Pegozafermin Improved Liver Histology, Liver-Related Non-Invasive Tests (NITs) and Metabolic Profiles 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

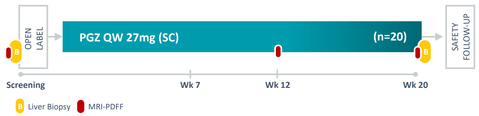
- Previously reported data from Part 1 of a Phase 1b/2a study in subjects with NASH showed that pegozafermin (PGZ) demonstrated:
  - Significant effect on liver and cardio-metabolic parameters
  - Low incidence of treatment-related adverse events (AEs)
  - Potential for every two-week dosing
- Herein,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



METHODS *CONT'D*

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.

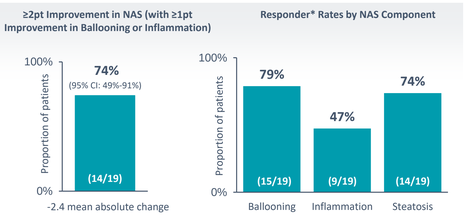
RESULTS

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

RESULTS *CONT'D*

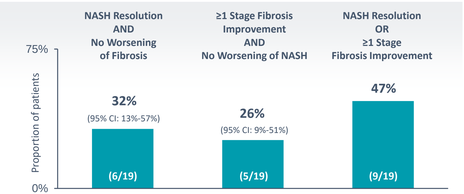
PGZ Robustly Improved NAFLD Activity Score (NAS) and all Components of NAS



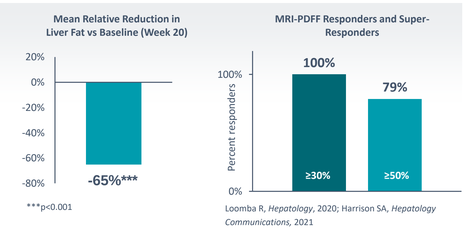
- **63%** of patients had ≥2-point improvement in NAS and no worsening of fibrosis* (nominal primary endpoint).
- **100%** of patients had improvement or no change in ballooning and inflammation.

*with ≥1-point improvement in ballooning or inflammation

PGZ Demonstrated Clinically Meaningful Changes on Key Histological Efficacy Endpoints



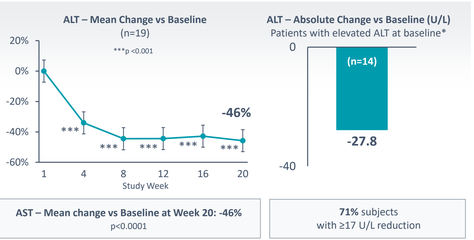
Robust Liver Fat Reduction With High Responder Rates as Assessed by MRI-PDFF



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

- 30% and 50% reductions in MRI-PDFF have been correlated with improved histology

PGZ Demonstrated Clinically Significant Reduction in ALT



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

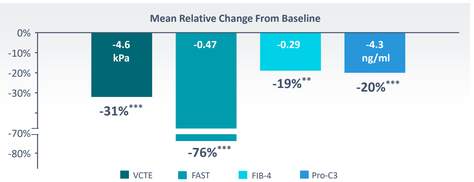
71% subjects with ≥17 U/L reduction

p value for change from baseline based on MMRM analysis

Elevated ALT: ≥30 U/L for women and ≥40 U/L for men
Loomba R, *Hepatology*, 2020

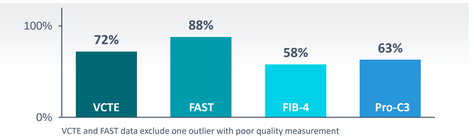
- ALT reduction ≥17 U/L has been correlated with favorable histological outcomes

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



**p<0.01 ***p<0.001
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

PGZ Had High Percentages of Responders Based on Clinically Relevant Thresholds* for Non-Invasive Tests (NITs)



VCTE and FAST data exclude one outlier with poor quality measurement

***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

PGZ 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 -0.5% (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).

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.