Biomarker Response in Metabolic Dysfunction-Associated Steatohepatitis (MASH) Patients With High-Risk Baseline FAST scores: Observations From the ENLIVEN Phase 2b Trial With Pegozafermin

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BACKGROUND

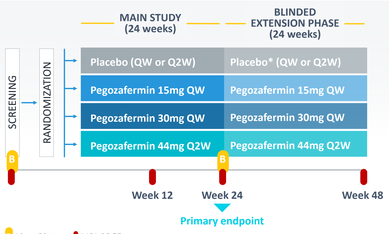
- Non-invasive tests (NITs) are increasingly being used to identify at-risk MASH patients as well as for prognostic applications.
- The FibroScan-AST (FAST) score utilizes data from FibroScan [liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) and controlled attenuation parameter (CAP)], combined with AST results and has been shown to identify patients with a NAFLD Activity Score (NAS) ≥4 and fibrosis stage ≥F2.
- Pegozafermin (PGZ), an FGF21 analog, has demonstrated improvements in both liver and extrahepatic metabolic derangements in patients with MASH.
- ENLIVEN, a phase 2b trial, evaluated the efficacy and safety of PGZ given weekly (QW) or every 2 weeks (Q2W) versus placebo in MASH patients with NAS ≥4 and biopsy-proven F2/F3 fibrosis.

OBJECTIVE

- The objective of this post-hoc analysis was to evaluate categorical shifts in risk category and changes in NITs in ENLIVEN patients at 24 and 48 weeks based on baseline FAST scores.

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stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).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without steatohepatitis and a NAS score of 0-1 for inflammation, 0 for ballooning and any value for steatosis (FDA draft guidance).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.

- The FAST Score[1] was calculated at baseline using Fibroscan (VCTE and CAP scores) and AST as follows:

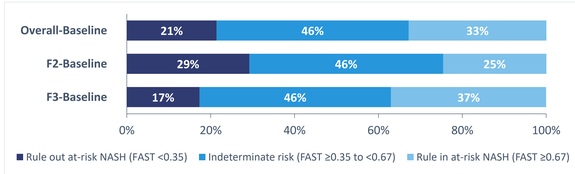
$$FAST^{TM} = \frac{e^{-1.65+1.07\ln(LSM)+2.66*10^{-5}xCAP^{3}-63.3xAST^{-1}}}{1+e^{-1.65+1.07\ln(LSM)+2.66*10^{-5}xCAP^{3}-63.3xAST^{-1}}}$$

- These scores were then used to categorize subjects into prespecified low risk (<0.35), indeterminate risk (≥0.35 to <0.67), or high risk (≥0.67) groups.[1]
- NIT responses at 24 weeks were compared to baseline FAST to assess predictive potential.

[1] Newsome et al. *Lancet Gastroenterol Hepatol.* 2020;5(4):362-373.

RESULTS

FAST Score by Cutoffs – Distribution in Overall ENLIVEN Population at Baseline



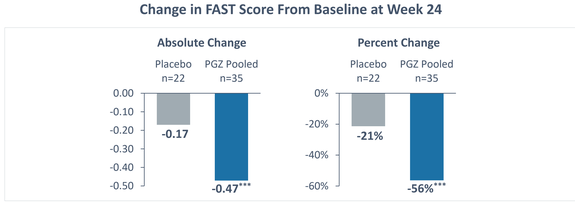
Proportions at each timepoint are based on total subjects included in the FAS.

- In this biopsy-proven F2/F3 ENLIVEN population (N=192), the FAST Score correctly ruled-in about one-third of patients.
- This analysis will focus on treatment responses in subjects assigned to the high-risk (most advanced) group.
- Full FAST/AGILE3+ analyses presented at Poster 2014.

Baseline Characteristics of Subjects at High-Risk NASH at Baseline (FAST Score ≥0.67)

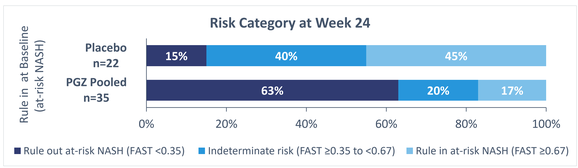
Parameter Mean or %	HIGH-RISK Placebo (n=24)	HIGH-RISK PGZ Pooled (n=40)	HIGH-RISK Total High Risk (n=64)	Total Randomized (N=222)
Age (years)	55.1	53.5	54.1	55.6
Female (%)	54.2%	62.5%	59.4%	60.8%
Weight (kg)	117.7	104.0	**109.1**	**102.2**
BMI (kg/m^2)	40.2	37.0	**38.2**	**36.6**
Type 2 Diabetes	66.7%	52.5%	**57.8%**	**66.2%**
Hypertension	87.5%	77.5%	**81.3%**	**73.9%**
Liver Fat Content (MRI-PDFF)	18.2%	17.0%	**17.5%**	**16.4%**
Liver Stiffness (VCTE, kPa)	19.2	17.6	**18.2**	**13.0**
Liver Steatosis (CAP, dB/m)	366	351	**357**	**340**
ELF Score >9.8	87.5%	67.5%	**75.0%**	**50.0%**
PRO-C3 (ng/mL)	59.6	62.3	**61.3**	**52.8**
ALT (U/L)	69.6	81.7	**77.2**	**55.8**
AST (U/L)	57.8	65.8	**62.8**	**43.6**
HbA1c, overall population (%)	6.94	6.74	6.81	6.66
Triglycerides (mg/dL)	175.8	177.3	176.8	171.9
Adiponectin (ug/ml)	5.0	5.4	5.2	4.9

Changes in FAST Score Among Subjects at High-Risk NASH at Baseline (FAST Score ≥0.67)



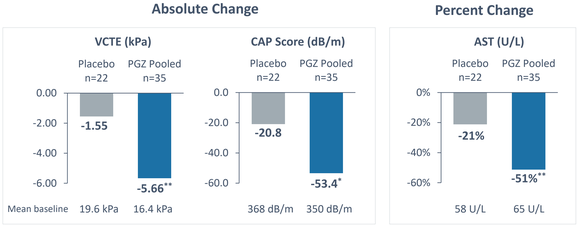
Mean Baseline=0.81 (placebo) and 0.77 (PGZ pooled [30mg QW + 44mg Q2W]) Source: Full Analysis Set in subjects with High-Risk FAST Score (≥0.67) at Baseline. Analysis via MMRM. ***p<0.001 versus placebo.

Shift in FAST Score by Risk Cutoffs – Categorical Regression From Baseline at Week 24 Among Subjects at High-Risk NASH (FAST score ≥0.67)



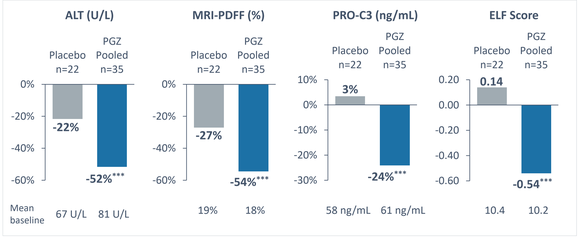
Source: Full Analysis Set in subjects with High-Risk FAST Score (≥0.67) at Baseline. PGZ pooled=30 mg QW + 44 mg Q2W.

Changes in FAST Score Components Among Subjects at High-Risk NASH at Baseline (FAST score ≥0.67) at Week 24



Source: Full Analysis Set in subjects with High-Risk FAST Score (≥0.67) at Baseline. Analysis via ANCOVA for VCTE and CAP; MMRM for AST. *p<0.05, **p<0.01 versus placebo.

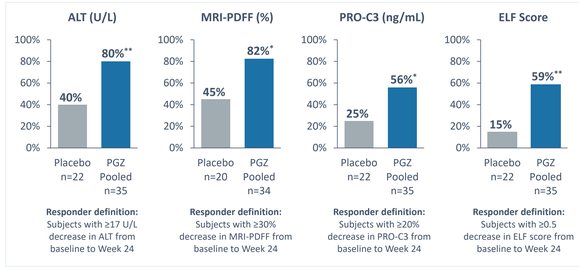
Reductions Across Liver NITs in Subjects at High-Risk NASH at Baseline (FAST score ≥0.67)



Source: Full Analysis Set in subjects with High-Risk FAST Score (≥0.67) at Baseline. Analysis via MMRM. ***p<0.001 versus placebo.

- PGZ responses were similar at Week 48 for all NITs.

High Responder Rates in Liver NITs Among Subjects at High-Risk NASH at Baseline (FAST Score ≥0.67)



Source: Full Analysis Set in subjects with High-Risk FAST Score (≥0.67) at Baseline. Analysis via CMH. *p<0.05, **p<0.01 versus placebo.

CONCLUSIONS

- In this population, baseline FAST Scores were not a robust diagnostic tool; however, they appear to stratify participants across the biopsy spectrum.
- FAST reductions were evident across all 3 components of the score.
- PGZ treatment shifted the majority of patients from high- to low-risk categories.
- Significant improvement across multiple NITs demonstrates PGZ therapy has a robust and consistent effect in this advanced subgroup.
- These data suggest PGZ can be highly efficacious in non-cirrhotic patients with the greatest need for treatment.
- Phase 3 clinical trials in non-cirrhotic and cirrhotic MASH patients are currently underway.

DISCLOSURES

Naim Alkhouri, MD: Consultant: 89Bio, Inc., AbbVie/Allergan, Echosens, Fibronostics, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, Zydus. **Quentin M. Anstee: Consultancy** on behalf of Newcastle University Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Inc., Boehringer Ingelheim, Bristol Myers Squibb, Corcept, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest, Poxel, Prosciento, Resolution Therapeutics, Roche, Ridgeline Therapeutics, RTI, Shionogi, Terns Zydus. **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. **Manal F. Abdelmalek, MD, MPH: Consultant:** 89Bio, Inc., Hanmi, Inventiva, Madrigal, Novo Nordisk Boehringer Ingelheim. **Kris Kowdley, MD: Consultant:** 89bio, Inc., CymaBay, Enanta, Genfit, Gilead, HighTide, Inipharm, Intercept, Madrigal, Mirum, NGM, Pfizer. **89bio, Inc. (MM, GDA, SF, CLH, HM):** Employees and stockholders. **Arun J Sanyal, MD: Consultant:** 89bio, Inc., Albireo, Alnylam, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Covance, Genefit, Genentech, Gilead, Hemoshear, HistoIndex, Inventiva, Jannsen, Lilly, Madrigal, Malinckrodt, Merck, NGM Bio, Novartis, Novo Nordisk, PathAI, Pfizer, Prosciento, Poxel, Regeneron, Roche, Salix, Siemens, Terns.