CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

maralixibat (Livmarli)

(Mirum Pharmaceuticals Inc.)

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

May 15, 2023

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Stakeholder Input

Disclaimer: The views expressed in each submission are those of the submitting organization or individual and not necessarily the views of CADTH or of other organizations. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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Patient Input: Canadian Liver Foundation

Name of the Drug and Indication	**Maralixibat (Livmarli) for the treatment of cholestatic pruritis in patients with Alagille syndrome 2 months of age and older.**
Name of the Patient Group	**Canadian Liver Foundation**
Author of the Submission	**Nem Maksimovic**
Name of the Primary Contact for This Submission	**Nem Maksimovic**
Email	[redacted]
Telephone Number	[redacted]

About Your Patient Group

Founded in 1969, the Canadian Liver Foundation (CLF) was the first organization in the world dedicated to supporting education and research into all forms of liver disease. Today, the CLF continues to be the only national health charity committed to reducing the incidence and impact for Canadians of all ages living with or at risk for liver disease. The CLF is the only registered charity in Canada directing funds specifically for liver disease research in all its forms and has invested nearly $39 million in the scientific search for causes, preventative measures and potential treatments for liver disease. The CLF reaches millions of Canadians through our public and professional education programs, patient support programs and other awareness, fundraising and outreach efforts.

Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include when the data were gathered; if data were gathered in Canada or elsewhere; demographics of the respondents; and how many patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

The CLF reached out to patients and caregivers who contacted the foundation over the last several years regarding their Alagille syndrome diagnosis. We anticipated that this submission could be challenging as it relates to the procurement of patient and caregiver input due to the rare nature of this disease, coupled with limited number of patients accessing the therapy under review who may not be available to respond to our request for patient input. On April 27th, 2023, the CLF contacted the U.S.-based patient advocacy group, the Alagille Syndrome Alliance, to request assistance with patient recruitment. The Alagille Syndrome Alliance were keen to conduct outreach through their networks and channels (May 2nd – May 5th).

Fortunately, our collaborative requests via email to various patients and caregivers living with Alagille syndrome resulted in 10 respondents who expressed interest in supporting this patient input request. This outreach effort resulted in **eight** Canadian patient and caregiver responses, with **four** having experience with the drug under review.

The data was gathered via phone and virtual interviews. The interviews were conducted by the CLF between May 3rd and May 10th, 2023. The patients and caregivers provided firsthand compelling, and relevant qualitative input regarding their:

- Experience with respect to the diagnosis of their Alagille syndrome
- Experience as caregivers/loved ones for someone with Alagille syndrome
- Disease experience
- Experience with respect to previous therapies
- Experience with respect to the therapy under review

The qualitative data from the interview will be referenced throughout this submission. Quotes from respondents in the virtual interviews are included in ***italics*** in various sections of this submission. To add to this critically important patient evidence submission, the CLF also used evidence from the Patient-Centered Outcomes Research (PCOR) developed by the Alagille Syndrome Family Survey called "What Matters to You in ALGS Research" in 2019 at the 8th International Symposium and Scientific Meeting on Alagille Syndrome in Cincinnati, Ohio, USA. The evidence obtained from this family survey in addition to the testimonials were sought and incorporated into this

submission in the most comprehensive manner possible to ensure the Alagille syndrome patient and caregiver voice is provided to help inform this committee's deliberations.

Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to- day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Alagille syndrome is a genetic, multisystem disease that can affect different parts of the body, including the liver. Alagille syndrome is estimated to affect between one in 30,000 to one in 50,000 individuals and is caused by mutations in one of two genes, JAGGED1 or NOTCH2. For people who have Alagille syndrome, bile does not properly drain from the liver because the bile ducts are too small, they are formed improperly, and/or there are fewer than normal. This means that bile and bile acids have difficulty being removed from the liver. When bile acids build up in the liver, it can cause damage and prevent the liver from working properly to remove waste from the bloodstream. This causes an increase in bile acids throughout the entire body. Bile build-up can cause many problems in people with Alagille syndrome, but the most troublesome symptom is often severe itching (pruritus). Other signs and symptoms arising from liver damage in Alagille syndrome may include a yellowish tinge in the skin and the whites of the eyes (jaundice) and small skin blemishes that happen due to a buildup of fats under the surface of the skin (xanthomas). The itchy skin has been shown to disturb sleep and affect everyday activities. The size and number of xanthomas may change appearance or affect vision, eating, or movement.

The treatment considerations for Alagille syndrome are primarily medical and not surgical. This is based on attempting to increase the flow of bile from the liver, maintain normal growth and development, and prevent or correct any of the specific nutritional deficiencies that often develop. Due to bile flow from the liver to the intestine being slow in patients with Alagille syndrome, medications designed to increase the flow of bile are frequently prescribed. These medications can decrease the damage in the liver and may improve the digestion of fat and fat-soluble vitamins.

The overall life expectancy for children with Alagille syndrome is unknown, but depends on several factors: the severity of scarring in the liver and/or the need for liver transplantation, the risk of stroke, and whether heart or lung problems develop because of the narrowing in the pulmonary artery. There is presently no procedure that can correct the loss of the bile ducts within the liver. In 20-30% of patients, cirrhosis advances to a stage where the liver fails to perform its functions, and liver transplantation is then considered.

Most families affected by Alagille syndrome expressed the feeling of uncertainty. Pruritus affects up to 88% of children with Alagille syndrome and is among the most severe pruritus in any chronic liver disease, negatively impacting quality of life, physical health, and psychosocial health. When asking parents and/or caregiver of loved one's living with Alagille syndrome, respondents indicated how an Alagille syndrome diagnosis has severely impacted the lives of their loved ones and affected their day-to-day activities, while adding physical and emotional stressors and worries:

> ***"We struggled from day one with our son, with failure to thrive, not eating, not sleeping. We live in a very rural community and the access to any type specialist was not there. No one really knew what was going on with him. He would scratch his entire body raw all the time. For the first 6 years of life, we never had the option of sleeping through the night because he was always up." – Parent***
>
> ***"I do feel when we got the diagnosis, for myself anyways, it was hard, because I didn't know, because it's rare right, it's different" – Parent***
>
> ***"I constantly feel helpless…nothing works for his itch and he is miserable" – Parent "I can't work***
>
> ***because we have to travel too often for treatment" – Parent "Exhaustion, fear and worry about***
>
> ***the future" – Parent***
>
> ***"Sleeplessness – the kids, the siblings, the parents. It really affects the whole family." – Caregiver***
>
> ***"Day to day management of appointments, tests, medication, insurance calls" – Parent "Nutrition***
>
> ***issues and medication side effects" – Caregiver***
>
> ***"Her first few years of life, the itch and scratching was every night, all day and all night. The stress of not sleeping, it was a lot." – Parent***

"We used to wake up regularly to bloody crib sheets and skin lesions. The amount of money we spent on over-the-counter lotions. It was challenging and it was also frustrating to have people who were well-meaning offering suggestions. " – Parent

"Lost wages because I have to care for my child around the clock" – Parent

"With my son, the main symptom used to be extreme pruritus, that was the hardest day-to day issue with him, he has some bone deformities that he has adapted to, but most days we don't have much to deal with. My son has to do some things more carefully, he has to do adapted programs, he just has to be more careful and aware than other kids. For myself, I have heart palpitations, really intense muscle and joint pain all the time, I'm changing my diet all the time to try and balance between kidney disease and diabetes. It's the muscle and joint pain that's the biggest day to day issue." – Patient & Caregiver

"Financial burdens and fighting with insurance" – Parent

"For me, very few, if any. I've been very lucky, it's mild, its mostly been subclinical findings, a notice of heart abnormalities as part of a workup when I was younger, but never a functional impairment." – Patient

"Oh gosh, it became our entire life, as a parenting team, when you have a medically fragile kid. We went from husband and wife and parents to co-case managers. You go into survival mode, and it just becomes your entire life – you're changing bloody sheets constantly. When they have that internal itch that they can't scratch, it's like watching your kid's body torture themselves and there's nothing you can do, it's all consuming and it's just awful. With medications, we can look at nutrition and other things special- needs parents might deal with, but it's not as all-consuming as when the itch is there." – Parent

"There was no sleep. We try all night to help in whatever way, while watching your child suffer. It was almost traumatic because you can't control any of it. All you can do is help in the best way you can, and that almost always failed." – Parent

"It limits her to doing physical activities, she has a timed schedule because she doesn't eat very much by mouth, she has energy but sometimes struggles to keep up with her peers, balance, communication." – Parent

"In day to day life, I had to stop working due to COVID and her health as well, she couldn't go to school, that was hard for both of us, she's back in school now, and she loves it, I'm not working now in case we have to go to Toronto, or even a simple cold can cause a hospital visit, one little sniffle can be a hospital visit away. I feel like she's generally happy, but she sometimes has more questions than what I can answer about what's going to happen with her liver, and those kinds of things, I think she has a bit of anxiety about what's going to happen in the future." – Parent

"The biggest thing for her would be sleep apnea, she sleeps very poorly, and on the subsequent day to day struggles that go with sleep deprivation, she has also been recently diagnosed with autism, so some regulation issues, she has a lot of medical trauma, a very medical life, has a hard time coping." – Parent

Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers. Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments).

Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

The treatment for patients with Alagille syndrome is tailored to each individual, but most patients will require treatment for their liver disease. The available treatments are often prescribed to address symptoms associated with Alagille syndrome, including itching, poor growth, and nutritional issues. Medications such as ursodeoxycholic acid can help to improve bile flow and reduce itching. Ursodeoxycholic acid can also aid to reduce blood cholesterol levels and jaundice. Antihistamines, such as diphenhydramine and hydroxyzine, can also be used to control itching and improve overall sleep patterns. Other medications such as rifampin, cholestyramine and colesevelam, may help to remove bile salts from the body. In severe cases, surgery to remove excess bile (partial external biliary diversion or ileal exclusion) can help with severe itching. Finally, skin moisturizers, keeping baths and showers short, and trimming fingernails to prevent skin damage from scratching is also recommended by health care professionals.

42% of respondents who responded to the PCOR Alagille Syndrome Family Survey indicated that the current medication is not effective:

> ***"Her liver is still deteriorating." – Parent***
>
> ***"Itching remains an issue, vitamins are still deficient." – Parent***
>
> ***"Still significant itch, disruption of sleep, tired, lack of appetite." – Parent "He continues***
>
> ***to constantly itch." – Parent***
>
> ***"My son is still yellow and getting worse, still severely itchy, not gaining weight properly." – Parent***
>
> ***"The number of skin breaks because of itching has increase to levels we haven't seen previously. In addition his quality and length of sleep is incredibly impacted." –***
> ***Caregiver***
>
> ***"He is still beyond itchy 99.9% of the time." – Parent***

Respondents also indicated the challenges relating to treatment access, follow-up care, and limited knowledge about Alagille syndrome in the health care community:

> ***"We've had a lot of issues, we live in Saskatchewan, there were 2 pediatric gastroenterologists, then there was one, tomorrow we have our last appointment with the last gastroenterologist, and then she's closing her practice. It's a massive challenge for anyone living with a chronic illness in Saskatchewan. I've been***
> ***petitioning the government and they say they're finding someone, but it's not really happening. We now have to fly to Toronto for care. Our gastroenterologist was an IBS specialist, not a hepatologist ,which was not ideal for my daughter. What she really needs is a hepatologist." – Parent***
>
> ***"There are very few guidelines on what to do for adults getting diagnosed, it leaves a lot of uncertainty, as someone with mild presentation, there's some survivor's guilt seeing how much worse others have it. It can be quite impactful getting the diagnosis." – Patient***
>
> ***"Even though our doctor tries to learn, I always feel more educated about ALGS. I'm the most knowledgeable person I know about ALGS. It's extremely frustrating to have to always be my son's best advocate." – Parent***

Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and

quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

The PCOR Alagille Syndrome Family Survey findings were consistent with the perspective received by the patient interviews.

When asked what outcomes should be considered when evaluating new therapies and what improvements respondents would like to see in a new treatment that is not achieved in the currently available treatments, patients and caregivers thoughtfully provided the following:

> ***"Gosh, for my son I guess the only thing that would be more helpful would be if some of his therapies or something was funded, or his nutritional supplement were paid for, but generally, we feel comfortable he is getting what he needs from his current team, we are more worried about in 6 years when he has to age out." – Parent***
>
> ***"I suppose access to testing. Because I don't have any liver involvement, I don't even have a point of contact to make that happen cause I don't have a hepatologist or anything like that." – Patient***
>
> ***"I have a lot of trouble getting my doctors to take Alagille syndrome as a relevant diagnosis for any of my treatments. In adult care, they only look at symptom and symptom management." - Patient***
>
> ***"One of the issues I had was to begin with was that there's no good guidelines for adults with Alagille, but one of the things that was recommended was to do an angiogram of the brain, and that's not covered by OHIP, so I needed a reason/justification by my doctor. As a PhD student studying epidemiology, I was able to pull a paper that showed the benefit of this test which was used to help justify me getting this, and when they did the scan it showed a small brain aneurysm, so I'm glad they did it. High barriers to getting this." – Patient***

Alagille syndrome accounts for about 4% of all pediatric liver transplants in North America. Given the rare nature of this disease and its ability to cause liver damage along with being associated with a range of other features such as heart and kidney issues, there is a strong need to prioritize patient centered outcomes such as quality of life. There is also a strong need for education, research, and awareness on Alagille syndrome among health care providers and investigators.

According to the various patient and caregiver input received, the therapy under review addresses and provides these desired improvements.

Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

Maralixibat (brand name: Livmarli) is a treatment that is specifically designed to treat the itch in Alagille syndrome. It is FDA approved for patients with Alagille Syndrome who are 3 months of age and older. Maralixibat targets and temporarily blocks the ileal bile acid transporter. In doing so, this treatment lowers bile acids in the body by interrupting bile acids from going back into the liver, and by increasing the amount of bile acids that are removed from the body in feces. Maralixibat is an oral treatment that is taken once daily. It is available in a grape-flavored liquid medicine that is taken approximately 30 minutes before a meal in the morning.

Four respondents indicated having experience with the drug under review. Respondents indicated that the primary method of access to the drug under review was through clinical trial. One respondent indicated that they were unable to gain access to the treatment due to their condition not being considered severe enough.

When asked about side-effects or symptoms with the drug under review, the following input was received from patients and caregivers:

"I think it was his AST and GGT that climbed, it was tricky, because his doctor felt completely comfortable giving him the medication, before the trial we were discussing a transplant for his liver, it was frustrating that there was a drug that was helping him that we couldn't give him cause it was still in the drug trial. I think the only side effect he had was that he had some loose stool for the first 2 weeks. He had no other side effects other than that." – Parent/Caregiver

"The side effects was mainly stomach upset initially, but it went away quite quickly." – Parent

"We had no specific issues with side-effects, at least nothing that affected her negatively." – Parent

The interview respondents expressed the improvements in their overall quality of life once they began treatment and limited challenges with obtaining the treatment:

"I hesitate to use life-changing because it's so cliché, but it completely changed him. It was the first time we got to see his personality, and felt like we got to meet our child for the first time. Before the maralixibat, he just cried, and scratched, and we were up every 2 hours, he was being tortured by his body all the time. He began to eat, he slept, he could play, he could think, it took the itch completely away." – Parent

"The treatment – you can't even compare the treatments, none of the other ones worked, and the maralixibat worked, we tried every other therapy and treatment, we tried everything we could, and nothing helped." – Patient

"The end-result has been wonderful, and my daughter is currently on maralixibat and it has been life-changing for all of us in our household" – Parent

"Access for us was complicated initially. We had to get it from Toronto, and we were 3 hours away, but now there is no challenges." – Parent

"Dr. Kamath from SickKids has been a godsend to us. She was the one that was able to get us on maralixibat and it was life-changing." – Parent

"Before maralixibat, the itch was just unbearable for him. He was so unhappy. We have since been on maralixibat for 2 years now. He is turning into a man, he is eating better, the biggest thing is that there is no itch, at all. The biggest impact, is that we see this incredible young man, he has such a fun sense of humor that we have never seen before. None of this would have happened if we were not on this medication. Is it a miracle drug? Yeah. " – Parent

Companion Diagnostic Test

Not applicable – this drug does not require a companion diagnostic test.

Anything Else?

The Canadian Liver Foundation believes that liver disease patients, their caregivers and health care providers should have access to the most effective treatment options regardless of geographical location, financial status, treatment status or disease severity in order to ensure the best possible outcomes.

The aim of treatment is to maximize the effectiveness and minimize the adverse side effects with the hope for improved patient outcomes. It is important to ensure greater and more equitable access to important treatments for Alagille syndrome patients while expanding therapeutic options for patients and healthcare professionals. We think it is crucial that patients across the country have equitable access to all treatments for liver disease and that provincial borders should not be a barrier.

When asked what questions would patients with Alagille syndrome ask researchers in the field, they indicated:

"With regard to xanthomas, is there anything we are seeing to improve the visibility and elimination of these deposits on the skin?" – Patient

"We are desperate for answers. What can we do to help advance science?" – Parent "I would say

the most helpful thing is connecting with other Alagille patients and caregivers, we're the ones who know the most about it than anyone, so that connection has probably been the most helpful thing that we've had." – Patient

The hope is that access to maralixibat will mean that patients and caregivers will have improved and increased access to treatment. However, if accessing maralixibat is not seamlessly and readily available as part of various provincial reimbursement programs, then patients will not have access to these treatments. We therefore strongly support and urge that a positive funding recommendation be issued for maralixibat for the treatment of cholestatic pruritis in patients with Alagille syndrome. We believe a positive funding recommendation aligns well with the identified patient need for a new, effective, easily administered treatment option that is capable of maintaining a high quality of life and durable response.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No outside assistance was utilized to complete this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No outside assistance was utilized to collect or analyze data used in this submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

The Canadian Liver Foundation (CLF) is committed to bringing liver research to life for all Canadians through liver research, education, patient support and advocacy. The CLF receives funding from a variety of sources with the majority coming from donations from individuals across the country. We use these funds to support CLF liver awareness, education, patient support and research grant programs. The CLF receives some program funding in the form of unrestricted educational grants from pharmaceutical companies. Grant agreements are established in support of activities initiated by the CLF and prohibit the funder from having any input or influence in program objectives or deliverables.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
N/A				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Nem Maksimovic
Position: Director, Support and Education Patient Group: Canadian Liver Foundation Date: May 15th, 2023

Patient Input: Alagille Syndrome Alliance

Name of Drug: Livmarli
Indication: Alagille Syndrome
Name of Patient Group: Alagille Syndrome Alliance
Author of Submission: Roberta Smith, President, and Cher Bork, Executive Director

About Your Patient Group

The Alagille Syndrome Alliance (ALGSA) is 501c3 non-profit organization dedicated to promoting education, advocacy, and support for families affected by Alagille Syndrome globally.

The ALGSA was founded in 1993 and has since become the leading ALGS-focused organization helping families through a variety of programs and services including an annual international family conference, financial assistance programs, disease literacy, and family support programs. The ALGSA is also deeply involved in science and research including funding the first 3 years of the Global ALagille Alliance (GALA), developing the ALGSA Collaborative Scientific Research Grant, having the only 3-way Cooperative Research And Development Agreement (CRADA) in partnership with the NIH/NCATS and Travere Therapeutics, hosting a biennial ALGSA Scientific Meeting, having a patient registry, and more.

The organization collaborates with clinicians, researchers, pharmaceutical companies, other advocacy groups and all stakeholders to advance and improve patient outcomes.

Website = alagille.org

Information Gathering

The ALGSA manages and/or is a part of 19 support groups on social media around the world including a specific support page for Canadian families with over 76 members, and an international page with over 2500+ members including caregivers and patients in Canada. The staff of the ALGSA logs over 1,500 personal conversations with patients and families each year, including interactions with Canadian families. Data is gathered through family surveys, personal conversations, topic specific discussions in the support groups, and focus groups in specific geographic locations. In an ALGSA family survey conducted in September 2020, we found that the #1 symptom of Alagille Syndrome that affects patients the most was itch.

Disease Experience

Alagille Syndrome can affect multiple organ systems, including the liver, heart, and kidneys. It can also cause developmental delays and cognitive impairments. The severity of symptoms can vary widely from person to person, but in general, the condition can have a significant impact on the day-to-day life and quality of life of both patients and caregivers.

Patients with Alagille Syndrome may experience chronic liver disease, which can cause a variety of symptoms such as jaundice, itching, and fatigue. These symptoms can be mild or severe but typically make it difficult for patients to carry out normal daily activities, such as going to school or work, socializing with friends, or participating in physical activities. Patients may also require frequent doctor/specialist visits, blood tests, and imaging to monitor their liver function and manage their symptoms, which can be time-consuming and disruptive to their daily routines. The diagnostic odyssey for ALGS can be complicated and long. It may involve multiple physicians, specialists, imaging, labwork, etc. Many Alagille patients are misdiagnosed with Biliary Atresia, many undergoing the very invasive Kasai procedure before the correct diagnosis is made, which is devastating. Along with this, many patients are not immediately diagnosed with a syndrome, especially adults who have gone undiagnosed. Many tend to be diagnosed with one medical diagnosis, like liver disease, but not correlated genetically or clinically with Alagille Syndrome as a whole.

In addition to liver disease, patients with Alagille Syndrome may also experience heart and kidney problems, which can further impact their day-to-day life. For example, heart problems may limit physical activity and require additional, frequent medical appointments, while kidney problems may require patients to undergo dialysis or other treatments.

Caregivers of patients with Alagille Syndrome may also experience significant challenges. They may need to manage their loved one's complex medical needs, including administering medications, monitoring symptoms, and coordinating medical appointments. This can be emotionally and physically exhausting, particularly if the patient requires frequent hospitalizations or suffers from severe itch associated with Alagille Syndrome. Caregivers may also need to advocate for their loved one's needs in a variety of settings, such as at school or in

the workplace, which can be time-consuming and stressful. Caregivers, parents, and teen and adult patients can experience varied levels of depression and anxiety associated with medical set-backs, long hospital stays, anticipation of major surgeries like transplant or open heart surgery, as well as toward fear of the unknown and what the future may bring. Many teenagers, young adults, adults, and caregivers worry significantly about mortality as survival rates through literature have been low over 18 years of age with native liver. We hear frequently from patients in their early 20's and older, that their doctors always indicated to their parents and to them personally in clinical settings that they would have a shortened life-span. We see deep-rooted emotional and mental consequences of these early predictions by physicians to family members and the long-term effects they created and work to combat these through social media messaging, one on one conversations with patients, and by offering financial assistance for patients to get professional mental health help to deal with this very damaging language used.

The most important aspects that must be controlled in Alagille Syndrome include:

1. Liver function and pruritus: The liver is one of the most important organs affected by Alagille Syndrome for the largest number of patients. Patients with Alagille Syndrome may have a buildup of bile in the liver, which can lead to liver damage and scarring. It is important to control liver function by managing the buildup of bile and monitoring the liver function through regular blood tests. Addressing pruritus is a heavy and significant challenge that patients and their families struggle to deal with. Controlling this with Livmarli can improve quality of life without the severe impact itching has on the family as a whole.
2. Nutritional status: Patients with Alagille Syndrome may have difficulty absorbing nutrients from food. Nutritional deficiencies can cause growth delays, weakness, and fatigue. It is important to monitor the patient's nutritional status and provide vitamins and supplements as needed. Weight gain is a significant stressor for numerous patients and caregivers, leading to additional emotional and mental health impacts. Unwarranted guilt, shame, feelings of failure by not meeting the weight requirements set by clinicians and facing tube feedings if the weight milestones are met feel threatening and impossible. Nutritional implications of ALGS are an extremely emotional and challenging aspect of daily pressure and stress heaped atop the already heavy burden of disease overall and the significant emotional burden of itch.
3. Cardiovascular health: Alagille Syndrome can affect the heart in several ways, including narrowing of the pulmonary artery and other heart defects such as Tetralogy of Fallot and more. Those with heavy cardiac involvement undergo a heavy medical schedule that includes invasive and noninvasive testing, procedures, and imaging including catheterizations, balloonings, open heart surgery for different cardiac related repairs, and so on. It is important to monitor cardiovascular health and manage any related conditions to prevent complications.
4. Bone health: Patients with Alagille Syndrome may have weak bones due to vitamin D deficiency and other factors. It is important to monitor bone health and provide appropriate supplements and treatments to prevent fractures, rickets, and other complications. Many patients experience bone breaks in the long bones, slow bone repair, and multiple bone breaks in their lifetime.
5. Genetic counseling: Alagille Syndrome is a genetic disorder that can be passed down from parents to their children. Genetic counseling is important to help families understand the risk of passing on the condition and to discuss options for family planning. Reproductive health and significant diseases literacy surrounding genetics and reproduction alternatives is extremely important.

Experiences With Currently Available Treatments

Before the FDA approval of Livmarli, patients were given a regimen of multiple drugs to combat itching, or one drug, and then the introduction of multiple or different drugs based on progress and effectiveness in combating the severe pruritus. For example, the first drug typically prescribed for itching is Rifampin, an old archaic antibiotic used to treat Tuberculosis. This drug is able to only mildly address pruritus, if at all, and typically only in combination with hydroxyzine, cholestyramine, naltrexone, or ursodiol. Patients and caregivers really grasp at anything that they think MIGHT give relief such as lotions that might provide a relaxing effect, or supplements like melatonin, ginkgo biloba, or any number of oatmeal bath mixes, etc. None of these, even in combination, are significantly effective. Severe pruritus that was not improved by the above antidotes, can lead to liver transplant evaluation or other invasive surgical approaches to relieve the day to day suffering.

Challenges with the medications listed above are managing dosages with frequency, time of day, restrictions of taking around other meds in the list, and coordinating with food, refrigeration, and school or work schedules.

Outside of the medications, vitamins, supplements, and creams described above, invasive surgeries like internal or external biliary diversion and liver transplant would be considered depending on severity of disease, severity of itch, or quality of life implications. Transplant does not cure Alagille Syndrome. Transplant is a very invasive surgery that comes with high risks and a probability of being unsuccessful resulting in death, especially due to the increased vascular involvement in some patient's Alagille Syndrome make-up.

Improved Outcomes

Patients and caregivers are desperate for relief from severe pruritus which is not managed well with current medication options outside of Livmarli in the US. This itch can be described as debilitating, unrelenting, a terrible burning or fire feeling under the skin, unreachable, deep into the body, uncontrollable, intense, and a persistent sensation that can be impossible to alleviate. The itching can be so severe that it completely disrupts sleep continually, night after night, and year after year for the patient and everyone in the family. This extreme fatigue and exhaustion, as we have learned through our support pages, one on one conversations with families, my own personal experience, can be emotionally and mentally draining. It has been known to lead to bickering and fighting between spouses, high irritability, low emotional tolerance levels, and reduced functionality and productivity at home and at work. Adult patients with itch struggle to maintain employment, deal with extreme discomfort, and try to adjust their environment in ways that improve quick access to make-shift tools like back scratchers, scratching gadgets, rough carpets to rub their feet on, canvas laundry baskets and ottomans with rough surfaces, bristle brushes to scratch the skin, and more. Continually adjusting the environment and thinking and planning for this is exhausting, expensive, and all-consuming. Pruritus is absolutely draining for everyone in the family. Livmarli has been life changing for patients and families in the US, renewing hope and providing a much improved quality of life for everyone in the home.

Patient's views of what outcomes should be considered when evaluating new therapies

How might daily life and quality of like be different with new treatment

Patients' views of what outcomes should be considered when evaluating new therapies really boils down to everything described above. Daily comfort, reduced itch which would allow functionality in school or in the workplace, peace with the body and mind, sleep, and clear skin free of cuts, scabs, and bloody excoriations. Stillness, freedom to travel and visit family without preparations of scratch tools, medications, and escape plans for when itching becomes too unbearable to continue an outing. In the September 2020 ALGSA survey conducted, itch was found to be the #1 research priority for survey respondents including both patients and caregivers. The overall impact of itch on a patient's daily physical life, social life, and financial impact was 73% daily impact.

What improvements would patients and caregivers like to see in a new treatment that is not currently achieved

Improvements not seen outside of Livmarli use include consistent and overall reduced itching long-term. Temporary solutions are not improvements on quality of life. Having alternatives to major surgeries like transplant and biliary diversion are so important, as liver transplant comes with potentially tragic high risks which can be avoided by having a medication option.

What trade-offs do patients, families, and caregivers consider when choosing therapy

In general with OTHER drugs outside of Livmarli but in terms of drugs used by Alagille Syndrome patients, trade-offs may include long-term effects of prescription drug use vs very mild uncertain relief from itch (Rifampin), high risk of transplant vs medication drug intervention that may prolong the need for liver transplant (Livmarli), life-time of reduced immune response and suppression with transplant vs mortality (Tacrolimus).

Quote from Article

"Maralixibat Takes Out the Itch of Rare Liver Disease"
Quote by:
Rohit Kohli, MBBS, MS
Chief, Division of Gastroenterology, Hepatology and Nutrition
Director, The George Donnell Society for Pediatric Scientists
Associates Chair in Liver and Intestinal Research
Associate Director, The Saban Research Institute (Teaching and Education)
Clinical Scholar and Professor of Pediatrics, Keck School of Medicine of USC

"These children had debilitating itching; scratching themselves to bleed," he said. "If you weren't trained in pediatrics to recognize this, you would think these children were abused -- the itching could be that bad."

Reference

Hein, I. (2022, November 9). *Maralixibat Takes Out the Itch of Rare Liver Disease*. MedPage Today. Retrieved May 3, 2023, from https://www.medpagetoday.com/meetingcoverage/aasld/101663?fbclid=IwAR3bosCBs2xTMhj0GNyQ_Bb_ZCYBB-N7Erj38iQ19po4IXNqpxE2NliwhIM

Experience With Drug Under Review

With the approval of Livmarli in the United States, and through clinical trials around the world, including in Canada, we have seen positive impacts on patients using the drug as either maralixibat or Livmarli depending on their vehicle of exposure to the drug ie clinical trial, expanded access program, or public use.. Through our support pages and personal interactions with Alagille patients, we have documented testimonies of patients indicating how Livmarli has contributed to 1) lessened day to day suffering from pruritus for the patients, 2) Lessened fatigue for the patient and all family members, 3) improved mental and physical health for the patient and all family members, 4) improved anxiety, depression, feelings of guilt, and physical health and overall wellbeing for patient and all family members, 5) improvements on feelings of hopelessness and helplessness, 6) improvements on overall burden of disease impact day to day, and 7) improvements on physical health of patient including reduction or complete relief of pruritus, improvements in weight gain, height, hair and nail growth, and appetite.

Benefits experienced, when compared to previous drugs used (because there weren't any set therapies for itch) are significantly higher impact with the reduction of itch or near expulsion of itch. All other medications used to try and treat pruritus would only take the edge off or be a short-term improvement.

Disadvantages, I'm not aware of any.

Noted side effects discussed in ALGSA private support groups included very mild to severe abdominal cramping and diarrhea most typically lasting only a few weeks with marked improvement within the first week and non-recurring side effects once the initial side-effect ended.

Livmarli use is much easier than previous drugs used because of the notable and significant improvement of itch. If a patient stops taking the drug, the itch will return within a few weeks, driving the patient to continue taking the drug consistently so they do not experience the severe itch again.

In summary, the values important to patients and caregivers regarding Livmarli include long-term relief of pruritus, long-term relief from extreme sleep deprivation, having an alternative to transplant and other invasive surgical interventions, prolonged preservation of native liver, improved overall family dynamic atmosphere with less stress, pressure, guilt, and emotional pain.

Personal Caregiver Perspective

Current Day Personal Testimony

President of the Alagille Syndrome Alliance - Michigan, USA
May 3, 2023

Through the ALGSA we are working on this patient input submission to support of Livmarli provincial reimbursement in Canada. Along with being a patient advocate and nonprofit leader, I am most importantly the mother of twin daughters who are 19 yrs old, one having Alagille Syndrome. My daughter Cloe started maralixibat, now Livmarli, through clinical trial in March 2016, after many years of severe pruritus which consisted of debilitating discomfort and pain due to itch along with self-inflicted abrasions, excoriations and skin tears. This led to scarring, extreme fatigue and exhaustion, sleep deprivation, continual frustration and upset, isolation from friends and family, low self-esteem, and decreased positive self-image. Just heartbreaking to watch as a parent, and itch affected everyone in the household. I personally suffered from long-term extreme fatigue and exhaustion, trying to aid her by scratching throughout the day and evening. I was also affected emotionally, watching her suffer daily was profound and extremely upsetting. I was helpless and could not prevent her from tearing her skin, bleeding all over her bed sheets at night, crying and suffering through the pain and discomfort, or resolve it in any way other than to be there for her and try to provide comfort. I felt absolutely hopeless and spent time worrying, fearing for her future, trying to find solutions with lotions, creams, medications, and nutrition, all of which made little to no impact. Once started, Livmarli improved my daughter's pruritus within a few weeks. Her skin started to heal, she began falling asleep at bedtime which was unheard of, and starting sleeping through the night. I also noticed her body changing in that she looked healthier and her personality and humor started to blossom. I attribute this to getting consistent sleep, experiencing vastly reduced daily pain and suffering, and feeling the freedom to enjoy life without the limitations and restrictions pruritus imposed on her life before Livmarli. To date, my daughter is still doing well with Livmarli and continues to enjoy significantly reduced itch and is living her life without having to focus on adjusting daily tasks, plans, and work around the extreme daily challenges of pruritus.

Past Personal Testimony

President of the Alagille Syndrome Alliance - Michigan, USA
November 13, 2019 (3 years after daughter started maralixibat through clinical trial)
Letter to Mirum in support of Maralixibat FDA approval

"Everyday I look at Cloe and marvel at how she's grown. Her hair has thickened, her skin has cleared, her personality has blossomed, mer mentality has sharpened, and her fatigue has fallen to the wayside. She's blossomed into such a beautiful teenager and I attribute that to maralixibat and the opportunity you've given my family (to be free of itch). I have a position that allows me insight into the dynamic of many Alagille homes. The gift maralixibat will be for these families is immeasurable, and you're taking it to the home plate with a home run."

Responses to Post in Private International ALGSA support page on Facebook

Original post dated January 10, 2022
*"How is Maralixibat/Livmarli working out for those of you who are using it?
Experiencing improvements?"*

6. Response by Mom of ALGS child from North Carolina, USA: "All I can say is we slept through the night for the 1st time in 5 years a few days after starting it"
7. Response by Mom of ALGS teenager from Washington, USA: "It's life changing for Emma"
8. Response by Mom of ALGS child from Texas, USA: "I have seen first hand how much it has given Samuel quality of life and he is able to sleep and be a child"
9. Response by **Canadian** Mom of ALGS child from Hanover, Ontario: "Life changing! We have a kid with a hilarious sense of humour that we're just getting to see! Sleep is significantly better. Lack of appetite continues to be a concern. It's a miracle drug in our house!"
10. Response by Mom of ALGS child from Utah, USA: "We have seen relief after only a few days. He was causing sores a lot and now he's only doing so occasionally. We're about 3 weeks in, and doing labs this week to see how things look."
11. Response by Mom of ALGS child from California, USA: "Insurance covered and we have noticed improvement ❤️. Taylor wasn't super itchy to begin with, but she says she's sleeping much better, and not as tired during the day. We've also noticed some changes in her hair- it's growing and much healthier, which was unexpected."
12. Response by Mom of ALGS young adult from Washington, USA: "My son has been on it for 4yrs now, it helped him immediately with the itching."
13. Response by **Canadian** Mom of an ALGS child from Saskatoon, Saskatchewan: "Ella has been on it for about 4 months now and it's working beautifully for her itch. She is having a lot of trouble with the watery stool side effects. She's needed to frequently and urgently get to a washroom. I'm hoping that over time, these side effects will diminish, but so far we haven't seen much improvement in this department."

One on one communication with Canadian Mom of child with ALGS NOT on maralixibat/Livmarli from Toronto

Email communication
Dated August 1, 2019
"The itch aspect is so important for me. These kids (Alagille kids) are just suffering. Knowing there's a medication that stops the itch and that my son can't have it because of "business" and not health is challenging. I once heard someone say that children shouldn't have to prove their worth to government…tough to swallow."

Companion Diagnostic Test

Patient and caregiver experiences with diagnosis can vary. Doctors can diagnose Alagille Syndrome through the presence of clinical features of the disease. Doctors can also easily confirm diagnosis by completing genetic testing.

Anything Else?

No

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Mirum Pharmaceuticals				X
Albireo Pharma/Ipsen				X
Travere Therapeutics				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Roberta Smith
Position: President
Patient Group: Alagille Syndrome Alliance
Date: April 20, 2023

Clinician Group Input

CADTH Project Number: SR0780-000
Generic Drug Name (Brand Name): maralixibat (Livmarli)
Indication: Alagille syndrome
Name of Clinician Group: Canadian Association for the Study of the Liver
Author of Submission: Binita M. Kamath

About Your Clinician Group

CASL is a non-profit organization that seeks to eliminate liver disease through research, education and advocacy. Our members are experts on liver disease in Canada: hepatologists, gastroenterologists, pediatricians, surgeons, radiologists, researchers, nurses, trainees, community advocates, and patients and family partners. https://hepatology.ca

Information Gathering

The data and information presented here are gathered from a review of the published literature about Alagille syndrome and Maralixibat and attendance at conferences and abstract presentations about Maralixibat. Further the information is based on collective expert opinion drawn from decades of experience managing patients with Alagille syndrome.

Current Treatments and Treatment Goals

Alagille syndrome (ALGS) is an autosomal dominant multi-system disorder characterized by bile duct paucity, chronic cholestasis, cardiac anomalies, typical facies, vertebral and eye findings, renal disease, and vascular malformations. Bile duct paucity in ALGS can lead to profound cholestasis, often presenting in infancy. Many patients suffer from severe pruritus, xanthomas, fat-soluble vitamin deficiencies (FSVD) and growth failure. Elevated GGT, total bile acids, and cholesterol serum levels are typical laboratory findings in patients with ALGS. For the purposes of this response, only the treatment paradigm for liver disease will be described (and not the extrahepatic features).

Treatment strategies in ALGS aim at managing cholestasis and its associated complications, such as nutritional support, FSVD, and pruritus. There are currently no curative therapies for ALGS-liver disease and the treatment paradigm described below is supportive and aims to ameliorate symptoms, however none of the therapies target the underlying disease mechanism of bile duct paucity. The management strategies described are all standard of care in Canada. There are no practice guidelines that outline this treatment paradigm due to the rarity of the disease and limited published data that meet the standards for a guideline, however multiple review articles encompass this information.

Nutritional Management

Children with ALGS require at least 125% of the recommended daily allowance of calories, and may need more for catch up growth. This is typically secondary to decreased intake, fat malabsorption and cardiac disease.[51-53] Medium chain triglyceride-rich foods are encouraged for ease of absorption, as well as other calorie dense foods. In children not being able to meet their caloric demands, tube feeding (nasogastric or via gastrostomy) is often required, especially in the context of end-stage liver disease.

Supplementation with fat-soluble vitamins is crucial. To aid with adherence and cost, cholestasis-specific formulations are available in Canada (e.g., DEKAs) via the special access pharmacy and are the preferred strategy. However, individual vitamin supplementation is acceptable if generic multivitamin preparations are the only available option.

Management of Pruritus

Pharmacological treatments

Treatment of pruritus requires a stepwise approach. Antihistamines are initiated first but are typically not effective but can be considered in mild cases and to augment sleep. Ursodeoxycholic acid promotes bile excretion rendering it more hydrophilic.[54] Due to its attractive safety profile, it is typically used as early in the management of cholestasis. Next, cholestyramine, a bile salt-binding agent may be considered. Cholestyramine decreases bile acid pool size by binding bile salts in the ileum. However, poor palatability and interference with absorption of other drugs (specifically fat-soluble vitamins) limits its use and in practice it is almost never used.[54] Rifampin is much preferred to treat pruritus instead of cholestyramine. Rifampin has been reported to improve pruritus in 50% of ALGS patients (n=39) and it is well-tolerated.[54] Through its enzymatic induction in the liver, it is thought to increase the metabolism of pruritogens. Opioid antagonists such as naltrexone, are sometimes added to the regimen if pruritus persists and may provide modest additional benefit. Opioid withdrawal symptoms which may occur in one-third of patients limits its use in clinical practice.[54] Lastly, sertraline, a selective serotonin reuptake inhibitor (SSRI), has been used in refractory cases. Its mechanism of action is poorly understood. Limited pediatric studies support its use as adjunctive therapy intractable pruritus and it is infrequently used in clinical practice.[55]

Surgical interventions

In patients with drug-refractory pruritus, biliary diversion procedures that interrupt the enterohepatic circulation and decrease bile pool size are considered. Partial external biliary diversion where a jejunal conduit is used to drain the gallbladder externally, is the most commonly performed procedure. In a large multi-centered North American study examining biliary diversion procedures among cholestatic infants, biliary diversion in 20 ALGS patients resulted in decreased serum cholesterol, resolution of xanthomas, and a significant drop in patient-reported pruritus.[56]

It should be noted that due to the biliary hypoplasia in ALGS, less bile acids reach the small intestine in some patients. Therefore, these procedures are generally less effective in ALGS than in other cholestatic liver diseases such as progressive familial intrahepatic cholestasis. These procedures therefore may not alleviate pruritus or prevent the progression of liver disease in many ALGS patients.[57,58] Fewer of these procedures are being performed in Canada due to low efficacy and families' preference not to have a stoma.

Liver Transplantation (LT)

The main indications for LT in ALGS fall under two categories: 1) patients with severe cholestasis and/or associated complications (growth failure, FSVD, and intractable pruritus); and 2) patients with cirrhosis and complications secondary to portal hypertension (ascites and variceal bleeding).

In children with cholestasis from teriary referral centres, LT is required in up to 75% of patients by the age of 18[59]. Outcomes post-LT are similar to most other indications of pediatric LT.[60]

Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The treatment goals for liver disease in ALGS are to ameliorate the symptoms, primarily pruritus, optimize nutritional goals, including treating FSVD. To date there are no therapies that target bile duct paucity and the underlying mechanisms of cholestasis in ALGS.

The treatment paradigm described above falls short for many patients with ALGS-cholestatic liver disease. Patients with even moderate cholestasis typically suffer from severe, debilitating pruritus. Anti-histamines are rarely effective, cholestyramine is unpalatable, and although rifampin does provide some symptomatic relief for pruritic patients, it is usually ineffective in substantially ameliorating or eradicating pruritus. Sertraline and naltrexone provide marginal additional benefit, if at all. Therefore current medical treatment paradigms for pruritus are insufficient for many cholestatic patients with ALGS. Thus surgical options have to be considered. An external biliary diversion can be offered to ALGS patients with pruritus that is refractory to medical

therapies, however it is only effective in approximately half of patients and leaves the child with a stoma which is unacceptable to most families. An internal biliary diversion is less effective in patients with ALGS. Finally between 50-75% of cholestatic liver disease end up requiring liver transplantation and pruritus is a leading indication for this. Liver transplantation is, of course, associated with mortality and morbidity associated with a major surgery and lifelong immune suppression.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

As described above, many patients with ALGS and cholestatic pruritus have inadequately treated pruritus with standard of care medical therapy. Maralixibat would be added to the current toolkit of available medical therapies. Maralixibat would be used in combination with the other available medications. None of the currently available therapies interrupt enterohepatic circulation of bile acids and lower serum bile acids by blocking bile acid uptake in the ileum. It is true that cholestyramine is a bile acid-binding resin and can also reduce bile acid return to the liver, however it is not as efficacious as blocking the intestinal bile acid transporter and more importantly it is unpalatable and almost never used in clinical practice.

Maralixibat treats symptomatic pruritus which is very debilitating for patients and disrupts sleep for children and the whole family with wide-ranging impacts on health-related quality of life. Maralixibat is a symptomatic treatment, however there are also emerging data that patients treated with maralixibat may have a reduction in clinically important liver events, including the need for liver transplantation. Since the primary indication for Maralixibat is treatment of pruritus, it would be used in patients who have persistent pruritus on ursodexycholic acid, antihistamines and rifampin. Maralixibat would be added in to the treatment plan (rather than as a replacement for these other medications). It is possible that some patients may be able to wean off some of the standard medications once they are established on Maralixibat. Naltrexone and sertraline are rarely offered in clinical practice due to very limited efficacy and tenuous safety profiles and therefore I would NOT recommend that these be attempted prior to offering Maralixibat.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients with ALGS and cholestatic pruritus, which is persistent on standard of care medical treatment would be eligible for treatment. Since the mechanism of action of Maralixibat is to lower serum bile acids, it is reasonable to anticipate that patients with elevated serum bile acids are most likely to respond to treatment. Patients with moderate to severe pruritus, as determined by clinician evaluation and parent/caregiver/patient report, would be at most need.

The diagnosis of ALGS is relatively straightforward. It is an autosomal dominant condition and a genetic diagnosis can be confirmed in >95% of patients with clinical features. Also a clinical diagnosis can be made by the presence of clinical features in 3/7 organ systems. With the advent of molecular testing, a misdiagnosis is infrequent.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The primary outcomes in the clinical trials were patient-reported assessments of pruritus severity and serum bile acids. The exact tool to assess pruritus in the trials is not feasible in clinical practice as it requires twice daily scores over 2 weeks. In clinical practice pruritus severity is assessed by asking the patient/family about severity of pruritus, sleep disturbance and then

examining the skin for evidence of excoriations. The physical examination can be scored according the Clinician Scratch Scale and this was also included in the clinical trials. Serum bile acids can also be used, however in clinical practice these are not sent routinely due to cost and logistics as this test is often sent to specialized laboratories and is not readily available in all gastroenterology practice settings.

A clinically meaningful response would be patients/families reporting an improvement in pruritus, improvement in sleep duration which can be objectively measured by asking how often the child wakes at night or by documenting improvements in skin excoriations.

What factors should be considered when deciding to discontinue treatment with the drug under review?

The most likely reason to discontinue treatment with Maralixibat would be if a patient's liver disease progresses and they undergo liver transplantation. The safety profile of the drug is excellent and I have not had to discontinue it for any side effects.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Maralixibat should be prescribed and monitored by a paedaitric gastroenterologist or hepatologist.

Additional Information

No

Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Binita M. Kamath
Position:
Division Head (interim)
Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children
Senior Associate Scientist, Research Institute
Professor, University of Toronto
Lead, CASL Canadian Pediatric Hepatology Research Group (CPHRG)
Date: 12-05-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Mirum: Consultant Unrestricted Educational Grant			X (Consultant)	X (Grant)
Albireo: Consultant Unrestricted Educational Grant			X (Consultant)	X (Grant)
Audentes (Astellas) Consultant		x		

* Place an X in the appropriate dollar range cells for each company.