SMC2806

maralixibat oral solution (Livmarli®)

Mirum Pharmaceuticals AG

08 August 2025 (*Issued 07 November 2025*)

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a second resubmission assessed under the orphan medicine process

maralixibat (Livmarli®) is accepted for restricted use for use within NHSScotland.

Indication under review: treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

SMC restriction: for use in patients whose condition has not responded to standard of care medicines.

In a double-blind, randomised withdrawal, phase IIb study, maralixibat maintained reduced serum bile acid levels, compared with a significant increase with placebo, in children (age 1 to 18 years) with ALGS.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Maralixibat is an ileal bile acid transporter (IBAT) inhibitor that acts in the distal ileum to block intestinal reabsorption of bile acids, thereby increasing their excretion and decreasing their serum levels which can improve cholestatic pruritus.[1, 2] Maralixibat is administered via an oral syringe at an initial dose of 190 micrograms/kg once daily for one week, followed by an increase to target dose of 380 micrograms/kg once daily. The maximum dose, for patients ≥ 70 kg, is 28.5 mg daily. Alternative treatment should be considered in patients for whom no benefit can be established following three months of continuous daily treatment with maralixibat. Further details are included in the Summary of Product Characteristics.[2]

1.2. Disease background

Alagille syndrome (ALGS) is a rare genetic disorder[1], with defects in the notch signalling pathway most commonly due to mutations in JAGGED1 gene and, in a small proportion, the NOTCH2 gene.[3] It affects multiple systems in the body, with severity varying from mild symptoms and normal life expectancy to debilitating symptoms and life-threatening complications.[1, 4] Patients with ALGS are typically born with a reduced number or impaired bile ducts in the liver resulting in cholestasis, which can cause severe pruritus, xanthomas, limited growth and fatigue. The clinical burden of cholestasis can be so severe that, even in the absence of end-stage liver disease, it is an indication for liver transplantation for some patients.[1]

1.3. Company proposed position

The submitting company considered that maralixibat would be used in patients whose condition has not responded to standard of care medicines.

1.4. Treatment pathway and relevant comparators

Other than maralixibat[2], there are no licensed treatments for cholestatic pruritus in ALGS. Current management involves the use of off-label treatments including cholestyramine, rifampicin, and ursodeoxycholic acid, as well as adjunctive therapies like antihistamines, naltrexone, and sertraline. Where symptoms remain severe despite treatment with medicines, surgical options include partial external biliary diversion and liver transplantation.[1, 5] The submitting company deemed standard of care to primarily include ursodeoxycholic acid, rifampicin, and phenobarbital; clinical experts contacted by SMC were in broad agreement, citing ursodeoxycholic acid and rifampicin as the predominant pharmacological treatments they use.

1.5. Category for decision-making process

Eligibility for a PACE meeting

Maralixibat meets SMC orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of maralixibat for the indication under review comes from the ICONIC study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study

Criteria	ICONIC study.[1, 6, 7]
Study design	Double-blind, randomised withdrawal, phase IIb study.

Eligible patients	• Children aged 12 months to 18 years with Alagille syndrome.
	• Evidence of cholestasis, defined as at least one of:
	  ○ Total serum bile acid or gamma-glutamyl transferase >3 x ULN for age
	  ○ Conjugated bilirubin >1 mg/dL
	  ○ Fat soluble vitamin deficiency or intractable pruritus otherwise unexplainable
	• ItchRO average daily score >2 for two consecutive weeks in the screening period.

Treatments	Following an 18-week open-label run-in of maralixibat (6-week titration to target dose of 380 micrograms/kg daily and 12 weeks of a stable dose), patients were randomised to a 4-week double-blind, placebo-controlled withdrawal. Then, all received open-label maralixibat 380 micrograms/kg daily to Week 48, with option to continue it in a long-term extension study.
Randomisation	Equal randomisation during the 4-week double-blind withdrawal period.
Primary outcome	Mean change in fasting serum bile acid levels from Week 18 to 22 (withdrawal period) in patients who received study treatment to Week 18 and had ≥50% reduction in serum bile acid from baseline through to Week 12 or 18 (mITT).
Selected secondary outcomes	In enrolled patients who received ≥1 dose of study drug (ITT), mean change from Week 18 to 22 for: fasting serum bile acid level; pruritus assessed by caregiver, ItchRO(Obs), and patient, ItchRO(Pt); and liver function tests.
Statistical analysis	Exploratory study with no formal sample size calculation. Differences between groups in change from Week 18 to 22 analysed by ANCOVA for continuous data and by Chi-square or Fischer's exact test for binary data. No adjustment for multiplicity.

Abbreviations: ItchRO = Itch Reported Outcome instrument, scored from 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) itch; ItchRO(Obs) completed by caregiver; ItchRo(Pt) completed by patient if > 9 years old and with caregiver help if 5 to 8 years old. ITT = intention-to-treat; mITT = modified intention-to-treat; ULN = upper limit of normal.

In the randomised withdrawal period (Week 18 to 22), maralixibat maintained reduced serum bile acid levels, compared with a significant increase with placebo in the modified intention-to-treat (mITT) population, that is the primary outcome, with similar results in the ITT population.[1]

Table 2.2. Primary and selected secondary outcomes results of ICONIC study.[1, 6]

Primary outcome assessed in the modified intention-to-treat (mITT) population			
Mean change from:	**Maralixibat (n=5)**	**Placebo (n=10)**	**Difference (95% CI)**
Week 18 to 22 in sBA (micromoles/L)	-21.73	95.55	-117.28 (-232.38 to -2.18)
Selected secondary outcomes in the intention-to-treat (ITT) population			
Mean change from:	**Maralixibat (n=29)**		**Difference (95% CI)**
Week 0 to 18 in sBA (micromoles/L)	-87.73		-
	Maralixibat (n=13)	**Placebo (n=16)**	
Week 18 to 22 in sBA (micromoles/L)	-18.74	95.21	-113.95 (-212.68 to -15.21)
	Maralixibat (n=29)		
Week 0 to 18 in ItchRO(Obs)	-1.704		-
	Maralixibat (n=12)	**Placebo (n=16)**	
Week 18 to 22 in ItchRO(Obs)	0.217	1.700	-1.483 (-2.122 to -0.844)

	Maralixibat (n=14)		
Week 0 to 18 in ItchRO(Pt)	-2.072		
	Maralixibat (n=5)	**Placebo (n=9)**	
Week 18 to 22 in ItchRO(Pt)	-0.149	1.839	-1.988 (-3.009 to -0.967)

CI = Confidence Interval; ItchRO = Itch Reported Outcome instrument, scored from 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (very severe) itch; ItchRO(Obs) completed by caregiver; ItchRo(Pt) completed by patient if > 9 years old and with caregiver help if 5 to 8 years old; sBA = Serum bile acid.

In the ICONIC study, 23 patients continued maralixibat after Week 48 in the optional open-label long-term extension, with 15 remaining on treatment at Week 204. After Week 100, patients with serum bile acid levels >8 micromole/L (upper limit of normal [ULN]) or pruritus, defined by Itch Reported Outcome Observer instrument, ItchRO(Obs) ≥1.5, increased maralixibat dosing to twice per day (up to a total daily maximum of 760 micrograms/kg), which is higher than the licensed dose. Results for serum bile acid and ItchRO(Obs) suggest generally maintained efficacy with maralixibat through to Week 204.[1, 6]

2.2. Evidence to support the positioning proposed by the submitting company

The proposed positioning is for patients whose condition has not responded to standard of care medicines. Supportive of the positioning, 94% (29/31) of all patients in the ICONIC study had a history of receiving treatments for pruritus with ursodeoxycholic acid (81%) and rifampicin (74%) being the most common treatments, whilst a smaller proportion (13%) were on phenobarbital.[2, 6] Concomitant use of these medicines were allowed during the study but dose adjustments were prohibited during the first 22 weeks.[2]

2.3. Health-related quality of life outcomes

Health-Related Quality of Life was assessed in the ICONIC study using the Pediatric Quality of Life Inventory (PedsQL) core (parent) generic module and the PedsQL multidimensional fatigue scale. Results for both suggest improvements after the run-in (Week 18) and over prolonged treatment to Week 48 with maralixibat. However, there were no significant differences between maralixibat and placebo during the randomised withdrawal period.[6]

2.4. Supportive studies

Two double-blind, dose-finding, phase II studies, IMAGO[8] and ITCH[9], recruited children (1 to 18 years old) with ALGS, cholestasis and moderate to severe pruritus and assessed maralixibat doses lower than the licensed target dose. In IMAGO, there were no significant differences between the maralixibat 140 (n=6) or 280 micrograms/kg/day (n=8) groups compared with placebo (n=6) for the primary outcome, change from baseline to week 13 in fasting serum bile acid levels (-82.9 and -49.4 versus -42.2 micromole/litre), ItchRO(Pt) or ItchRO(Obs).[8] In ITCH, there were significant differences between the maralixibat 70 (n=8), 140 (n=11) micrograms/kg/day groups, but not the 280 micrograms/kg/day (n=6) group, compared with placebo (n=12) for the primary outcome, change from baseline to week 13 in ItchRO(Obs) (-1.5, -1.5, -0.6 versus -0.6). There were no significant differences between groups for change from baseline to week 13 in serum bile acids.[9]

Two long-term extension studies, IMAGINE and IMAGINE II, recruited 19 and 34 patients, from IMAGO and ITCH, respectively, and they received open-label maralixibat 280 micrograms/kg once daily (with 280 micrograms/kg twice daily permitted after Week 124 in IMAGINE). Study outcomes

included the mean change from baseline in fasting serum bile acids level and pruritus assessed through ItchRO(Obs), and were assessed up to week 220 in IMAGINE II or 288 weeks in IMAGINE (with week 0 set at the initiation of IMAGINE or IMAGINE II). These long-term open-label studies demonstrated maintained efficacy in pruritus and serum bile acid at most time points with maralixibat.[1, 10-12]

An open-label, multicentre, phase II study (RISE) recruited infants (≥ 2 to <12 months old) with cholestatic liver disease (ALGS or progressive familial intrahepatic cholestasis).[13, 14] A regulator reviewed interim data (data cut off September 2023) from 16/17 included patients with ALGS (mean age 6.5 months) who were treated with maralixibat for at least 13 weeks. This showed clinical improvement in pruritus in 47% of patients as well as a numerical benefit in serum bile acid levels over the observation period. Despite issues with incomplete data sets for some outcomes, it was concluded that these results justify the clinical benefit of maralixibat in infants aged 3 months and older.[15]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

There was an indirect comparison of long-term outcomes in pooled maralixibat studies versus a historical control group treated with standard of care in the Global Alagille Alliance (GALA) clinical research database.[16] Results from this comparison were used in the economic base case.

Table 2.3: Summary of indirect treatment comparison.[1, 16]

Criteria	Overview
Design	External historical cohort comparison using Cox proportional hazards regression analysis
Population	Patients aged from 1 to 18 years with Alagille syndrome, cholestasis and pruritus who resided in North America, Europe and Australia.
Comparators	Standard of care
Studies included	**Maralixibat**: 84 patients from the ICONIC study[6, 7], IMAGO[8] and its extension study IMAGINE; ITCH[10] and its extension study IMAGINE II. **Standard of care:** 469 patients in the GALA registry[16], who aligned with the inclusion criteria of maralixibat studies and resided in North America, Europe and Australia.
Outcomes	Event-free survival, where events included: liver transplant; surgical biliary diversion; liver decompensation (which encompasses variceal bleeding and the need for ascites therapy); and death.
Results	Primary analysis (with adjustments for age, sex, bilirubin, and alanine transaminase) suggests that maralixibat, compared with standard of care, has longer event-free survival, with an adjusted HR 0.305 (95% CI: 0.189 to 0.491; p<0.0001).

CI = Confidence Interval; HR = Hazard Ratio; GALA = Global Alagille Alliance clinical research database.

3. Summary of Safety Evidence

Across the clinical study programme, the most common adverse events were diarrhoea, vomiting and abdominal pain. In the ICONIC study, gastrointestinal adverse events were reported by 71% (22/31) of patients during the initial 18-weeks (with diarrhoea, abdominal pain and vomiting noted by 42%, 39% and 36% of patients, respectively) and by 2 and 3 patients (15% versus 19%) within the maralixibat and placebo groups, respectively, during the randomised withdrawal phase. In the long-term extension (Week 48 to 204), 70% (16/23) of patients reported gastrointestinal events. Duration of these events was generally limited, and there were dose adjustments to mitigate.[6]

During the 4-week randomised drug withdrawal period of the ICONIC study (Week 18 to 22), adverse events were reported in 54% (7/13) and 75% (12/16) of the maralixibat and placebo group, respectively, including pruritus reported as an adverse event in 7.6% and 31%. Other frequently reported adverse events included infections (46% versus 25%); and skin and subcutaneous tissue disorders (15% versus 31%).[6]

Regulators concluded that maralixibat is generally well tolerated. However, uncertainty remains about potential liver toxicity, especially in very young patients. Therefore, monitoring and data collection are ongoing, in particular, the LEAP study is expected to provide further information on potential hepatotoxicity.[1]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- The differences observed with maralixibat when compared with placebo in serum bile acid levels and pruritus, as measured using the ItchRO instruments, during the ICONIC study's double-blind withdrawal phase, were regarded as clinically relevant. In patients with ALGS, increased levels of serum bile acids are assumed to cause pruritus and contribute to liver damage. Pruritus is a challenging and distressing symptom, and severe pruritis may lead to surgical interventions like biliary diversion or liver transplantation in patients with ALGS.[1]
- Maralixibat is the first medicine licensed for the treatment of cholestatic pruritis in ALGS.[2]

4.2. Key uncertainties

- ICONIC, was a phase II exploratory study, with a very small sample size.[1] Due to the rare nature of ALGS, no formal sample size calculation was performed. The planned sample size of 30 evaluable patients was based on the practicalities of running the study rather than powering it to detect differences.[6] Additionally, the placebo-controlled experimental phase of this study was limited to only 4 weeks.[1, 17] Of note, the primary efficacy analyses were conducted only in responders, further reducing the number of patients and causing an imbalance in group sizes (with only five patients in the maralixibat group and ten in the placebo group).
- Uncertainty remains around the long-term efficacy and safety of maralixibat. From Week 100, eligible patients in ICONIC could receive a dose of maralixibat of 760 micrograms/kg per day, limiting longer term data with the licensed recommended target dose of 380 micrograms/kg.[1] In addition, only 15 patients remained enrolled as of 204 weeks. Only uncontrolled, open-label data are available with prolonged use with maralixibat, which complicates interpreting subjective outcomes such as pruritis. In this context, the marketing authorisation was granted under exceptional circumstances, and further data on long-term efficacy and safety of maralixibat from a prospective study are to be provided to the regulator.[1]
- In the submission, an indirect comparison of pooled maralixibat studies versus the GALA cohort supports an assumption of improvement in long-term clinical outcomes, such as liver decompensation, liver transplant, surgical biliary diversion and death, which were included in the definition of event-free survival (EFS). In the EFS analysis, in the maralixibat (n=84) and control groups (n=469) respectively, 25% and 35% of patients had an event, which included liver transplants (12% versus 23%) and surgical biliary diversion (4.8% versus 7.0%). The clinical

studies excluded patients unlikely to complete them, for example due to imminent liver transplant or surgical biliary diversion, whereas these patients may not be excluded from the GALA registry. The regulator noted issues with comparisons with historical controls, including the risk of unaccounted factors influencing results and the susceptibility to selection bias, making accurate analysis difficult.[1]

- Some factors may affect the generalisability of the available data to the eligible Scottish population. Patients with severe complications were excluded (for example, decompensated liver cirrhosis).[6] There is limited data available in patients from 3 to 12 months of age, and for adults.[15]

4.3. Clinical expert input

All clinical experts consulted by SMC consider that maralixibat in the treatment of cholestatic pruritus in patients with ALGS is a therapeutic advance due to its mechanism of action and efficacy in a group of patients with substantial symptoms and limited treatment options.

4.4. Service implications

All clinical experts consulted by SMC considered that the introduction of maralixibat would not have a significant impact on services.

5. Patient and clinical engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of maralixibat, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Patients with ALGS can suffer debilitating, intractable itch (pruritus) that causes pain, skin damage and scarring. The continual discomfort can affect sleep, eating and ability to focus and participate in everyday activities, thereby limiting educational and social development. Some younger patients require artificial feeding and many fail to achieve development milestones. Overall, it markedly reduces quality of life and has a substantial negative impact on mental health.

- Often, itch is not adequately controlled with existing, sometimes off-label, treatments. It can be so severe that patients, sometimes with otherwise healthy livers, opt to find relief by undergoing a liver transplant. Some patients, who cannot have a transplant due to limited organ availability or comorbidities, have no effective options. There is an unmet need for effective therapies to treat itch associated with ALGS.

- The immense burden of managing the symptoms of ALGS has an impact on the patient's family, in practical terms and in relationships. Parents may have to reduce or stop work to help their child, leading to financial issues and they can feel overwhelmed, helpless and guilty for having less time to spend with their other children and spouse. Siblings can be upset to see the patient constantly distressed. Overall, it has a substantial negative psychological impact on the whole family.

- Maralixibat is specifically licensed to treat itch in ALGS. It considerably reduces itch and thereby can improve the patient's skin condition, pain and discomfort. This may lead to better sleep, eating and focus on educational and social activities. With fewer symptoms, they may attend healthcare services less often. PACE participants reported that maralixibat has enabled some patients to discontinue artificial feeding and some to stop their other medicines for itch, which has helped with polypharmacy issues. Overall, it has been reported to have a substantial positive impact on mental health and general wellbeing. Clinicians report that maralixibat has had a life-changing effect on children, with some who were previously miserable and non-verbal becoming happy and chatty. It may avoid escalation to a liver transplant with its potentially serious complications.
- If maralixibat effectively controls the patient's itch, the patient's family would benefit from a reduced carer's burden, improved quality of family life and more time with the patient and with each other. It may allow the patient's parents to participate more in work and in helping their other children with school and after school activities. Overall, it could have a substantial positive impact on the whole family's mental health, and it may allow them to use regular childcare facilities and have more options in terms of holidays and social activities.
- PACE clinicians consider that maralixibat would be used for patients who have failed on other treatments. They note that it could be delivered by Homecare, which would be efficient for the clinician and the family. They advised that monitoring would be included in standard follow-up procedures (after a short initial period of increased monitoring).

Additional Patient and Carer Involvement

We received a patient group submission from The Children's Liver Disease Foundation, which is a registered charity. The Children's Liver Disease Foundation has received 12% pharmaceutical company funding in the past two years, including from the submitting company. A representative from The Children's Liver Disease Foundation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (100 years)
Population	Patients 2-months of age and older with ALGS and cholestatic pruritis.
Comparators	Standard of care (SoC) medicines, which included ursodeoxycholic acid, rifampicin and phenobarbital.
Model description	The model compared two treatment arms, maralixibat in addition to SoC compared to SoC. The company utilised a Markov state-transition model with 8 discrete health states: cholestasis and pruritus, responsive to medication; severe cholestasis with pruritis, unresponsive to medication;

	cirrhosis; portal hypertension (PHT); ascites; liver transplant (LTx); post-LTx; and an all-absorbing dead state. In the maralixibat arm, patients entered the model in the responsive to medication health state. Patients in the responsive to medication health state could only transition to the unresponsive to medication or dead health state. Only patients in the responsive to medication health state continued treatment with maralixibat. In the SoC arm, patients entered the model in the unresponsive to medication health state; this reflects the positioning. Patients in the unresponsive to medication health state had a chance of transitioning to the cirrhosis health state. Patients in the cirrhosis health state could enter the PHT health state. From the PHT health state patients could enter the ascites health state. Patients without cardiac or renal involvement could transition to the LTx health state from any health state except the responsive to medication health state and dead. All patients who received a LTx moved to the post-LTx health state after one model cycle, except those who were assumed to require re-transplantation who remained in the post-LTx health state. Patients could enter the death health state from any other health state in any cycle. The model was run twice to account for patients who were eligible for LTx and those ineligible due to cardiac/renal involvement, these results were weighted and combined.
Clinical data	Clinical data from the ICONIC study informed baseline patient weight and response to maralixibat at 12 weeks (1st model cycle). Beyond the first model cycle the probability of transitioning from the responsive to unresponsive to medication health state was according to the proportion of patients who discontinued maralixibat due to adverse events at 18-weeks in ICONIC. Transition probabilities from the unresponsive health state to cirrhosis, cirrhosis to PHT, PHT to ascites, unresponsive to LTx, and LTx to death were from ALGS literature. Transition probabilities from the cirrhosis, PHT and ascites health states to LTx, the re-transplantation from the LTx health state, and mortality in the cirrhosis, PHT, ascites, post-LTx health states were from non-ALGS literature.
Extrapolation	Mortality for patients in the unresponsive to medication health state was extrapolated using parametric survival modelling applied to reconstructed Kaplan-Meier data from the GALA study. The company selected the midpoint curve (log-logistic) due to the similarity of visual and statistical fit (AIC/BIC) for each of the candidate distributions, the potential range was validated by a clinician. Mortality was adjusted in the responsive to medication health state according to the event-free survival (EFS) hazard ratio (0.305) from the indirect treatment comparison.
Quality of life	Health state-specific utility weights were obtained from a time-trade off vignette study conducted by the company for caregivers of and patients with ALGS. Utility decrements from the literature were applied for patients in the progressed liver disease health states. Caregiver disutilities were calculated by the difference between the caregiver utility in the vignette study and age-matched general population utility. The submitting company has included caregiver disutilities in a scenario analysis.
Costs and resource use	Costs included medicine acquisition, management of adverse events, monitoring and disease management, surgical management and end-of-life costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

*Other data were also assessed but remain confidential.**

6.2. Results

SMC would wish to present the with-PAS cost-effectiveness results that were used for decision-making. However, SMC is unable to publish these results due to commercial in confidence concerns regarding the PAS.

6.3 Sensitivity analyses

Deterministic sensitivity analyses found that the model was most sensitive to varying the age limit at which the GALA study mortality rate is applied (0 years in base case to 18 years in sensitivity analysis), the probability of discontinuation of maralixibat, inclusion of caregiver disutilities, inclusion of SBD (surgical biliary diversion) as a health state and varying the proportion of the cohort ineligible for liver transplantation.

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.2.

Table 6.2: Scenario Analyses

	Parameter	**Base case**	**Scenario**
1	Caregiver disutility	Excluded	Included
2	Probability of response to maralixibat	ICONIC study ≥50% reduction in sBA from baseline at week 12	RISE response rate
3			ItchRO response at 18 weeks (52.92%) from ICONIC
4			ItchRO response at 13 weeks (76%)
5			sBA response at 48-weeks (16.6% per cycle)
6	Post-LTx mortality	3.1%	Rate from NICE HST17 (0.03%)
7	Weight band	5th percentile	75th percentile
8	Proportion ineligible for LTx	30%	0%
9			76%
10	LTx utility	AIC	0.71
11	Discontinuation rate	AIC	AIC
12	Utility values	Vignette study	Kamath study
13	Transition to SBD	Exclude	Include
14	OS distribution	Log-logistic with adjustment for all-cause mortality	Exponential
15			Gompertz
16	Adverse event rates	ICONIC study	IMAGINE study
17	Adverse events	Include portal hypertension and ascites	Exclude portal hypertension and ascites
18	Mortality	Additional mortality allowed from age 0 onwards	No additional mortality vs. GALA until 18

Abbreviations: AIC = academic in confidence; ItchRO, itch reported outcome; LTx, liver transplant; NICE HST = NICE highly specialised technologies; OS, overall survival; sBA, serum bile acid; SBD, surgical biliary diversion.

6.4 Key strengths

- Availability of randomised evidence from the ICONIC study that, despite small numbers, as expected for a rare disease, reported that treatment with maralixibat had a statistically significant effect on reducing pruritis symptoms and serum bile acid in patients with ALGS.
- Data were available from the GALA database to inform the natural history of liver disease in a population of patients with ALGS.
- The submitting company had made amendments since the previous resubmission to reflect SMC guidance on the exclusion of carer disutilities from the base case, and the positioning has also been clarified.

6.5 Key uncertainties

- The modelling of mortality in the patient population eligible for treatment with maralixibat was highly uncertain. Data to provide external validation of the modelled mortality in patients presenting with cholestasis and pruritis were not available but survival estimates of patients presenting with neonatal cholestasis from a registry study reported greater than double the number of patients alive at 18 years compared to those in the standard of care arm of the model. It was uncertain whether the excess mortality applied in the model for patients who transitioned to progressed liver disease health states or to surgical interventions would be reflective of that observed in Scottish clinical practice. Scenarios that adjusted mortality in the model to reflect more closely that observed in the GALA cohort led to higher estimates of cost-effectiveness (see scenario 18 in Table 6.2).
- There was a lack of direct evidence for the health effects of maralixibat compared to standard of care medicines beyond serum bile acid levels and pruritus. The use of the event-free survival HR to estimate mortality in the responsive to medication health state compared to patients in the unresponsive to medication health state was uncertain. The event-free survival endpoint was difficult to interpret due to it capturing multiple competing risks that represented different patient experiences in terms of health outcomes, such as liver transplant and decompensated liver disease and death.
- The ongoing discontinuation rate of maralixibat seemed uncertain as it was based on the rate of AEs observed at 18-weeks in the ICONIC study. It is then extrapolated over the time horizon at a constant rate. The rate of maralixibat discontinuation that would be observed in Scottish clinical practice remains uncertain. In a scenario that halved the rate of discontinuation (Scenario 11), a large increase in the ICER was observed.

*Other data were also assessed but remain confidential.**

7 Conclusion

The Committee considered the benefits of maralixibat in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as maralixibat is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted maralixibat for restricted use in NHSScotland.

8 Guidelines and Protocols

The European Association for the Study of the Liver (EASL) published the EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. This was published in August 2024.[5]

9 Additional Information

9.1 Product availability date

01 December 2025

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Maralixibat 9.5 mg/mL oral solution	**190 micrograms/kg once daily for one week, then 380 micrograms/kg once daily (maximum for patients ≥70 kg, 28.5 mg [3 mL])**	**131,910 to 1,626,890**

Costs from BNF online on 29 April 2025. Costs calculated based on patient weighting of 5 kg to 70 kg. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. The European Medicines Agency (EMA) European Public Assessment Report. Maralixibat (Livmarli®). EMEA/H/C/005857/0000. Published: 13 October 2022. Available at: https://www.ema.europa.eu/en/medicines [Accessed: 23 April 2025].
2. Mirum Pharmaceuticals International B.V. Maralixibat 9.5 mg/mL oral solution (Livmarli®) - summary of product characteristics. Last updated: 19 March 2024. Available at: https://products.mhra.gov.uk/ [Accessed: 22 April 2025].
3. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012 Mar;20(3):251-7. doi: 10.1038/ejhg.2011.181.
4. National Institute of Diabetes and Digestive and Kidney Diseases. Alagille Syndrome - Defintion & Facts. Last reviewed: January 2019. Available at: https://www.niddk.nih.gov/health-information/liver-disease/alagille-syndrome/definition-facts [Accessed: 23 April 2025].
5. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. 2024; 81(2):303-325. doi: 10.1016/j.jhep.2024.04.006.
6. Gonzales E, Hardikar W, Stormon M, Baker A, Hierro L, Gliwicz D, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. Lancet. 2021 Oct 30;398(10311):1581-1592. doi: 10.1016/S0140-6736(21)01256-3.
7. ClinicalTrials.gov. Document provided by Mirum Pharmaceuticals, Inc. Safety and Efficacy Study of LUM001 (Maralixibat) With a Drug Withdrawal Period in Participants With Alagille Syndrome (ALGS) (ICONIC). Study Protocol. Available from: https://clinicaltrials.gov/ [AccessedL 24 April 2025].
8. ClinicalTrials.gov. Infomation provided by Mirum Pharmaceuticals, Inc. Safety and Efficacy Study of LUM001 in the Treatment of Cholestatic Liver Disease in Patients With Alagille Syndrome (IMAGO). Available from: https://clinicaltrials.gov/. [Accessed: 24 April 2025].
9. ClinicalTrials.gov. Evaluation of LUM001 in the Reduction of Pruritus in Alagille Syndrome (ITCH). Available from: https://clinicaltrials.gov/study/NCT02057692 [Accessed: 24 April 2025].
10. Shneider BL, Spino CA, Kamath BM, Magee JC, Ignacio RV, Huang S, et al; for ChiLDReN and UK IMAGO/IMAGINE Investigators. Impact of long-term administration of maralixibat on children with cholestasis secondary to Alagille syndrome. Hepatol Commun. 2022 Aug;6(8):1922-1933. doi: 10.1002/hep4.1992.
11. ClinicalTrials.gov. Infomation provided by Mirum Pharmaceuticals, Inc. An Extension Study to Evaluate the Long-Term Safety and Durability of Effect of LUM001 in the Treatment of Cholestatic Liver Disease in Subjects With Alagille Syndrome (ALGS) (IMAGINE). Available from: https://clinicaltrials.gov/. [Accessed: 24 April 2025].
12. ClinicalTrials.gov. Infomation provided by Mirum Pharmaceuticals, Inc. An Extension Study to Evaluate the Long-Term Safety and Durability of Effect of LUM001 in the Treatment of Cholestatic Liver Disease in Pediatric Subjects With Alagille Syndrome (IMAGINE-II). Available from: https://clinicaltrials.gov/. [Accessed: 24 April 2025].
13. Rosenthal P, Thompson R, Jankowska I, Horslen S, Ekong U, Sokal E, et al. Abstract Number: 363 - Safety and tolerability of maralixibat in infants from 2 months of age with Alagille syndrome or progressive familial intrahepatic cholestasis: results from the RISE study. 2023 Oct; J. Pediatr. Gastroenterol. Nutr. 77(1 Suppl. 1), S260. doi: 10.1097/01.mpg.0000978680.30209.e4.
14. ClinicalTrials.gov. A Study to Evaluate the Safety and Tolerability of Maralixibat in Infant Participants With Cholestatic Liver Diseases Including Progressive Familial Intrahepatic Cholestasis (PFIC) and Alagille Syndrome (ALGS). (RISE). Available from: https://clinicaltrials.gov/study/NCT04729751 [Accessed: 24 April 2025].".
15. Swissmedic - Swiss Agency for Therapeutic Products. Swiss Public Assessment Report (SwissPAR) for maralixibat (Livmarli®). Published: 11 November 2024. Available at:

https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/swisspar.html [Accessed: 30 April 2025].
16. Hansen BE, Vandriel SM, Vig P, Garner W, Mogul DB, Loomes KM, et al; Global ALagille Alliance (GALA) Study Group. Event-free survival of maralixibat-treated patients with Alagille syndrome compared to a real-world cohort from GALA. Hepatology. 2024 Jun 1;79(6):1279-1292. doi: 10.1097/HEP.0000000000000727.
17. Gonzales E, Sturm E, Stormon M, Sokal E, Hardikar W, Lacaille F, et al. Phase 2 open-label study with a placebo-controlled drug withdrawal period of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with Alagille Syndrome: 48-week interim efficacy analysis. Journal of hepatology. 2019;70(1):e119-e20. doi: 10.1016/S0618-8278(19)30211-7.

This assessment is based on data submitted by the applicant company up to and including 03 October 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.