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An international, phase 2 randomized controlled trial of the dual PPAR α-δ agonist GFT505 in adult patients with NASH

Category: Steatosis and Steatohepatitis

Descriptor: QO2. Steatohepatitis: Clinical and Therapeutic

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Peroxisome proliferator-activated receptor α-δ dual agonists, such as GFT505, are a promising therapy for NASH as they improve hepatic insulin sensitivity, glucose homeostasis, lipid metabolism, and inflammation.

Methods: In this randomized controlled trial (56 European and US centers) 274 patients (pts) (full analysis set, FAS) with histologically-defined non-cirrhotic NASH received GFT505 80 mg or 120 mg QD vs placebo (PLB) for one year. The primary outcome was resolution of NASH without worsening of fibrosis. Data were analyzed according to baseline severity (histological NAS score) and center effect. Biopsies were read by a single pathologist.

Results: 237 pts had entry and end-of-treatment biopsies (ITT population). While the a priori primary endpoint did not meet significance, after controlling for baseline severity and center effect, pts in the 120 mg arm had a 1.94 (CI 1.08-3.48, p=0.027) higher relative risk (RR) of achieving the primary end-point compared to PLB, while the RR was 1.68 (0.92-3.05, p=0.091) for the 80 mg arm. Results were similar in the FAS where pts missing the second biopsy were counted as failures. In pts with moderate activity (NAS 4 or 5) the response rate was 27.5% in the 120 mg arm vs. 19.5% for the PLB arm. In those with severe activity (NAS>5) it was 14.8% vs. 0%, respectively. In the 120 pts with NAS>4 from centers that recruited >1 patient/arm, the response rate was 29% and 5% in the 120 mg and PLB arms, respectively, p=0.01. A >2 point NAS reduction was obtained in 48% and 21% of patients respectively, p=0.01. Compared to PLB, the 120 mg arm improved ballooning (45% vs. 23%, p=0.02), inflammation (55% vs. 33%, p=0.05) and steatosis (35.5% vs. 18%, NS). In the 120 mg arm, resolution of NASH, resulted in a significant improvement in fibrosis (mean change -0.67 vs. +0.09 in non-responders, p<0.001). In the ITT population, pts in the 120 mg arm had improved ALT, GGT and ALP, non-invasive fibrosis panels (NFS Angulo score and FibroTest) and systemic inflammatory markers, hsCRP, haptoglobin, fibrinogen, α2macroglobulin. Importantly, cardiometabolic risk markers such as triglycerides, LDL-C, HDL-C, improved significantly in the 120 mg group (ITT population) vs. PLB, as well as HbA1c and FFA in diabetic pts, all on top of standard of care therapies. Tolerability was excellent without weight gain, cardiac events or safety signal.

Conclusion: In NASH patients 120 mg daily of GFT505 induced histological improvement and resolution of NASH, significantly more often than PLB. The excellent safety and tolerability and the improvement in cardiometabolic risk profile makes GFT505 an ideal drug candidate to be tested in phase 3 trials

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