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Abstract

TITLE: ANALYSIS OF LONG-TERM SAFETY IN MARALIXIBAT-TREATED PARTICIPANTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: DATA FROM MARCH-ON

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ABSTRACT BODY:

Abstract Body : Background: Maralixibat (MRX) is a novel, minimally absorbed, orally-administered inhibitor of the ileal bile acid transporter (IBAT) that interrupts the enterohepatic circulation of bile acids to reduce toxic bile acids and improve cholestatic pruritus. In MARCH, a 26-week, randomized, placebo-controlled, Phase 3 study (N=93) for patients with progressive familial intrahepatic cholestasis (PFIC), MRX was well tolerated with mild/self-limiting diarrhea and abdominal pain being the most commonly reported gastrointestinal adverse events (AEs) and were more common in the treatment group vs placebo (PBO). Bilirubin increase and fat-soluble vitamin (FSV) deficiency events were more frequent in the PBO group, and ALT laboratory assessments were not different between groups. MARCH-ON is an ongoing, open-label, long-term extension study for participants who completed MARCH. In this interim safety analysis up to 106 weeks, we describe the evidence of safety with longer follow-up, and inclusion of the MARCH PBO participants into MARCH-ON, adding to the overall safety analysis.

Methods: Treatment-emergent AEs (TEAEs) and laboratory data from MARCH-ON were analyzed longitudinally for all participants who opted to enroll (N=85) as of June 23, 2022. Safety was assessed for participants who received PBO in MARCH and initiated MRX in MARCH-ON (PBO-MRX group: n=38) and for participants who received MRX in MARCH and continued beyond 26 weeks of treatment into MARCH-ON (MRX-MRX group; n=47). Data are reported below for events of interest using pooled FDA Medical Query (FMQ) terms (gastrointestinal events, transaminases increased, bilirubin increased, and FSV deficiency).

Results: In MARCH-ON, mean (SD) exposure in all MRX-treated participants was 340 (205) days [MRX-MRX: 386 (205) days; PBO-MRX: 284 (193) days]. There were 82 (96.5%) participants with a TEAE, with the most common affected system being gastrointestinal (n=63; 74.1%). Overall, 7 (8.2%) had a severe AE, none of which were considered related to MRX; 14 (16.5%) had a serious AE with 1 (1.2%) considered related to MRX (increased blood bilirubin). There was 1 (1.2%) death due to respiratory infection and not related to MRX. Three participants (3.5%) had 4 AEs (diarrhea; bilirubin and ALT increase; and cirrhosis) leading to discontinuation. The proportion of participants with AEs of interest from the PBO-MRX group in MARCH-ON were lower than those observed from the MRX-treated participants from MARCH for diarrhea (13 [34.2%] vs 27 [57.4%]), abdominal pain (8 [21.1%] vs 12 [25.5%]), hyperbilirubinemia (1 [2.6%] vs 7 [14.9%]), transaminases increased (5 [13.2%] vs 8 [17.0%]), and FSV deficiency (10 [26.3%] vs 13 [27.7%]). Participants who previously received MRX in MARCH and did not report an event were less likely to report an event in MARCH-ON. New initial onsets of the following terms were reported: diarrhea (n=3), increased bilirubin (n=3), transaminases increased (n=1), and FSV deficiency (n=4).

Conclusions: In this safety analysis of long-term treatment with MRX out to 106 weeks from MARCH-ON, no new safety signals were observed. The frequency of events was slightly lower than previously reported and decreased over time in participants with extended follow-up. MRX was well-tolerated overall, as evidenced by a low rate of discontinuation.

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

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