Pegozafermin Led to Improved Liver Histology, Liver-related Non-invasive Tests and Metabolic Profile, With Favorable Safety and Tolerability, in an Open-label Cohort of a Phase 1b/2a Study in Subjects With Non-alcoholic Steatohepatitis

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INTRODUCTION

- FGF21 is an endogenous hormone regulating carbohydrate, lipid, and energy metabolism.
- FGF21 analogs have demonstrated improvements in both liver and extra-hepatic metabolic derangements in non-alcoholic steatohepatitis (NASH).
- Pegozafermin (previously BIO89-100) is a long-acting glycoPEGylated recombinant human FGF21 analog currently in development for the treatment of NASH and other cardio-metabolic diseases.

BACKGROUND

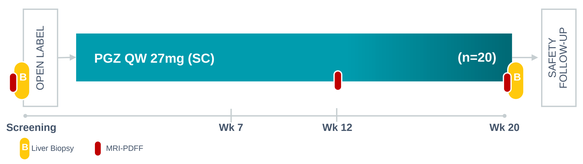
- Previously reported data from Part 1 of a Phase 1b/2a study in subjects with NASH showed that pegozafermin (PGZ) demonstrated:
  - Significant effect on liver and cardio-metabolic parameters
  - Low incidence of treatment-related adverse events (AEs)
  - Potential for every two-week dosing
- Herein, we present data from Part 2 of the Phase 1b/2a study, an open-label histology cohort in subjects with biopsy-confirmed NASH.

OBJECTIVE

To evaluate the effect of PGZ on liver histology in subjects with biopsy-confirmed NASH (NAFLD activity score [NAS] ≥4 and fibrosis stage F2 or F3 per NASH CRN system) following treatment for 20 weeks.

METHODS

Phase 1b/2a NASH Trial Design – Open-Label Cohort



KEY INCLUSION CRITERIA

- Stage 2 or 3 fibrosis; NAS ≥4 (with a ≥1 score in each of steatosis, ballooning, and lobular inflammation)
- MRI-PDFF ≥8%

KEY EXCLUSION CRITERIA

- History or evidence of cirrhosis
- Evidence of liver disease other than NASH
- Recently diagnosed diabetes or HbA1c ≥9.5%

KEY ENDPOINTS

- ≥2 point improvement in NAS
- NASH Resolution
- Fibrosis Improvement
- Safety and tolerability

19/20 (95%) patients completed treatment and had end-of-treatment biopsies; 1 patient discontinued treatment due to withdrawal of consent

Biopsies were centrally read at baseline and at end of treatment by a single pathologist

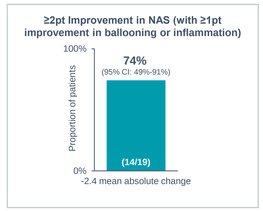
MRI dataset: 18 patients with Week 20 MRI; PD data: 19 subjects with Week 20 data

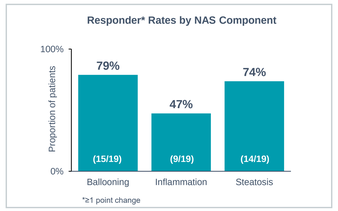
RESULTS

Baseline Characteristics

PARAMETER Mean or %	PGZ 27mg QW (n=20)
Age (years)	58.4
Female	75%
Weight (kg)	104.6
BMI (kg/m^2)	37.0
Type 2 Diabetes	85%
%F2/%F3	35%/65%
HbA1c (%)	6.6%
Triglycerides (mg/dL)	170.0
Non-HDL-C (mg/dL)	125.9
LDL-C (mg/dL)	92.0
HDL-C (mg/dL)	43.4
Adiponectin (µg/dL)	3.55

Pegozafermin Robustly Improved NAFLD Activity Score (NAS) and all Components of NAS

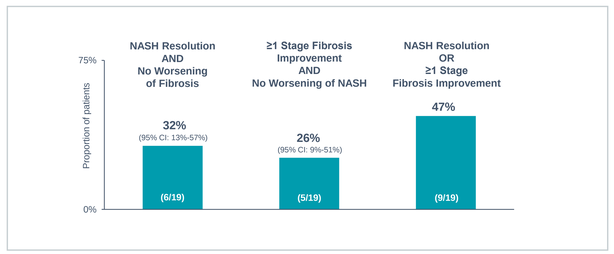




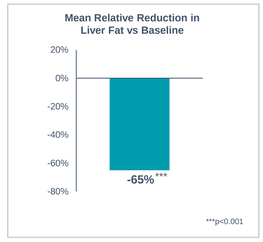
- **63%** of patients had ≥2 point improvement in NAS and no worsening of fibrosis* (nominal primary endpoint).
- **100%** of patients had improvement or no change in ballooning and inflammation.

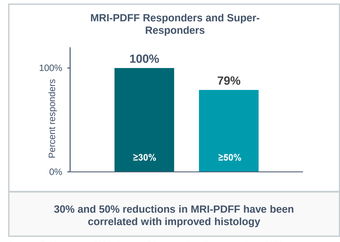
*with ≥1 point improvement in ballooning or inflammation

Pegozafermin Demonstrated Clinically Meaningful Changes on Key Histological Efficacy Endpoints



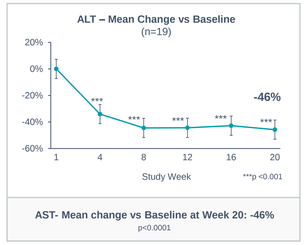
Robust Liver fat Reduction With High Responder Rates as Assessed by MRI-PDFF





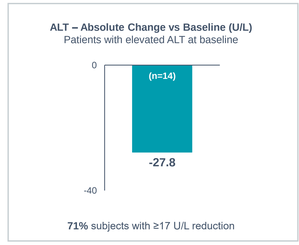
Loomba R, *Hepatology*, 2020; Harrison SA, *Hepatology Communications*, 2021

Pegozafermin Demonstrated Clinically Significant Reduction in ALT



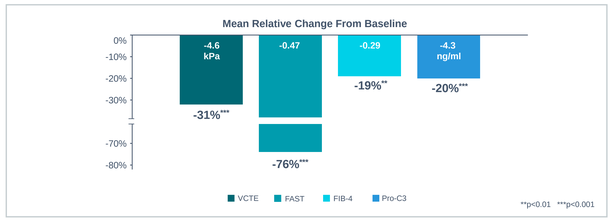
AST- Mean change vs Baseline at Week 20: -46%
p<0.0001

p value for change from baseline based on MMRM analysis



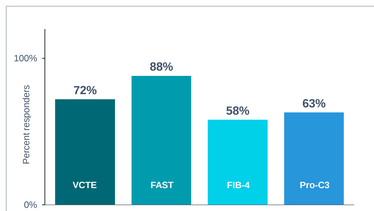
Elevated ALT ≥30 U/L for women and ≥40 U/L for men; Week 20
ALT reduction >=17 U/L has been correlated with favorable histological outcomes
Loomba R, *Hepatology*, 2020

Pegozafermin Substantially Improved Scores Across Non-Invasive Tests (NITs) Correlated With Advanced Fibrosis



Values in bars are absolute change versus baseline
p value for change from baseline based on MMRM analysis
VCTE and FAST exclude one outlier with poor quality measurement

Pegozafermin had High Percentages of Responders Based on Clinically Relevant Thresholds for Non-Invasive Tests (NITs)



***CLINICALLY RELEVANT THRESHOLDS**

- VCTE: >20% reduction correlates with fibrosis improvement
- FAST score: Score ≤0.35 predicts Fibrosis Stage F0/F1 and NAS <4
- FIB-4 score: Score <1.3 predicts Fibrosis Stage F0/F1
- Pro-C3: >15% reduction correlates with fibrosis improvement

*Tapper EB, *Am J Gastroenterol*, 2016; Newsome PN, *Lancet Gastroenterol Hepatol*, 2020; Kanwal F, *Gastroenterology*, 2021; Luo Y, *Scientific Reports*, 2018
VCTE and FAST data exclude one outlier with poor quality measurement

Pegozafermin Demonstrated Clinically Meaningful Improvements on HbA1c, Adiponectin, and Lipid Parameters With Notable Body Weight Reduction

- Absolute Change in HbA1c in the total population (n=19) was -0.05% (p<0.001)
  - In patients with baseline HbA1c≥6.5% (n=10), absolute change was -0.9% (p<0.01)
- Adiponectin was increased 87% (n=18)
- PGZ treatment also had significant favorable effects on various lipid parameters
  - TG levels were reduced 26% (p<0.001); in patients with elevated TG at baseline (≥150 mg/dL; n=11) the reduction was 32% (p<0.001)
  - Non-HDL-C decreased 18% (p<0.001)
  - LDL-C was lowered 13% (p<0.01)
  - HDL-C increased 23% (p<0.001)
- A weight change of -3.9% was observed in the total patient population (p<0.001)

Complete metabolic data presented at Poster SAT143 (Abstract 3654)

Pegozafermin Was Well Tolerated

	PGZ 27mg QW (n=20)
TEAEs leading to death	0
TEAEs leading to treatment discontinuation	0
Treatment-related serious adverse events	0
Treatment-related Grade 3+ adverse events	0
Treatment-related adverse events in ≥10% subjects (preferred term)	
Nausea	7 (35%)
Diarrhea	5 (25%)
Vomiting	2 (10%)
Decreased appetite	2 (10%)
Injection-site bruising	2 (10%)
Injection-site erythema	2 (10%)

- Most gastrointestinal AEs were mild and of short duration.
- No tremors or hypersensitivity AEs reported.

CONCLUSIONS

- In this Phase 1b/2a open-label histology cohort of subjects with NASH, treatment with PGZ (27mg QW for 20 weeks) demonstrated:
  - Meaningful changes on key histology endpoints (NAS >2-point reduction, NASH resolution, and improvement in fibrosis)
  - Reduction in liver fat as assessed by MRI-PDFF
  - Significant changes on liver-related non-invasive tests (NITs), glycemic control (HbA1c and adiponectin), lipid markers, and body weight
  - Favorable safety and tolerability profile
- These results extend the growing evidence of PGZ's potential as treatment for NASH.
- PGZ is currently being evaluated in NASH (NAS ≥4, F2-F3) in the ongoing Phase 2b ENLIVEN study NCT04929483.