No Increase in the Risk of Liver or Muscle Toxicity in Pegozafermin-treated Patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH) on Statin Background Therapy

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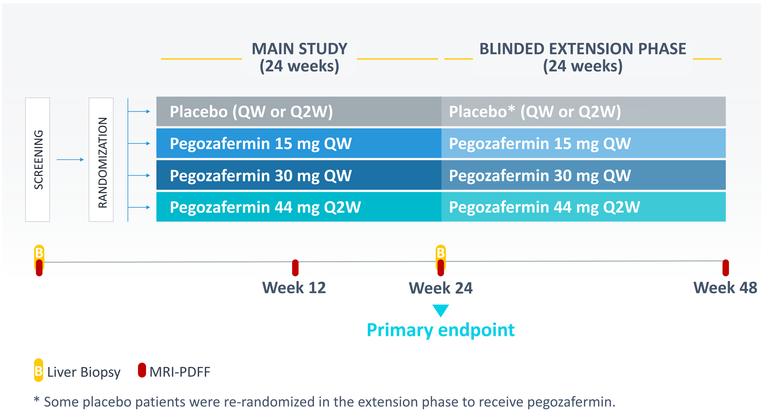
BACKGROUND

- 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).
- Administration of FGF21 has been suggested to decrease hepatic CYP3A4 activity (Woolsey et al., 2016).
- Statins, many of which are CYP3A4 substrates, are commonly used in patients with MASH and SHTG, raising a potential concern about increased statin exposure and toxicity, including liver or muscle toxicity.
- Overall, the objective of this post-hoc analysis from the ENLIVEN Phase 2b study presented herein was to assess for the presence of liver or muscle toxicity in PGZ-treated patients who were on background statin therapy as a potential manifestation of this putative Drug-Drug-Interaction (DDI).

METHODS

- ENLIVEN was a randomized, double-blind, placebo-controlled Phase 2b study to evaluate the efficacy, safety, and tolerability of PGZ administered subcutaneously (SC) in subjects with biopsy-confirmed MASH.

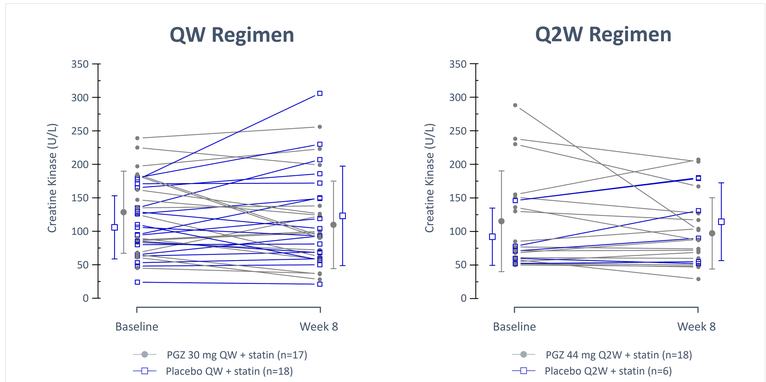


* Some placebo patients were re-randomized in the extension phase to receive pegozafermin.

- In the current analysis, patients were stratified based on treatment group and statin use:
  - Only statins metabolized by the hepatic isoenzyme CYP3A4 (atorvastatin, simvastatin and lovastatin) were considered.
- To account for differences in $t_{1/2}$ of statins (short and long-acting) and sufficient statin treatment duration, the analysis included only patients who were on statins continuously from baseline to at least Week 6.
- Adverse events (AEs) related to the liver or muscle toxicity were evaluated in all patients.
- Elevated creatine kinase levels were reviewed and assessed for potential safety signals resulting from statin administration.
- Changes in creatine kinase (CK), alanine transaminase (ALT), aspartate transferase (AST), low-density lipoprotein cholesterol (LDL-c), and triglycerides (TGs) were assessed in PGZ-treated and placebo patients on background treatment with statins.

SAFETY RESULTS

Figure 1. Creatine Kinase Comparison Before and After Treatment with Placebo or PGZ in MASH Patients on Background Statin Therapy



Note: Symbols with lines are individual observations; symbols with error bars represent mean and standard deviation for each respective group. One patient from the 44 mg Q2W cohort was excluded due to abnormally high baseline value (outlier). The subject in the QW regimen with a substantial increase in CK levels up to ~ 300 U/L was on placebo.

- No significant change in CK levels from baseline to Week 8 in placebo or in patients treated with the highest PGZ dose (30 mg QW or 44 mg Q2W) with statin background therapy.
- There was no evidence of an increase in CK levels when pegozafermin is co-administered with statins.

Table 1. Overview of Relevant Safety Events Related to Statin Use

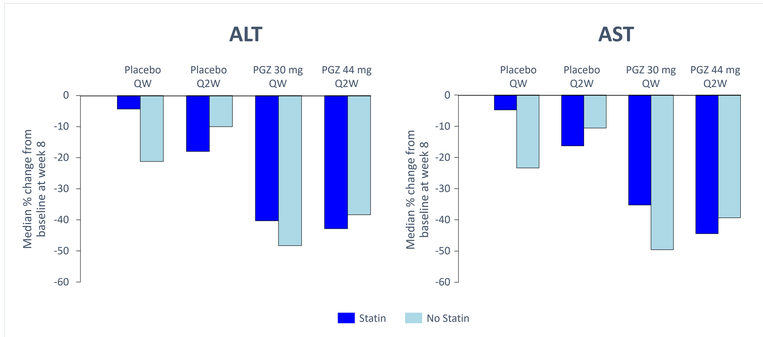
Event	Placebo (N=69)	15 mg QW (N=21)	30 mg QW (N=72)	44 mg Q2W (N=57)
Adverse event according to preferred term (Safety analysis population)*				
Muscle spasms, n (%)	1 (1)	1 (5)	7 (10)	0
Muscle strain, n (%)	0	0	1 (1)	2 (4)
Myalgia, n (%)	1 (1)	0	1 (1)	0
Muscular weakness, n (%)	1 (1)	1 (5)	0	0
Rhabdomyolysis, n (%)	0	1 (5)	0	0

* The safety analysis population included all the patients who received at least one dose of pegozafermin or placebo. Data from the placebo groups were pooled. All AEs were Grade 1 or Grade 2, except for one case of Grade 3 muscle strain (unrelated; pulled hamstring) in the 30 mg QW cohort.

- No difference in the AE profile of PGZ-treated patients with or without background statin therapy, including liver and muscle-related AEs.
- No hepatotoxic effects were observed.
- Myalgia, a common AE and reason for discontinuation of statin treatment, was reported in only two patients who were on background statin therapy (Table 1).
- Overall, no enhanced statin side-effects or trend of increased statin-induced muscle toxicity was observed.
- One case of worsening chronic rhabdomyolysis (Grade 2, deemed unrelated) was noted in the lowest PGZ cohort (15 mg QW), but was confounded by baseline CK levels being ~ 4-fold higher than the upper limit of normal (ULN).
  - No additional AEs suggestive of muscle toxicity were reported in this subject.

PD RESULTS

Figure 2. Effect on Liver Function Tests from PGZ With or Without Statins



Note: Number of subjects: placebo QW (n=18-22), placebo Q2W (n=6-13), PGZ 30 mg QW (n=17-48), PGZ 44 mg Q2W (n=19-34).

- Independent of statin co-administration, the benefits of PGZ on liver function enzymes were observed; no increase in liver function tests (ALT/AST) with the co-administration of statins (Figure 2).
- Separately, statistical analysis show that the reduction in lipids was not statistically different between subjects with or without statin background therapy. Median ratios (PGZ + statin/PGZ alone) for percent change from baseline at Week 8 ranged from 0.79 to 1.68 for LDL-c and from 1.13 to 1.28 for TG across dose groups.
- Potential DDI based on the PD biomarkers is therefore not supported.

CONCLUSIONS

- In this post-hoc analysis from the ENLIVEN Phase 2b study in MASH, there was no evidence of liver-related or muscle toxicity in PGZ-treated subjects on background statin therapy. These findings are reassuring, as they may indicate the absence of a clinically meaningful DDI between statins and PGZ that could result from putative decrease in CYP3A4 metabolism. Consequently, PGZ patients can continue their statin regimen in the absence of notable concerns about experiencing increased statin toxicity.

ACKNOWLEDGEMENTS

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REFERENCE

- Woolsey, S. J., Beaton, M. D., Mansell, S. E., Leon-Ponte, M., Yu, J., Pin, C. L., et al. (2016). "A Fibroblast Growth Factor 21-Pregnane X Receptor Pathway Downregulates Hepatic CYP3A4 in Nonalcoholic Fatty Liver Disease." *Mol Pharmacol* 90(4): 437-446.