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## Reimbursement Recommendation

# Maralixibat (Livmarli)

**Indication:** For the treatment of cholestatic pruritus in patients with Alagille syndrome

**Sponsor:** Mirum Pharmaceuticals Inc.

**Final recommendation:** Reimburse with conditions

**Corrected version:** Updated on April 2025 to correct condition 1 in Table 1

# Summary

## What Is the CADTH Reimbursement Recommendation for Livmarli?

CADTH recommends that Livmarli should be reimbursed by public drug plans for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Livmarli should only be covered to treat patients aged 12 months and older with a diagnosis of ALGS and who have impaired bile flow demonstrated by at least 1 of the following: elevated serum bile acids (sBAs), conjugated bilirubin, or gamma-glutamyl transferase; fat-soluble vitamin deficiency; and/or intractable itch. Patients must experience moderate to severe itch symptoms and must be currently or have been previously treated with systemic medication for itch.

### What Are the Conditions for Reimbursement?

Livmarli should only be reimbursed if it is prescribed under the care of a specialist with experience in managing ALGS, if patients experience an improvement in their itching after using Livmarli for 6 months, and if the cost of Livmarli is reduced. Livmarli should be stopped if the patient receives a liver transplant or biliary diversion surgery.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that, in patients with ALGS, treatment with Livmarli improves itching and sBA levels compared to placebo.
- ALGS is a rare disease, often accompanied by severe pruritis. Patients identified a need for effective treatments for ALGS that reduce itching, delay the course of the disease, avoid or delay the need for liver transplant, and improve health-related quality of life. Livmarli can reduce patients' pruritis and may improve their quality of life, although the evidence is uncertain.
- Based on CADTH's assessment of the health economic evidence, Livmarli does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Livmarli is estimated to cost the public drug plans approximately $132 million over the next 3 years.

# Summary

## Additional Information

### What Is ALGS?

ALGS is a rare inherited liver disease that disrupts the normal flow of bile acids. Patients experience severe itching and a build up of bile acids in the body that damage the liver. The itch can be severe enough to consider surgery or a liver transplant as treatment. ALGS is estimated to affect approximately 1,300 people in Canada.

### Unmet Needs in ALGS

Patients with ALGS need effective treatments that can cure the pruritus, relieve symptoms of itchiness, and reduce the risk of liver transplant and immunosuppression. Patients also identified a need for a reduced patient and caregiver fatigue and improved quality of life.

### How Much Does Livmarli Cost?

Treatment with Livmarli is expected to cost approximately $128,843 to $1,932,641 per patient per year in the first year of treatment and $130,094 to $1,951,404 per patient per year in subsequent years of treatment depending on patient weight.

## Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that maralixibat be reimbursed for cholestatic pruritus in patients with Alagille syndrome (ALGS).

## Rationale for the Recommendation

ALGS is a rare, life-threatening genetic disorder that presents with a range of clinical features, including cholestatic liver disease. Cholestatic pruritus is a significant management problem for patients with ALGS and their families; it has a considerable impact on sleep, growth, and school performance in children. The itch has been described by patient groups as debilitating, unrelenting, and impossible to alleviate. It is also a common reason for liver transplant in children living with ALGS. Currently available treatments are used off-label and yield only a partial response at best. Considering this, CDEC recognized that there is a significant unmet need in patients with cholestatic pruritus due to ALGS.

Evidence from a phase IIb, placebo-controlled, randomized, drug withdrawal study with open-label extension (ICONIC, N = 31) suggested that maralixibat treatment results in improvements in serum bile acid (sBA) and in pruritus compared to placebo from week 18 to week 22.

During the 4-week randomized withdrawal period of the ICONIC trial, the least squares (LS) mean difference between the maralixibat and placebo groups in change in sBA from week 18 to 22 was –117.28 µmol/L (95% CI, –211.699 µmol/L to –23.103 µmol/L; P = 0.0464) in favour of maralixibat.

Improvement in pruritus was identified as an important outcome according to patients and the clinical experts. The ICONIC trial reported on outcomes in pruritus based on caregiver- and patient-reported assessments using the Itch Reported Outcome(Observed) (ItchRO[Obs]) and ItchRO(Patient) (ItchRO[Pt]) weekly morning severity scores, respectively. The LS mean difference between the maralixibat and placebo groups from week 18 to week 22 for change in ItchRO(Pt) weekly average morning severity score was –1.98 (95% CI, –3.01 to –0.97; P = 0.0013) in favour of maralixibat. Similar results were reported for the ItchRO(Obs). Although not controlled for multiplicity, the results correspond to clinically meaningful improvements in pruritus and provide evidence to support the efficacy of maralixibat.

Patients identified a need for an effective treatment for cholestatic pruritus in ALGS that reduced the frequency and severity of pruritus, reduced patient and caregiver fatigue, and improved quality of life. CDEC concluded that maralixibat met some of the needs identified by patients in terms of improving pruritus.

Using the sponsor-submitted price for maralixibat plus best supportive care (BSC) and publicly listed price for all other drug costs, the incremental cost-effectiveness ratio (ICER) for maralixibat plus BSC was $2,775,887 per quality-adjusted life-year (QALY) gained compared with BSC alone. At this ICER, maralixibat is not cost-effective at a $50,000 per QALY gained willingness-to-pay (WTP) threshold for the treatment of cholestatic pruritus in patients with ALGS. A price reduction is required for maralixibat to be considered cost-effective at a $50,000 per QALY gained threshold.

## Table 1: Reimbursement Conditions and Reasons

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Initiation** | | |
| 1. Patients aged 12 months and older with a diagnosis of ALGS who have demonstrated the following:<br>1.1. evidence of cholestasis (must include at least 1 of the following):<br>1.1.1. total sBA > 3 × ULN for age<br>1.1.2. conjugated bilirubin > 1 mg/dL<br>1.1.3. fat-soluble vitamin deficiency otherwise unexplainable<br>1.1.4. GGT > 3 × ULN for age<br>1.1.5. intractable pruritus explainable only by liver disease<br>1.2. moderate to severe itch defined as an average daily score of 2 or more on the ItchRO or CSS for 2 consecutive weeks. | Evidence from the ICONIC trial supported the efficacy of maralixibat in patients aged between 12 months and 18 years with a diagnosis of ALGS, evidence of cholestasis, and moderate to severe itch at baseline. In the ICONIC trial, moderate to severe itch was defined as an average daily score of 2 or higher on the ItchRO questionnaire for 2 consecutive weeks in the screening period before dosing. The CSS was identified as an alternative physician-rated tool for the assessment of itch severity supported by the clinical experts. | — |
| 2. Patients currently treated with, or who have received an adequate trial with, a systemic treatment for pruritus before initiating maralixibat. | In the ICONIC trial, which supported the efficacy of maralixibat, approximately 93% of the overall population enrolled had a history of receiving any treatment for pruritus (81% reported a history of treatment with UDCA and 74% reported a history of treatment with rifampicin). This aligns with clinical practice in Canada based on input from the clinical experts who noted most patients with cholestatic pruritus due to ALGS are likely to have received prior treatment with UDCA or rifampin.<br>There is no direct evidence that maralixibat is clinically superior or inferior to any other available treatments currently reimbursed for the treatment of cholestatic pruritus in patients with ALGS. | An adequate trial was defined as a trial of 1 to 3 months with appropriate dosing of a systemic treatment for pruritus based on usual care. This may include UDCA, rifampicin, sertraline, naltrexone cholestyramine, or antihistamines. |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| 3. Patients with any of the following should not be eligible for reimbursement of maralixibat: biliary diversion, previous liver transplant, decompensated cirrhosis, or history or presence of other concomitant liver disease. | There is insufficient evidence for efficacy or safety of maralixibat in patients with the following comorbidities because these were excluded from the ICONIC trial: biliary diversion, previous liver transplant, decompensated cirrhosis, or history or presence of other concomitant liver disease. | — |
| **Renewal** | | |
| 4. The maximum duration of initial authorization is 6 months. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as an improvement in pruritus to minimal or no itch (a score of 1 or less) on the ItchRO or CSS. | An improvement in pruritus was observed within 18 weeks in the ICONIC trial. Assessment of response within 6 months of initiating treatment was considered appropriate and aligned with clinical practice in Canada based on input from clinical experts. | An alternative measure of beneficial clinical effect may be considered for patients who begin treatment with severe itch (equivalent to an ItchRO or CSS score of 4). An MID of 1 was identified as a clinically meaningful change for the ItchRO; as such, an improvement in pruritus by a score of 1 may be considered for patients with severe itch. |
| 5. For subsequent renewal, the physician must provide proof of maintenance of the change in CSS or ItchRO score from baseline every 6 months. | | — |
| **Discontinuation** | | |
| 6. Reimbursement of maralixibat should be discontinued if 1 or both of the following occurs:<br>6.1. patient receives liver transplantation or biliary diversion surgery. | There is no evidence to support the continued use of maralixibat following liver transplantation or biliary diversion surgery. | — |
| **Prescribing** | | |
| 7. The patient should be under the care of a hepatologist with experience in managing ALGS. | Accurate diagnosis and management of patients with ALGS and cholestatic pruritus is important to ensure that maralixibat is prescribed for appropriate patients. | — |
| **Pricing** | | |
| 8. A reduction in price. | The ICER for maralixibat plus BSC is $2,775,887 compared with BSC alone.<br>A price reduction of 96.5% would be required for maralixibat to achieve an ICER of $50,000 per QALY compared to BSC alone. | — |

ALGS = Alagille syndrome; BSC = best supportive care; CSS = Clinician Scratch Scale; GGT = gamma glutamyltransferase; ICER = incremental cost-effectiveness ratio; ItchRO(Obs) = Itch Reported Outcome (Observed); ItchRO(Pt) = Itch Reported Outcome (Patient); MID = minimal important difference; QALY = quality-adjusted life-year; UDCA = ursodeoxycholic acid; ULN = upper limit of normal.

## Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse maralixibat for the treatment of cholestatic pruritus in patients with ALGS. The reconsideration request outlined 5 issues with the initial recommendation which were discussed during the reconsideration meeting.
- During the initial and reconsideration meetings, CDEC discussed the uncertainty in the clinical evidence and 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. Given the rarity of the condition and the lack of effective options for patients, CDEC concluded that the limitations and uncertainty of the submitted evidence were balanced with the significant unmet need and rarity of cholestatic pruritus associated with ALGS.
- In their request for reconsideration, the sponsor submitted individual participant data on additional efficacy outcomes of pruritus (ItchRO[Obs] and Clinician Scratch Scale [CSS]) assessed at week 48 in the ICONIC trial. The sponsor also presented data regarding the proportion of patients with minimal to no itch (ItchRO[Obs] score ≤ 1) across different points of the trial. CDEC concluded that the interpretability of patient-level data on a population level remains limited; however, the new information provided supportive evidence of the treatment effect observed in the trial based on the correlation between the ItchRO and CSS data as well as the proportion of patients who exhibited minimal to no itch.
- Although data from ICONIC may show an association between decreased fasting sBA levels and improvement in pruritus 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 pruritus in patients with cholestatic liver diseases.
- CDEC noted that patients expect new treatments for cholestatic pruritus in ALGS to improve quality of life; however, no conclusion could be reached regarding the effects of maralixibat on quality of life because of the limitations of the available evidence. During the reconsideration meeting discussion, CDEC acknowledged feedback from the clinical experts that highlighted the magnitude of effect that was observed; however, this did not outweigh the limitations of the health-related quality of life (HRQoL) analysis, such as substantial missing data, particularly for a small sample size.
- CDEC also heard from clinical experts that improvement in pruritus 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 patients with ALGS treated with maralixibat with an external control cohort. Although the results of the natural history study suggested improvements in event-free survival and transplant-free survival with maralixibat, limitations inherent to the observational study design warrant concern when interpreting the results. During the reconsideration meeting discussion, it was noted that the natural history study provides supportive information on the potential of maralixibat to decrease liver transplant compared to an external control; however, given

the limitations noted previously, it is not possible to rule out potential unmeasured confounders on the treatment effect.

- During the initial and reconsideration meetings, CDEC discussed ethical and equity considerations related to maralixibat, including those related to the significant physical, emotional, and psychosocial burden of living with and caring for someone with Alagille syndrome, especially due to cholestatic pruritus. The committee also discussed how pediatric patients can be considered uniquely vulnerable because it can be difficult for them to understand and make sense of their suffering and because they depend on their caregivers to provide them with necessities and to advocate and facilitate access to their diagnosis and support for their condition. During the reconsideration meeting, CDEC also discussed that although there is limited evidence regarding the long-term safety and efficacy of maralixibat as well as uncertainty about the association of sBA levels with pruritus, maralixibat may help address a substantial unmet need for effective treatment for cholestatic pruritus that improves patients' and families' quality of life with fewer serious adverse events (SAEs) than currently used off-label therapies or surgical alternatives. The committee also discussed the potential advantages for patients in accessing and using maralixibat as an orally administered medication. CDEC noted the need for robust informed consent processes in pediatric and adult contexts to discuss the evidentiary uncertainty and likelihood that maralixibat may not halt the progression of the underlying liver disease that causes pruritus.
- CDEC noted that the sponsor's pharmacoeconomic model was premised on the relationship between sBA level and pruritis severity. The evidence to support a proxy relationship between sBA level and pruritis severity was highly uncertain. Clinical expert feedback received by CADTH for this review suggested that sBA is not used in clinical assessment and that clinical decision-making is made based on pruritis severity. Because of this and other limitations identified by CADTH in the appraisal of the economic evidence, the estimated QALY benefit that patients would experience with maralixibat compared to BSC is highly uncertain. At the sponsor's submitted price, the drug acquisition cost of maralixibat was expected to be an additional $11.4 million per patient over the course of their lifetime compared to BSC.

## 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 sBA 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 IIb, double-blind, randomized controlled trial (RCT); 1 long-term extension of the RCT; and 2 additional studies addressing gaps in evidence
- patients' perspectives gathered by 2 patient groups, 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, the Canadian Association for the Study of the Liver (CASL)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to maralixibat
- information submitted as part of the request for major reconsideration (described subsequently).

## 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 people living in Canada who are impacted by liver diseases. The ALGSA is a nonprofit organization based in the US dedicated to support families affected by ALGS globally. The CLF submission included phone or virtual interviews conducted in May 2023 with 8 patients and caregivers living in Canada. 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 and focus groups that included at least 76 members in Canada.

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 causing those affected to be fatigued, anxious, depressed, irritable, and worried. Patients said they feel isolated in school and it is challenging to maintain employment. Also, patients and families have difficulty finding a specialist who could recognize and make a 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 transplantation and immunosuppression. Patients who have been on maralixibat during clinical trials said that their itchiness was resolved with minor side effects, such as upset stomach and diarrhea; they could become more like themselves; they could 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 responses 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 patients with ALGS who have cholestatic pruritus that is refractory to medical therapies; however, these are not very effective and seldomly used in clinical practice. The experts stated that between 50% to 75% of patients with cholestatic liver disease will require a liver transplant and cholestatic pruritus is a leading indication for a transplant. Liver transplant is associated with increased morbidity, mortality, and lifelong immune suppression. As such, the experts noted 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 approximately 1 in 30,000 to 50,000, with approximately 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 approximately one-third of patients in a clinical expert's practice. Patients who are 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 achieving 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 that 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 was 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 if they experience severe adverse events (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 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 the clinical experts, the clinician group stated that treatment goals are mainly improvement in pruritus, improvement in quality of life (i.e., sleep duration), and optimizing nutritional goals (i.e., treating fat-soluble vitamin deficiency). Both groups also 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 of maralixibat would be considered; the clinical experts stated that if there was no effect on itch as measured clinically, discontinuation would be considered after adequate trial (i.e., 6 months). Otherwise, both groups agree that AEs would be an unlikely reason to discontinue because maralixibat is well-tolerated. The clinician group and clinical experts agree that maralixibat should be prescribed by a pediatric gastroenterologist or hepatologist. None of the clinician group or clinical experts consulted by CADTH had declared experience with maralixibat.

## Drug Program Input

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

### Table 2: Responses to Questions From the Drug Programs

| Implementation issues | Response |
|---|---|
| **Considerations for initiation of therapy** | |
| Most patients in clinical trials had the documented *JAGGED1* mutation. Can the study results be extrapolated to patients with other mutations? | CDEC agreed with the clinical experts that the study results can be extrapolated to patients with other mutations (i.e., *NOTCH2).* |
| **Considerations for continuation or renewal of therapy** | |
| Is a reduction in the ItchRO scale of greater than 1 point from baseline clinically significant?<br>Are the ItchRO scales used in clinical practice? | The clinical experts noted that although scales such as the ItchRO are often used in clinical trials, they are not commonly used in clinical practice. The experts noted that changes in pruritus in clinical practice would likely be evaluated via subjective family reporting or patient reporting for older children of symptoms, including itching and sleep disturbances, as well as by visual assessments of excoriations on the patient's skin that are often indicative of severe pruritus. CDEC considered input by the clinical experts and agreed a reduction of 1 point in the ItchRO scale is clinically meaningful. |

CDEC = Canadian Drug Expert Committee; ItchRO = Itch Reported Outcome.

# Clinical Evidence

## Systematic Review

### Description of Studies

The pivotal trial LUM001-304 (ICONIC) was a phase IIb open-label study to evaluate the safety and efficacy of maralixibat in children with ALGS aged 1 to 18 years. A total of 31 patients enrolled in 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 an 18-week open-label run-in period during which all patients received maralixibat, up to 380 mcg/kg/day (0 to 18 weeks); a 4-week randomized, double-blind, placebo-controlled drug withdrawal phase (weeks 18 to 22) during which 13 patients continued receiving active treatment while 16 patients shifted to placebo; followed by a 26-week stable-dosing period (weeks 23 to 48) during which all patients received active treatment at doses up to 380 mcg/kg/day. There was also an optional long-term treatment period. 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 levels, change in pruritus assessed using the ItchRO(Obs) and ItchRO(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 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 diarrhea, abdominal pain, and fat-soluble vitamin deficiency, as well as SAEs.

In the overall study population (N = 31), there were more men (19 of 31; 61.3%) than women (12 of 31; 38.7%) at baseline. There were also more men in the maralixibat (9 of 13; 69.2%) and placebo groups (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 in the maralixibat and placebo groups. Most patients were from Australia and France (9 of 31; 29.0% from 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 patients (25.8%) had a family history of ALGS; 1 of 13 patients (7.7%) in the maralixibat group and 7 of 16 patients (43.8%) in the placebo group had a family history. 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 end point 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 at the primary end point (5 randomized to maralixibat; 10 to placebo). The LS mean difference in change from week 18 to week 22 in sBA levels between the maralixibat and placebo groups was –117.28 µmol/L (95% confidence interval [CI], –211.699 µmol/L to –23.103 µmol/L; P = 0.0464) 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 scale (0 = none; 4 = very severe), which comprises 2 clinical outcome assessment instruments: ItchRO(Obs), the caregiver-reported version of the ItchRO, and ItchRO(Pt), the patient-reported version for patients aged 9 years and older. The change from week 18 to week 22 in ItchRO(Obs) weekly average morning severity score was a secondary end point. 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 end point) with a mean change of –1.70 (95% CI, –2.05 to –1.36; P < 0.0001) and from baseline to week 48 (additional end point) 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 cut-off for completion of the ItchRO(Pt) (≥ 9 years or ≥ 5 years with the assistance of their caregiver) in the pivotal trial. The LS mean difference between the maralixibat and placebo groups from week 18 to week 22 for the change in ItchRO(Pt) weekly average morning severity score was –1.98 (95% CI, –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 end point) with a mean change of –2.07 (95% CI, –2.65 to –1.50; P < 0.0001) and from baseline to week 48 (additional end point) 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 U/L (95% CI, –52.6 U/L to 72.6 U/L; P = 0.7455) compared to placebo. From week 18 to week 22,

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

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 time point 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 end points. The LS mean difference from week 18 to week 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 AEs was similar during the open-label, the after randomized withdrawal and long-term extension phases, with at least 25 of 29 patients (86.2%) experiencing any AEs in these treatment periods. During the randomized withdrawal phase, patients who stayed on maralixibat had a lower incidence of AEs (7 of 13 patients; 38%) compared with patients on placebo (12 of 16 patients; 75%). 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 patients (7.7%) on maralixibat and 1 of 16 patients (6.3%) 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 reported during the study. During the randomized withdrawal phase, patients who stayed on maralixibat had a similar incidence of diarrhea and abdominal pain (1 of 13 patients; 7.7%) compared with those on placebo (1 of 16 patients; 6.3%). 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 patients (9.7%) discontinuing due to an AE through 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. The data may show an association between sBA and Itch(RO) in some patients, but because the data were descriptive in nature and the assessment was conducted post hoc on a small number of patients (n = 28), the extent to which sBA levels may be associated with pruritus in patients with cholestatic liver diseases is unclear.

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 align with the clinical experts' expectations of a clinically meaningful change. The number of patients assessed for the PedsQL Multidimensional Fatigue Scale score was low during the randomized withdrawal phase; 9 of 13 patients (69.2%) in the maralixibat group and 12 of 16 patients (75.0%) in the placebo group contributed to the analysis of mean change from week 18 to week 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 the 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 affect the generalizability of the patient population in this study. The clinical trial only enrolled patients aged 12 months or older with a *JAGGED1* mutation; however, the clinical experts noted that the trial results would be applicable to patients younger than 12 months as well as patients with a *NOTCH2* mutation.

Although race and ethnicity data were not assessed in the pivotal trial, the clinical experts stated that the results would be applicable to the patient population in Canada.

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 because 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 as PedsQL are frequently used in clinical trials, they are not typically used in clinical practice.

The double-blind phase in the pivotal ICONIC trial was 4 weeks long, which limits the ability to assess the long-term efficacy and safety of maralixibat compared to placebo for the indicated dosage of 380 mcg/kg/day. Although maralixibat has been approved by Health Canada for use in patients with ALGS aged 2 months and older for the treatment of cholestatic pruritus, the ICONIC trial only enrolled patients aged 12 months and older. As such, there is a lack of comparative efficacy and safety data assessing maralixibat versus placebo among patients younger than 12 months 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 younger than 12 months based on clinical experts' feedback. 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 AEs, including, diarrhea, abdominal pain, and fat-soluble vitamin deficiency, and SAEs.

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

## Table 3: 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 week 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. |
| **Pruritus** | | | | | | | |
| Change in pruritus as measured by ItchRO(Obs) weekly average morning severity score from week 18 to week 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 week 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 week 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. |

| Outcome and follow-up[a] | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Maralixibat | Difference | | |
| Change in ALT (U/L) from week 18 to week 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 week 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 uncertainty about the clinical importance of the estimates. |
| Change in direct bilirubin (mg/dL) from week 18 to week 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, noncomparative) | 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, noncomparative) | 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, noncomparative) | 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. |

| Outcome and follow-up[a] | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Maralixibat | Difference | | |
| Change in body weight (z scores) from baseline to week 100 (LOCF)<br>Follow-up: 100 weeks | 31 (1 RCT, noncomparative) | 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<br>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<br>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. |
| **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 compared with placebo. |
| Patients with 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 compared with placebo. |
| Patients with 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 compared with placebo. |
| Patients with 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 compared with placebo. |

AE = adverse event; ALP =alkaline phosphatase; ALT = alanine aminotransferase; CI = confidence interval; ItchRO(Obs) = Itch Reported Outcome (observed); LOCF = last observation carried forward; NA = not applicable; NR = not reported; PedsQL =Pediatric Quality of Life; RCT = randomized controlled trial; SAE = serious adverse event; sBA = serum bile acid.

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 the confidence interval was unlikely to include both important benefit and harm.

[e]In the absence of a comparator group at the assessed time point, 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 patients (75.0%) 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, that compares disease outcomes among patients with ALGS treated with maralixibat (n = 84) with an external controls cohort from the GALA clinical research database (n = 469) including follow-up data up to 6 years. Outcomes assessed included event-free survival (EFS) — a composite end point of first event of liver decompensation (ascites, variceal bleeding), surgical biliary diversion, liver transplantation, and death — and transplant-free survival (TFS). The natural history comparisons were conducted independent of the sponsor (Mirum).

Results from patient-level data from 3 long-term studies of patients with ALGS treated with maralixibat, 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 is presented in this report.

#### *Efficacy Results*

Results from the natural history comparison study showed a 70% improvement in EFS in patients treated with maralixibat compared with the GALA control group (hazard ratio = 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 (hazard ratio = 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) showed 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. The study showed statistically and clinically significant reduction in liver transplants, death, and other associated events in patients who received maralixibat treatment compared with patients who received standard of care; however, there is uncertainty in the results and they 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 pruritus 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 pruritus 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 pruritus in ALGS due to its devastating effects 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 pruritus and may result in little to no difference in SAEs compared to placebo; however, there is evidentiary uncertainty concerning its safety and efficacy (particularly concerning its effect on long-term treatment outcomes and HRQoL), 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:** The clinical experts voiced that they would prescribe maralixibat based on the currently available evidence because of its potential to address a substantial unmet need for the treatment of ALGS-associated cholestatic pruritus 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 pruritus (for which there is no curative, nonsurgical 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

### Table 4: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov model |
| **Target population** | Cholestatic pruritus in patients with ALGS aged 12 months and older |
| **Treatment** | Maralixibat plus BSC |
| **Dose regimen** | Week 1: 190 mcg/kg daily<br>Week 2 and onward: 380 mcg/kg daily up to 28.5 mg per (or 3 mL) daily for patients who weigh more than 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 kg, ≥ 20 kg to < 25 kg, ≥ 25 kg to < 32 kg, ≥ 32 kg to < 46 kg, ≥ 46 kg to < 51 kg, 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, comprising ursodeoxycholic acids, rifampin, antihistamines (cetirizine hydrochloride, hydroxyzine hydrochloride), alimemazine tartrate (trimeprazine tartrate), naltrexone, and sertraline |
| **Perspective** | Canadian publicly funded health care payer |
| **Outcomes** | QALYs, life-years |
| **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 naive comparison of the ICONIC trial and the GALA clinical database. Among other methodological limitations, this comparison did not control for baseline 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 effect of maralixibat on clinically important outcomes.<br>• Based on the product monograph, maralixibat dosing is weight based. In the model, patient weight increases with patient age. The method used to incorporate patient weight resulted in a cohort that weighed considerably less in adulthood than the average weight of an adult in Canada, which potentially underestimates the cost of maralixibat. |
| **CADTH reanalysis results** | • Given the limitations identified within the 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 threshold of $50,000 per QALY gained compared to BSC alone. |

| Component | Description |
|---|---|
| | • 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; QALY = quality-adjusted life-year; sBA = serum bile acid.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. The proportion of patients with native liver 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. The 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 budget impact analysis model had programmatic errors, making it unclear if changes to default values were propagated throughout calculations.

In the 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 suggest that the overall budget impact to the public drug plans of introducing maralixibat for the treatment of cholestatic pruritus in patients with ALGS aged 2 months and older increases to $130,727,100 over 3 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. Patient age and weight were key drivers of the estimated budget impact.

# Request for Major Reconsideration

The sponsor filed a request for major reconsideration of the draft recommendation for maralixibat, indicated for the treatment of cholestatic pruritus in patients with ALGS. In their request, the sponsor identified 5 issues:

- **Relevance of ICONIC trial design**: Concern was raised that the design of the pivotal ICONIC study may not allow for the adequate assessment of the value of maralixibat in this submission. The sponsor requested that the reassessment take into consideration the totality of maralixibat clinical data. These considerations include the ICONIC study design rationale, the integrated analysis from 86 patients with ALGS studied in the clinical trial program along with the GALA natural history comparison.
- **Assessment of cholestatic pruritus benefit**: Concern was raised about the level of certainty in which the open-label phase of ICONIC was able to inform on the cholestatic pruritus benefit of maralixibat. The sponsor requested reconsideration of the durability of maralixibat's cholestatic pruritus benefit.
- **Natural history comparison study**: Concern was raised by CDEC about the level of certainty in which the natural history study is able to inform the long-term benefits of maralixibat in the real-

world setting. The sponsor requested reconsideration of the significance of the treatment effect demonstrated by maralixibat in the natural history comparison study.

- **Impact of maralixibat on quality of life of patients with ALGS**: Concern was raised by CDEC that maralixibat does not lead to improvement in quality of life of patients with ALGS. The sponsor requested reconsideration of the long-term HRQoL demonstrated by maralixibat in the ICONIC study.
- **Appropriate application of Section 9.3.1(c) of the CDRR Procedures**: CDEC acknowledged the applicability of Section 9.3.1(c) and the ability to accept additional uncertainty in the evidence. However, they concluded the submitted evidence was insufficient to draw conclusions on whether maralixibat will provide benefit in the real-world setting. The sponsor requested CDEC reconsider their conclusion based on the totality of the evidence submitted and in recognition of the significant clinical need in patients with ALGS, the majority of whom are children, who are at high risk of liver transplantation with no other approved treatment options.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following sources of information:

- information from the initial submission related to the issues identified by the sponsor
- new information provided by the sponsor to address an important clear gap in the evidence identified by CDEC
- feedback from 3 clinical specialists with expertise in the diagnosing and treating of patients with ALGS
- feedback from 5 patient groups, Canadian PBC Society; PFIC Advocacy and Resource Network, Inc.; Canadian Liver Foundation; Alagille Syndrome Alliance; and Children's Liver Disease Foundation
- feedback from 9 clinician groups, Alberta Children's Hospital, Pediatric Liver Centre, Calgary; University of Alberta, Alberta Transplant Institute, Edmonton; Canadian Pediatric Hepatology Research Group Canadian Association for the Study of the Liver (CASL), Special Interest Group; Children's Hospital of Eastern Ontario (CHEO), Ottawa; IWK Health Centre, Dalhousie University, Department of Pediatrics; Montreal Children's Hospital, McGill University Health Centre; North American Society for Pediatric Gastroenterology Hepatology & Nutrition, Hepatology Committee; Pacific Gastroenterology Associates, Vancouver; Autoimmune and Rare Liver Disease Clinical Programme, Toronto Centre for Liver Disease, Toronto General Hospital.
- feedback on the draft recommendation from the public drug plans that participate in the CADTH review process.

All stakeholder feedback received in response to the draft recommendation is available on the CADTH website.

# CDEC Information

## Initial Meeting Date: September 27, 2023

### 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, 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

**Regrets**: 2 expert committee members did not attend.

**Conflicts of interest**: None

## Reconsideration Meeting Date: February 29, 2024

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed

**Regrets**: 3 expert committee members did not attend.

**Conflicts of interest**: None

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