Utility of FibroScan® CAP Score in Monitoring Metabolic Dysfunction-Associated Steatohepatitis (MASH): Post-hoc Analysis from the ENLIVEN Study

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Disclosure

- Maya Margalit, Cynthia L Hartsfield, Shibao Feng, Hank Mansbach and Mildred D Gottwald are employees of 89bio and hold 89bio stock.
- Rohit Loomba and Phillip N Newsome are consultants to 89bio.

Background

- Pegozafermin (PGZ) is a long-acting fibroblast growth factor 21 (FGF21) analog, in development for non-cirrhotic and cirrhotic MASH.
- PGZ was evaluated in MASH patients with biopsy-proven stage F2/F3 fibrosis and NAS score ≥ 4 points fibrosis in the ENLIVEN Phase 2b trial.[1]
- PGZ had a significant and robust effects on liver histology and multiple liver-related non-invasive tests.
  - Fibrosis regression without worsening of MASH, MASH resolution without worsening of fibrosis
  - NAS score reduction of ≥2 points
  - Magnetic resonance imaging-proton-density fat fraction (MRI-PDFF)
  - FibroScan® VCTE score, ELF, ProC3, cT1

[1]Loomba et al, *N Engl J Med* 2023;389:998.

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Background (2)

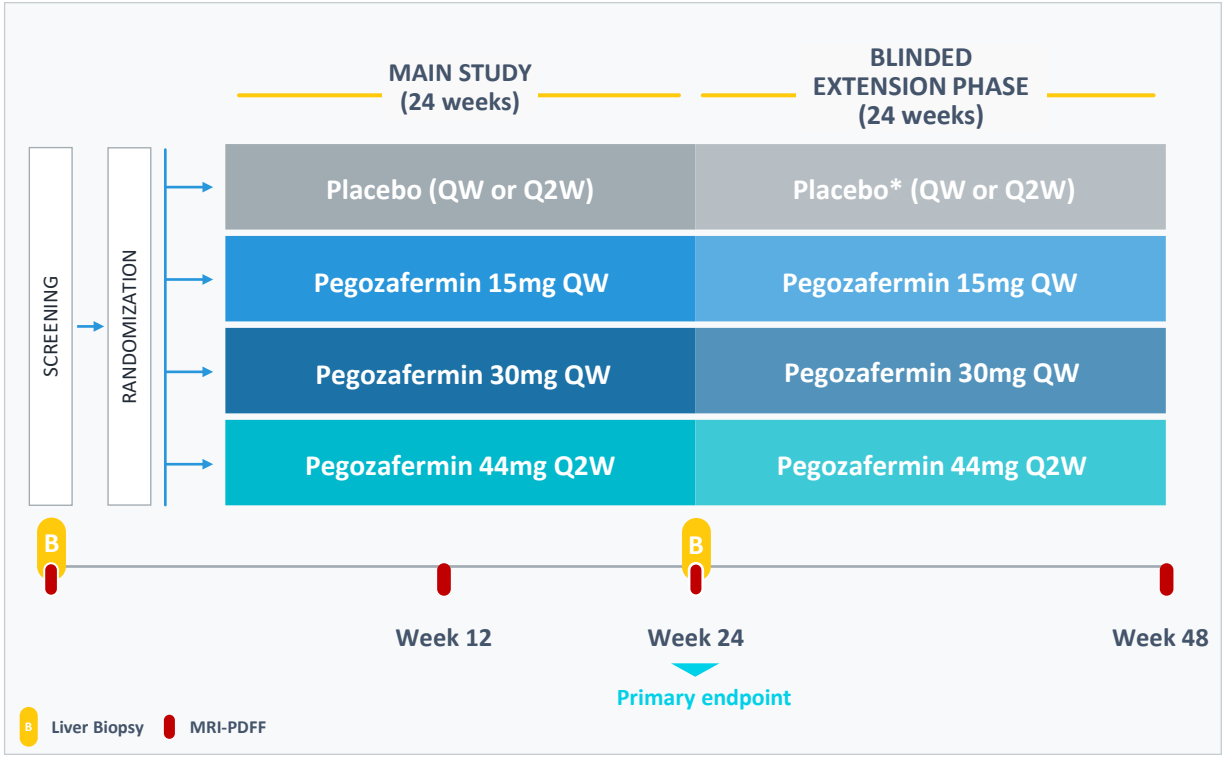
- ≥30% reduction in MRI-PDFF (MRI-PDFF response) has been associated with a ≥2-point reduction in the NAFLD Activity Score (NAS) in patients with MASH[1].
- The FibroScan® controlled attenuation parameter (CAP) score, which assesses hepatic steatosis, is less costly than MRI-PDFF and readily available at point of care.
- Few interventional studies have reported changes in CAP.
- Thresholds of meaningful changes in CAP have not been established, and the utility of CAP in monitoring on-treatment changes remains unclear.

[1]Loomba et al, *Hepatology* 2020 ;72(4): 1219–1229.

Objective

- To assess the performance of CAP score changes to predict MASH-related histological changes or ≥30% reduction in MRI-PDFF in the ENLIVEN Phase 2b trial (post-hoc).

ENLIVEN – Study Design for Phase 2b Trial



PRIMARY ANALYSIS POPULATION

- F2-F3 MASH; NAS ≥4

PRIMARY ENDPOINTS

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

KEY SECONDARY EFFICACY ENDPOINTS

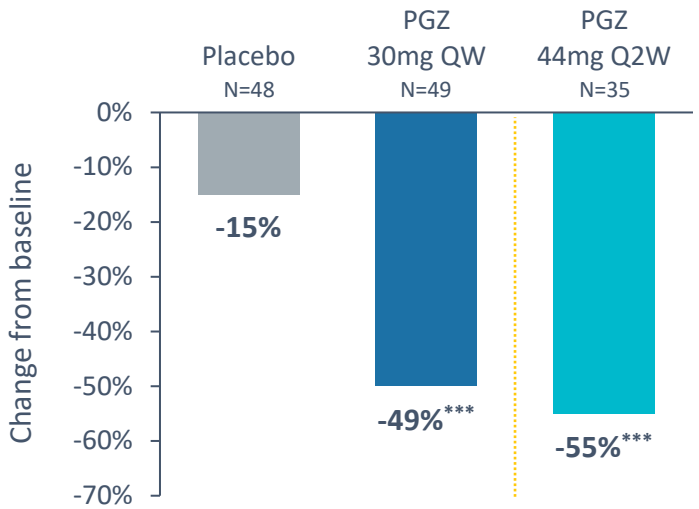
- ≥2-point change in NAS with no worsening of fibrosis
- Non-invasive liver markers (liver fat, liver injury, fibrosis markers)

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.
Loomba et al, *N Engl J Med* 2023;389:998.

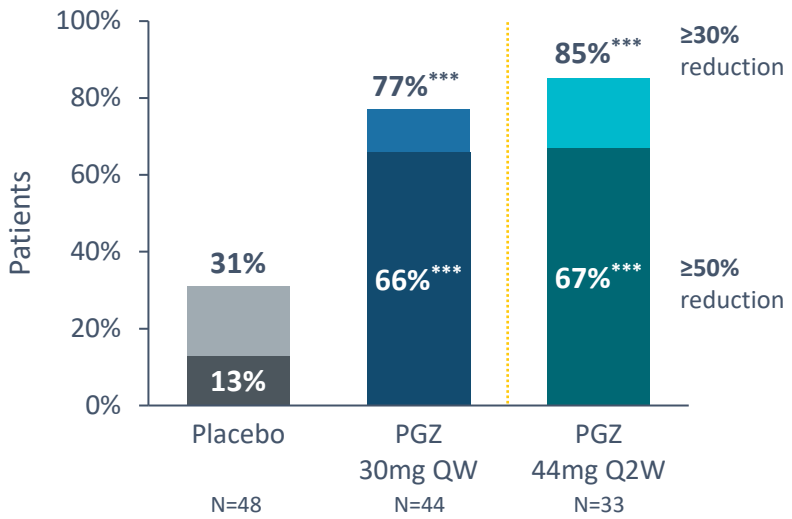
Pegozafermin Demonstrated Robust Liver Fat Reduction with High Responder Rates by MRI-PDFF at Week 24

MRI-PDFF Analysis set in Subjects with >10% Liver Fat at Baseline

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



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

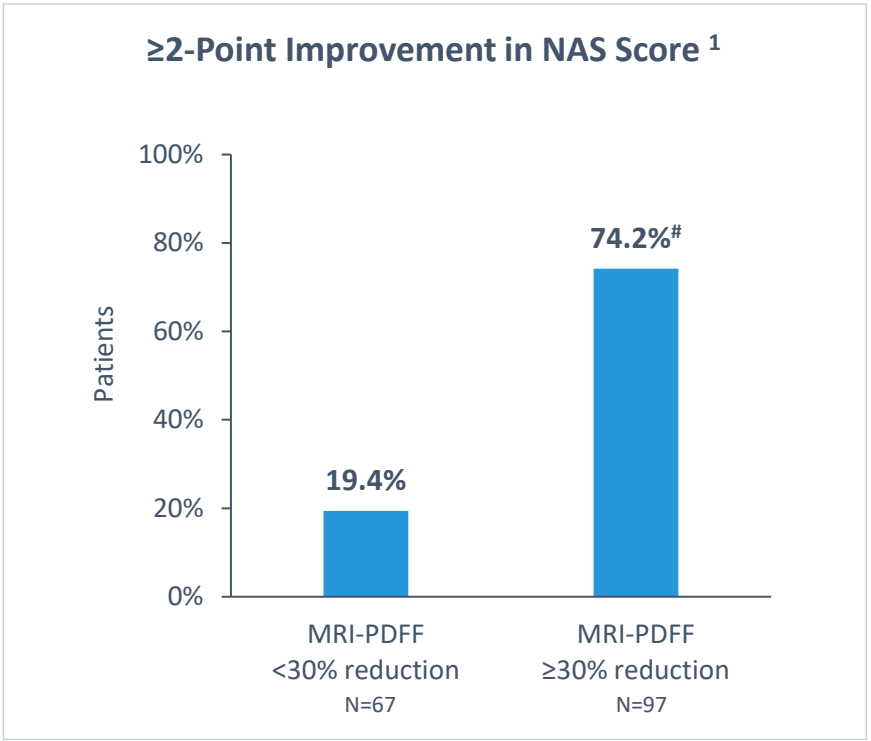


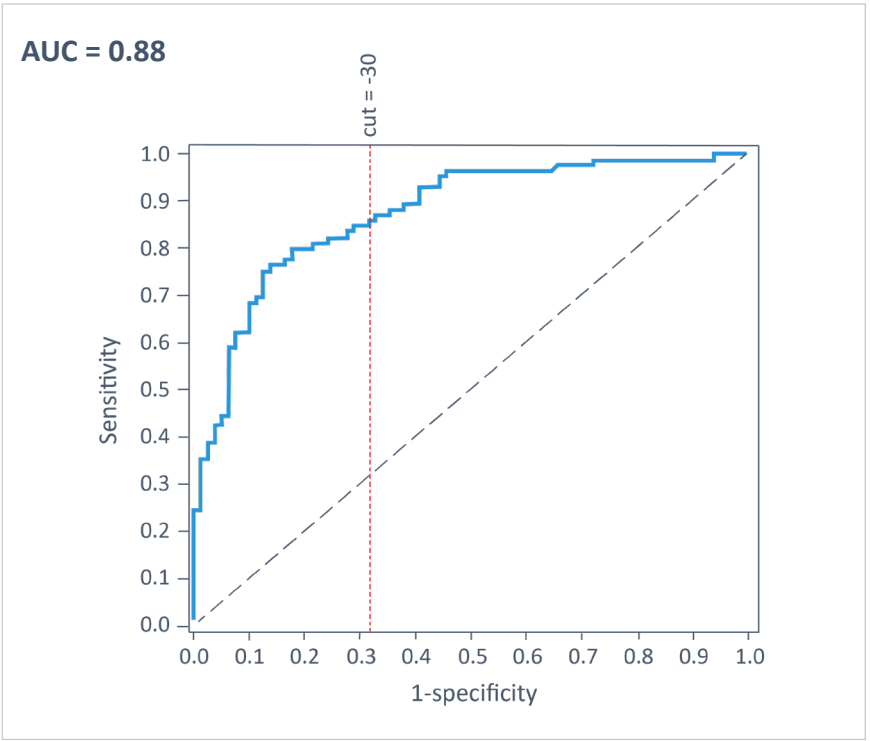
Results for the 15mg QW dose: -33%

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.
Loomba et al, *N Engl J Med* 2023;389:998.

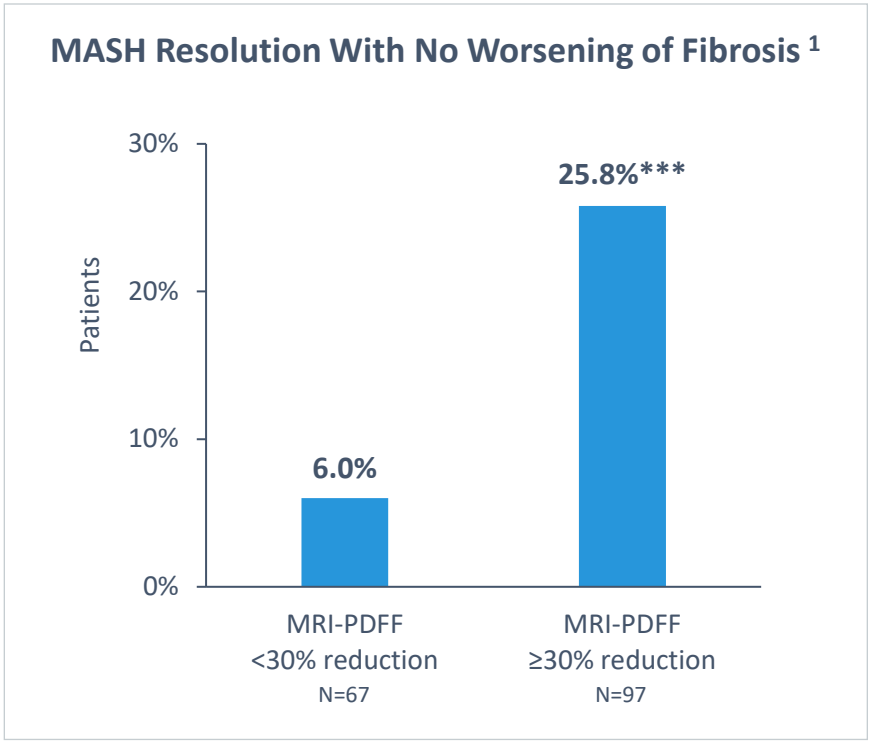
MRI-PDFF Reduction is Associated with ≥2-point NAS Improvement at Week 24

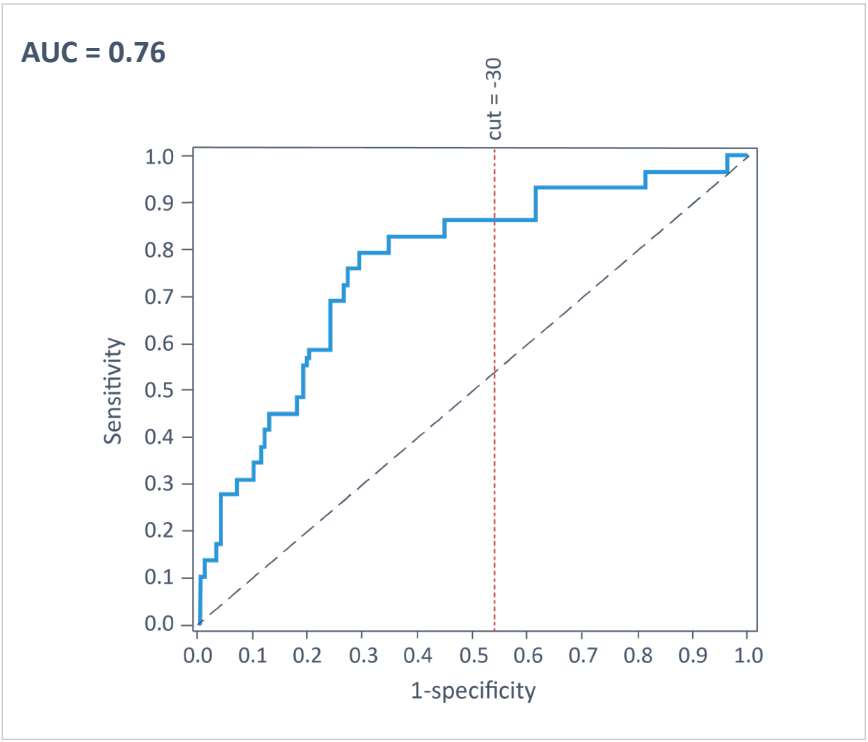




1. Analyses were based on the number of subjects with non-missing assessments at both baseline and week 24 for the corresponding parameters. The p-value was obtained via Cochran-Mantel-Haenszel (CMH) test stratified by T2DM status (yes vs. no) and fibrosis stage (F2 vs. F3).
# p<0.0001

MRI-PDFF Reduction Correlates to MASH Resolution





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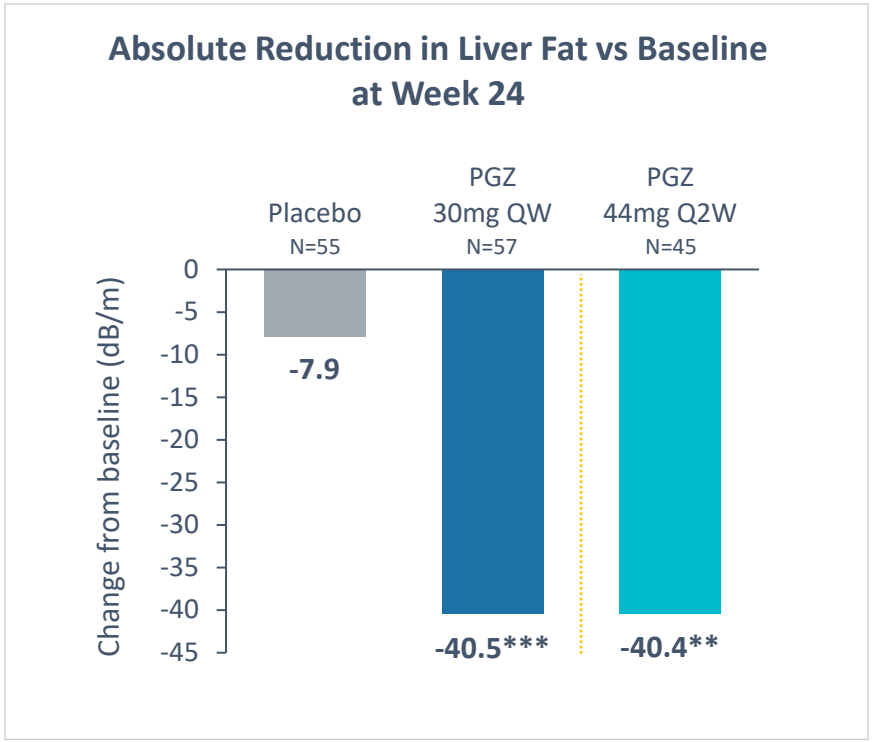
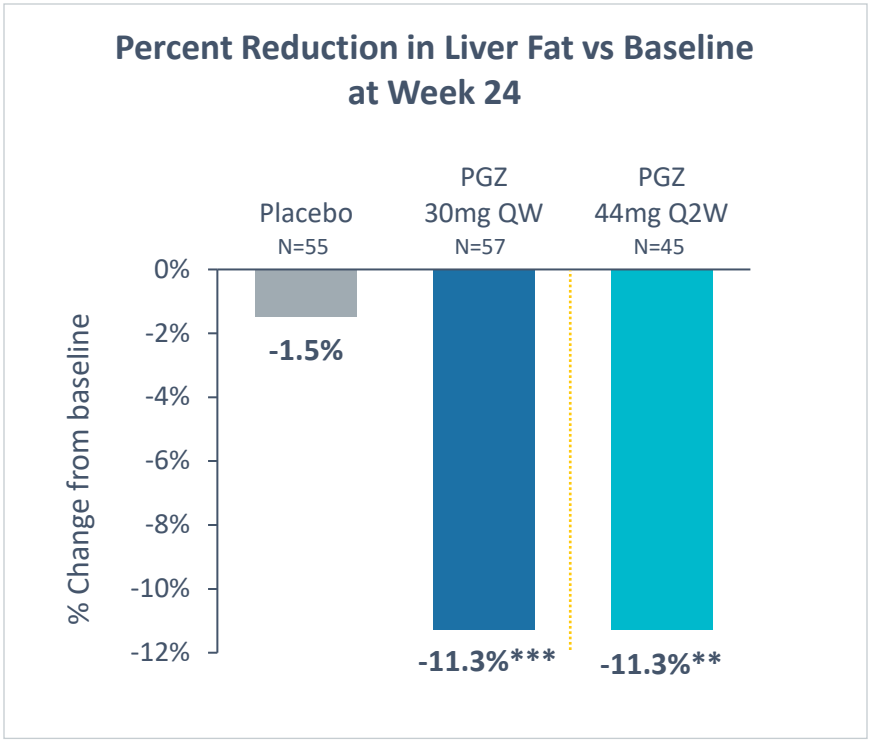
***p≤0.001

Pegozafermin led to Significant Liver Fat Reduction by CAP at Week 24

Mean baseline CAP score was 348 dB/m, 330 dB/m and 338 dB/m for placebo, PGZ 30 mg QW and PGZ 44 mg Q2W, respectively

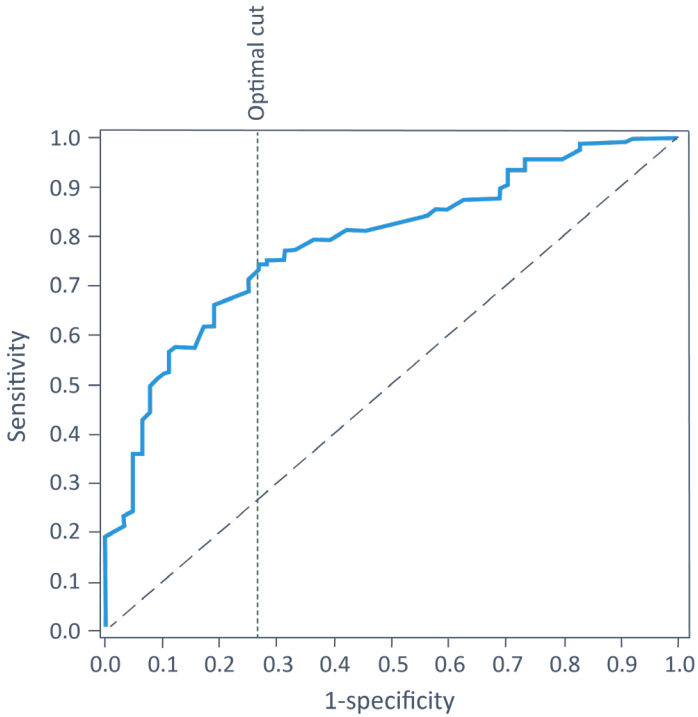




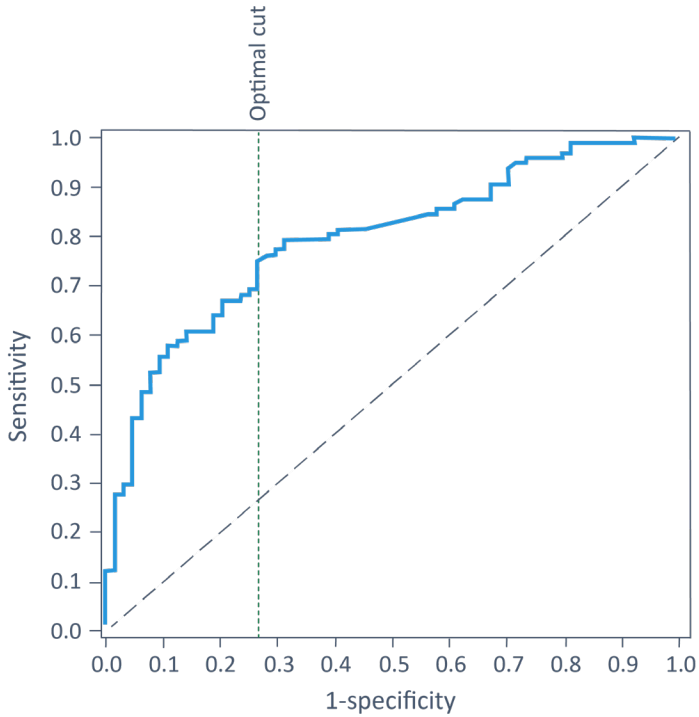
LS means was calculated based on ANCOVA with covariates of baseline CAP score, T2DM status (yes vs. no) and fibrosis stage (F2 vs. F3).
**p<0.01; ***p<0.001 versus placebo.

MRI-PDFF 30% Reduction vs. CAP Change

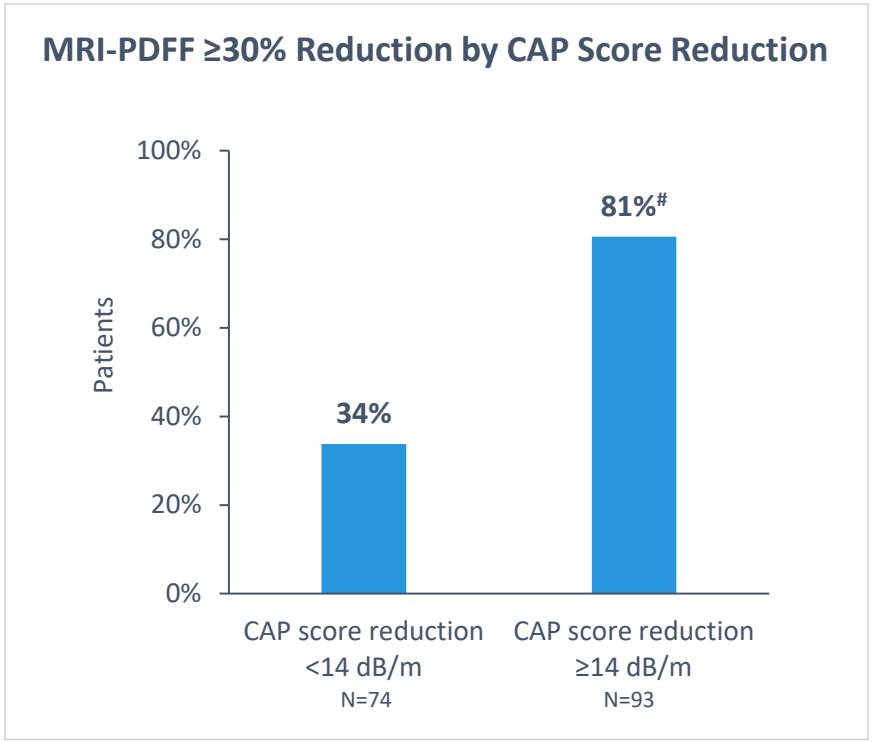
AUC = 0.79, Optimal Cut for CAP Absolute Change = -14 dB/m

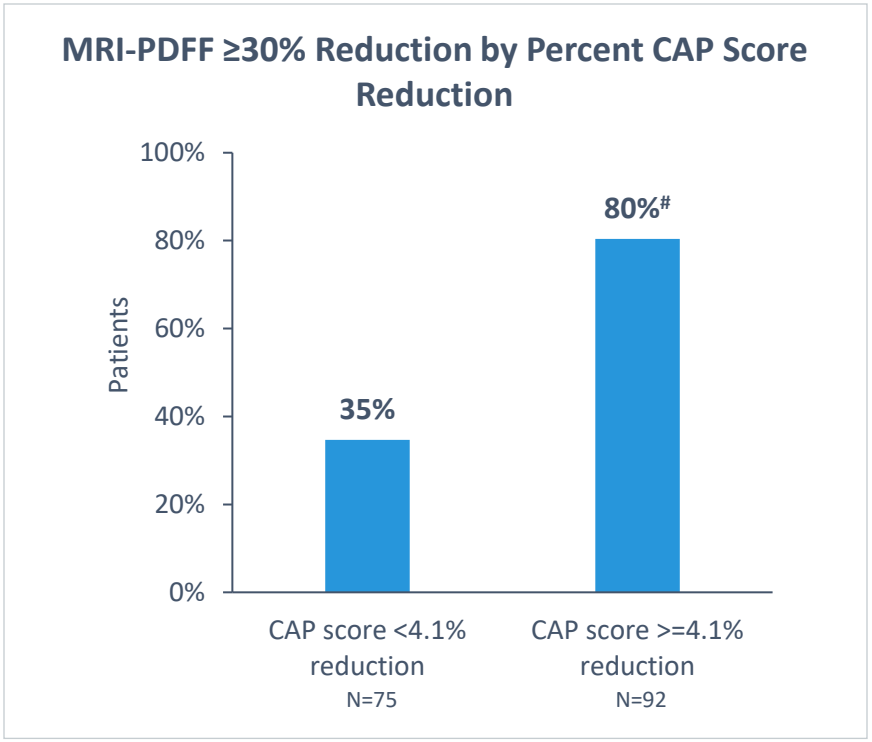


AUC = 0.80, Optimal Cut for CAP Percent Change = -4.1%



Association Between MRI-PDFF ≥30% Reduction and CAP Score Reduction



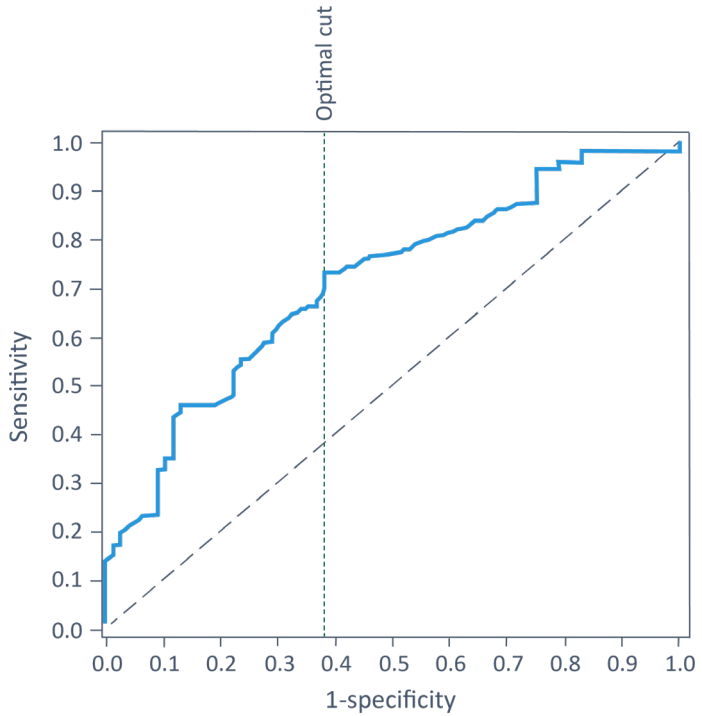


Analyses were based on the number of subjects with non-missing assessments at both baseline and week 24 for the corresponding parameters. The p-value was obtained via Cochran-Mantel-Haenszel (CMH) test stratified by T2DM status (yes vs. no) and fibrosis stage (F2 vs. F3).

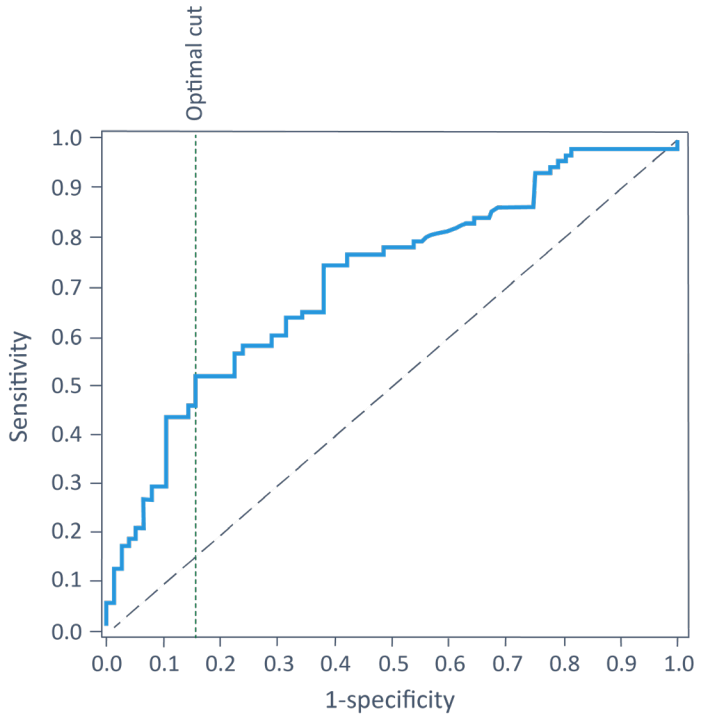
#p<0.0001

NAS ≥2-Point Change vs. CAP Score Change

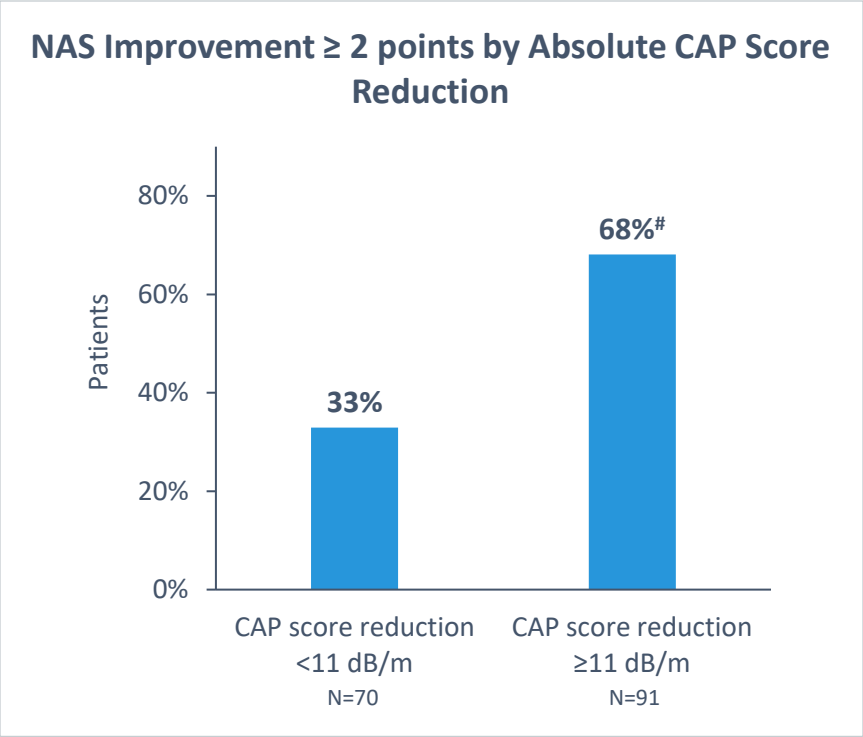
AUC = 0.71, Optimal Cut for CAP Absolute Change = -11 dB/m

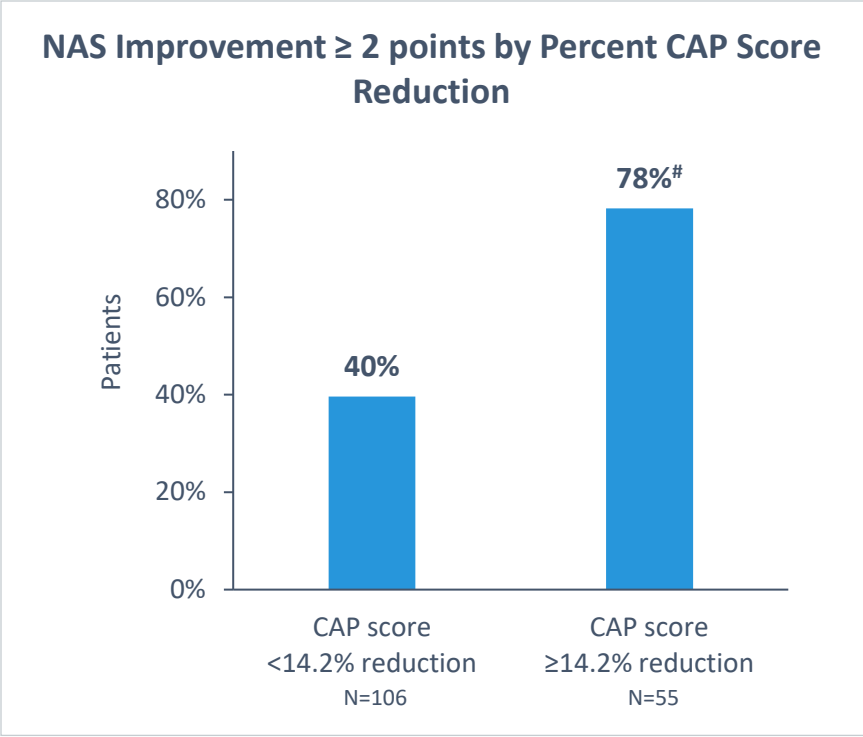


AUC = 0.71, Optimal Cut for CAP Percent Change = -14.2%



Reduction in CAP Score is Associated with ≥2-point NAS Improvement at Week 24





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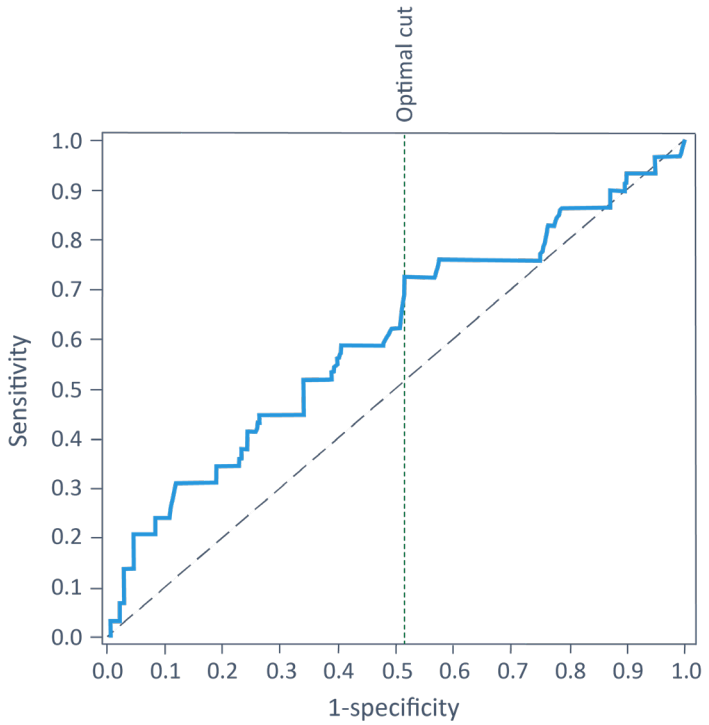
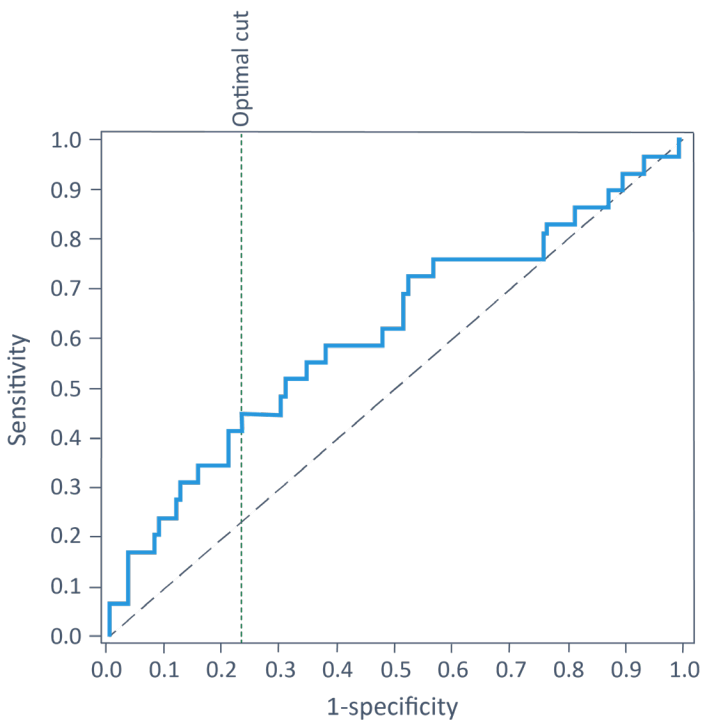
# $p<0.0001$

MASH Resolution Change vs. CAP Change

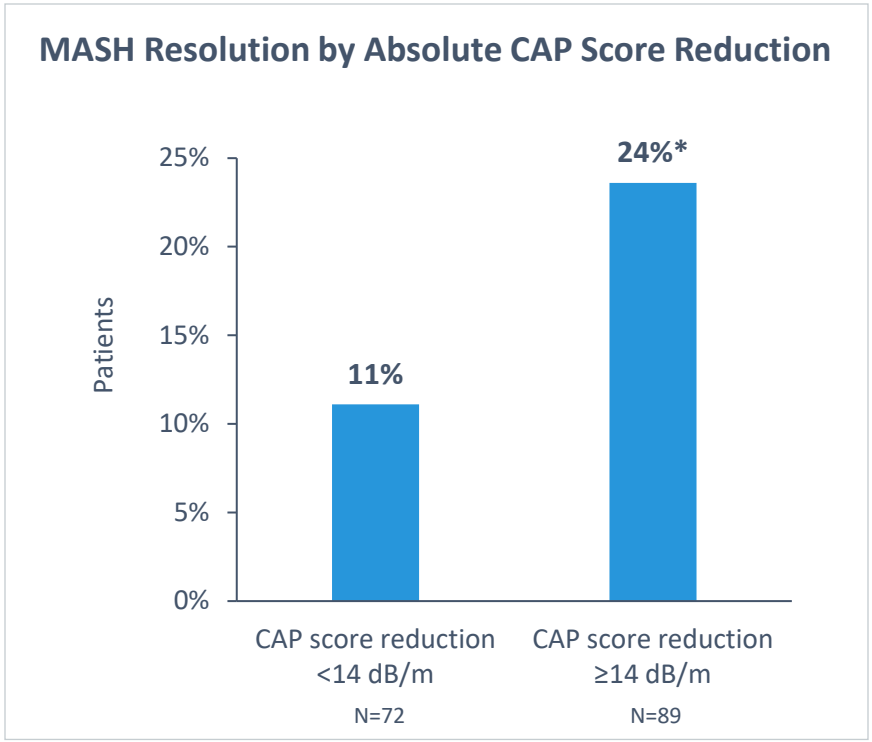
AUC = 0.60, Optimal Cut for CAP Absolute Change = -14 dB/m

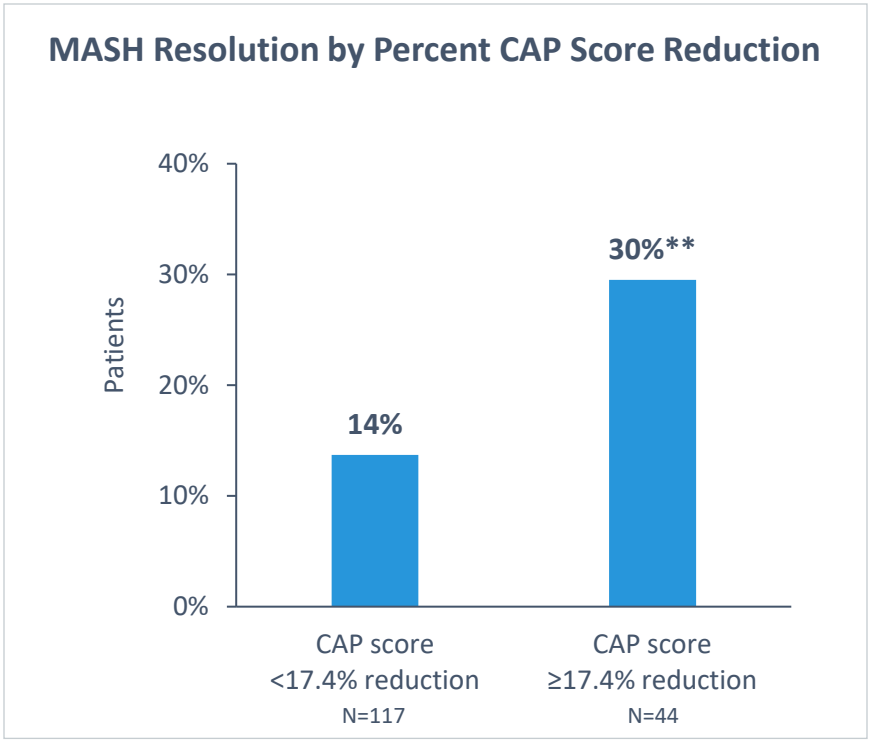


AUC = 0.61, Optimal Cut for CAP Percent Change = -17.4%



Reduction in CAP Score is Associated with MASH Resolution





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*p=0.03; **p=0.0094

Positive and Negative Predictive Values in treated subjects:

Assessment	Cutoff	Endpoint	PPV	NPV
MRI-PDFF	-30%	NAS≥2 reduction	85%	68%
MRI-PDFF	-30%	MASH resolution	34%	91%
CAP	-14 dB/m	MRI-PDFF response	92%	42%
CAP	-4%	MRI-PDFF response	92%	41%
CAP	-11 dB/m	NAS≥2 reduction	80%	52%
CAP	-14 %	NAS≥2 reduction	87%	45%
CAP	-14 dB/m	MASH resolution	31%	85%
CAP	-17%	MASH resolution	38%	81%

Conclusion

- In ENLIVEN, a ≥30% reduction in MRI-PDFF predicted a ≥2-point improvement in NAS score and MASH resolution.
- Although absolute and percent changes in CAP score are numerically modest even in the presence of significant reduction in steatosis, CAP score reductions were associated with MRI-PDFF response, ≥2-point reduction in NAS score and MASH resolution.
- The AUC of CAP score change to detect MRI-PDFF response and NAS ≥2-point reduction was acceptable (0.80 and 0.71, respectively), with informative PPV and NPV values in PGZ-treated subjects.
  - Challenge: Optimal cut-offs were within the reported variability range for CAP.
- Small improvements in CAP may indicate clinically meaningful benefit.
- Further studies are needed to evaluate the generalizability of these findings and utility of CAP to monitor in MASH.

Thank you