Pegozafermin Reduced Progression to Cirrhosis: A Post-Hoc Analysis From the Phase 2b ENLIVEN Study

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BACKGROUND

- FGF21 analogs such as pegozafermin (PGZ) have direct effects on liver fibrosis and other hepatic and extrahepatic benefits in patients with MASH.
- The Phase 2b ENLIVEN trial demonstrated statistically significant improvements in fibrosis regression and MASH resolution at week 24 (W24) with PGZ versus placebo (PBO) in MASH patients with F2/F3 fibrosis.[1]
- The primary goal in noncirrhotic patients is to prevent progression to cirrhosis.

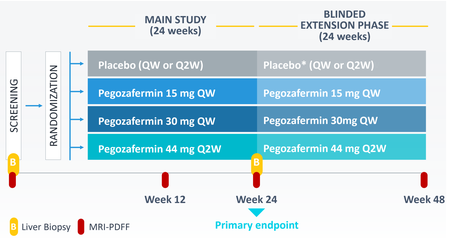
[1] Loomba et al. *N Engl J Med*. 2023.

OBJECTIVE

- The objective of this post-hoc analysis was to evaluate the effect of PGZ on histological progression to cirrhosis at W24 in the phase 2b ENLIVEN trial.

METHODS

ENLIVEN Trial Design



PRIMARY ANALYSIS POPULATION

- F2-F3 NASH; NAS ≥4

PRIMARY ENDPOINTS

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

KEY SECONDARY ENDPOINTS

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

*Some placebo patients were re-randomized in the extension phase to receive PGZ.
[†]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stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).
[‡]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without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis (FDA draft guidance).
MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAS, NAFLD activity score; Q2W: every 2 weeks; QW: every week.

METHODS

- In the phase 2b ENLIVEN study, subjects were randomized to PGZ 15 mg QW, 30 mg QW, or 44 mg Q2W or PBO (N=222).
- Biopsies [Baseline (BL) and W24] were evaluated by a panel of 3 pathologists using a robust consensus read methodology for NASH CRN NAS components and fibrosis stage.
- The full analysis set (N=192) excluded 27 subjects whose BL biopsy, initially assessed by 1 pathologist, did not meet the histological inclusion criteria based on panel read, and 3 subjects who were randomized but did not receive study drug.
- A total of 133 subjects had Stage 3 fibrosis at BL in the randomized analysis set.
- This post-hoc analysis included the 106 F3 subjects among the 164 subjects in the full analysis set who had baseline and Week 24 liver biopsies.
- The proportion of PGZ and PBO-treated subjects who progressed to cirrhosis at W24, additional histological parameters and non-invasive tests were evaluated.

RESULTS

Progressors to Cirrhosis

- Of the 106 total patients with Stage F3 fibrosis (FAS) on baseline liver biopsy, 13 (12.3%) progressed to cirrhosis at W24.
- No subject with ≤ Stage F2 fibrosis on baseline liver biopsy (n=58) progressed to F4.

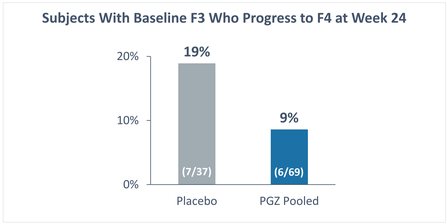
Baseline Characteristics of Progressors to Cirrhosis

Parameter Mean or %	F3 PROGRESSORS (n=13) Placebo (n=7)	PGZ Pooled (n=6)	Total F3 Progressors (n=13)	Total F3 Randomized Population (n=133)	Total ENLIVEN Randomized Population (N=222)
Age (years)	58.7	63.7	61.0	55.9	55.6
Female	71.4%	66.7%	69.2%	62.4%	60.8%
Weight (kg)	99.8	97.1	98.6	101.3	102.2
Type 2 Diabetes	42.9%	66.7%	53.8%	64.7%	66.2%
Hypertension	100.0%	83.3%	92.3%	75.2%	73.9%
Liver Fat Content (MRI-PDFF)	13.8%	11.1%	12.6%	15.8%	16.4%
Liver Stiffness (VCTE, kPa)	16.0	27.0	21.1	13.7	13.0
ELF Score >9.8%	85.7%	83.3%	84.6%	54.1%	50.0%
PRO-C3 (ng/mL)	58.4	46.2	52.8	54.2	52.8
ALT (U/L)	53.8	47.4	50.8	57.2	55.8
AST (U/L)	49.2	40.0	44.9	46.6	43.6
Triglycerides (mg/dL)	149.0	124.8	137.8	168.2	171.9

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

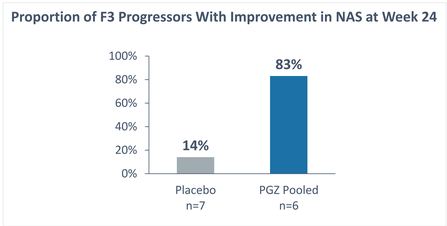
RESULTS

PGZ Decreased Progression to Cirrhosis



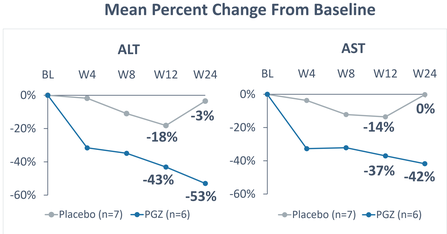
Post-hoc analysis. PGZ pooled is 30 mg QW and 44 mg Q2W. Full Analysis Set.

NAS Improved in a High Proportion of PGZ-Treated F3 Progressors



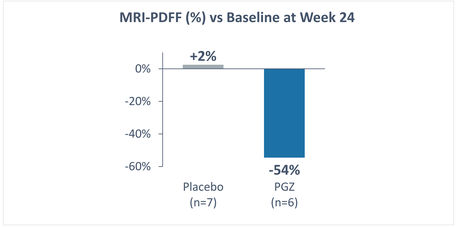
Post-hoc analysis. PGZ pooled is 30 mg QW and 44 mg Q2W. Full Analysis Set.

Significant Improvements in ALT and AST Over Time in PGZ-Treated Progressors



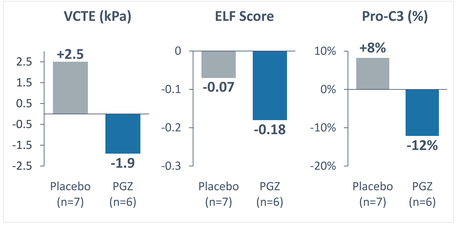
MMRM analysis at week 12 and 24. Data presented as percent means at week 4 and 8 and percent LS means at week 12 and 24.

Significant Reduction in MRI-PDFF in PGZ-Treated F3 Progressors



Source: Full Analysis Set. MRI-PDFF reported as LS mean change from baseline; MMRM analysis. Subject level data based on listings.
Post-hoc analysis.

Benefits on Fibrosis Markers in Pegozafermin-Treated F3 Progressors



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

Overview of Treatment Emergent Adverse Events in F3 Progressors

- Pegozafermin was safe and well tolerated in F3 progressors, aligned with the safety and tolerability profile of the overall ENLIVEN study population.
- No serious adverse events or TEAEs leading to treatment discontinuation were reported.
- Frequency of TEAEs was lower in PGZ-treated F3 progressors than in F3 progressors on placebo.

CONCLUSIONS

- Baseline NITs in F3 progressors indicated more advanced fibrosis compared to all F3 subjects. Mean VCTE and % subjects with ELF score >9.8 were similar to values previously reported in ENLIVEN subjects with F4 fibrosis at baseline.[2]
- Treatment with PGZ led to a reduction in the proportion of subjects with BL fibrosis stage F3 who progressed to cirrhosis.
- Relative to PBO F3 progressors, PGZ-treated progressors demonstrated improvement in histological disease activity and multiple liver-related NITs, indicating that PGZ may have clinical benefits even in patients with histological fibrosis progression.
- Pegozafermin was safe and well tolerated in PGZ-treated F3 progressors.
- Consistent improvement in multiple fibrosis NITs may be a more sensitive indicator of therapeutic benefit on fibrosis than biopsy at Week 24. Benefits on histology may be seen with longer follow-up.
- PGZ is currently being studied in Phase 3 studies in non-cirrhotic and cirrhotic MASH. The reduction in progression to cirrhosis observed in ENLIVEN adds to the promise of PGZ to address one of the key treatment goals in MASH.

[2]Loomba et al. Fibrosis Improvement with Pegozafermin Treatment in MASH Patients with F4 Fibrosis. Presented at The Liver Meeting AASLD, November 2023.

DISCLOSURES

Jörn Schattenberg, MD: Consultant: 89Bio, Inc., Akero, Alentis Therapeutics, Astra Zeneca, Boehringer Ingelheim, GSK, Ipsen, Inventiva Pharma, Madrigal, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineers. **Arun J Sanyal, MD: Consultant:** 89bio, Inc., Albireo, Alnylam, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Covance, Genefit, Genentech, Gilead, Hemoshear, HistoIndex, Inventiva, Janssen, Lilly, Madrigal, Malinckrodt, Merck, NGM Bio, Novartis, Novo Nordisk, PathAI, Pfizer, Prosciento, Poxel, Regeneron, Roche, Salix, Siemens, Terns. **Manal F. Abdelmalek, MD, MPH: Consultant:** 89Bio, Inc., Hanmi, Inventiva, Madrigal, Merck, Novo Nordisk, Boehringer Ingelheim. **89bio, Inc. (MM, GDA, MDG, SF, LT, CLH, HM):** Employees and stockholders. **Rohit Loomba, MD, MHSc: Consultant:** 89bio, Inc., Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Boston Pharmaceuticals, Bristol Myers Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, Terns Pharmaceuticals, Viking Therapeutics.