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JKB-121 in patients with nonalcoholic steatohepatitis: A phase 2 double blind randomized placebo control study

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Background and Aims: NASH is a rapidly growing cause of chronic liver disease worldwide with significant medical need for effective treatments. TLR-4 is a key mediator of obesity-associated inflammation, insulin resistance and hepatic inflammation and fibrosis. JKB-121 is a weak antagonist of the TLR-4 receptor demonstrated to prevent NASH in a methionine/choline deficient diet fed rat model of NAFLD, decrease NASH and fibrosis in STAM model and inhibit hepatic stellate cell activation and collagen expression in vitro. The aim of this study was to assess the safety/tolerability and biologic activity of JKB-121 in patients with biopsy-proven NASH.

Methods: This is a multicenter, randomized (1:1:1), double-blind, placebo-controlled study in adults with biopsy-proven NASH with a NAS ≥ 4 (1 point in each component), stage 1-3 fibrosis, ≥6 % liver fat content (LFC) by MRI-PDFF, and elevated liver aminotransferases (ALT > 40 U/l for women and > 60 U/l for men). Randomization was stratified by diabetes status. Patients received JKB-121 5 mg, 10 mg, or placebo twice daily for 24 weeks. The primary endpoint was reduction in LFC by MRI-PDFF and/or serum ALT at 24 weeks. Exploratory endpoints included serum biomarkers (FIB4, Fibro Test).

Results: 65 patients were randomized (median age, 51.0 years; woman, 68%; type 2 diabetes 66%; median BMI 35.2; median LFC 17.3%; median ALT 69 ± 36 U/l). Baseline characteristics, including histologic grade and stage, LFC, and biochemical parameters were comparable among groups. At week 24, median relative and absolute LFC improved in all groups with no difference in JKB-121 treatment groups compared to placebo ($p>0.05$). At week 24, in JKB-121 5 mg, 10 mg vs placebo, change in ALT was -5.4 U/l, -3.8 U/l, and -15.2 U/l, $p> 0.05$) with biochemical remission (ALT< 40 U/l on two consecutive measures) in 28.5%, 18.2%, and 31.8%, respectively, ($p>0.05$). JKB-121 did not improve BMI, glycosylated hemoglobin, HOMA-IR, total-, LDL-, HDL-cholesterol or triglycerides compared to placebo. Fib4 improved in the placebo group ($p< 0.05$). The most frequent drug-related adverse events (AEs) in JKB-121-treated patients were nausea (26.4% vs 22.7% in placebo), dizziness (36% vs 0%), constipation (9.1% vs 4.5%), vomiting (14.3% vs 4.5%), fatigue (9.1% vs 4.5%), and most AEs were mild. Serious AEs occurred in two patients; neither were considered drug-related. There were no deaths. Drug-related AEs leading to withdrawal in 10 mg, 5 mg vs placebo occurred in 27.3%, 9.5% vs 0%, respectively.

Conclusions: A notable improvement in LFC, ALT and FIB4 was observed in the placebo group in this 24 week NASH study. JKB-121 did not further improve the response rate in patients with NASH (F1-F3) compared to placebo. Given the multiple relevant biologic pathways of TLR-4 in pathogenesis NASH, further investigation of TLR-4 inhibition, as well as factors contributing to higher placebo response rates, is warranted.

Table 1			
	Placebo (n=22)	JKB-121 5 mg (n=21)	JKB-121 10 mg (n=22)
Median relative LFC Δ (SE) from baseline to week 24 *vs placebo*	-2.30% (4.27%) *	1.10% (4.82%) *p=0.03*	-2.40% (5.15%) *p=0.17*
Median absolute LFC Δ (SE) from baseline to week 24 *vs placebo*	3.30% (3.27%)*	3.20% (2.88%)* *p=0.57*	4.40% (2.55%)* *p=0.66*
Patients with>5% relative reduction in LFC (% pts)	63%	41%	64%
20% reduction in ALT at week 24 (% patients)	91%	57%	41%
Biochemical Remission	33.3%	27.8%	30.8%
Δ in Fibro Test (SE) from baseline to week 24	-0.036 (0.06)	0.002 (0.09)	0.013 (0.12)
Δ in Fib4 (SE) from baseline to week 24	-0.38 (0.67)*	-0.09 (0.61)	0.08 (0.80)
Completed Study	21 (95.5%)	18 (85.7%)	13 (59.1%)
Drug-related adverse events	0	2 (9.5%)	6 (27.3%)
Withdrawal /Lost to follow-up	1 (4.8%)	1(4.8%)	3 (13.6%)
**** p<0.05***			