An integrated analysis of long-term clinical safety in maralixibat-treated patients with Alagille syndrome

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Introduction

• Alagille syndrome (AGS) is a rare, life-threatening, autosomal dominant, multisystem disease, characterized by bile duct paucity and failure to thrive; the pruritus associated with AGS can be extremely debilitating and lead to sleep deprivation.1

• Maralixibat (MRX) is a selective sodium taurocholate cotransporter (NTCP) inhibitor that interrupts the enterohepatic circulation of bile acids, leading to significant and durable reductions in serum bile acids and cholestatic pruritus.2

• Maralixibat has been approved by the US FDA for the treatment of cholestatic pruritus in patients with AGS at least 1 year of age.

• The safety database for MRX now comprises 1800 participants, including 88 patients with AGS, which is the largest database for AGS.

Aim

• To evaluate the overall clinical safety of MRX in an integrated population of patients with AGS when treated with MRX for 5 years.

• To conduct a sub-analysis of safety data in the 13-week placebo-controlled, LUM001-303, and LUM001-302 studies.

Methods

• Study design—Patients entered from three Phase 3 clinical studies (and their extension studies) of MRX-treated patients with AGS and were included in an integrated analysis of adverse events (AEs):
  - Studies LUM001-303 (NCT02057692) and LUM001-302 (NCT01903460) were 13-week, randomized, placebo-controlled, Phase 2 studies.
  - Study LUM001-301 (NCT02117713) and LUM001-303 (NCT03737813) were 13-week, randomized, placebo-controlled, Phase 2 studies.

• MRX was administered according to a dose-escalation schedule over the first 5 weeks of treatment in studies LUM001-301 and LUM001-302 up to 295 µg/kg/day.

• In LUM001-304, MRX was administered according to a dose-escalation schedule over 6 weeks of treatment to a final dose of 295 µg/kg/day. Patients were increased to BID dosing, starting after week 113.

• Ongoing patients from studies LUM001-303, LUM001-303, and LUM001-302 were rolled over into the long-term safety study MRX-800 (NCT04168385).

Statistical analysis

• Safety data were analyzed across the integrated population, including treatment-emergent AEs (TEAEs) and laboratory parameters (multiple Medical Dictionary for Regulatory Activities [MedDRA] categories).

• AEs were reported for all patients who had baseline data and were exposed to treatment and were analyzed for reported treatments, either as a single event, or time-to-first-event and potential dose-response relationships.

• The data set for the present analysis was taken on December 1, 2019.

Results

Baseline characteristics and treatment duration

• In total, 38 patients with AGS treated with MRX were included in this integrated safety analysis.

• Baseline patient demographics and sub-analysis populations are shown in Table 2.

• Mean age of treatment exposure was 32.2 months, with a total of 39 months of treatment with MRX (>5 years). (Table 2)

• The most common TEAEs were pruritus, severe skin rash, and abdominal pain.

• The mean CSS score (SD) was 4.9 (1.7) at baseline.

• The number of TEAEs evaluated as moderate or severe was higher in the placebo group compared to the MRX group.

• Treatment-emergent adverse events

• A total of 62 patients (71.7%) had at least 1 TEAE reported to be potentially related to study treatment (Table 3).

• Most TEAEs were mild to moderate in severity, treated with 13-week placebo-controlled studies (≤30.5%); serious AEs (≥1.5%) occurred in 4 patients (3.6%).

• Fourteen patients (16.3%) had a TEAE that led to MRX discontinuation (Table 3).

• The most common TEAEs were diarrhea and abdominal pain, and the incidence was highest in the subgroup of patients who experienced diarrhea or abdominal pain in nature, and resolved with no action taken with MRX (Table 4).

• The majority of gastrointestinal (GI) events lasted for less than 2 days for diarrhea and 1 day for abdominal pain.

• Treatment-emergent GI events occurring in at least 5% of MRX patients.

Conclusions

• MRX was well tolerated over 5 years across an integrated ALGS population (N = 86).

• Mild-to-moderate GI effects were observed in the first weeks of treatment and lasted less than 1 week in duration:

  - Placebo-controlled data indicate that GI effects occur in the background of ALGS.

  - There were no discontinuations of MRX treatment due to diarrhea or abdominal pain.

  - ALT elevations appear to be consistent with the natural history of ALGS.

• This integrated analysis demonstrated that up to 5 years of treatment with MRX is well tolerated, and that MRX has an acceptable safety profile.