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Abstract

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

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ABSTRACT BODY:

Abstract Body : 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 with all PFIC types at higher doses than previously studied.

Methods: Participants aged 1-18 years had moderate to severe pruritus and elevated serum bile acid (sBA) levels. Participants were randomized 1:1 to maralixibat 570 µg/kg twice daily or placebo for 26 weeks. Primary and key secondary endpoints were mean change from Baseline in pruritus and sBA, respectively, in participants with non-truncating BSEP deficiency (BSEP cohort). Mean change in pruritus and sBA were also analyzed in the All-PFIC cohort (BSEP cohort plus other PFIC types).

Results: 93 participants were enrolled (maralixibat=47, placebo=46): 31 in the BSEP cohort, 64 in the All-PFIC cohort (31 BSEP, 13 FIC1, 9 MDR3, 7 TJP2, 4 MYO5B) and 29 in the exploratory cohort (heterozygosis, variants not found, post-surgical, intermittent sBA). Mean baseline age, sBA, pruritus, and liver biochemistries were balanced between groups. Mean reduction in pruritus (0-4 ItchRO scale) for maralixibat vs placebo was -1.7 vs -0.6 ($p=0.0098$) in the BSEP cohort and -1.8 vs -0.6 ($p<0.0001$) in the All-PFIC cohort. 64% (maralixibat) vs 26% (placebo) of participants achieved a 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 the BSEP cohort and -157.5 vs. 3 µmol/L ($p<0.0001$) in the All-PFIC cohort. In the All-PFIC cohort, total and direct bilirubin and weight significantly improved under maralixibat vs placebo. The most common adverse event was diarrhea (57.4% maralixibat vs 19.6% placebo; mostly mild and transient, median duration 5.5 days).

Conclusions: In the largest clinical study in children with PFIC, maralixibat significantly reduced pruritus and sBA and improved bilirubin and growth, with a well-tolerated safety profile.

(No Image Selected)

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DISCLOSURE STATEMENT: Study conforms to the principles of the Declaration of Helsinki.

DISCLOSURE STATEMENT: Study conforms to the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society.

Disclosure of Relevant Financial Relationships : Financial relationships to disclose.

Extra Info: Mirum Pharmaceuticals, Inc.:Consulting Fee:Consulting

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