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Early assessment of safety and efficacy of tropifexor, a potent non bile-acid FXR agonist, in patients with primary biliary cholangitis: An interim analysis of an ongoing phase 2 study

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Background and Aims: In patients with primary biliary cholangitis (PBC), incomplete response to first-line therapy with ursodiol (UDCA) is associated with increased risk of cirrhosis and death. The bile acid FXR agonist obeticholic acid is approved as second-line therapy for PBC. Tropifexor (LJN452) is a selective and highly potent, non-bile acid FXR agonist that reduces cholestasis and hepatocellular damage in rodent models. This trial was designed to test the safety, tolerability and preliminary efficacy of tropifexor in PBC patients.

Method: This ongoing multi-part, international, double blind, placebo controlled, ascending dose Phase 2 study enrolled PBC patients with an inadequate response to UDCA (ALP≥1.67xULN or Bilirubin >ULN), who were taking UDCA. Patients were randomized in cohorts (approx. 10 active to 5 placebo) to receive 30 µg, 60 µg or 90 µg of tropifexor once daily, or matching placebo, for 4 weeks. A planned interim analysis was conducted on completion of Cohort 3 (90 µg tropifexor). The pre-specified primary efficacy outcome was change in GGT from baseline to avoid the confounding effect of FXR mediated induction of ALP. Safety analyses included number of subjects to discontinue, evaluation of adverse events and laboratory markers.

Results: There were no deaths, non-fatal serious adverse events or discontinuations due to adverse events or itch. Baseline demographic and biochemical parameters were similar across groups (ALP 358, 317, 281 and 323 iU for pooled placebo, 30, 60 and 90 µg tropifexor arms). There was a brisk decrease in GGT, ALP, ALT and AST (tabulated below) with 72% reduction in GGT at 90 µg tropifexor at day 28. Biochemical markers had not yet reached their maximum changes at completion of dosing. Reductions in HDL of 33% and 26% occurred at doses of 60 µg and 90 µg tropifexor respectively and returned to baseline by end of study. There was no increase in total or LDL cholesterol at any dose of tropifexor tested.

Conclusion: Tropifexor was generally safe and well tolerated at the doses tested. The dose dependent activity on markers of cholestasis (GGT) and hepatocellular damage (ALT) indicates the potential benefit of FXR agonism by tropifexor in PBC. The absence of discernible increase in itch raises the possibility that tropifexor may have a tolerability advantage over obeticholic acid. Tropifexor shows promise as a potential future therapy for PBC and longer term studies are warranted.

Figure: Summary of mean change (%) from baseline at day 28 and repeated measures analysis for LFT parameters

%change	Placebo (n=16)	Tropifexor 30 µg (n=10)	Tropifexor 60 µg (n=9)	Tropifexor 90 µg (n=12)
GGT	-15	-26	-59**	-72**
ALP	-2	-10	-26*	-15
Bilirubin	-9	-9	-1	-17
Albumin	-1	2	-3	1
ALT	0	10	-30*	-41**
AST	-5	9	-14	-26*

*p<0.05 **p<0.001 vs placebo by repeated measures of analysis of covariance of log-transformed ratio to baseline