1-INTRODUCTION

A polymorphism of patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M, is strongly associated with the risk for and the progression of nonalcoholic steatohepatitis (NASH). Lanifibranor, a pan-PPAR agonist, has shown efficacy on histological disease activity and fibrosis as well as on metabolic-immune markers of NASH in the phase 2b NATIVE study, corresponding to the role of PPAR signaling in the disease biology of NASH. We evaluated the impact of the PNPLA3 variant I148M on the histologic and metabolic-immune response to lanifibranor.

2-MATERIAL/METHODS

NATIVE [2] evaluated lanifibranor 800 and 1200 mg/d versus placebo in 247 patients with non-cirrhotic NASH for 24 weeks of treatment. Of these, 219 patients consented to genotyping for the PNPLA3 rs738409 SNP. Sixty five were II, 105 IM and 49 MM, which is highest risk for disease severity and progression. Paired liver biopsy results were available for 207/219 patients. Histologic and metabolic-immune marker response was evaluated by PNPLA3 genotype.

3-RESULTS

There was no significant difference in demographics between the PNPLA3 types, although those with MM genotype were younger (mean age 50.9 vs 55.4 for II and 53.1 for IM) and were more likely to have Type 2 Diabetes (45% MM, 38% II, 41% IM).

There was no significant difference in response to lanifibranor by PNPLA3 genotype, despite the fact that MM genotype patients had more activity on biopsy than the II or IM patients (82% NAs≥E, vs 74%, 70%), while there was no difference in fibrosis.

4-CONCLUSION

The efficacy of lanifibranor on both liver histology and markers of cardiometabolic health appears to be independent of PNPLA3 status, despite MM genotype patients having more severe activity on liver biopsy.

References:


Contact information:
Vice President Clinical Development, INVENTIVA, Louis H. Griffel: Louis.GRiffel@inventivapharma.com