Diagnostic Potential of FAST and AGILE3+ Scores for F2/F3 Fibrosis: An Analysis of the Phase 2 ENLIVEN Study

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BACKGROUND

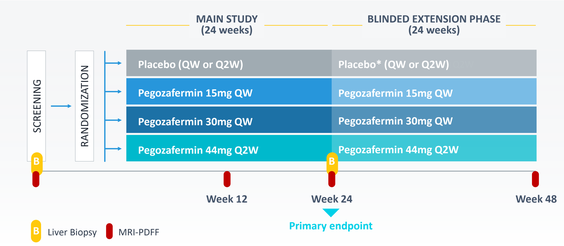
- Non-invasive tests (NITs) are commonly used to identify at-risk patients with metabolic dysfunction-associated steatohepatitis (MASH).
- In clinical trials, NITs can reduce screen-fail rates, while in clinical practice, NITs can be used for patient stratification for therapy decisions.
- The FAST and AGILE3+ scores are FibroScan-based NITs, which could be useful in these settings:
  - The FAST score, which combines FibroScan results (LSM by VCTE and CAP) with AST, identifies patients with ≥F2 fibrosis and NAS ≥4.
  - AGILE3+ utilizes FibroScan results (LSM by VCTE and CAP), AST, ALT, platelets, diabetes status and age, to identify patients with advanced fibrosis (≥F3).
- FGF21 analogs, such as pegozafermin (PGZ), have demonstrated improvements in both liver and extrahepatic metabolic derangements in patients with MASH.
- The phase 2b ENLIVEN trial evaluated the efficacy and safety of PGZ given weekly (QW) or every 2 weeks (Q2W) versus placebo in MASH patients with biopsy-proven F2/F3 fibrosis. The primary histology endpoints were assessed at week 24, followed by a 24-week blinded extension phase for a total of 48 weeks.

OBJECTIVE

- The objective of this analysis was to characterize the diagnostic potential of FAST and AGILE3+ in the ENLIVEN population.

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stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).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

- All patients had FibroScan conducted at baseline, which allowed for calculation of FAST and AGILE3+ scores.
- Based on established cut-off scores for FAST (low-risk <0.35, moderate risk ≥0.35 to <0.67, high-risk NASH ≥0.67) and AGILE3+ (low-risk <0.451, indeterminate-risk ≥0.451 to <0.679, high-risk NASH ≥0.679), patient's baseline score was compared to their biopsy staging to assess the accuracy of FAST and AGILE3+ scores.

Risk Stratification

Rule Out (low-risk NASH)	Indeterminate (moderate-risk NASH)	Rule In (high-risk NASH)
FAST Score <0.35 AGILE3+ Score <0.451	FAST Score ≥0.35 to <0.67 AGILE3+ Score ≥0.451 to <0.679	FAST Score ≥0.67 AGILE3+ Score ≥0.679

Newsome et al. *Lancet Gastroenterol Hepatol.* 2020;5:362–73.
Younossi et al. "Agile3+ development and validation: novel FibroScan based score to diagnose advanced fibrosis In non-alcoholic fatty liver disease patients". Poster presented at: EASL Digital NAFLD Summit; Sept 16-17, 2021.

RESULTS

Baseline Characteristics

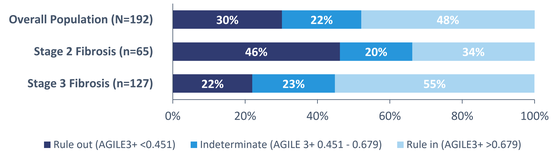
Parameter Mean or %	FAST SCORE (FAS POPULATION) N=192: Rule out (FAST Score <0.35) (n=41)	FAST SCORE (FAS POPULATION) N=192: Indeterminate zone (FAST score ≥0.35 to <0.67) (n=88)	FAST SCORE (FAS POPULATION) N=192: Rule in (FAST Score ≥0.67) (n=63)	AGILE3+ SCORE (FAS POPULATION) N=192: Rule out (AGILE3+ Score <0.451) (n=58)	AGILE3+ SCORE (FAS POPULATION) N=192: Indeterminate zone (AGILE3+ Score ≥0.451 to <0.679) (n=43)	AGILE3+ SCORE (FAS POPULATION) N=192: Rule in (AGILE3+ Score ≥0.679) (n=91)	Total Randomized N=222
Type 2 Diabetes	61	68.2	60.3	43	55.8	81.3	66.2
Liver Fat Content (MRI-PDFF)	13.5	17.1	18.0	18.5	15.7	15.9	16.4
Liver Stiffness (VCTE, kPa)	9.4	11.6	17.2	9.4	11.3	16.1	13.0
PRO-C3 (ng/mL)	44.3	49.4	61.9	49.3	54.7	53.2	52.8
ELF Score >9.8 (%)	22.0	42.0	73.0	24.1	51.2	61.5	50.0
ALT (U/L)	32.5	50.4	75.7	59.4	57.0	51.0	55.8
AST (U/L)	23.2	38.2	63.5	39.1	42.7	46.3	43.6
HbA1c, overall population (%)	6.28	6.64	6.89	6.26	6.35	7.02	6.66

- In the total randomized population, the mean age was 56 years, 61% were female, and the mean BMI was 37 kg/m^2.

PROC-C3 were analyzed on Cobas e801.
Source: Full Analysis Set for FAST and AGILE3+ score (N=192) and randomized population for total study (N=222).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; PRO-C3, N-terminal type III collagen propeptide; VCTE, vibration-controlled transient elastography.

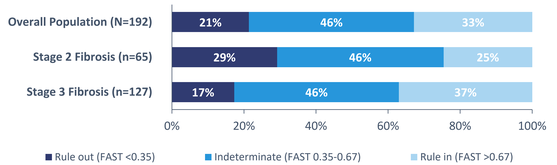
RESULTS

AGILE3+ Score by Cutoffs – Distribution in Overall FAS Population at Baseline



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

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



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

Summary of Baseline FAST and AGILE3+ Scores by Risk Categories

		Rule out at-risk NASH		Indeterminate risk		Rule in at-risk NASH	
	N	FAST <0.35	AGILE3+ <0.451	FAST ≥0.35 to <0.67	AGILE3+ ≥0.451 to <0.679	FAST ≥0.67	AGILE3+ ≥0.679
Overall population	192	21%	30%	46%	22%	33%	48%
Stage 3 Fibrosis	127	17%	22%	46%	23%	37%	55%
Stage 2 Fibrosis	65	29%	46%	46%	20%	25%	34%

- ENLIVEN enrolled 192 patients with F2 (n=65) and F3 (n=127) fibrosis.
- Both scoring systems performed comparably at identifying their respective populations, with 21% of F2/F3 patients misclassified as "rule-out" by FAST and 22% of F3 patients for AGILE3+.
- The AGILE3+ score accurately identified as "rule-in" 55% of the patients staged as F3 by histology, whereas the FAST score identified as "rule-in" only 33% of F2/F3 and NAS ≥4 patients.
- While categorizing more patients as indeterminate (46%), the FAST score was less likely to rule out patients who had F2 (29%) or F3 (17%) by histology compared to AGILE3+ (F2: 46%; F3 22%).
- AGILE3+ misclassified 34% of F2 patients as having at-risk NASH (F3+).

Pegozafermin Was Well Tolerated Across All Patients in ENLIVEN Through 48 Weeks

- The most common drug-related TEAEs were diarrhea, nausea, injection site reactions, and increased appetite.
  - Most TEAEs were Grade 1 and Grade 2

	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].

CONCLUSIONS

- Both FAST and AGILE3+ performed reasonably well in identifying their target populations in ENLIVEN.
- AGILE3+ correctly identified more patients for rule in, FAST resulted in less people incorrectly categorized as rule out.
- While these data suggest either score could be used for clinical trial screening (depending on the objective), more importantly these tools can be useful to physicians for identifying patients who could benefit from treatment and/or who need additional testing in the real-world setting.

DISCLOSURES

Naim Alkhouri, MD: Consultant: 89Bio, Inc., AbbVie/Allergan, Echosens, Fibronostics, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, Zydus. **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. **89bio, Inc. (GDA. SF, LT, NR, MDG, MM, HM):** Employees and stockholders. **Rohit Loomba, MD, MHSc: Consultant:** 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, 89bio, Terns Pharmaceuticals, Viking Therapeutics.