Pegozafermin Led to Significant Metabolic Benefits, in Addition to Robust Beneficial Effects on the Liver, in an Open-label Cohort of a Phase 1b/2a Study in Subjects with Non-alcoholic Steatohepatitis (NASH)

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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 NASH.
- Pegozafermin (previously BIO89-100), a long-acting glycoPEGylated recombinant human FGF21 analog in development for NASH, significantly improved liver and cardiometabolic parameters, and demonstrated favorable safety and tolerability, in a Phase 1b/2a study in NASH.

BACKGROUND

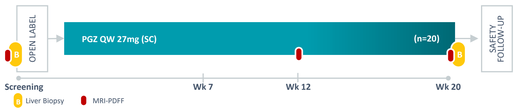
- Obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and dyslipidemia are commonly associated with NAFLD/NASH.
- Metabolic disorders are key drivers of NASH and significant risk factors for cardiovascular (CV) morbidity and mortality in NASH patients, that increases with advancing fibrosis.
- While treatments for NASH would ideally address both liver injury and metabolic perturbations in this population, metabolic liabilities (such as increases in LDL cholesterol) have been a drawback in several NASH drug development programs.

OBJECTIVE

The objective of this open label, 20-week study was to examine the effect of pegozafermin (PGZ) on extra-hepatic metabolic parameters in a biopsy-proven NASH population.

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 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

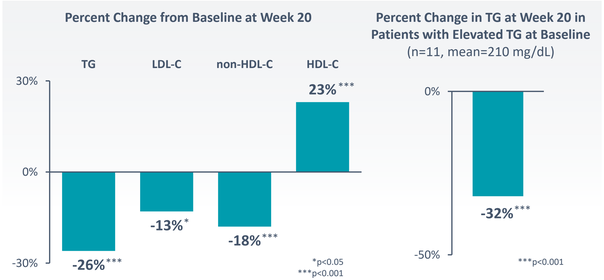
PARAMETER Mean or %	PGZ 27mg QW (n=20)
Age (years)	58.4
Female	75%
Weight (kg)	104.6
BMI (kg/m^2)	37.0
Type 2 Diabetes	85%
%F2/%F3	35%/65%
HbA1c (%)	6.6
Triglycerides (mg/dL)	170.0
Non-HDL-C (mg/dL)	125.9
LDL-C (mg/dL)	92.0
HDL-C (mg/dL)	43.4
Adiponectin (µg/dL)	3.55

Most Common Treatments for Diabetes and Hyperlipidemia

TREATMENT	NUMBER OF SUBJECTS * (subjects may be on more than one treatment)
Metformin	15/19
GLP-1 agonist	5/19
Sulfonylurea	4/19
Statin	11/19

*Subjects who completed treatment (N=19)

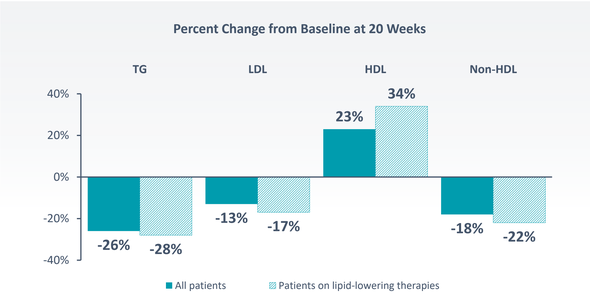
Pegozafermin Demonstrated Clinically Meaningful Improvements in Lipid Parameters



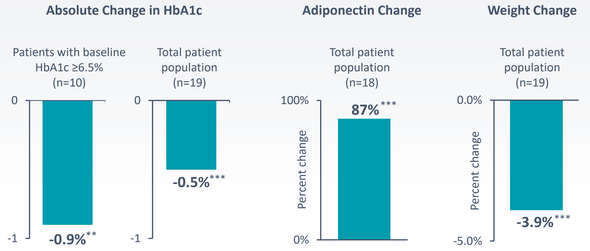
p value for change from baseline based on MMRM analysis

Elevated TG: TG ≥150 mg/dL

Pegozafermin Treatment Demonstrates Meaningful Lipid Benefits for Patients on Background Lipid Lowering Therapies (N=12)



Pegozafermin Demonstrated Clinically Meaningful Improvement on HbA1c and Adiponectin with Notable Body Weight Reduction



HbA1c: Baseline: 7.3%; Week 20: 6.4%

**p<0.01
***p<0.001

Patients with baseline HbA1c ≥6.5% were on an average of 2 anti-diabetic medications

p value for change from baseline based on MMRM analysis

***p<0.001

***p<0.001

Pegozafermin was Well Tolerated

- No treatment related SAEs or AEs leading to discontinuation.
- Most common AEs were nausea and diarrhea.
- Most gastrointestinal AEs were mild and of short duration.
- No tremors or hypersensitivity AEs reported.

CONCLUSIONS

- In a cohort of mostly diabetic NASH subjects with advanced fibrosis, many of whom were on treatment for diabetes, hyperlipidemia or both, PGZ (27 mg QW for 20 weeks) led to meaningful reductions in extra-hepatic metabolic parameters:
  - Significant improvement in serum lipids (TG, LDL-C, non-HDL-C, HDL-C), HbA1c, adiponectin and body weight
  - Marked improvement in serum lipids and HbA1c *on top of treatment for hyperlipidemia or diabetes*
- These benefits were additive to robust beneficial effects on liver histology and favorable safety and tolerability, and suggest a potential of PGZ to protect subjects with NASH not only from liver related outcomes, but also from CV risk
- PGZ is currently being evaluated in NASH subjects (NAS ≥ 4, F2-F3) in the ongoing Phase 2b ENLIVEN study. NCT04929483