ABSTRACT TITLE: EFFICACY AND SAFETY OF MARALIXIBAT IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (MARCH-PFIC): A RANDOMIZED PLACEBO-CONTROLLED PHASE 3 STUDY

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Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders resulting in disrupted bile composition, cholestasis, and pruritus. We evaluated maralixibat, an ileal bile acid transporter inhibitor, in a Phase 3 placebo-controlled study open to participants of all PFIC types at higher doses than previously studied.

Methods: Participants aged 1-18 years with moderate-severe pruritus and elevated serum bile acid (sBA) levels were randomized 1:1 to maralixibat 570 µg/kg BID or placebo for 26 weeks. Primary and key secondary endpoints were mean change from Baseline in pruritus (0-4 ItchRO scale) and sBA, in the BSEP cohort. Mean change in pruritus and sBA were also analyzed in All-PFIC cohort.

Results: 93 participants were enrolled (maralixibat=47, placebo=46): 31 in BSEP cohort, 64 in All-PFIC cohort (31 BSEP, 13 FIC1, 9 MDR3, 7 TJP2, 4 MYO5B), 29 in exploratory cohort. Mean Baseline age, sBA, pruritus, and liver biochemistries were balanced. Mean reduction in pruritus for maralixibat vs placebo was -1.7 vs -0.6 ($p=0.0098$) in BSEP cohort and -1.8 vs -0.6 ($p<0.0001$) in All-PFIC cohort. 64% (maralixibat) vs 26% (placebo) of participants achieved clinically meaningful 1-point pruritus reduction ($p=0.0023$). Mean reduction in sBA for maralixibat vs placebo was -176 vs. 11 µmol/L ($p=0.0013$) in BSEP cohort and -

157.5 vs. 2.9 ($p<0.0001$) in All-PFIC cohort. In All-PFIC cohort, total and direct bilirubin, and weight significantly improved under maralixibat. The most common adverse event, diarrhea, was mild and transient.

Conclusions: In the largest clinical study in PFIC, maralixibat significantly improved pruritus, sBA, bilirubin, and growth, and was well-tolerated.