Efruxifermin treatment improved histopathology and non-invasive markers of liver injury and fibrogenesis in NASHi patients across PNPLA3 genotypes: a post hoc analysis of the Ph2a BALANCED study

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BACKGROUND

Efruxifermin (EFX) is a long-acting Fc-FGF21 analogue being developed as a potential therapeutic for patients with fibrosis due to non-alcoholic steatohepatitis (NASH). In the phase 2A BALANCED study (NCT03788634) of patients with biopsy-confirmed NASH (F1–4), 8-week treatment with EFX significantly reduced liver fat content and improved markers of liver injury, bone, and lipid and glucose metabolism while demonstrating an acceptable safety and tolerability profile9.

Aims

This post hoc analysis evaluated the prevalence of PNPLA3 variants in a patient population, all of whom had biopsy-confirmed F1–F3 NASH. The study also evaluated clinical and biomarker characteristics present in 148M heterozygous or homozygous patients with NASHi. Finally, the effect of EFX treatment on histopathological markers of liver health and whole body metabolism were evaluated across PNPLA3 genotypes.

METHODS

58 patients were randomly assigned to the BALANCED main study (Fig. 1). Of those, 79 received at least one dose of study drug. Week 12 data were available for 68 patients, and at least one biopsy confirmed F1–3 NASH. The primary outcome across genotypes was post-hoc treatment biopsy, preventing meaningful within-group comparisons across genotypes.

RESULTS

• Table 1: Frequency of PNPLA3 genotypes in BALANCED Main Study

CONCLUSIONS

• In BALANCED, patients genetically predisposed to progressive disease, i.e., PNPLA3 I/M or M/M carriers, presented with differences in histopathology of comparable severity, but were younger and less insulin resistant than non-carriers.

Carriers of PNPLA3 I/M or M/M genotypes were at high risk of progression to ELD.

EFX improved markers of liver injury across PNPLA3 genotypes, notably among MM homozygotes, for whom these markers tended to worsen when untreated over 16 weeks.

EFX reduced markers of liver injury across PNPLA3 genotypes, notably among MM homozygotes, for whom these markers tended to worsen when untreated over 16 weeks.

EFX improved HDL cholesterol across PNPLA3 genotypes.

EFX improved metabolic health of liver both in patients whose NASHi carries a significant genetic component, but also in patients whose NASHi appears to be driven primarily by metabolic dysfunction, e.g., T2D.

ACKNOWLEDGMENTS

The authors wish to thank the patients, their families, and study investigators. This study and all analyses were funded by Akeo Therapeutics.

REFERENCES


Histological improvements were maintained in patients at high risk of progression to ELD.

EFX significantly improved liver manifestations of metabolic disease across PNPLA3 genotypes.