Pharmacokinetics (PK) and Pharmacodynamics (PD) of BIO89-100, a Novel GlycoPEGylated FGF21, in Nonalcoholic Steatohepatitis (NASH) Patients with Compensated Cirrhosis

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INTRODUCTION

- BIO89-100 (pegozafermin) is a long-acting glycoPEGylated analogue of fibroblast growth factor 21 (FGF21) in development for the treatment of non-alcoholic steatohepatitis (NASH) and severe hypertriglyceridemia (SHTG).
- There is a high unmet medical need in NASH as no approved therapy is currently available.
- In a Phase 1b/2a placebo-controlled, double-blind, multiple-ascending dose (MAD) study in noncirrhotic NASH patients (fibrosis stage F1-3), administration of pegozafermin resulted in clinically meaningful reductions in liver fat content and key lipid markers with a favorable safety and tolerability profile. PK/PD of pegozafermin was previously characterized in MAD study and a population PK/PD model was developed.
- The effect of compensated cirrhosis from NASH (fibrosis stage F4) on pegozafermin PK/PD was unknown.

AIM

- Current Phase 1 study was designed to characterize the PK/PD properties of pegozafermin in adult patients with NASH with compensated cirrhosis and evaluate the effect of cirrhosis on pegozafermin PK/PD.

METHOD

STUDY DESIGN

- This was a Phase 1, single center, open-label, single-dose PK study in the US in subjects with NASH with compensated cirrhosis.
- Eligible adults were 21-65 years of age with BMI between 18.5 and 50.0 kg/m^2, F4 fibrosis stage based on Liver Forum criteria and Child-Turcotte-Pugh (CTP) score <7 (Class A).
- Patients received a single 30-mg dose liquid formulation of pegozafermin to the abdomen via subcutaneous (SC) injection on Day 1.
- The primary endpoint was to evaluate PK of pegozafermin liquid formulation in subjects with NASH with compensated cirrhosis.
- Secondary and exploratory endpoints were safety and tolerability of pegozafermin and PD (key lipids and adiponectin levels).
- Blood samples for PK and PD assessment were collected before and at predetermined timepoints after pegozafermin administration and processed to serum.

PK AND PD ASSESSMENTS

- Serum levels of pegozafermin were quantified using a validated LC-MS/MS method.
- For the primary endpoint, PK parameters were estimated by non-compartmental analysis (NCA) methods using Phoenix® WinNonlin® (Ver. 8.3, Certara, Princeton, NJ).
- PD endpoints from the lipid panel (i.e., triglycerides [TGs], low-density lipoprotein cholesterol [LDL-C] and high-density lipoprotein cholesterol [HDL-C]) and adiponectin were evaluated as the absolute change and percent change from baseline to Day 8.
- PK/PD data were consequently compared to historic findings from cohorts 1-6 of the Phase 1b/2a MAD study.

METHOD *continued*

PK/PD Sampling Schedule

Study Day	1	2	3	4	5	6	7	8	15	22
Assessment	Week 1								Week 2	Week 3
PK	x*	x	x	x	x	x	x	x	x	x
Adiponectin	x							x		
Lipid panel	x							x		

* Intensive PK sampling on Day 1 at predose, and at 1hr, 6hr, and 12hr postdose.

KEY INCLUSION CRITERIA

- Male or female subjects must be 21 to 65 years of age with BMI between 18.5 and 50 kg/m^2.
- Diagnosis of NASH with compensated cirrhosis by a hepatologist based on Liver Forum criteria.
- Child-Turcotte-Pugh (CTP) score < 7 (Class A).
- FibroScan VCTE ≥14 kPa.
- Model for End-Stage Liver Disease (MELD) score <12.
- The subject must have had the following laboratory results at screening:
  - Albumin >3.5 g/dL
  - International normalized ratio (INR) <1.7 (without anticoagulant therapy)
  - Total bilirubin <2.0 mg/dL
  - Glomerular filtration rate (GFR) >30 mL/min/1.73 m^2 calculated using CKD-EPI equation
  - Platelet count > 75,000/mm^3

RESULTS

Table 1. Baseline Characteristics

Baseline Parameter	Mean (SD) or Percentages (N=8)
Age (years)	53.3 (11.1)
Female	62.5%
Body weight (kg)	103 (20.3)
BMI (kg/m^2)	37.4 (5.38)
Race, White	100%
T2DM	37.5%
ALT (U/L)	33.9 (19.5)
ALP (U/L)	137 (33.6)
AST (U/L)	39.1 (14.7)

Baseline Parameter	Mean (SD) or Percentages (N=8)
Triglycerides (mg/dL)	119 (31.7)
FibroScan VCTE (kPa)	28.9 (15.2)
LSM > 20 kPa	75%
FibroScan CAP (dB/m)	307 (37.9)
Platelet count (10^9/L)	150 (61.2)
Platelet counts <150 x 10^9/L	50%
Bilirubin (mg/dL)	0.91 (0.627)
Albumin (g/dL)	4.11 (0.356)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body-mass index; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; T2DM, Type 2 diabetes mellitus.

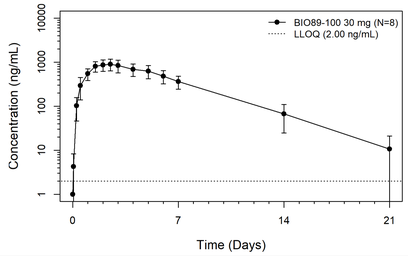
Table 2. Summary of Baseline FibroScan Results Relative to MAD Study

Statistic	FibroScan VCTE (kPa)		FibroScan CAP (dB/m)	
	F4 PK Study	MAD Study	F4 PK Study	MAD Study
N	8	81	8	81
Mean	28.9	7.29	307	352
SD	15.2	2.11	37.9	33.1

CAP, controlled attenuation parameter; SD, standard deviation; VCTE, vibration-controlled transient elastography.

RESULTS *continued*

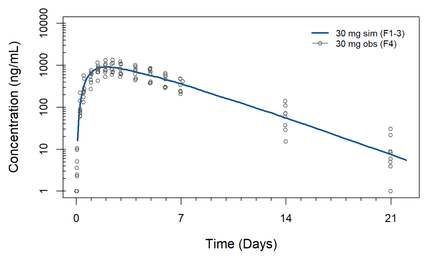
Figure 1. Mean PK Profile of Pegozafermin Following a Single 30-mg SC Dose of Pegozafermin in Patients with F4 NASH



PK RESULTS

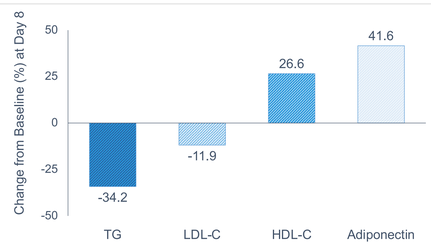
- PK profile of pegozafermin was well-characterized in NASH subjects with compensated cirrhosis following a single SC dose of 30 mg.
- Pegozafermin was slowly absorbed following SC administration with a median T_{max} of 57.2 hours (range, 34.7 to 70.2 hours).
- PK profile declined in monophasic fashion (Figure 1) with mean elimination $t_{1/2}$ of ~ 62 h consistent with those previously documented following single SC doses of pegozafermin in healthy volunteers.

Figure 2. Simulated (F1-F3) vs. Observed (F4) PK Profiles Following a 30-mg Single Dose of Pegozafermin



- Simulated PK profile using previously developed popPK model based on F1-3 data overlapped with the observed F4 PK data, indicating PK similarity between the two populations and that compensated cirrhosis does not affect pegozafermin PK (Figure 2).

Figure 3. Single Treatment with Pegozafermin Resulted in Metabolic Benefits in Key Biomarkers



RESULTS *continued*

PD RESULTS

- Assessment of the effect of pegozafermin on prespecified lipid biomarkers (HDL-C, LDL-C, and triglycerides) indicated a robust metabolic benefits (Figure 3).
- Pegozafermin also demonstrated significant increases in adiponectin (mean increase, 41.6%), a hormone associated with anti-steatotic, anti-inflammatory, and anti-fibrotic properties.
- PD effects are in alignment with the prior MAD data and did not indicate differences between F4 vs. F1-F3 population.

SAFETY

- Treatment-emergent AEs (TEAEs) were reported for 6 subjects (75.0%); all mild (Grade 1) in severity.
- None of the TEAEs were considered treatment-related.
- There were no deaths, adverse events with of special interest (AESIs), serious adverse events (SAEs), or discontinuations due to AEs during the study.
- There were no clinically meaningful trends or changes in clinical laboratory tests, vital signs, 12-lead ECGs, or physical examinations that were attributable to pegozafermin.
- Overall, single dose of pegozafermin in liquid formulation administered subcutaneously in adult subjects with NASH with compensated cirrhosis at 30 mg was safe and well tolerated with no treatment-related SAEs.

CONCLUSIONS

- Pegozafermin elicits a robust PK/PD effect independent of NASH fibrosis stage. These findings highlight the feasibility of assessing treatment response in F4 patients with compensated hepatic function without requiring dose adjustment.
- A favorable safety and tolerability profile was observed following a single 30-mg dose.
- Overall, these PK/PD properties warrant further investigation to allow assessments of effectiveness of pegozafermin in a larger F4 population.

ACKNOWLEDGEMENTS

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REFERENCES

Pegozafermin is currently investigated in a Phase 2b trial for NASH (ENLIVEN; NCT04929483) and a Phase 2 trial for SHTG (ENTRIGUE; NCT04541186).

Learn more about the pegozafermin trials at clinicaltrials.gov.