Effect of Moderate and Severe Hepatic Impairment on Pharmacokinetics, Safety and Tolerability of Pegozafermin After Subcutaneous Administration

Eric Lawitz[1], Leo Tseng[2], Kemal Balic[2], Hank Mansbach[2], Mildred Gottwald[2], Madhavi Rudraraju[3]

[1]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, Texas, USA, [2]89bio, Inc., R&D, San Francisco, California, USA, [3]Pinnacle Clinical Research, San Antonio, Texas, USA

INTRODUCTION

- Pegozafermin (PGZ) is a long-acting glycoPEGylated analog of fibroblast growth factor 21 (FGF21) in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and severe hypertriglyceridemia (SHTG).
- The liver plays a crucial role in drug disposition, and hepatic impairment (HI) may alter the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a drug such that dosage adjustments could be required.
- PGZ is presumed to be metabolized by proteases/peptidases into amino acids, with renal excretion being the predominant elimination pathway.
- Understanding PK in the HI population is essential to inform dosing recommendations for the PGZ program.

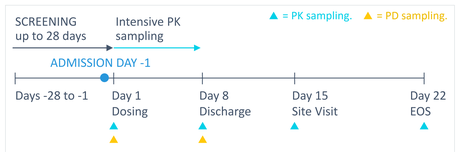
AIM

- This Phase 1 study was designed to assess the PK, safety and tolerability of PGZ in subjects with moderate and severe hepatic impairment (HI) from any etiology, including those with MASH.
- The subset of HI subjects with MASH was included to evaluate if there was a disease-specific effect.
- Findings from this study will guide dosing recommendations in patients with varying degrees of HI.

METHODS

Study Design

- Open-label, multicenter, parallel-group, Phase 1 PK study enrolled subjects with moderate (n=8) and severe (n=6) hepatic impairment (including 2 MASH subjects in each category) and 12 healthy control subjects matched by age, sex, and body weight.



- Hepatic impairment was classified according to the Child-Turcotte-Pugh (CTP) score at screening.[1]
- Subjects were administered a single SC dose of PGZ 30 mg via prefilled syringe on Day 1.

METHODS

PK/PD Assessments and Statistical Analyses

- Serial PK samples were collected predose through 21 days postdose and analyzed for PGZ serum concentrations using a validated LC-MS/MS method.
- PK parameters were calculated by standard non-compartmental methods using Phoenix® WinNonlin® (version 8.3; Certara, Princeton, NJ, USA).
- Analysis of covariance (ANCOVA) on the log-transformed C_{max} and AUC was performed in SAS; geometric least-squares (LS) mean ratios and 90% CIs were constructed. The model included hepatic function and sex as classification factors, and body weight and age as continuous covariates.
- Exploratory biomarkers (adiponectin and lipid panel) were assessed as change from baseline to Day 8.
- Standard safety assessments (laboratory tests, vital signs, ECGs, physical exam) were conducted across groups.

RESULTS

Baseline Characteristics

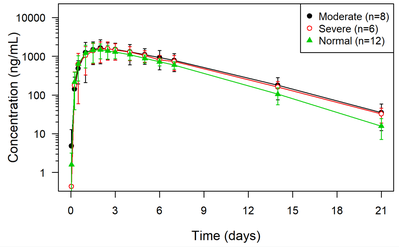
Characteristic	Normal (n=12)	Moderate HI (n=8)	Severe HI (n=6)
Age (years)	50.6 (8.98)	58.1 (5.33)	48.2 (10.7)
BMI (kg/m²)	31.5 (6.84)	31.0 (6.33)	38.1 (8.95)
CTP Score	NA	7.9 (0.83)	10.8 (0.75)
MELD Score	NA	9.8 (1.49)	16.5 (3.62)
Male, n (%)	8 (66.7)	6 (75.0)	4 (66.7)
Race, n (%)			
White	10 (83.3)	7 (87.5)	6 (100)
Black or African American	1 (8.3)	0	0
American Indian or Alaska Native	1 (8.3)	1 (12.5)	0
Ethnicity, n (%)			
Hispanic or Latino	7 (58.3)	5 (62.5)	4 (66.7)
MASH, n (%)			
Yes	0	2 (25.0)	2 (33.3)
Other Baseline Parameters/Exploratory Biomarkers			
Adiponectin (µg/mL)	7.6 (3.3)	15.8 (11.9)	29.1 (23.6)
HDL-c (mg/dL)	52.6 (7.0)	53.9 (11.5)	56.8 (23.6)
Triglycerides (mg/dL)	89.3 (33.5)	81.5 (39.1)	84.0 (11.4)
LDL-c (mg/dL)	110 (37.3)	79.8 (24.5)	83.0 (51.3)

BMI = body mass index; CTP = Child-Turcotte-Pugh; MASH = metabolic dysfunction-associated steatohepatitis; MELD = Model for End-Stage Liver Disease; NA = not applicable.
Data are presented as mean (SD) or proportions, as appropriate.

RESULTS

PK RESULTS (PRIMARY ENDPOINT)

Mean PK Profiles by Hepatic Function Group After Single SC 30 mg Dose of PGZ



Comparison between subjects with HI and healthy controls show:

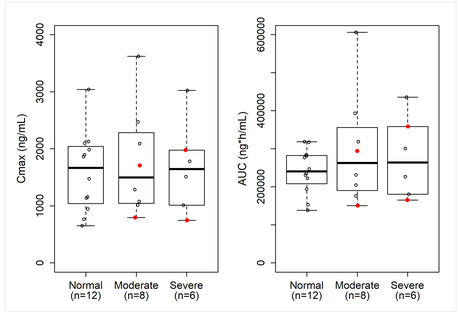
- No trend in exposure relative to hepatic impairment degree.
- Comparable T_{max} (median: 54 to 60 hours), indicating no effect of HI on absorption profile of PGZ.
- Mean apparent clearance was similar between groups (0.121 – 0.133 L/h), confirming that moderate or severe HI did not meaningfully affect the elimination of PGZ.

Statistical Analysis Summary of PGZ Serum PK Parameters

Parameter	Comparison	N	Geometric LS Mean	Ratio (90% CI)
C_{max} (ng/mL)	Normal	12	1502	--
	Moderate/Normal	8	1787	1.19 (0.792, 1.79)
	Severe/Normal	6	1578	1.05 (0.670, 1.65)
$AUC_{0\text{-}inf}$ (ng*h/mL)	Normal	12	238701	--
	Moderate/Normal	8	278732	1.17 (0.862, 1.58)
	Severe/Normal	6	284432	1.19 (0.852, 1.67)

- No clinically significant difference in exposure across different HI groups consistent with elimination pathway of PGZ.
  - Geometric LS mean C_{max} and AUC in moderate and severe HI were within 20% of healthy controls

Comparison of Serum PGZ Exposure in MASH vs. Non-MASH Subjects and Across Hepatic Function Groups



Symbols indicate individual observations; solid red symbol denotes subjects with MASH. Box shows IQR; whiskers extent to the min and max values.

- Serum exposure (C_{max} and AUC) in MASH subjects was within the range observed in non-MASH subjects.
- Overall, hepatic impairment had no clinically relevant effect on PGZ exposure.

PD RESULTS (EXPLORATORY)

- Mean baseline adiponectin levels were approximately 2- to 4-fold higher in the HI groups compared with healthy controls.
- Adiponectin, a hormone associated with anti-fibrotic, anti-inflammatory, and anti-steatotic properties, was increased with PGZ treatment across all groups.
- Assessment of the effect of PGZ on lipid biomarkers also indicated metabolic benefits (↑HDL-c, ↓TG) across all hepatic function groups.

SAFETY/TOLERABILITY

- Single SC dose of 30 mg PGZ was safe and well tolerated in adult subjects with varying degrees of HI.
- Treatment-emergent AEs (TEAEs) were reported in 11 subjects (42.3%): 5 in normal, 4 in moderate and 2 in severe HI group.
- No notable safety differences or trends in laboratory values were observed between HI and healthy controls.
- There were no deaths, sponsor-defined events to monitor, serious adverse events (SAEs), or discontinuations due to AEs during the study.
- No new or unexpected safety concerns were identified.

Summary of Most Common TEAE by Hepatic Function Group

TEAE	Normal (N=12) n (%)	Moderate (N=8) n (%)	Severe (N=6) n (%)
Diarrhea	0	2 (25.0)	0
Vomiting	1 (8.3)	1 (12.5)	0
Increased Appetite	1 (8.3)	1 (12.5)	0
Headache	2 (16.7)	0	0
Hypertension	2 (16.7)	0	0

TEAE = treatment-emergent adverse event.

CONCLUSIONS

- PGZ was safe and well tolerated across subjects with HI and healthy controls.
- Moderate and severe HI, including the presence of MASH, had no clinically meaningful effect on the pharmacokinetics of PGZ.
- No dose adjustment is warranted for subjects with varying degrees of hepatic function impairment.

REFERENCES

1. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the esophagus for bleeding esophageal varices. *Br J Surg.* 1973;60(8):646-649.

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DISCLOSURES

- Eric Lawitz, MD: **Researcher:** 89bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Cour Pharmaceuticals, Corcept Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., Northsea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, Zydus Pharmaceuticals.
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