Fibrosis Improvement with Pegozafermin Treatment in MASH Patients with F4 Fibrosis

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FGF21: Proposed Direct and Indirect Effects on Fibrosis

HEPATIC FIBROSIS → **ANTI-FIBROTIC MECHANISM** → **FIBROSIS REGRESSION**

Direct effects on fibroblasts

- Attenuates activation of hepatic stellate cells
- Decreases markers of fibrosis

Anti-inflammatory

- Direct inhibition of pro-inflammatory cytokines
- Increases adiponectin

Regulate oxidative stress and apoptosis

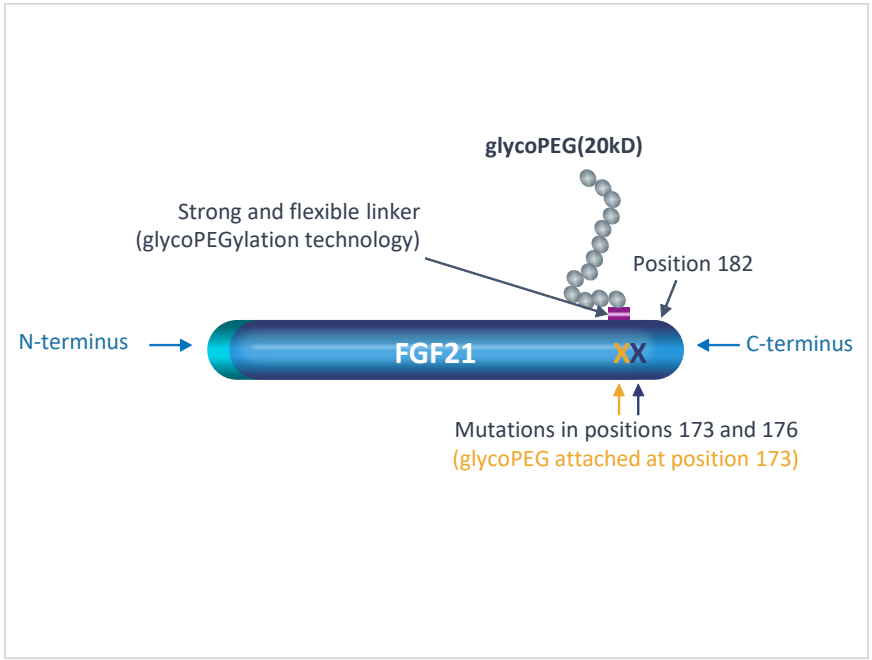
- Activates AMP-activated protein kinase (AMPK)

Reduce hepatic steatosis

- Decreases liver fat infiltration
- Decreases accumulation of FFA
- Increases LPL activity

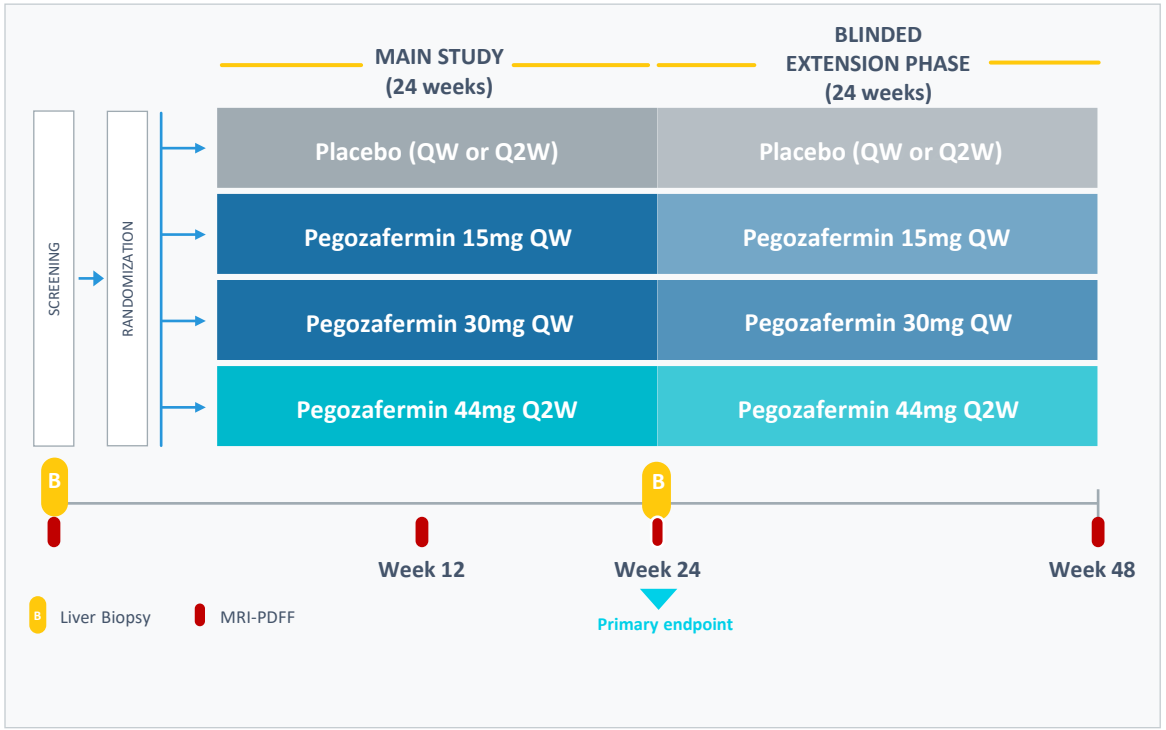
Figure adapted from Jia et.al Oxidative Medicine and Cellular Longevity 2022;Article ID 5042762Front. Endocrinol, 2020;11:601290

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



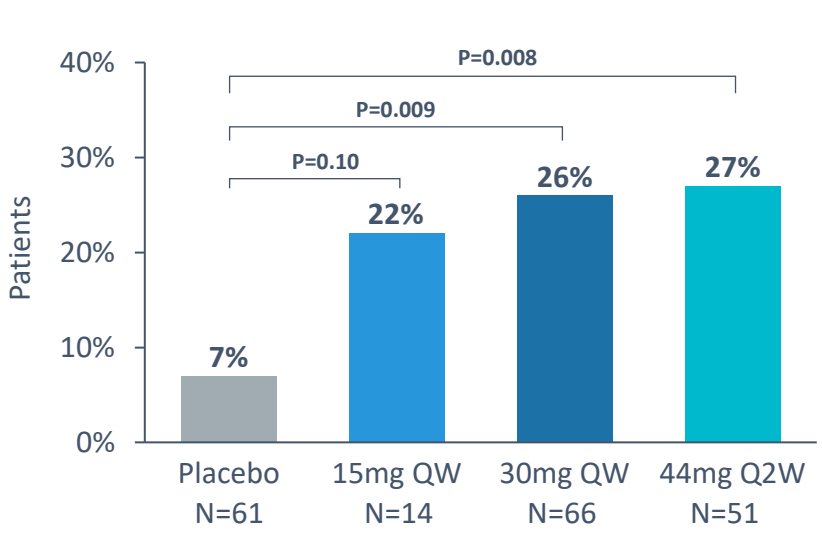
- Built using glycoPEGylation technology with site-specific mutations
- Low nanomolar potency against FGF receptors 1c, 2c, 3c, similar to native FGF21
- Comparable PK profiles between patients with noncirrhotic and well-compensated cirrhotic NASH

ENLIVEN: Main Results Published in NEJM



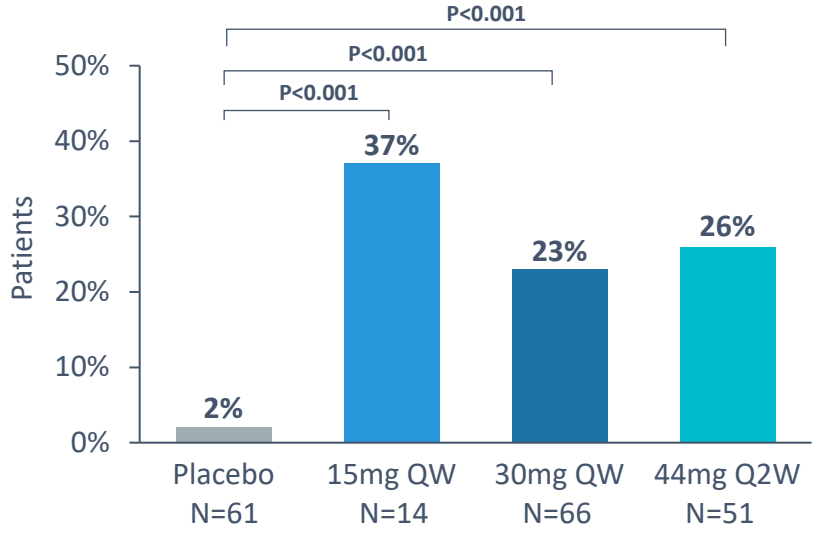
ENLIVEN Main Results (F2/F3): Pegozafermin Treatment Led to a Significant Improvement on Primary Endpoints at Week 24

Fibrosis Improvement ≥1 Stage Without Worsening of NASH



Relative Risk*	1	**2.9**	**3.7**	**4.1**
95% CI		**0.8, 10.8**	**1.2, 10.8**	**1.3, 12.9**

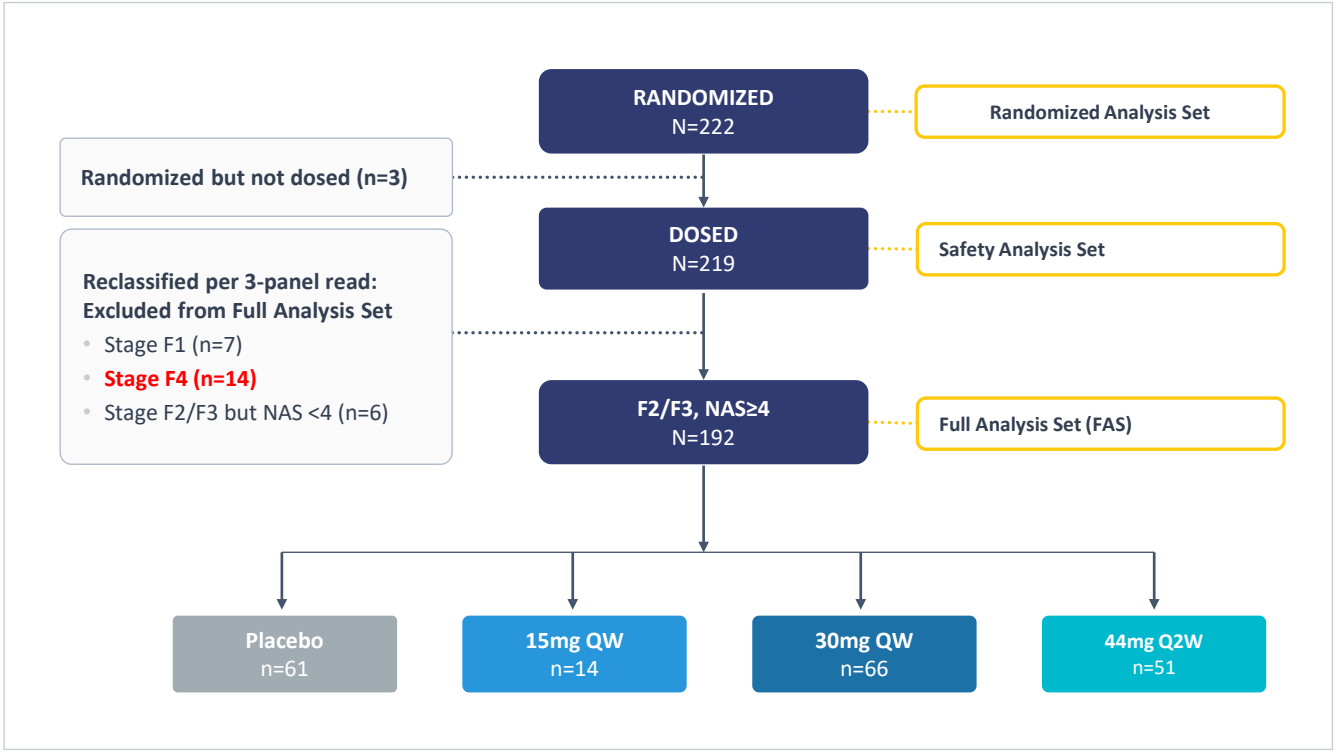
NASH Resolution Without Worsening of Fibrosis



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).

Fourteen ENLIVEN F2/F3 Subjects Were Reclassified as F4 By 3-Panel Read



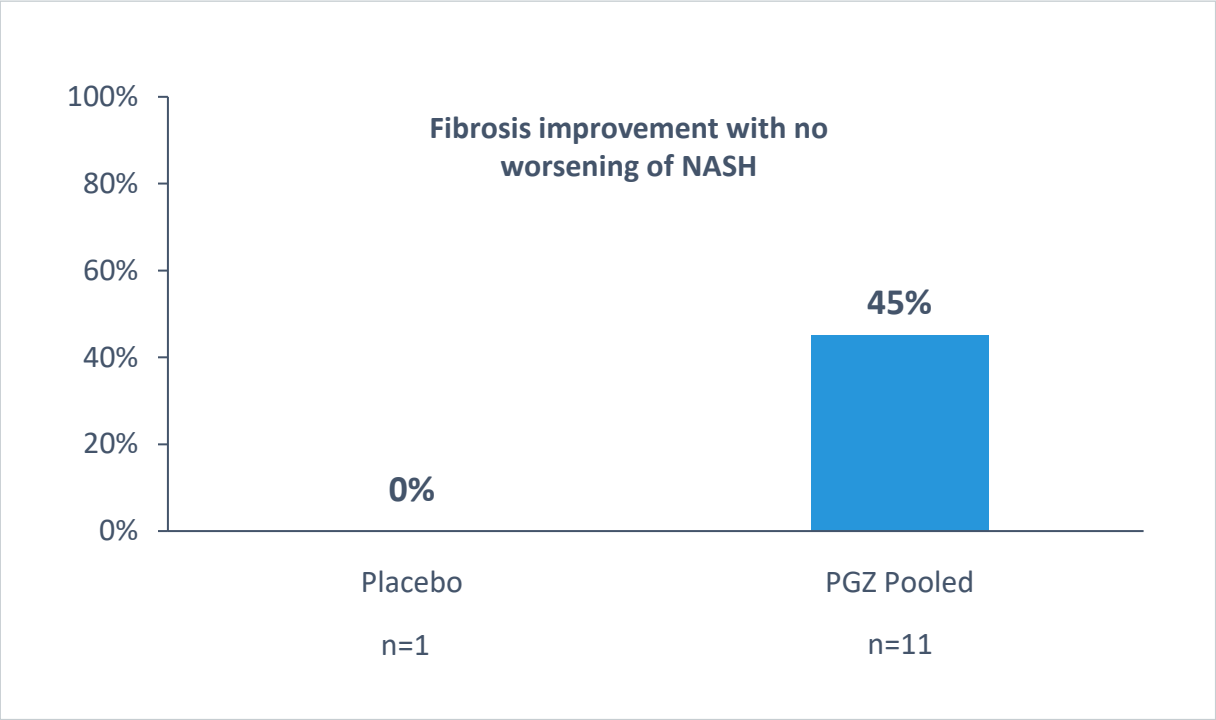
Eligibility biopsies were initially assessed by one of two central pathologists; during the study, a novel 3-panel consensus scoring method was introduced

Baseline Characteristics of Reclassified F4 Subjects are Consistent With Well-Compensated Cirrhosis Due to NASH

Parameter Mean or %	**ENLIVEN F4** (n=14)
Age (years)	**56**
Female (%)	**57%**
BMI (kg/m^2)	**37**
Type 2 Diabetes (%)	**86%**
NAFLD Activity Score	**4.9**
Liver Stiffness (VCTE, kPa)	**17.6**
PRO-C3 (ng/mL)	**65**
ELF Score >9.8 (%)	**79%**
Platelets ($10^9/L$)	**222**
ALT (U/L)	**73**
AST (U/L)	**56**

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.

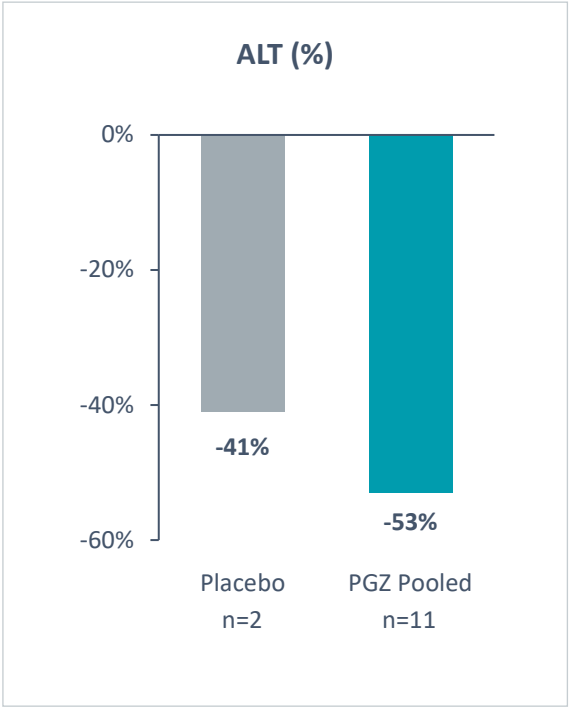
Pegozafermin Is Associated with Fibrosis Improvement at Week 24 in Patients With Well-Compensated Cirrhosis at Baseline

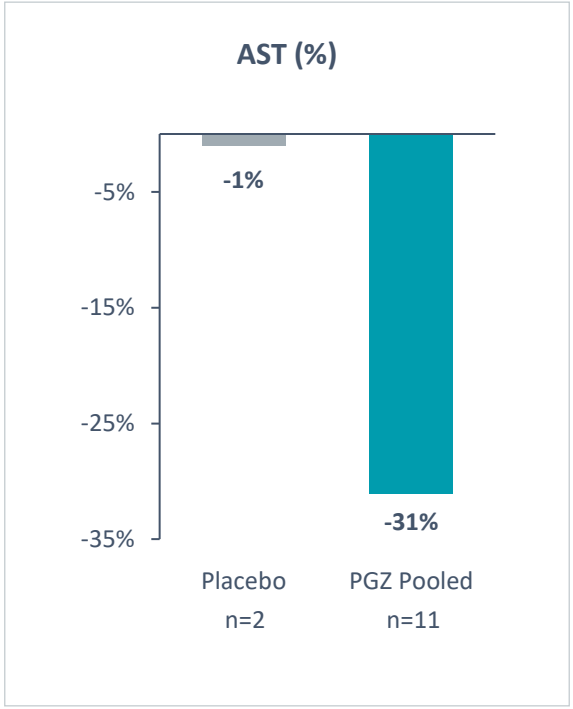


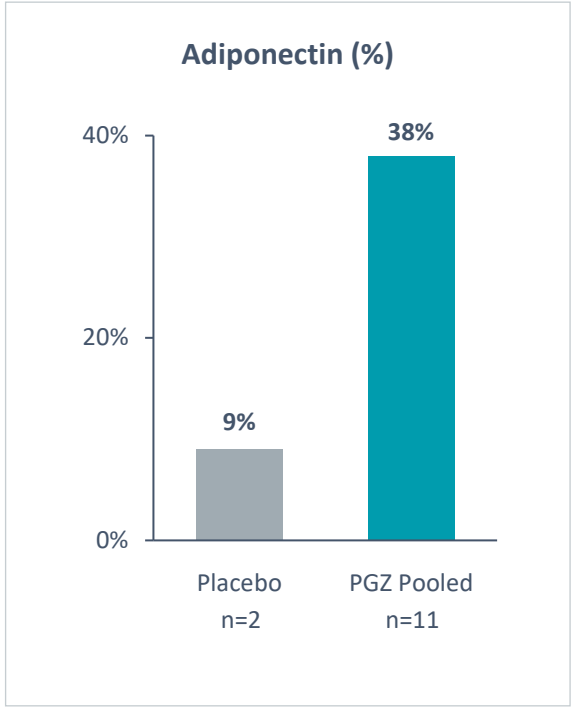
82% (9/11) of patients had fibrosis improvement

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

Pegozafermin Improves Transaminases and Increases Adiponectin in ENLIVEN F4 Subjects at Week 24

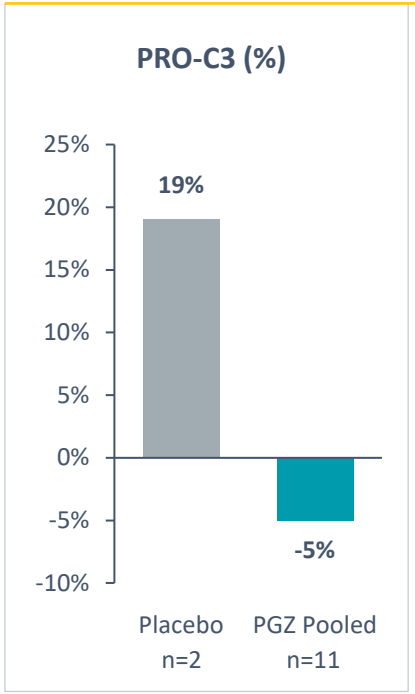


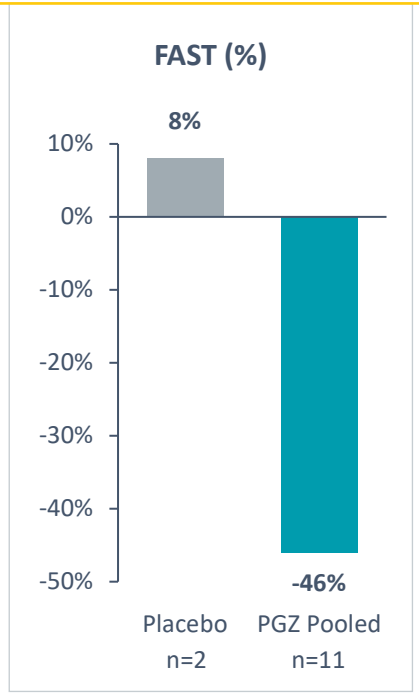


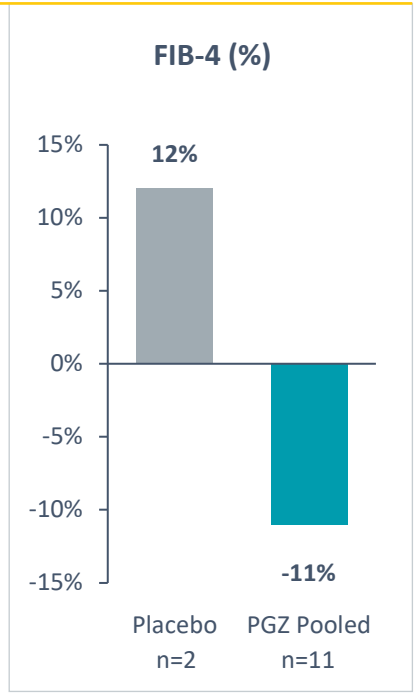


Data reported as LS mean percent change from baseline

Pegozafermin Improved Non-Invasive Markers of Fibrosis in ENLIVEN F4 Subjects at Week 24

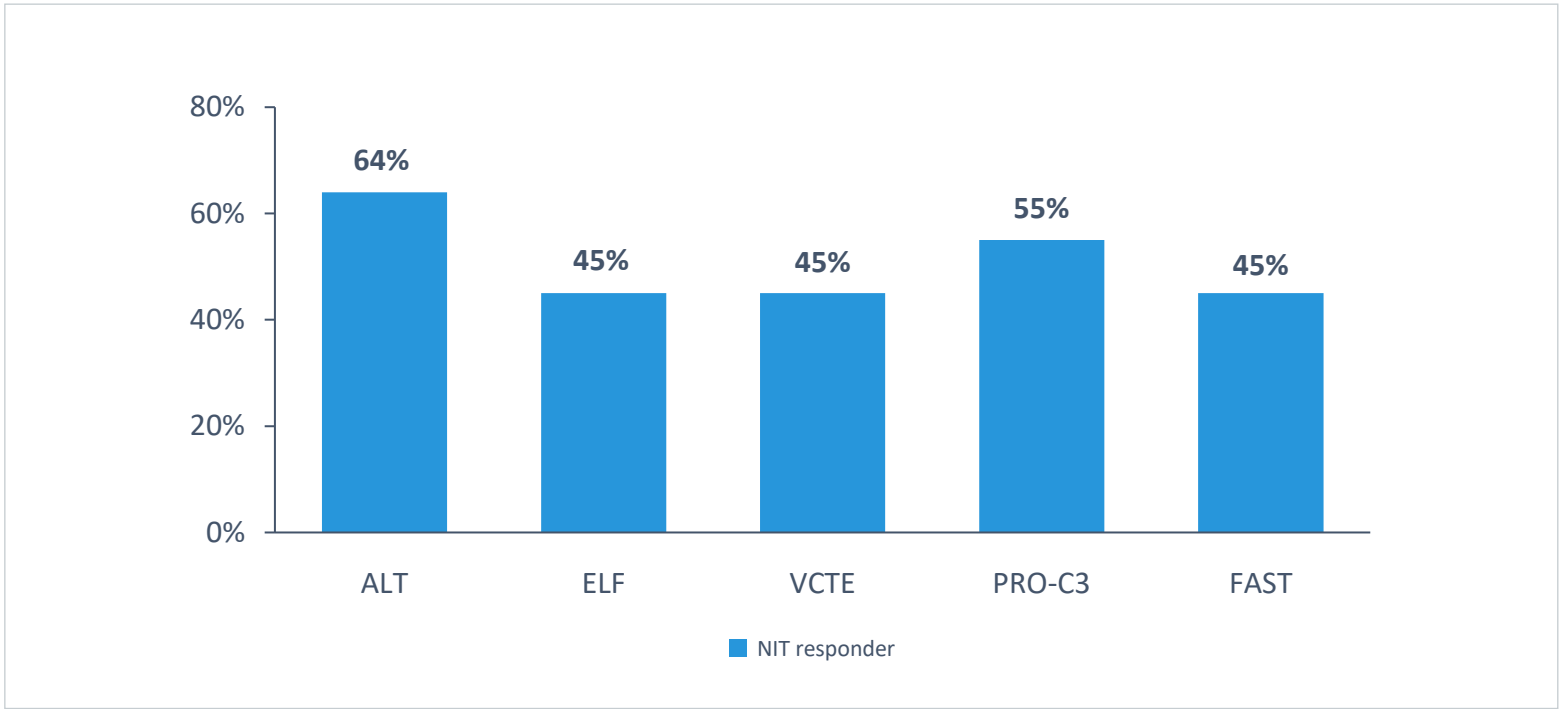






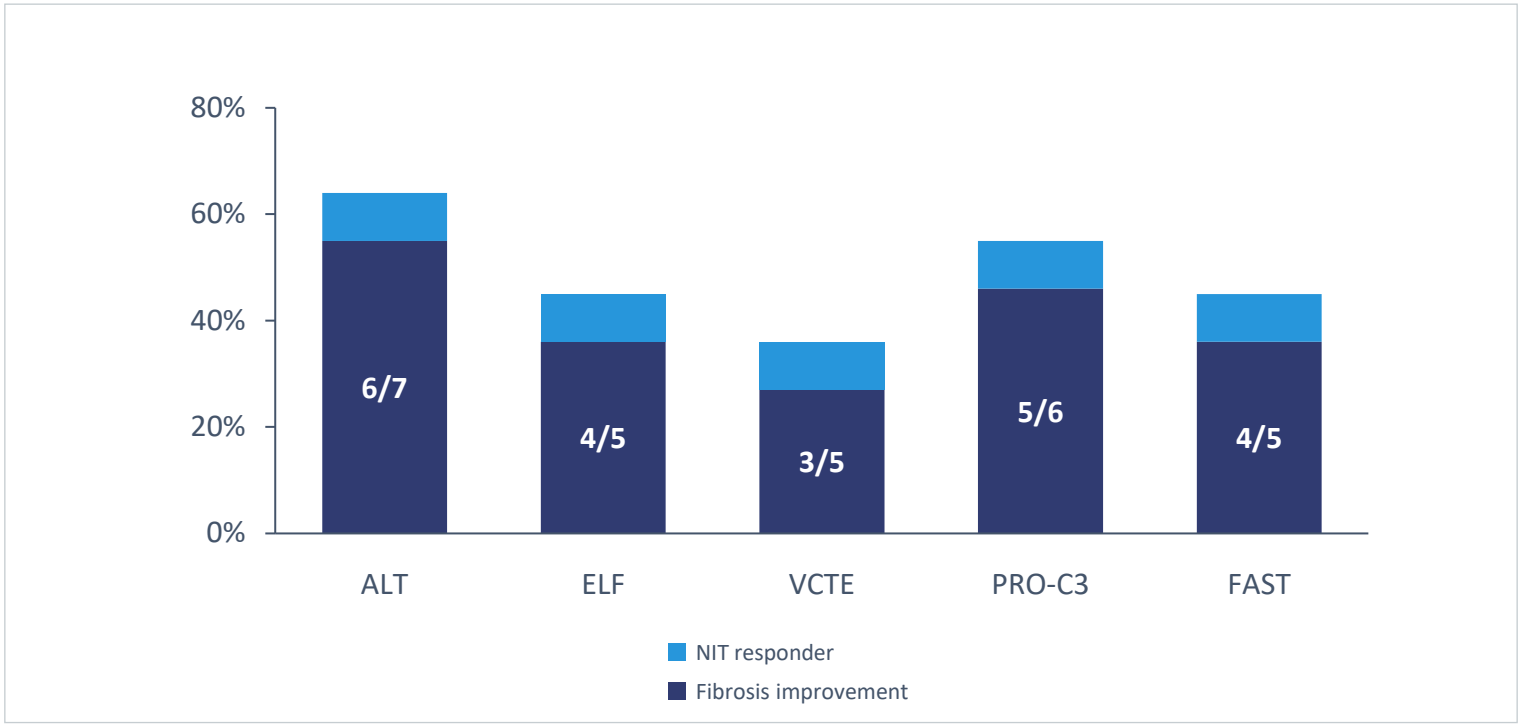
VCTE reported as median change from baseline; PRO-C3 reported as LS mean percent change from baseline; FAST and FIB-4 reported as median percent change from baseline

Responder Rates Varied Between 45% and 64% for Non-Invasive Tests in the ENLIVEN F4 Population at Week 24



Responders defined as: ALT reduction ≥17U/L; MRI-PDFF reduction ≥30%; ELF reduction ≥ 0.5; VCTE reduction ≥20%; PRO-C3 reduction >15%; FAST score <0.35; n=11

Fibrosis Improvement was Highly Associated with Responder Rates for Various Non-Invasive Tests in the ENLIVEN F4 Population at Week 24



Responders defined as: ALT reduction ≥17U/L; MRI-PDFF reduction ≥30%; ELF reduction ≥ 0.5; VCTE reduction ≥20%; PRO-C3 reduction >15%; FAST score <0.35

Pegozafermin Was Well Tolerated in a F4 Population With a Low incidence of Treatment-Related TEAEs

Drug-related TEAEs in ≥10% of patients

Preferred Term	Placebo Pool (n=2)	PGZ pooled (n=12)
Diarrhea	50%	8%
Injection site erythema	0	17%
Injection site pruritus	0	8%
Increased appetite	0	8%
Abdominal pain lower	0	17%

There were no TEAEs grade 3 or above. No DILI or tremor reported.

	Placebo Pool (n=2)	F4 (n=12)
Drug-related AEs leading to discontinuation	0	0
Drug-related Serious Adverse Event (SAE)	0	0

Source: Safety Analysis

Limitations of this Dataset

- Patients were identified by amended biopsy methodology
- Small sample size
- *Post hoc* analyses

Conclusions

- Fibrosis improvement without worsening of NASH was seen in 45% of ENLIVEN F4 subjects at week 24
- Improvement in key non-invasive tests for NASH, along with high correlation between NIT responders and fibrosis improvement, support the observed improvement in histology
- Pegozafermin was well tolerated in F4 patients with a similar safety profile to the F2/F3 population
- These promising results are hypothesis-generating and need to be validated in a dedicated study of patients with compensated cirrhosis
- Planning for the pegozafermin Phase 3 program in NASH is underway