Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening.

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Résumé en anglais	BACKGROUND & AIMS: Elafibranor is an agonist of the peroxisome proliferator-activated receptor-α and peroxisome proliferator-activated receptor-δ. Elafibranor improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation. We assessed the safety and efficacy of elafibranor in an international, randomized, double-blind placebo-controlled trial of patients with nonalcoholic steatohepatitis (NASH). METHODS: Patients with NASH without cirrhosis were randomly assigned to groups given elafibranor 80 mg (n = 93), elafibranor 120 mg (n = 91), or placebo (n = 92) each day for 52 weeks at sites in Europe and the United States. Clinical and laboratory evaluations were performed every 2 months during this 1-year period. Liver biopsies were then collected and patients were assessed 3 months later. The primary outcome was resolution of NASH without fibrosis worsening, using protocol-defined and modified definitions. Data from the groups given the different doses of elafibranor were compared with those from the placebo group using step-down logistic regression, adjusting for baseline nonalcoholic fatty liver disease activity score. RESULTS: In intention-to-treat analysis, there was no significant difference between the elafibranor and placebo groups in the protocol-defined primary outcome. However, NASH resolved without fibrosis worsening in a higher proportion of patients in the 120-mg elafibranor group vs the placebo group (19% vs 12%; odds ratio = 2.31; 95% confidence interval: 1.02-5.24; P = .045), based on a post-hoc analysis for the modified definition. In post-hoc analyses of patients with nonalcoholic fatty liver disease activity score ≥4 (n = 234), elafibranor 120 mg resolved NASH in larger proportions of patients than placebo based on the protocol definition (20% vs 11%; odds ratio = 3.16; 95% confidence interval: 1.22-8.13; P = .018) and the modified definitions (19% vs 9%; odds ratio = 3.52; 95% confidence interval: 1.32-9.40; P = .013). Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared with those without NASH resolution (mean reduction of 0.65 ± 0.61 in responders for the primary outcome vs an increase of 0.10 ± 0.98 in nonresponders; P < .001). Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation were significantly reduced in the elafibranor 120-mg group vs the placebo group. Elafibranor was well tolerated and did not cause weight gain or cardiac events, but did produce a mild, reversible increase in serum creatinine (effect size vs placebo: increase of 4.31 ± 1.19 µmol/L; P < .001). CONCLUSIONS: A post-hoc analysis of data from trial of patients with NASH showed that elafibranor (120 mg/d for 1 year) resolved NASH without fibrosis worsening, based on a modified definition, in the intention-to-treat analysis and in patients with moderate or severe NASH. However, the predefined end point was not met in the intention to treat population. Elafibranor was well tolerated and improved patients' cardiometabolic risk profile. ClinicalTrials.gov number: NCT01694849.
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