Pegozafermin inhibits NASH-induced hepatocellular carcinoma in the STAM™ mouse model

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INTRODUCTION

Pegozafermin (PGZ)

- FGF21 is an endogenous hormone that regulates carbohydrate, lipid, and energy metabolism.
- FGF21 exerts its biological effect through the activation of FGFR1c, FGFR2c, and FGFR3c, and requires co-activation of the transmembrane protein cofactor KLB, which is predominantly expressed in metabolic organs, including the liver, white adipose tissue, and the pancreas, and therefore confers organ specificity to FGF21. FGF21 does not activate FGFR4, which has been associated with mitogenic effects.
- PGZ, a long-acting glycoPEGylated recombinant human FGF21 analog in development for NASH, has demonstrated activation of FGFR1c, 2c, and 3c at low nanomolar potency without activation of R4.
- In a phase 2b study in NASH patients (ENLIVEN), PGZ 30mg QW and 44mg Q2W significantly improved liver histology, non-invasive liver tests, and cardiometabolic parameters, with favorable safety and tolerability.

NASH-associated hepatocellular carcinoma (HCC) and the Stelic Animal Model (STAM™)

- HCC, previously viewed as a complication of cirrhotic NASH, is increasingly diagnosed in pre-cirrhotic NASH.
- In the STAM™ mouse model, administration of streptozocin to newborn C57BL/6 mice, followed by feeding of a high fat diet, causes progressive NASH, fibrosis, and—ultimately—HCC.
- HCC appears at ~16 weeks of age and develops universally at ~20 weeks of age. In HCC prevention studies, treatment typically begins between 6-12 weeks of age.
- PGZ dosed SC at 0.1mg/kg, 0.5mg/kg, 2mg/kg, and 6mg/kg 3 times a week was shown to improve liver histology, liver transaminases, and various metabolic parameters in STAM™ mice in a previous study.

OBJECTIVE

The objective of this study was to evaluate the effect of PGZ on the development of HCC in the STAM™ mouse model.

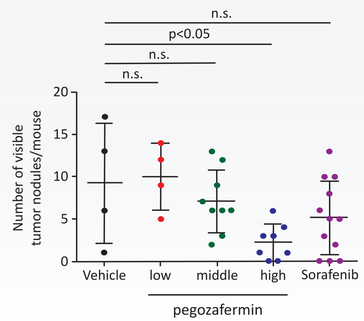
METHODS

NASH-associated hepatocellular carcinoma and the STAM™ model

- STAM™ mice (12 or 13 weeks old, male, n=20 per group) were treated by vehicle, PGZ (previous name BIO89-100) at 1 of 3 doses (low dose: 0.3mg/kg; middle dose: 1.0mg/kg; high dose: 3.0mg/kg) 3 times a week, or a positive control, sorafenib (30mg/kg once daily).
- Mice were treated for 9 weeks, starting at Week 12 (n=16 per group) or Week 13 (n=4 per group).
- All surviving animals were sacrificed at 20 or 21 weeks of age.
- At time of sacrifice, the number of surviving animals and liver weight, liver weight/body weight ratio, and the number of visible tumor nodules on the liver surface in surviving mice were assessed.

RESULTS

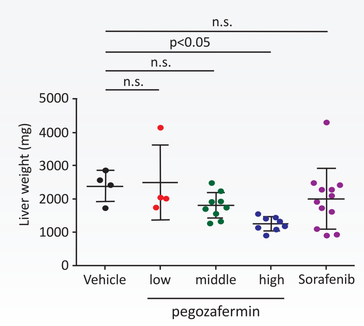
Effect of PGZ on the Number of Macroscopic Tumor Nodules



Treatment arm	Visible tumor nodules per mouse mean (±SD)
Vehicle	9 ± 7
Low-dose PGZ	10 ± 4
Middle-dose PGZ	7 ± 4
High-dose PGZ	2 ± 2*
Sorafenib	5 ± 4

*p<0.05

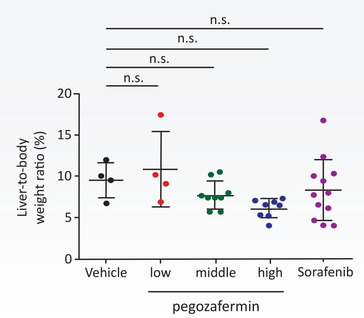
Effect of PGZ on the Liver Weight



Treatment arm	Liver weight mean (±SD) (mg)
Vehicle	2391 ± 473
Low-dose PGZ	2498 ± 1120
Middle-dose PGZ	1802 ± 391
High-dose PGZ	1252 ± 210*
Sorafenib	2013 ± 916

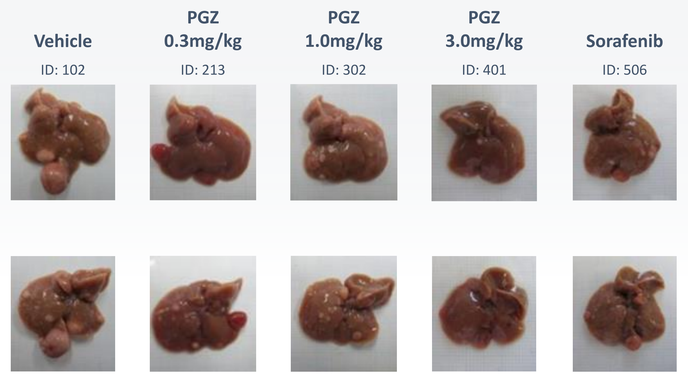
*p<0.05

Effect of PGZ on Liver Weight/Body Weight Ratio



Treatment arm	Liver weight/body weight mean (±SD)
Vehicle	9.6 ± 2.2
Low dose PGZ	11.0 ± 4.6
Middle dose PGZ	7.8 ± 1.7
High dose PGZ	6.2 ± 1.1
Sorafenib	8.4 ± 3.8

Representative Macroscopic Appearance of Liver at Week 20/21



Effect of Pegozafermin on Survival

Treatment arm	Survival at Week 20/21 N (%)
Vehicle	4/20 (20%)
Low-dose PGZ	4/20 (20%)
Middle-dose PGZ	9/20 (45%)
High-dose PGZ	8/20 (40%)
Sorafenib	12/20 (60%)

Differences were not statistically significant

CONCLUSIONS

- In STAM™ mice, PGZ treatment led to a dose-related decrease in HCC tumor nodules and tumor burden relative to vehicle, that was statistically significant and comparable to that achieved with the positive control sorafenib for the PGZ 3mg/kg dose.
- The mechanism of this anti-tumor effect remains to be fully elucidated, and may be speculated to be related to the beneficial effects of PGZ on NASH and fibrosis or to a direct anti-tumor effect.
- The STAM™ model recapitulates the human NASH–HCC sequence. Translation of the observed benefits in this model would add to the potential for PGZ to become an important treatment for NASH patients.
- Planning is underway for PGZ to enter phase 3 in NASH.