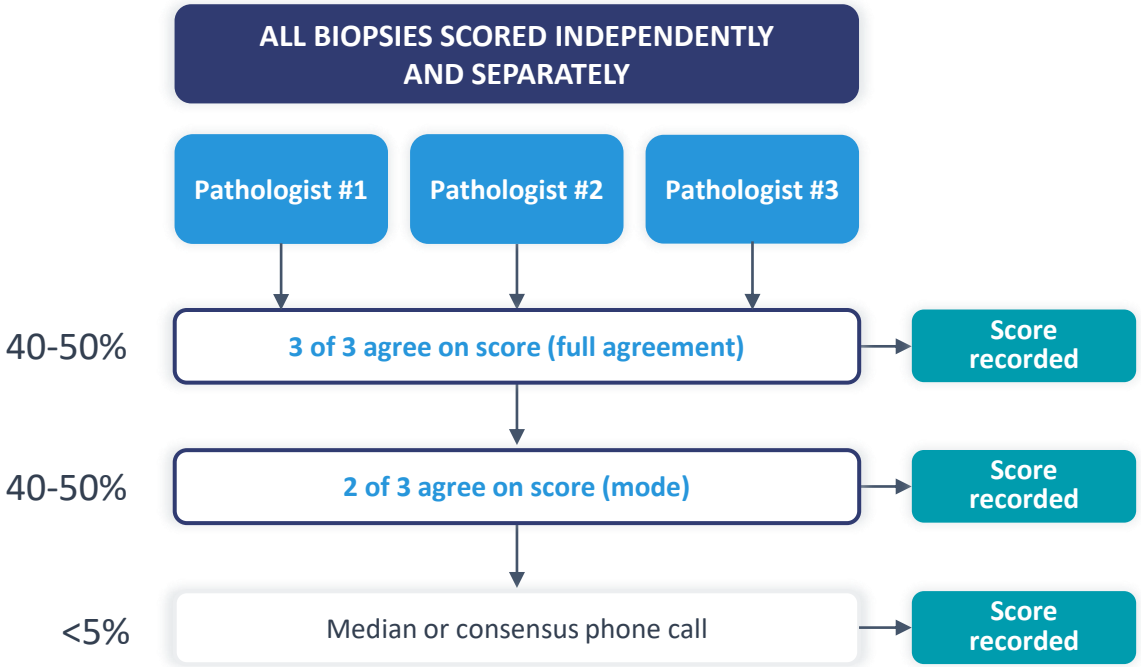
- ≥1-stage fibrosis improvement with no worsening of NASH[1]
- NASH resolution with no worsening of fibrosis[2]

KEY SECONDARY EFFICACY ENDPOINTS

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

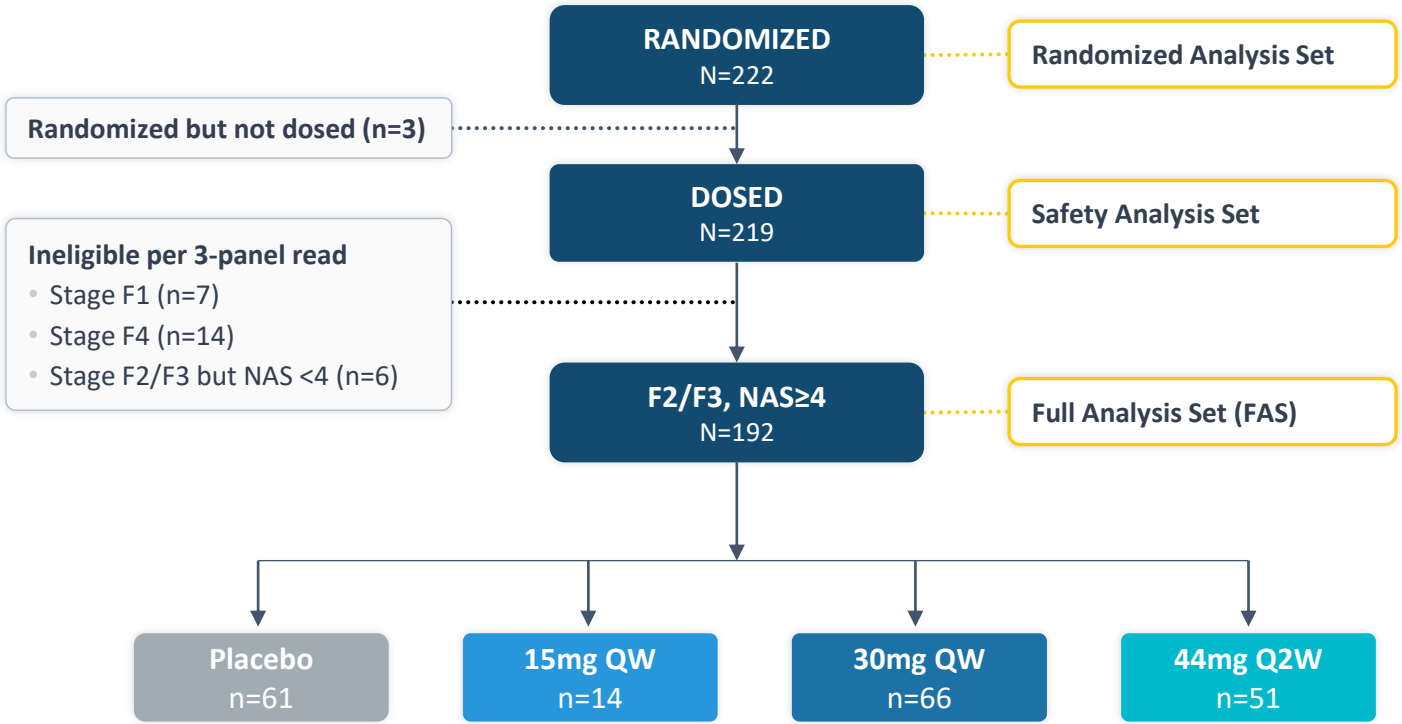
1 Improvement in liver fibrosis by ≥1 stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).
2 Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis (FDA draft guidance).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

ENLIVEN Used Objective Methodology Designed to Reduce Histology Scoring Biases and Variability



<1% of scores required consensus phone call

Patient Disposition and Analysis Sets



Analysis Sets were prospectively defined
Completer Analysis Set = FAS subjects with biopsies at both baseline and Week 24 (n=164).
MRI-PDFF Analysis Set = all subjects in FAS with baseline and at least one post-baseline MRI-PDFF assessment (n=181).

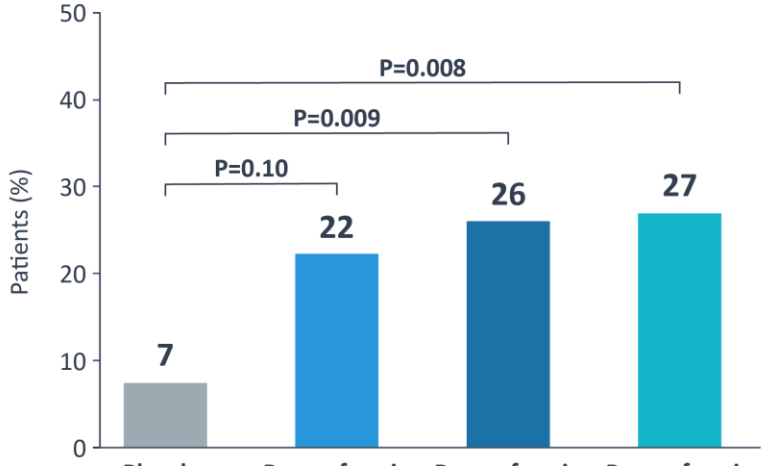
Baseline Characteristics Well Balanced Across Dose Groups

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.

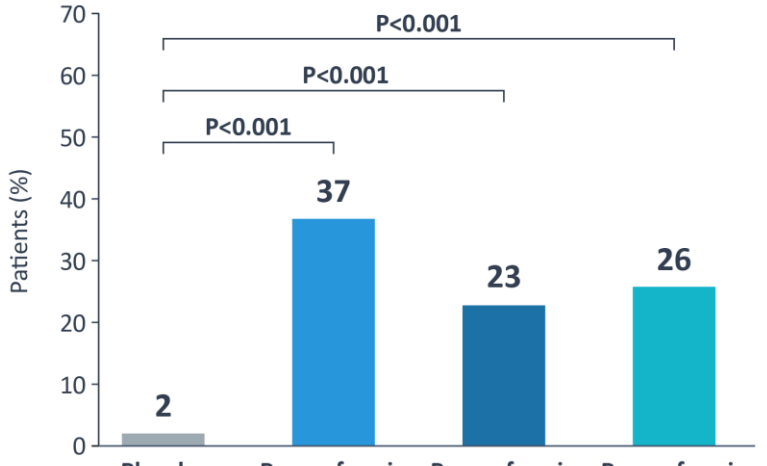
Pegozafermin Treatment Led to a Significant Improvement on Primary Endpoints at Week 24

Fibrosis Improvement ≥1 Stage Without Worsening of NASH



	Placebo (N=61)	Pegozafermin 15mg QW (N=14)	Pegozafermin 30mg QW (N=66)	Pegozafermin 44mg Q2W (N=51)
Relative risk	1	2.9	3.7	4.1
95% CI		0.8, 10.8	1.2, 10.8	1.3, 12.9

NASH Resolution Without Worsening of Fibrosis



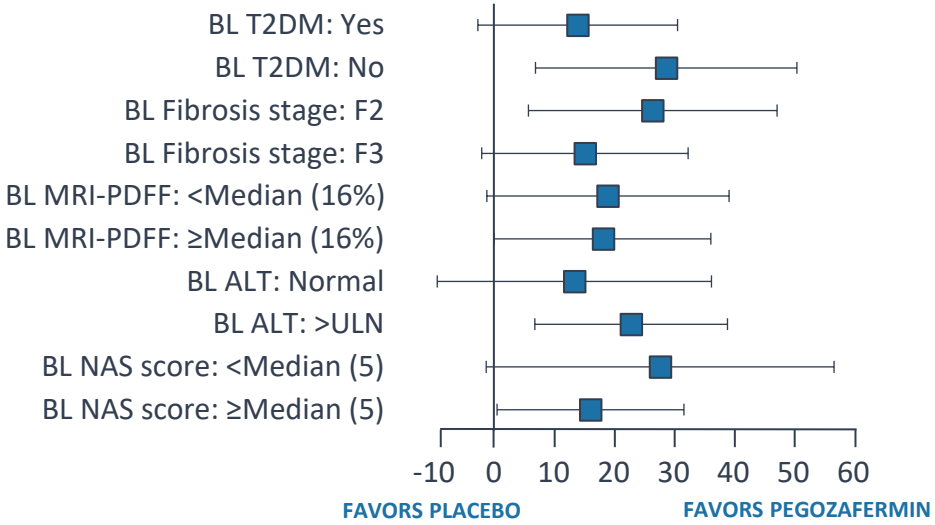
	Placebo (N=61)	Pegozafermin 15mg QW (N=14)	Pegozafermin 30mg QW (N=66)	Pegozafermin 44mg Q2W (N=51)
Relative risk	1	18.9	12.8	12.7
95% CI		3.2, 113.1	1.7, 97.1	1.9, 84.5

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).

Pegozafermin Showed Consistent and Significant Benefit in Achieving Fibrosis Improvement Across Prespecified Subgroups

Pegozafermin 30mg QW

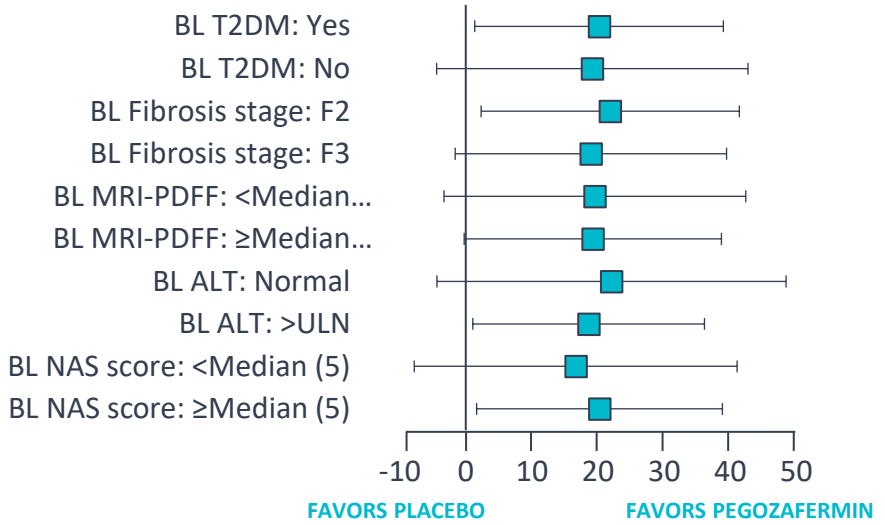
Proportion Achieving Fibrosis Improvement



Est. proportion difference (95% CI)

Pegozafermin 44mg Q2W

Proportion Achieving Fibrosis Improvement

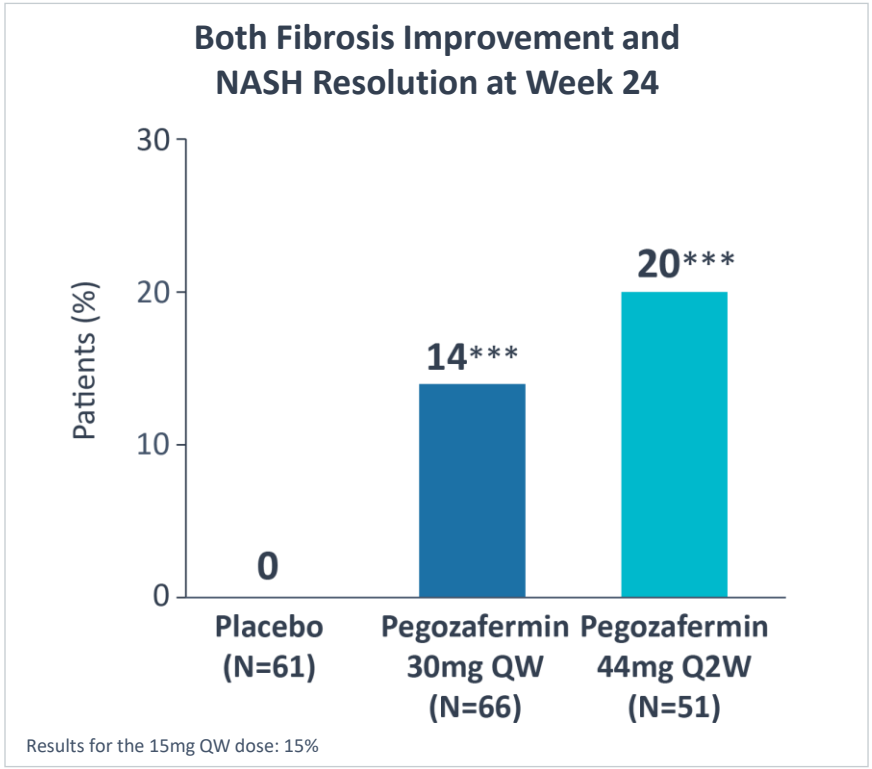


Est. proportion difference (95% CI)

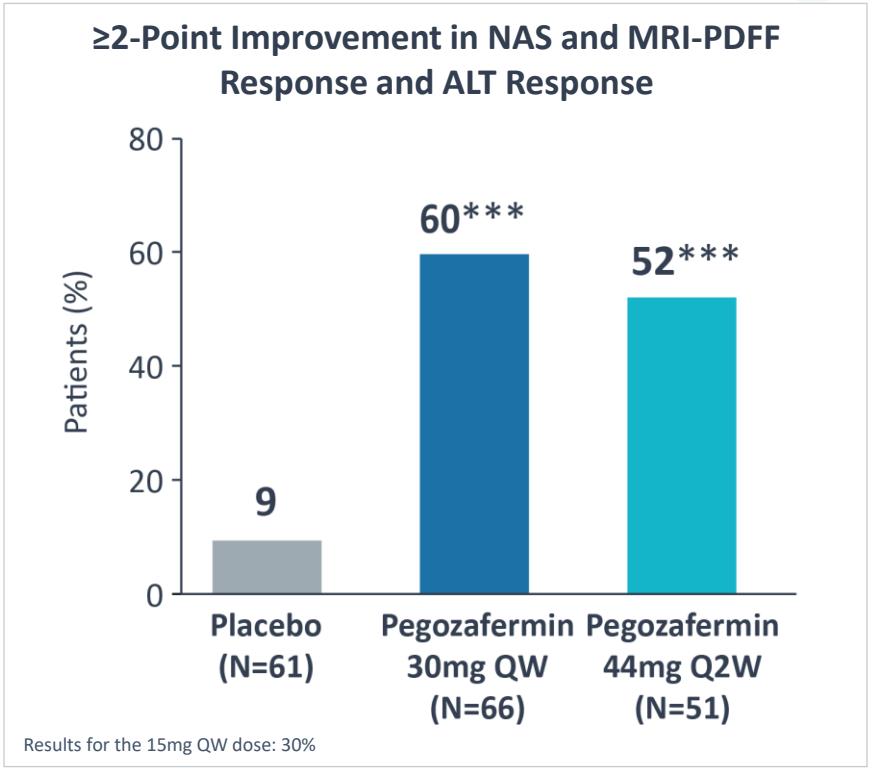
Source: Full Analysis Set

ALT, alanine aminotransferase; BL, baseline; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAS, Nonalcoholic fatty liver disease Activity Score; NASH, nonalcoholic steatohepatitis; Q2W, every 2 weeks; QW, once weekly; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal.

Statistically Significant Results on the Combined Endpoint of Fibrosis Improvement and NASH Resolution



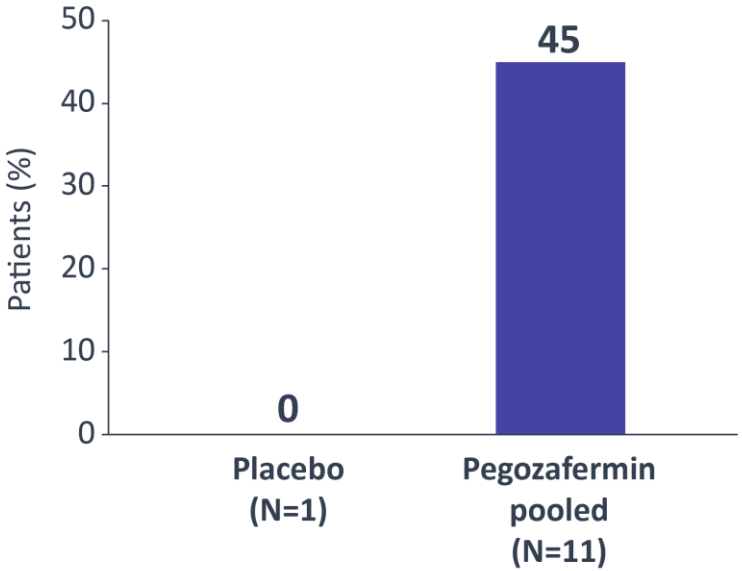
Results for the 15mg QW dose: 15%



Results for the 15mg QW dose: 30%

Source: Full Analysis Set; multiple imputation analysis via Cochran-Mantel-Haenszel (CMH) test stratified by T2DM status (yes vs. no) and fibrosis stage (F2 vs. F3).
MRI-PDFF responder defined as ≥30% reduction in liver fat content; ALT responder defined as ≥17U/L reduction.
MRI-PDFF, magnetic resonance imaging-proton density fat fraction; ALT, alanine transaminase
***p<0.001 versus placebo.

Fibrosis Improvement Without Worsening of NASH in 45% of Patients with F4 Fibrosis at Baseline



12/14 F4 patients enrolled in ENLIVEN had follow-up biopsies at week 24

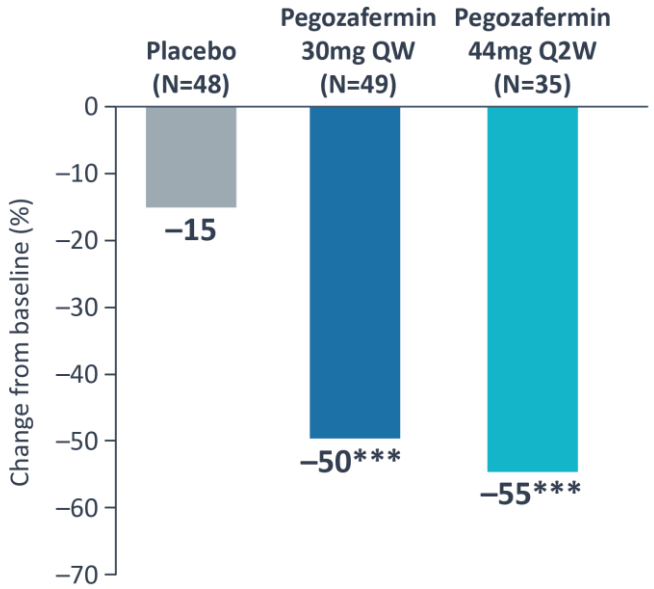
Parameter	Mean Change from Baseline on Pegozafermin (n=12)
MRI-PDFF	-33%
ALT	-53%
AST	-31%
ELF	-0.4 units
cT1	-87 msec

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.

Pegozafermin Demonstrated Robust Liver Fat Reduction with High Responder Rates by MRI-PDFF at Week 24

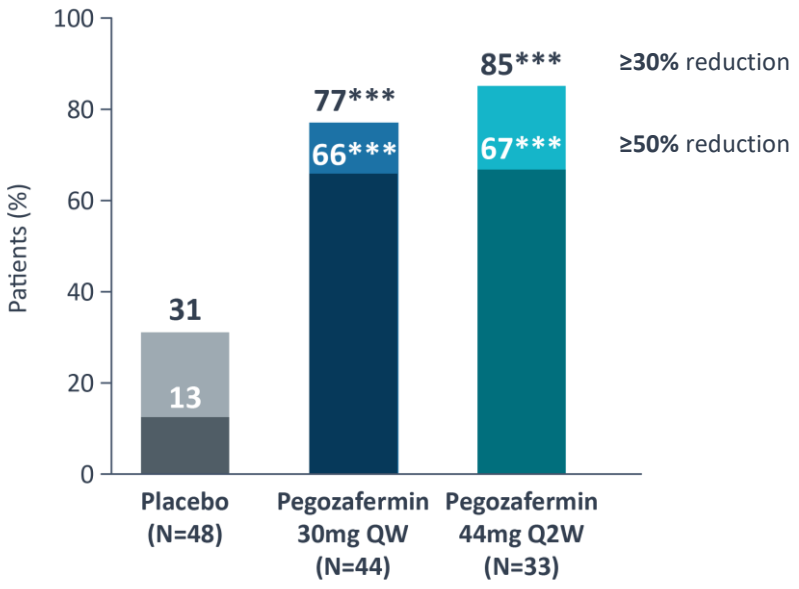
MRI-PDFF Analysis Set in subjects with >10% liver fat at baseline

Mean Relative Reduction in Liver Fat vs Baseline[1] at Week 24



Results for the 15mg QW dose: -33%

Patients Achieving ≥30% and ≥50% Reduction in Hepatic Fat Fraction Versus Baseline[2]

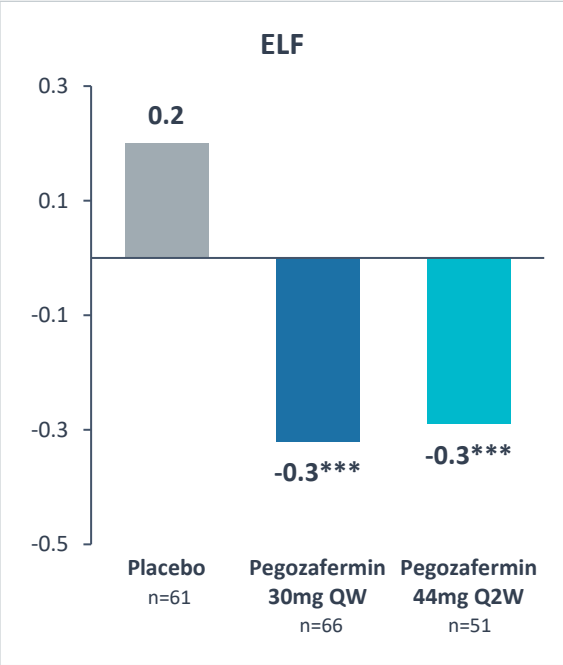


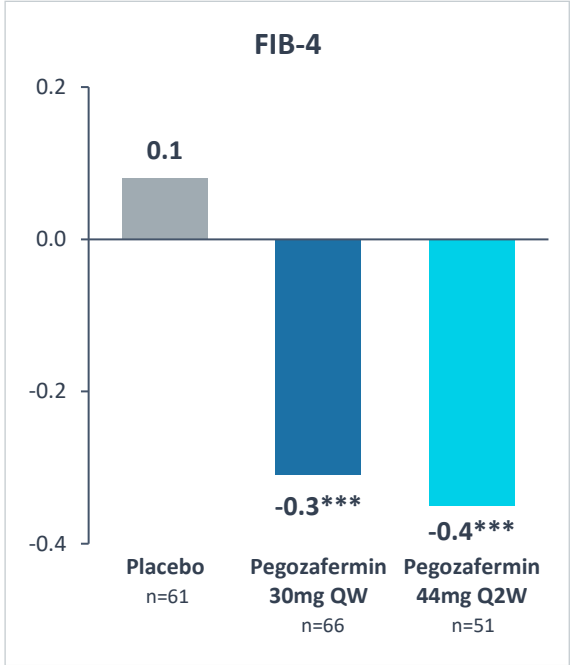
Results for the 15mg QW dose: 50%; 33%

[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.

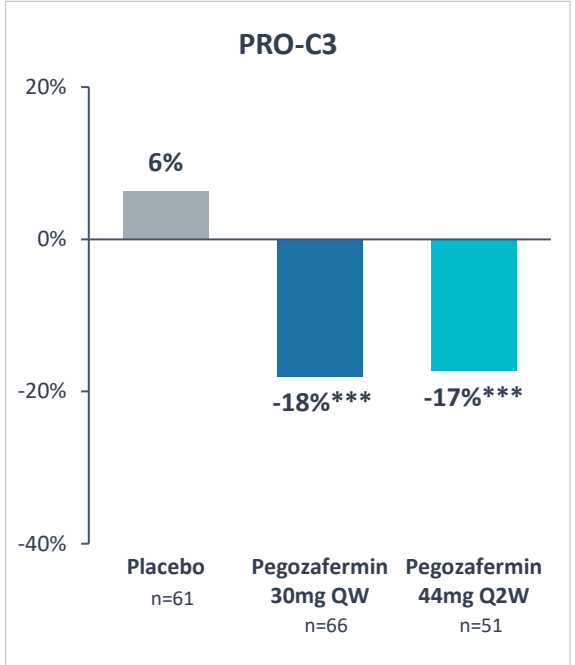
Pegozafermin Demonstrated Significant Improvements on Non-Invasive Markers (NITs) for Fibrosis

Absolute Change from Baseline at Week 24





Percent Change from Baseline at Week 24

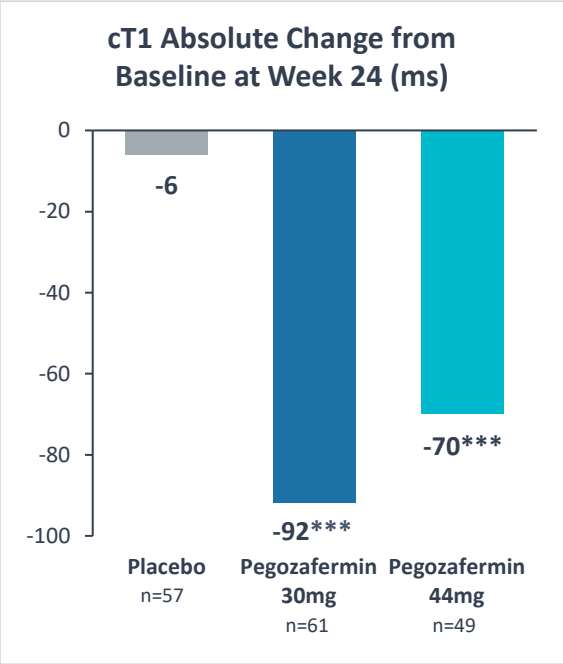


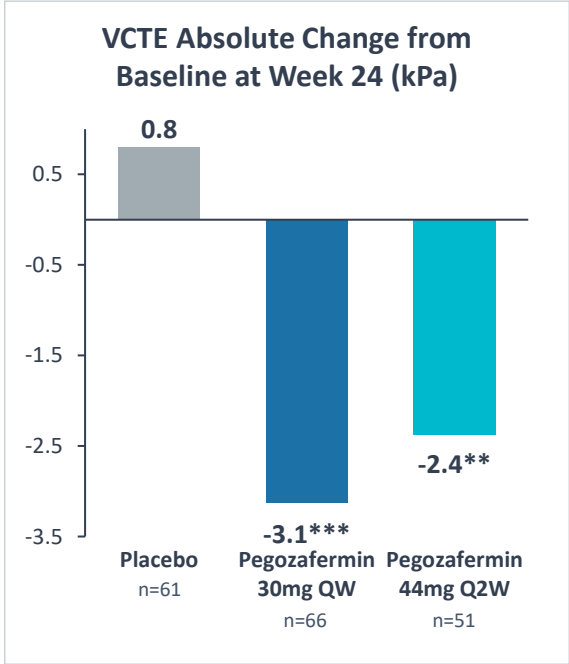
Results for the 15mg QW dose: ELF: -0.33 (n=14); FIB-4: -.45 (n=14); PRO-C3: -5% (n=14).

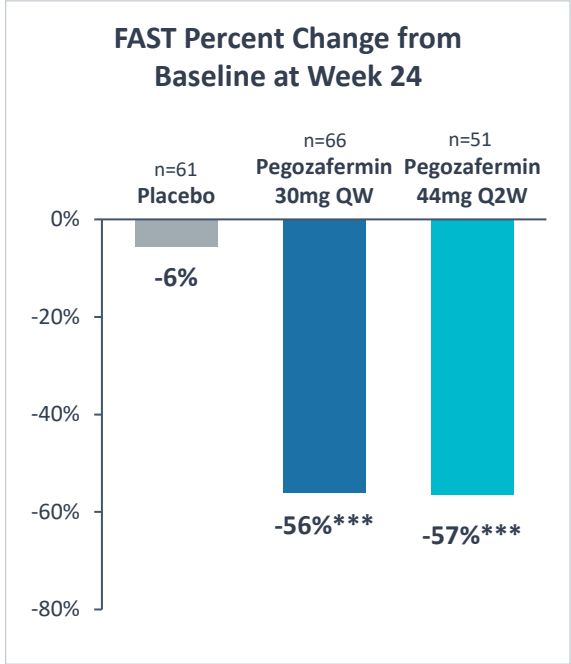
Source: Full Analysis Set. NITs reported as LS means with changes from baseline (absolute or %)

***p<0.001 versus placebo.

Pegozafermin Demonstrated Significant Reductions in Non-Invasive Markers (NITs) of Hepatic Inflammation and Fibrosis



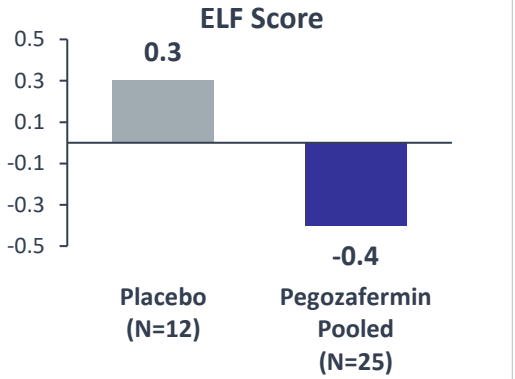


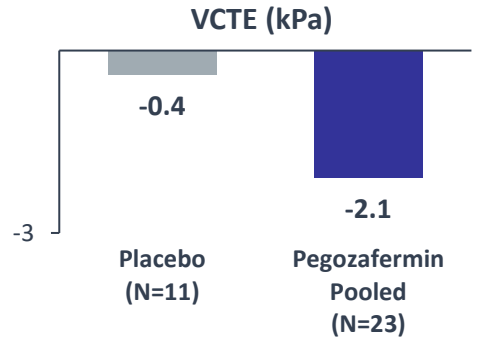


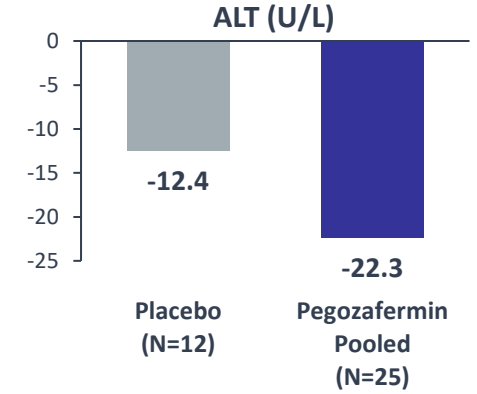
Results for the 15mg QW dose: cT1: -47 (n=10); VCTE: -1.42 kPa (n=14); FAST:-33% (n=14).

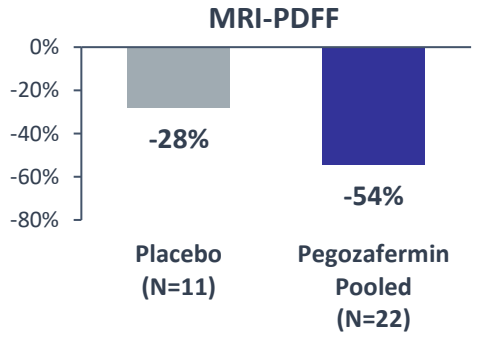
Source: Full Analysis Set for FibroScan and PRO-C3 assessments and MRI-PDFF analysis set for cT1, Analysis via MMRM for cT1 and PRO-C3, ANCOVA for VCTE. A patient is designated a cT1 responder with ≥80 msec reduction as compared to baseline. cT1 analysis was performed at sites where available.
*p<0.05, **p<0.01 ,***p<0.001 versus placebo.

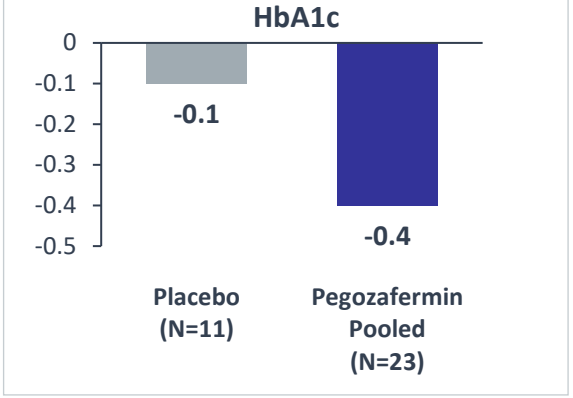
In Patients on Background GLP-1 Therapy, Greater Reductions Observed on Key Markers when PGZ is Added Versus Placebo











- **Acceptable tolerability with nausea as most common AE. No treatment-related discontinuations**
- **Pooled results include 30mg and 44mg groups as results were consistent across both groups.**

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

Pegozafermin Was Well Tolerated Across Doses
Low incidence of treatment-related TEAEs

Drug-related TEAEs in ≥10% of patients

Preferred Term	Placebo (n=69)	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	3%	14%	14%	5%
Injection site rash	1%	0	10%	4%
Increased appetite	0	10%	13%	5%

Most TEAEs were grade 1 or 2. No DILI or tremor reported. No clinically relevant changes observed on vitals, bone biomarkers or DXA.

	Placebo	15mg QW	30mg QW	44mg Q2W
Drug-related AEs leading to discontinuation	0	5%[a]	6%[b]	2%[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].
Unrelated discontinuations: Angina [placebo]; Colon CA [30 mg QW]; COVID-19 [30 mg QW].

Source: Safety Analysis Set. AE table cutoff ≥10% of patients for placebo, 30mg QW and 44mg Q2W doses.

Conclusions

- **Pegozafermin significantly improved:**
  - Fibrosis improvement without worsening of NASH
  - NASH resolution without worsening of fibrosis
  - Key non-invasive tests for NASH
- **Treatment effects were consistent across various subgroups, including in subjects on background GLP-1 therapy**
- **Efficacy similar with weekly and every-two-week dosing intervals**
- **Pegozafermin demonstrated a favorable safety and tolerability profile**
- **These data appear very promising for the planned Phase 3 program**

ENLIVEN: Study Results Published in NEJM in Conjunction with EASL Presentation

Thank you!

Happy to take any questions: roloomba@ucsd.edu