Zone-Specific Fibrosis Reductions Induced by Pegozafermin Over 24 Weeks are Similar in Non-Cirrhotic (F2/F3) and Cirrhotic (F4) MASH

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BACKGROUND

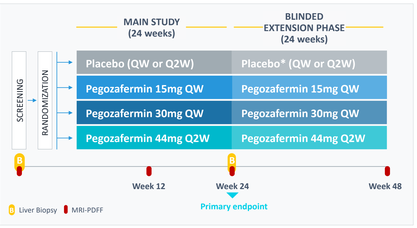
- Fibroblast growth factor 21 (FGF21) analogs such as pegozafermin (PGZ) have potent anti-fibrotic effects as well as metabolic benefits in patients with MASH.
- PGZ, a GlycoPEGylated, long-acting (FGF21) analog, led to fibrosis regression in MASH patients with proven F2/F3 fibrosis in the ENLIVEN Phase 2b trial as assessed by conventional pathology[1] and HistoIndex's Second Harmonic Generation digital pathology platform (qFibrosis).
- Histoindex's AI-based digital pathology platform enables assessment of histological improvement beyond conventional fibrosis stage scoring, including zonal quantification of fibrosis changes.
- qFibrosis features in the portal, periportal, and zone 2 regions have previously been reported to be predictive of hepatic decompensation and all-cause mortality.[2]

OBJECTIVE

- To assess hepatic zone-specific effects of PGZ in non-cirrhotic and cirrhotic MASH using qFibrosis zonal analysis

METHODS

ENLIVEN—Study Design for Phase 2b Trial



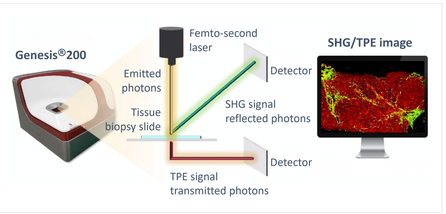
PRIMARY ANALYSIS POPULATION
- F2-F3 MASH; NAS ≥4

PRIMARY ENDPOINTS
- ≥1-stage fibrosis improvement with no worsening of MASH[a]
- MASH resolution with no worsening of fibrosis[b]

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

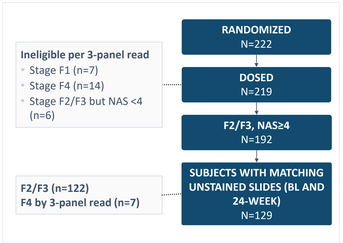
[a]Improvement in liver fibrosis by ≥1 stage and no worsening of steatohepatitis defined as no increase in NAS for ballooning, inflammation, or steatosis (FDA draft guidance).
[b]Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis 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.

Stain-Free Digital Pathology that Provides Consistent High-Resolution & Collagen-Specific Images for Analysis



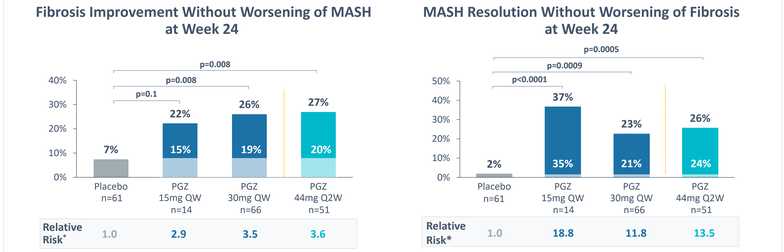
The simplified schematic diagram is for illustration only and does not represent the actual setup within the Genesis Imaging System.[3]

ENLIVEN: Patient Disposition and Analysis Sets



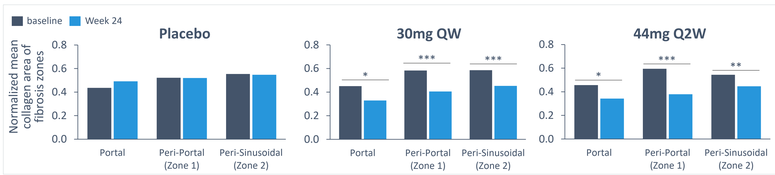
RESULTS

Primary Endpoints: PGZ Demonstrated Statistical Significance on Fibrosis Improvement and MASH Resolution at 30mg QW and 44mg Q2W Dose[1]



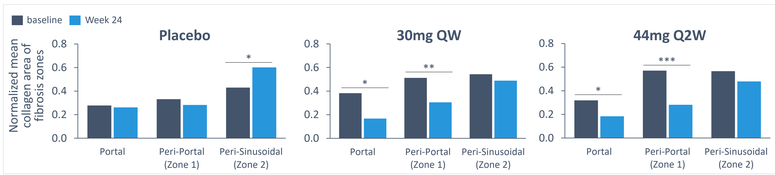
*Relative risk presented is calculated by dividing the drug response by placebo response. Relative risk calculated using statistical methods show similar results.
Source: Full Analysis Set; multiple imputation analysis via Cochran-Mantel-Haenszel (CMH) test stratified by type 2 diabetes mellitus (T2DM) status (yes vs. no) and fibrosis stage (F2 vs. F3).

Fibrosis Zonal Analysis for F2/F3 Shows PGZ Significantly Reduces Fibrosis in Portal, Peri-Portal Zones and Zone 2 for both 30mg QW and 44mg Q2W at Week 24



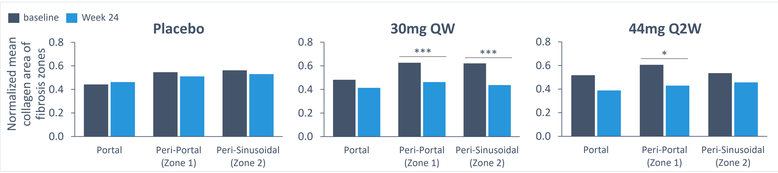
Steatosis-corrected; N=122 (122 cases were F2/3 at baseline by consensus pathology)
Paired t-test is used to determine significance between the Week 24 versus baseline.
*p < 0.05, **p < 0.01, ***p < 0.001

Fibrosis Zonal Analysis for F2/3 at Baseline: Patients with Fibrosis Improvement (≥1-Stage Reduction) According to Consensus Pathology



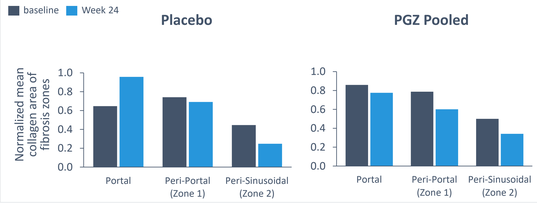
Steatosis-corrected. Paired t-test is used to determine significance between the Week 24 versus baseline.
*p < 0.05, **p < 0.01, ***p < 0.001

Fibrosis Zonal Analysis for F2/3 at Baseline: Patients with No-Change According to Consensus Pathology



Steatosis-corrected. Paired t-test is used to determine significance between the Week 24 versus baseline.
*p < 0.05, **p < 0.01, ***p < 0.001

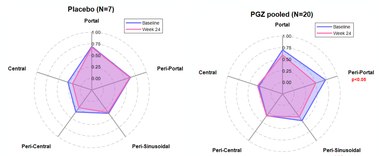
Fibrosis Zonal Analysis for F4 Showing Fibrosis Reduction in Zones 1 and 2 According to Consensus Pathology



- In pathologist-determined F4 patients, similar fibrosis regression was seen in zones 1 and 2, with more modest reductions in other zones.

Steatosis-corrected; N=7 (F4 cases identified at baseline by consensus pathology).
Paired t-test is used to determine significance between the Week 24 versus baseline.

F4 patients staged by qFibrosis: Fibrosis Zonal Analysis Showed Significant Fibrosis Reduction in Zones 1 and 2



Steatosis-corrected; N=27 (F4 cases identified at baseline by qFibrosis staging).
Paired t-test is used to determine significance between the Week 24 versus baseline.

CONCLUSIONS

- Treatment with pegozafermin (PGZ) in MASH patients with F2/F3 fibrosis led to highly significant fibrosis regression and MASH resolution at 24 weeks
- PGZ led to consistent fibrosis improvement trends in portal zone, peri-portal (zone 1), and peri-sinusoidal (zone 2) regression across both non-cirrhotic (F2-F3) and cirrhotic (F4) patients with MASH at 24 weeks.
- Improvement in zonal regions appear to be detectable prior to discernible histologic changes.
- This is the first report of qFibrosis regression in MASH cirrhosis within these clinically meaningful zones.
- The ENLIGHTEN MASH Phase 3 program, evaluating PGZ in both cirrhotic (F4) and non-cirrhotic (F2/F3) populations, is currently underway.

References

[1]Loomba et al, *N Engl J Med* 2023;389:998; [2]Kendall et al. *Liver Int.* 2024; [3]Sun W, Chang S, Tai D C, et al. *Journal of Biomedical Optics*, 2008, 13(6):7-0.