Canada's Drug and Health Technology Agency

**CADTH Reimbursement Review**

# CADTH Reimbursement Recommendation

(Draft)

Maralixibat (Livmarli)

Indication: For the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS).

Sponsor: Mirum Pharmaceuticals Inc.

Recommendation: Do Not Reimburse


Version: 1.0
Publication Date: October 2023
Report Length: 17 Pages


**Single Technology**

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## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that maralixibat not be reimbursed for cholestatic pruritis in patients with Alagille syndrome (ALGS).

## Rationale for the Recommendation

CDEC recognized that pruritus can be a severe symptom of ALGS and that current treatment options are generally not effective. However, based on the evidence reviewed, CDEC identified several limitations in the evidence that did not allow the committee to draw conclusions on whether maralixibat will provide benefit for patients in the real world setting. Evidence from 1 phase 2b, open-label, placebo-controlled study (ICONIC) suggested during the withdrawal phase of the study, patients who continued on maralixibat exhibited improvements in serum bile acid (sBA), the primary efficacy endpoint, and maintained improvements in pruritis (secondary efficacy endpoint not adjusted for multiple comparison) as assessed by the ItchRO(Observed) [ItchRO(Obs)] and ItchRO(Patient) [ItchRO(Pt)] weekly morning severity scores compared to placebo from week 18 to week 22. CDEC noted that sBA is not of relevance in clinical practice since it is not often assessed due to high costs and logistical limitations, and that there is a lack of evidence validating the correlation between sBA levels and improvement in pruritis. In addition, CDEC noted the enrichment trial design, small numbers of participants analyzed as part of the primary endpoint (only 5 participants received maralixibat), and the short duration of the randomized withdrawal portion of the trial (4 weeks) thus limiting the ability to assess the long-term efficacy and safety of maralixibat.

Patients identified a need for an effective symptomatic and curative treatment for cholestatic pruritis in ALGS that reduced the frequency and severity of pruritis, reduced patient and caregiver fatigue. CDEC was unable to determine whether maralixibat would meet any of these needs given the concerns with evidence previously described.

## Discussion Points

- Given the uncertainty in the clinical evidence, CDEC considered the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. CDEC acknowledged the rarity of this condition and concluded that the criteria allowing for additional uncertainty in the evidence were met. However, CDEC concluded that the submitted evidence was insufficient to determine the value of maralixibat as a treatment option for patients with ALGS and cholestatic pruritis in Canada.
- Although data from ICONIC may show an association between decreased fasting sBA and improvement in pruritis scores as assessed by the ItchRO(Obs) and ItchRO(Pt) weekly morning severity scores, the data were descriptive in nature and the assessment was conducted post-hoc on a small number of patients (n=28). Therefore, CDEC noted that it is unclear the extent to which sBA levels may be associated with pruritis in patients with cholestatic liver diseases.
- CDEC noted that although patients expect new treatments for cholestatic pruritis in ALGS to improve quality of life, this expectation was not met by maralixibat, because no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence. CDEC also heard from clinical experts that improvement in pruritis may result in delaying the need for liver transplantation, possibly by years, and even reducing mortality. To address this gap, the sponsor submitted a natural history study comparing maralixibat-treated patients with ALGS to an external control cohort. Despite the results of the natural history study suggesting improvement with maralixibat on event-free and transplant-free survivals, limitations inherent to the observational study design warrant concern when interpreting the results.
- CDEC noted that during the long-term extension phase of the ICONIC pivotal trial (week 103) eligible patients could have received a dose of maralixibat of up to 760 mcg/kg/day (given as twice-daily doses of 380 mcg/kg) which is outside of the proposed Health Canada indication of 380 mcg/kg /day. As such, CDEC concluded that efficacy and safety data after this period is not aligned with the recommended dose.
- CDEC discussed ethical and equity considerations related to maralixibat, including those related to the significant physical, emotional, and psychosocial burden of living, and caring for someone, with ALGS, especially due to cholestatic pruritus. The committee also discussed how pediatric patients may be considered particularly vulnerable as they depend on their parents to provide the necessities of life, and in the context of ALGS, to advocate and facilitate access to their diagnosis and support for their condition. The committee discussed the limitations of considering the opportunity costs of reimbursing maralixibat as a high-cost drug for a rare disease in the context of a single drug review. Additionally, the committee noted the need for broader discussions around Canadian values, health system priorities, and system sustainability to inform considerations of opportunity costs.

## Background

ALGS is a rare, life-threatening, genetic disorder that that presents with a range of clinical features including cholestatic liver disease, failure to thrive, cardiovascular disease, skeletal abnormalities, ocular abnormalities, renal and vascular abnormalities, and distinct facial features. Elevated levels of serum bile acids (sBAs) and jaundice (elevated bilirubin) are hallmarks of ALGS and indicate the presence of impaired bile flow, also known as cholestasis. Cholestasis could manifest as debilitating and intractable pruritus, which typically presents in the first few years of life and as early as 3 months of age and is the leading cause of liver transplant in patients with ALGS. The reported incidence of ALGS is 1 in 30,000 to 50,000 births. There is currently no approved treatment for cholestatic pruritus associated with ALGS. Off-label drugs, including antihistamines, ursodeoxycholic acid, rifampicin, cholestyramine, sertraline, and naltrexone may be used, although patients often find them ineffective and may require surgical interventions (surgical biliary diversion and liver transplant).

Maralixibat has been approved by Health Canada for the treatment of cholestatic pruritus in patients with ALGS. It is an ileal bile acid transporter inhibitor. It is available as a 9.5 mg/mL oral solution and the dosage recommended in the product monograph is 380 mcg/kg once daily in the morning after 1 week of a starting dose of 190 mcg/kg orally once daily. The maximum daily dose in volume for patients above 70 kg is 3 mL.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal phase 2b, double-blind, RCT, 1 long-term extension of the RCT, and 2 additional studies addressing gaps in evidence
- patients' perspectives gathered by 2 patient groups, including the Canadian Liver Foundation (CLF) and the Alagille Syndrome Alliance (ALGSA)
- input from public drug plans that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating cholestatic pruritus in patients with ALGS
- input from 1 clinician group, including the Canadian Association for the Study of the Liver
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to maralixibat

## Stakeholder Perspectives

### Patient Input

Two patient groups, the CLF and the ALGSA, provided input. The CLF is the only national health charity committed to support Canadians impacted by the liver diseases. Based in the U.S., the ALGSA is a non-profit organization dedicated to support families affected by ALGS globally. The CLF submission included phone/virtual interviews conducted in May 2023 with 8 Canadian patients and caregivers. Of those, 4 respondents had experiences with maralixibat through clinical trials. The ALGSA gathered data online through family surveys (2020), personal conversations, and topic specific discussions among support/focus groups including at least 76 Canadian members. Both groups stated that the itchiness (pruritus) is the most bothersome symptom that affects patients' and caregivers' lives. For example, the itchiness interrupts patients and families' sleep making those affected fatigued, anxious, depressed, irritable, and worried. Patients said they feel isolated in school and challenging to maintain employment. Also, patients and families have difficulty finding the specialist who could recognize and make proper diagnosis of ALGS and manage disease treatment. Patients and families from both groups want a new therapy that can provide significant relief of itchiness with long-term effects without high risks such as liver transplant and immunosuppression. Patients who have taken maralixibat during clinical trials said that their itchiness has been resolved with minor side effects, such as upset stomach and diarrhea, could become more of themselves, engage in normal day-to-day activities, and their households were also positively changed.

## Clinician Input

### *Input From Clinical Experts Consulted by CADTH*

The clinical expert panel stated that cholestatic pruritus remains a very significant management problem for patients with ALGS and their families, due to partial, incomplete, or null response to currently available treatments. Current treatments are used off-label and are supportive in nature. The experts noted that surgical options such as an external or internal biliary diversion can be offered to ALGS patients with cholestatic pruritus that are refractory to medical therapies, however, these are not very effective and seldomly used in clinical practice. Finally, the experts stated that between 50 to 75% of patients with cholestatic liver disease will require a liver transplantation and cholestatic pruritus is a leading indication for a transplant. Liver transplantation is associated with increased morbidity, mortality, and lifelong immune suppression. As such, the experts noted that there is an unmet need for effective symptomatic and curative treatment for cholestatic pruritus in the indicated patient population.

The clinical experts stated that maralixibat would likely be used in combination with current off-label treatments in patients experiencing ongoing pruritus, and that it is possible some patients could discontinue some of the off-label treatments once they are established on maralixibat and their pruritus is under control. The experts noted that if easily accessible, maralixibat may be used as an initial therapy for new patients presenting with severe pruritus. The clinical experts stated that the estimated incidence of ALGS in Canada is about 1 in 30,000 to 50,000 with about 200 new cases each year. The experts noted that pediatric patients with ALGS most suited for treatment with maralixibat are those who present with cholestatic pruritus that is persistent with current off-label treatments which makes up about a third of patients in a clinical expert's practice. Patients least suited to treatment with maralixibat are those who have minimal liver involvement (i.e., minimal liver enzyme abnormalities and no fat-soluble vitamin deficits) and patients who do not experience cholestatic pruritus.

According to the expert panel, a clinically meaningful response to treatment would include a reduction in the frequency and severity of pruritus, a reduction in sleep deprivation among patients and their caregivers, the ability for patients and their caregivers to attend school or work, reduced damage to the patients' skin, and improved patient weight and growth. The clinical experts consulted on this review noted that response to therapy would likely be evaluated via subjective family reporting of symptoms including itching and sleep disturbances as well as by visual assessments of excoriations on the patient's skin which are often indicative of severe cholestatic pruritus. Standard scratch scales are not commonly used in clinical practice according to the experts. Measurements of sBA could be used to assess response to therapy, however the experts noted that this is not common in clinical practice due to the high cost and limited availability of such testing in some practice settings. The clinical experts would initially assess patients monthly for approximately 3 months, at which time the frequency of visits would be reduced to every 3 to 6 months if a response to treatment is evident. The clinical experts stated that treatment with maralixibat will likely be lifelong for most patients. The panel noted that that treatment discontinuation may be considered if there is no effect on cholestatic pruritus after approximately 6 months of treatment initiation, if a patient's liver disease progresses and they undergo liver transplantation, or due to severe AEs, however, the experts stated that AEs associated with maralixibat are likely self-limited and may be addressed by titrating the dose of maralixibat. The clinical experts noted that a pediatric or adult liver or GI specialist would be the preferred specialist to prescribe and monitor treatment with maralixibat.

### *Clinician Group Input*

One clinician from Canadian Association for the Study of the Liver (CASL) provided input. The clinician group and 2 clinical experts consulted by CADTH agree on the unmet need, which is a lack of effective therapy specifically indicated for cholestatic pruritus associated with ALGS refractory to current off-label treatments. They also agree that all the existing therapies are not effective at reducing cholestatic pruritus associated with ALGS and there are no guidelines for treating cholestatic pruritus in patients with ALGS. In alignment with clinical experts, the clinician group stated that treatment goals are mainly improvement in pruritus, improvement in quality of life (i.e., sleep duration), optimizing nutritional goals (i.e., treating fat-soluble vitamin deficiency). Also, both groups agree that patients with ALGS and cholestatic pruritus that is persistent on standard of care medical treatment would be eligible population. The clinician group stated that if a patient's liver disease progresses and they undergo liver transplantation, discontinuation is considered and the clinical experts stated that if there is no effect on itch as measured clinically then discontinuation is considered after adequate trial, i.e., 6 months. Otherwise, both groups agree that adverse events would be unlikely reason to discontinue since maralixibat is well-tolerated. Lastly, all the clinician group and

clinical experts agree that maralixibat should be prescribed by pediatric gastroenterologist or hepatologist. None of the clinician group or clinical experts consulted by CADTH had declared experience with maralixibat.

### Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for maralixibat:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

## Clinical Evidence

### Systematic Review

#### *Description of Studies*

The pivotal trial LUM001-304 (ICONIC) was an open-label, phase 2b study to evaluate the safety and efficacy of maralixibat in children with ALGS between the ages of 1 to 18 years. A total of 31 patients enrolled into the study which was conducted at 10 clinical sites in Australia, Europe, and the UK between November 25, 2014, and September 11, 2015. The study comprised of an 18-week open-label run-in period during which all patients received maralixibat, up to 380 mcg/kg/day (0-18 weeks), a 4-week randomized, double-blind, placebo-controlled drug-withdrawal phase (week 18-22) during which 13 patients continued receiving active treatment while 16 patients shifted to placebo, followed by a 26-week stable-dosing period (week 23-48) during which all patients received active treatment at doses up to 380 mcg/kg/day, and an optional long-term treatment period. It should be noted that during the long-term extension phase (as of week 103) eligible patients could have received a dose of maralixibat of up to 760 mcg/kg/day (given as twice-daily doses of 380 mcg/kg) which is outside of the proposed Health Canada indication of 380 mcg/kg /day. As such, efficacy and safety data after this period is not aligned with the recommended dose. Assessed efficacy outcomes included change in sBA, change in pruritus assessed using the itch reported outcome (ItchRO) observed (Obs) and patient (Pt) tools, change in liver biomarkers and enzymes (alanine transaminase [ALT], alkaline phosphatase [ALP], total, and direct bilirubin), change in body height and weight z-scores, and health-related quality of life (HRQoL) as measured by the Pediatric Quality of Life (PedsQL) total score (parent) and the PedsQL multidimensional fatigue scale score (parent). Assessed harms included AEs such as harms including diarrhea, abdominal pain, and fat-soluble vitamin deficiency and serious adverse events (SAEs).

In the overall study population (N = 31), there were more males (19 of 31 [61.3%]) than females (12 of 31 [38.7%]) at baseline and in the maralixibat (9 of 13 [69.2%]) and placebo groups (n = 10 of 16 [62.5%]) during the randomized withdrawal period. The mean age in the overall study population was 5.4 years (range: 1 to 15 years) and was similar between the maralixibat and placebo groups. Most patients were from Australia and France (9 of 31 [29.0%] each) in the overall study population. The mean time since the original diagnosis of ALGS was 66.2 months in the overall study population, with 64.5 months in maralixibat group and 73.2 months in the to placebo group during the randomized withdrawal phase. In the overall study population, 8 of 31 (25.8%) of patients had a family history of ALGS (1 of 13 [7.7%] and 7 of 16 [43.8%] in the maralixibat and placebo group, respectively). All enrolled patients had the *JAGGED1* mutation present. Race and ethnicity data were not collected in the ICONIC trial.

#### *Efficacy Results*

In the ICONIC trial, the primary efficacy endpoint was the change in sBA during the 4-week randomized withdrawal phase in the modified intent to treat (mITT population; patients with sBA reduction ≥ 50% at week 12 or week 18). A total of 15 participants were in the mITT population and were analyzed in the primary endpoint (5 randomized to maralixibat; 10 to placebo). The least squares (LS) mean difference in change from week 18 to 22 in sBA between the maralixibat and placebo groups was –117.28 (95% confidence interval [CI], –211.699 to –23.103; p = 0.0464) µmol/L, in favour of maralixibat. A consistent difference was observed in the overall randomized ITT population.

In the ICONIC pivotal trial, pruritus was assessed using the ItchRO (0 = none; 4 = very severe), which comprises of 2 clinical outcome assessment instruments—namely, ItchRO(Obs), the caregiver-reported version, and the ItchRO(Pt), the patient-reported version for patients greater than or equal to 9 years of age. The change from week 18 to 22 in ItchRO(Obs) weekly average morning severity score was a secondary endpoint. The LS mean difference between the maralixibat and placebo groups was –1.48 (95% CI, –2.12 to –0.84; p < 0.0001), in favour of maralixibat. In the overall population, there was a decrease (improvement) in ItchRO(Obs) weekly average morning severity score from baseline to week 18 (secondary endpoint) with a mean change of –1.70 (95% CI, –2.05 to –1.36; p < 0.0001) and from baseline to week 48 (additional endpoint) with a mean change of –1.62 (95% CI, –2.12 to –1.12; p < 0.0001). The prespecified sensitivity analyses for ItchRO(Obs) weekly average morning severity score was consistent with the results of the ItchRO(Obs). A total of 14 patients met the age cutoff for completion of the ItchRO(Pt) (≥ 9 years of age or ≥ 5 years of age with the assistance of their caregiver) in the pivotal trial. The LS mean difference between the maralixibat and placebo groups from week 18 to 22 for the change in ItchRO(Pt) weekly average morning severity score was –1.98 (–3.01 to –0.97; p = 0.0013), in favour of maralixibat. In the overall population, there was a decrease (improvement) in ItchRO(Pt) weekly average morning severity score from baseline to week 18 (secondary endpoint) with a mean change of –2.07 (95% CI, –2.65 to –1.50; p < 0.0001) and from baseline to week 48 (additional endpoint) with a mean change of –2.25 (95% CI, –2.84 to –1.67; p < 0.0001).

From week 18 to week 22 the LS mean difference between the maralixibat and placebo groups for ALP was 10 (95% CI, –52.6 to 72.6; p = 0.7455) U/L, compared to placebo. From week 18 to week 22, the LS mean difference between treatment groups for ALT was 15.1 (95% CI, –25.1 to 55.2; p = 0.4472) U/L. From week 18 to week 22 the LS mean difference between the maralixibat and placebo groups for total bilirubin was –0.14 (95% CI, –0.88 to 0.60; p = 0.7000) mg/dL. From week 18 to week 22 the LS mean difference between the maralixibat and placebo groups for direct bilirubin was –0.02 (95% CI, –0.56 to 0.53; p = 0.9517) mg/dL.

In the overall study population, there was an increase from baseline to week 100/last observation carried forward (LOCF) in mean height z-scores with a mean change of 0.25 (95% CI, –0.86 to 2.04; p = 0.0216). In the overall study population, there were no major changes from baseline in mean weight z-scores at any timepoint with a mean change from baseline to week 100/LOCF of –0.05 (95% CI, –0.12 to 0.23; p = 0.5306).

The pivotal trial assessed HRQoL using the PedsQL (0 to 100 points, higher scores indicate better HRQoL) as additional efficacy endpoints, and the LS mean difference from week 18 to 22 in the PedsQL total score (parent) between the maralixibat and placebo groups was 2.33 (95% CI, –10.08 to 14.75; p = 0.7018). In the overall population, the mean change in the PedsQL total score (parent) from baseline to week 18 was 10.73 (95% CI, 4.43 to 17.03; p = 0.0016). The LS mean difference for the PedsQL multidimensional fatigue scale score (parent) from week 18 to week 22 between the maralixibat and placebo groups was 14.03 (95% CI, –2.78 to 30.84; p = 0.0966). In the overall population the mean change in the PedsQL multidimensional fatigue scale score (parent) from baseline to week 18 was 20.30 (95% CI, 8.98 to 31.63; p = 0.0013).

### *Harms Results*

The incidence of adverse events (AEs) was similar during the open label, the after randomized withdrawal and long-term extension phases, with at least 25 of 29 (86.2%) patients experiencing any AEs in these treatment periods. During the randomized withdrawal phase, patients that stayed on maralixibat had a lower incidence of AEs (7 of 13 [38%] patients) compared with patients on placebo (12 of 16 [75%] patients). The most frequently reported AEs (> 30% in at least 1 phase) were abdominal pain; pyrexia; diarrhea; nasopharyngitis; vomiting; cough; and pruritus. During the randomized withdrawal phase, SAEs were reported for 1 of 13 (7.7%) patients on maralixibat and 1 of 16 (6.3%) patients on placebo. None of the SAEs were considered related to study medication. A total of 6 patients (2 each in the open label, after randomized withdrawal, and long-term extension phases) experienced AEs leading to study drug discontinuation. No deaths were noted during the study. During the randomized withdrawal phase, patients that stayed on maralixibat had a similar incidence of diarrhea and abdominal pain (1 of 13 [7.7%] patients) compared with those on placebo (1 of 16 [6.3%] patients). No patients experienced events associated with fat-soluble vitamin deficiency during the randomized withdrawal phase.

### *Critical Appraisal*

During the open-label phases of the pivotal trial, patients' and/or caregivers' knowledge of treatment assignment may have biased subjective outcomes such as ItchRO(Obs), ItchRO(Pt), and PedsQL in favour of maralixibat. Reporting of harms could

also have been biased, potentially in favour of maralixibat. Discontinuation was low with 3 of 31 (9.7%) patients discontinuing due to an AE through to week 48. Regarding differences in baseline characteristics between patients in the maralixibat and placebo groups, the clinical experts noted that patients in the maralixibat group may have had a higher degree of disease severity than those in the placebo group as indicated by the higher sBA, ALT, and bilirubin values which may have biased results in favour of placebo. Descriptive post-hoc data from the ICONIC pivotal trial found that reductions in sBA from baseline to week 48 were associated with reductions in mean ItchRO(Obs) weekly average morning severity scores (Appendix 1). The data may show an association between sBA and Itch(RO) in some patients, but as the data was descriptive in nature and the assessment was conducted post-hoc on a small number of patients (n = 28), it is unclear the extent to which sBA levels may be associated with pruritus in patients with cholestatic liver diseases.

The clinical experts consulted on this review noted that a minimal important difference (MID) of 1 for the ItchRO tool is clinically meaningful, however the experts noted that such tools are not commonly used in clinical practice. HRQoL was assessed using the PedsQL as an additional efficacy outcome in the pivotal trial and MID estimates of 4 to 5 points aligns with the clinical experts' expectations of a clinically meaningful change. It should be noted that the number of patients assessed for the PedsQL Multidimensional Fatigue Scale Score was low during the randomized withdrawal phase with 9 of 13 (69.2%) patients in the maralixibat group and 12 of 16 (75.0%) patients in the placebo group contributing to the analysis of mean change from week 18 to 22. The impact of missing data on this outcome is unclear in the absence of sensitivity analyses.

The clinical experts consulted on this review stated that patients included in the ICONIC trial generally align with the selection criteria for candidates for maralixibat, although patients with mild cholestatic pruritus would not necessarily be excluded from treatment in clinical practice. Nonetheless, the clinical experts did not expect the exclusion of these patients to significantly impact on the generalizability of the patient population in this study. The clinical trial only enrolled patients greater than or equal to 12 months of age with a *JAGGED1* mutation however the clinical experts note that the trial results would be applicable to patients less than 12 months of age as well as patients with a NOTCH2 mutation, respectively. Although race and ethnicity data were not assessed in the pivotal trial, the clinical experts stated that the results would be applicable to the Canadian patient population. The efficacy outcomes measured in the study were of clinical importance to patients and clinicians, including change in sBA. However, the clinical experts noted the change in sBA is not often assessed in clinical practice due to high costs and logistical limitations as sBA testing is often sent to specialized laboratories and is not readily available in all gastroenterology practice settings. The clinical experts consulted for this review indicated that although tools such PedsQL are frequently used in clinical trials they are not typically used in clinical practice. Furthermore, the double-blind phase in the pivotal ICONIC trial was 4 weeks in length, limiting the ability to assess the long-term efficacy and safety of maralixibat compared to placebo for the indicated dose of 380 mcg/kg/day. While maralixibat has been approved by Health Canada for use in patients for the treatment of cholestatic pruritus in patients with ALGS, 2 months of age and older, the ICONIC trial only enrolled patients greater than or equal to 12 months of age. As such, there is an absence of comparative efficacy and safety data assessing maralixibat versus placebo among patients less than 12 months of age in the ICONIC trial due to challenges of conducting a controlled clinical trial in this age group. However, the trial results are expected to be applicable to patients less than 12 months of age based on clinical experts' feedback. Furthermore, during the long-term extension phase of the ICONIC pivotal trial (as of week 103) eligible patients could have received a dose of maralixibat of up to 760 mcg/kg/day (given as twice-daily doses of 380 mcg/kg) which is outside of the proposed Health Canada indication of 380 mcg/kg /day. As such, efficacy and safety data after this period is not aligned with the recommended dose.

## GRADE Summary of Findings and Certainty of the Evidence

### *Methods for Assessing the Certainty of the Evidence*

For the pivotal study (ICONIC) identified in the sponsor's systematic review, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[14,15] Following the GRADE approach, evidence from the pivotal study started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes

was finalized in consultation with expert committee members: change in fasting sBA levels, change in pruritus as measured by ItchRO(Obs) and ItchRO(Pt) weekly average morning severity scores, change in liver biomarkers and enzymes (ALT, ALP, total, and direct bilirubin), change in body height and weight z-scores, HRQoL as measured by the PedsQL total score (parent) and the PedsQL multidimensional fatigue scale score (parent), and adverse events including SAEs, diarrhea, abdominal pain, and fat-soluble vitamin deficiency.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence or absence of any (non-null) effect for all outcomes except the ItchRO and PedsQL due to the lack of a formal MID estimate.

### *Results of GRADE Assessments*

Table 1 presents the GRADE summary of findings for maralixibat versus placebo for the treatment of cholestatic pruritus in pediatric patients with ALGS.

## Table 1: Summary of Findings for Maralixibat Versus Placebo For the Treatment of Cholestatic Pruritus In Patients With ALGS

| Outcome and follow-up[a] | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Maralixibat | Difference | | |
| **Serum bile acids** | | | | | | | |
| Change in fasting sBA levels (µmol/L) from week 18 to 22 in patients who previously responded to treatment with maralixibat<br>Follow-up: 4 weeks | 15 (1 RCT) | NA | 95.55 | –21.73 (–115.69 to 72.23) | –117.28 (–232.38 to –2.18) | Low[b] | Maralixibat may result in a decrease (improvement) in fasting sBA levels when compared with placebo. The clinical importance of the decrease is unclear. |
| **Pruritis** | | | | | | | |
| Change in pruritus as measured by ItchRO(Obs) weekly average morning severity score from week 18 to 22 in patients who previously responded to maralixibat treatment<br>Follow-up: 4 weeks | 31 (1 RCT) | NA | 1.70 | 0.22 (–0.27 to 0.70) | –1.48 (–2.12 to –0.84) | Low[c] | Maralixibat may result in a clinically important improvement in ItchRO(Obs) weekly average morning severity score when compared with placebo. |
| Change in pruritus as measured by ItchRO(Pts) weekly average morning severity score from week 18 to 22 in patients who previously responded to maralixibat treatment<br>Follow-up: 4 weeks | 31 (1 RCT) | NA | 1.84 | –0.15 (–0.97 to 0.67) | –1.99 (–3.01 to –0.97) | Low[c] | Maralixibat may result in a clinically important improvement in ItchRO(Pts) weekly average morning severity score when compared with placebo. |
| **Biochemical outcomes** | | | | | | | |
| Change in ALP (U/L) from week 18 to 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NA | –7.2 | 2.8 (–43.6 to 49.1) | 10 (–52.6 to 72.6) | Low[d] | Maralixibat may result little to no difference in ALP when compared with placebo. There is some uncertainty about the clinical importance of the estimates. |
| Change in ALT (U/L) from week 18 to 22 Follow-up: 4 weeks) | 31 (1 RCT) | NA | 19.4 | 34.5 (5.6 to 63.4) | 15.1 (–25.1 to 55.2) | Low[d] | Maralixibat may result little to no difference in ALT when compared with placebo. There is some uncertainty about the clinical importance of the estimates. |
| Change in total bilirubin (mg/dL) from week 18 to 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NA | 0.46 | 0.32 (–0.23 to 0.86) | –0.14 (–0.88 to 0.60) | Low[d] | Maralixibat may result little to no difference in total bilirubin levels when compared with placebo. There is some |

| Outcome and follow-up[a] | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Maralixibat | Difference | | |
| | | | | | | | uncertainty about the clinical importance of the estimates. |
| Change in direct bilirubin (mg/dL) from week 18 to 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NA | 0.14 | 0.13 (–0.28 to 0.53) | –0.02 (–0.56 to 0.53) | Low[d] | Maralixibat may result in little to no difference in direct bilirubin levels when compared with placebo. There is some uncertainty about the clinical importance of the estimates. |
| **Height and weight outcomes** | | | | | | | |
| Change in body height (z-scores) from baseline to week 48<br>Follow-up: 48 weeks | 31 (1 RCT, non-comparative) | NA | NR | NR | 0.18 (–0.02 to 0.23) | Very low[e] | The evidence is very uncertain about the effect of maralixibat on body height z-scores when compared with any comparator. |
| Change in body height (z-scores) from baseline to week 100/LOCF<br>Follow-up: 100 weeks | 31 (1 RCT, non-comparative) | NA | NR | NR | 0.25 (0.04 to 0.46) | Very low[e] | The evidence is very uncertain about the effect of maralixibat on body height z-scores when compared with any comparator. |
| Change in body weight (z-scores) from baseline to week 48<br>Follow-up: 48 weeks | 31 (1 RCT, non-comparative) | NA | NR | NR | 0.02 (–0.15 to 0.18) | Very low[e] | The evidence is very uncertain about the effect of maralixibat on body weight z-scores when compared with any comparator. |
| Change in body weight (z-scores) from baseline to week 100/LOCF<br>Follow-up: 100 weeks | 31 (1 RCT, non-comparative) | NA | NR | NR | 0.05 (–0.12 to 0.23) | Very low[e] | The evidence is very uncertain about the effect of maralixibat on body weight z-scores when compared with any comparator. |
| **HRQoL** | | | | | | | |
| Change in PedsQL total score (parent) from week 18 to week 22 (Follow-up: 4 weeks | 31 (1 RCT) | NA | –9.03 | –6.69 (–15.97 to 2.59) | 2.33 (–10.08 to 14.75) | Low[f] | Maralixibat may result in little to no difference in the PedsQL total score (parent) when compared with placebo. |
| Change in PedsQL multidimensional fatigue scale score (parent) from week 18 to week 22 (Follow-up: 4 weeks | 31 (1 RCT) | NA | –16.99 | –2.96 (–15.67 to 9.74) | 14.03 (–2.78 to 30.84) | Low[g] | Maralixibat may result in improvement of the PedsQL multidimensional fatigue scale score (parent) when compared with placebo. |

| Outcome and follow-up[a] | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Maralixibat | Difference | | |
| **Harms** | | | | | | | |
| Patients with SAEs from week 18 to week 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NR | 63 per 1,000 | 77 per 1,000 (NR) | NR | Very low[h] | The evidence is very uncertain about the effect of maralixibat on SAEs when compared with placebo. |
| Diarrhea, from week 18 to week 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NR | 63 per 1,000 | 77 per 1,000 (NR) | NR | Very low[h] | The evidence is very uncertain about the effect of maralixibat on the proportion of patients with diarrhea when compared with placebo. |
| Abdominal pain, from week 18 to week 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NR | 63 per 1,000 | 77 per 1,000 (NR) | NR | Very low[h] | The evidence is very uncertain about the effect of maralixibat on the proportion of patients with abdominal pain when compared with placebo. |
| Fat-soluble vitamin deficiency, from week 18 to week 22<br>Follow-up: 4 weeks | 31 (1 RCT) | NR | 0 per 1,000 | 0 per 1,000 (NR) | NR | Very low[h] | The evidence is very uncertain about the effect of maralixibat on the proportion of patients with fat-soluble vitamin deficiency when compared with placebo. |

AE = adverse event; CI = confidence interval; RCT = randomized controlled trial [add definitions to abbreviations list as required in alphabetical order].

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] Statistical testing for all outcomes was not adjusted for multiplicity. The potential for type I error (false positive results) is increased.

[b] Rated down 2 levels for very serious imprecision, evidence from 1 trial with small sample size. The small sample size raises concerns about the potential for prognostic imbalance and potential overestimation of the true effect. No known MID so target of certainty appraisal was any effect; 95% CI did not cross the null.

[c] Rated down 2 levels for very serious imprecision, evidence from 1 trial with small sample size. The small sample size raises concerns about the potential for prognostic imbalance and potential overestimation of the true effect. The 95% CI did not considerably cross the threshold of importance (based on an MID of 1).

[d] Rated down 2 levels for very serious imprecision, evidence from 1 trial with small sample size. There is no known MID and the clinical experts consulted by CADTH could not provide a threshold of important difference, however the CADTH review team judged that the effect estimate was likely to correspond with no important difference, and confidence interval was unlikely to include both important benefit and harm.

[e] In absence of a comparator group at the assessed timepoint, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low. Rated down 2 levels for very serious imprecision, evidence from 1 arm of 1 trial with small sample size.

[f] Rated down 2 levels for very serious imprecision. The 95% CI for difference between groups included possible important benefit and important harm (based on MID of 4 to 5 points).

[g] Rated down 1 level for serious study limitations. Risk of bias due to missing outcome data, results of analysis available for 9 of 13 (69.2%) patients in the maralixibat group and 12 of 16 (75.0%) patients in the placebo group. Rated down 1 level for serious imprecision; the 95% CI for difference between groups included potential for little to no difference (based on MID of 4 to 5 points).

[h] Rated down 1 level for serious indirectness. The clinical experts noted that the 4-week randomized withdrawal period was not sufficient to fully assess the comparative safety of maralixibat to placebo for this outcome. Rated down 2 levels for serious imprecision; the sample size is small and the results are based on very few or no events in each group.

## Long-Term Extension Studies

The pivotal ICONIC trial included a long-term extension phase described in the systematic review section of this report. No other long-term extension studies were submitted.

## Indirect Comparisons

No indirect comparisons were conducted comparing maralixibat to other comparators for this submission.

## Studies Addressing Gaps in the Evidence From the Systematic Review

### *Description of Studies*

The sponsor submitted a natural history comparison study which is presented in this report comparing disease outcomes among maralixibat-treated patients with ALGS (N = 84) with an external controls cohort from the GALA clinical research database (n = 469), with follow-up data up to 6 years. Outcomes assessed included event-free survival (EFS, a composite endpoint of first event of liver decompensation [ascites, variceal bleeding], surgical biliary diversion, liver transplantation, and death) and transplant-free survival (TFS). Of note, the natural-history comparisons were conducted independent of the sponsor (Mirum).

Results from patient-level data from 3 long-term studies of maralixibat treated patients with ALGS including LUM001-303 (IMAGINE), the ICONIC pivotal trial (LUM001-304), and IMAGINE-II (LUM001-305) to identify predictors of EFS and TFS was submitted by the sponsor and presented in this report.

### *Efficacy Results*

Results from the natural history comparison study reported a 70% improvement in EFS with maralixibat treatment compared with the GALA control group (HR = 0.305; 95% CI, 0.189 to 0.491; p < 0.0001) and a 67% improvement in TFS with maralixibat treatment compared to the GALA control group (HR = 0.332; 95% CI, 0.197 to 0.559; p < 0.0001). Additional relevant evidence assessing patient-level data (n = 76) from 3 ALGS clinical trials (IMAGINE, IMAGINE-II, and ICONIC) stated that clinical parameters (sBA levels, total serum bilirubin, and change in pruritus from baseline as measured by the ItchRO[Obs]) obtained after 48 weeks of maralixibat treatment were potential predictors of subsequent TFS and EFS.

### *Critical Appraisal*

Concerns regarding the natural history comparison include the potential residual confounding, incomparability in disease severity, and the lack of sBA data available among patients in the GALA registry. Although the study showed statistically and clinically significant reduction in liver transplantation, death and other associated events in patients who received maralixibat treatment compared to patients who received standard of care, there is uncertainty in the results and should be interpreted with caution. Results from the 3 ALGS clinical trials (IMAGINE, IMAGINE-II, and ICONIC) are subject to uncertainty due to various limitations including the limited sample size, a lack of control group, and uncertainty if the improvements in EFS and TFS observed in this analysis are solely the result of improvements in pruritus.

# Ethical Considerations

Patient group, clinician group, clinical expert, and drug program input gathered during this CADTH review, as well as relevant literature, were reviewed to identify ethical considerations relevant to the use of maralixibat to treat cholestatic pruritis in people with ALGS.

Ethical considerations identified in this review included those related to:

- **Diagnosis, Treatment, and Experiences of ALGS:** Ethical considerations arising in the context of ALGS highlighted the significant physical, psychosocial, and financial impact of the condition and its associated cholestatic pruritis on patients and their families, and difficulties and harms associated with delays in accessing a timely diagnosis and routine treatment and care. Families with limited income, with multiple members with ALGS, or living far from specialized treatment centres may

experience disproportionate burden of managing the condition and difficulties accessing timely care. There is a significant unmet need for an effective treatment for cholestatic pruritis in ALGS due to its devastating impacts on patients and their families; the limited efficacy of and adverse effects associated with currently available off-label therapies; and the invasive, life-altering nature of surgical treatment alternatives such as liver transplantation.

- **Clinical and Economic Evidence used in the Evaluation of Maralixibat:** Clinical trial evidence indicated that maralixibat may result in a clinically meaningful decrease in pruritis and may result in little to no difference in serious adverse events compared to placebo; however, there is evidentiary uncertainty concerning its safety and efficacy (particularly concerning its effect on long-term treatment outcomes and health-related quality of life), which limits the assessment of clinical benefits and harms associated with its use as well as the accuracy of the pharmacoeconomic assessment of cost-effectiveness.
- **Clinical Use and Implementation of Maralixibat:** Clinical experts voiced they would prescribe maralixibat based on the currently available evidence, given its potential to address a substantial unmet need for the treatment of ALGS-associated cholestatic pruritis with a favourable safety profile. However, given the uncertainty of evidence and the likelihood that maralixibat may not halt the progression of the underlying liver disease causing pruritis (for which there is no curative, non-surgical treatment), robust informed consent processes are required in both pediatric and adult contexts. As an orally administered medication, maralixibat is relatively accessible for patients, but equitable access requires attending to potential diagnostic, geographic, and monitoring-related barriers to access.
- **Health Systems:** Ethical considerations for health systems related to the implementation of maralixibat highlight the challenges of funding decisions for high-cost drugs for rare diseases, assessments of opportunity costs, and the fair allocation of scarce resources, as well as issues related to pan-Canadian approaches to providing equitable reimbursement and access.

## Economic Evidence

### Cost and Cost-Effectiveness

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov model |
| **Target population** | Cholestatic pruritus in patients with ALGS 12 months of age and older |
| **Treatment** | Maralixibat plus best supportive care (BSC) |
| **Dose regimen** | Week 1: 190 mcg/kg daily<br>Week 2 and onwards: 380 mcg/kg daily up to 28.5 mg per (or 3 mL) daily for patients above 70 kg |
| **Submitted Price** | 9.5 mg / mL: $1,787.00 per mL ($53,610.00 per bottle) |
| **Treatment Cost** | The cost per maintenance dose was $1,251, $1,608, $1,787, $2,234, $3,127 and $4,021 for body weights of ≥17 kg to <20, ≥20 to < 25, ≥25 to < 32, ≥32 to < 46, ≥46 to < 51 and ≥51 kg, respectively. The estimated annual costs of maintenance treatment ranged between $ 456,891 and $1,468,579, depending on patient weight. |
| **Comparator** | BSC, comprised of ursodeoxycholic acids (UDCAs), rifampin, antihistamines (certrizine hydrochloride, hydroxyzine hydrochloride), alimemazine tartrate (trimeprazine tartrate), naltrexone and sertraline |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, LYs |
| **Time horizon** | Lifetime (94.65 years) |
| **Key data source** | The ICONIC trial and GALA clinical database |
| **Key limitations** | • The comparative clinical efficacy of maralixibat plus BSC vs BSC alone was estimated using a naïve comparison of the ICONIC trial and the GALA clinical database. Among other methodological limitations, this comparison did not control for baseline serum bile acid (sBA) levels, introducing considerable uncertainty to conclusions that can be drawn on the comparative clinical effects and for the economic analysis.<br>• The pharmacoeconomic model relied upon changes in sBA levels as the primary metric of treatment effectiveness. Clinical expert feedback solicited by CADTH suggested that the primary metric of effectiveness in actual practice is severity of itch. CADTH found insufficient evidence to support the use of sBA as a proxy for itch severity. This added additional uncertainty, limiting the model's ability to accurately reflect the impact of maralixibat on clinically important outcomes. |

| Component | Description |
|---|---|
| | • Based on the product monograph, maralixibat dosing is weight based. In the model, patient weight increases with patients' age. The method used to incorporate patient weight resulted in a cohort that weighed considerably less in adulthood than the average weight of a Canadian adult, which potential underestimates the cost of maralixibat. |
| **CADTH reanalysis results** | • Given the limitations identified within comparative clinical evidence and with the sponsor's economic analysis, CADTH was not able to use the model to provide a more reliable estimate of the cost effectiveness of maralixibat.<br>• Based on the sponsor's analysis, a 96.5% price reduction would be required for maralixibat plus BSC to be considered cost-effective at a willingness to pay (WTP) threshold of $50,000 per QALY gained, compared to BSC alone.<br>• Given the limitations in the submission that could not be addressed by CADTH, this price reduction is highly uncertain and further price reductions may be required. |

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY= quality-adjusted life-year; sBA = serum bile acid; UDCA = ursodeoxycholic acid

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. The proportion of patients with native liver and covered by public plans was uncertain. As such, the population size eligible for treatment with maralixibat has been underestimated. The rate of treatment discontinuation was uncertain because the reasons for discontinuation did not meet face validity. Treatment cost of maralixibat did not include drug wastage and was also uncertain. Dose escalation as observed in the ICONIC trial was not considered and the sponsor's submitted BIA model had programmatic errors, making it unclear if changes to default values were propagated throughout calculations.

In CADTH reanalyses, the proportion of patients with native liver was 70%, a coverage rate of 100% was adopted, no treatment discontinuation was assumed, and drug wastage was included. CADTH reanalyses results suggested that the overall budget impact to the public drug plans of introducing maralixibat for the treatment of cholestatic pruritus in patients with ALGS two months of age and older increased to $130,727,100 over three years (Year 1: $26,649,978; Year 2: $44,315,818; Year 3: $59,761,303).

The estimated budget impact increased as the eligible population size increased. The patient age and weight were key drivers of the estimated budget impact.

## CDEC Information

### Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

### Meeting date: September 27, 2023

### Regrets:

Two expert committee member(s) did not attend.

### Conflicts of interest:

None