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)

Naim Alkhouri[1], Rohit Loomba[2], Juan P Frias[3], Linda Morrow[4], Shibao Feng[5], Leo Tseng[5], Germaine D Agollah[5], Will R Charlton[5], Hank Mansbach[5], Maya Margalit[5], Stephen Harrison[6]

[1]Arizona Liver Health, Tucson, AZ; [2]USCD NAFLD Research Center, La Jolla, CA; [3]Velocity Clinical Research, Los Angeles, CA; [4]Prosciento Inc., San Diego, CA; [5]89bio Inc., Herzliya, Israel, and San Francisco, CA, [6]Pinnacle Clinical Research, San Antonio, TX.

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 (PGZ, 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

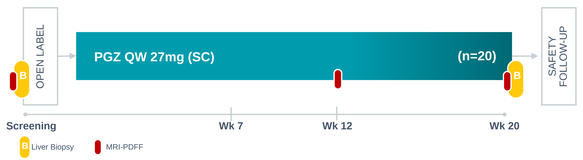
- Obesity, insulin resistance, type 2 diabetes (T2DM) and dyslipidemia are commonly associated with NAFLD/NASH.
- Metabolic disorders are key drivers of NASH and significant risk factors for cardiovascular (CV) morbidity and mortality in NASH patients, that increases with advancing fibrosis.
- While 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 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 (must be stabilized on medication for 3-6 months) 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

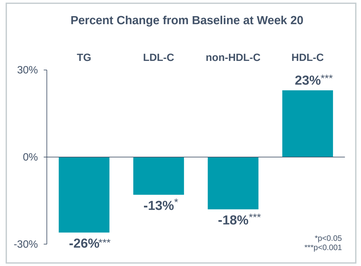
PARAMETER Mean or %	PGZ 27mg QW (n=20)
Age (years)	58.4
Female	75%
Weight (kg)	104.6
BMI (kg/m^2)	37.0
Type 2 Diabetes	85%
%F2/%F3	35%/65%
HbA1c (%)	6.6
Triglycerides (mg/dL)	170.0
Non-HDL-C (mg/dL)	125.9
LDL-C (mg/dL)	92.0
HDL-C (mg/dL)	43.4
Adiponectin (µg/dL)	3.55

Most Common Treatments for Diabetes and Hyperlipidemia

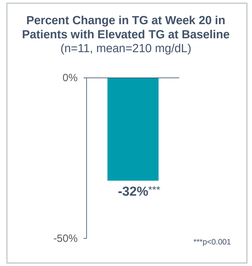
TREATMENT	NUMBER OF SUBJECTS * (subjects may be on more than one treatment)
Metformin	15/19
GLP-1 receptor agonist	5/19
Sulfonylurea	4/19
Statin	11/19

*Subjects who completed treatment (N=19)

Pegozafermin Demonstrated Clinically Meaningful Improvements in Lipid Parameters

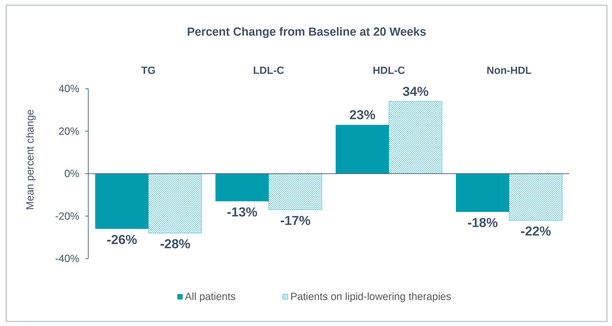


p value for change from baseline based on MMRM analysis

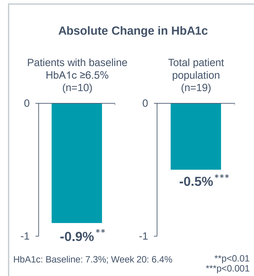


Elevated TG: TG ≥150 mg/dL

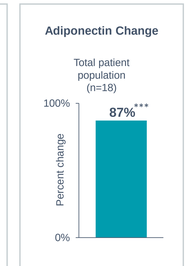
Pegozafermin Treatment Demonstrates Meaningful Lipid Benefits for Patients on Background Lipid Lowering Therapies (N=12)

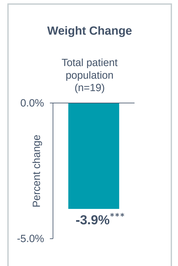


Pegozafermin Demonstrated Clinically Meaningful Improvement on HbA1c and Adiponectin with Notable Body Weight Reduction



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

Pegozafermin was Well Tolerated

- No treatment related SAEs or AEs leading to discontinuation.
- Most common AEs were nausea and diarrhea, 35% and 25% of participants respectively.
- Most gastrointestinal AEs were mild and of short duration.
- No tremors or hypersensitivity AEs reported.

CONCLUSIONS

- In a cohort of NASH subjects with advanced fibrosis, 85% of which had T2D, and 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
- Topline histology and NIT data presented at Poster SAT139 (Abstract 3535)
- PGZ is currently being evaluated in NASH subjects (NAS ≥ 4, F2-F3) in the ongoing Phase 2b ENLIVEN study. NCT04929483