Single Technology Appraisal

Maralixibat for treating cholestatic pruritus in Alagille Syndrome [ID3941]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Maralixibat for treating cholestatic pruritus in Alagille Syndrome [ID3941]

Contents:

The following documents are made available to stakeholders:

The final scope and final stakeholder list are available on the NICE website.

1. **Company submission from** Mirum Pharmaceuticals**:**
    a. Full submission
    b. Company addendum
    c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
    a. Children's Liver Disease Foundation

4. **Expert statements**
    a. Caitlin Mulholland, Patient expert, nominated by Children's Liver Disease Foundation

5. **External Assessment Report** prepared by Warwick evidence
    a. Main Report
    b. Report Addendum

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Maralixibat for treating cholestatic disease in Alagille Syndrome [ID3941]

Document B

Company evidence submission

December 2023

File name	Version	Contains confidential information	Date
ID3941 Document B	**V2**	**Yes**	**15/12/2023**

Table of contents

Table of figures

Table of tables

Table of abbreviations

AE	Adverse event	**MedDRA**	Medical Dictionary for Regulatory Activities
AIC	Akaike Information Criteria	**MHRA**	Medicines and Healthcare products Regulatory Agency
ALGS	Alagille syndrome	**MITT**	Modified intent-to-treat
ALP	Alkaline phosphatase	**MMRM**	Mixed-effects model for repeated measures
ALT	Alanine aminotransferase	**MRX**	Maralixibat
ANCOVA	Analysis of covariance	**NAFLD**	Non-alcoholic fatty liver disease
AP	Alkaline phosphatase	**NHS**	National health Service
AST	Aspartate aminotransferase	**NICE**	National Institute for Health and Care Excellence
BIC	Bayesian Information Criteria	**NLS**	Native liver survival
BID	Twice a day	**NOTCH**	NOTCH signalling pathway
BIM	Budget impact model	**OL**	Open label
BMI	Body mass index	**ONS**	Office for National Statistics
BSEP	Bile salt export pump	**OS**	Overall survival
CEM	Cost-effectiveness model	**PAS**	Patient Access Scheme
CHMP	Committee for Medicinal Products for Human Use	**PBO**	Placebo
CI	Confidence interval	**PEBD**	Partial external biliary diversion
CIC	Caregiver Impression of Change	**PedsQL**	Paediatric Quality of Life Inventory
CMH	Cochran-Mantel-Haenszel	**PFIC**	Progressive familial intrahepatic cholestasis
CRD	Centre for reviews and dissemination	**PHT**	Portal hypertension
CSS	Clinician scratch scores	**PIC**	Patient Impression of Change
CTCAE	Common terminology criteria for adverse events	**PRO**	Patient reported outcome
DSA	Deterministic sensitivity analyses	**PSA**	Probabilistic sensitivity analysis
EFS	Event-free survival	**PSS**	Parent satisfaction survey
EMA	European Medicines Agency	**PSSRU**	Personal Social Services Research Unit
EOT	End of treatment	**QALY**	Quality-adjusted life years
FDA	Food and Drug Administration	**QoL**	Quality of Life
FSV	Fat-Soluble Vitamin	**RCT**	Randomised controlled trial
GALA	Global ALagille Alliance	**RMSE**	Root mean square error
GD	Graft dysfunction	**RWD**	Real-world data
GGT	Gamma-glutamyl transferase	**RWP**	Randomised withdrawal phase
GI	Gastrointestinal	**SAE**	Serious adverse event
HADS	Hospital Anxiety and Depression Scale	**sBA**	Serum bile acid
HCC	Hepatocellular carcinoma	**SBD**	Surgical biliary diversion
HR	Hazard ratio	**SD**	Standard deviation
HRQoL	Health-related quality of life	**SE**	Standard error
HST	Health-state transition	**SLR**	Systematic literature review
IBAT	Ileal bile acid transporter	**SmPC**	Summary of product characteristics
ICER	Incremental cost-effectiveness ratio	**SoC**	Standard of care
ItchRO	Itch-reported outcome	**SSRI**	Selective serotonin reuptake inhibitor
ITT	Intent-to-treat	**TEAE**	Treatment-emergent adverse event
KS	Kolmogorov-Smirnov	**TR**	Transplantation rate
LDL	Low-density lipoprotein	**TTO**	Time trade off
LOCF	Last observation carried forwards	**UDCA**	Ursodeoxycholic acid
LR	Likelihood ratio	**ULN**	Upper limit of normal
LTx	Liver transplant	**US**	United States
LY	Life years	**VAS**	Visual analogue scale
LYG	Life year gained	**WPAI**	Work productivity and activity impairment
WTP	Willingness to pay		

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem presented in this document is described in Table 1. The clinical and economic analysis are in line with the NICE Reference Case, with no major deviation from the final scope.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with cholestatic pruritus related to Alagille syndrome (ALGS)	People with cholestatic pruritus related to ALGS	NA
Intervention	Maralixibat (in addition to established clinical management)	Maralixibat (in addition to established clinical management)	NA
Comparator(s)	Established clinical management without maralixibat, which may include: • Off-label drug treatments such as ursodeoxycholic acid (UDCA), cholestyramine, rifampicin, ondansetron, naltrexone, selective serotonin reuptake inhibitor (SSRIs), and antihistamines • Dietary changes • Surgical interventions such as LTx	Established clinical management without maralixibat, including: • Off-label drug treatments such as UDCA, cholestyramine, and rifampicin • Surgical interventions such as LTx (with surgical biliary diversion (SBD) in a scenario)	A simplifying assumption was made, as there were no data available for the parametrisation of drug use beyond UDCA, rifampicin, and cholestyramine (i.e., ondansetron, naltrexone, SSRIs, and dietary changes). However, these were not expected to impact the economic analysis.
Outcomes	The outcome measures to be considered include: • Change in symptoms of cholestasis including pruritus • Change in sBA level • Change in xanthomas • Change in sleep disturbance	The model includes: • Change in sBA levels and corresponding pruritus • Time to liver event and progression of liver disease (transplant, cirrhosis, ascites and portal hypertension (PHT)) • Adverse events	The outcomes selected in the model were based on clinical opinion and the documented literature on possible outcomes for patients with ALGS. Change in xanthomas and bilirubin could not be directly linked to ALGS patient quality of life, survival, or costs incurred, and were therefore omitted. Survival is modelled indirectly using natural history

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Change in liver enzymes and bilirubin levels • Time to liver event (surgery, transplant, or liver cancer) • Measures of faltering growth and failure to thrive • Adverse events • Health-related quality of life (patient and carer-reported) • Overall survival • Transplant-free survival • Number of patients requiring surgical interventions	• Health-related quality of life • Overall survival • Measures of faltering growth • Transplant-free survival • Number of patients requiring surgical interventions	data, as ICONIC did not collect long-term survival outcomes. Quality of life is included in the model using a vignette study, and time to surgery/pre-transplant survival is based on the literature.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.	The main outcome of the economic analysis is the incremental cost per quality-adjusted life year. The time horizon is a lifetime (100 years maximum), as ALGS is expected to impact patients and caregivers across their lifetimes. In the base-case, costs and outcomes are those that apply to the NHS and PSS only. A commercial agreement exists for maralixibat, which is included in the analysis.	–
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The current dossier covers maralixibat within its marketing authorisation only.	–

***Abbreviations**: ALGS, Alagille syndrome; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; sBA, serum bile acid; SSRI, selective serotonin reuptake inhibitor; UDCA, ursodeoxycholic acid.*

B.1.2 Description of the technology being evaluated

Table 2 presents an overview of the drug being evaluated (maralixibat). Please see Appendix C for the summary of product characteristics and UK public assessment report for maralixibat.

Table 2: Technology being evaluated

<table>
<tr><td>UK approved name and brand name</td><td>Maralixibat (Livmarli)</td></tr>
<tr><td>Mechanism of action</td><td>Maralixibat is a minimally absorbed, reversible, potent, selective inhibitor of the ileal bile acid transporter (IBAT
Maralixibat acts locally in the distal ileum to decrease the reuptake of bile acids and increase the clearance of
acids through the colon, reducing the concentration of bile acids in the serum. By pharmacologically inhibiting
entry of bile acids into enterocytes, maralixibat inhibits the reuptake of bile acids and increases their excretion
reducing the level of circulating bile acids and associated pruritus.</td></tr>
<tr><td>Marketing authorisation/CE mark status</td><td>9.5mg/mL oral solution of maralixibat (PLGB 56642/0001) was approved by the Medicines and Healthcare pro
Regulatory Agency (MHRA) on 10 February 2023 for the treatment of cholestatic pruritus in patients with ALG
months of age and older. In coming to its decision, the MHRA relied on an EC decision on 9th December 2022
(EMEA/H/C/005857), in accordance with advice from the Committee for Committee for Medicinal Products for
Use (CHMP).</td></tr>
<tr><td>Indications and any restriction(s) as described in the SmPC</td><td>Maralixibat is indicated for the treatment of cholestatic pruritus in patients with ALGS 2 months of age and old</td></tr>
<tr><td>Method of administration and dosage</td><td>Treatment with maralixibat should be initiated under the supervision of a physician experienced in the manage
patients with cholestatic liver diseases.

Maralixibat is provided as an oral solution. The recommended target dose is 380 µg/kg once daily. The startin
is 190 µg/kg once daily and should be increased to 380 µg/kg once daily after one week. Please see the dose
of solution to be given for each weight range below:

<table>
<tr><td rowspan="2">Patient weight (kg)</td><td colspan="2">Days 1 to 7
(190 µg/kg once daily)</td><td colspan="2">From Day 8 and after
(380 µg/kg once daily)</td></tr>
<tr><td>Volume once daily (mL)</td><td>Oral syringe size (mL)</td><td>Volume once daily (mL)</td><td>Oral syringe (mL)</td></tr>
<tr><td>5-6</td><td>0.1</td><td rowspan="8">0.5</td><td>0.2</td><td rowspan="3">0.5</td></tr>
<tr><td>7-9</td><td>0.15</td><td>0.3</td></tr>
<tr><td>10-12</td><td>0.2</td><td>0.45</td></tr>
<tr><td>13-15</td><td>0.3</td><td>0.6</td><td rowspan="4">1</td></tr>
<tr><td>16-19</td><td>0.35</td><td>0.7</td></tr>
<tr><td>20-24</td><td>0.45</td><td>0.9</td></tr>
<tr><td>25-29</td><td>0.5</td><td>1</td></tr>
<tr><td>30-34</td><td>0.6</td><td rowspan="4">1</td><td>1.25</td><td rowspan="5">3</td></tr>
<tr><td>35-39</td><td>0.7</td><td>1.5</td></tr>
<tr><td>40-49</td><td>0.9</td><td>1.75</td></tr>
<tr><td>50-59</td><td>1</td><td>2.25</td></tr>
<tr><td>60-69</td><td>1.25</td><td rowspan="2">3</td><td>2.5</td></tr>
<tr><td>70 or higher</td><td>1.5</td><td>3</td></tr>
</table>

In case of poor tolerability, dose reduction from 380 µg/kg/day to 190 µg/kg/day, or treatment interruption can
considered. Renewed dose escalation can be attempted as tolerated. The maximum recommended daily dos
patients above 70 kg is 3 mL (28.5 mg).

Alternative treatment should be considered in patients for whom no treatment benefit can be established follow
months of continuous daily treatment with maralixibat.</td></tr>
</table>

Additional tests or investigations	No additional tests or investigations are required. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard
List price and average cost of a course of treatment	£43,970 per 30ml bottle of 9.5mg/ml maralixibat oral solution
Patient access scheme (if applicable)	A Patient Access Scheme (PAS) is available for MRX [redacted]

Information provided from the summary of product characteristics and UK public assessment report for maralixibat (Appendix C).
***Abbreviations**: ALGS, Alagille syndrome; CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; EMEA, European Medicines Agency; IBAT, ileal bile acid transporter; kg, kilogram; MHRA, Medicines and Healthcare products Regulatory Agency; mL, millilitre; SmPC, Summary of Product Characteristic; UK, United Kingdom.*

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease area

B.1.3.1.1 Clinical presentation

B.1.3.1.1.1. Bile duct paucity

ALGS is a rare inherited disorder, with an incidence of [redacted] live births (see Appendix O). It is caused by autosomal dominant mutations in the genes encoding JAG1 or NOTCH2, both of which are involved in the NOTCH signalling pathway (1). In ALGS patients, NOTCH signalling malfunction presents as abnormally narrow and malformed bile ducts which are reduced in number (2, 3). At least 65% of ALGS patients will present with bile duct paucity before 3 months of age (4). This bile duct paucity leads to the retention of toxic bile acids in the liver, and in turn the development of cholestasis (3, 5, 6).

B.1.3.1.1.2. Cholestasis

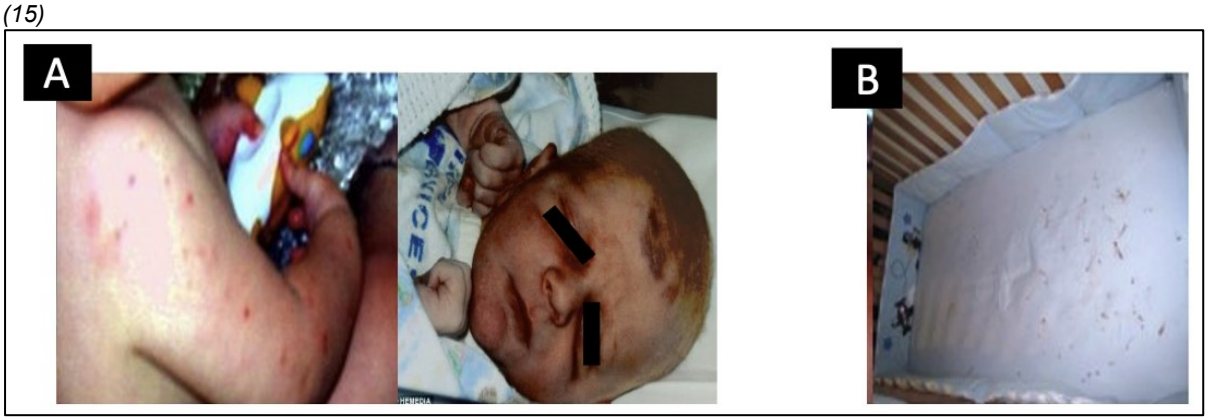
Cholestasis is defined by a reduction in bile flow, whereby bile acids are retained in hepatocytes. Through adaptive transport mechanisms that protect hepatocytes from the cytotoxic detergent effect of bile acids, some of these bile acids are eliminated from the hepatocyte and join the systemic circulation, leading to an increase in sBA and jaundice (elevated bilirubin) – both of these are key markers of cholestasis (3, 5, 6).

Cholestasis is the first and most serious feature of ALGS for most patients. It is reported in 85% of children with ALGS, and its first manifestation seen at a median age of 12 months (3, 5, 6). The retention of bile acids associated with cholestasis leads to a range of liver complications in ALGS patients, including cirrhosis (46% of patients), ascites (57% of patients), and PHT (40% of patients) (7, 8), as well as pruritus (9, 10).

B.1.3.1.1.2.1. Cholestatic pruritus

For many patients, the main clinical manifestation of cholestasis is severe and debilitating pruritus (11). Pruritus affects 74% to 88% of ALGS patients (3, 4, 12, 13); it is caused by retention of bile acids in the skin, which leads to the stimulation of the cutaneous nerve endings (9, 10). The first evidence of pruritus in ALGS patients is typically displayed 6 to 14 months after birth (3). Debilitating pruritus results in self-mutilation, skin lesions, and extensive scarring (see Figure 1), which has a profoundly negative impact on patient quality of life: itching has been identified as the aspect of ALGS that most impacts patients' lives, with a strong negative correlation between quality of life and severity of pruritus (r=0.74, p-value not reported) (3). The cholestatic pruritus associated with ALGS is among the most severe in any chronic liver disease (14).

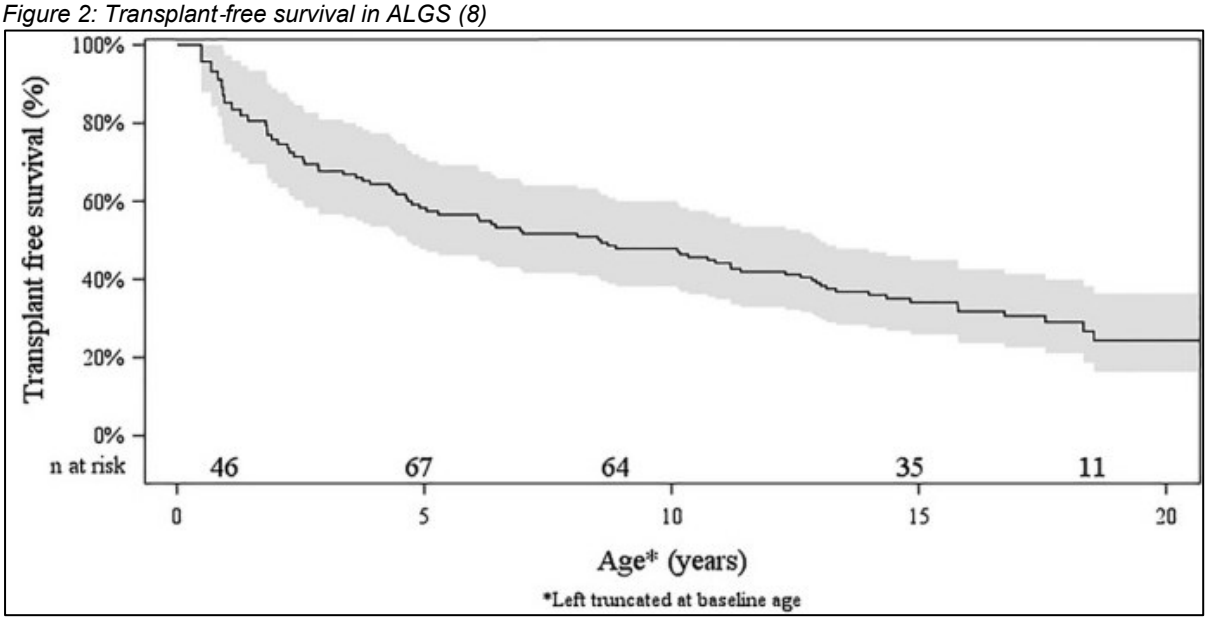
Figure 1: Illustrations of (A) scratching lesions and (B) bed stains by scratch lesions due to cholestatic pruritus (15)



Pruritus is the key indicator for LTx: 69% of LTxs in ALGS patients are conducted because of intractable pruritus (4). Data from children in the historical Global ALagille Alliance (GALA) ALGS cohort comprising of those diagnosed between January 1997 and August 2019 demonstrated shows that only 37.9% of children in Europe with a

history of neonatal cholestasis reach the age of 18 with a native liver, with 72% of the LTxs performed in these patients occurring within the first 5 years of life (4). Without transplantation, survival rates for ALGS patients rapidly decrease as they age, with only 24% of 18.5-year-olds surviving without a transplant, as shown in Figure 2 (8). LTx in ALGS has increased risk of complications and the likelihood of survival for patients with a transplant is around 87% 1-year post-transplantation (16).

Figure 2: Transplant-free survival in ALGS (8)



***Abbreviations**: ALGS, Alagille syndrome.*

In a study of GALA, (1,443 children of aged 12 months to 18 years), the mortality rate with ALGS is 7.2% at age 5 and nearly 12% at age 18, with a median age of death of 2.6 years in the GALA cohort aged 12 months to 18 years (4). The leading causes of death were LTx-related complications (22%) and cardiac complications (18%) (4, 14).

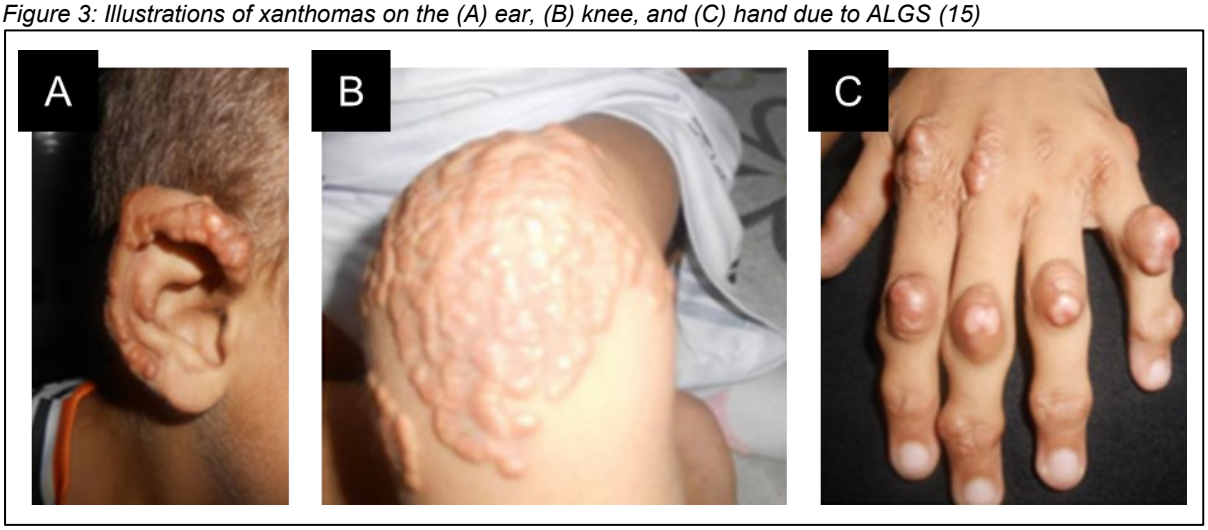
B.1.3.1.1.2.2. Extra-hepatic manifestations of cholestasis

Extra-hepatic manifestations of cholestasis in ALGS include (6):

- **Hypercholesterolemia,** which can result in xanthoma development (17) and cardiovascular disease (18). Hypercholesterolaemia affects 81-83% of ALGS patients with cholestasis (3).
- **Xanthomas** (fatty deposits on the extensor surfaces), which can impact survival rates (3) and restrict the ability of patients to take part in physical

activity (19). In addition, the impact of xanthomas on physical appearance (see Figure 3) can lead to mockery or exclusion from activities and difficulty with school, especially in childhood. This can have a large psychological impact on the patient (19), and often results in patients experiencing depression (14). Xanthomas affect 30-42% of ALGS patients. 61% of those patients affected by xanthomas experience an impact on their physical appearance, and 46% are impacted psychologically by their change in appearance (3, 19).

Figure 3: Illustrations of xanthomas on the (A) ear, (B) knee, and (C) hand due to ALGS (15)



***Abbreviations**: ALGS, Alagille syndrome.*

- **Growth failure,** which, much like xanthomas can further impact the physical appearance of patients with ALGS. It can sunukarky result in bullying, particularly in childhood, and subsequent depression (19). Growth failure affects between 50-87% of ALGS patients (3, 20).
- **Chronic fatigue and sleep disturbances,** which lead to reduced participation in activities and difficulty with school as a result of impaired psychosocial and cognitive development (11, 19, 21, 22). Chronic fatigue affects between 65-85% in cholestatic patients (23). Sleep disturbances affect 23-54% of ALGS patients with pruritus (3).
- **Neurocognitive deficits,** such as IQ deficiencies (24). Neurocognitive deficits affect more than 50% of ALGS patients (24).
- **Fat-Soluble Vitamin (FSV) deficiency** (malabsorption of fat-soluble vitamin A,D,E and K), which can lead to visual disturbances, osteodystrophy (abnormal changes in the growth and formation of bone), neurological

disorders, and bleeding disorders (25). Most cholestasis present with FSV deficiency, although the exact number is not known (26).

- **Dental damage,** which can lead to enamel opacities, hypomineralisation and hypoplasia of tooth enamel (27). Enamel hypoplasia and hypomineralisation affect over 50% of ALGS patients (28).

B.1.3.1.1.3. Extra-cholestasis complications

ALGS can also result in complications unrelated to cholestasis, including cardiovascular abnormalities (such as peripheral pulmonary artery branch stenosis and tetralogy of Fallot), skeletal abnormalities, characteristic facies, posterior embryotoxon/anterior segment abnormalities, retinitis pigmentosa, and renal dysplasia (29, 30).

Cardiovascular abnormalities may affect up to 94% of all patients with ALGS, and are most common in those with cholestatic liver disease (31). Significant cardiovascular disease could also impact the morbidity and mortality of ALGS patients, which may exclude these patients from LTx and thus leave them with limited treatment options for dealing with the clinical manifestations of cholestasis (32).

B.1.3.1.1.4. Patient quality of life (QoL)

Severe manifestations of ALGS and complications due to liver disease invariably exert a major influence on the QoL of patients and their families. Patient QoL is often impacted by sleep disorders, resulting in reduced school activities as a result of impaired psychological and cognitive development [9, 19, 21]. Symptoms associated with ALGS which impact physical appearance, such as pruritus, growth retardation, xanthomas, and facial dysmorphism, can lead to mockery or exclusion from activities, especially in childhood. This heavy psychological burden can eventually lead to depression and a decrease in psychosocial integration, which can significantly affect ALGS patients' independence, self-esteem, and development (19).

B.1.3.1.1.5. Impact on caregivers

Caring for a child with ALGS has a large impact on caregivers, with more severe disease being associated with reduced caregiver QoL (as shown in Table 3). Caregivers experience disrupted sleep, restrictions in the amount of time they have for parenting and usual activities, and anxiety as a result of their child's disease (Appendix M, (33)). Caregivers report spending an average of 85.6 (95% confidence interval: 67.9, 103.2) hours per week on caring for their child or other activities associated with the management of their child's condition (Appendix M). Caregivers also reported negative financial impact of caregiving due to lost productivity; those caregivers who remained employed reporting an average of 8 hours absenteeism per week.

Table 3: Caregiver vignettes – EQ-5D scores (33)

Description	EQ-5D index scores	
	Mean (SD)	Range
Progressive cholestasis	0.543 (0.175)	-0.059 to 0.892
Non-progressive cholestasis/successful LTx	0.837 (0.084)	0.338 to 0.987
Chronic LTx rejection	0.526 (0.174)	0.084 to 0.935

Non-progressive cholestasis and successful LTx states were merged due to the similarity in impacts experienced
***Abbreviations**: EQ-5D, European Quality of Life Five Dimension; SD, standard deviation.*

B.1.3.2 Clinical pathway

ALGS patients are diagnosed predominantly during the first year of life or during early childhood (3). Most diagnoses occur as a result of a patient presenting with at least three of the following seven clinical criteria (11):

- Hepatic abnormalities
- Cardiac abnormalities
- Ophthalmological abnormalities
- Renal abnormalities
- Vasculature abnormalities
- Bone abnormalities
- Characteristic facial features

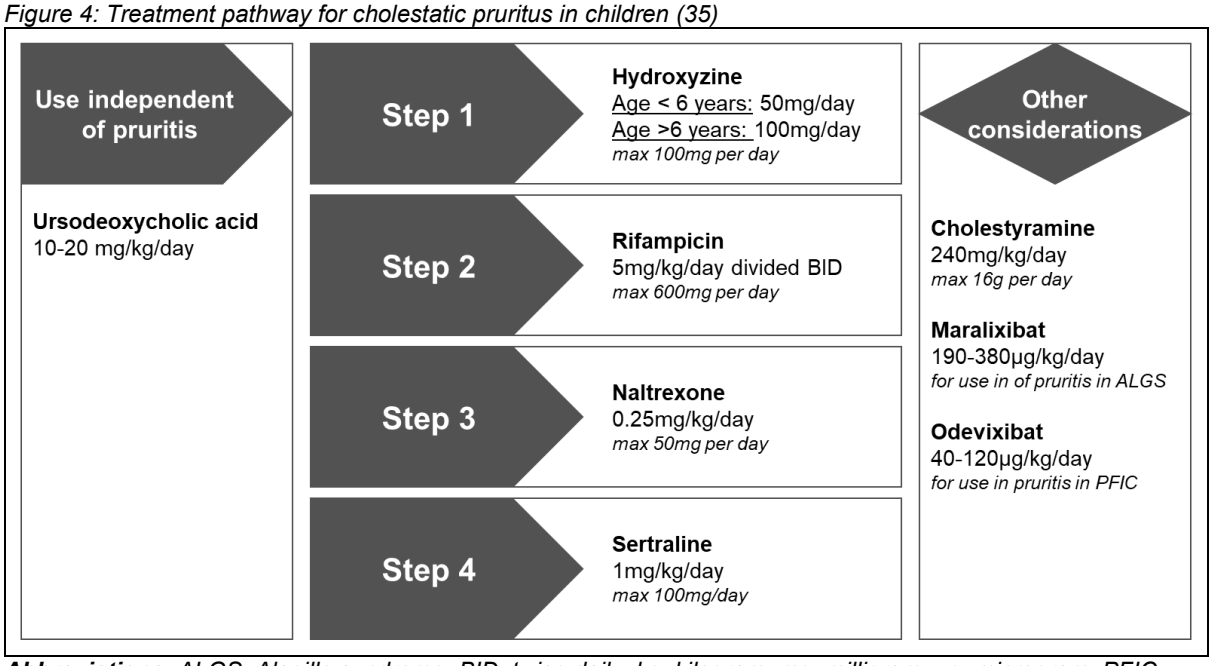
Genetic testing can be conducted for JAG1 or NOTCH2 mutations as part of the diagnosis of ALGS (3, 4). However, diagnosis through genotyping is complicated as there are no clear genotype-phenotype correlations: the phenotypic severity of ALGS is highly variable, ranging from no apparent clinical involvement to severe disease which requires LTx (3). As such, clinical presentation remains the key determining factor in ALGS diagnoses.

In the UK, paediatric liver specialists are centralised at one of three specialist academic centres: Kings College London, Birmingham Childrens Hospital, or Leeds Royal Infirmary. Patients are typically treated in secondary care by hepatologists, and may be referred to other specialists, such as cardiologists or nephrologists, for their wider complications (34).

Currently no specific guidelines are available for the treatment of cholestatic pruritus in patients with ALGS in the UK, and there are no pharmacotherapies approved for the treatment of ALGS patients in the UK.

Patients with ALGS may be treated with off-label supportive pharmacotherapy, as described by Rodrigo et al. 2023 (Figure 4) (35), which provides some symptomatic relief by optimising nutritional intake and attempting to control the consequences of cholestasis, but does not address the underlying disease (3).

Figure 4: Treatment pathway for cholestatic pruritus in children (35)



***Abbreviations**: ALGS, Alagille syndrome; BID, twice daily; kg, kilogram; mg, milligram; µg, microgram; PFIC, progressive familial intrahepatic cholestasis.*

Surgical intervention is available to manage ALGS and is primarily focused on LTx (reported in 29% of children with ALGS) (4). LTx is conducted in those with end-stage liver disease or hepatocellular carcinoma, or when other treatment options have been exhausted (20). LTx is often associated with complications, including procedural risks such as post-surgical infection, allograft failure, or rejection; the need for a new transplant; and the requirement for lifelong immunosuppressive therapy (which itself carries the risk of nephropathy, immune dysregulation, and increased risk of infection-related cancers) (3, 16, 36). Additionally, it should also be taken into account that some patients are not eligible for LTx due to extra-hepatic comorbidities, such as those with severe cardiovascular abnormalities (94% of ALGS patients experience cardiovascular complications such as peripheral pulmonary

artery branch stenosis and tetralogy of Fallot (31)). Without transplantation, survival rates for ALGS patients rapidly decrease as they age, with only 24% of 18.5-year-olds surviving without a transplant (8). The likelihood of survival for patients with a transplant is around 79% 1-year post-transplantation (7).

Another surgical option available to ALGS patients is surgical biliary diversion (SBD) (4). SBD is rarely used (reported in only 5% of children with ALGS (4)), which may be in part due to the fact that only patients with severe pruritus not effectively managed with medications are eligible (see Appendix N). Additionally, there is a significant medical and psychosocial burden to patients of having a permanent stoma (37, 38) and a significantly increased risk of death vs. LTx (hazard ratio (HR): 1.9; 95% confidence interval (CI): 1.4,2.6; $p < 0.001$) as a result of the procedure (37, 38). In addition, SBD is targeted at interrupting the enterohepatic circulation, but since the bile duct paucity associated with ALGS can result in less bile reaching the bowel, SBD is generally less effective in ALGS than in other cholestatic diseases (11).

B.1.3.2.1 Therapeutic need

As discussed in section B.1.3.2, patients with ALGS are currently treated with off-label supportive pharmacotherapy, which addresses ALGS symptoms but does not reduce sBA or improve cholestasis (3).

Surgical interventions available for ALGS (e.g. LTx and biliary diversion) are associated with a range of limitations and complications, such as the significant medical and psychosocial burden to patients of having a permanent stoma (37, 38); procedural risks such as post-surgical infection, allograft failure, or rejection; the need for a new transplant; and the requirement of lifelong immunosuppressive therapy (which itself carrying the risk of nephropathy, immune dysregulation, and increased risk of infection-related cancers) (3, 16, 36). Additionally, it should also be taken into account that some patients are not eligible for LTx due to extra-hepatic comorbidities, which leaves them with even fewer treatment options (11, 32)

Given the invasive nature of surgical treatment options, the lack of approved pharmacotherapeutics for cholestatic pruritus, and the morbidity and mortality

associated with the disease, there remains a high unmet medical need for safe and efficacious pharmacological treatment for treating cholestatic pruritus in patients with ALGS.

B.1.3.2.2 Proposed place in therapy

IBAT inhibitors directly inhibit the enterohepatic circulation of bile acids, leading to increased excretion of bile acids in the faeces and reduced levels of sBA (20). They are the only type of pharmacological treatment which addresses the pathophysiologic mechanism of cholestatic pruritus. As such, maralixibat, an IBAT inhibitor, provides an attractive and much-needed solution to the unmet medical need for pharmacological treatment of cholestatic pruritus in ALGS patients in the UK.

Data from the pivotal ICONIC study demonstrates that maralixibat provides clear benefits for ALGS patients (39):

- **Durable and clinically meaningful improvements in cholestasis**, the first and most serious feature of ALGS for most patients (3, 5, 6).
- **Significant improvement in cholestatic pruritus**, the main manifestation of cholestasis and key indicator for LTx, which profoundly impacts patient QoL (3, 4).
- **Substantial reduction in other cholestatic manifestations** such as xanthomas (fatty deposits on the extensor surfaces), growth impairment, and chronic fatigue (3, 19, 23). These manifestations can have an impact on patient survival (3) and physical and psychosocial wellbeing (11, 14, 19, 21, 22).
- **Significant improvements in patient and caregiver QoL**. ALGS has a profound impact on both patients and their families. Patients may experience sleep issues and psychological challenges due to the disease's physical symptoms, potentially leading to depression. Caregivers' QoL is closely linked to their child's condition, and they may suffer from disrupted sleep, limited time for daily activities, and increased anxiety (39).

- **Significant reduction in liver-related events.** End-stage liver disease, hepatocellular carcinoma, or treatment failure can necessitate LTx. However, LTx often entails post-surgical infections, graft failure, and lifelong immunosuppressive therapy (which comes with its own set of risks). Not all ALGS patients are eligible for LTx, and as they age, survival rates decline. SBD, an option primarily for severe uncontrollable pruritus, is rarely performed due to the significant medical and psychosocial burden of having a stoma and the heightened risk of mortality associated with the surgery (40).

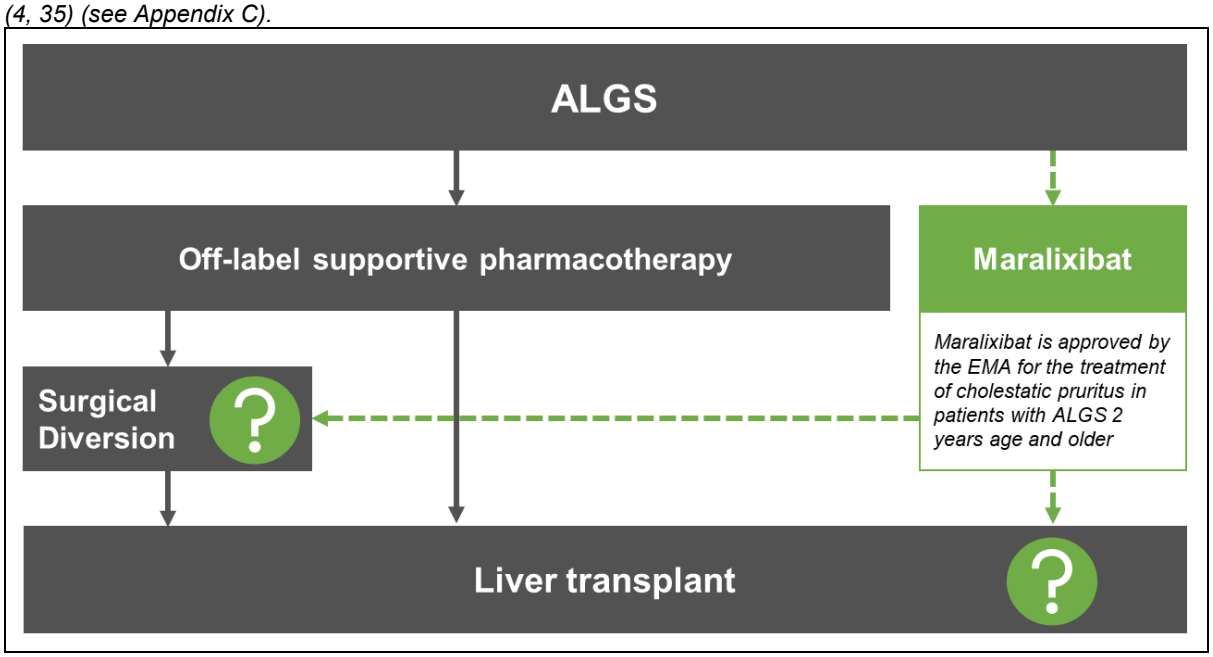
- **Ease of administration**. Maralixibat is convenient and easy to administer, potentially relieving some of the burden on health care professionals. Additionally, the oral route of administration means that maralixibat has a low level of invasiveness for patients and provides optimal absorption.

For more information on the clinical benefits of maralixibat, please refer to section B.2.6.

In addition, maralixibat has the advantage of being easily interrupted or discontinued in those patients who do not respond to such therapeutic intervention, which contrasts with the disfigurement and long-term complications of surgical treatment options (3, 16, 36).

Overall, maralixibat is a generally well tolerated pharmacological therapy which can be initiated early on in life, thereby offering the potential to postpone or even eliminate the need for surgical intervention (as shown in Figure 5). Maralixibat may represent the only treatment option for patients with ALGS cholestatic pruritus and severe cardiovascular involvement.

Figure 5: Proposed positioning of maralixibat in the treatment pathway for cholestatic pruritus in ALGS patients (4, 35) (see Appendix C).



***Abbreviations**: ALGS; Alagille syndrome; EMA, European Medicines Agency.*

B.1.4 Equality considerations

Informal caregiving is often a significant part of managing chronic diseases, typically taken on by family members. These family members play a crucial role in providing physical, emotional, and psychological support to those with chronic illnesses. However, caregiving responsibility can be demanding and emotionally taxing for caregivers. The majority of caregivers are women, and consequently, women may experience a greater caregiving burden.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Please see Appendix C, Appendix G, Appendix H, and Appendix I for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.1.1 Identification of published studies

Two systematic literature reviews (SLRs) were conducted to identify and summarise the results of published clinical studies examining the efficacy of maralixibat, both RCTs and non-RCTs.

The original SLR was produced in 2021; an updated SLR was conducted in 2023 to identify any additional data published between 11th October 2021 and 18th May 2023. At the time of submission (4th October 2023), those studies which were identified as being unavailable at full-text screen were re-reviewed for availability and relevance. The SLRs were conducted in accordance with the NICE requirements (see Appendix C) and Centre for Reviews and Dissemination (CRD) guidance (41).

The original and updated SLRs identified a total of 21 relevant clinical publications. Table 4 provides a summary of the published clinical evidence identified in the SLRs. Overall, one randomised controlled trial (RCT) (accounting for six publications) was identified as providing relevant clinical effectiveness evidence for inclusion in the model: the pivotal ICONIC study with open-label follow-up (36, 42-46). This study has been further described in an internal study report (39). In addition, one non-RCT (accounting for four publications) was also identified as relevant for the model: the GALA Cohort Comparison Study (47-50). This study has also been further described in an internal study report (40). Evidence on the efficacy of maralixibat in ALGS patients with cholestatic pruritus from these key studies is discussed in detail through Section B.2.2. to B.2.12.

Table 4: Summary of clinical publications identified in SLR (N=22)

Study name	Reference	Publication type	Intervention(s)	Study design	Included in model	Rationale for use/non-use in model (Section B.3.3)
ICONIC with open-label follow-up	Gonzales et al. 2019 (42)	Abstract	Maralixibat (≥380 µg/kg/day, ≥760 µg/kg/day) Placebo	Phase 2b RCT + open-label follow-up	Yes	Key study evidencing the efficacy and safety of maralixibat in ALGS patients with cholestatic pruritus. The response rate for maralixibat-treated ALGS patients has been taken from the rate of 'previous responders' in the ICONIC study, as measured by the proportion of patients who experienced a ≥50% reduction in sBA from baseline at Week 12 or 18. Furthermore, demonstrated reductions in pruritus severity associated with maralixibat are used to inform improved health-related QoL for patients responding to treatment with maralixibat. Further efficacy data for maralixibat from the ICONIC study (39) (e.g. the impact on biochemical markers of cholestasis, growth, xanthoma severity, and QoL) is explored in Section 0, as this provides a holistic overview of the patient-impact of maralixibat treatment. However, this data are not included in the economic model as it is not anticipated to be key drivers of either disease progression or the incremental difference in costs and benefits for patients treated with maralixibat.
	Gonzales et al. 2019 (43)	Abstract				
	Foster et al. 2020 (44)	Abstract				
	Gonzales et al. 2020 (45)	Poster				
	Gonzales et al. 2021 (46)	Full paper				
	Gonzales et al. 2021 (36)	Full paper				
GALA Cohort Comparison Study	Hansen et al 2021 (47)	Abstract	N/A	Application of eligibility criteria from ITCH/IMAGINE II, IMAGO/IMAGINE, and ICONIC with open-label follow-up to the GALA natural history registry assessing outcomes in patients with ALGS	Yes	Key study providing a robust natural history cohort comparison for maralixibat. Data from GALA provides the long-term reduction in hazard for liver-related event-free survival (SBD, LTx, decompensation event, or death) used in the health economic model to estimate reductions in individual components of event-free survival associated with maralixibat use.
	Hansen et al 2022 (48)	Abstract				
	Hansen et al 2023 (49)	Abstract				

Study name	Reference	Publication type	Intervention(s)	Study design	Included in model	Rationale for use/non-use in model (Section B.3.3)
IMAGINE	Baker et al. 2017 (51)	Abstract	Maralixibat (140 µg/kg/day, 280 µg/kg/day) Placebo	Phase 2b open-label follow-up	Yes (scenario)	ICONIC was used as the primary source of input for the model (efficacy and safety). As no responder analyses were collected as part of IMAGINE, this data were omitted. A scenario is provided with safety data collected across all MRX dose groups.
ITCH	Shneider et al.2017 (52)	Abstract	Maralixibat (70 µg/kg/day, 140 µg/kg/day, 280 µg/kg/day) Placebo	Phase 2 RCT	Yes (scenario)	ICONIC was used as the primary source of input for the model (efficacy and safety). However, as a responder analysis was included in the study report, a scenario is included in the model with sBA response at 13 weeks. The placebo arm was omitted, however, because GALA provided the largest and longest natural history data and was therefore considered more accurate of the comparator arm outcomes, such as time to liver events. As the safety data were similar to ICONIC, no additional scenario was included.
	Shneider et al. 2018 (53)	Full paper				
N/A	Kronsten et al. 2011 (54)	Abstract	N/A	Retrospective observational study of the management and outcomes of cholestatic pruritus in children	No	This study does not provide outcomes for patients treated with standard of care that can be used in the economic analysis. Outcomes are not comparable to those collected as part of the maralixibat clinical trial programme, and as such cannot be used to inform comparative effectiveness.
	Kronsten et al. 2013 (21)	Full paper				
N/A	Thebaut et al. 2017 (55)	Full paper	Sertraline (1 mg/kg/day with dose increase according to clinical response and at the physician's discretion)	Prospective observational study of sertraline use in children with ALGS cholestatic pruritus	No	Although sertraline is sometimes recommended in ALGS patients with cholestatic pruritus, there was insufficient data from GALA and ICONIC to include sertraline in the comparator arm of the model.
N/A	Kamath et al. 2021 (56)	Abstract	Maralixibat (66.5 µg/kg/day to 380 µg/kg/day, 380 µg/kg twice daily) Placebo	Pooled analysis of ITCH/IMAGINE II, IMAGO/IMAGINE, and ICONIC with open-label follow-up	No	There were no major differences between safety outcomes of ICONIC and this pooled analysis – as a result, ICONIC was selected in the base-case and no additional scenario was provided.

Study name	Reference	Publication type	Intervention(s)	Study design	Included in model	Rationale for use/non-use in model (Section B.3.3)
N/A	Raman et al 2021 (57)	Poster	Maralixibat (66.5 µg/kg/day to 380 µg/kg/day, 380 µg/kg twice daily) Placebo	Pooled analysis of ITCH/IMAGINE II, IMAGO/IMAGINE, and ICONIC with open-label follow-up	Yes (scenario)	This pooled analysis included the proportion of patients with Grade 3-4 adverse events (AEs) at 13 weeks and was used in a scenario in the model.
MRX-EAP	Gonzalez-Peralta et al 2022 (58)	Poster	Maralixibat	Outcomes of patients in the maralixibat Expanded Access Programme	No	This study provides case reports for three patients only, and as such is not robust enough to be relevant to this submission.
N/A	Kamath et al 2022 (59)	Poster	Maralixibat (66.5 µg/kg/day to 380 µg/kg/day, 380 µg/kg twice daily) Placebo	Pooled analysis of height weight z-scores from ITCH /IMAGINE II, IMAGO/IMAGINE, and ICONIC with open-label follow-up	No	This study only examined height and weight, pooling data from studies in maralixibat. Because baseline weight was available from ICONIC, and ICONIC was the primary source for the modelling, this study was not used for the model.
N/A	Shneider et al 2022 (60)	Full paper	N/A	Application of eligibility criteria from **ITCH** to a prospective longitudinal cohort study of children with cholestasis **(LOGIC)**	No	This source is a prospective study, and as RCT data were available, it was not deemed appropriate to include this study in the modelling.
N/A	Shneider et al 2022b (61)	Full paper	Maralixibat (70 µg/kg/day, 140 µg/kg/day, 280 µg/kg/day) Placebo	Pooled analysis of ITCH/IMAGINE II and IMAGO/IMAGINE	No	This study provided change from baseline outcomes and AEs for ITCH/IMAGO, IMAGINE II/IMAGINE, and IMAGINE II. Because no sBA or Itch-reported outcome (ItchRO) responder analysis was provided in this pooled analysis, and AEs are reported by combining two studies at a time, it was not included in the model.

***Abbreviations**: ALGS, Alagille syndrome; N/A, not applicable; RCT, randomised controlled trial, sBA, serum bile acid; SLR, systematic literature review.*

B.2.1.1 Identification of unpublished studies

The U.S. National Institutes of Health clinical trials registry and results database (ClinicalTrials.gov) was searched to identify study results that may not have been published. This search identified two relevant studies (IMAGINE I and IMAGINE II). As described in Table 4, these studies were included in scenario analyses for safety, because no responder analyses were available for efficacy.

B.2.2 List of relevant clinical effectiveness evidence

The clinical effectiveness of maralixibat in reducing sBA levels, bilirubin, and pruritus in ALGS patients was investigated through the Phase 2 ICONIC study (39) including open-label follow-up. Please see Table 5 for more details.

Table 5: Clinical effectiveness evidence: ICONIC (39)

	ICONIC (LUM001-304)
Study design	Multicenter, double-blind randomised Phase 2b study with open-label follow-up Duration of treatment: 204 weeks
Population	Children aged 12 months-18 years with ALGS and cholestasis, who experience moderate to severe pruritus as measured by a mean daily score ItchRO[Obs]≥2 for two consecutive weeks during the selection period 31 patients from across Australia and Europe, including 3 from the UK
Intervention(s)	Maralixibat (≥380 µg/kg/day, ≥760 µg/kg/day from Week 49 onwards)
Comparator(s)	Placebo
Indicate if study supports application for marketing authorisation	Yes
Reported outcomes specified in the decision problem	**Primary efficacy endpoint** • Mean change from Week 18 to Week 22 of fasting sBA levels in patients who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 in modified intention-to-treat (MITT) Population **Secondary efficacy endpoints** • Change from Week 18 to Week 22 in biochemical markers of cholestasis and liver disease (Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), total bilirubin, direct bilirubin) • Change from Week 18 to Week 22 in pruritus in subjects who previously responded to maralixibat treatment as measured by ItchRO(Obs)/ItchRO(Pt) • Change from baseline to Week 18 in fasting sBA levels • Change from baseline to Week 18 in biochemical markers of cholestasis and liver disease (ALT, ALP, total bilirubin, direct bilirubin)

	ICONIC (LUM001-304)
	• Change from baseline to Week 18 in pruritus as measured by ItchRO(Obs)/ItchRO(Pt) **Additional efficacy endpoints** • Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100, and change from baseline to Weeks 18, 22, and 48, and then every 12 for pruritus response rates as measured by ItchRO(Obs)/ItchRO(Pt) • Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 for clinician scratch scores (CSS) • Change from baseline to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale score • Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in fasting sBA levels • Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in biochemical markers of cholestasis and liver disease (ALT, ALP, total bilirubin, direct bilirubin, total cholesterol, low-density lipoprotein (LDL)-C) • Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in bile acid synthesis (7αC4) • Change from baseline at Weeks 18, 22, 48, 60, 72, 84, 96, and 100, and change from Week 18 to Week 22 for Paediatric quality of life inventory (PedsQL) • Patient Impression of Change (PIC), Caregiver Impression of Change (CIC) and Caregiver Global Therapeutic Benefit (CGTB) at Weeks 18, 22, 48, 84, 96, and 100 and change from Week 18 to Week 22 • Change from baseline in body height and weight at Weeks 3, 6, 12, 18, 18/last observation carried forwards (LOCF), 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
All other reported outcomes	Not applicable.

***Abbreviations**: ALGS, Alagille syndrome; ALP, alkaline phosphatase; ALT, alanine transaminase; BID, twice daily; CGTB, Caregiver Global Therapeutic Benefit; CIC, Caregiver Impression of Change; CSS, clinical scratch score; ItchRO, Itch-reported outcome; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; mITT, modified intention-to-treat; PedsQL, Paediatric Quality of Life Inventory; PIC, Patient Impression of Change; RCT, randomised controlled trial; sBA, serum bile acid.*

The GALA Cohort Comparison Study (40) was a cohort comparison conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry.

The GALA registry is the largest global ALGS registry, with a total of 1,543 children between the ages of 12 months to 18 years included (4). The registry specifically aimed to examine the rates of native liver survival (NLS) in children diagnosed with ALGS and a history of neonatal cholestasis, and to identify early laboratory

predictors of long-term hepatic outcomes. Furthermore, the study evaluated global patient and graft survival following LTx in children with ALGS (4).

The comparison study aimed to assess the impact of long-term maralixibat treatment on clinical outcomes in patients with ALGS. This evaluation involved a comparison between the maralixibat-treated cohort and the control group from the GALA study. The primary endpoint being studied was the event-free survival (EFS) duration, specifically the time it took for the first occurrence of any of the following events (40):

- LTx
- SBD
- Liver decompensation, which encompasses variceal bleeding and the need for ascites therapy
- Death

Please see Table 6 for more details of the GALA comparison study.

Table 6: Clinical effectiveness evidence: GALA Cohort Comparison Study (40)

	GALA Cohort Comparison Study
Study design	Cohort comparison study conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry
Population	Maralixibat cohort: those who took part in maralixibat studies (IMAGINE, ICONIC, and IMAGINE II). Children aged 12 months-18 years with ALGS and cholestasis, who experience moderate to severe pruritus as measured by a mean daily score ItchRO[Obs]≥2 for two consecutive weeks during the selection period 84 patients from across North America, Australia, and Europe GALA standard of care cohort: Children aged 12 months-18 years with ALGS and cholestasis 469 patients from across North America, Australia, and Europe
Intervention(s)	Maralixibat (dose based on prior trial dose)
Comparator(s)	Standard of care
Indicate if study supports application for marketing authorisation	No
Reported outcomes specified in the decision problem	Primary outcome: Time to first occurrence of any of the following listed events of the EFS: • LTx • SBD • Liver decompensation (variceal bleeding, ascites requiring therapy) • Death

All other reported outcomes	Not applicable

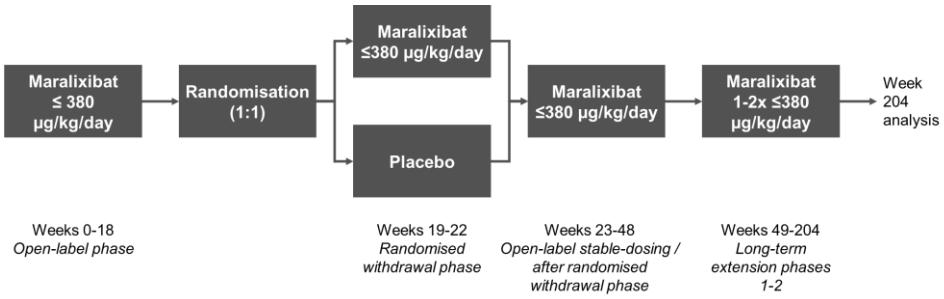
***Abbreviations**: ALGS, Alagille syndrome; ItchRO, Itch-reported outcome.*

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Summary of methodologies

A summary of the methodologies of the ICONIC study and (39) GALA Cohort Comparison Study (40) are shown in Table 7 and Table 8, respectively.

Table 7: Summary of methodology of the ICONIC study (39)

	ICONIC
Trial design	The ICONIC study (39) was a multicentre, double-blind, randomised Phase 2b study with open-label follow-up. As demonstrated in Figure 6, the ICONIC study consisted of five phases: • Open-label run-in phase: from baseline to Week 18, all patients received ≥380 µg/kg/day of maralixibat • Double-blind, placebo-controlled RWP: from Weeks 19-22, patients were randomised 1:1 to receive either ≤380 µg/kg/day of maralixibat, or placebo • Open-label, stable dosing phase: from Weeks 23-48, all patients received ≤380 µg/kg/day of maralixibat • First long-term follow-up phase: from Weeks 49-101, all patients received ≤380 µg/kg/day of maralixibat • Second long-term follow-up phase: from Weeks 101-204, all eligible patients received ≤380 µg/kg once per day or twice per day Figure 6: Trial design of pivotal ICONIC study for maralixibat in ALGS (39) 
Eligibility criteria	Male and female subjects aged between 12 months and 18 years could be enrolled in the study if they met the following key inclusion criteria: • Diagnosis of ALGS based on diagnostic criteria • Evidence of cholestasis (with at least one or more of the following): • Levels of sBA >3 x ULN • Conjugated bilirubin >1 mg/dl • Gamma-glutamyl transferase (GGT) levels >3 x UNL depending on age • Otherwise unexplained deficiency of fat-soluble vitamins • Resistant pruritus explainable only by liver disease

	ICONIC
	• Average daily ItchRO score >2 for two consecutive weeks during the screening period, prior to administration (0=none; 4=very severe pruritus) • Patients were excluded from entering the study based on the following exclusion criteria: • Surgical interruption of the enterohepatic circulation • LTx • Presence of decompensated cirrhosis • History or presence of clinically significant ascites • Presence of variceal haemorrhage and/or encephalopathy • History or presence of other concomitant liver disease, or history or presence of any disease or condition known to interfere with absorption, distribution, metabolism, or excretion of drug • Administration of bile acids or lipid-binding resins during the 28 days prior to screening and throughout the duration of the study • Patients who weighed more than 50 kg at screening or any other condition or abnormality that, in the opinion of the investigator or the supervising doctor, could compromise the safety of the participant or interfere with their participation
Settings and locations	The ICONIC study was conducted in ten clinical sites across seven countries, including three sites in the UK.
Trial drugs	All patients received ≥380 µg/kg/day of maralixibat during the open-label run-in phase (conducted from baseline to Week 18), the open-label, stable dosing phase (conducted from Weeks 23-48), and the first long-term follow-up phase (conducted from Weeks 49-101) During the double-blind, placebo-controlled RWP (conducted from Weeks 19-22), patients were randomised 1:1 to receive either ≥380 µg/kg/day of maralixibat, or placebo. During the second long-term follow-up phase (conducted from Weeks 101-204) all eligible patients received ≥380 µg/kg/day maralixibat, or ≥760 µg/kg/day maralixibat administered as two doses of ≥380 µg/kg per day.
Permitted concomitant medication	Patients had to stop bile acid chelating resins at least 28 days before initiation of the study and during the complete study period. In the first 22 weeks, no new drugs to treat pruritus could be added and the dosage of concomitant drug therapies should not be changed, with the exception of weight-related dose adjustments and vitamin supplementation, which should be documented. If a medicinal product other than this specified in the protocol was administered, a joint decision was taken by the investigator and the sponsor to continue or discontinue the study for the patient concerned.
Outcomes used in the economic model or specified in the scope	Proportion of patients who are classes as 'previous responders' to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18.

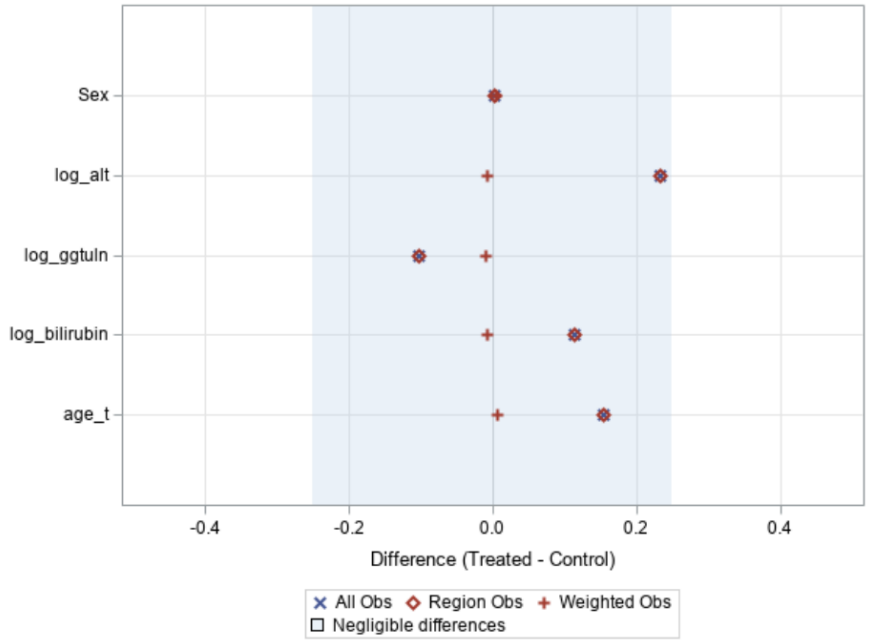
Pre-planned subgroups	Subgroup analysis was planned for:
	• ItchRO(Obs) responders
	• sBA responders
	• ItchRO(Obs) weekly average morning severity scores across:
	  ○ Age group (up to 24 months, 2-12 years, >12 years)
	  ○ Baseline sBA (<275 µmol/L, ≥275 µmol/L)
	  ○ Baseline total bilirubin (<3.8 mg/dL, ≥3.8 mg/dL)

	ICONIC
	○ Baseline ALT (<90 U/L, ≥90 U/L) ○ Baseline ItchRO(Obs) weekly average morning severity score (<3 pts, ≥ 3 pts) • sBA levels across: ○ Age group (up to 24 months, 2-12 years, >12 years) ○ Baseline sBA (<275 µmol/L, ≥275 µmol/L) ○ Baseline total bilirubin (<3.8 mg/dL, ≥3.8 mg/dL) ○ Baseline ALT (<90 U/L, ≥90 U/L) ○ Baseline ItchRO(Obs) weekly average morning severity score (<3 pts, ≥3 pts)

***Abbreviations**: ALGS, Alagille syndrome; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ItchRO, Itch-reported outcome; sBA, serum bile acid; ULN; upper limit of normal.*

Table 8: Summary of methodology of the GALA Cohort Comparison Study (40)

	GALA Cohort Comparison Study
Trial design	The GALA Cohort Comparison Study (40) was a prespecified 6-year EFS analysis in patients with ALGS treated with maralixibat, compared with a natural history external control group. This comparison included the aggregated data from the maralixibat clinical studies IMAGINE, ICONIC, and IMAGINE II (N=84). For patients who were still actively receiving maralixibat, outcome data and on-study AEs were collected. For patients who discontinued a maralixibat study, follow-up data on outcome events were collected through an appropriate institutional review board/ethics committee approval and consent process. Data files were sent electronically to the GALA statistician for independent analysis. The patient selection for the comparison with the maralixibat cohort followed a stepwise selection process to balance the cohorts with respect to the important baseline covariates: age at inclusion and total bilirubin. Only participants from the GALA clinical research database born after 1997 and who met the inclusion and exclusion criteria from maralixibat ALGS studies were included. These steps were designed to balance the two cohorts with respect to important baseline covariates. The approach is discussed in a survey of methods for the use of historic patient-level data (62). Distribution between the two cohorts was assessed for critical factors, including age, bilirubin, GGT, and ALT. Balance was assessed by examining a standardised differences plot (Figure 7) summarising differences between the treated and control groups. None of the standardised mean differences exceeded the upper limit of 0.25 for critical factors, meaning that the two cohorts were appropriately matched in the study.

	GALA Cohort Comparison Study
	Figure 7: Standardised mean differences for critical factors 

Eligibility criteria	The maralixibat cohort consisted of maralixibat-treated participants in the IMAGO/IMAGINE, ITCH/IMAGINE II, and ICONIC studies, with analyses are based on the final analysis datasets from these studies. Please see Table 7 for details on the eligibility criteria from the ICONIC study, and Table 9 for the eligibility criteria from the IMAGO/IMAGINE and ITCH/IMAGINE studies.
	
	Patients from the GALA database were included in the control group if they met the following key inclusion criteria:
	• Age at inclusion: >12 months and <18 years
	• Cholestasis, defined by one or more of the following:
	  ○ Total SBA >3 x ULN
	  ○ Conjugated or direct bilirubin >1 mg/dL
	  ○ Total bilirubin >2 mg/dL
	  ○ GGT >3 x ULN
	
	There was no criterion for severity of pruritus to be eligible for inclusion in the control arm.
	
	Patients were excluded from entering the study based on the following key exclusion criteria:
	• ALT >15 x ULN
	• Clinical event, defined as LTx, SBD, liver decompensation, or death prior to inclusion
	• Diagnosis of hepatocellular carcinoma (HCC) by biopsy-proven histopathology
	• Born prior to 1997 (based on the earliest birth date from the maralixibat studies)
	• Participant in any intervention clinical study at any time

Settings and locations	Please see Table 7 for details on the settings and locations from the ICONIC study, and Table 9 for details on the settings and locations from the IMAGO/IMAGINE and ITCH/IMAGINE studies.

	GALA Cohort Comparison Study
	The control group was made up of patients from the GALA database living in North America, Europe, and Australia, to match the study setting of the maralixibat cohort.
Trial drugs	Please see Table 7 for details on the trial drugs from the ICONIC study, and Table 9 for details on the trial drugs from the IMAGO/IMAGINE and ITCH/IMAGINE studies. Patients in the GALA control group were considered to be the external control group.
Permitted concomitant medication	Please see Table 7 for details on the permitted concomitant medication from the ICONIC study, and see Table 9 for details on the permitted concomitant medication from the IMAGO/IMAGINE, ITCH/IMAGINE studies. No permitted concomitant medication was described or recorded for the GALA cohort as part of the GALA Cohort Comparison Study.
Outcomes used in the economic model or specified in the scope	Time to first occurrence of any of the following listed events for the maralixibat cohort and GALA control group: • LTx • SBD • Liver decompensation (variceal bleeding, ascites requiring therapy) • Death
Pre-planned subgroups	Subgroup analysis was planned for: • Regions (Europe, Australia, North America) • HCC events • Baseline sBA • Overlapping GALA and maralixibat study sites

***Abbreviations**: ALGS, Alagille syndrome; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; ItchRO, Itch-reported outcome; sBA, serum bile acid; SBD, surgical biliary diversion; ULN, upper limit of normal.*

Table 9: Summary of methodology of the IMAGO/IMAGINE and ITCH/IMAGINE II studies (63-66)

	IMAGO (63)	IMAGINE (64)	ITCH (65)	IMAGINE II (66)
Trial design	Randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of 13 weeks of treatment with maralixibat in paediatric patients with ALGS	Multicenter, double-blind study of maralixibat in children >12 months of age diagnosed with ALGS who have completed participation in IMAGO	Randomised, double-blind, placebo-controlled, parallel group, multicenter study with 13 weeks of treatment with maralixibat in children with ALGS	Multicenter, double-blind study of maralixibat in children >12 months of age diagnosed with ALGS who have completed participation in ITCH
Eligibility criteria	This study enrolled male and female subjects aged between 12 months and 18 years (inclusive) with ALGS and evidence of cholestasis and an average daily score ≥2 on the ItchRO(Obs) questionnaire for 2	Male and female participants between the ages of 12 months and 18 years (inclusive) who completed participation in IMAGO were eligible to participate in the study. Participants must not have	This study enrolled male and female subjects aged between 12 months and 18 years (inclusive) with ALGS and evidence of cholestasis and an average daily score ≥2 on the ItchRO(Obs) questionnaire for 2	Male and female participants between the ages of 12 months and 18 years (inclusive) who completed participation in ITCH were eligible to participate in the study. Participants must not have

	IMAGO (63)	IMAGINE (64)	ITCH (65)	IMAGINE II (66)
	consecutive weeks in the screening period prior to randomisation. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15× ULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhoea requiring specific intravenous fluid or nutritional intervention, were excluded.	experienced an AE or serious adverse events (SAE) related to the study drug during IMAGO that led to the discontinuation from the study. Participants with a history or presence of gallstones or kidney stones, or with a history of non-adherence during the IMAGO study, were not eligible to participate.	consecutive weeks in the screening period prior to randomisation. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15× ULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhoea requiring specific intravenous fluid or nutritional intervention, were excluded.	experienced an AE or SAE related to the study drug during ITCH that led to the discontinuation from the study. Participants with a history or presence of gallstones or kidney stones, or with a history of non-adherence during the IMAGO study, were not eligible to participate.
Settings and locations	This study was conducted in 3 sites in the UK.	This study was conducted in 3 sites in the UK.	This study was conducted in 13 centres in the United States and Canada.	This study was conducted in 11 centres in the United States and Canada.
Trial drugs	Daily dosing of maralixibat occurred over 13 weeks and consisted of a dose escalation period, followed by a stable dose period, and a 4-week follow-up period. Subjects in Cohort A were randomly assigned to receive 140 µg/kg/day or placebo. Subjects in Cohort B were randomly assigned to receive 70 µg/kg/day, 280 µg/kg/day, or placebo.	Daily dosing of maralixibat occurred over up to 252 weeks of treatment and consisted of an initial dose escalation period followed by a dose optimisation period, stable dosing period, and long-term follow-up treatment period. Subjects received either 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day or 280 µg/kg/day, or 560 µg/kg/day based on response.	Daily dosing of maralixibat occurred over 13 weeks and consisted of an initial dose escalation period Subjects were randomly assigned to receive either placebo or 1 of 3 doses of maralixibat: 70 µg/kg/day, 140 µg/kg/day, or 280 µg/kg/day.	Daily dosing of maralixibat occurred over up to 213 weeks of treatment and consisted of an initial dose escalation period followed by a dose optimisation period, stable dosing period, and long-term follow-up treatment period. Subjects received either 35 µg/kg/day, 70 µg/kg/day, 140 µg/kg/day or 280 µg/kg/day, based on response.
Endpoints	The primary endpoint was mean change from baseline to Week 13/early termination (ET) in fasting sBA levels. The secondary endpoints included change from baseline to Week 13 for the combined treatment groups relative to placebo in ALT, Aspartate aminotransferase (AST), ALP, the weekly average daily	The primary efficacy endpoint was the mean change from maralixibat baseline to Week 48 in fasting sBA levels. The secondary endpoints included change from baseline to Week 48 in biochemical markers of cholestasis and liver disease, pruritus, and xanthomas.	The primary efficacy endpoint was the mean change from baseline to Week 13/ET in pruritus, as measured by the ItchRO(Obs) weekly average score (daily average). Secondary endpoints included changes from baseline to Week 13 for fasting sBA levels, ALT, AST, ALP, GGT, and total and direct bilirubin.	The primary objective was to evaluate the long-term safety and tolerability of maralixibat. The primary efficacy endpoint for this study was the mean change in fasting sBA levels from baseline to Week 48.

	IMAGO (63)	IMAGINE (64)	ITCH (65)	IMAGINE II (66)
	score of the ItchRO(Obs), and PedsQL.			
Results	The primary endpoint (change from baseline in sBA at Week 13/ET) was not met.	• A statistically significant reduction (improvement) in sBA concentrations was observed (mean [SD] change from maralixibat baseline to Week 48 (-94.40 [98.915] µmol/L; p=0.0012). • A statistically significant improvement in pruritus was noted at all time points in the study from maralixibat baseline through Week 216, as measured by ItchRO(Obs) weekly average morning severity scores. • Participants in this study experienced a growth benefit, as demonstrated by statistically significant improvements in height z-scores. Over the study duration, increases (improvements) from maralixibat baseline in height z-scores were observed at all visits (range: 0.008 [Week 2] to 0.568 [Week 252]). Statistically significant (p≤0.05) mean increases from maralixibat	• The primary efficacy endpoint comparing the ItchRO(Obs) in the higher dose maralixibat groups combined (140 and 280 µg/kg/day) with the placebo group at Week 13/ET was not met. • Responder analyses (defined as change from baseline of at least 1 point) based on ItchRO(Obs) weekly average severity scores at Week 13 showed a larger proportion of participants responded in the maralixibat group than in the placebo group: 70.8% of maralixibat-treated participants achieved a ≥1.0-point reduction in ItchRO(Obs) compared with 27.3% of placebo-treated participants who achieved these improvements (p=0.027)	• There was a sustained, long-term reduction (improvement) in pruritus levels, as measured by the ItchRO(Obs) weekly average morning severity score of approximately 1.8 points over the course of the study. The reduction from maralixibat baseline was statistically significant at most timepoints. • Statistically significant (p≤0.05) decreases (improvements) in mean change from maralixibat baseline in Clinician Xanthoma Scale score were observed at Weeks 24 through 48. • Participants in this study experienced growth benefit, as demonstrated by statistically significant (p≤0.05) increases (improvements) in height z-scores of around 0.3 observed at Week 24 and Weeks 48 through 168. Improvements in weight z-scores were similar but less pronounced, reaching statistical

	IMAGO (63)	IMAGINE (64)	ITCH (65)	IMAGINE II (66)
		baseline in height z-scores were observed at Weeks 36, 48, and 60. • Statistically significant improvements in weight z-scores were not observed.		significance at Weeks 84 and 108.
Permitted concomitant medication	No permitted concomitant medications were specified. The dosage and dosing regimen of concomitant drug were not permitted to change during the course of the study, with the exception of weight-based dose adjustments and vitamin supplementation. All modifications to a subject's concomitant drug therapy had to be carefully documented in the relevant case report forms. No new medications used to treat pruritus were permitted to be added during the course of the study. If drug therapy other than that specified by the protocol was taken, a joint decision was made by the investigator or investigator's designee and sponsor to continue or discontinue the subject.			

***Abbreviations**: AE, adverse event; ALGS, Alagille syndrome; ALT, alanine transaminase; ItchRO, Itch-reported outcome; SAE, serious adverse event; ULN, upper limit of normal.*

B.2.3.1.1 Baseline characteristics

Baseline characteristics of subjects in the ICONIC study (39) are presented in Table 10 and Table 11. Overall, the baseline characteristics of this study were well balanced between the maralixibat and placebo groups during the RWP.

Table 10: Patient demographics in the ICONIC study (39)

	Open-label phase (≤Week 18)	RWP (Weeks 19- 22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)
	MRX (n=31)	MRX (n=13)	Placebo (n=16)	MRX (n=29)	MRX (n=23)
Age, in years[a]					
Mean	5.4	5.5	5.8	5.7	6.2
SD	4.25	5.03	3.75	4.29	4.26
Median	5	4	5	5	5
Sex, n (%)					
Male	19 (61.3)	9 (69.2)	10 (62.5)	19 (65.5)	14 (60.9)
Country, n (%)					
Australia	9 (29.0)	5 (38.5)	4 (25.0)	9 (31.0)	9 (39.1)
Belgium	5 (16.1)	1 7.7)	2 (12.5)	3 (10.3)	3 (13.0)
France	9 (29.0)	3 (23.1)	6 (37.5)	9 (31.0)	6 (26.1)
Spain	3 (9.7)	2 (15.4)	1 (6.3)	3 (10.3)	1 (4.3)
Poland	2 (6.5)	0	2 (12.5)	2 (6.9)	1 (4.3)
United Kingdom	3(9.7)	2 (15.4)	1 (6.3)	3 (10.3)	3 (13.0)

***Abbreviations**: MRX, maralixibat; SD, standard deviation.*

Table 11: ALGS disease characteristics and history in the ICONIC study (39)

	Open-label phase (≤Week 18)	RWP (Weeks 19- 22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)
	MRX (n=31)	MRX (n=13)	Placebo (n=16)	MRX (n=29)	MRX (n=23)
Mutation Present, n (%)					

	Open-label phase (≤Week 18)	RWP (Weeks 19- 22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)
	MRX (n=31)	MRX (n=13)	Placebo (n=16)	MRX (n=29)	MRX (n=23)
JAGGED1	31 (100.0)	13 (100.0)	16 (100.0)	29 (100.0)	23 (100.0)
sBA, in µmol/L					
Mean	283.43	317.97	249.56	280.23	246.89
SD	210.569	233.671	196.804	212.952	203.319
Median	275.64	335.41	195.81	275.64	203.66
ItchRO(Obs) weekly Morning Average Severity (Item I) score [a]					
Mean	2.909	2.879	2.930	2.907	2.895
SD	0.548	0.538	0.559	0.541	0.509
Median	3.000	2.833	3.000	3.000	2.833
ItchRO(Obs) weekly Morning Average Frequency (Item 2) score [a]					
Mean	3.001	3.051	2.996	3.021	3.032
SD	0.599	0.615	0.519	0.554	0.546
Median	3.000	3.000	3.000	3.000	3.000
Clinician Scratch Scale Score					
Mean	3.3	0.3	3.5	3.3	3.3
SD	0.9	1.08	0.73	0.32	0.88
Median	4	0.3	4	4	4
Cholesterol, in mg/dL					
Mean	512,1	557,3	461	504,2	417,3
SD	419.82	552.49	317.87	432.81	273.51
Median	327.0	324.0	353.0	324.0	319.0
LDL Cholesterol, in mg/dL					
Mean	184.9	172.5	195.7	185.3	185.7
SD	58.37	54.56	64.48	60.34	62.63
Median	178.0	178.0	194.5	178.0	178.0
7αC4, in ng/mL					
Mean	10.32	14.77	6.53	10.22	7.05
SD	14.66	19.874	8.728	15.082	7.545
Median	4.5	7.6	2.9	4.0	3.5
Clinician Xanthoma Scale Score					
Mean	0.9		0.9	0.9	0.8
SD	1.26	1.29	1.31	1.28	1.17
Median	0.0	1.0	0.0	0.0	0.0
Height z-score at baseline visit					
Mean	-1.668	-1.541	-1,837	-1,705	-1,677
SD	1.3413	1.258	1.483	1.3708	1.3962
Median	-1.584	-1.668	-1.535	-1.584	-1.486

a. ItchRO average scores are based on the 7 days prior to the baseline visit date. Caregivers for all patients complete the ItchRO[Obs]
***Abbreviations**: ALGS, Alagille syndrome; ItchRO, Itch-reported outcome; LDL, low-density lipoprotein; MRX, maralixibat; sBA, serum bile acid; SD, standard deviation.*

Baseline characteristics of subjects in GALA Cohort Comparison Study (40) are presented in Table 12 and Table 13. Overall, the baseline characteristics of this study were well balanced between the GALA control group and the maralixibat group, aside from elevated sBA levels in the maralixibat group.

Table 12: Patient demographics in the maralixibat and GALA control groups of the GALA Cohort Comparison Study (40)

	Maralixibat cohort (N=84)	GALA control group (N=469)	p-value
Sex, n (%)			
Male	49 (58.3)	274 (58.4)	0.988
Female	35 (41.7)	195 (41.6)	
Age at baseline, in years			
Median (QI, Q3)	5.6 (2.7, 9.9)	4.3 (2.2, 9.6)	0.078
Region, n (%)			
Europe	41 (48.8)	229 (48.8)	0.945
North America	34 (40.5)	195 (41.6)	
Australia	9 (10.7)	45 (9.6)	

For continuous measures, a Wilcoxon rank-sum test was used to compare the treatment groups.

Table 13: ALGS disease characteristics and history in the maralixibat and GALA control groups of the GALA Cohort Comparison Study (40)

	Maralixibat cohort (N=84)	GALA control group (N=469)	p-value
Mutation, n (%)			
JAGGED1	81 (97.6)	330 (95.1)	0.55[a]
NOTCH2	2 (24)	17 (4.9)	
Other/unknown	1 (0.2)	37 (9.6)	
sBA[b] in µmol/L			
Median (QI, Q3)	200 (81, 371)	125 (39, 260)	0.003

For continuous measures, a Wilcoxon rank-sum test was used to compare the treatment groups.
a. Due to more than 20% of the cells having expected counts
b. Baseline sBA was available for 73 patients in the GALA control group. Approximately 85% of the sBA values were not available in the GALA clinical research database because frequent sBA measurement is not part of the clinical practice.
***Abbreviations**: sBA, serum bile acid.*

B.2.3.2 Expert elicitation

B.2.3.2.1 Clinical opinion and consensus report

Clinical opinion was sought to validate assumptions and outputs of the model. These questions included the adequacy of the model structure and health states, the proportion of patients which would be ineligible for LTx as a result of their cardiac or renal complications, the frequency and outcomes of SBD in clinical practice, patient QoL, and the proportion of patients on each standard of care drugs.

Broadly speaking, the clinician agreed with the methods and assumptions of the economic model. A number of changes were made to the economic model (in particular the exclusion of SBD) as a result of the interview. Please see Appendix N for further details.

B.2.3.2.2 Clinical engagement letter

Clinical expert opinion was sought regarding treatment of ALGS patients with cholestatic pruritus, with a focus on patient eligibility and treatment with maralixibat, in the form of a letter.

[redacted]

Please see Appendix O for further details.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analysis

A summary of the statistical analysis of the ICONIC and GALA Cohort comparison studies is displayed in Table 14 (39, 40).

Table 14: Summary of statistical analyses (39, 40)

	ICONIC	GALA Cohort Comparison Study
Hypothesis objectives	Primary efficacy outcomes: • Mean change from Week 18 to Week 22 of fasting sBA levels in patients	Primary efficacy outcomes: • Time to first occurrence of any of the following listed events

	ICONIC	GALA Cohort Comparison Study
	who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 in the MITT Population Secondary efficacy outcomes: • Change from Week 18 to Week 22 in: o Pruritus in subjects who previously responded to maralixibat treatment as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) o ALP o ALT o Total bilirubin o Direct bilirubin • Change from baseline to Week 18 in: o Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) o Fasting sBA levels o ALP o ALT o Total bilirubin o Direct bilirubin Additional efficacy outcomes: • Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in: o Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) o CSS • Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in: o Pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) o Fasting sBA levels o ALP o ALT o Total bilirubin o Direct bilirubin o Other biochemical markers of cholestasis o Bile acid synthesis (7αC4)	for the maralixibat cohort and GALA control group of the EFS: • LTx • SBD • Liver decompensation (variceal bleeding, ascites requiring therapy) • Death

	ICONIC	GALA Cohort Comparison Study
Statistical analysis	**For the analysis of primary outcomes:** The difference between the maralixibat and placebo groups in the change in sBA levels from Week 19 to Week 22 was assessed using an ANCOVA model with treatment group as a factor, and sBA levels from Week 19 as covariates. The mean within-group change between weeks 19 and 22 was tested using Student's t-test. **For the analysis of secondary outcomes:** Secondary and exploratory efficacy measures of continuous variables are analysed in the same way as efficacy analyses of the primary outcome. Secondary and exploratory efficacy measures of binary categorical variables were analysed using either the chi-square test or the Fisher exact test, depending on sample size. For non-binary ordinal results, the CMH was used. **For the analysis of continuous outcomes:** Analysis was conducted similarly to the primary and secondary outcomes, using summary statistics and, with the exception of PIC, CIC, and CGTB, by ANCOVA.	**For the analysis of primary outcomes:** Survival analysis techniques were used to summarise and analyse EFS. EFS was calculated as the number of days from baseline to the date of the first clinical event. Patients who did not reach the EFS endpoint were censored at the date of last contact. The time of a clinical event (SBD, LTx, decompensation event [variceal bleeding or ascites requiring therapy], or death) was compared between the maralixibat cohort and GALA control group. Depiction of the time to first occurrence of events was performed with Kaplan-Meier survival curves. In addition, the HR estimate of the treatment comparison with 95% CI was calculated with Cox proportional hazards regression analysis that included age, sex, baseline bilirubin, baseline ALT, and treatment as factors. The appropriateness of the proportional hazards model was assessed.
Interim analysis and stopping guidelines	A planned unblinded interim analysis was conducted after all subjects completed the study through Week 48 or discontinued the study before the Week 48 clinic visit. The final interim analysis for the 48-Week treatment period was performed on unblinded (actual) treatment codes. The purpose of this 1st interim analysis was to guide the future of the programme.	2 analyses of the outcomes were conducted comparing MRX and GALA cohorts. A preliminary analysis used all data available as of 8th Feb 2021, and a second analysis was conducted upon receipt of the final follow-up data.
Sample size, power calculation	Based on the rarity of the disease and practical considerations, the sample size for the ICONIC study was set at 30 evaluable patients.	No formal sample size calculations were performed. Available patients meeting the selection criteria were analysed.
Data management, patient withdrawals	Any subject who withdrew from the study was scheduled to undergo all procedures specified for the end of treatment (EOT)/ET visit. Per the protocol, the ET visits were scheduled within 7 days of the last dose of study drug. However, in the event an ET visit occurred more than 7 days after the date of last dose prior to the respective ET visit (i.e., Week 48/ET, 100/ET, and EOT/ET), visit-based assessments performed during that visit were not to be used in analysis summaries. For a subject who prematurely discontinued the study, their ET visit data was assigned to a protocol-specified visit window (for analysis purposes).	All data from time of study inclusion (the date that control group eligibility criteria were met) up to the time of study completion/withdrawal were included in the analysis, regardless of duration of treatment. The primary method for analysis of time-to-event endpoints was to be censored data after a participant's last follow-up. For maralixibat patients, the date of the clinical event was used in the time-to-event analysis unless the date was unavailable, in which case the date of last contact was used. Follow-up information for patients who had discontinued maralixibat ALGS studies was obtained. For the comparison analysis, follow-up information for events on the discontinued maralixibat-treated patients was collected.

Abbreviations: *ALGS, Alagille syndrome; ALP, alkaline phosphatase; ALT, alanine transaminase; ANCOVA, Analysis of Covariance; CGTB, Caregiver Global Therapeutic Benefit; CIC, Caregiver Impression of Change; CMH, Cochran-Mantel-Haenszel; EFS, event-free survival; EOT, end of treatment; ET, early termination; HR, harzard ratio; ItchRO, Itch-reported outcome; MRX, maralixibat PIC, Patient Impression of Change; sBA, serum bile acid; surgical procedure, SBD.*

Description of study populations

Please see Table 15 for a description of all study populations across the trials included in this submission (39, 40).

Table 15: Overview of study populations (39, 40).

	Study population	**Description**
ICONIC	Safety population	All patients who were enrolled and received at least one dose of the study drug.
	intention-to-treat (ITT)	All patients who were enrolled and received at least one dose of the study drug.
	MITT	All patients who were enrolled and received the study drug up to Week 18 and had a reduction from baseline of sBA of ≥50% at Week 12 or Week 18
GALA Cohort Comparison Study	Analysis	The maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry.

Abbreviations*: ITT, intent-to-treat; mITT, modified intent-to-treat.*

B.2.4.2 Patient disposition

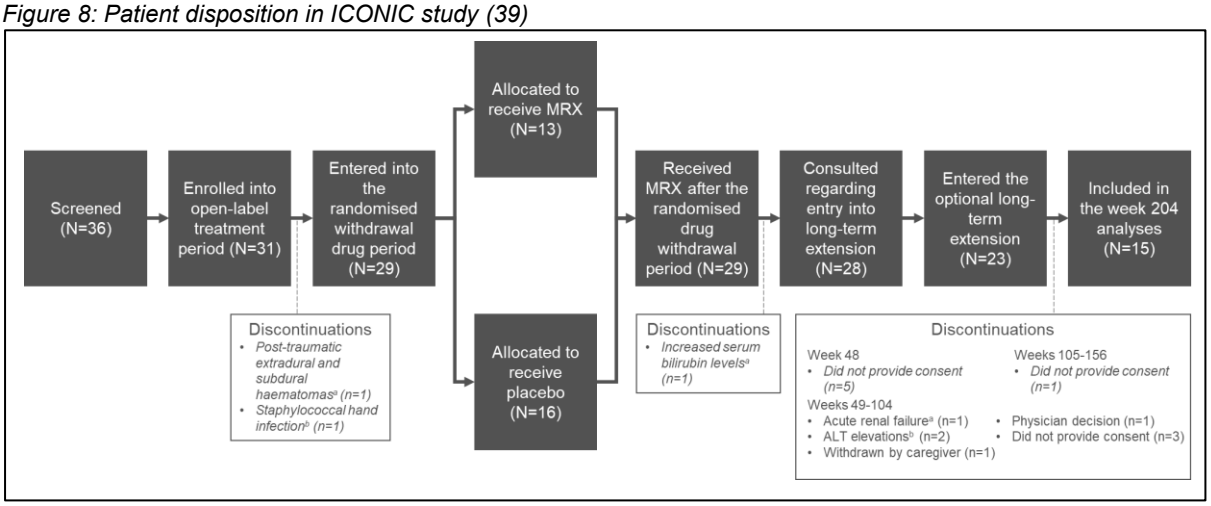
36 participants were screened to participate in the ICONIC study, of which 31 participants enrolled in the first open-label phase of the study, 29 (maralixibat n=13, placebo n=16) entered the RWP and completed the open-label stable dosing phase, and 23 entered the long-term extension phase (39).

Of the participants who discontinued the ICONIC study, two discontinued during the open-label phase due to an AE (staphylococcal infection of moderate intensity considered by the investigator to be possibly related to maralixibat, and extradural hematoma and subdural haemorrhage, both of which were considered by the investigator to be unlikely/remotely related to maralixibat), one discontinued during the open-label stable dosing phase due to an AE (blood bilirubin increased/acute kidney injury, both considered to not be related to maralixibat), and three discontinued during the long-term extension phase due to an AE (ALT increased in two participants and acute kidney injury in one participant). Two other participants

were withdrawn due to physician decision (one participant) and withdrawal by caregiver (one participant).

Patient disposition from the ICONIC study is further summarised in Figure 8.

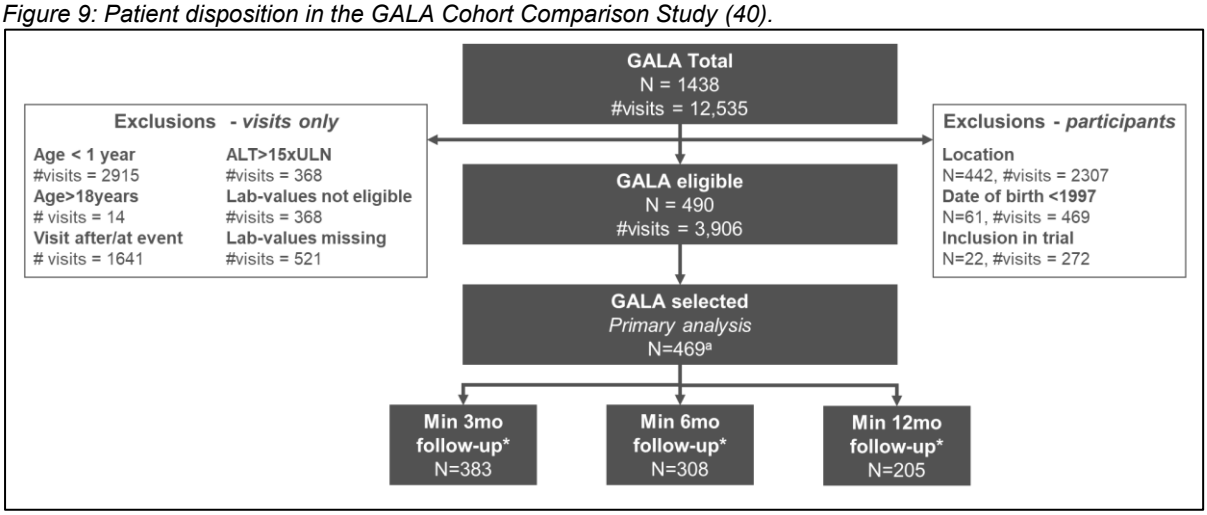
Figure 8: Patient disposition in ICONIC study (39)



a. Deemed unrelated to maralixibat by the investigator
b. Deemed possibly related to maralixibat by the investigator
***Abbreviations**: ALT, alanine transaminase; MRX, maralixibat.*

490 patients, with 3,906 visits, were included in the analyses in the GALA Cohort Comparison Study control group (40). Figure 9 summarises the selection of these patients from the overall GALA database (40). 84 patients were included in the maralixibat cohort from across the IMAGO/IMAGINE and ITCH/IMAGINE II studies (63-66).

Figure 9: Patient disposition in the GALA Cohort Comparison Study (40).



** To avoid early immortal time bias, all eligible patients must have had 3, 6, or 12 months of follow-up.*
a Among the 490 GALA eligible patients, only 469 patients had all covariates needed to perform the maximum likelihood selection
***Abbreviations**: ALT, alanine transaminase; ULN, upper limit of normal.*

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Please see Appendix C, Appendix G, Appendix H, and Appendix I for the complete quality assessment for each study. Table 16 and Table 17 assess the relevant clinical effectiveness evidence, using criteria taken from the NICE User Guide.

Table 16: Quality assessment of ICONIC (39)

Quality assessment criteria	Response
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, patients, and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No
Did the authors of the study publication declare any conflicts of interest?	Yes

***Abbreviations:** ITT, intent-to-treat.*

Table 17: Quality assessment of GALA Cohort Comparison Study (40)

Quality assessment criteria	Response
Was the cohort recruited in an acceptable way?	Yes
Was the exposure accurately measured to minimise bias?	Yes
Was the outcome accurately measured to minimise bias?	Yes
Have the authors identified all important confounding factors?	Yes

Quality assessment criteria	Response
Have the authors taken account of the confounding factors in the design or analysis, or both?	Yes
Was the follow-up of patients complete?	Yes
How precise are the results?	95% CI throughout

***Abbreviations**: CI, confidence interval.*

B.2.6 Clinical effectiveness results of the relevant studies

Summary

- The efficacy and safety of maralixibat in ALGS has been established in the ICONIC study (39), a multicenter, double-blind, randomised Phase 2b study with open-label follow-up. Data from this study has shown that treatment with maralixibat results in:
    - Significant, durable, and clinically meaningful improvements in cholestasis (the retention of toxic bile acids in the liver) which can lead to cirrhosis, PHT, ascites, and cholestatic pruritus (7, 8). *See section B.2.7.1 for further details.*
    - Significant improvements in cholestatic pruritus, which is the main clinical manifestation of cholestasis and a key indicator for LTx. Cholestasis has a profoundly negative impact on patient QoL (3, 4, 11). *See section B.2.12.1.2 for further details.*
    - A significant reduction in wider cholestatic manifestations such as xanthomas, growth impairment, and fatigue. These manifestations can impact patient survival (3), have a deep psychological impact (14, 19), and lead to impaired psychosocial and cognitive development (11, 19, 21, 22). *See section B.2.6.2 for further details.*
    - A significant long-term improvement in the QoL of ALGS patients, meaning patients can live a more fulfilling life without the burden of their symptoms (39). *See section B.2.6.3 for further details.*
- The GALA Cohort Comparison Study (40) was a cohort comparison conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry, providing a historical control comparison for maralixibat in ALGS patients. Data from the GALA Cohort Comparison Study shows that maralixibat treatment is associated with:
    - A significant reduction in liver-related events including LTx, SBD, liver decompensation, and even death over 6 years. These implications for morbidity and mortality are profound and represent a transformative therapeutic advance for patients suffering with ALGS. *See section B.2.12.1.5 for further details.*
- In addition, it is anticipated that by alleviating the symptoms of cholestasis and its associated complications in ALGS patients, caregivers will experience an improvement in their QoL. This improvement will be driven by a reduction in the demanding nature of their caregiving responsibilities (33).

B.2.6.1 Maralixibat provides durable and clinically meaningful improved control of cholestatic pruritus for ALGS patients

Summary

- In many patients, main clinical manifestation of cholestasis is severe and debilitating pruritus (11), which has a profoundly negative impact on patient QoL through self-mutilation, skin lesions, and extensive scarring (3). Cholestatic pruritus is also the key indicator for LTx in ALGS patients (4)
- Data from the ICONIC study (39) showed that treatment with maralixibat is associated with:
    - Sustained ItchRO scores across the RWP, which differed significantly from placebo treatment (ItchRO scores +0.201[SE 0.2180] vs. +1.712 [SE 0.2513], p<0.0001) Significant long-term improvement was also shown in ItchRO scores (see Figure 10), which is consistent with that shown for cholestasis markers (sBA, bilirubin, LDL-C, cholesterol, 7αC4, ALP and ALT)
    - Sustained CSS scores (a clinician-based measure of pruritis) across the RWP, which differed significantly from placebo treatment (CSS scores +0.4 [SE0.35] vs. +1.6 [SE0.41])

Debilitating pruritus results in self-mutilation, skin lesions, and extensive scarring, which has a profoundly negative impact on patient QoL. Itching has been identified as the aspect of ALGS that most impacts patients' lives, with a strong negative correlation between QoL and severity of pruritus (r=0.74, p-value not reported) (3). In addition, pruritus is the key indicator for LTx, with 69% of LTx conducted in ALGS patients attributed to intractable pruritus (4).

ItchRO is a validated tool (3) designed to assess the impact of pruritus in children with cholestatic liver disease, including ALGS. Patients treated with maralixibat during the RWP of the ICONIC study (39) showed sustained ItchRO scores across the RWP, compared with the significant progression in ItchRO scores seen with placebo treatment; this was true for both observer and patient-based measures. The prevention of pruritus progression with maralixibat was also demonstrated (and was statistically significant) using clinician-based measures (CSS scores). This data is summarised in Table 18.

Table 18: Mean change in pruritus scores during RWP in the overall population (ITT) (39)

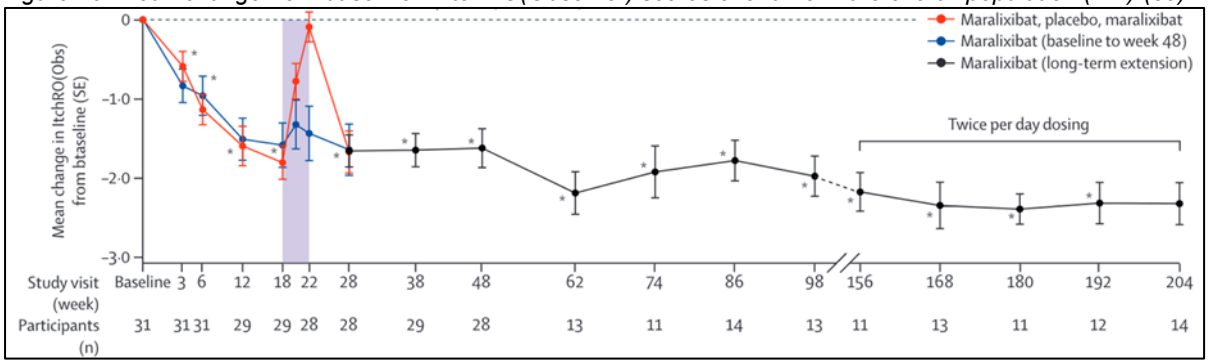
		Maralixibat (n=13)	**Placebo (n=16)**
ItchRO(Observer) n=23	**Mean change in score during RWP [SE]**	+0.201 [0.2180]	+1.712 [0.2513]
	p-value*	p=0.3754	p<0.0001
	Difference**	p < 0.0001	
ItchRO(Patient) n=23	**Mean change in score during RWP [SE]**	-0.095 [0.4611]	+1.808 [0.3789]

	p-value*	p=0.8465	p=0.0014
	Difference**	p=0.0013	
CSS n=23	**Mean change in score during RWP [SE]**	+0.4 [0.35]	+1.6 [0.41]
	p-value*	p=0.2930	0.0016
	Difference**	p=0.0311	

**Student's t-test used to test if mean change was statistically significant*
***Difference was calculated through an ANCOVA model*
***Abbreviations**: ANCOVA, Analysis of Covariance; CSS, clinical scratch score; ItchRO, Itch-reported outcome; ITT, intent-to-treat; SE, standard error.*

For the overall population (ITT) of the ICONIC study (39), statistically significant long-term decreases from baseline in ItchRO (Obs) weekly average morning severity scores were observed at each timepoint, as demonstrated in Figure 10. This significant long-term improvement in cholestatic pruritus is consistent with that for the markers of cholestasis (i.e. sBA, bilirubin, LDL-C, cholesterol, ALT, ALP and 7αC4), as described above (39).

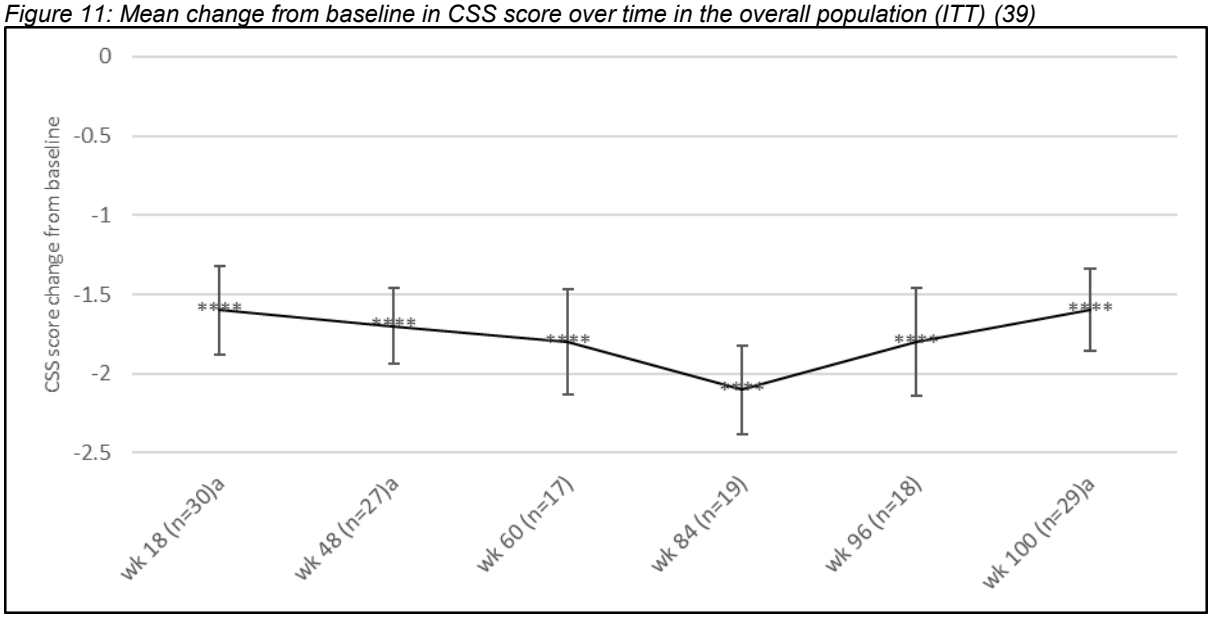
Figure 10: Mean change from baseline in ItchRO(Observer) scores over time in the overall population (ITT) (39)



Dashed lines represent data not shown between Week 98 to Week 156. Asterisks in represent paired t-test comparing the change from baseline (testing if the change was equal to zero or not). 12 patients went to twice per day dosing on the basis of raised sBA in the open-label extension.
**95% CI excludes zero (compared with baseline, overall population (ITT)).*
†The maralixibat, placebo, maralixibat group (n=16) received placebo during the RWP (purple-shaded area), whereas the maralixibat treatment group (n=13) continued to receive maralixibat.
***Abbreviations**: CI, confidence interval; ItchRO, itch-reported outcome; ITT, intent-to-treat; sBA, serum bile acid.*

Statistically significant long-term decreases from baseline in CSS scores were also observed at each timepoint for the overall population (ITT) of the ICONIC study (39), as demonstrated in Figure 11.

Figure 11: Mean change from baseline in CSS score over time in the overall population (ITT) (39)



*Student's t-test used to test if mean change is statistically significant: ****p<0.0001*
Error bars show SE. Data from RWP not included
a. Last observation carried forwards (LOCF)
***Abbreviations**: CSS, clinical scratch score; ITT, intent-to-treat; SE, standard error.*

B.2.6.2 Maralixibat significantly improves wider manifestations of cholestasis, such as xanthomas, growth impairment and fatigue

Summary

- Cholestasis can present with a range of extra-hepatic manifestations, such as xanthomas (fatty deposits on the extensor surfaces), growth impairment, and chronic fatigue (3, 19, 23). These manifestations can have an impact on patient survival (3) and the physical appearance of patients (with a subsequent psychological impact) (14, 19), as well as impacting the ability of patients to take part in activities and schooling. This leads to impaired psychosocial and cognitive development (11, 19, 21, 22)
- Data from the ICONIC study (39) shows that maralixibat treatment is associated with:
    - A significant reduction in the severity of xanthomas (Xanthoma Severity Score from baseline to Week 48, ITT -0.4 [SE 0.13], p=0.0095)
    - A significant improvement in growth at several timepoints (z-score data shown in Figure 12)
    - A significant improvement in fatigue at several timepoints (PedsQL multidimensional fatigue scale score data shown in
    - Table 20).

Cholestasis can present with a range of wider extra-hepatic manifestations. One such example is the development of xanthomas – fatty deposits on the extensor surfaces – which can impact patient survival (3, 6), restrict the ability of patients to take part in physical activity (19), and impact physical appearance (19). This can

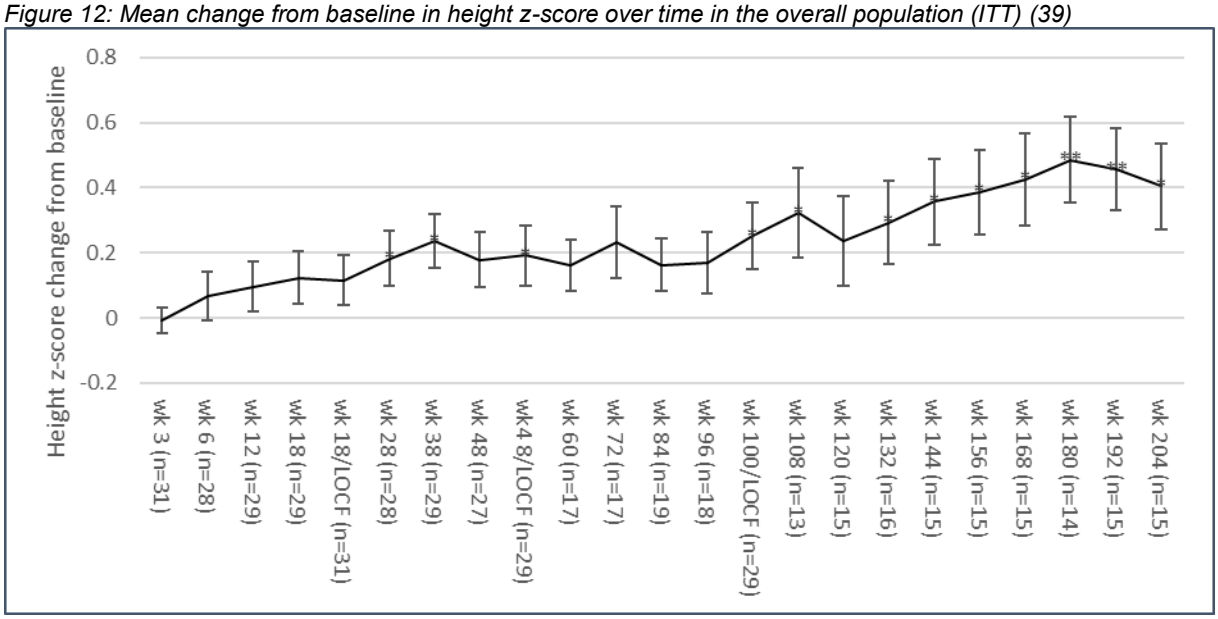
lead to mockery or exclusion from activities and difficulty with school, with an associated psychological impact on the patient (especially in childhood) (14, 19).

Data from the ICONIC study (39) shows that maralixibat treatment results in a significant reduction in Xanthoma Severity Score at Week 48 compared with baseline in the overall population (ITT) (-0.4 [SE 0.13], p=0.0095).

Growth impairment, another manifestation of cholestasis (6), can further impact the physical appearance of patients with ALGS, and much like xanthomas can result in bullying, particularly in childhood, and subsequent depression (19).

Data from the ICONIC study (39) shows that treatment with maralixibat is associated with increased growth for ALGS patients, with a statistically significant increase from baseline in mean height z-score at several timepoints in the overall study population (see Figure 12).

Figure 12: Mean change from baseline in height z-score over time in the overall population (ITT) (39)



*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations:** ITT, intent-to-treat; RWP, randomised withdrawal phase; SE, standard error.*

In addition, chronic fatigue is common in ALGS patients (23), and can lead to reduced participation in activities and difficulty with school and impaired psychosocial and cognitive development (11, 19, 21, 22). A statistically significant improvement in fatigue was seen for maralixibat at all time points in the ICONIC study (39), as measured by PedsQL multidimensional fatigue scale score (see Table 19).

Table 19: Mean change from baseline in PedsQL fatigue scores over time in the overall population (ITT) (39)

		Mean change from baseline (SE)	p-value
Peds QL fatigue score	wk 18 (n=30) [a]	20.39 (5.520)	0.0013
	wk 48 (n=27) [a]	20.20 (5.176)	0.13
	wk 60 (n=17)	24.57 (5.430)	0.0007
	wk 84 (n=19)	23.51 (7.515)	0.0080
	wk 96 (n=18)	12.85 (3.826)	0.0043
	wk 100 (n=29) [a]	9.84 (3.610)	0.0123

Student's t-test used to test if mean change was statistically significant
Data from RWP not included
a. Last observation carried forwards
***Abbreviations**: ITT, intent-to-treat; PedsQL, Paediatric Quality of Life Inventory; SE, standard error.*

B.2.6.3 Maralixibat improves overall quality of life of ALGS patients

Summary

- Compared to the general population, patients with ALGS and their carers are more likely to have a significantly lower QoL due to the burden of both the illness and providing care.
- Data from the ICONIC study (39) shows that maralixibat treatment is associated with a significant improvement in QoL at several timepoints (PedsQL total score data shown in Table 20).
- Furthermore, the positive outcomes associated with disease management due to maralixibat can also substantially improve caregivers' QoL.

ALGS patient QoL is often impacted by sleep disorders resulting in reduced school activities and impaired psychological and cognitive development (11, 19, 21). Symptoms associated with ALGS which impact physical appearance, such as pruritus, growth retardation, xanthomas, and facial dysmorphism, can lead to mockery or exclusion from activities, especially in childhood. This heavy psychological burden can eventually lead to depression in ALGS patients and a decrease psychosocial integration, which can significantly affect independence, self-esteem, and psychosocial development (19).

Maralixibat treatment is associated with a long-term improvement in QoL of ALGS patients, as demonstrated by the PedsQL total scores from the ICONIC study (39), wherein the improvement was statistically significant at most time points (Table 20).

Table 20: Mean change from baseline in PedsQL scores over time in the overall population (ITT) (39)

		Mean change from baseline (SE)	p-value
PedsQL total score	wk 18 (n=30)[a]	10.36 (2.983)	0.0017
	wk 48 (n=27) [a]	8.40 (3.392)	0.0196
	wk 60 (n=17)	12.71 (5.302)	0.0310
	wk 84 (n=19)	12.43 (5.151)	0.0290
	wk 96 (n=18)	8.10 (3.570)	0.0366
	wk 100 (n=29) [a]	5.31 (2.745)	0.0633

Student's t-test used to test if mean change was statistically significant
Data from RWP not included
a. Last observation carried forwards
***Abbreviations**: ITT, intent-to-treat; PedsQL, Paediatric Quality of Life Inventory; SE, standard error.*

Caring for a child with ALGS can significantly affect caregivers, with their QoL closely tied to the state of their child's disease. Caregivers often endure disrupted sleep, face limitations on their time for both parenting and regular activities due to their child's care needs, and frequently experience anxiety because of their child's condition (33). Therefore, the positive improvements in disease management and overall QoL observed with maralixibat can have a substantial, positive impact on the QoL of caregivers as well.

B.2.6.4 Maralixibat significantly reduces the risk of liver-related events and death in ALGS patients

Summary

- The likelihood of an ALGS patient experiencing an 'event' is high. 62.1% of ALGS patients will receive a LTx by the age of 18, and 40-57% of ALGS patients will experience a liver complication such as cirrhosis, ascites, or PHT. Furthermore, the mortality rate in children with ALGS is 7.2% at age 5 and nearly 12% at age 18, with a median age of death of 2.6 years in the GALA cohort aged 12 months to 18 years (4).
- Data from the GALA Cohort Comparison Study (40) demonstrates that maralixibat treatment is associated with:
    - A significant reduction in the risk of liver-related events over 6 years compared to the GALA control group (HR 0.305, 95% CI: 0.189-0.491; p<0.0001).
    - A significant reduction in the risk of LTx over 6 years vs. the GALA control group (HR 0.332, 95% CI: 0.197-0.559; p<0.0001) (40).

The likelihood of an ALGS patient requiring a LTx or developing a liver complication is high. Only 37.9% of children in Europe with a history of neonatal cholestasis reach the age of 18 with a native liver, with 72% of the LTxs performed in these patients occurring within the first 5 years of life (4).Cirrhosis, ascites, and PHT affect 46%, 57%, and 40% of ALGS patients, respectively (7, 8).

In addition, the mortality rate in children with ALGS is 7.2% at age 5 and nearly 12% at age 18, with a median age of death of 2.6 years in the GALA cohort aged 12 months to 18 years (4). The leading causes of death for ALGS patients are LTx-related complications (22%) and cardiac complications (18%) (4, 14).

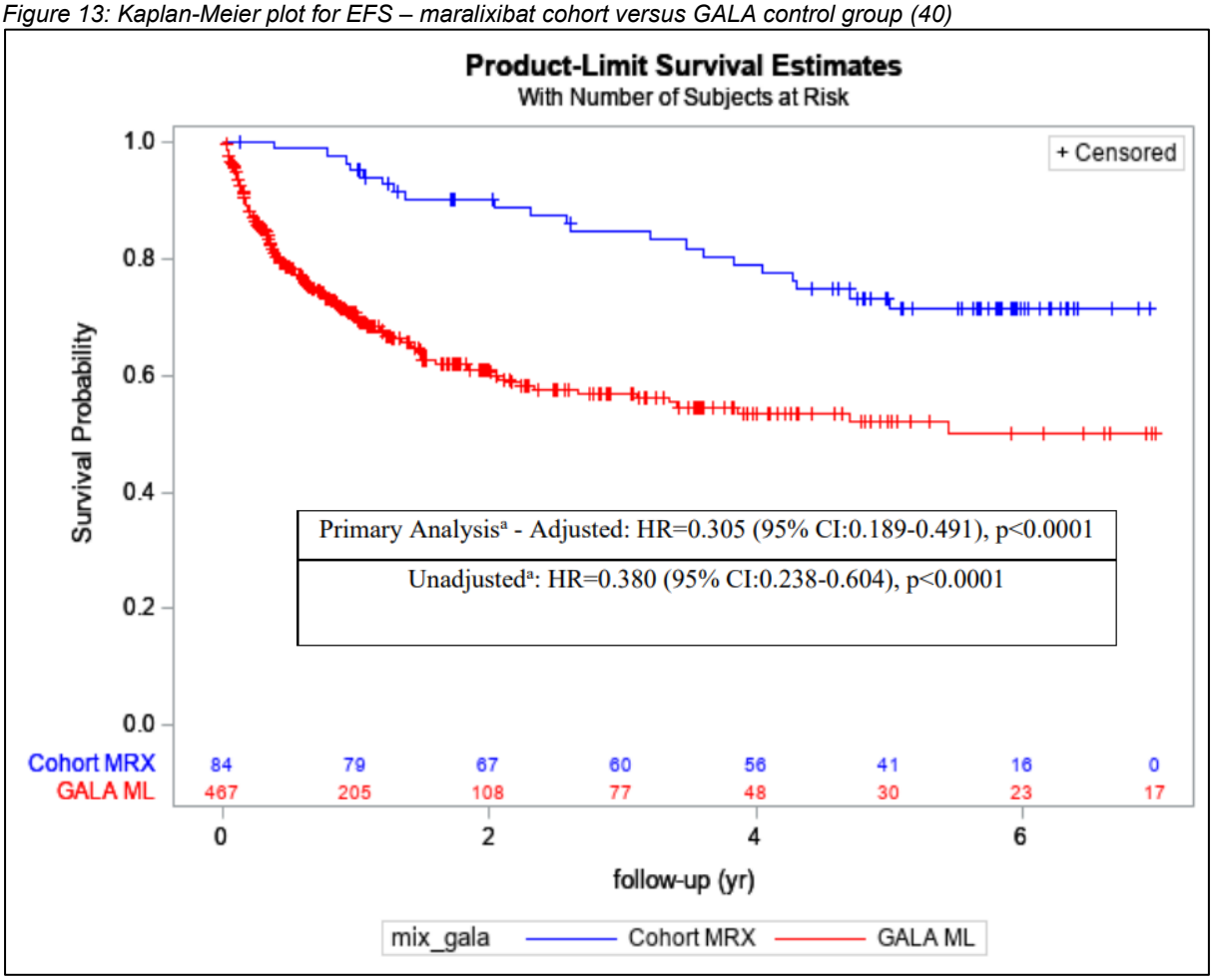
Data from the GALA Cohort Comparison Study (40) shows that adjusted 6-year EFS, (with an event being defined as LTx, liver decompensation event (variceal bleeding or ascites), SBD, or all-cause death), was statistically significantly higher in the maralixibat ITT cohort compared with the GALA control group (HR: 0.305; 95% CI: 0.189, 0.491; p<0.0001). Time to a clinical event in the maralixibat cohort was delayed compared with the GALA control group (see Figure 13). This data demonstrate that maralixibat treatment is associated with a significant ~70% reduction in the risk of liver-related events (LTx, SBD, liver decompensation), which are common for ALGS patients (67), as well as death.

In addition, an unadjusted (or crude) model was performed with the only covariate being treatment. EFS was higher in the maralixibat cohort than in the GALA control group (HR: 0.380; 95% CI: 0.238, 0.604; p<0.0001), indicating a 62% improvement in EFS with maralixibat treatment (see Figure 13).

Subgroup analyses conducted in the GALA Cohort Comparison Study (40) on EFS were significant across various baseline visit definitions (barring first eligible visit), regional subgroups, when including the GALA control group at overlapping study sites as a site conducting a maralixibat study, and for those patients for which baseline sBA was available (see section B.2.7.3) (40). This suggests that the findings of significant improvement in EFS with maralixibat treatment are robust.

Furthermore, LTx-free survival was statistically significantly higher in the maralixibat cohort compared with the GALA control group (HR: 0.332; 95% CI: 0.197, 0.559; p<0.0001), indicating a 67% reduction in risk of LTx or death in patients receiving maralixibat.

Figure 13: Kaplan-Meier plot for EFS – maralixibat cohort versus GALA control group (40)



a Cox regression models - effect of MRX vs. GALA log likelihood test adjusted for age, sex, bilirubin, and ALT
***Abbreviations**: ALT, alanine aminotransferase; CI, confidence interval; HR, hazard ratio; MRX, maralixibat.*

A recently published study by Sokol et al., identified as relevant but unavailable at the time of the SLR (50), describes how clinically meaningful reductions in ItchRO(Obs) (>1 point, p=0.005), bilirubin (<6.5 mg/dL p<0.0001), and sBA (<200 µmol/L; p=0.001) from baseline to Week 48 of maralixibat treatment were significantly correlated with 6-year EFS. This further stresses the importance of improvements in cholestasis and cholestatic pruritus being critical in reducing the likelihood of events (such as LTx and death) in ALGS patients.

B.2.6.5 Supporting evidence

The efficacy and safety of maralixibat is further supported by the results of ITCH, IMAGO, IMAGINE, and IMAGINE II clinical trials, as well as pooled analyses of ITCH, IMAGO, IMAGINE, IMAGINE II, and ICONIC presented by Kamath et al. (2021), Raman et al. (2021), Kamath et al. (2022), and Schneider et al (2022b).

Additional national history evidence based on a post-hoc analysis of a prospective, longitudinal cohort study of children with cholestasis based on the inclusion criteria of ITCH has also been presented by Schneider et al. (2022). These studies, while not reporting evidence that can be directly incorporated in the health economic model (Table 4), support the use of maralixibat as an efficacious and well-tolerated treatment for ALGS.

B.2.6.5.1 ITCH (LUM001-301) and IMAGINE II (LUM001-305)

Summary: ITCH

- Maralixibat was associated with improvements in pruritus based on ItchRO(Obs) score in comparison with placebo, showing a meaningful, although not statistically significant improvement of -0.473 (SE=0.3281; p=0.1594) over 13 weeks.
- In the secondary endpoint of change from baseline to Week 13 sBA, a statistically significant improvement was observed in the overall maralixibat treatment group (-117.401 [SE=46.2352; p=0.0163]).
- A numerical improvement was observed in sBA in all maralixibat treatment groups in comparison with placebo.

Summary: IMAGINE II

- The reduction in mean change from maralixibat baseline in sBA was statistically significant in the overall study population at Weeks 2 through 36, Weeks 60 through 120, and Weeks 156 through 192.
- A statistically significant reduction in the ItchRO(Obs) weekly average morning severity score was observed at Week 218 (mean change from maralixibat baseline: [redacted]). Over the study duration, the mean reduction from maralixibat baseline in ItchRO(Obs) weekly average morning severity score in the overall study population ranged from [redacted] (Week 2) to -[redacted] (Week 218).

Overall takeaway from both trials

- The findings of ITCH and IMAGINE II support the long-term efficacy and safety of maralixibat as a treatment for ALGS.

ITCH (LUM001-301) (65) is a Phase 2, randomised, double-blind, placebo-controlled, parallel group, multicentre study with 13 weeks of treatment in children with ALGS. The study included a 4-week screening period, a 5-week dose escalation period, an 8-week stable dose period, and a 4-week follow-up period. Subjects were

randomly assigned to receive either placebo (n=12) or 1 of 3 doses of maralixibat: low dose (70 µg/kg/day, n=8), mid dose (140 µg/kg/day, n=8), or high dose (280 µg/kg/day, n=8). ITCH enrolled male and female subjects aged between 12 months and 18 years (inclusive) with ALGS and evidence of cholestasis and an average daily score ≥2 on the ItchRO(Obs) questionnaire for 2 consecutive weeks in the screening period prior to randomisation. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15xULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhoea requiring specific intravenous fluid or nutritional intervention, were excluded from participating.

The primary efficacy endpoint of ITCH was the mean change from baseline to Week 13 in pruritus, assessed through ItchRO(Obs), in the two highest tolerated dose groups of maralixibat in comparison with placebo. The study also included secondary efficacy endpoints of change from baseline to Week 13 in fasting sBA level, and other liver-related parameters, including ALP, ALT, AST, GGT, and total and direct bilirubin. The study also assessed the occurrence of treatment-emergent adverse events (TEAEs), SAEs, and TEAEs leading to permanent discontinuation of study drug.

Maralixibat was associated with improvements in pruritus based on ItchRO(Obs) score in comparison with placebo, showing a meaningful, although not statistically significant improvement of -0.473 (SE=0.3281; p=0.1594) over 13 weeks. In the overall maralixibat treatment group, the ItchRO(Obs) mean change from baseline was -1.192 points (SE=0.1766; p<0.0001) and the change from baseline for the placebo group was -0.580 points (SE=0.2453; p=0.0242). In the secondary endpoint of change from baseline to Week 13 sBA, a statistically significant improvement was observed in the overall maralixibat treatment group (-117.401 [SE=46.2352; p=0.0163]). A numerical improvement was observed in sBA in all maralixibat treatment groups in comparison with placebo, although these improvements did not reach statistical significance. In the overall maralixibat treatment group, 22 subjects (88.0%) experienced ≥1 TEAE, and 15 subjects (60%) experienced a TEAE potentially related to the study drug. In the placebo group, a total of 12 subjects (100%) reported at least 1 TEAE, and 7 subjects (58.3%) reported a TEAE that was potentially related to the study drug.

IMAGINE II (LUM001-305) (66) was a long-term extension study based on the participants enrolled in ITCH (LUM001-301). In ITCH, participants were randomised to receive either placebo or active maralixibat; in IMAGINE II all participating subjects were treated with maralixibat. The study was divided into 6 parts: a dose escalation period, a dose optimisation period, a stable dosing period, a safety monitoring period, and 2 long-term optional follow-up treatment periods. Participants randomised to receive placebo received weekly dose increases of maralixibat up to a target dose of 140 µg/kg/day, and participants who received maralixibat in ITCH continued to receive the Week 13 dose. Following completion of the 4-week dose escalation period, participants entered an 8-week dose optimisation period. During this period, the investigator had the option of adjusting maralixibat dosing with the objective of achieving optimal control of pruritus at a dose level that was tolerated by the participant up to a maximum daily dose of 280 µg/kg maralixibat or 20 mg total dose.

The primary objective of IMAGINE II was to evaluate the long-term safety and tolerability of maralixibat in paediatric participants with ALGS. Secondary objectives were to evaluate the long-term effect of maralixibat on sBA levels (mean change from maralixibat baseline to Week 48, and from baseline to Week 220) and pruritus (mean change from maralixibat baseline through to Week 220 assessed though the ItchRO(Obs) instrument and clinician scratch scale), and to assess the long-term effect of maralixibat on other biochemical markers of cholestasis and liver disease.

A total of 34 participants were screened and enrolled in IMAGINE II. In the overall study population, the mean treatment duration was 953.2 days, with a mean average dose of 218.8 µg/kg/day. The primary efficacy endpoint was the mean change from maralixibat baseline to Week 48 in fasting sBA level, where baseline was defined as the last observation obtained before the first dose of maralixibat (either in ITCH or IMAGINE II). Overall, a reduction in sBA was observed following treatment with maralixibat, with a mean change from maralixibat baseline to Week 48 of -28.59 µmol/L (SD=89.456). A reduction in sBA from maralixibat baseline to Week 216 was also observed for the overall study population (-12.71; SD=51.276), with 26 patients remaining in the study as of Week 216. The reduction in mean change from maralixibat baseline in sBA was statistically significant in the overall study population

at weeks 2 through 36, weeks 60 through 120, and weeks 156 through 192. Furthermore, a statistically significant reduction in the ItchRO(Obs) weekly average morning severity score was observed at Week 218 (mean change from maralixibat baseline: [redacted]). Over the study duration, the mean reduction from maralixibat baseline in ItchRO(Obs) weekly average morning severity score in the overall study population ranged from [redacted] (Week 2) to [redacted] (Week 218). In IMAGINE II, all participants experienced at least 1 TEAE. In the overall study population, TEAEs related to maralixibat were experienced by 22 participants (64.7%). Overall, 6 participants (17.6%) experienced at least 1 treatment-emergent SAE and 2 participants (5.9%) experienced at least 1 treatment-emergent SAE related to the study drug. A total of 6 participants (17.6%) experienced at least 1 TEAE that led to discontinuation of maralixibat. No deaths were observed during IMAGINE II.

In summary, treatment with maralixibat resulted in reductions from maralixibat baseline in sBA at Week 48 (primary efficacy endpoint) and over time through Week 216 (secondary efficacy endpoint). Statistically significant improvements in sBA were reported in the overall study population at Weeks 2 through 36, Weeks 60 through 120, and Weeks 156 through 192. Additionally, a statistically significant improvement in pruritus was noted at all time points in the study from maralixibat baseline through Week 216 in the overall study population, as measured by ItchRO(Obs) weekly average morning severity scores and CSS scores. The findings of ITCH and IMAGINE II support the long-term efficacy and safety of maralixibat as a treatment for ALGS.

B.2.6.5.2 IMAGO (LUM001-302) and IMAGINE (LUM001-303)

Summary: IMAGO

- An analysis of the PedsQL Scale (parent and subject) scores showed a significant improvement in patients treated with maralixibat 140 µg/kg/day and the overall maralixibat treatment groups, in comparison with placebo.
- Change from baseline in PedsQL (Parent and Subject) scores were significantly higher at Week 13 in the maralixibat 140 µg/kg/day and 280 µg/kg/day treatment groups.

Summary: IMAGINE

- The reduction (improvement) in mean change from maralixibat baseline in sBA was statistically significant (p≤0.05) in the overall population at Weeks 4 through 60, Weeks 132 through 156, and Weeks 192 through 252.
- A statistically significant decrease from maralixibat baseline in ItchRO(Obs) weekly average morning severity score was observed, with patients experiencing a mean 1.095 reduction (SD = 0.7173; p<0.0001) at Week 48.
- In the overall study population, statistically significant improvements from maralixibat baseline were observed in mean PedsQL Total Scale Score (Parent) at Week 24 (p=0.0217), Week 48 (p=0.0018), and Week 72 (p=0.0386).

Overall takeaway from both trials

- The findings from IMAGO and IMAGINE demonstrate the short and long-term efficacy and safety of maralixibat, with treatment with maralixibat resulting in clinically and statistically significant improvement in sBA and pruritus.

ITCH IMAGO (LUM001-302) (63) is a Phase 2, randomised, double-blinded, placebo-controlled study to evaluate the safety and efficacy of maralixibat as a treatment for ALGS. The study enrolled UK patients between the ages of 12 months and 18 years old with native liver, across three sites. Enrolled patients were required to have a confirmed diagnosis of ALGS, cholestasis (sBA > 3xULN), intractable pruritus determined as an average daily ItchRO score of ≥2 for two consecutive weeks prior to randomisation. Two dose cohorts were considered, with eligible subjects were randomly assigned in a ratio of 2:1 (maralixibat to placebo). Cohort A were treated with 140 µg/kg/day maralixibat oral solution (n=6), or placebo (n=3), and Cohort B received either 70 or 280 µg/kg/day maralixibat oral solution (n=6), or placebo (n=3). The study participation period consisted of a screening period of up to 4 weeks, a 13-week treatment period (including a dose escalation period up to 5 weeks depending on dose group), a stable dose period (up to 11 weeks depending on dose group), and a 4-week follow-up period.

The primary efficacy endpoint of IMAGO was change in fasting sBA level from baseline to Week 13 (or early termination) in comparison with placebo. Change from baseline to Week 13 in ALT, AST, ALP, and pruritus measured by ItchRO, and PedsQL, were assessed as secondary efficacy endpoints. AEs occurring during the study were also collected and reported.

For the primary efficacy evaluation, there were no significant differences in the mean sBA levels versus placebo treatment for the overall maralixibat treatment group. Although no significant difference in the average daily scores for ItchRO(Pt) or ItchRO(Obs) were seen for the maralixibat treatment groups in comparisons with placebo treatment, an analysis of the PedsQL Scale (parent and subject) scores showed a significant improvement in patients treated with maralixibat 140 µg/kg/day and the overall maralixibat treatment groups in comparisons with placebo. Change from baseline in PedsQL (Parent and Subject) scores were also significantly better at Week 13 in the maralixibat 140 µg/kg/day and 280 µg/kg/day treatment groups. No SAEs or deaths were reported during the conduct of the study. One subject in the placebo arm discontinued study participation due to a TEAE.

IMAGINE (LUM001-303) (64) was the long-term extension study for patients enrolled in IMAGO (LUM001-302). The objective of the study was to evaluate the long-term efficacy, safety, and tolerability of maralixibat in paediatric participants with ALGS. Study endpoints included the mean change from maralixibat baseline to Week 48 in fasting sBA level (primary); mean change in ALT, AST, ALP, GGT and total and direct bilirubin; pruritus assessed through ItchRO(Obs); and xanthomas.

In IMAGO, participants were randomised to receive either placebo or active drug (maralixibat). All participants received active drug (maralixibat) in IMAGINE. The study was divided into 5 parts: a dose escalation period, a dose optimisation period, a stable dosing period, a 52-week follow-up treatment period, and a long-term follow-up treatment period for eligible participants who chose to stay on treatment with maralixibat. Participants who were randomised to receive placebo during IMAGO received weekly dose increases of maralixibat up to a target dose of 140 µg/kg/day or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose). Participants who received maralixibat in IMAGO remained on the same dose. During this long-term follow-up treatment period (52 weeks plus), participants could have their dose of maralixibat increased to a maximum of 560 µg/kg/day (280 µg/kg twice daily).

A total of 19 participants were enrolled and treated in the core study (up to Week 72), with 5 of these participants assigned placebo in IMAGO and 14 of these

participants assigned to any dose level of maralixibat in IMAGO. In the overall trial population, a statistically significant reduction in sBA from baseline to Week 48 (-94.40, SD = 98.915; p=0.0012) was observed. The reduction (improvement) in mean change from maralixibat baseline in sBA was statistically significant (p≤0.05) in the overall population at weeks 4 through 60, weeks 132 through 156, and weeks 192 through 252. In addition, a statistically significant mean decrease from maralixibat baseline in ItchRO(Obs) weekly average morning severity score was observed, with patients experiencing a mean 1.095 reduction (SD = 0.7173; p<0.0001) at Week 48. In the overall study population, statistically significant mean improvements from maralixibat baseline were observed for the PedsQL Total Scale Score (Parent) at Week 24 (p= 0.0217), Week 48 (p=0.0018), and Week 72 (p=0.0386). In the overall population, 18 participants (94.7%) had at least 1 TEAE and 15 (78.9%) had at least 1 AE that was related to study drug; 6 participants (31.6%) had at least 1 SAE and 1 participant (5.3%) had at least 1 SAE that was related to study drug.

Overall, IMAGO and IMAGINE demonstrated the short and long-term efficacy and safety of maralixibat, with treatment with maralixibat resulting in clinically and statistically significant improvement in sBA and pruritus. The reduction in mean change from maralixibat baseline in sBA was statistically significant in the overall population at weeks 4 through 60, weeks 132 through 156, and weeks 192 through 252. A statistically significant improvement in pruritus was noted at all time points in the study from maralixibat baseline through Week 216 in the overall study population, as measured by weekly average morning severity ItchRO(Obs) scores.

B.2.6.5.3 Kamath et al. (2021)

In an abstract, Kamath et al. assessed the gastrointestinal tolerability of maralixibat in ALGS (56). Data from ITCH, IMAGO, IMAGINE II, IMAGINE, and ICONIC were combined in an integrated analysis. The analysis was specific to TEAEs of diarrhoea and abdominal pain. A total of 49 (57%) patients had an event of diarrhoea and 46 (53%) patients had an event of abdominal pain; 33 (38%) patients had both events, of which 20 (23%) patients had both events concurrently. Most events were mild to moderate in severity and resolved with no action taken. No patients discontinued maralixibat due to either event. The analysis demonstrated that the majority of these

events were mild to moderate in severity, transient in nature, and did not result in discontinuation of treatment.

B.2.6.5.4 Raman et al. (2021)

In a poster, Raman et al. performed an integrated analysis of long-term clinical safety in maralixibat-treated patients with ALGS (57). Data from ITCH, IMAGO, IMAGINE II, IMAGINE, and ICONIC were combined in an integrated analysis of AEs. A sub-analysis of safety data in ITCH and IMAGO was also conducted.

All 86 patients (100%) had ≥1 treatment-emergent AE. A total of 62 patients (72.1%) had a treatment-emergent AE reported to be potentially related to study treatment. Most were mild to moderate in severity. The most common treatment-emergent AEs were diarrhoea and abdominal pain, and the incidence was highest during the first 4 weeks of treatment. The majority of gastrointestinal (GI) events lasted for less than 1 week.

B.2.6.5.5 Kamath et al. (2022)

In an abstract, Kamath et al presented a 4-year analysis demonstrating growth improvement in patients with ALGS (59). Height and weight z-scores were evaluated in patients who participated in ITCH, IMAGO, and ICONIC, as well as their respective long-term extension studies. Only patients for whom height and weight data were available at both baseline and Week 204 follow-up were included.

Overall, mean height z-score increased significantly to -1.29 (1.03) at Week 204 (change: 0.37; P=0.0004). The greatest catch-up height gain was observed among those within the lowest baseline quartile height z-scores, increasing from -3.1 (0.71) at baseline to -2.38 (0.82) at Week 204 (change: 0.72; P=0.018), and there was a significant correlation between change in height and baseline height (r=-0.48; P=0.004). Among patients with sBA <200 mmol/L at Week 48, height z-score increased from -1.58 (1.23) at baseline to -1.16 (1.00) at Week 204 (Δ: 0.42; P=0.001), whereas there was no significant change in height z-score among patients with sBA >200 mmol/L.

B.2.6.5.6 Schneider et al. (2022)

Shneider et al. applied inclusion and exclusion criteria from ITCH to a prospective longitudinal cohort of children with cholestasis (LOGIC) to derive contextual comparator data for evolving clinical trials of intestinal bile acid transport inhibitors in ALGS (60). A natural history cohort of 59 participants who met adapted inclusion and exclusion criteria of ITCH was identified from 252 LOGIC participants with ALGS with their native liver. Frequency weighting was used to match the age distribution of ITCH and yielded a cohort that was very similar to the baseline status of ITCH participants. During a 2-year prospective follow-up of the natural history cohort, there was a significant reduction in pruritus assessed through CSS (−1.43, 95% CI: −1.99, −0.87). In contrast, total bilirubin, albumin, and alanine aminotransferase levels were unchanged.

B.2.6.5.7 Schneider et al. (2022b)

Shneider et al. investigated the long-term efficacy and safety outcomes of maralixibat on children with cholestasis secondary to ALGS. The analysis was conducted by pooling data from IMAGO, ITCH, IMAGINE, and IMAGINE II, while taking into account all doses of maralixibat (ranging from 140 to 560µg/kg/day) (61). Changes from baseline (pretreatment at Week 13) to Week 48, Week 72, and end of treatment efficacy outcomes (after Week 48) in the extension studies were summarised. Linear mixed-effects models were fitted to estimate the significance of the change from baseline to Week 48. 57 participants with ALGS were enrolled in IMAGO (n=20) and ITCH (n=37). The characteristics of the participants were similar in both studies. Fifty-three of these participants enrolled in the extension studies (IMAGO→IMAGINE n = 19; ITCH→IMAGINE II, n = 34). By 4 weeks, change in ItchRO and CSS relative to baseline was similar in participants who received either placebo or maralixibat in the placebo-controlled phase of either study. As such, participants originally receiving placebo and maralixibat were combined as a single group for analyses of efficacy outcomes after Week 24.

Clinically and statistically significant improvements in pruritus and QoL relative to baseline were observed at Week 48. One point or greater reduction in ItchRO and CSS was observed in 73% and 68% of the participants, respectively, at Week 48.

Clinically significant 10 point or greater increases in PedsQL and the multidimensional fatigue, and family impact scales were observed in 45%, 52%, and 56% of participants, respectively. Mean sBA and cholesterol levels were significantly reduced (-80μM and -75mg/dl, respectively) from baseline, while total bilirubin was unchanged.

Changes observed at Week 48 were maintained by Week 72 or end of treatment. A reduction in ItchRO(Obs) extended from Week 48 to Week 72 (ItchRO(Obs) -1.61 Week 48, -2.00 Week 72).

During the median follow-up of 3.9 years, there were no deaths and two LTx in the four studies. 52 participants (91%) had treatment-emergent AEs; in IMAGINE and IMAGINE II, participants averaged seven AEs per person per year. Treatment-emergent GI AEs occurred in 42 participants (74%): 90% were mild, and the rate in the randomised phase of the studies was identical in participants receiving placebo or maralixibat.

B.2.7 Subgroup analysis

B.2.7.1 Maralixibat provides significant, durable, and clinically meaningful improved control of cholestasis for ALGS patients

Summary

- Cholestasis is defined as the retention of toxic bile acids in the liver. It can lead to cirrhosis, PHT, and ascites, as well as severe and debilitating pruritus (7, 8, 11). Increased sBA levels and jaundice (elevated bilirubin) are known markers of cholestasis (5).
- Data from the ICONIC study (39) showed that maralixibat treatment is associated with:
    - A significant and durable reduction in sBA levels vs. placebo (-21.73 μmol/L [standard error (SE) 43.125]) vs. +95.55 μmol/L ([SE 30.488], p=0.0464)
    - Significant reduction in total and direct bilirubin levels at several timepoints (see Figure 15 and Figure 16 respectively)
    - Significant improvement in other markers of cholestasis and healthy bile acid synthesis at several timepoints, including total cholesterol, LDL-C, ALT, ALP, and 7αC4 levels

Cholestasis is defined by a reduction in bile flow whereby bile acids are retained in hepatocytes. Through adaptive transport mechanisms that protect hepatocytes from the cytotoxic detergent effect of bile acids, some of these bile acids are eliminated

from the hepatocyte and join the systemic circulation leading to an increase in sBA and jaundice (elevated bilirubin) which are key markers of cholestasis (3, 5, 6). Cholestasis is the first and most serious feature of ALGS for most patients: it is reported in 85% of children with ALGS and its first manifestation is seen at a median age of 12 months (3, 5, 6). This retention of bile acids leads to a range of liver complications in ALGS patients, including cirrhosis (46% of patients), ascites (57%), and PHT (40%) (7, 8).

Patients treated with maralixibat during the RWP of the ICONIC study (39) showed a significant reduction in sBA levels compared with placebo, thus demonstrating a clinically meaningful effect on cholestasis in ALGS. This is true for both 'previous responder' (MITT) patients and the overall ITT population, as shown in Table 21.

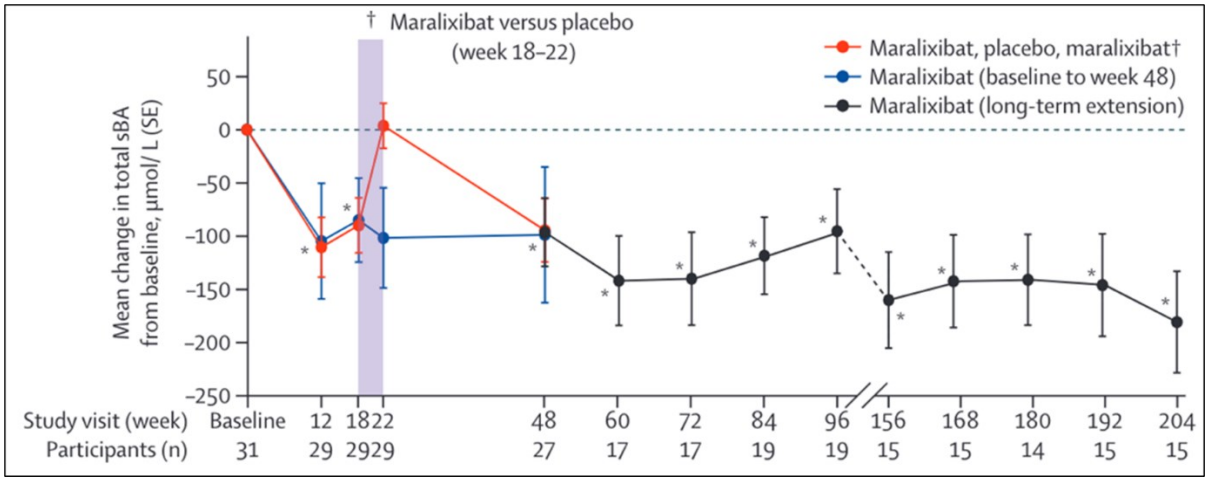
Table 21: Mean change in sBA during RWP (39)

		Maralixibat	**Placebo**
Previous responders MITT n=15	**n**	5	10
	Mean change in sBA during RWP [SE] (µmol/L)	-21.73 [43.125]	+95.55 [30.488]
	p-value*	p=0.6234	p=0.0086
	Difference**	p=0.0464	
Overall population (ITT) n=23	**n**	13	16
	Mean change in sBA during RWP [SE] (µmol/L)	-16.73 [30.412]	+93.58 [33.219]
	p-value*	p=0.5923	p=0.0130
	Difference**	p=0.0254	

'Previous responders' to maralixibat treatment refers to those patients who experienced a ≥50% reduction in sBA from baseline at Week 12 or 18.
**Student's t-test used to test if mean change is statistically significant*
***Difference was calculated through an ANCOVA model*
***Abbreviations**: ANCOVA, Analysis of Covariance; ITT, intent-to-treat; MITT, modified-intent-to-treat; RWP, randomised withdrawal phase; sBA, serum bile acid; SE, standard error.*

Data from the ICONIC study (39) also supports the long-term nature of the impact of maralixibat on sBA levels. Statistically significant mean decreases from baseline in sBA over time were seen in the overall population (ITT) for most timepoints, as demonstrated in Figure 14.

Figure 14: Mean change from baseline in sBA from over time in the overall population (ITT) (36)



Dashed line depicts data not shown between weeks 96 and 156. 12 patients went to twice per day dosing based on raised sBA in the open-label extension.
**95% CI excludes zero (compared with baseline, overall population (ITT); maralixibat treatment group vs placebo group).*
†The maralixibat, placebo, maralixibat group (n=16) received placebo during the RWP (purple-shaded area), and the maralixibat treatment group (n=13) continued to receive maralixibat.
***Abbreviations**: CI, confidence interval; ITT, intent-to-treat; sBA, serum bile acid; SE, standard error.*

Patients treated with maralixibat during the RWP of the ICONIC study (39) showed no significant difference in total and direct bilirubin levels compared with placebo, as shown in Table 22. However, as shown in Figure 15 and Figure 16 respectively, there was an overall downward numerical trend in total and direct bilirubin levels over time versus baseline with maralixibat treatment, which was significant at several timepoints, further supporting the data on sBA levels showing maralixibat treatment is associated with long-term reduction in bilirubin and thus cholestasis.

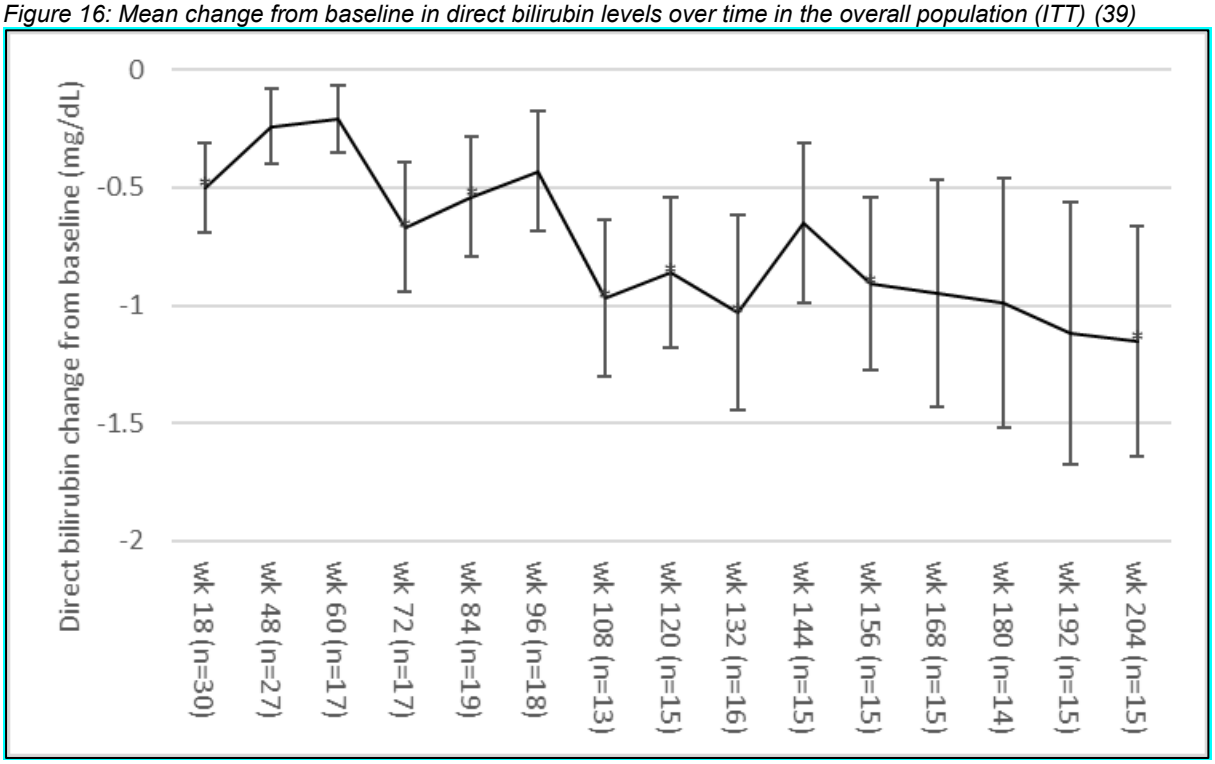
Table 22: Mean change in total and direct bilirubin during RWP in the overall population (ITT) (39)

		Maralixibat	Placebo
Total bilirubin	**n**	[redacted]	[redacted]
	Mean change in total bilirubin during RWP [SD] (mg/dL)	[redacted]	[redacted]
	p-value*	[redacted]	[redacted]
	Difference**	[redacted]	
Direct bilirubin	**N**	[redacted]	[redacted]
	Mean change in direct bilirubin during RWP [SD] (mg/dL)	[redacted]	[redacted]
	p-value*	[redacted]	[redacted]
	Difference**	[redacted]	

**Student's t-test used to test if mean change was statistically significant*
***Difference was calculated through an ANCOVA model*
***Abbreviations**: ANCOVA, Analysis of Covariance; ITT, intent-to-treat; RWP, randomised withdrawal phase; SD, standard deviation.*

Figure 15: Mean change from baseline in total bilirubin levels over time in the overall population (ITT) (39)
[redacted]*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations:** ITT, intent-to-treat; RWP, randomised withdrawal phase; SE, standard error.*

Figure 16: Mean change from baseline in direct bilirubin levels over time in the overall population (ITT) (39)

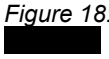


*Student's t-test used to test if mean change is statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations:** ITT, intent-to-treat; RWP, randomised withdrawal phase; SE, standard error.*

Total cholesterol levels and LDL-C are biochemical markers for cholestasis (68). In addition, total cholesterol levels are typically elevated in ALGS patients (3), which can result in wider complications such as xanthoma development (17) and cardiovascular disease (18). [redacted]

Figure 17: Mean change from baseline in total cholesterol levels over time in the overall population (ITT) (39)
[redacted]
*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations**: ITT, intent-to-treat; RWP, randomised withdrawal phase; SE, standard error.*

Figure 18: Mean change from baseline in LDL-C levels over time in the overall population (ITT) (39)



*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005; ***p<0.001*
Error bars show SE. Data from RWP not included
***Abbreviations**: ITT, intent-to-treat; RWP, randomised withdrawal phase; SE, standard error.*

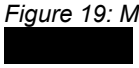
ALT and ALP are also biochemical markers for cholestasis, although due to its role in the aetiology of the disease, levels of ALT are not increased to the same extent as ALP and other measures of cholestasis (69, 70). Patients treated with maralixibat during the RWP of the ICONIC study (39) showed no significant difference in ALT and ALP levels compared with placebo, as shown in Table 23. However, as shown in Figure 19 and Figure 20, respectively, there is an overall downward numerical trend in ALT and ALP levels over time vs. baseline with maralixibat treatment, which was significant at several timepoints – further supporting the data on sBA levels showing that maralixibat treatment is associated with long-term reduction in bilirubin and thus cholestasis.

Table 23: Mean change in ALT and ALP during RWP in the overall population (ITT) (39)

		Maralixibat	Placebo
ALT	**n**	[redacted]	[redacted]
	Mean change in ALT during RWP [SD] (U/L)	[redacted]	[redacted]
	p-value*	[redacted]	[redacted]
	Difference**	[redacted]	
ALP	**N**	[redacted]	[redacted]
	Mean change in ALP during RWP [SD] (U/L)	[redacted]	[redacted]
	p-value*	[redacted]	[redacted]
	Difference**	[redacted]	

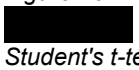
**Student's t-test used to test if mean change was statistically significant*
***Difference was calculated through an ANCOVA model*
***Abbreviations**: ALP, alanine aminotransferase; ALT, alanine transaminase; ANCOVA, Analysis of Covariance; ITT, intent-to-treat; RWP, randomised withdrawal phase; SD, standard deviation.*

Figure 19: Mean change from baseline in ALT levels over time in the overall population (ITT) (39)



*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included.
***Abbreviations**: ALT, alanine transaminase; ITT, intent-to-treat; SE, standard error*

Figure 20: Mean change from baseline in ALP levels over time in the overall population (ITT) (39)



*Student's t-test used to test if mean change was statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations**: ALP, alanine aminotransferase; ITT, intent-to-treat; SE, standard error*

In addition, data from the ICONIC study (39) showed that statistically significant increases in mean 7αC4 levels (a marker of healthy/non-cholestatic bile acid synthesis (71)) from baseline were observed for most time points in the overall

population (ITT) (Figure 21). This further supports the long-term clinically meaningful impact of maralixibat on sBA in ALGS patients.

Figure 21: Mean change from baseline in 7αC4 levels over time in the overall population (ITT) (39)
[redacted]*Student's t-test used to test if mean change is statistically significant: *p<0.05, **p<0.005*
Error bars show SE. Data from RWP not included
***Abbreviations**: ITT, intent-to-treat; SE, standard error.*

B.2.7.2 Data from the ICONIC study

Subgroup analyses conducted in the ICONIC study (39) on ItchRO(Obs) differences between the maralixibat and placebo groups between Week 18 and Week 22 were statistically significant across various statistical methods, as described in Table 24.

Table 24: Subgroup analysis on ItchRO(Obs) differences between the maralixibat and placebo groups between Week 18 and Week 22 (39)

Statistical method	Timeframe (wk)	n		Mean difference (95% CI)	p-value
		MRX	PBO		
t-test (baseline vs. endpoint for all participants) [a]	[redacted]				
ANCOVA [b]					
ANCOVA with Subject 050007 Week 22 Date Adjustment [b, d]					
ANCOVA using minimum of 3 (rather than 4) daily scores to define a compliant week [b]					
ANCOVA controlling for sba responder group [b]					
ANCOVA controlling for presence of paucity [b]					
ANCOVA controlling for baseline CSS [b]					
ANCOVA controlling for baseline sBA level [b]					
ANCOVA controlling for baseline total bilirubin [b]					
ANCOVA Controlling for Baseline 7αC4 Level [b]					
ANCOVA controlling for age (months) at baseline [b]					
ANCOVA Controlling for BMI at Baselineb					
ANCOVA controlling for baseline ALT level [b]					
ANCOVA controlling for family history of ALGS [b]					
ANCOVA controlling for baseline cholesterol level [b]					
ANCOVA controlling for baseline GGT level [b]					
ANCOVA controlling for baseline Clinician Xanthoma Severity Score [b]					
MMRM [c]					

Statistical method	Timeframe (wk)	n		Mean difference (95% CI)	p-value
		MRX	PBO		
MMRM with participant 050007 Week 22 date adjustment [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM using minimum of 3 (rather than 4) daily scores to define a compliant week [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM controlling for sBA responder group [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM controlling for BMI at baseline [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MMRM controlling for sex, and age (months) and BMI at baseline [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a t-test: For examining change from baseline to Week 18 and Week 48 (all participants on maralixibat), a one-sample (2-sided) t-test was used. A negative mean difference indicates the ItchRO(Obs) weekly morning average severity scores decreased over that time period. For the t-test the values under the mean difference heading represent the difference from baseline to endpoint for all participants in the trial. For all other analysis methodologies the values under the mean difference header represent the difference between the MRX and PBO treated participants during the RWP.
b ANCOVA: For comparing treatment group differences in change from Week 18 to 22, an ANCOVA using a mixed model with treatment group as a fixed effect and baseline value as a covariate was used. The ANCOVA uses a residual REML estimation method for the covariance parameters. Least squares means on the change from Week 18, and 2-sided 95% confidence limits and p-values, are presented. Additional covariates were added to the model, as main effects, as indicated.
c MMRM: Change from Week 18 in ItchRO(Obs) weekly average morning and evening scores over the RWP (Weeks 19, 20, 21, and 22) were analysed via a REML-based repeated measures approach. The analysis model included the fixed, categorical effects of treatment, study visit, treatment by visit interaction, and continuous covariates of baseline (Week 18) score, and baseline score-by-visit interaction. An unstructured covariance structure shared across treatment groups was used to model the within-participant errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. The primary comparison was the contrast (difference in least squares mean) between treatments at the last visit (Week 22). Additional covariates were added to the model, as main effects, as indicated.
d A sensitivity analysis was performed to account for a participant (050007) who was hospitalised during the RWP for a SAE of polytraumatism/splenic rupture which made it impossible for the participant to comply with in-clinic visits. It was decided by the medical monitors that this participant should discontinue study medication until the SAE resolved and the participant was able to comply with study requirements. This participant was on placebo for the first 5 weeks of the RWP and then came off study drug for 13 weeks before their Week 22 clinic visit. The planned analysis used the Week 22 clinic visit date in deriving Week 19-22 ItchRO weekly average scores, using the principle of intent-to-treat, rather than using ItchRO data from the 4 weeks immediately following this participant's Week 18 clinic visit. For this sensitivity analysis, the 4-Week time period immediately after the Week 18 Visit date was used to derive ItchRO weekly scores (for Weeks 19-22).
Note: Responder definitions (participant specific): sBA responder: ≥50% reduction in sBA level from baseline to Week 12 or 18 (unless otherwise specified); ItchRO responder: ≥1.0 point reduction in ItchRO(Obs) weekly morning average severity from baseline to Week 12 or 18.
***Abbreviations**: ALGS, Alagille syndrome; ANCOVA, Analysis of Covariance; ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CSS, clinical scratch score; GGT, gamma-glutamyl transpeptidase; HR, hazard ratio; ItchRO, Itch-reported outcome; LOCF, last observation carried forward; MMRM, Mixed Models for Repeated Measures; MRX, maralixibat; PBO, placebo; PIC, Patient Impression of Change; REML, restricted maximum likelihood; SAE, serious adverse event; sBA, serum bile acid.*

For ItchRO(Obs) weekly average morning severity scores, the results remained statistically significant across all methods. When controlling for various baseline characteristics including sBA responder status, presence of bile duct paucity, baseline CSS, sBA, bilirubin, 7αC4, age, BMI, ALT, family history of ALGS, GGT, cholesterol, and Xanthoma Severity Score, the results remain internally consistent, with all treatment effect p-values statistically significant. The results are also

statistically significant when using the MMRM analysis method when controlling for multiple variables.

Results for subgroups of baseline age, sBA, bilirubin, ALT, and ItchRO(Obs) weekly average morning severity score were statistically significant, except where there were very small numbers in the category (n≤4), and also in the maralixibat group from Week 18 to Week 22 (when a change in pruritus would not be expected).

Sensitivity analyses conducted on ItchRO(Obs) differences between the maralixibat and placebo groups between Week 18 and Week 22 were also statistically significant across various subgroups.

B.2.7.3 Data from the GALA Cohort Comparison Study

No patient in the GALA control group had a first clinical event of HCC; therefore, this subgroup analysis was not performed as it would be identical to the primary analysis.

Subgroup analyses conducted in the GALA Cohort Comparison Study (40) on EFS were significant across various baseline visit definitions (barring first eligible visit), as described in Table 25.

Table 25: Subgroup analysis on EFS HR by baseline visit definition

Baseline visit definition	EFS HR (95% CI)	p-value
First Eligible Visit[a]	0.618 (0.369-1.036)	p=0.068
Last Eligible Visit	0.241 (0.148-0.392)	p<0.0001
Random Visit 1 Method 1[b]	0.457 (0.284-0.734)	p=0.0012
Random Visit 2 Method 1[b]	0.486 (0.304-0.777)	p=0.0026
Random Visit Method 2[c]	0.439 (0.274-0.703)	p=0.0006
Date of Birth[a]	0.504 (0.320-0.795)	p=0.0032

a. Prespecified analysis
b. Refers to selection of an eligible visit at random
c. Refers to selection of a random visit among all available visits for a calendar year
***Abbreviations**: CI, confidence interval; EFS, event-free survival; HR, hazard ratio.*

Subgroup analyses conducted for differences in EFS between the maralixibat and GALA control groups were also statistically significant across regional subgroups, as described in Table 26 (40).

Table 26: Subgroup analysis on EFS HR by region (40)

Region	EFS HR (95% CI)	p-value
Europe	0.360 (0.187-0.693)	p=0.0022
North America	0.249 (0.114-0.542)	p=0.0005
Australia	0.140 (0.024-0.832)	p=0.031

***Abbreviations**: CI, confidence interval; EFS, event-free survival; HR, hazard ratio.*

Differences in EFS between the maralixibat and GALA control groups were also statistically significant when classifying the GALA control group at overlapping study sites as a site conducting a maralixibat study (the analysis controlled for standard of care as a confounding variable by using the same study centres in the analyses): HR=0.359; 95% CI: 0.219, 0.587; p<0.0001 (40).

In addition differences in EFS between the maralixibat and GALA control groups was also statistically significant for those patients for which baseline sBA was available: HR=0.245; 95% CI: 0.124, 0.483; p<0.0001 (40).

B.2.8 Meta-analysis

No relevant meta-analyses were conducted for inclusion in this submission.

B.2.9 Indirect and mixed treatment comparisons

No relevant indirect or mixed treatment comparisons were conducted for inclusion in this submission.

B.2.10 Adverse reactions

- Data from the ICONIC study (39) demonstrates that maralixibat treatment is generally well tolerated in ALGS patients, with a low frequency of high-grade or treatment-related AEs as well as SAEs.

B.2.10.1 F*requency and severity of AEs*

The incidence of maralixibat-treated patients experiencing AEs during the ICONIC study (39) remained similar across the open-label phase, after randomised withdrawal and long-term extension phases, with the majority of patients (86.2 to 100%) experiencing AEs. However, only 34.8 to 38.7% of patients experienced AEs potentially related to maralixibat treatment (see B.2.10.3 for more details).

During the RWP, patients that stayed on maralixibat had a lower incidence of AEs and AEs potentially related to maralixibat treatment (53.8% and 7.7%, respectively) compared with patients on placebo (75% and 18.8%, respectively).

The most frequently reported AEs (> 40% in total) were abdominal pain, diarrhoea, vomiting, fever, cough, and nasopharyngitis. The incidence of AEs in each study phase is presented in Table 27.

Table 27: Incidence of AEs (preferred term) in two or more patients in any phase for the safety population (39)

	Open-label phase (≤ Week 18)	**RWP (Weeks 19- 22) a**		**After RWP (Weeks 23-48)**	**Long-term efficacy phase (>Week 48)**
n (%)	MRX n=31	MRX n=13	Placebo n=16	MRX n=29	MRX n=23
Number of patients with at least 1 AE	30	7 (53.8)	12 (75.0)	25 (86.2)	23 (100.0)
Congenital familial and genetic disorders	0	0	0	0	2 (8.7)
Phimosis	0	0	0	0	2 (8.7)
Ear and labyrinth disorders	2 (6.5)	0	0	3 (10.3)	3 (13.0)
Ear pain	1 (3.2)	0	0	3 (10.3)	1 (4.3)
Gastrointestinal disorders	22 (71.0)	2 (15.4)	3 (18.8)	14 (48.3)	16 (69.6)
Diarrhoea	13 (41.9)	1 (7.7)	1 (6.3)	5 (17.2)	7 (30.4)
Abdominal pain	12 (38.7)	1 (7.7)	1 (6.3)	6 (20.7)	12 (52.2)
Vomiting	11 (35.5)	1 (7.7)	1 (6.3)	3 (10.3)	8 (34.8)
Dental caries	0	0	0	0	1 (87)
Pale faeces	2 (6.5)	0	0	0	1 (4.3
Nausea	1 (3.2)	1 (7.7)	0	1 (3.4)	2 (8.7)
General disorders and administration site conditions	7 (22.6)	0	0	10 (34.5)	12 (52.2)
Pyrexia	6 (19.4)	0	2 (12.5)	7 (24.1)	10 (43.5)
Influenza-like illness	0	0	0	2 (6.9)	2 (8.7)
Infections and infestations	0	6 (46.2)	1 (25)	15 (51.7)	17 (73.9)
Upper respiratory infection	6 (19.4)	2 (15.4)	0	3 (10.3)	4 (17.4)
Nasopharyngitis	4 (12.9)	1 (7.7)	0	8 (27.6)	9 (39.1)
Ear infection	3 (9.7)	0	0	4 (13.8)	5 (21.7)
Gastroenteritis	0	0	1 (6.3)	2 (6.9)	5121.7)
Bronchitis	0	0	0	1 (3.4)	2 (8.7)
Influenza	2 (6.5)	1 (7.7)	0	1 (3.4)	2 (8.7)
Lower respiratory infection		0	0	0	2 (8.7)
Otitis media	2 (6.5)	0	0	0	2 (8.7)
Pharyngitis		0	1 (6.3)	0	3 (13.0)
Rotavirus infection	2 (6.5)	0	0	0	

n (%)	Open-label phase (≤ Week 18)	RWP (Weeks 19- 22) a		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)
	MRX n=31	MRX n=13	Placebo n=16	MRX n=29	MRX n=23
Viral infection	1 (3.2)	1 (7.7)		1 (3.4)	4 (17.4)
Injury, poisoning, and procedural complications	8 (25.8)	0	1 (6.3)	6 (20.7)	11 (47.8)
Fall	4 (12.9)	0	0	3 (10.3)	
Nasal injury	0	0	0	2 (6.9)	1 (4.3)
Procedural pain	0	0	0		1 (8.7)
Head injury	2 (6.5)	0	0	1 (3.4)	1 (4.3)
Skin abrasion	2 (6.5)	0	0	1 (3.4)	1 (4.3)
Skin laceration	1 (3.2)	0	0	1 (6.9)	1 (4.3)
Contusion	1 (3.2)	0	0	0	3 (13.0)
Muscle strain	1 (3.2)	0	0	1 (3.4)	2 (8.7)
Investigations	3 (9.7)	0	0	1 (3.4)	6 (26.1)
Alanine aminotransferase increased	0	0	0	0	4 (17.4)
Aspartate aminotransferase increased	0	0	0	0	2 (8.7)
Metabolism and nutrition disorders	2 (6.5)	1 (7.7)	0	1 (3.4)	1 (4.3)
Decreased appetite	2 (6.5)	0	0		
Musculoskeletal and connective tissue disorders	1 (3.2)	0	0	1 (3.4)	8 (34.8)
Pain in extremity		0	0		4 (17.4)
Nervous system disorders	7 (22.6)	0	1 (6.3)	2 (6.9)	5 (21.7)
Headache	5 (16.1)	0	0	2 (6.9)	4 (17.4)
Lethargy	2 (6.5)	0	0	0	
Psychiatric disorders	3 (9.7)	0	1 (6.3)	0	2 (8.7)
Insomnia	1 (3.2	0	0	0	2 (8.7)
Respiratory, thoracic, and mediastinal disorders	8 (25.8)	0	0	7 (24.1)	10 (43.5)
Cough	3 (9.7)	0	0	3 (10.3)	8 (34.8)
Rhinorrhoea	2 (6.5)	0	0	1 (3.4)	1 (4.3)
Epistaxis	1 (3.2)	0	0		2 (8.7)
Oropharyngeal pain	1 (3.2)	0	0	3 (10.3)	3 (13.0)
Skin and subcutaneous tissue disorders	4 (12.9)	2 (15.4)	5 (31.3)	3 (10.3)	4 (17.4)
Pruritus	3 (9.7)	1 (7.7)	5 (31.3)	1 (6.9)	0

Subjects who terminated the study during the Open-label Phase are not included.
Adverse events were coded using MedDRA version 22.1. Treatment groups are based on the dose received at the onset of the AE. Patients were counted only once for each SoC and preferred term (PT). SoC and PT are sorted in the order of most frequent in the OL phase.
Abbreviations: AE, adverse events; MedDRA, Medical Dictionary for Regulatory Activities; MRX, maralixibat; OL, open-label; SoC, PT, preferred term.

B.2.10.2 Grade 3-5 AEs

As shown in Table 28, most AEs experienced by maralixibat-treated patients across all phases of the ICONIC study (39) were of mild to moderate severity (Grades 1-2). No patients experienced a Grade 5 AE (i.e., there were no deaths associated with placebo or the study drug), and there was a greater incidence of life-threatening AEs (Grade 4) in the placebo-treated patients vs. the maralixibat-treated patients in the RWP: 1 patient (6.3%) versus 0 patients, respectively.

The Grade 4 AEs experienced by maralixibat-treated patients were as follows:

- Extradural haematoma and subdural haemorrhage (one patient, open-label phase)
- Acute kidney injury (one patient, after RWP)
- Aplasia pure red cell, toxicity to various agents; verbatim term: voluntary rifadine intoxication (one participant, long-term extension phase)
- Increased ALT (one participant, long-term extension phase)
- Marrow hyperplasia (one participant, long-term extension phase)
- Shock haemorrhagic and splenic rupture (one participant, RWP)

Table 28: Incidence of AEs by severity and study phase for the safety population (39)

	Open-label phase (≤ Week 18)	RWP (Weeks 19-22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)
n (%)	MRX n=31	MRX n=13	Placebo n=16	MRX n=29	MRX n=23
Any system organ class any event (total)	30 (96.8)	7 (53.8)	12 (75.0)	25 (86.2)	23 (100.0)
Grade 1 (mild)	13 (41.9)	6 (46.2)	3 (18.8)	13 (44.8)	4 (17.4)
Grade 2 (moderate)	13 (41.9)	1 (7.7)	8 (50.0)	9 (31.0)	11 (47.8)
Grade 3 (severe)	3 (9.7)	0	0	2 (6.9)	5 (21.7)
Grade 4 (life-threatening)	1 (3.2)	0	0	1 (3.4)	3 (13.0)
Grade 5 (fatal)	0	0	0	0	0

Severity grades are reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If the CTCAE does not have a grading for a particular adverse event, the severity of the event is reported by the investigator as mild, moderate, or severe.
Treatment groups are based on the dose received at the onset of the AE. A participant with multiple events per system organ class or per preferred term is counted only once at the maximum reported severity grade.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MRX, maralixibat.

B.2.10.3 Treatment-related AEs

As shown in the table below, the incidence of patients who experienced treatment-related AEs with maralixibat in the ICONIC study (39) was moderately low, occurring in 12 patients in the open-label phase (38.7%), 8 patients (34.8%) in the long-term extension phase, and only 1 patient (3.4%) between week 23 and 48. During the RWP, patients that stayed on maralixibat had a lower incidence of treatment-related AEs compared with patients on placebo: 1 patient (7.7%) versus 3 patients (18.8%), respectively.

Table 29: Incidence of treatment-related AEs in two or more patients in a study phase for the safety population (39)

	Open-label phase (≤ Week 18)	RWP (Weeks 19- 22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48) a
n (%)	MRX n=31	MRX n=13	Placebo n=16	MRX n=29	MRX n=23
Number of patients with at least one treatment-related AE	12 (38.7)	1 (7.7)	3 (18.8)	1 (3.4)	8 (34.8)
Abdominal pain	9 (29.0)	0	0	0	4 (17.4)
Diarrhoea	6 (19.4)	0	0	1 (3.4)	1 (4.3)
Vomiting	3 (9.7)	0	0	0	0
Increased alanine aminotransferase	0	0	0	0	4 (17.4)
Aspartate aminotransferase	0	0	0	0	2 (8.7)
Pruritus	0	1 (7.7)	3 (18.8)	0	0

a) Subjects that terminated the study during the Open-label Phase are not included.
Adverse events were coded using MedDRA version 22.1. Treatment groups are based on the dose received at the onset of the AE. Patients were counted only once for each System Organ Class and Preferred Term. Events are included in the table if PT had two or more patients in at least one of the study phases.
Abbreviations: AE, adverse event; MRX, maralixibat.

B.2.10.4 SAEs

The occurrence of SAEs with maralixibat in the ICONIC study (39) was low; in total, 14 patients experienced a total of 33 SAEs. None of the SAEs were considered by

the investigator to be related to the study drug. Infections and infestations (reported by seven patients) and GI events (reported by three patients) were the most frequently reported types of SAEs. The incidence of SAEs was similar during the open-label and after the RWP (four patients, 12.9% and five patients, 17.2%, respectively) and was slightly higher during the long-term extension phase (6 patients, 26.1%), as would be expected from the longer exposure. During the RWP, patients that stayed on maralixibat had a similar incidence of SAEs compared with patients on placebo (one participant, 7.7% and one participant, 6.3%, respectively).

B.2.10.5 Discontinuations and/or dose modifications due to adverse events

As demonstrated in Table 30, the incidence of AEs which led to permanent treatment discontinuation of maralixibat in the ICONIC study (39) was low, only occurring in six patients in total: 2 patients (6.5%) in the open-label phase, 2 patients (6.5%) after the RWP, and 2 patients in the long-term extension phase (8.7%). No such events occurred during the RWP.

In the open-label phase, one participant had an extradural haematoma and subdural haemorrhage, both of which were Grade 4 in severity and considered by the investigator to be unlikely/remotely related to the study drug. One participant had a staphylococcal infection of moderate intensity that was considered by the investigator to be possibly related to the study drug. In after the RWP, one participant had acute kidney injury that was Grade 4 in severity and considered by the investigator to be not related to the study drug, and one participant had blood bilirubin increase of severe intensity that was considered by the investigator to be not related to the study drug. No discontinuations in the after-randomisation withdrawal phase were due to the study drug. In the long-term extension phase, one participant had ALT of severe intensity that was considered by the investigator to be related to the drug, and one participant had increased ALT of moderate intensity that was considered by the investigator to be possibly related to the study drug.

Table 30: Incidence of AEs that led to permanent treatment discontinuation in the safety population (39)

	Open-label phase (≥Week 18)	RWP (Weeks 19- 22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)a
n (%)	MRX	MRX	Placebo	MRX	MRX

	n=31	n=13	n=16	n=29	n=23
Number of patients with at Least 1 AE	2 (6.5)	0	0	2 (6.9)	2 (8.7)
Staphylococcal infection	1 (3.2)	0	0	0	0
Extradural haematoma	1 (3.2)	0	0	0	0
Subdural haemorrhage	1 (3.2)	0	0	0	0
Increased blood bilirubin increased	0	0	0	1 (3.4)	0
Increased alanine aminotransferase	0	0	0	0	2 (8.7)
Acute kidney injury	0	0	0	1 (3.4)	0

Subjects who terminated the study during the OL phase are not included.
Adverse events were coded using MedDRA version 22.1.
Abbreviations: AE, adverse event; MRX, maralixibat; OL, open-label.

B.2.11 Ongoing studies

Patients from the IMAGINE, ICONIC, and IMAGINE II studies are being followed up in the ongoing open-label long-term safety study, MERGE (MRX-800) (72). Please see Table 31 for more details.

The safety and efficacy of maralixibat in infants (<12 months of age) with cholestatic liver disease, including but not limited to ALGS, is also currently being investigated in the RISE (MRX-801) study (73). Interim results from [redacted]. These interim results were used to support European marking authorisation (see Appendix C). Full results of RISE are expected in Q3 2024. Please see the tables below.

Table 31: Ongoing studies: MERGE (72)

Study	**MERGE (MRX-800)**
Study design	Multicenter, open-label extension study for the IMAGINE, ICONIC, and IMAGINE II studies This study is currently underway, with treatment continuing until the drug is commercially available or at the discretion of the sponsor.
Population	Those who completed the IMAGINE, ICONIC, and IMAGINE II studies without tolerance issues
Intervention(s)	Maralixibat (dose based on prior trial dose)
Comparator(s)	None
Outcomes	Primary objective: • Evaluate the long-term safety of maralixibat in subjects with cholestatic liver disease including, but not limited to, ALGS, PFIC, and biliary atresia Secondary objectives: • Evaluate the long-term effect of maralixibat on pruritus • Evaluate the long-term effect of maralixibat on sBA levels • Evaluate the long-term effect of maralixibat on total serum bilirubin • Evaluate the long-term effect of maralixibat on time to liver-associated outcomes (e.g., partial external biliary diversion [PEBD] or LTx) • Evaluate the long-term effects of maralixibat on growth • Exploratory objectives:

	• Evaluate the long-term effects of maralixibat on long-term healthcare utilisation • Evaluate the long-term effects or maralixibat on caregiver burden • Evaluate the efficacy of maralixibat on health-related QoL • Assess palatability of the maralixibat formulation (ALGS and PFIC)

***Abbreviations**: ALGS, Alagille syndrome; PEBD, partial external biliary diversion; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.*

Table 32: Ongoing studies: RISE (73)

Study	RISE (MRX-801)
Study design	Multicenter, open-label Phase 2 study This study is currently underway, with duration of treatment planned to be 13 weeks with a long-term follow-up period.
Population	Infants aged <12 months (weighing ≥2.5kg) with PFIC or ALGS
Intervention(s)	Maralixibat (≥400 µg/kg/day)
Comparator(s)	None
Outcomes	Primary objective: • Evaluate the safety and tolerability of maralixibat in infant patients with ALGS or PFIC Secondary objectives: • Evaluate the treatment effect of maralixibat on sBA levels • Evaluate the effect on liver enzymes (ALT, AST) and bilirubin • Evaluate the effect on lipid-soluble vitamins • Evaluate the pharmacokinetics of maralixibat in infant patients Exploratory objectives: • Evaluate the impact of maralixibat on pruritus in study patients with pruritus at baseline • Evaluate the effect of maralixibat on growth • Evaluate the impact of maralixibat on healthcare resource utilisation • Evaluate the impact of maralixibat on caregiver burden

***Abbreviations**: ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, Aspartate transaminase; PEBD, partial external biliary diversion; PFIC, progressive familial intrahepatic cholestasis; sBA, serum bile acid.*

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Summary of clinical efficacy

B.2.12.1.1 Maralixibat provides significant, durable, and clinically meaningful improved control of cholestasis for ALGS patients

Cholestasis is defined by a reduction in bile flow whereby bile acids are retained in hepatocytes. Through adaptive transport mechanisms that protect hepatocytes from the cytotoxic detergent effect of bile acids, some of these bile acids are eliminated from the hepatocyte and join the systemic circulation, leading to an increase in sBA and jaundice (elevated bilirubin) – key markers of cholestasis (3, 5, 6) Cholestasis is the first and most serious feature of ALGS for most patients: it is reported in 85% of children with ALGS and its first manifestation seen at a median age of 12 months (3, 5, 6). This retention of bile acids leads to a range of liver complications in ALGS

patients, including cirrhosis (46% of patients), ascites (57% of patients), PHT (40% of patients) (7, 8), and pruritus (9, 10).

Patients treated with maralixibat during the RWP of the ICONIC study (39) showed a significant reduction in sBA levels compared with placebo (-21.73 µmol/L [SE 43.125] vs. +95.55 µmol/L [SE 30.488], p=0.0464), which was maintained long-term (see Table 21). In addition, as shown in Figure 15 and Figure 16 respectively, there was an overall downward numerical trend in total and direct bilirubin levels over time vs. baseline with maralixibat treatment, which was significant at several timepoints – further supporting data on sBA levels which shows that maralixibat treatment is associated with long-term reduction in bilirubin and thus cholestasis.

Durable control of cholestasis was further supported by data from the ICONIC study (39) on markers of cholestatic pruritus and healthy bile acid synthesis, with total cholesterol and LDL-C, ALT, and ALP levels (68). ALT and ALP are also biochemical markers for cholestasis, although the levels of ALT are not increased to the same extent as ALP and other measures of cholestasis due to its role in the aetiology of the disease (69, 70). Patients treated with maralixibat during the RWP of the ICONIC study (39) showed no significant difference in ALT and ALP levels compared with placebo, as shown in Table 23. However, there was an overall downward trend in ALT and ALP levels over time versus baseline with maralixibat treatment. In addition, 7αC4 levels (a marker of healthy/non-cholestatic bile acid synthesis (71)) increased statistically significantly from baseline for most time points in the overall population (ITT).

Furthermore, these improvements in cholestasis management are substantiated by improvements in liver chemistry markers, with statistically significant reductions in ALP levels at Week 38 and Week 48 (39). Reduction in cholesterol should also

reduce the likelihood of wider complications of cholestasis in ALGS such as xanthoma development (17) and cardiovascular disease (18)

B.2.12.1.2 Maralixibat provides durable and clinically meaningful improved control of cholestatic pruritus for ALGS patients

Cholestatic pruritus is the main clinical manifestation of cholestasis, which can cause self-mutilation, skin lesions, and extensive scarring (3, 11). In addition, pruritus is the key indicator for LTx, with 69% of LTxs conducted in ALGS patients necessitated by intractable pruritus (4). ItchRO is a validated tool (3) designed to assess the impact of pruritus in children with cholestatic liver disease, including ALGS. Patients treated with maralixibat during the RWP of the ICONIC study (39) showed sustained ItchRO scores during the RWP, compared with the significant progression in ItchRO scores seen with placebo treatment (ItchRO scores +0.201[SE 0.2180] vs. +1.712 [0.2513], $p<0.0001$), which was maintained long-term. The same significant relationship between maralixibat prevention of progression of pruritus was also demonstrated for a clinician-based measure (CSS scores +0.4 [SE0.35] vs. +1.6 [SE0.41]) (39).

This significant long-term improvement in cholestatic pruritus is consistent with that for the markets of cholestasis at several timepoints as described above (i.e. sBA, bilirubin, LDL-C, cholesterol, ALT, ALP, and 7αC4) (39).

B.2.12.1.3 Maralixibat significantly improves wider manifestations of cholestasis, such as xanthomas, growth impairment, and fatigue

Cholestasis can also present with a range of wider extra-hepatic manifestations, for instance the development of xanthomas (3). Xanthomas are fatty deposits on the extensor surfaces which can impact patient survival (3), restrict the ability of patients to take part in physical activity (19), and impact physical appearance (19). This can lead to mockery or exclusion from activities and difficulty with school (especially in childhood), with a subsequent psychological impact on the patient (14, 19). Maralixibat treatment is associated with a significant reduction in xanthoma severity, as shown in the ICONIC study (Xanthoma Severity Score: -0.4 [SE 0.13] Week 48 vs. baseline, $p=0.0095$) (39).

Cholestasis-induced growth limitations can further impact the physical appearance of patients with ALGS, compounding the psychological impact of ALGS for patients (19). Maralixibat treatment is associated with a significant improvement in growth impairment over several timepoints, as demonstrated in the ICONIC study (see Figure 12) (39).

In addition, fatigue affects between 65-85% ALGS patients, leading to a reduction in participation in activities, difficulties with school, and impaired psychosocial and cognitive development (11, 19, 21-23). A statistically significant improvement in fatigue was seen for maralixibat at all time points in the ICONIC study (see Table 19), as measured by PedsQL multidimensional fatigue scale score (39).

B.2.12.1.4 Maralixibat improves overall quality of life of ALGS patients

Overall, these improvements in ALGS clinical manifestations result in a long-term improvement in the QoL of ALGS patients (39). Maralixibat treatment is associated with a long-term improvement in QoL of ALGS patients, as demonstrated by statistically significant improvement in the PedsQL total scores at several timepoints in the ICONIC study (see Table 20) (39). It is also anticipated that caregivers of ALGS patients would encounter a notable improvement in their QoL as the burdensome clinical manifestations that previously caused them stress and financial difficulties are alleviated (33).

B.2.12.1.5 Maralixibat significantly reduces the risk of liver-related events and death in ALGS patients

Furthermore, the likelihood of an ALGS patient experiencing a liver-related event is high: 62.1% of ALGS patients will receive a LTx by the age of 18, and 40-57% of ALGS patients will experience a liver complication such as cirrhosis, ascites, and PHT. The mortality rate in children with ALGS is 7.2% at age 5 and nearly 12% at age 18, with a median age of death of 2.6 years in the GALA cohort aged 12 months to 18 years (4).

Data from the GALA Cohort Comparison Study (40) demonstrates that maralixibat treatment is associated with a significant reduction in the risk of liver-related events

(HR=0.305 vs. GALA control group; 95% CI:0.189, 0.491; p<0.0001), as well as a significant reduction in the risk of LTx (HR=0.332 vs. GALA control group; 95% CI: 0.197, 0.559, p<0.0001) over 6 years.

B.2.12.2 Summary of clinical safety

The incidence of maralixibat-treated patients experiencing AEs during the ICONIC study (39) was similar during the open-label, after randomised withdrawal, and long-term extension phases, with the majority of patients (86.2 to 100%) experiencing AEs. However, only 34.8-38.7% of patients experienced AEs potentially related to maralixibat treatment. During the RWP, patients that stayed on maralixibat had a lower incidence of AEs and AEs potentially related to maralixibat treatment (53.8% and 7.7%, respectively) compared with patients on placebo (75% and 18.8%, respectively). The most frequently reported AEs (> 40% in total) were abdominal pain, diarrhoea, vomiting and fever, cough, and nasopharyngitis.

Most AEs experienced by maralixibat-treated patients across all phases of the ICONIC study (39) were of mild to moderate severity (Grades 1-2). No patients experienced a Grade 5 AE (i.e. there were no deaths associated with placebo or the study drug), and there was a greater incidence of life-threatening AEs (Grade 4) in the placebo-treated patients vs. the maralixibat-treated patients in the RWP: 1 patient (6.3%) versus 0 patients, respectively.

Treatment-related AEs with maralixibat in the ICONIC study (39) were moderately low, occurring in 12 patients in the open-label phase (38.7%), eight patients (34.8%) in the long-term extension phase, and only one patient (3.4%) in the after RWP. During the RWP, patients that stayed on maralixibat had a lower incidence of treatment-related AEs compared with patients on placebo: 1 patient (7.7%) versus 3 patients (18.8%), respectively.

In the ICONIC study (39) occurred in 14 patients treated with maralixibat, with a total of 33 SAEs. None of the SAEs were considered by the investigator to be related to the study drug. Infections and infestations (reported by seven patients) and GI events (reported by three patients) were the most frequently reported types of SAEs.

The incidence of AEs which led to permanent treatment discontinuation of maralixibat in the ICONIC study (39) was low, only occurring in four patients in total: 2 patients (6.5%) in the open-label phase, and two patients in the long-term extension phase (8.7%). No such events occurred during the RWP. Two patients (6.5%) did discontinue the study in the after RWP, but these were considered by the investigator to not be related to the study drug.

B.2.12.3 Strengths and limitations of the clinical evidence base

B.2.12.3.1 Strengths of the clinical evidence base for maralixibat

The efficacy and safety of maralixibat in ALGS has been established in the ICONIC study (39), a multicentre, double-blind, randomised Phase 2b study with open-label follow-up.

The randomised withdrawal design used in the ICONIC study (39) is an established alternative to the classic parallel group design in rare disease:

- A randomised withdrawal design allows for the reduction of the number of subjects exposed to a long-term therapy in case of lack of efficacy, as well as reducing the time that subjects receive placebo (74). This is important as it would be unethical to force patients to receive no treatment for long when their disease is so burdensome
- The efficiency of the randomised withdrawal design has been established across in several therapeutic areas, including in the field of paediatrics (75-77).
- Through the randomised withdrawal design, reliable efficacy results were obtained, as demonstrated by significant improvement vs. baseline within 3 weeks for pruritus (ItchRO(Observer) score), 12 weeks for sBA levels, and 18 weeks for other key endpoints such as: other measures of cholestasis (direct bilirubin, total cholesterol and LDL-C), another measure of pruritus (CSS), and measures of healthy bile acid synthesis (7αC4), height (z-scores), fatigue (PedsQL fatigue score), and patient QoL (PedsQL total score)
- The duration of the RWP in the ICONIC study (39) was sufficient to show clear statistically significant differences between maralixibat and placebo:

21.73 µmol/L [SE 43.125] reduction in sBA levels, compared with the 95.55 µmol/L increase seen with placebo [SE 30.488], p=0.0464).

- The randomised withdrawal design of the ICONIC study provided robust data with minimal risk of bias. Adequate concealment of treatment allocation and successful blinding was also achieved during the RWP, (39) wherein patients, investigators, study staff, and the sponsor were blinded to the study drug assignment. The patient demographics and disease characteristics and history at baseline of the patients who took part in the ICONIC study were generally balanced.

In addition, the sample size of the ICONIC study (39) was demonstrated to be of adequate size for a rare disease such as ALGS (11): primary and secondary efficacy endpoints were statistically significant and consistent across all prespecified analyses, and 84% of participants saw clinically meaningful improvements in pruritus, maintained for 4 years.

Further, the overall duration of the ICONIC study was sufficient to provide long-term safety and efficacy data for up to 204 weeks (39). This was shown by maintenance of a significant improvement from baseline at several timepoints from weeks 18-204 for measures of cholestasis (sBA, total and direct bilirubin, total cholesterol, LDL-C, ALT and ALP), healthy bile acid synthesis (7αC4), pruritus (ItchRO(Observer) score, and height (z-scores). In addition, a significant improvement from baseline was maintained for most timepoints from Week 18-100 for another measure of pruritus (CSS), as well as measures of fatigue (PedsQL fatigue score), and patient QoL (PedsQL total score).

To validate the efficacy from the ICONIC study, the GALA Cohort Comparison Study was conducted (40). This was a cohort comparison conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry. The comparison study aimed to assess the impact of long-term maralixibat treatment on clinical outcomes in patients with ALGS. This evaluation involved a comparison between the maralixibat-treated cohort and the control group from the GALA study.

The GALA Cohort Comparison Study (40) provides a historical control comparison, which has been proven to be useful in cases when there are ethical concerns in recruiting patients for control arms in life-threatening diseases (78). To further support its robustness as a historical control comparison, the GALA Cohort Comparison Study was conducted in line with the draft Food and Drug Administration (FDA) Guidance, Rare Diseases: Natural History Studies for Drug Development (79).

The GALA Cohort Comparison Study (40) provides robust data, with the GALA registry being the largest global ALGS registry, with a total of 1543 children between the ages of 12 months to 18 years (4). For the natural history control comparison, an independent statistician followed a stepwise selection process to balance the patients from the GALA registry with those in the maralixibat cohort with respect to the important baseline covariates: age at inclusion and total bilirubin. Distribution between the two cohorts was assessed for critical factors, and balance was assessed by examining a standardised differences plot (Figure 7) which summarised differences between the treated and control groups. None of the standardised mean differences exceeded the upper limit of 0.25 for critical factors, meaning that the two cohorts were appropriately matched in the study (4).

The duration of the GALA Cohort Comparison Study (40) was sufficient to show clear statistically significant differences between maralixibat and the GALA control group in terms of EFS over 6 years of follow-up (HR=0.305; 95% CI:0.189-0.491; p<0.0001).

In addition, the GALA Cohort Comparison Study (40) provides data with minimal risk of bias: the cohorts were selected appropriately and distribution between groups was assessed for critical factors, including age, bilirubin, GGT, and ALT. Balance was assessed by examining a standardised differences plot that summarised differences between the treated and control groups. Per the SAP, the standardised mean differences must not have exceeded the upper limit of 0.25. None of the standardised mean differences exceeded the upper limit of 0.25 for critical factors. In addition, data was presented controlling for a range of critical factors, including the primary endpoint which was controlled for age, sex, and bilirubin and ALT levels.

Further, the findings from the ICONIC study (39) and the GALA Cohort Comparison Study (40) are relevant to the real-life ALGS population, providing data for the key clinical events experienced by ALGS patients (liver decomposition, SBD, LTx and death) (67); sBA, total and direct bilirubin, cholesterol, LDL-C, ALT, ALP, and 7αC4 levels as measures of cholestasis and healthy bile acid synthesis (5, 9, 10, 71); ItchRO as a measure of the impact of pruritus in children with cholestatic liver disease; and growth and xanthoma severity as measures of the impact on wider manifestations of cholestasis (6). Management of these complications is important for patient QoL, as demonstrated by the PedsQL total scores from the ICONIC study (39), wherein the improvement was statistically significant at most time points. In addition, a statistically significant improvement in fatigue was seen for maralixibat at all time points, as measured by PedsQL multidimensional fatigue scale score. Chronic fatigue in ALGS can lead to reduced activities and difficulty with school and impaired psychosocial and cognitive development (11, 19, 21, 22).

B.2.12.3.2 Limitations of the clinical evidence base for maralixibat

The duration of the placebo-controlled period in the ICONIC study was limited to 4 weeks. However, long-term comparisons against a control group would not be possible in a randomised, placebo-controlled study in this setting. Such a burdensome condition, the risks of forgoing treatment that a patient would otherwise receive outside of a study are so high that it would not be ethical to ask participants to accept them (80). Historical control comparison is useful in such cases when there are ethical concerns in recruiting patients for control arms in life-threatening diseases (78), which is why the GALA Cohort Comparison Study was conducted.

The sample size of the ICONIC study was limited, but this is to be expected from such a rare disease (11). Due to the severity of ALGS, the minimisation of both the number of subjects on placebo and the length of the placebo period as part of an effective and rigorous study design is deemed to be ethically correct.

B.2.12.4 Conclusion

The clinical effectiveness of maralixibat in reducing sBA levels, bilirubin and pruritus in ALGS patients has been investigated through the Phase 2 ICONIC study (39)

including open-label follow-up. Data from this study showed that maralixibat treatment is associated with:

- A significant and durable reduction in sBA levels (-21.73 µmol/L [standard error (SE) 43.125]) vs. +95.55 µmol/L ([SE30.488], p=0.0464) vs. placebo. In addition, as shown in Figure [redacted] and Figure 16, there was a significant reduction in direct bilirubin levels over time at several timepoints. Increased sBA levels and jaundice (elevated bilirubin) are known markers of cholestasis (the retention of toxic bile acids in the liver), which can lead to cirrhosis, PHT, and ascites, as well as severe and debilitating pruritus (7, 8, 11).
- A significant improvement in other markers of cholestasis and healthy bile acid synthesis at several timepoints, including total cholesterol, LDL-C, 7αC4, ALP, and ALT levels.
- Sustained ItchRO scores across the RWP, which differed significantly from placebo treatment (ItchRO scores +0.201[SE 0.2180] vs. +1.712 [SE 0.2513], p<0.0001). Significant long-term improvement was also shown in ItchRO scores, which is consistent with improvements shown for cholestasis markers (sBA, bilirubin, LDL-C, cholesterol, 7αC4, ALP, and ALT). ItchRO is a validated tool (3) designed to assess the impact of pruritus in children with cholestatic liver disease, including ALGS. Pruritis is the main clinical manifestation of cholestasis and has a profoundly negative impact on patient QoL through self-mutilation, skin lesions, and extensive scarring (3, 11). Cholestatic pruritus is also the key indicator for LTx in ALGS patients (4).
- Sustained CSS scores (a clinician-based measure of pruritis) across the RWP, which differed significantly from placebo treatment (CSS scores +0.4 [SE0.35] vs. +1.6 [SE0.41]).
- Significant improvement in extra-hepatic manifestations of cholestasis, including the severity of xanthomas (Xanthoma Severity Score from baseline to Week 48, ITT -0.4 [SE 0.13], p=0.0095), growth (z-score data at several timepoints), and fatigue (PedsQL multidimensional fatigue scale score data at several timepoints.
- The wider extra-hepatic manifestations of cholestasis can have an impact on patient survival (3) and the physical appearance of patients (with subsequent

psychological impact) (14, 19), as well as impacting the ability of patients to take part in activities and schooling – leading to impaired psychosocial and cognitive development (11, 19, 21, 22).

- Significant long-term improvement in QoL as measured by PedsQL total scores at several timepoints (39). ALGS patient QoL is often impacted by sleep disorders resulting in reduced school activities and impaired psychological and cognitive development (11, 19, 21, 22). Symptoms associated with ALGS which impact physical appearance, such as pruritus, growth retardation, xanthomas, and facial dysmorphism, can lead to mockery or exclusion from activities, especially in childhood. This heavy psychological burden can eventually lead to depression in ALGS patients and a decrease in psychosocial integration, which can significantly affect their independence, self-esteem, and development (19).
- A low frequency of high-grade or treatment-related AEs as well as SAEs, proving to be generally well-tolerated in ALGS patients.

The GALA Cohort Comparison Study (40) was a cohort comparison conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, as well as a historical international cohort of standard-care treated patients from the GALA clinical research registry, providing a historical control comparison for maralixibat in ALGS patients.

Data from the GALA Cohort Comparison Study (40) demonstrates that: maralixibat treatment is associated with (40):

- A significant reduction in the risk of liver-related events over 6 years compared to the GALA control group (HR 0.305, 95% CI: 0.189-0.491; p<0.0001)
- A significant reduction in the risk of LTx over 6 years vs. the GALA control group (HR 0.332, 95% CI: 0.197-0.559; p<0.0001)
- The likelihood of an ALGS patient requiring a LTx or developing a liver complication is high. 62.1% of ALGS patients will receive a LTx by the age of 18, and 40-57% of ALGS patients will experience a liver complication such as cirrhosis, ascites, and PHT. Further, the mortality rate in children with ALGS is

7.2% at age 5 and nearly 12% at age 18, with a median age of death of 2.6 years in the GALA cohort aged 12 months to 18 years (4).

As such, maralixibat has the potential to mitigate a wide range of complications associated with cholestasis, including those that affect survival and patients' QoL. The positive outcomes associated with disease management due to maralixibat treatment can also substantially improve the QoL of caregivers, who often endure disrupted sleep, face limitations on their time for both parenting and regular activities due to their child's care needs, and frequently experience anxiety because of their child's condition (33).

B.3 Cost-effectiveness

The company would like to make it known that commercial surgery negotiations with NHS England are ongoing to identify a commercially viable agreement for maralixibat, at a cost-effective price. The goal is to complete negotiations ahead of a final decision from NICE.

Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

B.3.1 Published cost-effectiveness studies

The SLR, conducted in May 2023, identified no publications that met the inclusion criteria for review question three: ‘What cost-effectiveness analysis evidence is available for treatment of ALGS?’. Therefore, no comparison of methods and results can be provided. A previous single technology appraisal was submitted to NICE for odevixibat in the treatment of PFIC (an analogous indication) (81), and is used as precedent for the modelling.

B.3.2 Economic analysis

Summary

- A cost-utility analysis is presented for maralixibat in ALGS, using clinically meaningful health states which capture the progressive and debilitating nature of the condition.

- The benefit of maralixibat is captured primarily in the delayed time to progression to progressive stages of liver disease and LTx, which is associated with long-term costs and increased risk of acute mortality.
- The comparator for the analysis is standard of care, which consists of off-label anti-pruritic medication, and is associated with low rates of response. Another surgical procedure (SBD) is explored in scenario analysis, as it is reported in the literature, but not routinely used in clinical practice.

B.3.2.1 Patient population

Maralixibat is indicated for the treatment of cholestatic pruritus in ALGS in patients two months or older and was designated an orphan medicine by the MHRA in 2023 (See Appendix C). This is the population considered in the cost-effectiveness analysis, which is consistent with the population examined in the ICONIC trial and GALA study, and reflects the population covered by the EMA marketing authorisation as well as the final scope.

B.3.2.2 Model structure

The model is constructed as a multi-state Markov model, with the following health states:

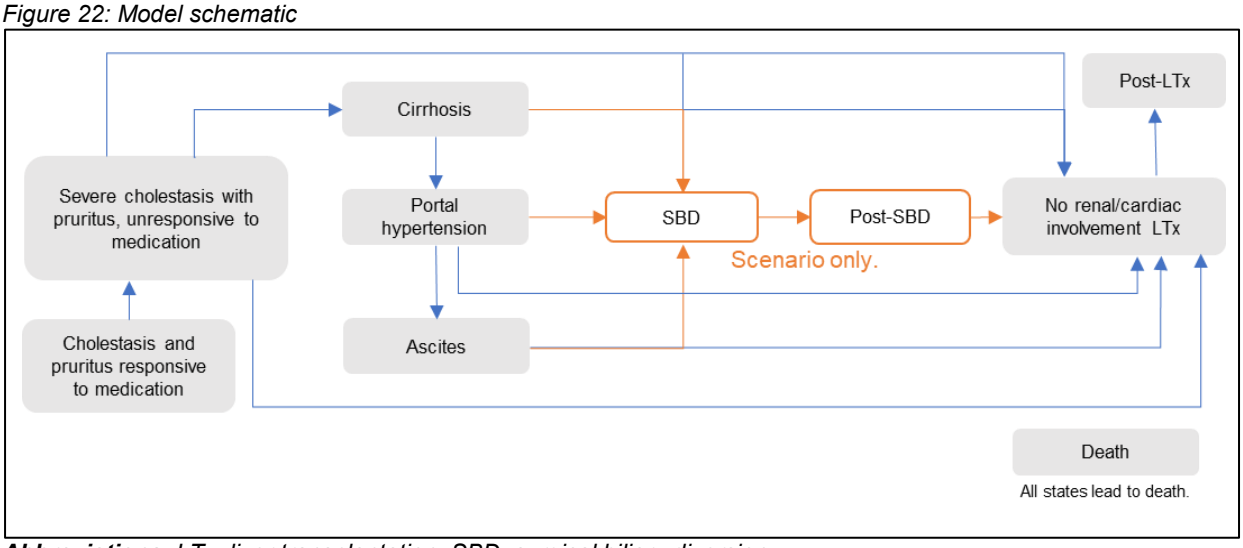
1. Cholestasis and pruritus, with response to treatment
2. Cholestasis and pruritus, with loss of response to treatment
3. Cirrhosis
4. Portal hypertension (PHT)
5. Ascites
6. Surgical biliary diversion (SBD) (scenario only)
7. Post-SBD (scenario only)
8. LTx (without cardiac or renal involvement, with a proportion of patients remaining in cycle to capture re-transplant).
9. Post-LTx
10. Death (absorbing state)

Health states were informed by the literature on ALGS, as well as being validated by a clinical expert (see Appendix N) and are considered to reflect the progressive and debilitating nature of the disease.

ALGS is a multi-system and multi-organ disease which impacts the heart and kidneys in addition to the liver (8). The involvement of multiple organs results in a proportion of patients not being eligible for LTx, as described in the literature (11, 32). As such, individuals with severe cardiac or renal complications are not eligible for LTx in the model. In the model base-case, a conservative estimate of 30% was used, which reflects the proportion of ALGS patients in severe cardiac and/or renal involvement, but estimates of 76%–94% are reported in the literature and used in scenario analysis (82).

The cycle length chosen is 12 weeks, which aligns with how quickly maralixibat-treated patients are expected to respond (as confirmed by a clinical expert, see Appendix N) and the discontinuation recommendation in case of non-response in the SmPC (see Appendix C). Although clinical data were available for a longer duration as part of the ICONIC study, 12-week results were used to avoid any bias in the estimation of efficacy of maralixibat, as the full 48-week study design included a RWP prior to the long-term exposure. However, a scenario is presented using long-term data, as this was considered appropriate by a clinical expert (see Appendix N). A 12-week cycle length was therefore selected to capture all progression events of ALGS over time. Half-cycle correction is applied using the lifetable method, where the time in a given cycle is estimated by taking the average of the number of patients at the start and end of the cycle. The model's structure is presented in Figure 22.

Figure 22: Model schematic



***Abbreviations**: LTx, liver transplantation; SBD, surgical biliary diversion.*

The model was developed in Microsoft Excel and captures the differences in costs and health outcomes between maralixibat and SoC. Disease progression is driven by patients' sBA response. Treatment with maralixibat is assumed to slow down the progression of ALGS to severe stages of liver disease (cirrhosis, PHT, and ascites), and eventually surgery (SBD or LTx). Cholestasis is defined by a reduction in bile flow whereby bile acids are retained in hepatocytes. Through adaptive transport mechanisms that protect hepatocytes from the cytotoxic detergent effect of bile acids, some of these bile acids are eliminated from the hepatocyte and join the systemic circulation leading to an increase in sBA (3, 5, 6). An sBA response was therefore assumed to lead to a corresponding response in pruritus (35, 83). Once progressed to 'unresponsive to medication', patients' liver disease progresses until indicated for a LTx.

Surgical biliary diversion is rarely used (reported in 5% of children with ALGS (4)), which may be in part due to the fact that only those patients with severe pruritus which is not effectively managed with medications are eligible ((4), see Appendix N). SBD has been reported to cause relief from severe pruritus (84), and is therefore included in a scenario analysis. However, since SBD is targeted at interrupting the enterohepatic circulation and the bile duct paucity associated with ALGS can result in less bile reaching the bowel, SBD is generally less effective in ALGS than in other cholestatic diseases (11). In the model base-case, the transition to SBD is therefore set to 0%. A scenario explores SBD from pre-LTx states, using data in PFIC (85). A

number of intermediate and sequential liver disease states are included in the model to capture the progressive nature of ALGS (cirrhosis, PHT, and ascites), which are documented in the literature and were validated by a clinician (see Appendix N) (8, 12). The progression of ALGS to cirrhosis, PHT, and ascites is documented in the literature (8). These health states are associated with increasingly poorer health outcomes as patients' liver disease progresses, with the only treatment option being LTx – ascites and PHT are complications of cirrhosis, which are among the primary causes of death in patients with end-stage liver disease (86, 87). Although HCC is reported in the literature as a possible outcome of ALGS, it is not well documented, and no data were identified to parameterise this transition (88).

A proportion of patients require a re-transplant, which is assumed to occur once in the subsequent cycle to their initial LTx (89).

There are no NICE technology appraisals for the same indication, although one appraisal has been published for PFIC (HST17) (81). Although ALGS and PFIC are caused by different pathogenic variants, the diseases and treatment options are comparable. Unlike PFIC, ALGS causes additional cardiac and renal complications, which are captured in the model, whereby a proportion of patients are not indicated for LTx given the severity of their cardiac involvement (30% in the base-case (8)), which was verified by a clinician (Appendix N).

Table 33 summarises the key inputs and assumptions used in the economic model.

Table 33: Features of the economic analysis

	Previous evaluations	**Current evaluation**	
Factor	**HST 17**	**Chosen values**	**Justification**
Time horizon	Lifetime.	Lifetime (maximum age of 100).	MRX is expected to be administered for a lifetime, and the benefits of treatment are expected to be applicable to a lifetime horizon. This is in line with the NICE Reference Case.
Treatment waning effect	Only discontinuation is modelled.	Only discontinuation is modelled.	Only discontinuation is modelled as no waning in treatment efficacy is expected.
Source of utilities	Vignette study + literature for disutilities.	A vignette study is used for patients and caregiver QoL (EQ-5D-5L).	Although ICONIC collected PedsQL scales, these could not be mapped to EQ-5D due to patient age being <2 months and school functioning scales not being collected as a result. The chosen source for utility values meets the NICE Reference Case criteria.
Source of costs	Perspective of the NHS and PSS in England and Wales, with a scenario	Perspective of the NHS and PSS in England and Wales.	All costs relate NHS and PSS resources and are valued using the prices relevant to the NHS and PSS.

Factor	Previous evaluations	Current evaluation	
	HST 17	Chosen values	Justification
	including wider societal costs.		

Abbreviations: *HST, highly specialised technology; MRX, maralixibat; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PEBD, partial external biliary diversion; PSS, Personal and Social Services; QoL, quality of life.*

B.3.2.3 Intervention technology and comparators

There are currently no licensed treatments for ALGS, and the comparator in the economic analysis is SoC. This primarily includes off-label oral drug treatments to optimise nutritional intake and manage cholestasis-related symptoms such as FSV deficiency and pruritus: UDCA, rifampicin, and phenobarbital are included in the model (90). Although these treatments are usually used sequentially, a simplification was made in the model to avoid the additional complexity of modelling sequential lines of treatment, which was not expected to have a significant impact on costs. The cost is applied as a lump sum each cycle. All patients in the SoC arm will eventually progress to advanced stages of liver disease and surgery, limited only by patient life expectancy. SBD is part of the treatment pathway for ALGS, although not all patients undergo the procedure before progressing to LTx. Biliary diversion is not included in the base-case, but when it is used in a scenario, it is available to patients in cirrhosis, PHT, and ascites health states, as well as non-responders.

B.3.3 Clinical parameters and variables

Summary

- Clinical parameters used in the economic evaluation are sourced from the ICONIC study and GALA and supplemented with estimates from published literature.
- Parameters relating to baseline characteristics, treatment response, and discontinuation were taken from the ICONIC study and GALA, whereas transitions to progressive stages of liver disease and mortality are informed by the literature.
- The mortality benefit in maralixibat is modelled both indirectly by proxy of reduced sBA, and directly by assuming a mortality benefit equivalent to the comparison of maralixibat and GALA.

The clinical data used in the economic evaluation include:

- Patient and general population characteristics
- Response and discontinuation to treatment
- Transition probabilities to and from cirrhosis, PHT, and ascites

- Transition probabilities to and from LTx and SBD
- Mortality

However, it is important to note that given the heavy burden of ALGS, not all impacts are captured in these parameters (further detail is given in Section B.3.12). This is particularly true in relation to caregiver outcomes, long-term career and productivity outcomes, and the emotional and mental health of patients and caregivers (91).

B.3.3.1 Patient characteristics

The baseline age applied in the model is two months old, consistent with the indication for maralixibat. A weight distribution is applied to the model and used in the calculation of drug doses. Weight data are taken from the World Health Organization and the Office for National Statistics (ONS), and weight is set to the 5th percentile of the general population. Patients in ICONIC were shorter and lighter than the general population (as is expected in ALGS), which is explained by their difficulty digesting fats and absorbing fat-soluble vitamins (39). This is demonstrated by a baseline z-score of -1.7 and corresponds to the 5th percentile weight band. The proportion of female patients is 39.7% as reported in the ICONIC study. An extreme scenario is performed on the 75th percentile weight band.

B.3.3.2 Transition probabilities

A summary of the transition probabilities used in the model are reported in Table 34.

Table 34: Transition probabilities derived and used in the cost-effectiveness model (CEM)

Transition	Reported value	Value (12-week cycle)	Source
Response to MRX	[redacted]	[redacted]	ICONIC (39)
Response to SoC	–	0%	Assumption
Discontinuation of MRX	2/31 at 18 weeks	4.51%	ICONIC (39)
Discontinuation of SoC	[redacted]	[redacted]	Clinical opinion (Appendix M)
Unresponsive → Cirrhosis	41/94 at 10 years	1.31%	Lykavieris (12)
Cirrhosis → PHT	40% at 30 years	0.39%	Kamath (8)
PHT → ascites	36% at 30 years	0.34%	Kamath (8)
Unresponsive → LTx	47% at 4 years	3.58%	Quiros-Tejeira (92)
Cirrhosis → LTx	7.27% at 1 year	1.72%	Hagstrom (93)
PHT → LTx	23% at 1 year	5.9%	Krasinskas (94)
Ascites → LTx	–	5.9%	Assumed equal to PHT→ LTx
Post-SBD → LTx	0% in the base-case 36% at 18 years	0% or 0.6%	NAPPED (95)
LTx → LTx (re-transplantation)	22% at 1 year	5.55%	Adam (89)
Unresponsive → SBD	0% in the base-case	0% in the base-case 6.38% in a scenario	Foroutan (85)
Cirrhosis → SBD			

Transition	Reported value	Value (12-week cycle)	Source
PHT → SBD	50% at 29 months in a scenario		
Ascites → SBD			

Abbreviations: *CEM, cost-effectiveness model; PHT, portal hypertension; LTx, liver transplantation; MRX, maralixibat; SBD, biliary diversion; SoC, standard of care*

Transition probabilities are described in further detail below. Where possible, Kaplan-Meier curves were digitised and an exponential rate fit to the last reported value to derive a per-cycle probability of transitioning from one state to the next. All individuals start in the 'response' state in the first cycle. All states can transition to mortality. Rationale for the selected studies for maralixibat is provided in Table 4.

Response to maralixibat is derived from ICONIC;

- Response to maralixibat is derived from the ICONIC 12-week results, using a patient-level data analysis of patients who had an sBA response of >50% reduction at 12 weeks ([redacted]) and a scenario using the ItchRO (Obs) change from baseline ≤-1.0 at 18 weeks (52.9% probability per cycle). Another scenario is presented using long-term (48-week) data ([redacted] at 48 weeks, [redacted]% per cycle).
- Patients who do not respond after 3 months discontinue treatment with maralixibat, as per the SmPC recommendation (see Appendix C). Discontinuation is assumed equivalent to the proportion of patients who discontinued maralixibat due to AEs in the first 18 weeks of LUM001-304, in the first model cycle, which is equivalent to a discontinuation probability of 2/31, 4.51%. Following the first cycle, the probability of discontinuation is applied based on the longer-term follow-up data from ICONIC (18-week discontinuation, only considering discontinuations in the maralixibat arm in the RWP to avoid confounding due to discontinuations from placebo). This captures both patients discontinuing due to AEs over a long-term period and those declining to proceed into the next phase of the study, under the assumption that withdrawal of consent to participate is likely to reflect that a patient no longer responding to treatment. This approach differs from treatment efficacy, where 12-week response is used to determine which patients remain on treatment – long-term discontinuation is considered in the model, whereby effective efficacy of treatment with maralixibat varies in the model over time as patients discontinue.

- Response to SoC is assumed to be zero. As is described in the literature, off-label drugs are only used symptomatically and do not alter the mechanism of the disease (3). Furthermore, maralixibat is expected to be used in patients who do not respond to SoC; the relevant comparator population is therefore one which does not respond to off-label drugs.

Progression from unresponsive to:

- **SBD** (in a scenario only) is derived from the literature in PFIC (Foroutan (85)), using 29-month outcomes in partial internal biliary diversion.
- **Cirrhosis** is derived from the literature in ALGS (Lykavieris (12)).
- **LTx** is derived from a study in ALGS (Quiros-Tejeira (92)).

Progression from cirrhosis to PHT and PHT to ascites is derived from a study in ALGS (Kamath (8)). Progression from cirrhosis, PHT, and ascites to LTx is taken from the literature in non-ALGS populations (Hagstrom (93), Krasinskas (94)). Progression from post-SBD to LTx is derived from a registry in PFIC, and was considered a reasonable proxy for SBD outcomes in ALGS (NAPPED (95)). The outcomes used were specifically in bile salt export pump (BSEP) patients, which is a 'milder' form of PFIC and responds better to LTx (in contrast to PFIC 1, which has poorer post-LTx outcomes). Because ALGS patients are expected to generally respond well to LTx, this estimate was considered reasonable. A small proportion of patients are expected to require a second transplant after rejection – a large cohort study in European patients was used to inform the proportion of re-LTx (Adam (89)).

B.3.3.3 Mortality

Mortality transitions are summarised in the table below.

Table 35: Summary of mortality transitions

Mortality from state:	Reported value	Per-cycle value	Source(s)
Responsive to medication	HR-adjusted (0.305)	0.41%	Kamath et al (8) GALA (40)
Unresponsive to medication	18-year mortality: 9.3%	Dependent on distribution, log-logistic in base-case	Vandriel et al (4)
Cirrhosis (compensated)	10-year mortality: 40%	1.2%	D'Amico et al (96)
PHT	5-year mortality: 48%	2.9%	Santambrogio et al (97)
Ascites	5-year mortality: 4.5%	4.5%	Tonon et al (98)
SBD/post-SBD	-	Dependent on distribution	Assumed identical to unresponsive mortality
LTx	1-year mortality: 29%	5.3%	Emerick et al (7)

Mortality from state:	Reported value	Per-cycle value	Source(s)
Post-LTx	Pooled 5-year survival is 80%	1.02%	Hou et al (99)

Abbreviations: *HR, hazard ratio; LTx, liver transplantation; PHT, portal hypertension; SBD, surgical biliary diversion.*

Risk of mortality for children with ALGS who presented with cholestasis at birth was reported in the GALA study for the first 18 years of life (4). Here, risk of death without transplantation was 6.1% (95% CI, 4.7-7.7), 7.8% (95% CI, 6.1-9.8), and 9.3% (95% CI, 7.1-11.8), at 5, 10, and 18 years, respectively.

Patient-level data were reconstructed based on a digitisation of published cumulative incidence plots, from which the risk of death from the GALA study was calculated, assuming absence of competing risks. This data, alongside the reported number of patients at risk, was then used as inputs for an iterative K-M estimation algorithm as described in Liu et al (2022) (100), to reconstruct patient-level time-to-event data.

Accuracy of the reconstructed patient-level data against the extracted data coordinates was assessed via a series of summary statistics, including the root mean square error, measuring the difference in survival probabilities calculated using reconstructed data, and the extracted data coordinates, as well as the mean absolute error and the max absolute error. As a guideline, root mean square error <0.05 and mean absolute error <0.02 indicate that the extracted data coordinates are sufficiently well-captured by the reconstructed patient-level data (100). The Kolmogorov-Smirnov test statistic was also calculated (Table 36).

Table 36: Summary statistics of accuracy assessment for reconstructed patient-level data

Summary statistic	Value
Root mean square error	0.001
Mean absolute error	0.001
Max absolute error	0.001
Kolmogorov-Smirnov test statistic (p-value)	0.11 (0.996)

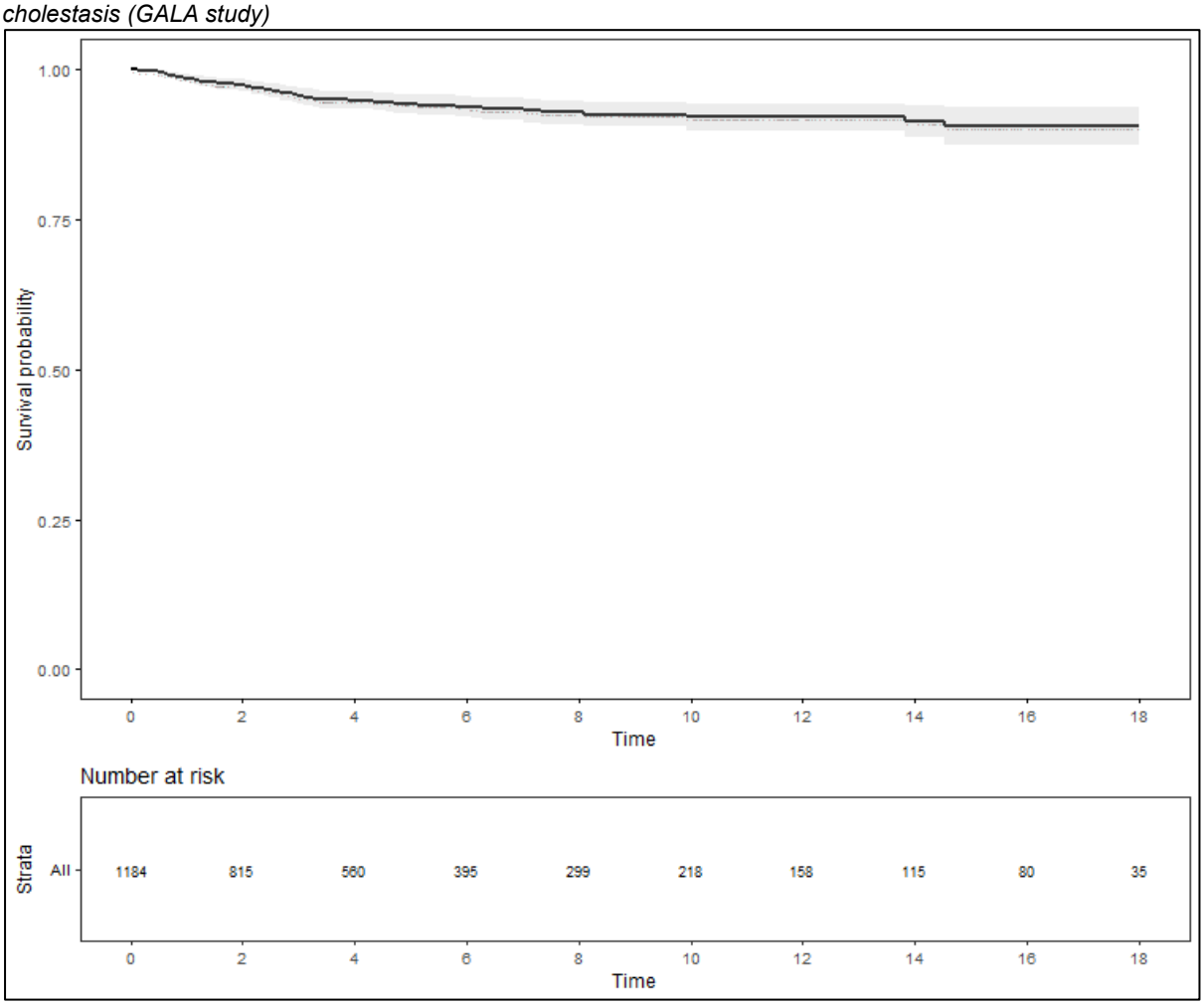
Individual parametric models were used to extrapolate the reconstructed patient-level data to the end of the model horizon (100 years). In accordance with NICE DSU Technical Support Document (TSD) 14 (101), the following standard parametric functions were considered: Exponential, Weibull, Gompertz, log-logistic, log-normal, Gamma, and Generalised Gamma.

Goodness of fit for each of the candidate distributions was assessed based on Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores,

with smaller values indicating better fit. Model fit was also assessed via visual inspection against the Kaplan-Meier plot.

Figure 23 shows a Kaplan-Meier plot for the survival of children with ALGS who presented with neonatal cholestasis, based on reconstructed patient-level data from the GALA study. The survival probability at 5, 10, and 18 years was, 94.3% (95% CI, 92.7-95.9), 92.1% (95% CI, 89.9, 94.3), and 90.5% (95% CI, 97.4, 93.7), respectively. The RMSE and mean absolute error of difference between the survival probabilities, calculated using reconstructed patient-level data and the extracted data coordinates from published mortality plots, were 0.001.

Figure 23: Kaplan-Meier plot of the survival probabilities of children with ALGS who presented with neonatal cholestasis (GALA study)



Abbreviations: *ALGS, Alagille syndrome.*

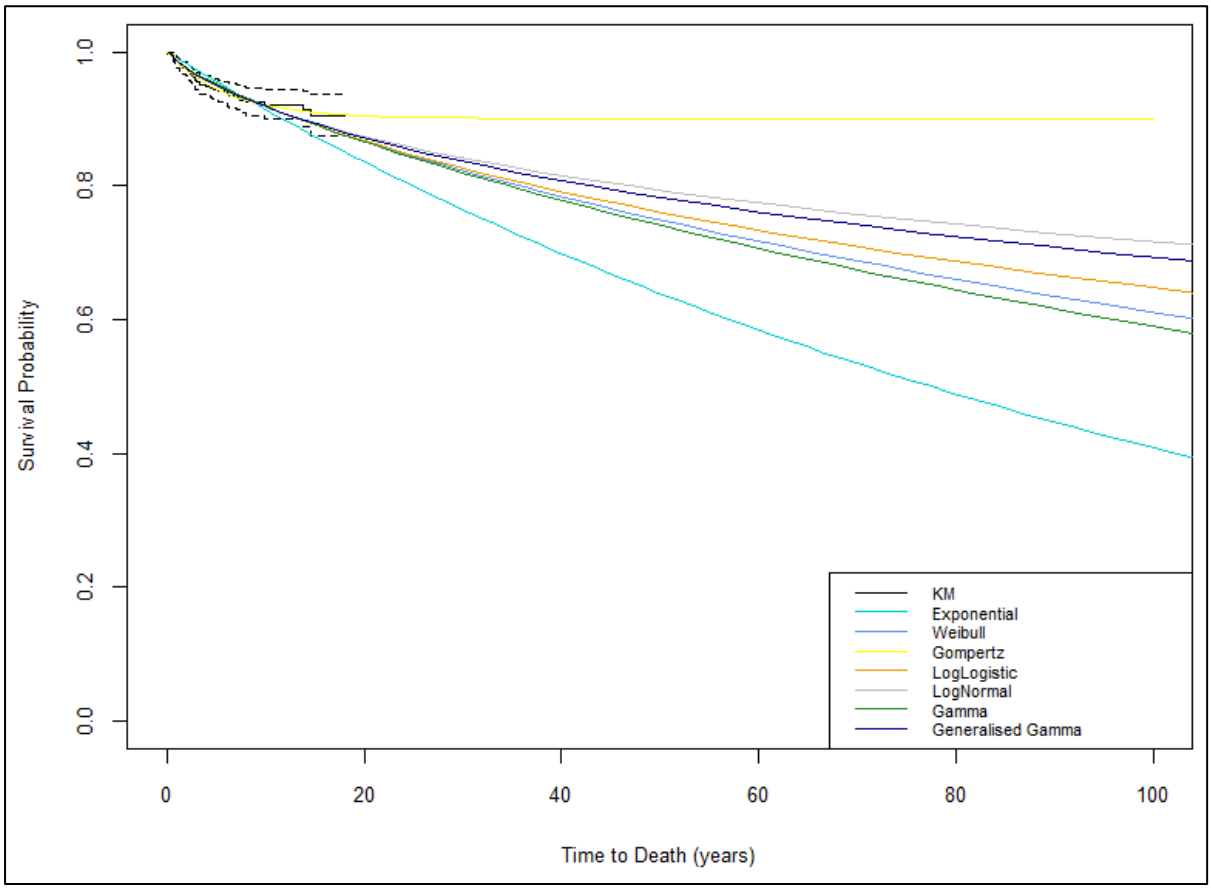
Parametric extrapolations of the reconstructed patient-level data are shown in Figure 24, with goodness of fit tests (AIC and BIC values), presented in

Table 37. Survival probabilities at 10, 18, 50, and 100 years, based on the parametric extrapolations are shown in Table 38, together with the predicted median survival.

All candidate distributions fit the reconstructed patient-level data well up to 20 years. The trajectories of the curves then varied quite substantially, with the exponential model producing the most conservative estimate of survival, and Gompertz the least conservative. The best statistical fit (i.e., the lowest AIC and BIC values) was achieved by the Gompertz model. However, when plotted in the model including mortality from all other subsequent states, all distributions overlapped; when presented with the curves, a clinical expert confirmed the range was broadly representative of expected outcomes. As such, the midpoint curve was selected in the base-case (log-logistic).

Based on a visual inspection of the plots, none of the parametric extrapolations produced reasonable estimations of survival for children with ALGS, with predicted median survival times in most instances being larger than average life expectancy in the UK (82 years). As a result, these models were used to predict disease-specific mortality, which was combined with lifetable estimates to generate a combined estimate of all-cause mortality in this patient population. The potential for double counting is considered to be minimal, with mortality rates being extremely low in the first 18 years of life for the general population. Because ALGS is an extremely rare condition, the impact of ALGS related mortality already present in the life tables is negligible.

Figure 24: Parametric extrapolations of the survival of children with ALGS who presented with neonatal cholestasis



Abbreviations: *ALGS, Alagille syndrome; KM, Kaplan-Meier.*

Table 37: Goodness of fit test for parametric survival extrapolation

Distribution	AIC	Rank	BIC	Rank
Exponential	665.1	7	670.1	**4**
Weibull	660.7	6	670.8	**5**
Log-normal	654.3	2	664.4	**2**
Log-logistic	660.0	4	670.0	**3**
Gompertz	651.0	1	661.1	**1**
Gamma	661.1	5	671.2	**6**
Generalised gamma	658.0	3	673.2	**7**

Abbreviations: *AIC, Akaike information criterion; BIC, Bayesian information criterion.*

Table 38: Survival probabilities at different ages

Distribution	Year 10	Year 18	Year 50	Year 100	Median survival (years)
Observed survival [a]	92.1%	90.5%	-	-	**NE**
Exponential	91.4%	85.1%	63.9%	40.9%	**77.4**
Weibull	92.0%	87.6%	74.9%	61.1%	**156.0**
Log-normal	91.8%	88.1%	79.3%	71.6%	**497.4**
Log-logistic	91.9%	87.7%	76.1%	64.8%	**216.6**
Gompertz	92.0%	90.6%	90.0%	90.0%	**NE**
Gamma	92.0%	87.6%	74.1%	59.0%	**138.8**
Generalised Gamma	91.8%	88.0%	78.3%	69.6%	**339.0**

[a] *observed survival is based on reconstructed patient-level data form the GALA study*
Abbreviations: *NE, not estimable.*

From the cirrhosis health state, mortality is derived from a natural history study of survival in cirrhosis (D'Amico et al (96). The Kaplan-Meier curve for compensated

cirrhosis was digitised and an exponential rate applied to extrapolate the curve across the model time horizon, resulting in a 10-year probability of 40%, or a per-cycle probability of 1.2%.

Mortality in PHT is derived from a study in hepatocellular carcinoma (HCC) (Santambrogio et al (97), which reports survival in patients with and without PHT. The patient population of this study includes patients undergoing hepatic resection for HCC, which is reported as a possible outcome for patients with ALGS (82). It was therefore considered an appropriate population to model mortality from PHT. However, incidence and outcomes of HCC in ALGS are poorly reported and therefore could not be included in the model. The study used was included in an SLR and meta-analysis (102) which reported 5-year survival estimates ranging from 28.9 to 56%. A midpoint of 5-year overall survival (OS) was selected from the reported sources as 47.7%, which resulted in a per-cycle probability of 3.3%.

Mortality in ascites is derived from a study in cirrhotic patients (Tonon et al (98). The survival curve for Grade 1 ascites was digitised and an exponential rate applied to the 60-month data to obtain a per-cycle probability of death of 4.5%.

LTx mortality is divided into short-term mortality (LTx mortality, applied to the cycle in which patients undergo surgery) and long-term mortality (post-LTx mortality, all cycles subsequent to the surgery). LTx mortality is derived from an ALGS study (Emerick et al (7)), which reports 1-year survival of 21% and results in a per-cycle probability of 5.3%. Post-LTx mortality is derived from a systematic review and meta-analysis of LTx in infants (99), and the pooled survival of >1-5 years was applied in the base-case (71%), assuming a midpoint of 2.5 years and a constant exponential rate. This resulted in a per-cycle probability of 3.1%.

Mortality from SBD, when applied in scenario analysis, is also divided into short- and long-term mortality – however, as no literature was identified to derive these transitions, and there is no additional mortality associated with similar procedures (i.e. partial internal biliary diversion) (103), they were assumed identical to non-responder mortality (i.e. mortality per cycle of 1.6%). This was confirmed by a clinical expert (Appendix N). This is potentially a conservative estimate, as there could be additional complications associated with SBD as a procedure.

As many of the above studies were in adult populations, it is expected that these are not fully reflective of mortality in a paediatric population. However, no data was identified in paediatric patients specifically.

B.3.4 Measurement and valuation of health effects

Summary

- QoL is modelled using primarily a vignette study in ALGS and the literature.
- The trial-collected PedsQL could not accurately be mapped to EQ-5D due to participant age. A scenario is presented using the literature.
- The base-case is presented applying the caregiver disutilities from the vignette study, given the significant burden of ALGS on caregivers.
- QoL is a key driver of the model results, and based on results from ICONIC. Treatment with maralixibat is expected to significantly improve patient and caregiver QoL.

B.3.4.1 Health-related quality of life data from clinical trials

B.3.4.1.1 Data from ICONIC

The primary efficacy endpoint of ICONIC evaluated mean change from baseline of the ItchRO (Obs) patient reported outcome (39). Additionally, an exploratory endpoint evaluated change in baseline in PedsQL Total Score (Parent) from Weeks 18-100. The PedsQL total scores from ICONIC outlined in Table 20 illustrates the improvement was statistically significant at most time points. In addition, a statistically significant improvement in fatigue was seen for maralixibat at all time points, as measured by PedsQL multidimensional fatigue scale score (See Table 19).

B.3.4.2 Mapping

The scales reported for ICONIC were the Psychosocial Health Summary Scores, Physical Health Summary Scores, Multidimensional Fatigue Scale Scores, and Family Impact Total Scores. These scales were not mappable to EQ-5D, as participant age made it impossible to map from PedsQL. The School Functioning scores of the PedsQL scales were not collected, given the cohort age of ICONIC was younger than school age. As a result, PedsQL could not accurately be mapped to EQ-5D using published algorithms (e.g. Khan et al (104)), and as a result, trial

health-related quality of life (HRQoL) outcomes were not used in the economic model.

B.3.4.3 Health-related quality of life studies

Ten publications reported HRQoL results in the SLR from May 2023, of which several used the PedsQL reporting tool and one used the CHQ-PF50 reporting tool. None of these publications tried to map PedsQL to the EuroQoL-5 Dimensions Questionnaire (EQ-5D) for utility value reporting. Of the three publications reporting outcomes of the ICONIC clinical trial, two reported that patient QoL and fatigue both improved significantly as a result of maralixibat treatment at both time points (Week 18 and Week 48), which aligned with significant reductions in sBA levels at these same time points. Two publications also reported that PedsQL scores improved with maralixibat, as shown in the ICONIC long-term extension. Kamath et al 2022 (59) reported the ICONIC study HRQoL findings: that responders (those with an ItchRO response) to maralixibat reported significant improvements across HRQoL from baseline to 48 weeks. Several studies describe the QoL burden experienced by patients with ALGS (particularly the impact of pruritus) and their carers explaining the effects of providing care on a loved one's everyday activities, employment, social life, relationships, emotional health, and sleep (33).

B.3.4.4 Adverse reactions

AEs recorded in the ICONIC study have been detailed below, alongside the associated utility decrements and 12-week probabilities. Only abdominal pain was considered to have an impact on QoL, for which a disutility was taken from Sullivan et al (155, Other Gastrointestinal Disorders) (105).

Table 39: Summary of adverse events used in the model

Adverse event	Disutility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)
Abdominal Pain	–0.0512028 (0.005311)	–0.0616124 – 0.0407931	B.2.10
ALT Increased	0	–	

Abbreviations: *ALT, alanine aminotransferase; NA, not available.*

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

B.3.4.5.1 Vignette study

In the economic model, a vignette study was used to populate HRQoL throughout the health states. The full report is provided Appendix M. [redacted] The health states identified are summarised in Table 40.

Table 40: Summary of health states used in the vignette study

State	Description
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: *sBA, serum bile acid.*

[redacted]

Table 41: Patient health-state vignettes EQ-5D-5L index scores

State	Mean (SD)	Standard error	Range	95% CI
Progressive cholestasis	[redacted]	[redacted]	[redacted]	[redacted]
Non-progressive cholestasis	[redacted]	[redacted]	[redacted]	[redacted]
Successful LTx	[redacted]	[redacted]	[redacted]	[redacted]
Chronic LTx rejection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *CI, confidence interval; SD, standard deviation.*

Table 42: Caregiver health-state vignettes EQ-5D-5L index scores

State	Mean (SD)	Standard error	Range	95% CI
Progressive cholestasis	[redacted]	[redacted]	[redacted]	[redacted]
Non-progressive cholestasis/ Successful LTx	[redacted]	[redacted]	[redacted]	[redacted]
Chronic LTx rejection	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *CI, confidence interval; SD, standard deviation.*

B.3.4.5.1.1.1. Methods and key conclusions of the vignette study:

[redacted]

In addition to the utility values reported in the vignette study, additional inputs are used to derive the utilities in the cirrhosis, PHT, ascites, and SBD health states. Given no direct estimates were available from the literature, composite utility values

were produced using Sullivan et al. (105) and HST17 (81). These are summarised in Table 43. The stoma disutility multiplier was constructed using a 2006 study in ulcerative colitis, and the ratio of TTO utility weights in the remission and ileostomy populations calculated to obtain 0.57 ÷ 0.79 = 0.72.

Table 43: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Responsive to medication	[redacted]	[redacted]	Page 105 – Measurement and valuation of health effects	Vignette study (see Appendix M)
Unresponsive to medication	[redacted]	[redacted]		
Cirrhosis	[redacted]	[redacted]		Sum of unresponsive utility and 'liver disease' disutility (–0.04) from Sullivan et al (105)
PHT	[redacted]	[redacted]		Sum of cirrhosis utility and 'liver disease' disutility (–0.04) from Sullivan et al (105)
Ascites	[redacted]	[redacted]		Sum of PHT utility and 'gastrointestinal disorder' disutility (–0.05) from Sullivan et al (105)
SBD	[redacted]	[redacted]		Assumed equivalent to LTx utility
Post-SBD	[redacted]	[redacted]		SBD utility multiplied by the stoma multiplier (0.72) used in HST17 (81)
LTx	[redacted]	[redacted]		Vignette study, weighted average of progressive cholestasis and LTx rejection (see Appendix M)
Post-LTx	[redacted]	[redacted]		Vignette study, successful LTx (see Appendix M)
Death	0	NA	–	–

***Abbreviations**: LTx, liver transplantation; NA, not applicable; PHT, portal hypertension; SBD, surgical biliary diversion.*

Caregiver utilities are applied by calculating the utility loss between those reported in the vignette and age-matched general population EQ-5D using Ara and Brazier for the UK (109). Age-matched utility ([redacted] years, based on mean age from the vignette study) was [redacted]. These were considered appropriate to apply in the base-case, given the impact of ALGS on caregivers, who are often parents of young children. A summary of the caregiver utilities applied in the model is provided in Table 44.

Table 44: Summary of utility values for cost-effectiveness analysis

State	Caregiver utility	Caregiver disutility
Responsive to medication	[redacted]	[redacted]
Unresponsive to medication	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]
PHT	[redacted]	[redacted]

Ascites	[redacted]	[redacted]
SBD	[redacted]	[redacted]
Post-SBD	[redacted]	[redacted]
LTx	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]
Death	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; NA, not applicable; PHT, portal hypertension; SBD, surgical biliary diversion.*

B.3.4.5.2 Literature

A scenario was performed using the PedsQL outcomes reported in Kamath et al. (22) in ALGS. A mapping algorithm was used (Khan et al (104)), for which the individual scales and calculated EQ-5D utilities are reported in Table 45. The obtained EQ-5D values are applied to the 'unresponsive to medication' and 'responsive to medication' states, respectively, while others are maintained (i.e. calculations from unresponsive or responsive states dynamically changed with the new utilities, whereas others were not adjusted). As can be seen in Table 45, the difference between ALGS and healthy patients' utility is very small (0.04), which could be a result of caregivers and patients becoming used to the burden of ALGS and pruritus, and therefore no longer reporting accurate quantitative estimates of their burden over time. It has been validated by clinicians globally, as well as the leading clinician in the UK, that carers 'normalise' the pruritus, meaning carer-reported utility scores are likely underestimated (see Appendix N).

Table 45: Summary of PedsQL scores reported in Kamath et al (22) and mapping algorithm from Khan (104)

Scale	**PedsQL**		**Mapped EQ-5D**	
	ALGS	**Healthy**	**ALGS**	**Healthy**
Total score	69.86	83.91	0.76	0.80
Physical functioning	72.52	87.77		
Emotional functioning	69.13	79.21		
Social functioning	69.11	84.97		
School functioning	67.28	81.31		
Age	9.5 years (22)			
Gender	39% female (22)			

Abbreviations: *PedsQL, Paediatric Quality of Life Inventory TM.*

An additional scenario was performed using the LTx utility value reported in the DFK NICE submission (0.71) (110).

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Summary

- The costs included in the analysis include drug, healthcare resource, surgery and mortality costs which are incurred by the NHS to treat patients with ALGS as they progress through all stages of their liver disease.
- The model does not capture the indirect and long-term financial impact of the disease or the resulting societal cost savings as a result of introducing maralixibat.

B.3.5.1 Intervention and comparators' costs and resource use

The following sections describe the sources, methodology, and values used for costs and resource use in the economic model. Frequencies were primarily informed by a clinical expert, whereas costs were sourced from NHS reference costs (111) and the Personal Social Services Research Unit (PSSRU) (112).

B.3.5.1.1 Drug acquisition costs

The acquisition cost of drugs included in the SoC arm are reported in Table 46. Drug costs were sourced from eMIT. The SoC drugs are cumulative to maralixibat and are therefore included in equal proportions in both arms of the model, in all states prior to LTx. See Appendix K for more details.

Table 46: Drug costs included in the cost-effectiveness model

Technologies	Price per pack	Units per pack
MRX – list price	£43,970	30mL vial (9.5mg/mL)
MRX – PAS price	[redacted]	
UDCA	£6.59	60 x 150mg
Rifampicin	£41.18	100 x 300mg
Phenobarbital	£1.24	28 x 60mg

Abbreviations: *PAS, patient access scheme; UDCA, ursodeoxycholic acid.*

As described in the prefix for B.3, a PAS price that will be commercially viable for the company is currently being negotiated with NHS-E via commercial surgery.

Maralixibat is administered based on patient weight. To calculate cost per cycle, weight bands reported in the SmPC were used (see Appendix C). For each set of low and high weight bands, a daily dose of maralixibat (mL) was applied and multiplied by the cost/mL) for maralixibat to calculate a weekly cost which could then be converted into a final cost per cycle. Differential cycle costs between cycle 1 and 2+ differ due to separate maralixibat doses applied to patients within week 1 and

weeks 2 onwards. Given maralixibat is expected to be administered at home, vial sharing is applied in the base-case.

Patients with ALGS are expected to be shorter and lighter than the general population, which is explained by their difficulty digesting fats and absorbing fat-soluble vitamins, leading to malnutrition. The 5th percentile weight band is used in the base-case (as demonstrated in the ICONIC trial (39), baseline z-score of -1.7), with patients assumed to be normally distributed about the mean value. Within the model engine, normal distributions based upon weight and SD in each given cycle were used instead of cohort means to estimate average cohort doses for maralixibat at each timepoint, to capture the cost of maralixibat treatment more robustly. The maralixibat cycle cost is only applied to the treatment response health-state (within the maralixibat treatment arm) in order to calculate a cohort cost per cycle within both cost engines.

SoC costs are applied within the treatment response health-state, using a weighted average cost per cycle for UDCA, rifampicin, and phenobarbital, taking into consideration the proportion of patients on each drug (this proportion was based on ICONIC baseline characteristics). Unit costs were sourced from the British National Formulary. Individual average costs for each comparator were derived directly from unit costs and dosing data (see Table 47) to calculate cost per mg and cost per day and determine a cost per cycle. Similarly, SoC costs were only applied to the treatment responders.

Table 47: Drug costs for the SoC treatment arm

Comparator	dose per day	% patients	Unit size (mg)	Cost per pack	Units per pack	cost/cycle
UDCA	10mg	80.60%	150	£6.59	60	£0.62
Rifampicin	10mg	72.40%	300	£41.18	100	£1.15
Phenobarbital	120mg	12.90%	60	£1.24	28	£7.44

Abbreviations: *SoC, Standard of Care; UDCA, ursodeoxycholic acid*.

B.3.5.1.2 Administration costs

No administration costs are included in either arm of the model. Maralixibat is administered as an oral solution by a caregiver or the patient and requires no special administration. SoC medication is also taken without special administration.

B.3.5.2 Health-state unit costs and resource use

A summary of the health-state costs included in the model are reported in Table 48 and corresponding units per health-state in Table 49. These were sourced from the latest PSSRU and NHS reference costs. A summary of healthcare resource use costs per cycle is provided in Table 50. No cost is included for the post-LTx health-state, as this is modelled separately using an aggregate figure for Year 1, 2, and 3 following LTx from NICE guidance on non-alcoholic fatty liver disease, which includes drug and monitoring costs (113) (see Table 48).

The final costs per cycle (Table 48) were calculated by multiplying the unit resource cost by the number of units per health-state to provide a total resource use cost. For each individual health-state, these were then summed to give a total cost per cycle.

Table 48: Health-state costs included in the cost-effectiveness model

Resource	Unit cost	Source
Paediatrician visit	£113.00	PSSRU 2021/22 (112)
Hepatologist visit	£113.00	PSSRU 2021/22 (112)
Dietician visit	£100.00	PSSRU 2021/22 (112)
Endocrinologist visit	£113.00	PSSRU 2021/22 (112)
Lab tests	£43.81	NHS reference costs (DAPS02) (111)
Cardiologist visit	£113.00	PSSRU 2021/22 (112)

Abbreviations: *NHS, National Health Service; PSSRU, Personal Social Services Research Unit.*

Table 49: Health-state units per cycle included in the cost-effectiveness model

	Units per health-state						
Resource	Response	Loss of response	Loss of response, cardiac	Cirrhosis	PHT	Ascites	Response
Paediatrician visit	0.23	0.12	0.12	0.12	0.12	0.12	0.23
Hepatologist visit	0.23	0.69	0.69	0.69	0.69	0.69	0.23
Dietician visit	0.23	1.38	1.38	1.38	1.38	1.38	0.23
Endocrinologist	0.00	0.23	0.23	0.23	0.23	0.23	0.00
Lab tests	0.23	0.69	0.69	0.69	0.69	0.69	0.23
Cardiologist visit	0.00	0.00	0.23	0	0	0	0.00

Source: *Clinical expert opinion, see Appendix N*
Abbreviations: *PHT, PHT.*

Table 50: Summary health-state costs

Health-state	Cost per cycle
Responsive to medication	£96.26
Unresponsive to medication	£305.60
SBD	£18,179.82
Post-SBD	£16,835.63
Cirrhosis	£305.60
PHT	£305.60
Ascites	£305.60
LTx	£44,244.32
Post-LTx	£0[1]
Death	£1,279.00

Abbreviations: *LTx, liver transplantation; PHT, portal hypertension; SBD, surgical biliary diversion.*
[1]Separate health-state costs are allocated post-LTx and described below.

B.3.5.3 Adverse reaction unit costs and resource use

AEs are considered in the model base-case. The unit costs reported in Table 51 are applied to the proportion of patients experiencing AEs in the SoC and maralixibat arms based on the findings of the ICONIC clinical trial (see Clinical Section B.2.10 and Table 51). These values were then applied to the treatment response health-state in each treatment arm as a final cost per cycle.

Table 51: Adverse Event unit costs

Adverse event	Cost per event	Frequency (MRX arm)	Frequency (SoC arm)	Cost per cycle (MRX)	Cost per cycle (SoC)
Abdominal pain	£0	6.45%	0%	£0.00	£0.00
ALT increased	£1.55	6.45%	0%	£0.10	£0.00

Abbreviations: *ALT, alanine transaminase; MRX, maralixibat; SoC, standard of care.*

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 Cost of surgery

In the scenario where it is applied, a unit cost of £18,127.00 is applied to patients receiving an SBD. Post-SBD, a further £16,836 per cycle is applied to account for the increased monitoring in patients who have had an SBD. A proportion of patients undergo a reversal of their SBD, which is associated with a slightly lower cost of reoperation of £14,056.50, whereas some patients have infections and bowel prolapse. Table 52 provides a breakdown of the proportion of patients who may experience some of the short-term SBD procedures and their subsequent costs. Within the model, the cost of £16,836 attached to the first cycle of new patients entering the post-SBD health-state was determined by calculating a weighted average of these three possible procedures.

Long-term healthcare costs detailed in Table 52 were again calculated by taking a weighted average of the three long-term healthcare resource use costs post-SBD. This was then applied as a final cost per cycle in the post-SBD health-state of both treatment arms. Similarly, a unit cost of £44,244.32 is applied to patients undergoing LTx, with a further £15,199 applied to the first year (£3,800 per cycle) following their LTx. Post-LTx, patients incur a per-cycle cost of £1,180 (£4,720 annual) in Year 2

following their LTx, and £539 per cycle from Year 3 onwards. These costs were taken from the NICE guidance on non-alcoholic fatty liver disease and include the additional monitoring and immunosuppression expected for post-LTx patients (113). All costs associated with LTx are displayed within Table 53.

Table 52: Breakdown of costs associated with SBD

Procedure/ resource use	Unit cost	Number of units	Source
Cost of an SBD	£18,127.00	–	NHS reference costs 21/22, Complex hepatobiliary or pancreatic procedure. Average of NHS reference costs total HRGs. (111)
Short-term post-SBD procedures and costs			
Cost of reoperation	£14,056.50	67%	Paediatric intermediate infection, CC score 0-5+. Average score. (111) Bjornland et al (114)
Infection treatment	£2,089.00	43%	Paediatric other gastrointestinal disorders, CC scores 0-4+. Average score. (111) Bjornland et al (114)
Surgery for bowel prolapse	£688.96	7%	Paediatric other gastrointestinal disorders, CC scores 0-4+. Average score. (111) Bjornland et al (114)
Long-term healthcare resource use and costs post-SBD			
Laboratory blood test	£43.81	Once every 3 months	NHS reference costs 21/22, DAPS02. (111) Foroutan et al (85)
Ultrasound	£374.66	Once every 3 months	NHS reference costs 21/22, Cost of an ultrasound. (111) Foroutan et al (85)
Hepatologist visit	£113.00	Once every 3 months	PSSRU 21/22, Cost of a hospital-based consultant. (112) Foroutan et al (85)

Abbreviations: *CC, comorbidity and complications; NHS, National health Service; PSSRU, Personal Social Services Research Unit; SBD, surgical biliary diversion.*

Table 53: Breakdown of costs associated with LTx

Procedure/resource use	Unit cost	Source
One-off cost of LTx	£44,244.32	NHS reference costs 21/22. Average of GA15A, B, and C. (111)
Cost of LTx (cycles 1-4) per cycle	£3,800	NICE draft guidance consultation | Non-alcoholic fatty liver disease (NAFLD): assessment and management. (113) Inflated from 2016.
Post-LTx (cycles 4-8) per cycle	£1,180	
Post-LTx (cycles 5+) per cycle	£539	

Abbreviations: LTx, liver transplantation; NHS, National health Service.

B.3.5.4.2 Cost of mortality

A cost of £1,279.00 has been applied as a one-off cost to all patients entering the Death health-state to reflect additional costs associated with required care. This cost was taken from the 2014 Nuffield trust report on end-of-life costs (inflated to 2023) (115). Although the model uses a lifetime horizon in base-case analysis, and as such all patients will eventually incur these costs, patients treated with maralixibat are anticipated to experience survival benefits in comparison with SoC resulting from slowed disease progression. As a result, overall costs associated with mortality will differ due to discounting in the model base-case.

It is important to note that, given the heavy burden of ALGS, not all costs are captured in the economic analysis (further detail is given in Section B.3.12), particularly costs required for specialist nutritional needs and medical appointments, and the financial burden on caregivers who are unable to attend work or require mental health support. As such, the long-term costs included in the analysis are likely underestimated.

B.3.6 Severity

ALGS is a severe genetic disorder which affects multiple organ systems, including the liver, cardiovascular system, renal system, as well as the formation of the skeleton. Patients with ALGS may experience a range of symptoms, including intractable and severe pruritus, xanthomas, and stunted growth. Patients with ALGS also have significantly shorter life expectancy than the general population on average, with 92.8%, 91.2% and 88.1% of patients surviving to age 5, 10, and 18, respectively.(4) This translates to approximately a 21-fold increase in the risk of mortality by the age of 18 in comparison with the general population in the UK.

The summary features of the QALY shortfall analysis conducted to support the submission are presented in Table 54. Patient sex distribution is based on the baseline characteristics of the ICONIC clinical trial, and the starting age is based on the SmPC or maralixibat, with patients to be treated from the age of 2 months old.

Table 54: Summary features of QALY shortfall analysis

Factor	Value	Source
Sex distribution	61.3% male	ICONIC baseline characteristics; Table 10, section B.2.2.1.1.
Starting age	0.17 years (2 months)	SmPC; Table 2, section B.1.2.

The summary of time spent in each health state, and the associated utility value for patients treated with SoC is presented in Table 56. In general, patient health related quality of life is poor in patients who are not responding to treatment, or who have not received a liver transplant.

Table 55: Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value: mean (standard error)	Undiscounted life years
Treatment response	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]
Ascites	[redacted]	[redacted]

State	Utility value: mean (standard error)	Undiscounted life years
LTx	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]

Abbreviations: LTx, liver transplantation
** standard error assumed 10% of mean value*

In total, this translates to undiscounted benefits of [redacted] QALYs gained in patients treated with SoC, or [redacted] QALYs when discounted at 3.5% per annum. This is a significant absolute and proportional shortfall when compared with general population estimates. An age and sex matched general population would be expected to accrue [redacted] total QALYs, resulting in an absolute shortfall of [redacted] QALYs for patients with ALGS, or a proportional shortfall of [redacted], based on a calculation using English lifetables, the 1993 MVH EQ-5D-3L value set (116), health state profiles from the Health Survey for England 2014 (117), and using the ALDVMM model proposed by Hernandez Alava, et al (118).

These estimated shortfalls justify a severity modifier for QALY weighting of 1.2 according to NICE guidance, based on an absolute shortfall between 12 and 18 QALYs. As such, the proposed economic analysis includes a 1.2 multiplier on incremental per patient QALYs. The severity modifier has not been applied to incremental benefits to caregivers.

B.3.7 Managed access proposal

Managed access is not relevant for this submission.

B.3.8 Uncertainty

Summary

- The uncertainty present in the model is tested in sensitivity analysis. However, it is important to note that with ALGS being a rare and debilitating condition, the economic analysis is unlikely to have captured all the long-term savings and benefits associated with the introduction of maralixibat and are likely underestimated.

ALGS is a rare multi-organ condition which affects a range of patient and caregiver outcomes. Given the relative paucity and variation in the data, there is uncertainty in the evidence available and used in the economic model. As a result, sensitivity analysis explores the uncertainty linked to key drivers of cost-effectiveness, such as utility values and mortality.

While the natural history of ALGS indicate heightened risk of mortality, primarily due to chronic liver failure and the inability to have a LTx in patients whose heart/kidney is involved, this generally represents a longer-term risk (3). As a result of this, differences in mortality between treatment arms in ICONIC are not captured.

As described in the parameterisation of the model, treatment efficacy is measured by means of response in sBA levels and pruritus. As sBA is a biochemical indicator of disease severity and correlates with pruritus, sBA levels drive the need for a LTx, and more generally, progression of liver disease. Patients who respond to treatment have an sBA response >50% (change from baseline) and remain in a favourable health-state with reduced mortality, or disease progression associated with greater mortality. The proportion of patients receiving a LTx have high pruritus, as this is the greatest indicator for LTx in ALGS and those experiencing pruritus also have high levels of sBA – it was therefore considered clinically accurate to assume a link between sBA, pruritus, and LTx. Although no direct link is modelled between sBA and mortality, sBA non-responders progress to health states which are associated with greater mortality (such as cirrhosis, ascites, PHT, and surgery). A significant proportion of patients end up receiving a LTx in both arms across the modelled cohort and time horizon, but a greater proportion of patients are held back in 'response' in the maralixibat vs SoC arm, resulting in fewer patients dying. As such, mortality is modelled by proxy of sBA, which drives liver cirrhosis and subsequent liver failure and/or LTx. The mortality estimates predicted by the model are conservative in comparison with published estimates, due to the paucity of data available.

Additionally, the multi-system nature of the condition suggests there is uncertainty in which patients are eligible for LTx or SBD, based on the severity of their cardiac and/or renal involvement. This is explored in sensitivity analysis, as the exclusion of LTx leads to significantly poorer health outcomes. As described in further detail in Section B.3.12, there is a substantial burden associated with ALGS and the current SoC, especially surgery, on patients and their caregivers. A majority of patients will require a LTx early on in childhood, which presents both an emotional and financial burden on patients and caregivers. This is not captured in the economic analysis, as quantitative outcomes in post-LTx only account for the cost and outcomes

associated with long-term post-LTx care, which are favourable. However, as described in a later section, there are many aspects of patients' and caregivers' lives that cannot be quantified, but that would be positively affected by maralixibat. As a result, the model outcomes are likely underestimating the full benefits of introducing maralixibat in the treatment pathway for patients with ALGS.

B.3.9 Summary of base-case analysis inputs and assumptions

Summary

- The key assumption made in the model revolves around the mechanism of action of maralixibat, whereby reductions in sBA are correlated to reduced pruritus and therefore delayed progression of ALGS.
- Other important assumptions include the sources used for mortality, that treatment responders have a mortality benefit over non-responders equivalent to the comparison of maralixibat with GALA, and that a proportion of patients are not eligible for LTx as a result of multi-organ involvement.

B.3.9.1 Summary of base-case analysis inputs

A summary of the base-case cost-effectiveness analysis inputs is provided in Table 56.

Table 56: Summary of variables applied in the economic model

Variable	Value	Standard error	Distribution	Reference to section in submission
General settings				
Time horizon (years)	100.00	NA	–	Economic analysis
Discount rate (costs and benefits)	0.035	NA	–	
Cycle length (years)	0.23	NA	–	
Discount on vial (%)	[redacted]	NA	-	
Baseline demographics				
Baseline age (years)	0.17	NA	–	Section: Patient population
Caregiver age (years)	[redacted]	NA	–	
Weight band	5th %ile	NA	–	
Sex (% cohort female)	0.39	NA	–	
Cardiac complications (% of cohort)	0.30	0.03	Beta	
Transitions				
MRX response - probability of patients responding to MRX	[redacted]	[redacted]	Beta	Clinical parameters and variables
SoC response - probability of patients responding to SoC	[redacted]	[redacted]	Beta	
Discontinuation of MRX - responder to loss of response - Cycle 1	0.045	0.00	Beta	
Discontinuation of SoC - responder to non-response	[redacted]	[redacted]	Beta	
Probability of cirrhosis – non-responder to cirrhosis	0.013	0.00	Beta	
Probability of PHT - cirrhosis to PHT	0.004	0.00	Beta	
Portal hypertension to ascites	0.003	0.00	Beta	
Non-responder to LTx	0.036	0.00	Beta	
Cirrhosis to LTx	0.017	0.00	Beta	
Portal hypertension to LTx	0.059	0.01	Beta	
Ascites to LTx	0.059	0.01	Beta	
Post BD to LTx	0.006	0.00	Beta	

Variable	Value	Standard error	Distribution	Reference to section in submission
LTx to death	0.053	0.01	Beta	
Post-LTx to death	0.031	0.00	Beta	
Re-transplantation - LTx to LTx	0.056	0.01	Beta	
Cirrhosis to death	0.012	0.00	Beta	
Portal hypertension to death	0.029	0.00	Beta	
Ascites to death	0.045	0.00	Beta	
Non-responder to BD	0.064	0.01	Beta	
Cirrhosis to BD	0.000	0.00	Beta	
Portal hypertension to BD	0.064	0.01	Beta	
Ascites to BD	0.064	0.01	Beta	
Adverse event - MRX	0.065	0.01	Beta	
Adverse event - SoC	0.000	0.00	Beta	
HR of mortality (responder vs. non-responder)	0.305	0.03	Normal	
SoC mortality - type of parametric distribution	4.000	NA	NA	
SoC mortality – Parameter 1	0.789	NA	NA	
SoC mortality – Parameter 2	216.563	NA	NA	
SoC mortality – Parameter 3	0.000	NA	NA	
Utilities				
Treatment response	[redacted]	[redacted]	Gamma	Section: Adverse reactions AEs recorded in the ICONIC study have been detailed below, alongside the associated utility decrements and 12-week probabilities. Only abdominal pain was considered to have an impact on QoL, for which a disutility was taken from Sullivan et al (155, Other Gastrointestinal Disorders) (105). Table 39: Summary of adverse events used in the model
No treatment response	[redacted]	[redacted]	Gamma	
Cirrhosis	[redacted]	[redacted]	Gamma	
Portal hypertension	[redacted]	[redacted]	Gamma	
Ascites	[redacted]	[redacted]	Gamma	
SBD	[redacted]	[redacted]	Gamma	
Post-SBD	[redacted]	[redacted]	Gamma	
LTx	[redacted]	[redacted]	Gamma	
Post-LTx	[redacted]	[redacted]	Gamma	
Disutility multiplier - stoma	0.72	0.07	Beta	
Disutility - liver disease	-0.04	0.00	Gamma	

Adverse event	Disutility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)
Abdominal Pain	–0.0512028 (0.005311)	–0.0616124 – 0.0407931	B.2.10
ALT Increased	0	–	

Variable	Value	Standard error	Distribution	Reference to section in submission
Disutility - GD	-0.05	-0.01	Gamma	***Abbreviations:*** *ALT, alanine aminotransferase; NA, not available.* Health-related quality of life data used in the cost-effectiveness analysis
Utility - AE disutility - ALP	-0.05	-0.01	Gamma	
Utility - AE disutility - ALT	0.00	0.00	Gamma	
Disutility - per cycle - MRX	-0.003	0.00	Gamma	
Disutility - per cycle - SoC	0.000	0.00	Gamma	
Carer disutility - TR	[redacted]	[redacted]	Gamma	
Carer disutility - LR	[redacted]	[redacted]	Gamma	
Carer disutility - Cirrhosis	[redacted]	[redacted]	Gamma	
Carer disutility - PT	[redacted]	[redacted]	Gamma	
Carer disutility - ascites	[redacted]	[redacted]	Gamma	
Carer disutility - SBD	[redacted]	[redacted]	Gamma	
Carer disutility - post-SBD	[redacted]	[redacted]	Gamma	
Carer disutility - Ltx	[redacted]	[redacted]	Gamma	
Carer disutility - post-LTx	[redacted]	[redacted]	Gamma	
Carer disutility - death	0	-0.00	Gamma	
Utility - caregiver disutility	1.00	-	N/A	
Multiplier for SBD (stoma)	0.72	-	N/A	
Disutility for liver disease	-0.04	-	N/A	
Disutility gastro disorders	0.05	-	N/A	
Health-state costs				
Health-state costs				
Health-state cost - treatment response	85.06	8.51	Gamma	Intervention and comparators' costs and resource use
Health state cost - non-response	285.75	28.57	Gamma	
Health-state cost - cirrhosis	285.75	28.57	Gamma	
Health-state cost - portal hypertension	285.75	28.57	Gamma	
Health-state cost - Ascites	285.75	28.57	Gamma	
Health-state cost - SBD	18127.00	1812.70	Gamma	
Health-state cost - post-SBD	16835.63	1683.56	Gamma	
Health-state cost - LTx	44244.32	4424.43	Gamma	

Variable	Value	Standard error	Distribution	Reference to section in submission
Health-state cost - post-LTx	0.00	0.00	Gamma	
Health-state cost - death	1279.00	127.90	Gamma	
Health-state cost - CC - TR	85.06	8.51	Gamma	
Health-state cost - CC - non-response	311.74	31.17	Gamma	
Health-state cost - CC - cirrhosis	285.75	28.57	Gamma	
Health-state cost - CC - PHT	285.75	28.57	Gamma	
Health-state cost - CC - Ascites	285.75	28.57	Gamma	
Health-state cost - CC - SBD	18127.00	1812.70	Gamma	
Health-state cost - CC - post-SBD	16835.63	1683.56	Gamma	
Health-state cost - CC - LTx	44244.32	4424.43	Gamma	
Health-state cost - CC - post-LTx	0.00	0.00	Gamma	
Health-state cost - CC - death	1279.00	127.90	Gamma	
Cost - post-SBD (long-term)	531.47	53.15	Gamma	
Cost - LTx (1-4)	7599.78	759.98	Gamma	
Cost - post-LTx (4-8)	2360.47	236.05	Gamma	
Cost - post-LTx (5+)	1078.77	107.88	Gamma	
Cost - AE - abdominal pain - MRX	0.00	0.00	Gamma	
Cost - AE - ALT increased - MRX	0.10	0.01	Gamma	
Cost - AE - abdominal pain - SoC	0.00	0.00	Gamma	
Cost - AE - ALT increased - SoC	0.00	0.00	Gamma	
Cost - standard of care cost	2.29	0.23	Gamma	
Surgical costs				
Cost of reoperation	14056.50	-	N/A	Health-state unit costs and resource use
Treatment for infections	2089.00	-	N/A	
Surgery for bowel prolapse	688.96	-	N/A	
Standard of care inputs				

Variable	Value	Standard error	Distribution	Reference to section in submission
Ursodeoxycholic acid – dose (mg)	10	-	N/A	Intervention and comparators' costs and resource use
Rifampicin – dose (mg)	10	-	N/A	
Phenobarbital – dose (mg)	120	-	N/A	
Ursodeoxycholic acid – % patients	80.6%	-	N/A	
Rifampicin – % patients	72.4%	-	N/A	
Phenobarbital – % patients	12.9%	-	N/A	
Ursodeoxycholic acid – Units per pack	60	-	N/A	
Rifampicin – Units per pack	100	-	N/A	
Phenobarbital – Units per pack	28	-	N/A	
Other resource use				
Laboratory blood test – unit per cycle	0.69	-	N/A	Cost and healthcare resource use identification, measurement and valuation
Ultrasound – unit per cycle	0.69	-	N/A	
Hepatologist – unit per cycle	0.69	-	N/A	
Adverse event probabilities				
Adverse event – probability per cycle – MRX abdominal pain	6.45%	Beta	N/A	Measurement and valuation of health effects
Adverse event – probability per cycle – MRX ALT increased	6.45%	Beta		
Adverse event – probability per cycle - SoC	0%	-	N/A	
Unit, response				
Units, response - paediatrician	0.23	-	N/A	Cost and healthcare resource use identification, measurement and valuation
Units, response - hepatologist	0.23	-	N/A	
Units, response - dietician	0.23	-	N/A	
Units, response - endocrinologist	0.00	-	N/A	
Units, response - lab tests	0.23	-	N/A	

Variable	Value	Standard error	Distribution	Reference to section in submission
Units, response - cardiologist	0.00	-	N/A	
Units, non-response - paediatrician	0.12	-	N/A	
Units, non-response - hepatologist	0.69	-	N/A	
Units, non-response - dietician	1.38	-	N/A	
Units, non-response - endocrinologist	0.23	-	N/A	
Units, non-response - lab tests	0.69	-	N/A	
Units, non-response - cardiologist	0.00	-	N/A	
Units, CC - paediatrician	0.12	-	N/A	
Units, CC - hepatologist	0.69	-	N/A	
Units, CC - dietician	1.38	-	N/A	
Units, CC - endocrinologist	0.00	-	N/A	
Units, CC - lab tests	0.23	-	N/A	
Units, CC - cardiologist	0.00	-	N/A	
Units, cirrhosis - paediatrician	0.12	-	N/A	
Units, cirrhosis - hepatologist	0.69	-	N/A	
Units, cirrhosis - dietician	1.38	-	N/A	
Units, cirrhosis - endocrinologist	0.23	-	N/A	
Units, cirrhosis - lab tests	0.69	-	N/A	
Units, cirrhosis - cardiologist	0.00	-	N/A	
Units, PHT - paediatrician	0.12	-	N/A	
Units, PHT - hepatologist	0.69	-	N/A	
Units, PHT - dietician	1.38	-	N/A	
Units, PHT - endocrinologist	0.23	-	N/A	
Units, PHT - lab tests	0.69	-	N/A	
Units, PHT - cardiologist	0.00	-	N/A	

Variable	Value	Standard error	Distribution	Reference to section in submission
Units, ascites - paediatrician	0.12	-	N/A	
Units, ascites - hepatologist	0.69	-	N/A	
Units, ascites - dietician	1.38	-	N/A	
Units, ascites - endocrinologist	0.23	-	N/A	
Units, ascites - lab tests	0.69	-	N/A	
Units, ascites - cardiologist	0.00	-	N/A	
Units, response - paediatrician	0.23	-	N/A	
Units, response - hepatologist	0.23	-	N/A	
Units, response - dietician	0.23	-	N/A	
Units, response - endocrinologist	0.00	-	N/A	
Units, response - lab tests	0.23	-	N/A	
Units, response - cardiologist	0.00	-	N/A	
Units, non-response - paediatrician	0.12	-	N/A	
Units, non-response - hepatologist	0.69	-	N/A	
Units, non-response - dietician	1.38	-	N/A	
Units, non-response - endocrinologist	0.23	-	N/A	
Units, non-response - lab tests	0.69	-	N/A	
Units, non-response - cardiologist	0.00	-	N/A	

Abbreviations: *AE: adverse event; ALT: alanine transaminase; ALP: alkaline phosphatase; BD: biliary diversion; CC: cardiac complications; GD: gastric decompression; LTx: LTx; MRX: maralixibat; PHT: portal hypertension; SoC: Standard of care; SBD: SBD; TR: treatment response.*

B.3.9.2 Assumptions

The list of assumptions used in the economic model is summarised in Table 57.

Table 57: Assumptions of the economic analysis

Assumption	Chosen methodology	Justification
Treatment waning effect	Only discontinuation is modelled.	Only discontinuation is modelled as no waning in treatment efficacy is expected.
Mortality in responders	Responders receive mortality from the non-responder arm adjusted using the EFS HR from the comparison of MRX patients vs GALA patients (i.e. SoC patients).	It was not deemed appropriate to use general population mortality for the responder arm, as liver (and heart or kidney) damage can have long-term implications on patients' mortality risk. A parsimonious approach was therefore selected and was confirmed with a clinician expert (Appendix N).
Transition to LTx	Only available to individuals without renal/cardiac involvement (30% are not eligible for LTx)	The literature reports between 30% and 94% of heart defects (8, 82). A conservative estimate of 9% was applied in the base-case based on a conversation with a clinician, reflective of the proportion of patients with cardiac or renal involvement which die from their complications (Appendix M).
Utilities	A vignette study was used instead of the ICONIC trial-reported utilities.	PedsQL collected in ICONIC could not be adequately mapped to EQ-5D as patients included were not of school age; the vignette study was therefore used instead. This approach was validated by a clinician (Appendix M).
Transition to SBD	SBD is only available in a scenario.	As SBD is not routinely used in clinical practice in the UK, it is not included in the base-case.
SBD and post-SBD mortality	SBD mortality is assumed identical to non-responder mortality when it is used in a scenario.	PEBD is reported in the literature not to be associated with additional mortality. Mortality was therefore assumed identical to non-responder mortality (103).
Weight band	Weight-based dosing is applied to the 5th percentile weight band, with patients assumed to be normally distributed about the mean value.	Patients in ICONIC (39) were shorter and lighter than the general population, which is explained by their difficulty digesting fats and absorbing fat-soluble vitamins. This is demonstrated by a baseline z-score of -1.7.
Severity modifier	MRX qualifies for a 1.2 multiplier.	Based on the absolute shortfall criteria, the number SoC quality-adjusted life years (QALYs) accumulated across the time horizon is [redacted] QALYs. This equates to an absolute shortfall of [redacted] QALYs.

Abbreviations: *EFS, event-free survival; HST, highly specialised technology; LTx, liver transplantation; MRX, maralixibat; NHS, National Health Service; NICE, The National Institute for Health and Care Excellence; PEBD, partial external biliary diversion; PSS, Personal and Social Services; QoL, Quality of Life; SBD, surgical biliary diversion.*

B.3.10 Base-case results

Summary

- In the base-case, the incremental cost-effectiveness ratio (ICER) for maralixibat vs SoC is [redacted], which represent [redacted] incremental QALYs and [redacted] incremental costs.
- At PAS price, the ICER is [redacted] incremental costs). Based on the absolute shortfall criteria, maralixibat qualifies for a threshold multiplier of 1.2.
- Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

B.3.10.1 Base-case incremental cost-effectiveness analysis results

A summary of the base-case results (list price) is provided in Table 59. A PAS is available for maralixibat ([redacted]), for which the base-case results are included in Table 59. A summary of the disaggregated costs and outcomes is provided in Table 61 to Table 66. Given the absolute shortfall severity modifier criteria, maralixibat qualifies for a 1.2 incremental QALY multiplier. This is calculated using the absolute shortfall criteria of 7.03 QALYs (results excluding caregiver disutilities).

It is important to note that, given the heavy burden of ALGS, not all impacts are captured in these results (further detail is given in Section B.3.12), particularly in relation to caregiver and patient health outcomes, long-term career and productivity outcomes, and the emotional and mental health of patients and caregivers (which are frequently young children and their parents).

Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

Table 58: Base-case results

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs†	
MRX	[redacted]						[redacted]
SoC	[redacted]						

†Please note, the severity modifier is applied to incremental QALYs, excluding those for caregivers. As a result, the subtraction of Total QALYs reported in this table don't align with the Incremental QALYs in this table.
***Abbreviations:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.*

Table 59: Base-case results (PAS price)

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs†	
MRX	[redacted]						[redacted]
SoC	[redacted]						

†Please note, the severity modifier is applied to incremental QALYs, excluding those for caregivers. As a result, the subtraction of Total QALYs reported in this table don't align with the Incremental QALYs in this table.
***Abbreviations:** ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.*

Table 60: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000
MRX	[redacted]				
SoC	[redacted]				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.

Table 61: Undiscounted costs

Health-state	SoC	MRX	Incremental
Treatment response (list)	£44	[redacted]	[redacted]
Treatment response (PAS)	£44	[redacted]	[redacted]
Loss of response	£10,309	£10,290	-£19
Cirrhosis	£6,468	£6,455	-£13
Portal hypertension	£567	£566	-£1
Ascites	£38	£38	£0
SBD	£0	£0	£0
Post-SBD	£0	£0	£0
LTx	£1,110	£701	-£409
Post-LTx	£979	£844	-£136
Death	£1,276	£1,276	-£0
Total (list)	**£20,792**	[redacted]	[redacted]
Total (PAS)	**£20,792**	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 62: Discounted costs

Health-state	SoC	MRX	Incremental
Treatment response (list)	£44	[redacted]	[redacted]
Treatment response (PAS)	£44	[redacted]	[redacted]
Loss of response	£7,582	£7,189	-£394
Cirrhosis	£3,230	£3,063	-£167
Portal hypertension	£222	£211	-£11
Ascites	£12	£12	-£1
SBD	£0	£0	£0
Post-SBD	£0	£0	£0
LTx	£1,097	£693	-£404
Post-LTx	£861	£704	-£157
Death	£773	£735	-£38
Total (list)	**£13,820**	[redacted]	[redacted]
Total (PAS)	**£13,820**	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; PAS, patient access scheme; SBD, surgical biliary diversion; SoC, standard of care.*

Table 63: Undiscounted life years (LYs)

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]
SBD	[redacted]	[redacted]	[redacted]
Post-SBD	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 64: Discounted LYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]
SBD	[redacted]	[redacted]	[redacted]
Post-SBD	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]

Post-LTx	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 65: Undiscounted QALYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	1.41
Loss of response	[redacted]	[redacted]	-0.01
Cirrhosis	[redacted]	[redacted]	-0.01
Portal hypertension	[redacted]	[redacted]	0.00
Ascites	[redacted]	[redacted]	0.00
SBD	[redacted]	[redacted]	0.00
Post-SBD	[redacted]	[redacted]	0.00
LTx	[redacted]	[redacted]	0.00
Post-LTx	[redacted]	[redacted]	-0.01
Death	[redacted]	[redacted]	0.00
Caregiver	[redacted]	[redacted]	0.20
Total	[redacted]	[redacted]	**1.58**

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 66: Discounted QALYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	1.24
Loss of response	[redacted]	[redacted]	-0.16
Cirrhosis	[redacted]	[redacted]	-0.07
Portal hypertension	[redacted]	[redacted]	0.00
Ascites	[redacted]	[redacted]	0.00
SBD	[redacted]	[redacted]	0.00
Post-SBD	[redacted]	[redacted]	0.00
LTx	[redacted]	[redacted]	0.00
Post-LTx	[redacted]	[redacted]	-0.13
Death	[redacted]	[redacted]	0.00
Caregiver	[redacted]	[redacted]	0.25
Total†	[redacted]	[redacted]	**1.13**

†Please note, total reported in this table doesn't account for the severity modifier.
Abbreviations*: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

B.3.11 Exploring uncertainty

Summary

- Uncertainty in the model is explored by means of deterministic, probabilistic, and scenario analyses.
- These analyses demonstrated the model's sensitivity to QoL, efficacy, and discontinuation of maralixibat and post-LTx mortality.
- Probabilistic sensitivity analysis was deemed to accurately demonstrate the range of uncertainty present in the model, and the reliability of the base-case results.
- Probabilistic results were relatively congruent with the deterministic results. The ICER in the probabilistic analysis resulted in an ICER of [redacted] and [redacted] at PAS price.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 1,000 iterations are presented in Table 67 and Table 68. The mean incremental costs and QALYs of

maralixibat compared with SoC alone were calculated to estimate the probabilistic ICER.

The probabilistic results were comparable with the deterministic results. The incremental QALYs and costs in the probabilistic analysis results were [redacted] and [redacted], respectively, compared to [redacted] and [redacted] in the deterministic analysis results. At the PAS price, the incremental QALYs and costs in the probabilistic analysis were [redacted] and [redacted], respectively. A scatterplot presents the total number of simulations (Figure 25).

The ICER in the probabilistic analysis resulted in an ICER of [redacted]. At PAS price, this was [redacted]. At PAS price, the probability of cost-effectiveness is [redacted] at a willingness to pay (WTP) threshold of [redacted] (Table 69).

Table 67: Probabilistic results (list price)

	MRX	SoC	Incremental	ICER
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	

Abbreviations: *LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SoC, standard of care.*

Table 68: Probabilistic results (PAS price)

	MRX	SoC	Incremental	ICER
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	

Abbreviations: *LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SoC, standard of care.*

Figure 25: Cost-effectiveness plane from PSA (list price) (1,000 simulations) – PAS price

[redacted]

Abbreviations*: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

Table 69: Proportion of simulations cost-effective

Threshold	% simulations cost-effective at PAS price
£145,000	[redacted]
£170,000	[redacted]
£195,000	[redacted]
£220,000	[redacted]
£235,000	[redacted]

Abbreviations: *PAS, patient access scheme.*

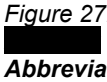
Figure 26: *Cost-effectiveness acceptability curve from PSA (list price) (1,000 iterations) – PAS price*

Abbreviations: *PSA, probabilistic sensitivity analysis.*

B.3.11.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The most impactful inputs on the ICER are presented in Figure 27 using the list price for maralixibat. Results were also displayed in descending order in as a tornado plot in Figure 27. The cost-effectiveness of maralixibat is most sensitive to changes in the responder health utility value, the discount rate in costs and benefit, weight band, and the inclusion of SBD. Varying the responder utility is a driver of maralixibat cost-effectiveness as it impacts the number of QALYs gained, which is more significant in the maralixibat vs SoC arm. Similarly, varying the discounting of benefits and costs varies the value of QALYs and costs across the time horizon, and therefore has a significant impact on the ICER. As the dosing of maralixibat is based on weight, and cost is a key model driver, varying weight bands also has a significant impact on results.

Figure 27: Tornado plot of DSA (most impactful parameters – List price)



Abbreviations*: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LR, loss of response; LTx, liver transplantation; MRX, maralixibat; QALY, quality-adjusted life year; SBD, surgical biliary diversion; TR, treatment response*

Table 70: One-way sensitivity analysis results – list price

Parameter	Lower bound ICER	Upper bound ICER
Apply GALA mortality only to age limit [0.000 - 18.000]		
Health state utilities - Treatment response [ ]		
Include SBD as a health state? (1 = Yes, 2 = No) [2.000 - 1.000]		
Annual discount rate - benefits (%) [0.000 - 0.050]		
Weight band [1.000 - 4.000]		
Annual discount rate - costs (%) [0.000 - 0.050]		
Disutilities - care giver [ ]		
Probability - Discontinuation of MRX - Responder to non-response [ ]		
% of cohort that are Ineligible for LTx [0.000 - 0.760]		
Carer disutility - LR [ ]		
Health state utilities - No treatment response [ ]		
Carer disutility - TR [ ]		
Health state utilities -Post liver transplant [ ]		
Carer disutility - Cirrhosis [ ]		
Probability - Post LTx to death [0.025 - 0.037]		
Health state utilities - Cirrhosis [ ]		
Probability - non responder to LTx [0.029 - 0.043]		

Patient characteristics - Baseline age [0.133 - 0.200]	[redacted]	[redacted]

Abbreviations: *ICER, incremental cost-effectiveness ratio; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care; LTx, LTx.*

B.3.11.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken analyses and the results of the scenario analyses, presented as the ICER of maralixibat compared to SoC are shown in the tables below.

Table 71: Summary of scenario analysis with ICER results at list price

Scenario	ICER	% change
Base-case	[redacted]	-
Discount rate = 1.5%	[redacted]	-5.53%
Discount rate = 5%	[redacted]	2.06%
Post-LTx mortality = HST17 (0.03% per cycle)	[redacted]	35.93%
Weight band = 75th percentile	[redacted]	34.74%
Caregiver disutility not applied	[redacted]	24.28%
Ineligible for LTx = 0%	[redacted]	7.90%
Ineligible for LTx = 76%	[redacted]	-10.09%
LTx utility = 0.71	[redacted]	0.10%
Discontinuation of MRX = halved	[redacted]	58.00%
Response to MRX = ItchRO response at 18 weeks ([redacted] from ICONIC	[redacted]	-0.86%
Utility values from Kamath	[redacted]	15.40%
Transition to SBD = include	[redacted]	42.29%
Parametric distribution = exponential	[redacted]	0.66%
Parametric distribution = Weibull	[redacted]	0.06%
Parametric distribution = Gompertz	[redacted]	-1.06%
Parametric distribution = Log-normal	[redacted]	-0.30%
Parametric distribution = Gamma	[redacted]	0.11%
Parametric distribution = Gen. Gamma	[redacted]	-0.19%
No additional health state mortality until cohort reaches age 18	[redacted]	57.06%
Exclude ascites and PHT from the model	[redacted]	0.00%
Adverse event rates from IMAGINE	[redacted]	-1.56%
Response to MRX = ItchRO response at 13 weeks from ITCH ([redacted])	[redacted]	4.33%
Response to MRX = sBA response at 48-weeks from ICONIC ([redacted] per cycle)	[redacted]	-5.53%

Abbreviations: *ICER, incremental cost-effectiveness ratio; MRX, maralixibat; LTx, liver transplantation; PHT, portal hypertension; SBD, surgical biliary diversion.*

Table 72: Summary of scenario analysis with ICER results at PAS price

Scenario	ICER	% change
Base-case	[redacted]	-
Discount rate = 1.5%	[redacted]	-5.46%
Discount rate = 5%	[redacted]	2.01%
Post-LTx mortality = HST17 (0.03%)	[redacted]	35.94%
Weight band = 75th percentile	[redacted]	34.79%
Caregiver disutility not applied	[redacted]	24.28%
Ineligible for LTx = 0%	[redacted]	7.89%
Ineligible for LTx = 76%	[redacted]	-10.08%
LTx utility = 0.71	[redacted]	0.10%
Discontinuation of MRX = halved	[redacted]	58.14%
Response to MRX = ItchRO response at 18 weeks ([redacted]) from ICONIC	[redacted]	-0.86%
Utility values from Kamath	[redacted]	15.40%
Transition to SBD = include	[redacted]	41.72%
Parametric distribution = exponential	[redacted]	0.66%

Parametric distribution = Weibull	[redacted]	0.06%
Parametric distribution = Gompertz	[redacted]	-1.05%
Parametric distribution = Log-normal	[redacted]	-0.30%
Parametric distribution = Gamma	[redacted]	0.11%
Parametric distribution = Gen. Gamma	[redacted]	-0.19%
No additional health state mortality until cohort reaches age 18	[redacted]	42.57%
Adverse event rates from IMAGINE	[redacted]	0.00%
Response to MRX = ItchRO response at 13 weeks from ITCH ([redacted])	[redacted]	-1.54%
Response to MRX = sBA response at 48-weeks from ICONIC([redacted] **per cycle)**	[redacted]	4.33%
Exclude PHT and ascites	[redacted]	0.14%

Abbreviations: *ICER, incremental cost-effectiveness ratio; MRX, maralixibat; LTx, liver transplantation; PHT, portal hypertension; SBD, SBD.*

Scenario analyses demonstrated that the ICER is particularly sensitive to decreasing the discontinuation of maralixibat (i.e. halving discontinuation leads to a +58% in the ICER). The ICER is also impacted by the risk of mortality in patients; a scenario excluding additional health state mortality associated with progressed liver disease increased the ICER by 57%, as the relative reduction in mortality associated with treatment results in fewer absolute numbers of deaths avoided. Additionally, as seen in the other sensitivity analyses, the ICER is sensitive to changes in utility values – using the utility values from Kamath et al. leads to +15% in the ICER, where the difference in the utility gain between responders and non-responders is smaller, and patients therefore gain fewer QALYs versus SoC. The ICER is not particularly sensitive to changes in the extrapolation of survival (<2%). The ICER is sensitive to changes in post-LTx mortality; applying the mortality estimate used in the PFIC submission, the ICER increases by 36%. However, the source selected in the analysis was deemed more appropriate given the design and population of the study (meta-analysis in infants) (99). Removing caregiver disutilities, which is an important consideration for treatment of ALGS, increased the ICER by 24%.

B.3.12 Subgroup analysis

No subgroup analysis was performed in the economic evaluation. Although subgroup analyses are presented as part of the clinical data (Section B.2.7), there was no rationale for presenting an economic analysis on specific cohorts.

B.3.13 Benefits not captured in the QALY calculation

Summary

- A broad number of additional benefits should be taken into account when estimating and interpreting the cost-effectiveness results for maralixibat vs SoC in ALGS, which could not be included quantitively in the analysis due to the absence of data.
- These impact both patients and their caregivers over the long-term.

There are potential health benefits of maralixibat that are not captured in the economic modelling; the overall benefits to patients and caregivers may therefore be underestimated.

Maralixibat is associated with statistically significant reduction in xanthomas (Xanthoma Severity Score from baseline to Week 48, ITT -0.4 [SE 0.13], p=0.0095). Xanthomas can impact patient survival (3, 6), restrict patients ability to participate in physical activity, and impact physical appearance (19). This can lead to mockery or exclusion from activities and difficulty with school, with an associated psychological impact on the patient, particularly in childhood (14, 19). Because no evidence was identified that allowed the direct incorporation of the impact of xanthomas on patient outcomes in the health economic model, these benefits are not included in the overall estimated QALY gain.

Maralixibat treatment also resulted in statistically significant improvements in growth at several timepoints in comparison with baseline based on z-score. Growth impairment can also impact the physical appearance of patients with ALGS, and can result in bullying, particularly in childhood, leading to adverse mental health outcomes (19).

In addition to these factors, there are wider benefits to patients, caregivers and societal productivity that are not captured in the economic modelling, such as:

- **Time spent by family members providing care:** family members of individuals with ALGS frequently provide a substantial amount of unpaid care. This may negatively affect their work, social life, and physical and mental health. In 2022, a caregiver survey was completed by 105 caregivers of children with ALGS who either experience itch or have had a LTx, across seven countries (Canada, France, Germany, Italy, Spain, UK, US). The results showed that caregivers spent an average of 85 hours caregiving a week. 79% of caregivers reported a negative financial impact associated with

informal care, and 51% reported negative impact on their families overall. Importantly, if patients experience reduced itch as a result of treatment of maralixibat, this may reduce the need for informal caregiving. This, in turn, may lead to increased productivity and earnings for carers, potentially improving their overall QoL.

- **Career progression and societal impact:** maralixibat could have a positive impact on patients' careers, whereby effective treatment enables young children to reach developmental milestones and later academic achievement, enabling career progression which would otherwise not be attainable. This could have implications on wider societal productivity gains, as this would allow a greater number of individuals to work compared to current SoC. Treatment with maralixibat could also limit mental health disorders in patients with ALGS by enabling activities which support mental health.

- **Organ availability** is not accounted for in the economic analysis. there may be difficulty in finding an adequate liver for a LTx, causing time spent on waiting lists, and potentially a worsening of a patient's symptoms. This is also associated with an emotional toll on caregivers.

- **Costs to government bodies other than the NHS**: maralixibat could also have cost implications for other government bodies, such as the Department for Education and the Department for Work and Pensions. For example, if maralixibat improves children's ability to attend school and learn, this could lead to increased educational attainment and future earnings.

- **Costs borne by patients that are not reimbursed by the NHS:** patients with ALGS may face some costs that are not reimbursed by the NHS, such as the cost of travel to and from hospital appointments, the cost of special diets, and the cost of complementary therapies.

B.3.14 Validation

Summary

- The model was thoroughly validated to ensure freedom of error, and outcomes compared against the literature, which resulted in consistent and accurate results.

- A clinical expert was consulted to validate model assumptions.

B.3.14.1 Validation of cost-effectiveness analysis

Internal quality assurance measures were undertaken throughout the model development. The model was validated using extreme values and formula auditing to ensure the consistency of model estimates.

The model structure and inputs were critiqued and validated by a clinician and health economics consultant. Where appropriate, any errors were amended. Overall, the validation identified no issues with the structural or computational accuracy of the model. The model was tested for external validity using the literature, particularly mortality. The proportion of patients in the mortality state was taken from age 5, 10, 15, and 20 years and compared to Kamath et al. and Vandriel et al., which report natural history for ALGS. As can be seen in Figure 2, survival in Kamath is lower at age 5, with a plateau at around 18 years. In Vandriel et al (4), a plateau is observed around 10 years, with deaths not exceeding 10% until age 18 (Figure 28). The results from the model predict a survival rate that sits in between these two estimates (Figure 29, Table 73).

Figure 28: Mortality and LTx from Vandriel et al [7]

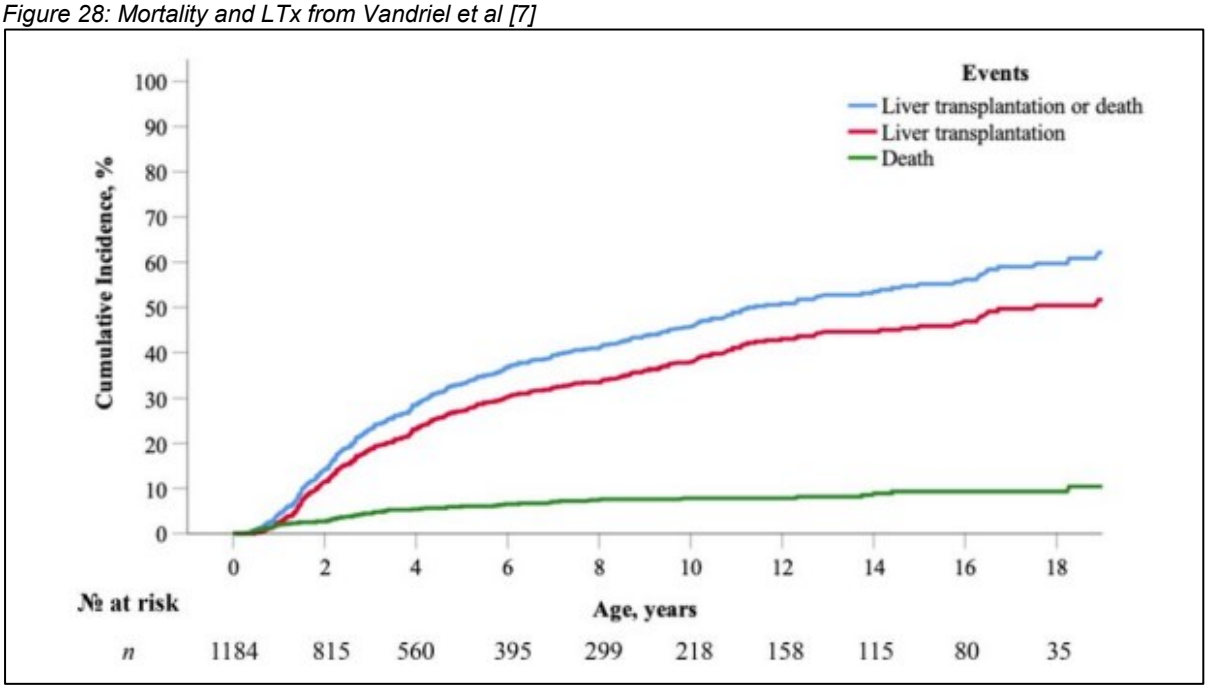


Figure 29: Mortality curves from the model

Abbreviations: *MRX, maralixibat; SoC, standard of care.*

Table 73: Comparison of mortality with the literature

Age	Survival			
	Kamath (8)	Vandriel (4)	SoC arm	MRX arm
5	60%	93%	89.09%	91.57%
10	45%	92%	72.87%	77.26%
15	35%	92%	58.69%	63.35%
20	25%	NA	47.40%	51.60%

Abbreviations: *SoC, standard of care; MRX, maralixibat.*

In addition to this, a clinical expert was consulted to ensure model assumptions were reflective of clinical practice. Questions revolved around the model structure, inclusion of SBD, and the proportion of patients eligible for LTx, and are described in further detail throughout the document.

B.3.15 Interpretation and conclusions of economic evidence

Summary

- A number of strengths support the accuracy of the current model results, such as the availability of trial data and long-term outcomes from GALA.
- ALGS being a rare and debilitating disease which affects many aspects of a patient's life, the benefit of maralixibat is likely underestimated in the analysis.
- Results and outcomes should be considered and interpreted alongside the unquantifiable long-term impact of treatment on caregivers and patients (which are oftentimes children and their parents).
- Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

This economic evaluation presents the cost-effectiveness of maralixibat in ALGS vs SoC, and is the first attempt at parameterising an economic model in this condition. In the base-case, the ICER for maralixibat vs SoC is [redacted], which represents

[redacted] incremental QALYs and [redacted] in incremental costs. At PAS price, the ICER is [redacted] incremental costs). Based on the absolute shortfall criteria (106), maralixibat qualifies for a threshold multiplier of 1.2. The ICER in the probabilistic analysis resulted in an ICER of [redacted] and [redacted] at PAS price, which is congruent with the deterministic analysis and demonstrates the limited extent of uncertainty in the model. Extreme scenarios are tested to explore this further, such as post-LTx mortality, discontinuation of maralixibat, and varying weight bands. All of these had a significant impact on the ICER.

Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

Treatment efficacy is derived from the pivotal trial (ICONIC), which demonstrated improvement in sBA and pruritus outcomes. The 12-week sBA responder analysis is used in the base-case, which is a key strength of this analysis. An additional strength of the analysis is that a wide range of scenarios have been performed to test the model's sensitivity to various parameters. The model is particularly sensitive to maralixibat discontinuation and post-LTx mortality. A key limitation of the analysis is the data paucity: where possible, ALGS-specific data were used, but small patient numbers and the limited number of studies available on long-term outcomes in ALGS resulted in model uncertainty (for instance, outcomes following cirrhosis, PHT and ascites, and the frequency and outcomes associated with SBD).

HRQoL was derived from a vignette study, which was considered the most appropriate source of QoL in the absence of mappable trial utilities. Costs were sourced from a range of NHS-specific sources and the literature. Maralixibat is expected to significantly improve QoL by maintaining patients in the 'treatment response' health-state, and delaying progression to severe liver disease and surgery, by means of controlling sBA and therefore pruritus. This was demonstrated in ICONIC, and is captured in the economic model.

Maralixibat is expected to have a significant impact beyond direct health benefits. The impact of itching/pruritus on patients can completely disrupt every aspect of life and can have serious long-term effects such as post-traumatic stress disorder, impulse control, and other social-emotional disabilities. The multi-system nature of

the condition leads to an increased mortality risk in patients, whereby a proportion of patients are not eligible for a LTx, and therefore have much poorer outcomes. Maralixibat improves symptoms such as pruritus, sleep, and growth (height and weight z-scores); delays disease progression; and avoids or delays surgical procedures and/or LTx. Therefore, it is also expected to have a positive impact on schooling and employment opportunities, as well as QoL and mental health, for people with ALGS and their caregivers.

B.3.16 Cost to the NHS and personal social services

Summary

- The cumulative budget impact across 5 years for the introduction of maralixibat is [redacted] at list price and [redacted] at PAS price. Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.
- The costs included in the analysis cover direct healthcare costs only. The expected societal savings resulting from the introduction of maralixibat are not accounted for and therefore underestimated.
- Long-term outcomes are not accounted for in the budget impact calculation and should be considered alongside the quantitative assessment presented here.

A budget impact model (BIM) is included in the CEM as a standalone sheet, drawing from CEM inputs for efficiency and consistency.

B.3.16.1 ***Patient numbers***

Existing literature places the incidence of ALGS between 1 in 30,000 (referring solely to confirmed genetic mutations in JAGGED1 or NOTCH2) and 1 in 100,000 live births. Using the midpoint, the prevalence would be 1 in 65,000. Mirum spoke to a leading author in ALGS, [redacted], who explained that clinical diagnosis is always completed prior to genetic confirmation. This gave a conservative prevalence figure of [redacted] (Appendix O). However, conversations with NICE suggested that current population numbers are unclear, with an estimated prevalence above 300, meaning maralixibat did not meet the HST criteria (119). NICE provided a prevalence range of between 565 and 1,885. A conservative estimate of 565 in Year 1, with an annual incidence of 1 in 30,000, is therefore applied. A summary of the budget impact calculation is provided in Table 74. Please see Appendix P for a summary of how cost-effectiveness is achieved for maralixibat.

Table 74: Summary of clinical parameters used in the BIM

Parameters	Value	Source
Prevalence	565 patients	Consultation with NICE
Incidence	53% of 1 in 30,000 live births (0.0018%)	Based on incidence of positive JAG1 or NOTCH2 mutations (120-122)
Percent covered by payer	100%	Assumption

Abbreviations: *ALGS, Alagille Syndrome; BIM, budget impact model; LTx, liver transplantation; ONS, Office for National Statistics.*

Table 75: Summary of patient numbers

	Year 1	Year 2	Year 3	Year 4	Year 5
Prevalence	565	-	-	-	-
Incidence	-	11	11	11	11
Total	565	576	587	597	608

Abbreviations: *LTx, liver transplant.*

The anticipated uptake of maralixibat is reported in Table 76. This was informed by launch data in the US. Discontinuation is also included, using the inputs from the CEM (Table 77). An estimated 81.83% of patients remain on maralixibat every year (39), and 95% on SoC (40).

Table 76: Summary of expected uptake of MRX

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX	25%	33%	45%	66%	75%
SoC	75%	67%	55%	34%	25%

Abbreviations: *MRX, maralixibat; SoC, standard of care.*

Table 77: Summary of patient population after discontinuation

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX	112	150	208	311	360
SoC	403	366	306	193	144
Total	**514**	**516**	**515**	**504**	**505**

Abbreviations*: MRX, maralixibat; SoC, standard of care.*

B.3.16.2 ***Costs***

The annual cost of maralixibat is based on weight. Assuming a baseline weight of 4.35kg at 2 months old (5th percentile weight), a weighted average cost per year is calculated using a cost per vial of £43,970 in the base-case. A scenario is presented with the PAS price [redacted]. The mean weighted cost per year accounts for a lower dose in Week 1, and maintenance dose in Week 2 and beyond.

An average annual cost of £9.95 is estimated for SoC, using average doses for UDCA, rifampicin, and phenobarbital (in equal doses to CEM calculations). The total cost of treatment without maralixibat is presented in

Table 78. The total cost of treatment with the introduction of maralixibat is presented in Table 79.

No additional costs are anticipated relating to the introduction of maralixibat, as regular monitoring is already in place for patients on SoC and is not expected to change dramatically as a result of treatment with maralixibat.

Productivity losses have not been quantified in the BIM but are likely to result in a wider societal saving, given the efficacy of maralixibat vs SoC has the potential to reduce the number of caregivers' missed days of work.

Table 78: Scenario without MRX

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX	£0	£0	£0	£0	£0
SoC	£5,623	£5,730	£5,838	£5,945	£6,054
Total	£5,623	£5,730	£5,838	£5,945	£6,054

Abbreviations: *MRX, maralixibat; SoC, standard of care.*

Table 79: Scenario with MRX

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX – list	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MRX – PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	£4,217	£3,839	£3,211	£2,021	£1,513
Total – list	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total – PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *MRX, maralixibat; PAS, patient access scheme; SoC, standard of care.*

B.3.16.3 Results

The estimated budget impact for maralixibat in ALGS is reported in Table 80 and Table 81.

Table 80: Total budget impact (list price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total/patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 81: Total budget impact (PAS price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Total/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total/patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *PAS; Patient access scheme.*

The main limitation of the assessment lies in the prevalence and incidence of the patient population, given the range reported in the literature. However, given these were confirmed in consultation with NICE, these are the most reliable estimates available. Discontinuation is based on the trial, and response to treatment may be measured differently, and therefore vary, in clinical practice. Additionally, as mentioned in the cost section, the budget impact does not capture the wider societal costs of introducing maralixibat, such as increased productivity. The true budget impact is therefore likely to vary from those presented here.

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B.5 Appendices

Appendix C. Summary of product characteristics (SmPC) and UK public assessment report

Appendix C.1. SmPC

Please see document ‘Appendix C – SmPC’

Appendix C.2. Public assessment report

Please see documents ‘Appendix C_Livmarli MHRA Public Assessment Report’ and ‘Appendix C_Livmarli European Public Assessment Report‘.

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix D.1. Identification and selection of relevant studies

Please see document ‘Appendix D, G, H, I – SLR Results’

Appendix D.2. Participant flow in the relevant randomised control trials

Included in the full submission, see Section B.2.4.2.

Appendix D.3. D.3 Critical appraisal for each study

Included in Appendix D, G, H, I – SLR Results Data extraction excel sheet.

Appendix E. Subgroup analysis

Included in the full submission, see section B.2.7.

Appendix F. Adverse reactions

No additional adverse reactions to report.

Appendix G. Published cost-effectiveness studies

Please see document ‘Appendix D, G, H, I – SLR Results’

Appendix H. Health-related quality of life studies

Please see document ‘Appendix D, G, H, I – SLR Results’

Appendix I. Cost and healthcare resource identification, measurement and valuation

Please see document ‘Appendix D, G, H, I – SLR Results’

Appendix J. Clinical outcomes and disaggregated results from the model

Included in the full submission, see Section B.38.

Appendix K. Price details of treatments included in the submission

See Document Appendix K: Price details of treatments included in the submission.

Appendix L. Checklist of confidential information

See Document Appendix L Checklist of confidential information.

Appendix M. Vignette study

See Document Appendix M Vignette Study

Appendix N. Clinical opinion and consensus report

See Document Appendix N Clinical opinion and consensus report.

Appendix O. Clinical opinion letter

See Document Appendix O Clinical opinion letter

Appendix P. Cost-effectiveness document

See Document Appendix P cost-effectiveness document

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Maralixibat for treating cholestatic disease in Alagille Syndrome [ID3941]

Updated commercial agreement

June 2024

File name	Version	Contains confidential information	Date
ID3941 Updated commercial agreement	**V1**	**Yes**	**07/06/2024**

Table of contents

Table of figures

Table of tables

B.1 Cost-effectiveness

The Company would like to present updated cost-effectiveness analysis results, based on the commercial agreement in principle with NHS England. Please note, all results presented in this section pertain to this updated commercial agreement.

B.1.1 Drug acquisition costs

The price per vial aligned to the new commercial agreement is [redacted]. Please see Table 1 for the acquisition cost of drugs included in the model.

Table 1: Drug costs included in the cost-effectiveness model

Technologies	Price per pack	Units per pack
MRX – PAS price	[redacted]	9.5mg x 30mL x 1 vial
UDCA	£6.59	60 x 150mg
Rifampicin	£41.18	100 x 300mg
Phenobarbital	£1.24	28 x 60mg

Abbreviations: *PAS, patient access scheme; UDCA, ursodeoxycholic acid.*

B.1.2 Base-case results

B.1.2.1 Base-case incremental cost-effectiveness analysis results

A summary of the base-case results with the updated commercial agreement ([redacted]) is provided in Table 2. A summary of the disaggregated costs and outcomes is provided in Table 4 to Table 9. Given the absolute shortfall severity modifier criteria, maralixibat qualifies for a 1.2 incremental QALY multiplier. This is calculated using the absolute shortfall criteria of 7.03 QALYs (results excluding caregiver disutilities).

Table 2: Base-case results

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs†	
MRX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

†Please note, the severity modifier is applied to incremental QALYs, excluding those for caregivers. As a result, the subtraction of Total QALYs reported in this table don't align with the Incremental QALYs in this table.
Abbreviations: *ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.*

Table 3: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £30,000
MRX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations*: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.*

Table 4: Undiscounted costs

Health-state	SoC	MRX	Incremental
Treatment response (PAS)	£44	[redacted]	[redacted]
Loss of response	£10,309	£10,290	-£19
Cirrhosis	£6,468	£6,455	-£13
Portal hypertension	£567	£566	-£1
Ascites	£38	£38	£0
SBD	£0	£0	£0
Post-SBD	£0	£0	£0
LTx	£1,110	£701	-£409
Post-LTx	£979	£844	-£136
Death	£1,276	£1,276	-£0
Total	**£20,792**	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 5: Discounted costs

Health-state	SoC	MRX	Incremental
Treatment response (PAS)	£44	[redacted]	[redacted]
Loss of response	£7,582	£7,189	-£394
Cirrhosis	£3,230	£3,063	-£167
Portal hypertension	£222	£211	-£11
Ascites	£12	£12	-£1
SBD	£0	£0	£0
Post-SBD	£0	£0	£0
LTx	£1,097	£693	-£404
Post-LTx	£861	£704	-£157
Death	£773	£735	-£38
Total	**£13,820**	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; PAS, patient access scheme; SBD, surgical biliary diversion; SoC, standard of care.*

Table 6: Undiscounted life years (LYs)

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]
SBD	[redacted]	[redacted]	[redacted]
Post-SBD	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 7: Discounted LYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]
SBD	[redacted]	[redacted]	[redacted]
Post-SBD	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 8: Undiscounted QALYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	1.41
Loss of response	[redacted]	[redacted]	-0.01
Cirrhosis	[redacted]	[redacted]	-0.01
Portal hypertension	[redacted]	[redacted]	0.00
Ascites	[redacted]	[redacted]	0.00
SBD	[redacted]	[redacted]	0.00
Post-SBD	[redacted]	[redacted]	0.00
LTx	[redacted]	[redacted]	0.00
Post-LTx	[redacted]	[redacted]	-0.01
Death	[redacted]	[redacted]	0.00
Caregiver	[redacted]	[redacted]	0.20
Total	[redacted]	[redacted]	**1.58**

Abbreviations: *LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

Table 9: Discounted QALYs

Health-state	SoC	MRX	Incremental
Treatment response	[redacted]	[redacted]	1.24
Loss of response	[redacted]	[redacted]	-0.16
Cirrhosis	[redacted]	[redacted]	-0.07
Portal hypertension	[redacted]	[redacted]	0.00
Ascites	[redacted]	[redacted]	0.00
SBD	[redacted]	[redacted]	0.00
Post-SBD	[redacted]	[redacted]	0.00
LTx	[redacted]	[redacted]	0.00
Post-LTx	[redacted]	[redacted]	-0.13
Death	[redacted]	[redacted]	0.00
Caregiver	[redacted]	[redacted]	0.25
Total†	[redacted]	[redacted]	**1.13**

†Please note, total reported in this table doesn't account for the severity modifier.
Abbreviations*: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.*

B.1.3 Exploring uncertainty

B.1.3.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. PSA results for 1,000 iterations are presented in **Error! Reference source not found.** and Table 10. The mean incremental costs and QALYs of maralixibat compared with SoC alone were calculated to estimate the probabilistic ICER.

The probabilistic results were comparable with the deterministic results. The incremental QALYs and costs in the probabilistic analysis results were [redacted] and [redacted] respectively, compared to 1.30 and [redacted] in the deterministic analysis results (**Error! Reference source not found.**).

The ICER in the probabilistic analysis resulted in an ICER of [redacted]. With the commercial agreement price, the probability of cost-effectiveness is [redacted] at a willingness to pay (WTP) threshold of [redacted] (Table 11).

Table 10: Probabilistic results (PAS price)

	MRX	SoC	Incremental	ICER
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	

Abbreviations: *LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SoC, standard of care.*

[redacted]

Abbreviations*: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.*

Table 11: Proportion of simulations cost-effective

Threshold	% simulations cost-effective at PAS price
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: *PAS, patient access scheme.*

[redacted]

Abbreviations: *PSA, probabilistic sensitivity analysis.*

B.1.3.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs. The most impactful inputs on the ICER are presented in

Table 12 using the list price for maralixibat. Results were also displayed in descending order in as a tornado plot in

Figure 1. The cost-effectiveness of maralixibat is most sensitive to changes in the responder health utility value, the discount rate in costs and benefit, weight band, and the inclusion of SBD. Varying the responder utility is a driver of maralixibat cost-effectiveness as it impacts the number of QALYs gained, which is more significant in the maralixibat vs SoC arm. Similarly, varying the discounting of benefits and costs varies the value of QALYs and costs across the time horizon, and therefore has a significant impact on the ICER. As the dosing of maralixibat is based on weight, and cost is a key model driver, varying weight bands also has a significant impact on results.

Figure 1: Tornado plot of DSA (most impactful parameters)

***Abbreviations**: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LR, loss of response; LTx, liver transplantation; MRX, maralixibat; QALY, quality-adjusted life year; SBD, surgical biliary diversion; TR, treatment response*

Table 12: One-way sensitivity analysis results

Parameter	Lower bound ICER	Upper bound ICER
Apply GALA mortality only to age limit [0.000 - 18.000]	[redacted]	[redacted]
Health state utilities - Treatment response [redacted]	[redacted]	[redacted]
Include SBD as a health state? (1 = Yes, 2 = No) [2.000 - 1.000]	[redacted]	[redacted]
Annual discount rate - benefits (%) [0.000 - 0.050]	[redacted]	[redacted]
Weight band [1.000 - 4.000]	[redacted]	[redacted]
Annual discount rate - costs (%) [0.000 - 0.050]	[redacted]	[redacted]
Disutilities - care giver [1.000 - 2.000]	[redacted]	[redacted]
Probability - Discontinuation of MRX - Responder to non-response [redacted]	[redacted]	[redacted]
% of cohort that are Ineligible for LTx [0.000 - 0.760]	[redacted]	[redacted]
Carer disutility - LR [redacted]	[redacted]	[redacted]
Health state utilities - No treatment response [redacted]	[redacted]	[redacted]
Carer disutility - TR [redacted]	[redacted]	[redacted]
Health state utilities -Post liver transplant [redacted]	[redacted]	[redacted]
Carer disutility - Cirrhosis [redacted]	[redacted]	[redacted]
Probability - Post LTx to death [0.025 - 0.037]	[redacted]	[redacted]
Health state utilities - Cirrhosis [redacted]	[redacted]	[redacted]
Probability - non responder to LTx [0.029 - 0.043]	[redacted]	[redacted]
Patient characteristics - Baseline age [0.133 - 0.200]	[redacted]	[redacted]

Abbreviations: *ICER, incremental cost-effectiveness ratio; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care; LTx, LTx.*

B.1.3.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model to alternative model inputs and assumptions. The details of the undertaken analyses and the results of the scenario analyses, presented as the ICER of maralixibat compared to SoC are shown in the tables below.

Table 13: Summary of scenario analysis with ICER results

Scenario	ICER	% change
Base-case	[redacted]	-

Scenario	ICER	% change
Discount rate = 1.5%	[redacted]	[redacted]
Discount rate = 5%	[redacted]	[redacted]
Post-LTx mortality = HST17 (0.03%)	[redacted]	[redacted]
Weight band = 75th percentile	[redacted]	[redacted]
Caregiver disutility not applied	[redacted]	[redacted]
Ineligible for LTx = 0%	[redacted]	[redacted]
Ineligible for LTx = 76%	[redacted]	[redacted]
LTx utility = 0.71	[redacted]	[redacted]
Discontinuation of MRX = halved	[redacted]	[redacted]
Response to MRX = ItchRO response at 18 weeks (52.92%) from ICONIC	[redacted]	[redacted]
Utility values from Kamath	[redacted]	[redacted]
Transition to SBD = Include	[redacted]	[redacted]
Parametric distribution = Exponential	[redacted]	[redacted]
Parametric distribution = Weibull	[redacted]	[redacted]
Parametric distribution = Loglogistic	[redacted]	[redacted]
Parametric distribution = Lognormal	[redacted]	[redacted]
Parametric distribution = Gamma	[redacted]	[redacted]
Parametric distribution = Gen. Gamma	[redacted]	[redacted]
Adverse event rates from IMAGINE	[redacted]	[redacted]
Response to MRX = ItchRO response at 13 weeks (76%)	[redacted]	[redacted]
Response to MRX = sBA response at 48-weeks (16.6% per cycle)	[redacted]	[redacted]

Abbreviations: *ICER, incremental cost-effectiveness ratio; MRX, maralixibat; LTx, liver transplantation; PHT, portal hypertension; SBD, surgical biliary diversion.*

B.1.4 Subgroup analysis

B.1.5 Interpretation and conclusions of economic evidence

In the base-case, the ICER for maralixibat versus SoC is [redacted], which represents 1.30 incremental QALYs and [redacted] in incremental costs. Based on the absolute shortfall criteria, maralixibat qualifies for a threshold multiplier of 1.2. Furthermore, at a willingness-to-pay threshold of [redacted] The ICER in the

probabilistic analysis resulted in an ICER of [redacted] with the updated commercial agreement price, which is congruent with the deterministic analysis and demonstrates the limited extent of uncertainty in the model.

B.1.6 Cost to the NHS and personal social services

A budget impact model (BIM) is included in the CEM as a standalone sheet, drawing from CEM inputs for efficiency and consistency.

B.1.6.1 ***Costs***

The annual cost of maralixibat is based on weight. Assuming a baseline weight of 4.35kg at 2 months old (5th percentile weight), a weighted average cost per year is calculated using a cost per vial of [redacted] in the base-case. The mean weighted cost per year accounts for a lower dose in Week 1, and maintenance dose in Week 2 and beyond.

Table 14: Scenario without MRX

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX	£0	£0	£0	£0	£0
SoC	£5,623	£5,730	£5,838	£5,945	£6,054
Total	£5,623	£5,730	£5,838	£5,945	£6,054

Abbreviations: *MRX, maralixibat; SoC, standard of care.*

Table 15: Scenario with MRX

Technologies	Year 1	Year 2	Year 3	Year 4	Year 5
MRX – PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	£4,217	£3,839	£3,211	£2,021	£1,513
Total – PAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *MRX, maralixibat; PAS, patient access scheme; SoC, standard of care.*

B.1.6.2 Results

The estimated budget impact for maralixibat in ALGS is reported in **Error! Reference source not found.** and Table 16.

Table 16: Total budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Total/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total/patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: *PAS; Patient access scheme.*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Maralixibat for treating cholestatic disease in Alagille syndrome [ID3941]

Summary of Information for Patients (SIP)

November 2023

File name	Version	Contains confidential information	Date
ID3941 SIP	V1	No	08th November 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article

SECTION 1: Submission summary

1a) Executive summary: In only a few sentences please provide a top-level summary to describe the medicine. Please outline the main patient population it is proposed to treat:

Maralixibat is an oral solution used to treat cholestatic pruritis (itching) in patients aged 2 months and older who have Alagille syndrome (ALGS). ALGS is a rare genetic disease which can lead to a build-up of bile acids in the liver. This build-up is called cholestasis. Cholestasis causes severe pruritus, fatty deposits under the skin (xanthomas), poor growth, and feeling tired; it can get worse over time.

Maralixibat works by reducing the build-up of bile acids in the liver. Bile acids are found in digestive fluid, called bile, which is produced by the liver. Bile acids move from the liver into the gut, where they help with digesting food. After this, they move back into the liver.

Maralixibat stops bile acids from being taken back to the liver once they have done their job in the gut. This allows them to pass out of the body in stools.

1b) Name of the medicine (generic and brand name):

Generic name: Maralixibat

Brand name: Livmarli®

1c) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Maralixibat is intended to be used for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) who are 2 months of age and older.

1d) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 10 February 2023, the Medicines and Healthcare Regulatory Agency (MHRA) approved maralixibat for use in cholestatic pruritis. The assessment report for the approval can be found here: https://mhraproducts4853.blob.core.windows.net/docs/6071fd17da427b1a92865371939132bd804864d2

1e) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Childrens liver foundation • *Grant for '*CLDFs initiatives that provide Information and support for patient advocacy and facilitate patient engagement for the paediatric liver community in the UK during the 2023 year' *(July 2023) – financial support provided* • *CLDF provided patient support letter to submit to Canadian authorities (CADTH) to support reimbursement in Canada (October 2023) – (no financial support provided)* • *Grant for '*CLDFs initiatives that provide Information and support for patient advocacy and facilitate patient engagement for the paediatric liver community in the UK during the 2021 year' *(January 2021) – financial support provided*

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Main conditions the medicine plans to treat: Maralixibat is a medicine which treats cholestatic pruritis, a condition causing itchy skin due to a build-up of bile acids in the liver, in patients who have Alagille syndrome (ALGS). ALGS reduces the tubes that carry bile from the liver to the bowel, referred to as bile ducts. Bile is a digestive fluid containing bile acids, which help with breaking down food in the gut. Normally, bile acids move back to the liver after digestion, but in ALGS, they

accumulate in the liver, which impacts the normal functioning of liver and other organs. This is called cholestasis (1, 2).

Main symptoms of the disease: Cholestasis affects up to 88% of ALGS patients, starting when they are between 6 and 14 months old (3). It results in intense pruritus, which can lead to skin damage and scarring. It is a significant aspect of ALGS which negatively affects the patients' quality of life: more severe pruritus is linked to a decrease in patient wellbeing (4-6). Many ALGS patients, around 69%, require a liver transplant to manage their itchy skin (7).

Cholestasis can cause further complications (8) such as high cholesterol (which increases the chances of heart disease (9)), fat build-up under muscles (referred to as xanthomas), and stunted growth. These affect physical appearance, which can have a negative impact on mental health (10). Additionally, cholestasis can lead to further liver-related issues, including liver scarring (cirrhosis) in 46% of patients; high blood pressure in the portal vein, a key blood vessel in the liver (portal hypertension) in 40% of patients; and fluid build-up in the abdomen (ascites) in 57% of patients. A liver transplant is often required to manage these complications (4, 11, 12).

Without transplantation, survival rates for ALGS patients rapidly decrease with age: only about 23% of 18-year-olds survive without a transplant (12). In addition to cholestasis, ALGS patients can experience cardiovascular (heart and blood vessel-related), skeletal (bone-related), renal (kidney-related), and ophthalmological (eye-related) issues, as well as abnormal facial appearance (5, 13).

The overall quality of life for caregivers of children with ALGS is significantly influenced by the condition of their children (14).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Patients are diagnosed with ALGS if they have three out of seven of the following symptoms (5-7, 15):

- Cholestasis
- Cardiac issues
- Vascular (blood vessel-related) issues
- Skeletal issues
- Renal issues
- Ophthalmological issues
- Abnormal facial appearance

Patients are commonly diagnosed during infancy and early childhood (4). Because ALGS is a genetic disease, doctors may perform a genetic test to confirm the diagnosis. (4, 7).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Currently, there is no specific guidance for doctors to follow when treating ALGS patients with cholestatic pruritis.

Patients with ALGS are currently treated with off-label medicines (meaning they are not currently approved for use in the UK) such as ursodeoxycholic acid, rifampicin and cholestyramine. Supplementation with fat-soluble vitamins (vitamins A, D, E and K) is also necessary. These medicines can help improve symptoms, but they do not address the underlying cause of the disease (4).

In some cases, especially when patients are very young, a liver transplant is the only option to manage the symptoms. However, liver transplants come with potential complications: infections after the surgery, rejection of the new liver, the need for another transplant, and the requirement for lifelong treatment with drugs that suppress the immune system. Immunosuppressant drugs can lead to kidney problems and increase the risk of infections and cancer (4, 12, 16-21).

Some patients are not eligible for liver transplantation due to other health issues such as cardiovascular disease, which is more likely to develop because of cholestasis (8, 9). This leaves them with fewer treatment options (15, 22).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Severe ALGS symptoms and liver disease consequences always have a significant impact on patients' and their families' quality of life. Sleep disturbances frequently have an adverse effect on a patient's quality of life, resulting in less school activities and delayed cognitive and psychological

development. The Alagille Syndrome (ALGS): Vignette development and utility valuation study and caregiver burden survey (Appendix M) reports:

- Over half (57%) of ALGS patients' education was reportedly impacted by missing school due to appointments or symptoms, and for 32% their concentration at school was impacted.
- The most commonly reported symptoms were pruritus (81% n=88), jaundice (71% n=77), arrhythmia (71%, n=77) and sleep problems (56% n=60). Xanthomas were reported for 33% (n=36) of people with ALGS.

Pruritus is considered the most troublesome symptom of ALGS. It can have a significant impact on a child's school and social activities, and pruritus is an indication for biliary diversion surgery or liver transplant (14). The impact of child itch severity on caregiver sleep quality and that caregivers of children who have had a liver transplant reported less anxiety than those whose child has not had a liver transplant (Appendix M).

The quality of life (QoL) of carers for children with ALGS is significantly impacted by the child's condition, with more severe disease being associated with reduced caregiver quality of life (Appendix M). An assessment of caregiver burden and HRQoL in ALGS (Appendix M), notes:

- The majority of caregivers (79%) reported a negative financial impact from caregiving, 80% (n=67) of those said the level of financial impact was at least moderate.
- Time spent travelling for appointments has a negative impact on the caregiver and their family for nearly half of caregivers (45%).
- Half (48%) of caregivers who had other children without ALGS reported a negative impact on their relationship with the other children; a similar proportion also reported a negative impact of caregiving on their family overall (51%).
- For 39% of caregivers, caring had a negative impact on their relationship with their partner.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

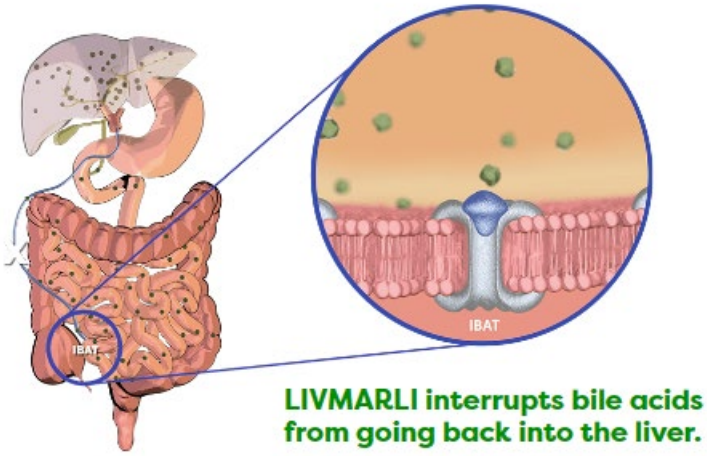
Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Maralixibat works by reducing the build-up of bile acids in the body (as measured by levels in the blood) by stopping bile acids from going back into the liver once they have done their work in the intestines. This means bile acids pass out of the body in stools, allowing the liver and other organs to function normally (1, 23).

Figure 1: The mechanism of action of maralixibat



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Maralixibat is not intended to be used in combination with any other medicine (2).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

ALGS patients should be started on maralixibat treatment under the supervision of a doctor experienced in the management of patients with ALGS or similar diseases (23).

Maralixibat is taken by mouth using an oral syringe and must be swallowed. Patients take the medicine together with food or on an empty stomach up to 30 minutes before eating in the morning. Maralixibat can be taken by patients themselves or administered by caregivers (23).

Please see the patient information leaflet for more information on how to take maralixibat:

https://products.mhra.gov.uk/product/?product=LIVMARLI%209.5%20MG%2FML%20ORAL%20SOLUTION

The dose of maralixibat is based on the patient's weight (23):

- The target dose is 380 micrograms of maralixibat for each kilogram of body weight, once daily.
- The starting dose is 190 micrograms for each kilogram of body weight, once daily.
- After one week, this dose will be increased to 380 micrograms for each kilogram of body weight, once daily.

The table below shows the correct oral syringe size for each prescribed dose:

Prescribed dose volume (mL)	Oral syringe size (mL)
0.1 to 0.5	0.5
0.6 to 1	1
1.25 to 3	3

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Several clinical studies have been performed for maralixibat.

The main clinical trial to study maralixibat for the treatment of cholestatic pruritis was the ICONIC study. The goal of the study was to test the safety and effectiveness of maralixibat. The study had four different phases (24):

- An 18-week open-label run-in period (OL phase): In this phase, all participants received maralixibat, and it was open-label, meaning that everyone knew they were getting the drug.

- A 4-week randomised, double-blind, placebo-controlled drug-withdrawal period (randomised withdrawal phase): In this phase, some participants continued to receive maralixibat, while others received placebo (a dummy treatment that has no active ingredients), and nobody knew who was receiving each treatment.
- A 26-week stable-dosing period at doses up to 400 µg/kg/day participants received maralixibat at various doses, up to 400 µg/kg/day.
- An optional long-term treatment period (long-term extension phase; LTE): In this phase, participants could continue to receive maralixibat, and their dose might be increased to a maximum of 800 µg/kg/day based on how well it worked and how safe it was.

31 patients across Australia and Europe took part, including three patients from the UK. Patients were included if they had evidence of cholestasis and an average daily Itch Reported Outcome ItchRO(Obs) score of more than two. The ItchRO tool is used to measure itch severity over time based on a 5-point scale, where 0 = 'not itchy at all' and 5 = 'extremely itchy'. Changes in ItchRO score by one point or more represent noticeable differences in the itch; for example, a change from 3 to 2 means that a patient went from feeling 'very itchy' to feeling 'somewhat itchy' (24).

The primary endpoint was a comparison of the change in serum bile acid (sBA) levels from week 18 to 22 between the treatment and placebo groups. The goal was to see if the drug lowered sBA levels more than placebo. Secondary endpoints included changes in itching (ItchRO), and indicators of liver health such as liver enzyme levels and bilirubin levels (24).

Additional clinical evidence came from the IMAGINE study and the ITCH study, which also tested the efficacy and safety of maralixibat. Two trials are still ongoing (RISE and MERGE) which include people who were enrolled in studies that have now ended (such as ITCH and ICONIC) to test how well maralixibat works in the long-term, and how safe it is.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the ICONIC study, maralixibat was associated with a significant reduction in liver-related issues, including the need for liver transplant surgery, as well as a long-term improvement in cholestasis and its associated complications, such as pruritus, xanthomas, and stunted growth.

Maralixibat offers long-lasting and significant improvement in controlling cholestasis for patients with ALGS.

During the randomised withdrawal phase of the ICONIC study (where those who have responded to a treatment are randomly assigned to continue receiving the treatment or to receive a placebo), patients who took maralixibat had a significant decrease in the levels of serum bile acids in their blood (24). Participants had previously responded to maralixibat, defined in the trial as having sBA reduced by ≥50% from baseline. In the maralixibat group, the levels of bile acids went

down by about 21.73 points, while in the placebo group, they went up by about 95.55 points. This suggests that maralixibat was effective in controlling serum bile acid even when patients had stopped taking the drug and suggests that the medicine has long-term benefits for those treated with it.

Maralixibat offers long-lasting and significant improvement in controlling cholestatic pruritis for patients with ALGS.

The ICONIC study showed that maralixibat was effective in controlling cholestasis and improving signs of cholestatic pruritus and healthy flow and elimination of bile (24). Specifically, maralixibat treatment led to a decrease in total cholesterol and LDL-C levels, indicating an improvement in cholestasis (3, 25).

Patients who received maralixibat during the randomised withdrawal period of the ICONIC study had stable ItchRO scores from weeks 18 to 22 of the study (24). This was in contrast to patients who received placebo, whose ItchRO scores increased significantly over the same time period (ItchRO scores +0.201 versus. +1.712) which was maintained throughout the long-term study.

Maralixibat significantly reduces other symptoms of cholestasis, such as xanthomas and growth impairment.

Maralixibat not only helps with pruritus, but leads to a decrease in other symptoms of cholestasis, such as xanthomas (8). In the ICONIC study, it was found that xanthoma severity decreased significantly from the start of the trial to 48 weeks into the trial. Additionally, there were significant improvements in the growth of patients, as indicated by improved height z-scores (a way to compare a child's height to the average height of children of the same age and sex) at several time points in the study (24).

Maralixibat significantly reduces the risk of liver-related events and death in ALGS patients.

The results for the maralixibat-treated patients who took part in the ICONIC trial were compared to the results for patients from the Global Alliance for Alagille Syndrome (GALA) database, who were treated with standard treatments. The GALA database is the largest worldwide collection of secure information from people who have ALGS. Data from a study comparing patients in the GALA database to those in the ICONIC trial (26), the GALA Cohort Comparison study, showed that maralixibat is associated with a significant reduction in the risk of liver-related events or death.

The hazard ratio (HR) is a measure of how much more likely one group of people is to experience an event than another group. In this comparison, the HR was 0.305, meaning that people who received maralixibat were 30.5% less likely to have a liver-related event or death than people who did not receive maralixibat (26).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Maralixibat improves long-term fatigue and overall quality of life of paediatric in ALGS patients.

ALGS patients often have sleep disorders, which can lead to missing school, and problems with thinking and learning. ALGS symptoms like pruritus, slow growth, xanthomas, and facial dysmorphism (unusual facial features) can lead to being teased or excluded from activities, especially in childhood. This can have a negative impact on the patient's mental health, leading to depression and problems integrating socially. These problems can make it difficult for ALGS patients to live independently and have a good quality of life.

The Paediatric Quality of Life Inventory (PedsQL) is a questionnaire used to measure how children and teenagers feel about their own quality of life. It helps to give insights into their physical, emotional, and social wellbeing, as well as how they cope with different aspects of their health and daily life, and includes parameters focused on fatigue.

Maralixibat treatment is associated with a long-term improvement in quality of life in children with ALGS, as demonstrated by significant improvement in PedsQL scores at several points during the ICONIC study (24).

Caring for a child with ALGS can also be difficult for caregivers. Caregivers often have to deal with disrupted sleep, less time for other parenting and personal activities, and anxiety about their child's condition (14). The improvements in disease management and quality of life that maralixibat can provide for ALGS patients can also have a positive impact on the quality of life of their caregivers.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Like all medicines, this medicine can cause side effects, although not everybody gets them. This safety data comes from a review of five clinical studies involving 86 patients aged between 1 and 17 years old, who had, on average, been treated with maralixibat 2.5 years. The most common side effects reported in patients with ALGS who were treated with maralixibat in clinical trials for over 5 years were diarrhoea, which affected 36.0% of patients older than 12 months of age, and abdominal pain, which affected 29.1% of these patients. In patients younger than 12 months of age, the most common side effects were also diarrhoea and abdominal pain (2).

For most patients, the reported diarrhoea and abdominal pain were mild to moderate in severity. Only one patient experienced severe abdominal pain. These side effects typically occurred within the first month of treatment, with diarrhoea lasting for an average period of 2 days and

abdominal pain for an average period of 1 day. In 4.7% of patients, treatment was interrupted, or the dose was reduced due to these gastrointestinal reactions. However, none of the patients had to stop taking maralixibat due to these side effects (2).

If a patient experiences persistent diarrhoea and/or abdominal pain with no other identified causes, the doctor may consider reducing the dose or temporarily stopping treatment. The doctor will monitor any signs of dehydration. If treatment is interrupted, the doctor will likely continue treatment once diarrhoea or abdominal pain improve (2).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There are currently no other therapeutic options approved by NICE for the treatment of cholestatic pruritus in ALGS. All other treatments are used off-label, meaning they are not specifically approved for treating this condition. Off-label treatments may have limited clinical data and side effect profiles that are not well understood.

Maralixibat is approved to treat cholestatic pruritus and its effectiveness has been shown in clinical trials. It is also a generally well-tolerated drug and can be started early in life. It is also minimally absorbed, meaning it has few side effects outside of the digestive system, and if a patient does have a side effect, it will be cleared out of the body quickly. In addition, maralixibat is an oral formulation which is appropriate for the target population.

If is it made available in the UK, maralixibat should replace or reduce the use of off-label treatments for cholestatic pruritus in ALGS. It also has the potential to postpone or even eliminate the need for liver transplantation in some people with ALGS.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?

- How the condition, taking the new treatment compared with current treatments affects your quality of life.

The economic model was created in Microsoft Excel and helps compare the costs and health outcomes of two different treatments, one being maralixibat.

How the model reflects the condition

The model uses various health states to represent how the disease progresses:

1. Cholestasis and pruritus, with response to treatment
2. Cholestasis and pruritus, with loss of response to treatment
3. Cirrhosis
4. Portal hypertension
5. Ascites
6. Surgical biliary diversion (SBD) (only in patients who have not got cirrhosis yet)
7. Post-SBD
8. Liver transplant (without cardiac or renal involvement, with some patients receiving a re-transplant)
9. Post-liver transplant
10. Death

ALGS is a complex condition that affects not only the liver but also the heart and kidneys. Some patients with severe heart or kidney problems cannot get a liver transplant, and this is taken into account in the model.

The model works in cycles of 12 weeks, which is about how long it takes for patients to respond to maralixibat. The choice of a 12-week cycle helps to avoid any bias in the analysis.

The progression of the disease is mainly driven by how patients respond to maralixibat. The treatment is assumed to slow down the disease from getting worse and helps with symptoms like pruritus. Once the disease becomes unresponsive to medication, it continues to progress until patients need a liver transplant or surgery.

The information used to evaluate maralixibat comes from two studies, the ICONIC and GALA studies, and additional information from published studies. The model includes details about the conditions of patients at the start, how they respond to treatment, and when they stop treatment.

Data regarding the likelihood of their condition changing to more severe stages like cirrhosis, portal hypertension, and ascites was used. It also looks at the chances of patients needing liver transplantation or another surgical procedure (SBD), as well as mortality rates. This information is mainly taken from the published literature rather than the clinical trials.

The main assumption in the analysis is that maralixibat works by reducing sBA, which is related to reducing pruritus and slowing down the progression of ALGS. It also assumes that people who respond well to treatment have a lower risk of death compared to those who do not respond, and that some patients cannot have liver transplants due to other health issues.

The analysis relies on data from a vignette study to provide data for quality of life. A vignette study is where researchers create fictional scenarios or "vignettes" to understand people's feelings or experiences to understand the patient's perspective.

Modelling how the costs of treatment differ with the new treatment

As noted earlier, the current treatment for Alagille syndrome consists of a combination of off-label medicines, that do not treat the underlying cause of the disease. This makes maralixibat comparatively expensive, however it is important to keep in mind the innovativeness of the medicine.

Healthcare resource costs are applied to the model, which represent any costs of doctor/nurse time, or tests that the patient may require. These costs change based on the health state that the patient is in.

The cost of surgery, such as liver transplantation or biliary diversion, would not be applicable to patients receiving maralixibat. This includes any follow-up for these procedures, and any costs of any complications that may occur following the procedure.

Cost effectiveness results

The Incremental Cost Effectiveness Ratio (ICER) is a measure used to decide if a treatment is worth its cost. It tells us how much more it costs to get more benefit from the treatment, using quality-adjusted life years (QALYs), which measure the quality and quantity of life that a treatment adds. In this case, when comparing maralixibat to the current treatments, maralixibat provides additional QALYs, meaning that it provides an improvement in both the length and quality of a patient's life. Taking into account the additional costs and QALYs, maralixibat brings good value for the money spent.

Additional factors

Maralixibat is expected to have a significant impact beyond direct health benefits. Cholestatic pruritus can disrupt every aspect of life and can have serious long-term effects. For example, it can lead to post-traumatic stress disorder, impulse control problems, and other social and emotional disabilities. ALGS is a complex disease that can increase the risk of death for patients, and not everyone can have a liver transplant, which makes their outlook much worse.

Maralixibat can improve pruritus, help with sleep, and support growth. It can also slow down the progress of the disease and potentially avoid or delay the need for surgery or a liver transplant. This is very positive for patients with ALGS and their families because it can make it easier for them to go to school, find a job, and improve their overall quality of life.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Maralixibat is an innovative medicine that has been given 'Orphan' status by the European Medicines Agency (EMA) and MHRA, because it is intended to treat a rare disease.

Currently, there are no effective approved treatments for cholestatic ALGS, and the standard medical approach is only supportive, which means it does not target the root cause of the disease. In some cases, patients have had to undergo invasive procedures like biliary diversion, which diverts bile away from the body through a stoma, requiring drainage bags and tubing.

Liver transplantation is another option for ALGS patients, but it is considered when all other treatments fail, and it is a complex surgery with substantial risks. Furthermore, finding suitable organ donors can be a challenge. Maralixibat offers a crucial treatment option, by improving symptoms such as pruritus, reducing bile acid levels, and delaying or avoiding the need for liver transplantation or invasive biliary diversion.

Beyond the physical and mental health impacts of ALGS, the disease can have broader consequences on education, work, social interactions, and more. With better control provided by medications like maralixibat, these wider aspects of a patient's life could be significantly improved.

Due to the small patient population, coupled with the paucity of available quality of life and utility data in the UK for patients with ALGS, there is little opportunity to fully characterise all of the above burden mentioned. Patients and carers often 'normalize' the pruritus and other symptoms of the disease, as they have to live with it, this means that when quality of life decrement is captured for patients with severe pruritus, scores are not too dissimilar from that of a child with a minor ailment, compared to a healthy child.

In addition, the lifelong cost of maralixibat, compared to a one-off cost of liver transplantation, appears as an extensive cost to the healthcare system. However, the impact of a paediatric liver transplantation, lifelong risk of rejection, re-transplantation, and death, must be considered in more detail than the QALY can demonstrate currently in the economic model, as the burden to children and carers is immense.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Informal caregiving is often a significant part of managing chronic diseases, and it is typically taken on by family members. Research indicates that a majority of informal caregivers are women (27, 28). These women play a crucial role in providing physical, emotional, and psychological support to those with chronic illnesses. However, this caregiving responsibility can be quite demanding and emotionally taxing for the women caregivers. Consequently, it can lead to a greater burden on women caregivers compared to caregivers of all genders, contributing to inequalities in the caregiving experience.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Term	**Meaning**
7αC4	A marker of healthy/non-cholestatic bile acid synthesis
AE	Side effect
Alagille syndrome/ALGS	A disease in which the number of bile ducts are reduced, which means that bile does not easily flow from the liver to the bowel, impacting the normal functioning of the liver and other organs
Ascites	Build-up of fluid in the abdomen
Bile acids	A key component of bile
Cardiac	Heart-related
Cardiovascular	Heart and blood vessel -related
Cholestasis/cholestatic	Abnormal bile flow
Cholestatic pruritis	Bile-related severe itching
Chronic fatigue	Severe tiredness
Cirrhosis	Scarring of the liver
ItchRO	measure of the impact of pruritis
LDL-C	Biochemical markers for cholestasis
Marketing authorisation	The process of reviewing and assessing the evidence to support a medicine, finalised by granting of a licence to be sold

Off-label	Not currently approved for use in the UK
Ophthalmological	Eye-related
PedsQL	Measure of patient quality of life
Portal hypertension	High blood pressure in a key liver blood vessel – the portal vein
Pruritis	Severe itching
Renal	Kidney-related
SAE	Serious side effects
SBA levels	Blood levels of bile acids
Skeletal	Bone-related
TEAE	Side effects
Vascular	Blood vessel -related
Xanthomas	Fat build-up underneath muscles

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Maralixibat for treating cholestatic pruritus in Alagille Syndrome [ID3941]

Clarification questions (updated)

December 2023

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Notes for company

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Section A: Clarification on effectiveness data

Document A

A1. Table 3, page 12: What is the dosing regimen in the maralixibat arm of the ICONIC trial and the GALA study? In the Table 3 of document A stated dosing is maralixibat ≤380 µg/kg/day (ICONIC) and maralixibat (≥380 µg/kg/day, ≥760 µg/kg/day from week 49 onwards) in GALA? In table 5 of document B, it is stated as ≥380 µg/kg/day for ICONIC. Which of this is correct (≤380 µg/kg/day or ≥380 µg/kg/day)?

Patients in the ICONIC study received maralixibat ≤380 µg/kg/day, increased to ≤760 µg/kg/day from week 49 onwards, as such Document A Table 3 should read "Maralixibat (≤380 µg/kg/day, ≤760 µg/kg/day from week 49 onwards)".

Document B

A2. B.2.1.1 Identification of published studies and B2.1.2, pages 26-28: why was IMAGO study only mentioned in the pooled analyses and not separately described?

The results of IMAGO (LUM001-302) were published as part of a pooled analysis which has been described in section B.2.1.1. accordingly. As such, it was not

included in section B.2.1.2 as outcomes including the study participants have been published and are described in section B.2.1.1. Additional information describing the conduct and standalone findings of IMAGO have been provided in section B.2.6.6. of the company submission.

A3. Priority question: B.2.2 List of relevant clinical effectiveness evidence, Table 5, page 28: What was the rationale for defining the primary efficacy endpoint (mean sBA level reduction) in the responders (sBA reduced ≥50%) as opposed to ITT (entire study) population?

The primary efficacy endpoint in ICONIC (LUM001-304) was estimated only in study participants who achieved an sBA reduction ≥50% from baseline. This was undertaken as the efficacy endpoint is calculated during a randomised withdrawal period, as such, patients who did not respond in terms of an sBA reduction from baseline would not be expected to either continue to achieve a response if randomised to maralixibat or have their sBA increase if randomised to placebo. This approach is consistent with the SmPC for maralixibat that states patients should discontinue treatment if they have not experienced a treatment benefit after 3 months of continuous treatment. However, the randomised withdrawal period and long-term extension conclusively demonstrate that the benefit of treatment with maralixibat is sustained in those who achieve an initial response, and that benefits in terms of reductions in sBA and pruritis are superior to standard of care alone.

A4. B.2.3.1 Summary of methodologies, page 33: Distribution between the two cohorts was assessed for critical factors, including age, bilirubin, GGT, and ALT. Balance was assessed by examining a standardised differences plot (Figure 7). Were the baseline sBA levels and itchRO scores compared across the maralixibat cohort and GALA control group? If not, why?

The GALA comparison cohort is based on an observational cohort of patients, as such, data collection is not as consistent or comprehensive as for the associated maralixibat clinical trials. As such, only 73 patients had measurements for baseline sBA in the GALA control group, however, a comparison was made based on patients who had a recorded baseline sBA level. Patients in the pooled maralixibat cohort had a median (inter-quartile range) of 200 µmol/L (81-371) in comparison with 125 µmol/L (39-260) in the GALA comparison cohort (Table 13, B.2.3.1. of company

submission). The difference between the groups was statistically significant (p = 0.003), with patients enrolled in the maralixibat cohort having higher baseline sBA on average. As such, differences in baseline characteristics with respect to sBA are likely to bias comparative efficacy results in favour of the GALA control group (i.e., reduced the estimated treatment effect of maralixibat) with respect to event-free survival. ItchRO was not captured in GALA as although ItchRO is frequently used in clinical trials as a standardised and validation measure of itch, it is not frequently collected by clinicians in clinical practice. As such, a baseline comparison between the two cohorts in terms of ItchRO is not possible.

A5. Priority question: B.2.3.1.1 Baseline characteristics, Tables 10-11, pages 38-39: Please provide a breakdown of patients meeting and not meeting the sBA ≥50% improvement from baseline to Week 12 or Week 18 criteria in the ICONIC study in the format below. Please stratify the data by treatment arms if feasible.

The breakdown of enrolled patient sBA at baseline, week 12, week 28 and week 22 are shown in Table 1. Please note that patients failing to meet sBA response criteria by week 12, did not continue to contribute sBA measurements in the clinical trial, as such this data has not been provided. The rationale behind this omission is described in the company response to question A3.

Table 1. Breakdown of patients meeting the sBA ≥50% from baseline to Week 12 or Week 18 criteria

sBA level (µmol/L)	Baseline (week 0)	Week 12			Week 18			Week 22	
		Overall	MRX-MRX-MRX	MRX-PBO-MRX	Overall	MRX-MRX-MRX	MRX-PBO-MRX	MRX	PBO
Total									
n	31	29	N/A	N/A	29	N/A	N/A	13	16
Mean (SD)	283.43 (210.569)	172.32 (181.805)	N/A	N/A	192.50 (161.278)	N/A	N/A	216.23 (207.335)	253.19 (208.380)
sBA responder									
n	15	N/A	5	10	N/A	5	10	5	10
Mean (SD)	244.91 (197.16)	N/A	66.91 (20.08)	83.29 (14.135)	N/A	100.22 (24.714)	132.13 (17.397)	68.83 (49.589)	232.50 (34.908)
sBA non-responder									
n	14	Not collected or analysed							
Mean (SD)	318.07 (229.849)								
Patients excluded for reasons other than response									
n	2	0	0	0	0	0	0	0	0

sBA level (µmol/L)	Baseline (week 0)	Week 12			Week 18			Week 22	
		Overall	MRX-MRX-MRX	MRX-PBO-MRX	Overall	MRX-MRX-MRX	MRX-PBO-MRX	MRX	PBO
Mean (SD)	329.88 (236.223)	N/A	N/A	N/A	N/A			N/A	N/A

Abbreviations: *MRX, maralixibat; PBO, placebo; sBA, serum bile acid; SD, standard deviation;*

A6. Please present a summary of baseline characteristics of patients in the ICONIC study in the format below, stratified based on whether patients met the sBA ≥50% response criteria or not at either week 12 or week 18. The requested tables should resemble Table 10 and Table 11 from Document B respectively.

Please see the requested data below in Table 2 to Table 5.

Table 2. Patient demographics in the ICONIC study for those who achieved sBA ≥50% at week 12 or week 18

	MRX (n=5)	Placebo (n=10)
Age, in years[a]		
Mean (SD)	7 (4.64)	6.4 (4.17)
Sex, n (%)		
Male	3 (60%)	7 (70%)
Country, n (%)		
Australia	4 (80%)	4 (40%)
Belgium	0 (0%)	2 (20%)
France	0 (0%)	1 (10%)
Spain	0 (0%)	1 (10%)
Poland	0 (0%)	1 (10%)
United Kingdom	1 (20%)	1 (10%)

Abbreviations: *MRX, maralixibat; SD, standard deviation.*

Table 3. Patient demographics in the ICONIC study for those who did not achieve sBA ≥50% at week 12 or week 18

	MRX (n=8)	Placebo (n=6)
Age, in years[a]		
Mean (SD)	4.5 (5.32)	4.8 (2.99)
Sex, n (%)		
Male	6 (75%)	3 (50%)
Country, n (%)		
Australia	1 (12.5%)	0 (0%)
Belgium	1 (12.5%)	0 (0%)
France	3 (37.5%)	5 (83.3%)
Spain	2 (25%)	0 (0%)
Poland	0 (0%)	1 (16.7%)
United Kingdom	1 (12.5%)	0 (0%)

Abbreviations: *MRX, maralixibat; SD, standard deviation.*

Table 4. ALGS disease characteristics and history in the ICONIC study: for patients who achieved sBA ≥50% at week 12 or week 18

	MRX (n=5)	Placebo (n=10)
Mutation Present, n (%)		
JAGGED1	5 (100%)	10 (100%)
sBA, in µmol/L		
Mean	288.81	222.96
ItchRO(Obs) weekly Morning Average Severity (Item l) score [a]		
Mean	2.929	2.936
ItchRO(Obs) weekly Morning Average Frequency (Item 2) score [a]		

	MRX (n=5)	Placebo (n=10)
Mean	3.086	2.964
Clinician Scratch Scale Score		
Mean	2.8	3.3
Cholesterol, in mg/dL		
Mean	313.8	375.0
Median	309.0	353.0
LDL Cholesterol, in mg/dL		
Mean	169.0	172.4
Median	178.0	168.0
7αC4, in ng/mL		
Mean	9.06	5.90
Median	10.00	3.00
Clinician Xanthoma Scale Score		
Mean	0.6	0.5
Median	0	0
Height z-score at baseline visit		
Mean	-0.759	-1.516
Median	-0.902	-1.535

***Abbreviations**: ALGS, Alagille syndrome; ItchRO, Itch-reported outcome; LDL, low-density lipoprotein; MRX, maralixibat; sBA, serum bile acid; SD, standard deviation.*

Table 5. ALGS disease characteristics and history in the ICONIC study: for patients who did not achieve sBA ≥50% at week 12 or week 18

	MRX (n=8)	Placebo (n=6)
Mutation Present, n (%)		
JAGGED1	8 (100%)	6 (100%)
sBA, in µmol/L		
Mean	336.19	293.90
ItchRO(Obs) weekly Morning Average Severity (Item l) score [a]		
Mean	2.848	2.921
ItchRO(Obs) weekly Morning Average Frequency (Item 2) score [a]		
Mean	3.030	3.048
Clinician Scratch Scale Score		
Mean	3.1	3.8
Cholesterol, in mg/dL		
Mean	709.5	604.3
Median	339.0	354.0
LDL Cholesterol, in mg/dL		
Mean	174.6	234.5
Median	167.0	217.5
7αC4, in ng/mL		
Mean	18.34	7.58
Median	5.45	1.40
Clinician Xanthoma Scale Score		
Mean	1.3	1.5
Median	1	1
Height z-score at baseline visit		
Mean	-2.029	-2.372
Median	-1.839	-1.667

***Abbreviations**: ALGS, Alagille syndrome; ItchRO, Itch-reported outcome; LDL, low-density lipoprotein; MRX, maralixibat; sBA, serum bile acid; SD, standard deviation.*

A7. Priority question: Among the ICONIC study participants, 15 out of 31 achieved a reduction of at least 50% in sBA levels at week 12 or 18. Is the company able to share the individual sBA levels for these responders, measured at baseline and at each assessment point up to week 204 or until discontinuation from the study, whichever happens first? If it's not possible to

provide individual sBA data for the 15 responders, but summary data (Mean (SD) sBA levels at each assessment point can be provided, it would also be helpful.

Please refer to Table 6 for summary data describing the least squares mean change in sBA from baseline and associated standard errors for patients meeting the sBA response criteria in ICONIC (LUM001-304). Data are provided by study visit from week 12 through to week 204 from baseline.

Table 6. Summary sBA levels at each timepoint for the mITT population, which includes all subjects who were enrolled, received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the week 12 or week 18 measurement (sBA responders).

sBA CFB (µmol/L)	MRX-MRX-MRX			MRX-PBO-MRX				
	n	LS Mean*	SE	n	LS Mean*	SE		
Week 12	5	66.91	20.080	10	83.29	14.135		
Week 18	5	100.22	24.714	10	132.13	17.397		
Week 22	5	68.83	49.589			10	232.50	34.908
Week 48	5	36.75	29.318			10	100.39	20.638
Week 60	5	50.49	40.488			7	103.31	34.135
Week 72	5	47.16	24.683			7	77.26	20.810
Week 84	5	58.67	33.001			9	115.78	24.481
Week 96	4	56.25	30.800			9	108.67	20.452
Week 120	3	24.80	51.371	7	150.85	33.294		
Week 132	3	105.81	49.964	8	100.88	30.068		
Week 144	3	31.47	52.716	7	107.33	33.959		
Week 156	3	67.24	40.745			7	86.45	26.248
Week 168	3	25.68	38.699			7	112.43	24.930
Week 192	3	-3.42	57.236			7	111.51	36.871
Week 204	3	-9.81	62.770			7	98.29	40.436

Abbreviations: *CFB, change from baseline; LS, least squares; SE, standard error; MRX, maralixibat; PBO, placebo;*
**Estimates are from a mixed model with treatment group as a fixed effect and baseline value as a covariate.*

A8. Priority question: B.2.3.1.1 Baseline characteristics. For the maralixibat cohort (n=84) and GALA control group (n=469) in the GALA Cohort Comparison Study, Table 13 only provided data on genetic mutation and sBA. Could data on other ALGS disease characteristics and history (i.e. the same measures reported in Table 11 for ICONIC study) be provided in the same format? Could the same information (patient demographics and ALGS disease

characteristics and history) be provided for the subgroups of UK patients within the maralixibat cohort and GALA control group respectively?

Individual patient data for the GALA comparison cohort is not available to the company, however, please see Table 7 for a summary of all available baseline characteristics for the GALA comparison study. Similarly, no more granular data stratified by country can be provided.

Table 7. Summary baseline characteristics for the GALA comparison study, stratified by study arm.

	Maralixibat cohort (N=84)	***GALA control group (N=469)***	***p-value***
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	
Age at baseline, in years			
Median (Ql, Q3)	[redacted]	[redacted]	[redacted]
Region, n (%)			
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	
Australia	[redacted]	[redacted]	
Mutation, n (%)			
JAGGED1	[redacted]	[redacted]	[redacted]
NOTCH2	[redacted]	[redacted]	
Other/unknown	[redacted]	[redacted]	
Total bilirubin in mg/dL			
Mean (SD)	[redacted]	[redacted]	-
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
<2 (n, %)	[redacted]	[redacted]	[redacted]
≥2 (n, %)	[redacted]	[redacted]	
GGT in log10 x ULN			
Mean (SD)	[redacted]	[redacted]	-
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
<3 (n, %)	[redacted]	[redacted]	[redacted]
≥3 (n, %)	[redacted]	[redacted]	
ALT in U/L			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]
sBA[b] in µmol/L			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (Q1, Q3)	[redacted]	[redacted]	[redacted]

For continuous measures, a Wilcoxon rank-sum test was used to compare the treatment groups.
a. Due to more than 20% of the cells having expected counts
b. Baseline sBA was available for 73 patients in the GALA control group. Approximately 85% of the sBA values were not available in the GALA clinical research database because frequent sBA measurement is not part of the clinical practice.
***Abbreviations**: GGT, gamma-glutamyl transpeptidase; Q, quartile; sBA, serum bile acid; ULN, upper limit of normal*

A9. B.2.3.1.1 Baseline characteristics: Could the baseline total bilirubin level (n, mean, standard deviation) for both patients in the ICONIC study and the maralixibat cohort and GALA control group in the GALA Cohort Comparison Study be provided?

Please see Table 8 for a summary of baseline total bilirubin levels in the ICONIC (LUM001-304) and GALA cohort comparison studies, stratified by treatment arm and study phase (ICONIC only).

Table 8. Baseline total bilirubin levels for patients in the ICONIC study and GALA cohort comparison study

Total bilirubin (mg/dL)	ICONIC					GALA cohort comparison study	
	Open-label phase (≤Week 18)	RWP (Weeks 19-22)		After RWP (Weeks 23-48)	Long-term efficacy phase (>Week 48)		
	MRX	MRX	PBO	MRX	MRX	MRX	Control
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

***Abbreviations**: MRX, maralixibat; PBO, placebo ; SD, standard deviation*

A10. B.2.3.1.1 Baseline characteristics: Could the company provide information on baseline non-maralixibat treatments (e.g. those listed as comparators in the NICE final scope) received by UK patients included in the maralixibat cohort and GALA control group in the GALA Cohort Comparison Study; and the same information for "previous responders" and "non-responders" in the ICONIC study? The company may also wish to provide any additional data from the broader GALA Clinical Research Registry or other literature with regard to patient characteristics and ALGS disease characteristics and history for UK patient population likely to be eligible for maralixibat treatment to justify the applicability of ICONIC results to the UK setting.

A summary of ICONIC (LUM001-304) participant concomitant medication use at baseline is presented in Table 9. A breakdown of medication use by country is not currently available; similarly, the company does not have access to GALA comparison cohort data and cannot provide a summary of concomitant medication use. However, sensitivity analysis conducted as part of the GALA comparison cohort study by geographic region showed that conclusions were consistent.

As ALGS is a rare condition, the company is not aware of published summary evidence describing the breakdown of medication use in the UK, however, concomitant medications used in ICONIC are well aligned with standard clinical guidelines for the management of ALGS, which include first line use of ursodeoxycholic acid ([redacted] of enrolled patients) and cholestyramine, and an

escalation to rifampicin ([redacted] of patients) in patients who continue to experience symptoms. Although only 3.2% of enrolled patients were in receipt of cholestyramine due to study inclusion criteria, patients enrolled in ICONIC were required to have intractable pruritus and extremely elevated sBA (over 3 x the upper limit of normal), as such, the lack of cholestyramine use in ICONIC is not anticipated to impact assessments of treatment efficacy, as patients should not be responding to existing treatments as a condition of study eligibility.

Table 9. Baseline concomitant medication use in ICONIC (LUM001-304).

Number of subjects taking prior pruritis medications	*Patients (n, %)*
Summary of concomitant medication use	
No medications	[redacted]
1 medication	[redacted]
2 medications	[redacted]
≥3 medications	[redacted]
Concomitant medications	
Rifampicin	[redacted]
Phenobarbital	[redacted]
Antihistamines for systemic use	[redacted]
Ursodeoxycholic acid	[redacted]
Ornithine aspartate	[redacted]
Cholestyramine	[redacted]
Naltrexone	[redacted]
Sertraline	[redacted]

A11. Priority question: Table 14, pages 41-43 – please clarify whether the primary efficacy calculation refers to "mean change from Week 18 to Week 22" (as mentioned in the Hypothesis and objectives section of Table 14) or "the difference between the maralixibat and placebo groups in the change in sBA levels from Week 19 to Week 22" (as stated in the Statistical analysis section of Table 14)? Which week – Week 18 or Week 19 – is used to calculate the change scores? Which day of the week was measurement done – is it the beginning (day 1) or the end (day 7) of the week?

The mean change in fasting sBA levels in participants who previously responded to maralixibat treatment (as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18) was calculated from Week 18 (and not week 19) to Week 22. Measurements for week 18 were taken within five days of the first day of Week 18

(i.e., day 126 ± 5 days). Similarly, measurements for Week 22 were taken within five days of the first day of Week 22 (i.e., day 154 ± 5 days).

A12. Table 14, pages 41-43 – mean changes for secondary efficacy endpoints were measured from baseline to week 18, 22, and 48 and onwards. Please clarify whether this was the single baseline (start of open label run-in screening phase) or different baselines for each study phase (e.g., randomized withdrawal, stable dosing, 1st long term extension, 2nd long term extension)?

Baseline refers to the observation obtained at study day 0 before the first dose of study drug. If study day 0 was not available/missing, the last value obtained during the screening period was used as the baseline (day 0) observation. An analogous approach was used to define the baseline for each of the 3 treatment phases (open label, randomised withdrawal, and after the randomised withdrawal). The reference period used varies by secondary efficacy endpoint:

- *Change from Week 18 (i.e., Week 18 baseline) to Week 22 in pruritus in subjects who previously responded to maralixibat treatment as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), ALP, ALT, total bilirubin, direct bilirubin*
- *Change from baseline (i.e. Week 0) to Week 18 in pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), fasting sBA levels, ALP, ALT, total bilirubin, direct bilirubin*

Similarly for additional efficacy outcomes:

- *Responder analysis versus study baseline (i.e. Week 0) at Weeks 18, 48, 60, 72, 84, 96, and 100 in pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), CSS*
- *Change from baseline (i.e. Week 0) to Weeks 18, 22, and 48, and then every 12 weeks in pruritus as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]), fasting sBA levels, ALP, ALT, total bilirubin, direct bilirubin, other biochemical markers of cholestasis, bile acid synthesis (7αC4)*

A13. Priority question: Table 14, page 42, Modified Intention to Treat (MITT) population: Please clearly define the Modified Intention to Treat (MITT) population, including the inclusion/exclusion criteria and how this group differs from the Intention to Treat (ITT) population. Please also specify the

number of individuals excluded from the MITT population compared to the ITT population.

MITT refers to all patients who were enrolled and received the study drug up to Week 18 and had a reduction from baseline of sBA of ≥50% at Week 12 or Week 18. In total, 15 patients were classed as sBA responders, and as such were part of the MITT. No other inclusion criteria defined the MITT patient population. ITT refers to all patients who were enrolled and received at least one dose of the study drug; in total, 31 patients received at least on dose of study drug and as such were part of the ITT.

A14. Table 14, page 42, Modified Intention to Treat (MITT) population: please clarify the primary endpoint's definition, which was stated as follows: "Mean change in fasting sBA levels from Week 18 to Week 22 in patients who had previously responded to maralixibat treatment, defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 in the modified intention-to-treat (MITT) Population." Does this imply that only patients whose sBA levels reduced by at least 50% at week 12 or week 18 compared to week 0 (baseline) values are included in the primary efficacy analysis?

The primary efficacy endpoint of this study was the mean change from Week 18 to Week 22 of fasting sBA levels in participants who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18. As such, only those patients whose sBA levels reduced by at least 50% at week 12 or week 18 compared with baseline were included in the primary efficacy analysis. The rationale for this approach is described in the company's response to question A3.

A15. Figure 9, page 44: It is not clear how the sample of 490 participants was obtained after excluding 525 (442+61+22) out of 1,438 participants; this leaves 913 (not 490) participants. Please clarify.

In addition to the 525 patients referenced, a proportion of potential visits were also excluded due to patient demographics at the time of the visit, or missing data. As such, some patients were excluded due to a lack of contributing data after visit inclusion/exclusion criteria were applied. In summary, 525 patients were excluded due to location, date of birth, or inclusion in a clinical trial. Removing ineligible visits resulted in an additional 423 patients no longer contributing data to the study. In

total, 948 patients were excluded from the original 1,438 patients, leaving 490 patients eligible for inclusion in the GALA comparison cohort.

A16. Figure 8, page 45: Out of the 36 children screened for the ICONIC trial (Figure 8 in Document B), 5 were not enrolled. Could the company please provide the reasons for the non-enrolment of these 5 children?

Of the 5 children who were not enrolled in the ICONIC study following screening, 1 was excluded due to decompensated cirrhosis, and the other 4 were excluded as they failed to meet the minimum itch requirement of an average daily ItchRO score over 2 for 2 consecutive weeks in screening.

A17. B.2.6.5, page 60: Please provide a breakdown by treatment cohort (maralixibat versus GALA control cohort) of the liver-related events and death that made up the composite outcome of Event Free Survival in the GALA Cohort Comparison Study.

The data available on breakdown of liver-related events and death that contribute to the estimation of event-free survival is presented in Table 10.

Table 10. Contributing events in the GALA comparison cohort, stratified by study arm

	Maralixibat Cohort (N=84)	***GALA Control Group (N=469)***
Total contributing events (first event only)	[redacted]	[redacted]
Liver transplantations (first event only)	[redacted]	[redacted]
Surgical biliary diversions (first event only)	[redacted]	[redacted]
Liver decompensations (first event only)	[redacted]	[redacted]
Deaths (first event only)	[redacted]	[redacted]
Liver transplantations (total)[a]	[redacted]	[redacted]
Deaths (total)[a]	[redacted]	[redacted]

[a] includes liver transplantations and deaths occurring following an initial event meeting the criteria for event-free survival.

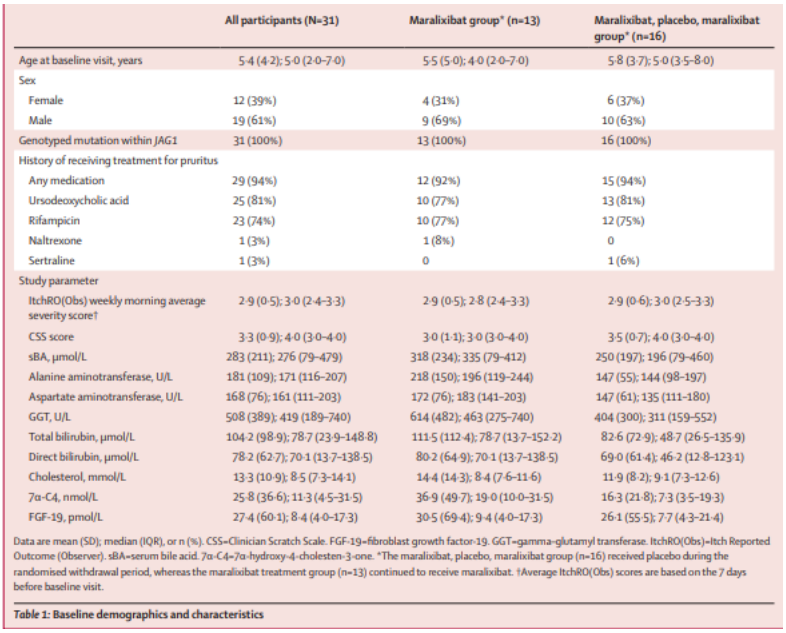
The company does not have access to the GALA comparison cohort data, and as such cannot provide a detailed breakdown of time-to-event for each outcome in tabular format as requested. However, a summary of the age of each participant at the incidence of each contributing event is shown in ***Error! Reference source not found.****.*

[redacted]

A18. B.2.5 Critical appraisal of the relevant clinical effectiveness evidence, Table 16-17, page 46: Could the company provide statements/explanations supporting the critical appraisal responses (only for 'Yes' and N/A)?

Please see Table 11 and Table 12 for additional supporting statements and evidence justifying responses during the quality assessment for ICONIC (LUM001-304) and the GALA cohort comparison study.

Table 11. Quality assessment of ICONIC

Quality assessment criteria	*Response*	*Explanation*
Was randomisation carried out appropriately?	*Yes*	*All participants were randomly assigned (1:1) in a blinded fashion to continue receiving the same dose of maralixibat or receive placebo for a period of 4 weeks. Randomisation used a permuted block algorithm stratified by predefined response criteria (≥50% sBA reduction from baseline to week 12 or week 18) and with entire blocks (size 4) assigned by study site using SAS software (version 9.4) by an unblinded statistician not involved in the conduct of the trial or analysis of the data.*[1]
Was the concealment of treatment allocation adequate?	*N/A*	*The randomisation code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code. Both maralixibat and placebo were identical in appearance. All participants, investigators, and laboratory staff were masked to treatment allocation.*[1]
Were the groups similar at the outset of the study in terms of prognostic factors?	*Yes*	*Baseline characteristics were well aligned between study groups, as reported by Gonzales et al. in the primary study publication.*[1] 
Were the care providers, patients, and outcome assessors blind to treatment allocation?	*Yes*	*All participants were randomly assigned (1:1) in a blinded fashion to continue receiving the same dose of maralixibat or receive placebo for a period of 4 weeks. Randomisation used a permuted block algorithm stratified by predefined response criteria (≥50% sBA reduction from baseline to week 12 or week 18) and with entire blocks (size 4) assigned by study site using SAS software (version 9.4)*

	All participants (N=31)	Maralixibat group* (n=13)	Maralixibat, placebo, maralixibat group* (n=16)
Age at baseline visit, years	5·4 (4·2); 5·0 (2·0–7·0)	5·5 (5·0); 4·0 (2·0–7·0)	5·8 (3·7); 5·0 (3·5–8·0)
Sex			
Female	12 (39%)	4 (31%)	6 (37%)
Male	19 (61%)	9 (69%)	10 (63%)
Genotyped mutation within *JAG1*	31 (100%)	13 (100%)	16 (100%)
History of receiving treatment for pruritus			
Any medication	29 (94%)	12 (92%)	15 (94%)
Ursodeoxycholic acid	25 (81%)	10 (77%)	13 (81%)
Rifampicin	23 (74%)	10 (77%)	12 (75%)
Naltrexone	1 (3%)	1 (8%)	0
Sertraline	1 (3%)	0	1 (6%)
Study parameter			
ItchRO(Obs) weekly morning average severity score†	2·9 (0·5); 3·0 (2·4–3·3)	2·9 (0·5); 2·8 (2·4–3·3)	2·9 (0·6); 3·0 (2·5–3·3)
CSS score	3·3 (0·9); 4·0 (3·0–4·0)	3·0 (1·1); 3·0 (3·0–4·0)	3·5 (0·7); 4·0 (3·0–4·0)
sBA, μmol/L	283 (211); 276 (79–479)	318 (234); 335 (79–412)	250 (197); 196 (79–460)
Alanine aminotransferase, U/L	181 (109); 171 (116–207)	218 (150); 196 (119–244)	147 (55); 144 (98–197)
Aspartate aminotransferase, U/L	168 (76); 161 (111–203)	172 (76); 183 (141–203)	147 (61); 135 (111–180)
GGT, U/L	508 (389); 419 (189–740)	614 (482); 463 (275–740)	404 (300); 311 (159–552)
Total bilirubin, μmol/L	104·2 (98·9); 78·7 (23·9–148·8)	111·5 (112·4); 78·7 (13·7–152·2)	82·6 (72·9); 48·7 (26·5–135·9)
Direct bilirubin, μmol/L	78·2 (62·7); 70·1 (13·7–138·5)	80·2 (64·9); 70·1 (13·7–138·5)	69·0 (61·4); 46·2 (12·8–123·1)
Cholesterol, mmol/L	13·3 (10·9); 8·5 (7·3–14·1)	14·4 (14·3); 8·4 (7·6–11·6)	11·9 (8·2); 9·1 (7·3–12·6)
7α-C4, nmol/L	25·8 (36·6); 11·3 (4·5–31·5)	36·9 (49·7); 19·0 (10·0–31·5)	16·3 (21·8); 7·3 (3·5–19·3)
FGF-19, pmol/L	27·4 (60·1); 8·4 (4·0–17·3)	30·5 (69·4); 9·4 (4·0–17·3)	26·1 (55·5); 7·7 (4·3–21·4)

Data are mean (SD); median (IQR), or n (%). CSS=Clinician Scratch Scale. FGF-19=fibroblast growth factor-19. GGT=gamma-glutamyl transferase. ItchRO(Obs)=Itch Reported Outcome (Observer). sBA=serum bile acid. 7α-C4=7α-hydroxy-4-cholesten-3-one. *The maralixibat, placebo, maralixibat group (n=16) received placebo during the randomised withdrawal period, whereas the maralixibat treatment group (n=13) continued to receive maralixibat. †Average ItchRO(Obs) scores are based on the 7 days before baseline visit.

Table 1: Baseline demographics and characteristics

[1] Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet*. 2021;398(10311):1581-1592. doi:10.1016/S0140-6736(21)01256-3

Quality assessment criteria	Response	Explanation
		by an unblinded statistician not involved in the conduct of the trial or analysis of the data. The randomisation code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code. Both maralixibat and placebo were identical in appearance. All participants, investigators, and laboratory staff were masked to treatment allocation.[1]
Were there any unexpected imbalances in drop-outs between groups?	*No*	*100% of patients in both study arms completed the randomised withdrawal phase between Week 18 and Week 22.*
Is there any evidence to suggest that the authors measured more outcomes than they reported?	*Yes*	*Key secondary endpoints were assessed in all study participants from baseline to weeks 18 and 48 and compared the maralixibat and placebo groups during the RWD, including sBA level and ItchRO(Pt) score. Other assessments included changes in CSS score, CXS score, height, weight, serum cholesterol, and 7α-C4. Changes in liver enzymes (alanine aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase), total and direct bilirubin, and safety and tolerability (adverse events and serious adverse events), including severity and relatedness, as evaluated by the investigator, were also assessed. Outcomes reported match those listed on clinicaltrials.gov.*
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	*No*	*N/A*
Did the authors of the study publication declare any conflicts of interest?	*Yes*	*Gonzales et al. declare all conflicts of interest in the primary study publication.*[1]

Abbreviations: *ITT, intent-to-treat.*

Table 12. Quality assessment of GALA Cohort Comparison Study

Quality assessment criteria	Response	Explanation
Was the cohort recruited in an acceptable way?	*Yes*	*The GALA clinical research database is well recognized globally by paediatric hepatologists who treat patients with ALGS, with most countries and tertiary referral centres participating in this clinical research database. The GALA clinical research database is composed of more than 100 physicians, surgeons, scientists, and research coordinators from 35 countries, contributing data from over 1400 patients into the clinical research database. For this natural-history comparison, the independent GALA statistician utilised well-selected historical control data from the GALA clinical research database that collects data from multinational centres using a robust data capture procedure.* *The cohort of MRX-treated patients with ALGS consists of: MRX-treated participants in studies LUM001-301/-302/303/-304/-305 and those contained within the natural history/standard of care cohort (GALA registry).*
Was the exposure accurately measured to minimise bias?	*Yes*	*As stated in the GALA data management and selection process a prospective, prespecified SAP was generated before patient selection or analysis was initiated. In line with FDA guidance on the use of external control groups the analysis plan defined detailed instructions for the selection process in order to adequately control for bias.*

Quality assessment criteria	*Response*	*Explanation*
		All data from study baseline, defined as the visit a patient had the maximum likelihood of being enrolled in the maralixibat group, up to the time of study completion/withdrawal were included in the analysis, regardless of duration of treatment. The primary method for analysis of time-to-event endpoints was to be censored data after a participant's last follow-up.
Was the outcome accurately measured to minimise bias?	*Yes*	*The impact of potential selection bias (i.e., heterogeneity between cohorts) on estimates of treatment differences was minimized using a same set of cohort eligibility criteria and adjustments of potential imbalanced covariates in Cox regression analysis. The statistical personnel were blinded to treatment outcomes prior to selection of the external controls.*
Have the authors identified all important confounding factors?	*Yes*	*The impact of potential bias (i.e. heterogeneity between cohorts) on estimates of treatment differences was minimised using a common set of cohort eligibility criteria.* *The HR estimate of the treatment comparison with 95% CI was calculated with Cox proportional hazards regression analysis that included age, sex, baseline bilirubin, baseline ALT, and treatment as factors. The appropriateness of the proportional hazards model was assessed.* *In the case of imbalance of potential confounders between cohorts, a weighted Cox analysis was performed with IPTW and HR estimate of the treatment comparison with 95% CI reported.*
Have the authors taken account of the confounding factors in the design or analysis, or both?	*Yes*	*Sensitivity analysis was conducted to explore the potential confounding effect of subtle differences in the standard of care across the regions. The analysis controlled for standard of care as a confounding variable by using the same study centre in both analyses. Analytical choices with respect to study inclusion date were also explored in sensitivity analysis with conclusions consistent across all sensitivity analyses conducted.*
Was the follow-up of patients complete?	*Yes*	*All patients included in the analysis must have had 3, 6 or 12 months of follow-up.*
How precise are the results?	*95% CI throughout*	*A 5% significance level and 95% confidence intervals (CIs) were used throughout.*

Abbreviations*: CI, confidence interval.*

A19. Priority question: Please provide data on number of patients achieving the ≥50% reduction in sBA levels from baseline at week-13 by treatment group for study LUM001-301 (ITCH).

Please see Table 13 for the number of patients achieving a ≥50% reduction in sBA levels from baseline at Week 13 by treatment group in ITCH (LUM001-301). Please note that although [redacted] *patient in the placebo arm of ITCH (LUM001-301) achieved a ≥50% reduction in sBA, ALGS is a chronic, incurable, and progressive condition, and while sBA has the potential to vary over time, achieving sustained response is not feasible without the use of additional intervention, either pharmacological in the case of maralixibat, or surgically through biliary diversion or transplant. Sustained response in terms of both sBA reductions have been demonstrated in the long-term*

follow-up phases of the maralixibat clinical trial programme, however, no similar supportive evidence is available for standard of care.

Table 13. Numbers of patients achieving ≥50% reduction in sBA at Week 13 in ITCH (LUM001-301)

	Maralixibat regimens			Placebo
	70 µg/kg	140 µg/kg	280 µg/kg	
Total number of patients randomised	[redacted]	[redacted]	[redacted]	[redacted]
Number meeting the ≥50% reduction in sBA criteria (%)	[redacted]	[redacted]	[redacted]	[redacted]

A20. Priority question: Please provide data on number of patients achieving the ≥50% reduction in sBA levels from baseline at week-13 by treatment group for study LUM001-302 (IMAGO).

Please see Table 14 for the number of patients achieving a ≥50% reduction in sBA levels from baseline at Week 13 by treatment group in IMAGO (LUM001-302). As stated in the response to question A19, it is important to note that although [redacted] *patient achieved a ≥50% reduction in sBA, no evidence supporting a sustained reduction in sBA is available for standard of care in contrast with maralixibat.*

Table 14. Numbers of patients achieving ≥50% reduction in sBA at Week 13 in IMAGO (LUM001-302)

	Maralixibat regimens		Placebo
	140 µg/kg	280 µg/kg	
Total number of patients randomised	[redacted]	[redacted]	[redacted]
Number meeting the ≥50% reduction in sBA criteria (%)	[redacted]	[redacted]	[redacted]

Section B: Clarification on cost-effectiveness data

Model inputs

B1. Priority question: in the company's model, the initial response rate for maralixibat treatment for the base case was calculated as [redacted]/31 with a note "LUM001-304 trial result (12 week), sBA % CFB > 50 (analysis of PLD)". The EAG could not locate this data in company's submission Document A or Document B and in the ICONIC trial report (Document B reference 39). Please confirm the source and accuracy of the data, and also provide justification why the response rate was not calculated in line with the definition of

responder (sBA≥50% from baseline to Week 12 *or Week 18*) used in the calculation of primary end point of the ICONIC trial.

In ICONIC (LUM001-304), a total of 12 patients achieved a ≥50% reduction in sBA from baseline to Week 12 based on a post-hoc analysis of individual patient data collected as part of the trial. This analysis was conducted at 12 weeks in contrast with the primary efficacy endpoint of ICONIC to align with the stopping rule included in the SmPC for maralixibat as a treatment for ALGS, which states that alternative treatment should be considered in patients who have not responded to treatment after three months of continuous daily use. This is also consistent with its application in the cost-effectiveness model, where patients who did not respond in terms of sBA reduction from baseline are assumed to discontinue treatment with maralixibat, and no longer accrue costs or benefits associated with treatment.

B2: Model input: The economic model assumes a 0% response rate to standard of care. Could the company provide a justification for this 0% assumption?

The ICONIC (LUM001-304) clinical trial enrolled patients with intractable pruritis, and total sBA more than 3 times the upper limit of normal for patients their age. Enrolled patients have been unable to achieve a sustained response to treatment in terms of either reductions in pruritus or sBA. ALGS is a chronic, incurable, and progressive condition, and while sBA has the potential to vary over time, and the severity of itch may change on a daily basis, achieving a sustained response is not feasible without the introduction of additional interventions, either pharmacological in the case of maralixibat, or surgically such as through biliary diversion or liver transplant. Sustained response in terms of both sBA reductions and pruritus have been demonstrated in the long-term follow-up phases of the maralixibat clinical trial programme, however, no similar supportive evidence is available for standard of care. As such, the model assumes that patients will continue to not respond to standard of care treatment.

B3. Priority question: The hazard ratio for mortality of [redacted] (described as 'maralixibat vs control group' in Document B, but as 'responder vs non-responder' in the model) obtained from the GALA Cohort Comparison Study and used in the model was the hazard ratio of event free survival, which was calculated as time from baseline to the first clinical event. Events included

liver transplantation, surgical biliary diversion, liver decompensation and death. The GALA Cohort Comparison Study reported [redacted] deaths in the maralixibat cohort (n=84) and [redacted] deaths (n=469) in the GALA control group. Can the company justify the use of hazard ratio chosen and provide an alternative hazard ratio using only death events in the GALA Cohort Comparison Study?

The GALA comparison cohort study demonstrated a statistically significant increase in the composite endpoint of event-free survival (comprising liver transplantation, biliary diversion, liver decompensation and death) for patients treated with maralixibat. No analysis was planned as part of the GALA comparison cohort study to compare outcomes based on overall survival only, as the comparison would not be powered sufficiently due to the rare nature of ALGS. However, the evidence available supports the application of the event-free survival hazard ratio to mortality alone, as death was a key component of the composite endpoint. It is also important to note the cause of death in the GALA control group, [redacted] died due to liver disease or sepsis, a consequence of cholestasis, that could be expected to be impacted by treatment with maralixibat. [redacted] died due to other, or unknown causes, and [redacted] of patients died of cardiac disease, non-cardiac vascular complications, or multi-organ failure. Consequently, [redacted] of deaths in the control group of GALA could have been influenced by treatment with maralixibat. As all deaths in the maralixibat treated group occurred post study and incidence was based on publicly available information available regarding the death, a similar breakdown of cause of death for maralixibat treated patients is unavailable.

The company does not have access to the GALA patient data and are consequently unable to provide an estimate of a hazard ratio relating to overall survival alone. However, reiterates that the HR of [redacted] applied in the economic model for event-free survival, including death, represents the best available evidence on the impact of maralixibat treatment on patient mortality in ALGS.

B4. Can the company clarify why transition from cirrhosis to biliary diversion (BD) is set to [redacted] while transitions from portal hypertension and ascites both have a cycle probability of [redacted]%?

The [redacted] transition probability from portal hypertension and ascites to SBD has been included in error, with the correct parameterisation reflecting that patients with cirrhosis, including portal hypertension and ascites, will require transplantation to ameliorate liver related symptoms. As SBD is not included in the model base case reflecting current clinical practice in the UK, only the scenario included in section B.3.9.3. of the company submission is impacted by an updated parameter set. Correctly setting transitions to SBD from portal hypertension and ascites health states to zero changes the scenario ICER from [redacted] to [redacted] per QALY gained at list price.

B5. Can the company justify why the mortality risk (from GALA study) for non-responders in all health state begins from birth in the economic model given that participants less than 1 year old were excluded from the GALA Cohort Comparison Study and the median age for the maralixibat and GALA control group was [redacted] and [redacted] respectively (Table 2 of the Integrated Clinical and Statistical Report for GALA [Reference 40 for Document B])?

ALGS is a rare disease and data robustly describing overall survival in these patients are limited. The evidence incorporated within the model was the best identified to appropriately capture survival outcomes in patients with ALGS, despite some limitations such as the baseline age of participants, which does not necessarily align with the target patient population who will be treated from 2 months old. It is also important to acknowledge that the survival data shows a decreasing risk of mortality over time, i.e. younger patients are at increased risk of death in comparison with older patients. This means that patients would spend more time at high risk of mortality had they been participating in the study from 2 months old as per the economic modelling. As such, the hazard ratio for mortality applied would result in increased numbers of deaths avoided over the early model horizon in comparison with the submitted basecase, as such this limitation is likely to present a conservative estimate of the survival benefit associated with maralixibat.

B6. Can the company clarify why study participants of the ICONIC study had to stop bile acid chelating resins before initiation of the study and during the complete study period? This could have implications for the validity of the assumption of 0% response rate to standard of care as mentioned in question B2.

Participants were not allowed to receive bile acid resins from 28 days prior to screening and through the duration of the study. This requirement was applied to reduce the risk of bias in the study and remove a potential confounder for measuring the treatment effect. Although bile acid resins are sometimes prescribed for patients experiencing cholestatic pruritis, they do not impact the underlying disease as is the case for maralixibat.

B7. Can the company justify the reason for using the vignette studies to elicit utility for care givers rather than collecting this information directly from care givers and valuing them with recommended value sets?

ALGS is a lifelong genetic condition, which means that patients with ALGS and their caregivers become normalised to the state of their disease which causes them to systematically underestimate the impact of the disease when measured through standard instruments such as EQ-5D when compared with a reference population. For example, a response regarding a patient or carers ability to take part in 'usual activities' as assessed through EQ-5D will be provided in the context of what the patient and the caregiver have been able to do since the patient was diagnosed with ALGS. This phenomenon is not specific to ALGS, and is frequently observed in patients with chronic conditions, where quality of life improves over time despite no change in the underlying symptom burden as patients and caregivers learn to adapt to limitations imposed on them by their condition. As such, opinions elicited from a vignette study conducted in participants from the general population can provide more impartial assessments of quality-of-life impact of disease. This was confirmed by a clinical expert consulted as part of the submission development process (Appendix N in the company submission.)

Furthermore, use of a general population sample provides a far larger number of potential participants in the study compared with ALGS, which is a rare disease; increasing statistical power and reducing uncertainty in addition to providing a more objective assessment of utility decrements for the reasons already stated.

Section C: Textual clarification and additional points

Document B

C1. Table 10, RWP (Weeks 19-22) Mean baseline Clinician Scratch Scale Score, MRX vs. placebo arm (mean [redacted]; median [redacted]) – please confirm if the data were correct.

This is a typographical error in the company submission; the correct data for maralixibat versus placebo here should read "mean 3.0 vs. 3.5; median 3.0 vs. 4".

Appendix D, G, H and I; the 'Systematic Literature Review Technical Report'

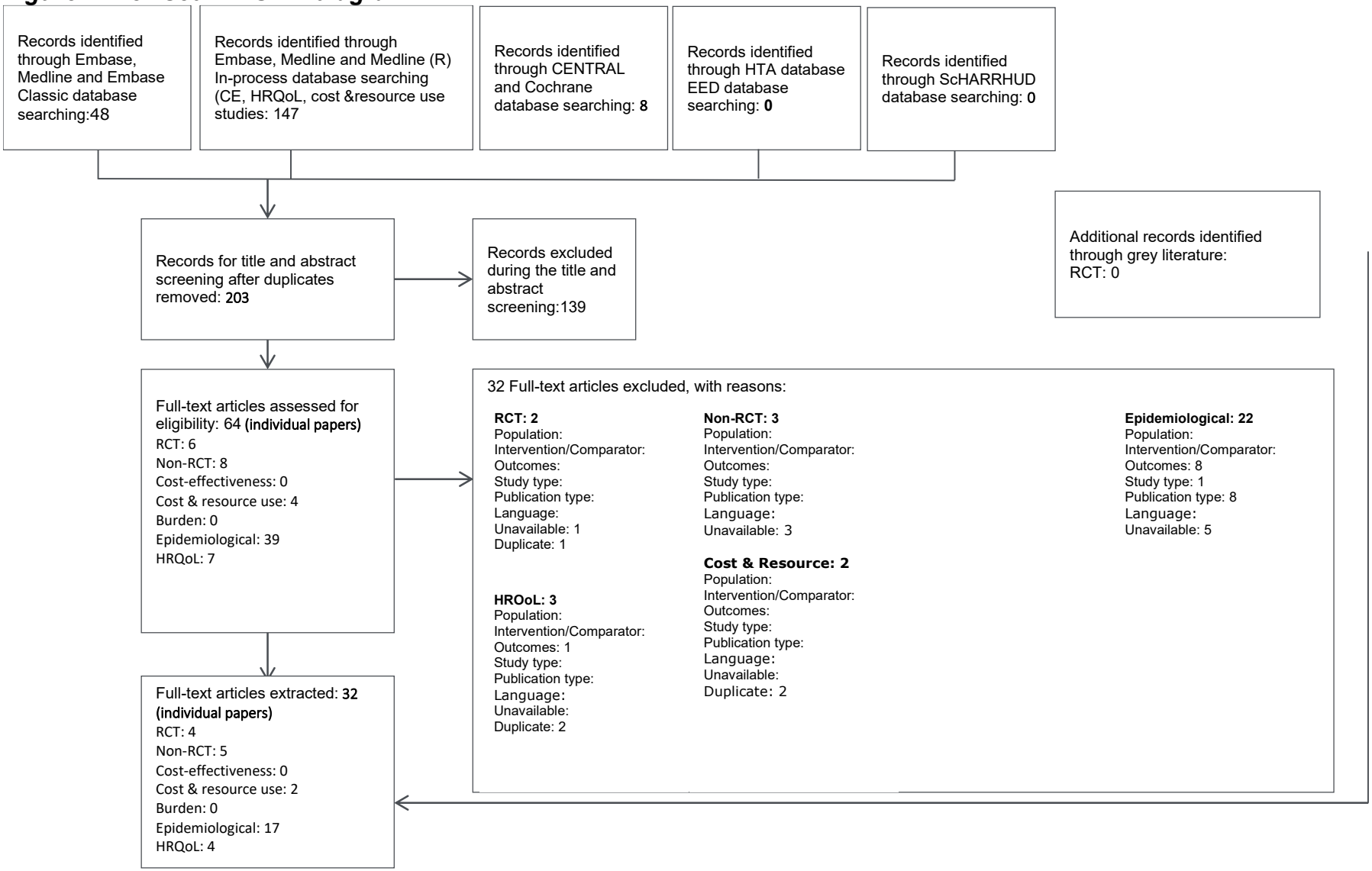
C2. Figure 1, PRISMA diagram for the October 2021 SLR: The numbers of full text articles screened, excluded and extracted do not add up. Please, explain why.

- 24 RCTs were assessed for eligibility and 12 excluded, which leave 12 for full text extraction (+ 3 identified through grey literature); not the 6 recorded in the final box.
- Non-RCTs: 24 assessed, 13 excluded, should leave 11 for extraction; not 7 as shown
- Epidemiological: 217 assessed, 149 excluded, should leave 68 for extraction; not 62
- HRQoL: 10 assessed, 6 excluded, should leave 4 for extraction; not 6.

[Company: please enter your answer to this question here]

The discrepancy is due to a reporting error in the submitted PRISMA diagram. Please find a revised version of the PRISMA diagram in Figure 1.

Figure 1. Revised PRISMA diagram.



C3. Figure 2, Updated SLR PRISMA (and related text in 4.1, page 16): The numbers of records identified through Embase and Medline searching do not correspond to those recorded in Appendix B Tables 24-27. Please clarify.

Data from Appendix B		*Data from Figure 2: PRISMA*	
Table 24 Embase + Table 25 Medline. RCTs/observational studies.	44 + 4 = **48** records	Embase & Medline RCTs/observational	**153** records
Table 26 Embase + Table 27 Medline CE, HRQoL, costs	94 + 53 = **147** records	Embase & Medline CE, HRQoL, costs	**31** records
Table 28 Cochrane databases	8 records	Cochrane databases	8 records
Total;	**203**		**192**
- 44 duplicates (text on page 16)			
	159		148

This discrepancy is due to a reporting error in the PRISMA diagram. Please see Figure 1 in the company response to question C2 for a revised version.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Maralixibat for treating cholestatic pruritus in Alagille Syndrome

ID3941

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Children's Liver Disease Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Children's Liver Disease Foundation (CLDF) is the only UK charity dedicated to fighting all childhood liver diseases. We do this by providing information to families and to health professionals, emotional/practical support to young people with liver disease and their parent/families, funds for research and a voice for all affected. CLDF currently provides emotional support and practical assistance to approximately 4,000 children, young people and their families affected by a childhood liver disease. We have 144 children and young people diagnosed with Alagille Syndrome engaged with our organisation. However, this does not include those who have not signed up to us as a member and their families, who may still access our online services and support without signing up to the charity. CLDF is reliant on voluntary donations to fund the work of the charity. Along with trust and grant funding, we also receive income via the fundraising efforts of the families and young people we support.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company,**	**Mirum pharmaceuticals** Amount – £25,000 grant Date – awarded in July 2023 Purpose – To contribute to funding of CLDF's information and support services.

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	▪ Discussions with CLDF's Children and Families Team who provide 1:1 support service, information, signposting and online opportunities to those affected by a childhood liver condition including Alagille Syndrome. ▪ Direct conversations with parents of children with Alagille Syndrome and patients with Alagille Syndrome. ▪ Survey sent to 61 parents of children with Alagille Syndrome (whose contact preferences allow us to e-mail).

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Alagille Syndrome impacts not only the life of the child diagnosed with the condition but also their parents/carers and siblings. The complexities of Alagille Syndrome and the associated symptoms and complications can significantly affect development, sleep, the child's education, social relationships and the work and home life of the family. There is also the psychological impact of living with a debilitating condition, especially where pruritus is severe. Anxiety and mental health issues are common for both the patient and the parents/caregivers. The syndrome can be difficult for young children and their carers to cope with and manage. Not being able to verbalise their pain and discomfort is incredibly distressing for all and can hinder development milestones when their focus is on the itch. In our discussions with those affected, the impact on siblings was also highlighted. Development and education for the children can be severely impacted, not only affecting their expected milestones and educational attainment but their social development/skills, peer groups and friendship circles. The financial burden is also huge as some parents are unable to work due to the number of appointments and level of care needed. This leads to household income being greatly reduced at a time when the financial burden of care increases the requirement for household income. Through conversations with parents and patients we would also like to note that there can be a tendency to normalise the symptoms of the condition. When a child/young person lives with a debilitating condition and

	symptoms of it, this is their 'normal'. They will often say things are fine and children will describe their symptoms as such because they do not know what life is like without the itch or other symptoms. To manage stress and anxiety parents are encouraged to cope positively with their lives and that can often mean minimising what is happening to allow them to function and to cope. **Impact on patient/child:** "Awful, I could write a whole book on the impact of itch on my life." "Alagille's has affected the entire family - we had to move countries and continents to get the correct care. Her whole life is curtailed by the disease. It impacts her in every aspect of her life as it affects so many of her organs. Her life is hard with Alagille's. She was transplanted before a year old. It's been hell." "My son gets very itchy at times. He scratches his skin until it bleeds sometimes, especially at night. He was mostly NG fed for his first 6 years because he struggles with lack of appetite and struggles to gain weight much." "When he was a baby ALGS prevented him from gaining weight, he vomited several times a day, the itch stopped him sleeping and made him scratch until he bled. He spent a lot of time crying and needed to be held and distracted. None of the anti-itch meds gave him much relief. Due to his size and lack of muscle tone he had physical developmental delays (sitting up, crawling, walking). He missed the window of opportunity to start eating, so struggled to eat solids and had speech delays. Even when he could eat solids, he had a very poor appetite and continued to struggle to gain weight. (He had overnight NG feeds from 3 months old and then overnight PEG feeds from 8 months old)." "Unpredictable. Having lived with a relatively mild presentation for years he has developed a host of complications in recent years including nephropathy, metabolic bone disease, multiple fractures and a subdural haematoma. He has lived with an itch that varies in intensity but can become debilitating, causing him to scratch until he bleeds. He has a poor appetite and is underweight. He has had suspected heart arrythmias which have caused loss of consciousness and required the placement of an internal loop monitor. He suffers badly with anxiety." "It is so tough! My son has pulmonary stenosis, intracranial hypertension with papilledema on both his brain and eyes as well as the worst itch. It has a huge impact on his life." "Very hard. Constant itching. Not sleeping. Not eating much so feeding tube." **Impact on parents/carers and siblings:** "The experience when he was young meant that his siblings' childhood was very different to normal. His xanthomas caused pain and discomfort, so he didn't want to play with others. He had a partial external diversion to assist with itching and he had several bleeds as his liver disease progressed, which his siblings witnessed. His sister suffers separation anxiety as she would wake up and I would be in hospital with her brother due to him becoming ill overnight."

	“I have put my whole life on hold to care for her. I have not been able to have a job, and we really need the money. Not a day goes past when I am not doing something to manage her - medicine, appointments, food etc. It is the loneliest journey as nobody understands quite how hard it is. It has affected all of us as we cannot often do all the things we want to do.” “I have to spend a lot of time taking my son to hospital check-ups and collecting prescriptions at the chemist. I have to encourage D to eat during most meals and he never feels hungry.” “Pre transplant life was very hard. 23 medications, NG tube and a biliary diversion. Under development, constant itch and debilitated child.” “He is one of twins and we also had older children. He spent a lot of time in hospital due to many complications. His older siblings were very worried about him and found it very hard when one or both of us had to be at the hospital with him and they were being looked after by relatives. At home it was hard to keep him calm, it felt like he took all the attention, so his twin got very little (other than the basic care).” “I have found it hard. It has caused a divorce and I have required therapy. It's hard to come to terms with not knowing and the panic that things are worsening. I am not the person I once was due to my son’s condition.” “An emotional rollercoaster. Feelings of overwhelm and helplessness. Reduced time with other children. Guilt. So much time off work and a loss of income as a result. Feeling like a carer or nurse instead of a parent. Reduced time with spouse. Post traumatic stress.” “It’s difficult to watch him when he’s itching constantly. Our other children get very upset when he has to go to hospital or the fact he has the peg. It has changed our entire family.” **Impact on education** “He didn't mix as children usually would. His sleep was disturbed, and his development was much slower.” “She had it from birth and is now 16.5 years. I think it has set her back by at least a year and a half.” “For 2 years my sons teachers say he is distracted by his itch. He has been moved down a group in english and maths because he wasn't getting his work complete due to always having to stop writing to itch somewhere on his body.” “Itch is horrendous. It stops children from sleeping and children that do not sleep cannot function properly. I felt very lucky that my son had his transplant before starting school. So many other ALGS parents would ask for help/ hints / ideas to help their children cope and be able to sleep at night and I felt awful knowing how badly those children were feeling. There are many stories from other ALGS parents about their children struggling to concentrate at school.” “The itching made my son not sleep at night and was tired for the following day and unable to learn.” “It effects his concentration at school. He has required more time off than his peers.” “The itching has been so tough for us from birth. My son has never been a great sleeper due to this. There's been

	periods where we've had to go to England for admission due to itching to be monitored. Which meant 1 week off school, he has had a lot of admissions and appointments which had meant a lot of time off school. We've recently done a parental application with the EA. My son had now got a full time one to one classroom assistant due to his medical needs."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are not specific to Alagille Syndrome patients (off label) so have varying levels of success. Often families are calling out for other practical ways to support their children to manage symptoms. This is because they understand that there are currently no treatments that are specifically for the reduction or removal of symptoms of their child's condition. "The drugs my son has took for itchy skin has never worked before. He'd still very itchy regardless if he takes the meds or not. I feel like he doesn't get seen or this is acknowledged enough." "I don't really know how 'expert' his consultants are. We feel sometimes when talking to the doctors we don't feel listened to and think they think we're making up the itching problem." "Treatments don't help."
8. Is there an unmet need for patients with this condition?	Yes, there is an unmet need as there are no treatments currently available specifically for Alagille Syndrome patients. Off label treatments may support with pruritus and other symptoms but with varying degrees of success. There is also a lack of mental health support for patients and parents dealing with such complex health issues and the impact on their psychological wellbeing. "My child's growth is slow. I feel like this is not met with treatment." "Mental health services need improvement. We know other people that have not been able to cope with the mental health side of liver disease, transplant etc and the support needs to be drastically improved to match the (physical) medical side. Children and young adults are falling through the cracks."

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	A specific drug for Alagille Syndrome patients provides hope and an option for these patients and their families where there is currently none. This is because current off label treatments don't work well in most cases. Many families rely on practical solutions unless/until it reaches the point of liver transplantation. However, this operation carries significant risk and many hope to delay the need for this as long as possible. Although a liver transplant is lifesaving, it is not a cure and patients require a lifetime of care and medication. The ongoing immunosuppression needed to prevent rejection has its own long-term risks; it increases the risk of infection and cancer and the child and family live with the ongoing concern that the new liver may fail at some stage, therefore leading to the need for further lifesaving transplants. "Hopefully this new med could help with my sons itch and maybe in time help with his appetite." "I think it would be really beneficial for new parents with the ALGS diagnosis which is frightening." "I would hope it would improve treatments and provide higher quality and more consistent care." "A new drug in the arsenal for treating a debilitating part of the disease. Even for patients considered to have mild disease, the itch feels unbearable. If you'd have told me that a child would talk about ending their life due to itching I wouldn't have believed you, but I've heard it." "Other Alagille's families won't have to go through the trauma of waiting for the meds that are so needed for these kids to have some quality of life."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patient/parent carers spoken to and surveyed only raised the issue of side effects and it not working for them/their child. "With it being a new drug, I would be cautious with any further side effects." "Might not work at all."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We understand that cholestasis affects up to 88% of Alagille Syndrome patients, starting within their first year. It can result in intense itching, which can lead to skin damage and scarring. It is a significant aspect of Alagille Syndrome which negatively affects the patients' quality of life. Therefore, the majority of Alagille Syndrome patients would benefit from this technology.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.

Other issues

13. Are there any other issues that you would like the committee to consider?	No.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The effects of cholestatic disease and pruritus in Alagille Syndrome patients can often be devastating and affect all areas of the child's life as well as those of their parents/carers and family. • There are currently no treatments available that are specifically for this group of patients. Therefore, any safe treatment that can significantly improve cholestatic disease and the pruritus which has such a devastating impact, and possibly delay or even remove the need for transplant, is vital. • •

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Maralixibat for treating cholestatic pruritus in Alagille syndrome [ID3941]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with cholestatic pruritus in Alagille syndrome or caring for a patient with cholestatic pruritus in Alagille syndrome. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 3rd July 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with cholestatic pruritus in Alagille syndrome

Table 1 About you, cholestatic pruritus in Alagille syndrome, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with cholestatic pruritus in Alagille syndrome? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with cholestatic pruritus in Alagille syndrome? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Children's Liver Disease Foundation
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with cholestatic pruritus in Alagille syndrome? **If you are a carer (for someone with cholestatic pruritus in Alagille syndrome) please share your experience of caring for them**	Having been diagnosed with Alagille syndrome at 6 days old and now 26 years old I have experienced living with cholestatic pruritus my whole life. Over the years I have been on various different treatments to help subside the itch, but none have been Alagille syndrome specific. The itch has affected every aspect of my life. As a baby I would scratch my skin to the point of bleeding, as well as prescribed medication, my parents would have applied many cooling lotions and wet wrapped me in my pyjamas, to help subside the constant need to scratch the skin. This also had a financial toll on my parents having to buy lots of different creams to try, and having to buy more clothes as a result of blood stains from breaking the skin. As I got older and into school age years, I was prescribed Alimemazine tartrate which was used as a sedative to help me stay asleep and not wake to itch in the middle of the night. However, with the side effects of feeling groggy and tired in the mornings, this affected my concentration levels in school. It also had a knock-on effect when paired with the diuretics I took for the heart problems I acquired as part of Alagille syndrome. As a side effect to the alimemazine my mouth was always dry and being paired with the diuretics, I was constantly drinking fluids, leaving me needing the toilet numerous times throughout the school day and often missing out on important class time. As well as missing out on important class time and low concentration levels, I would have to stop completing my work to itch my skin as I was never able to get rid of the 'warm fuzzy feeling' under my skin. When I joined secondary school the alimemazine as well as early mornings and long days didn't work. Therefore, I was left waking up several times throughout the night with the itch. The itch gets worse in the warm weather so in summertime it

	was very difficult to even get to sleep in the first place. Again, this had a knock-on effect of low concentration levels and constant tiredness. I would always say 'I don't know what it feels like not to be tired'. I feel I am in a constant state of tiredness due to lack of/interrupted sleep because of the pruritus. The pruritus has also had an impact on my relationships throughout my life. At nights my back and feet get extremely itchy and being the eldest of 6, I would often bribe a sibling with a fizzy drink or a couple of pounds to scratch my feet and back. However, this then backfired on me, and they began with the bribes, 'I'll scratch your feet if you give me a bottle of your Lucozade'. My siblings knew I would never give up the opportunity to have my feet or back scratched at any time of the day. Now as an adult and in a stable relationship, I would have my partner scratch my feet and back at night and to him it has become a chore which wasn't the intention. Although he has come to understand the frustration I have when itchy without relief. As for friendships, they would always ask why I scratched myself constantly and having to explain the situation over and over was a chore. I would always have scratch marks and scabs all over my skin which impacted my self-confidence. Where clothing was concerned, I always had to wear natural fibres such as cotton as they were less likely to cause irritation. This consisted of loose-fitting clothing rather than the likes of tight skinny jeans. I wasn't always able to follow the latest clothing trends as my friends did. This led to low self-confidence as I lived in baggy trousers and t-shirts. At home I often must wear baggy t-shirts on their own to reduce irritation to the legs. At night, the heat of a quilt would increase irritation and I would have to sleep outside the blankets, with short pj's on.

	When going on holidays we had to choose a destination that wouldn't be too hot as I have previously mentioned the heat exacerbates the irritation and itch. I have had to learn how to deal with the heat in other countries, and I do so by ensuring I can access air condition spaces and that there is shaded areas that I can frequent during the hottest parts of the day. At home when we are lucky enough to have hot weather, I mostly stay indoors as much as possible and have a cold fan in my bedroom for night time as to not exacerbate the irritation. As a teenager I took part in the Lumena drug trial, with their aim being that the drug would lower serum bile acids and alleviate severe itching. At the end of the trial, it turned out I had been on the placebo drug therefore would not have experienced the effects of it. Although the impact over the years from pruritus has been huge, as with any congenital condition it has become normal. During hospital appointments or any check ups where doctors would ask how my itch has been I would respond with 'it has been fine' meanwhile I am sat there scratching the face, arms legs etc off myself. Without a pruritus specific treatment I have had to learn to live with and adapt to the side effects.
7a. What do you think of the current treatments and care available for cholestatic pruritus in Alagille syndrome on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**A.** Currently there are no Alagille specific treatments for cholestatic pruritus. My experience with the treatments that are currently used is that although they help in subsiding the itch they do not fully eradicate the symptoms. In my opinion the current treatments can be used in the short term to help with management of symptoms but long term a specific treatment is needed.

	B. From my experience in talking to other patients and parents their views are the same as mine. A long term cholestatic pruritus treatment is needed.
8. If there are disadvantages for patients of current NHS treatments for cholestatic pruritus in Alagille syndrome (for example, how they are given or taken, side effects of treatment, and any others) please describe these	As with most treatments there are side effects to taking medication. Most of the treatments I have experienced have side effects that include toileting issues, which is very difficult when out and about in public places. This is mostly caused by being on various different treatments at the one time. As the treatments only subside the itch, most nights, I have a very broken sleep waking up during the night itchy. This in turn leads to low energy levels and a constant state of being tired. Patients are also at a disadvantage in terms of the mental toll this takes on them as there is a huge lack of mental health support available considering the patients are dealing with such complex and multifaceted conditions. For one, the recognition that they are unable to keep up with their peers due to various side effects of treatments and their condition alone is extremely mentally draining.
9a. If there are advantages of maralixibat over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does maralixibat help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a.** Any treatment that is going to improve quality of life is an advantage. The possibility of being able to get a full night's sleep not waking up to itch constantly is a miracle. That alone will have a ripple effect on all aspects of my life. Currently I must work from home some days if my itch is exceptionally worse, although I am in a lucky position that the organisation I work for are flexible and understanding of my condition and the symptoms/side-effects associated with it. Also, in terms of work life, having that much needed sleep will boost my energy, productivity and concentration levels ensuring I can reach my full potential as an employee and will be a more suitable candidate for promotions etc. Although I have been assessed three times for transplant, I have been lucky enough so far not to need one. However, any treatment that can delay the need for one at any stage is a huge advantage. Again, a transplant is another treatment not a cure.

	Another advantage would be an improvement in mental health. Not having to constantly scratch my skin leaving marks or breaking the skin, it would totally boost my confidence and I would be more able to keep up with the latest fashion trends like my peers. The possibility of keeping up with my peers more than I have been due to the domino effect of more sleep etc is huge. I wouldn't have to miss out on so much due to low energy levels and tiredness. **9B.** The most important advantage of all will be the improvement in quality of life as this addresses almost every aspect. **9C.** Maralixibat would help to overcome all the disadvantages I listed above. However, I am sure it comes with its own side effects. Although, being on one treatment alone would be more advantageous that being on various treatments to try combat the symptoms of cholestatic pruritus.
10. If there are disadvantages of maralixibat over current treatments on the NHS please describe these. For example, are there any risks with maralixibat? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are no disadvantages of maralixibat over other treatments due to the fact that there is no current condition specific treatment on the market for cholestatic pruritus in Alagille Syndrome.
11. Are there any groups of patients who might benefit more from maralixibat or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility,	From my understanding cholestatic pruritus affects almost 90% of patients with Alagille syndrome. It being one of the more prevalent side effects of Alagille Syndrome, the majority of those with a diagnosis of Alagille syndrome will benefit from maralixibat.

dexterity or cognitive impairments) that affect the suitability of different treatments	Depending on how maralixibat may contradict other medications, patients with other health conditions will not benefit from it as it will not be prescribed.
12. Are there any potential equality issues that should be taken into account when considering cholestatic pruritus in Alagille syndrome and maralixibat? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There are currently no specific treatments for cholestatic pruritus in Alagille Syndrome
- The cholestatic pruritus associated with Alagille Syndrome affects every aspect in a patients life as it is very debilitating
- This condition specific treatment would greatly improve the quality of life of Alagille Syndrome patients if it works as it is supposed to.

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Title: Maralixibat for treating cholestatic pruritus in Alagille Syndrome

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Contributions of authors
Henry Nwankwo (Assistant Professor) critiqued the economic modelling and undertook EAG modelling; Felix Achana (Honorary Senior Research Fellow) critiqued methodological and statistical aspects of the company submission (CS); Alexander Tsertsvadze (Honorary

Senior Research Fellow) critiqued the key trials included in the CS; Anna Brown (Information Specialist) critiqued the company's literature searches and conducted additional EAG searches; Pranshu Mundada (Research Associate) critiqued the cost-effectiveness review and modelling of the CS; Priyanka Chaudhuri (Research Associate) drafted the Introduction and Background and critiqued the decision problem in CS Naila Dracup (Information Specialist) assisted in critiquing literature searches. Yen-Fu Chen coordinated the project and critiqued the decision problem and methodology of the CS; all authors wrote and commented on draft versions of the report and contributed to the writing and editing of the final report.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

Table of Contents

Table of Tables

Table of Issues

Table of Figures

List of abbreviations

AE	Adverse Events
AESP	Adverse Events of Special Interest
AFP	Alpha-Fetoprotein
ALGS	Alagille Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ASBT	Apical Sodium-dependent Bile acid Transporter
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body Mass Index
CEAC	Cost Effectiveness Accessibility Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CQ	Clarification Questions
CRD	Centre for Review and Dissemination
CS	Company Submission
CSS	Clinician Scratch Scores
CXS	Clinician Xanthoma Scale
DB	Double Blind
DB-RWP	Double-Blind Randomised Withdrawal Phase
DSA	Deterministic Sensitivity Analysis
EAG	External Assessment Group
ECG	Electrocardiogram
EED	Economic Evaluation Database
EFS	Event Free Survival
EMA	European Medicines Agency
EOS	End of Study
EPAR	European Public Assessment Report
ET	Early Termination
FGF-19	Fibroblast Growth Factor-19
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HR	Hazard ratio
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IBAT	Intestinal Bile Acid Transport
ICERs	Incremental Cost-Effectiveness Ratios
INAHTA	International Network of Agencies for Health Technology Assessment
INR	International Normalized Ratio
IQR	Interquartile Range
ItchRO	Itch Reported Outcome
ItchRO(obs)	Itch-Observer-Reported Outcome

ItchRO(pt)	Itch-Patient-Reported Outcome
ITT	Intention To Treat
LDL-C	Low-density lipoprotein
LOCF	Last Observation Carried Forward
LR	Loss of Response
LS	Least Square
LTE	Long Term Extension
LTFP	Long Term Follow-up Phase
LTFU	Long Term Follow Up
LTx	Live Transplantation
LYG	Life Years Gained
MHRA	Medicines & Healthcare Products Regulatory Agency
mITT	Modified Intention to Treat
MMRM	Mixed-effects Model for Repeated Measures
MRX	Maralixibat
N	Number of subjects
N/A	Not Applicable
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NMB	Net Monetary Benefit
NORD	National Organization for Rare Disorders
NR	Not Reported
OL	Open Label
OS	Overall Survival
PAS	Patient Access Scheme
PBO	Placebo
PEBD	Partial External Biliary Diversion
PedsQL	Paediatric Quality of Life Inventory
PHT	Portal Hypertension
PP	Per Protocol
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Servies
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
Pts	Points
Pats	Patients
QALY	quality-Adjusted Life Year
QOL	Quality of Life
RCT	Randomised Control Trial
SAEs	Serious Adverse Events
SAF	Safety Population
sBA	Serum bile acid
SBD	Surgical biliary diversion
ScHARRHUD	School of Health and Related Research
SD	Standard Deviation
SE	Standard Error

SLR	Systematic Literature review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System Organ Class
SSRIs	Selective Serotonin Reuptake Inhibitors
TEAEs	Treatment-Emergent Adverse Event
TR	Treatment Response
TRAEs	Treatment related Adverse Events
TTO	Time Trade Off
Tx	Treatment
UDCA	Ursodeoxycholic Acid
UK	United Kingdom
ULN	Upper Limit of Normal
W	Week
Wk	Week
WTP	Willingness To Pay

Executive Summary

1 Executive summary

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report (page 26 onwards).

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1: Summary of key issues

ID3941	Summary of issue	Report sections
Issue 1	Discrepancy between the population covered by marketing authorisation and the population included in maralixibat (MRX) clinical studies presented in the company submission (CS)	1.3, 2.2.1 & 2.2.4
Issue 2	Potential ambiguity in eligibility criteria and stopping rules for MRX treatment in clinical practice	1.3
Issue 3	Prohibition of bile acid resins in MRX clinical studies deviated from standard practice	1.3, 2.2.1 & 3.2.4
Issue 4	Discrepancy between the target dose recommended in the marketing authorisation and doses received by participants of MRX clinical studies	2.2.1, 2.3.1, 2.3.2, 2.3.2.5
Issue 5	No evidence is presented to support the 50% reduction in serum bile acid (sBA) level as a measure for treatment response	2.2.1 & 3.2.2
Issue 6	Application of additional mortality risk from age 0	0 & 3.2.6.3
Issue 7	Hazard ratio for event free survival is used to predict overall survival in the MRX arm	0 & 3.2.6.3
Issue 8	Probability of response for standard of care (SoC) assumed to be zero	3.2.2 & 3.2.6.2
Issue 9	The choice of curve function for extrapolation of survival	3.2.6.3
Issue 10	Inclusion of disutility for carers and not using quality of life reported by carers	3.2.7
Issue 11	Utility values used for responders and non-responders.	3.2.7
Issue 12	Inclusion of severity modifier	3.2.9

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the response rate for standard of care (SoC, the 'usual practice' comparator), utility values used for response and loss of response health states, inclusion of caregiver utility, and removal of severity modifier from the incremental cost-effectiveness ratio.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Response rate used for maralixibat (MRX) and current standard of care (SoC, also known as 'usual care')
- Inclusion of caregiver disutility
- Inclusion of a severity modifier of 1.2 to the incremental QALYs.
- The utility difference between response and non-response health state.
- Inclusion of surgical biliary diversion (SBD) health state.
- Increased mortality risk for non-responders

Overall, the technology is modelled to affect costs by:

- The higher unit price for MRX compared to current treatments
- The proportion of cohort ineligible for liver transplant
- Weight distribution of cohort

The modelling assumptions that have the greatest effect on the ICER are:

- Assumption of 0% response rate for SoC
- Inclusion of caregiver utility
- Utility value of response and non-response health state
- Application of severity modifier
- Including SBD health state
- Weight distribution of cohort

1.3 The decision problem: summary of the EAG's key issues

Issue 1: Discrepancy between the population covered by marketing authorisation and the population covered by MRX clinical studies presented in the company submission (CS)

Report section	1.3, 2.2.1 & 2.2.4
Description of issue and why the EAG has identified it as important	The age ranged covered in the MRX clinical studies (1 year to 18 years old) was more limited compared with the marketing authorisation (2 months and older).
What alternative approach has the EAG suggested?	The discrepancy calls for caution in extrapolation of findings beyond the ages covered in maralixibat clinical studies.
What is the expected effect on the cost-effectiveness estimates?	The expected effect is uncertain. However as drug costs are an important driver of cost-effectiveness, the ICERs for MRX treatment are likely to be higher for people older than 18 as their body weight is greater.
What additional evidence or analyses might help to resolve this key issue?	The generalisability of evidence for individuals with cholestatic pruritus in Alagille Syndrome who are younger than 1 year or older than 18 years needs to be evaluated through additional studies that include patients aged below 1 year and above 18 years.

Issue 2: Potential ambiguity in eligibility criteria and stopping rules for MRX treatment in clinical practice

Report section	1.3
Description of issue and why the EAG has identified it as important	The licensed indication for MRX is broader than the patient population included in MRX clinical studies, through which the treatment effect was estimated. In addition to discrepancy in patient age highlighted in Issue 1, enrolment in the ICONIC study required persistent pruritus with an average daily ItchRO score >2 for two consecutive weeks. However, ItchRO is not routinely used in clinical practice and this may lead to alternative criteria being used for selecting patients for treatment, raising applicability concern. In addition, the suggestion for treatment discontinuation in the license ("no treatment benefit" after 3 months of treatment) is vague and could lead to varied interpretation. These could greatly impact on the number and characteristics of patients starting and staying on MRX treatment, which in turn may impact on the clinical and cost-effectiveness in practice.
What alternative approach has the EAG suggested?	The EAG suggests that clearer eligibility criteria for treatment and stopping rules, taking into account both available evidence, patient/carer preference and current clinical practice, need to be formulated alongside the technology appraisal.
What is the expected effect on the cost-effectiveness estimates?	The effectiveness and cost-effectiveness of using MRX in patients with disease characteristics that differ from those covered in MRX clinical studies is uncertain, but the cost-effectiveness may be less favourable for patients with less severe symptoms and those who might respond to current standard of care.
What additional evidence or analyses might help to resolve this key issue?	Evidence from further clinical studies in different patient population (e.g. not having received other current treatment) or studies evaluating different stopping rules.

Issue 3: Prohibition of bile acid resins in MRX clinical studies deviated from standard practice

Report section	1.3, 2.2.1 & 3.2.4
Description of issue and why the EAG has identified it as important	The use of bile acid resins, including cholestyramine, commonly employed in UK clinical practice, was prohibited from 28 days before study entry and throughout the study period in MRX clinical studies. This restriction applied to the ICONIC study, which contributed to estimating the initial treatment response for both the treatment and comparator groups in the model. The prohibition of bile acid resins in MRX clinical studies has the potential to introduce bias in favour of MRX, as newly prescribed or ongoing cholestyramine might provide some treatment benefits for the comparator arm.
What alternative approach has the EAG suggested?	Ideally, evidence for direct comparison between MRX and cholestyramine or adding MRX to standard practice including use of cholestyramine should be used. However, EAG could not identify clinical studies that provide estimates of the effectiveness of cholestyramine on serum bile acids or liver-related events.
What is the expected effect on the cost-effectiveness estimates?	The absence of cholestyramine in the comparator group may result in under-estimation of treatment response for standard practice, and therefore lead to biased estimate of cost-effectiveness in favour of MRX.
What additional evidence or analyses might help to resolve this key issue?	The issue is unresolved as the EAG is unaware of reliable comparative evidence between MRX and cholestyramine or adding MRX to cholestyramine that can be used. Collection of such evidence in future studies would help.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 4: Discrepancy between the target dose recommended in the marketing authorisation and doses received by participants of maralixibat clinical studies

Report section	2.2.1, 2.3.1, 2.3.2, 2.3.2.5
Description of issue and why the EAG has identified it as important	Although the marketing authorisation recommends a target dose of 380 µg/kg/day (which could be reduced to 190 µg/kg/day in case of poor tolerability), participants in MRX clinical studies received various doses, including sub-licensed doses (140 µg/kg/day or lower) and above-licensed doses (up to 560 µg/kg/day) at different phases. Since data from these studies, including their long-term extension, contributed to the GALA Cohort Comparison Study estimating the treatment effect (hazard ratio) on event-free survival for liver-related events, the deviation from licensed doses may impact the accuracy of the estimated treatment effect.
What alternative approach has the EAG suggested?	Given the rarity of the condition, EAG agrees that including all MRX-treated patients in the GALA Cohort Comparison is a sensible approach. Nevertheless, the EAG suggests the potential impact of including patients receiving unlicensed doses, particularly above-licensed doses, should be investigated possibly by subgroup or sensitivity analyses separating patients receiving licensed doses and above-licensed doses.
What is the expected effect on the cost-effectiveness estimates?	As the sub-licensed doses were used in early phases of the clinical studies and the above licensed doses were used in long-term extension phases, there could be an initial under-estimation followed by later over-estimation of treatment benefit using licensed doses, as the EAG noted in Section 2.2.5. The impact on ICER is uncertain as the cost of the drug would also need to be adjusted according to the actual doses used over time. However an increase in ICER is likely as the impact on cost would be significantly larger at higher doses (e.g. doubling the licensed dose would mean a net increase of 380 µg/kg/day, while half the licensed dose would result in a net decrease of 190 µg/kg/day and corresponding change in cost).
What additional evidence or analyses might help to resolve this key issue?	Patients who received sub-licensed doses in the early phases of the clinical studies received licensed or above-licensed doses subsequently. The impact on longer-term liver-related events is likely to be relatively small. However, the effect of the above-licensed doses may be more prominent given the additional treatment costs that would have been incurred but that were not considered in the model. Sensitivity analysis for estimating a hazard ratio for event-free survival excluding patients who received above-licensed doses during long-term extension studies or including the cost of actual doses used could be undertaken to evaluate the impact.

Issue 5: Use of 50% reduction in serum bile acid (sBA) level as a measure for treatment response

Report section	2.2.1 & 3.2.2
Description of issue and why the EAG has identified it as important	The decision to use the biomarker sBA levels with an arbitrary threshold, >50% reduction from baseline was not justified, particularly when other outcomes such as bilirubin levels and itchRO scores were available. The implications of converting a continuous outcome sBA levels, to a binary outcome (treatment response) was not accounted for.
What alternative approach has the EAG suggested?	The ERG believes that pruritus is the most clinically important outcome in ALGS, so should be the main outcome in assessing response to treatment. The EAG has explored a scenario using ItchRO scores from the ITCH study as a proxy for response rather than sBA levels. The EAG has also explored a scenario where the threshold for response was increased to >= 70% reduction in sBA levels.
What is the expected effect on the cost-effectiveness estimates?	Using alternative assumptions about treatment response significantly increased the ICER as seen in 5.1.2, Table 37 of the EAG Scenario analysis.
What additional evidence or analyses might help to resolve this key issue?	In the absence of evidence supporting the 50% reduction in sBA levels as marker of treatment response, sensitivity analyses should have been performed using alternative thresholds to define treatment response (e.g. 60%, 70%, etc.) to see the impact of a higher threshold on the ICER. For example, in the appraisal of Odexivibat for Progressive familial intrahepatic cholestasis (PFIC), which has similar mode of action as MRX, a higher threshold (>= 70% reduction in sBA levels from baseline) was used to define treatment response. Additionally, the response rate should have been derived from a randomised comparison of MRX and standard of care (SoC). Treatment outcomes could then be mapped onto the risk of developing important clinical events over the natural course of ALGS and explicitly modelled.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 6: Application of additional mortality risk from age 0

Report section	0 & 3.2.6.3
Description of issue and why the EAG has identified it as important	Additional mortality risks in all non-responder health states were set equivalent to mortality risks from the GALA cohort comparison study and applied from the beginning of the cohort. This implies that additional mortality risk is independent of age and disease history i.e., excluding background mortality, a 2-month-old has the same additional mortality risk as a 50-year-old. Given that patients in the SoC arm are assumed to have a 0% response rate, this biases the ICER in favour of MRX.
What alternative approach has the EAG suggested?	The EAG has proposed re-setting the age at which additional mortality applies to the model cohort to align with the GALA study from which these mortality risks were derived. The GALA study excluded ALGS patients who were less than 12 months old. The IQR for the cohort is 2.2 to 9.6 years with a median age of 4.3 years. The EAG prefers to set the age at which mortality risk is applied to the cohort equal to the lower quartile age of participants in the GALA study (2 years).
What is the expected effect on the cost-effectiveness estimates?	Increasing the age at which additional mortality risks applies slightly increases the ICER. See EAG preferred assumptions EAG 06.
What additional evidence or analyses might help to resolve this key issue?	The EAG explored a scenario in which the age additional mortality risk was applied to all non-responder health state was set equal to the median age of the GALA study (4 years).

Issue 7: Hazard ratio for event free survival is used to predict overall survival in the MRX arm

Report section	0 & 3.2.6.3
Description of issue and why the EAG has identified it as important	In the GALA study, the HR for Event Free Survival (EFS) includes the following events: liver transplantation (LTx), liver decompensation events, surgical biliary diversion and death. This HR estimate from this composite endpoint (0.305) was applied to the overall survival (OS) curve for responders. The computation of EFS (including all events above) is sensitive to the choice of baseline. For the primary analysis, baseline was chosen as the time MRX cohort entered the study. When other baseline definitions such as date of birth and first eligible visits were used, the HR increased to 0.618 (estimate not statistically significant at a 95% confidence level) and 0.504 respectively.
What alternative approach has the EAG suggested?	The EAG has considered a crude examination of deaths in both groups in the GALA Cohort Comparison Study, excluding all other events. Patients in the MRX group had [redacted]/24 ([redacted]%) death events while those in the SoC cohort had [redacted]/469 ([redacted]%) death events. This implies the risk of death is higher in the MRX group than in the control group. Given the uncertainties in the way the HR was estimated and the potentially higher risk of death in the MRX group, the EAG conservatively assumes equivalent mortality risk and sets the HR to 1.
What is the expected effect on the cost-effectiveness estimates?	The ICER slightly increased as seen in EAG03 of the EAG preferred assumptions.
What additional evidence or analyses might help to resolve this key issue?	A re-estimation of the HR for mortality between responders and non-responders that excludes all non-death events will provide a more reliable estimate.

Issue 8: Probability of response for standard of care (SoC) assumed to be zero

Report section	3.2.2 & 3.2.6.2
Description of issue and why the EAG has identified it as important	In the ICONIC study, all patients were initially treated with MRX and then a placebo-controlled random withdrawal period was followed. The study therefore did not provide a parallel comparator group of Standard of Care (SoC). In the absence of randomised comparative data, the company assumed a 0% response rate for SoC, which the EAG considers to be too pessimistic and would bias in favour of MRX.
What alternative approach has the EAG suggested?	The ITCH trial of MRX was a double-blind, placebo-controlled trial with similar inclusion criteria compared with the ICONIC study. The trial provided data on a reduction in serum bile acid (sBA) of ≥50 from baseline at 13 weeks, which was nearly identical to the definition of responder used in the ICONIC study and in the model. As sub-licensed doses were used in the MRX arms in the ITCH trial, the trial could not provide direct comparative evidence for the response rates between MRX and SoC. Nevertheless, the EAG considers that data from the placebo arm of the trial would provide the most suitable data for the response rate for SoC.
What is the expected effect on the cost-effectiveness estimates?	In the ITCH trial, [redacted] of patients in the placebo arm achieved a reduction in sBA of ≥50 at 13 weeks. Using this response rate for SoC in place of 0% assumed by the company substantially increased the ICER (see scenario analysis EAG02).
What additional evidence or analyses might help to resolve this key issue?	Data from a parallel, placebo-controlled trial that evaluates MRX at licensed dose added to SoC compared with SoC would provide the best estimate for relative response rate. However, no such trial is available.

Issue 9: The choice of curve function for extrapolation of survival

Report section	3.2.6.3
Description of issue and why the EAG has identified it as important	The OS curve used to model mortality for the treatment-naive population was derived from digitised KM curves from the GALA study. However, the GALA study was immature, and this was reflected in parametric extrapolations of median OS which ranged from 77 years to inestimable. The log-logistic curve chosen by the company implausibly estimates a median OS of 216 years.
What alternative approach has the EAG suggested?	In the absence of better data, The EAG prefers the exponential curve with a median OS of 77 years. Despite the optimistic OS estimation which rivals the UK life expectancy, it provides the most realistic extrapolation of the available curves.
What is the expected effect on the cost-effectiveness estimates?	The ICER slightly increases as seen in EAG01 of the EAG preferred assumption.
What additional evidence or analyses might help to resolve this key issue?	Given the immaturity of the GALA study and very limited alternative data in the literature, the uncertainty may need to be resolved by continued collection of longer-term data in ALGS population.

Issue 10: Inclusion of disutility for carers and not using quality of life reported by carers

Report section	3.2.7
Description of issue and why the EAG has identified it as important	Caregiver utilities were derived from a vignette study involving caregivers rather than directly from caregivers. The method used does not follow NICE recommendations which only allow for using alternative methods for utility elicitation when it is not feasible to estimate utility directly from respondents or proxies. The estimates from the vignette study were very favourable to responders and biased the ICER in favour of MRX. Caregiver NHS and PSS costs were not collected leading to accumulation of benefits without the costs.
What alternative approach has the EAG suggested?	The EAG has removed caregiver utility from its base case due to substantial methodological concerns in utility elicitation. The margin of benefit in the vignette study may be influenced by the description of the health state in the vignettes and may be unreflective of actual benefits of caregiver health-related quality of life.
What is the expected effect on the cost-effectiveness estimates?	Removing caregiver utility considerably increased the ICER as seen in EAG04 of the EAG preferred assumption
What additional evidence or analyses might help to resolve this key issue?	Collecting utility values directly from relevant caregivers may help resolve methodological issues with the source of utility.

Issue 11: Utility values for response and non-response health state

Report section	3.2.7
Description of issue and why the EAG has identified it as important	The utility values used for the response and non-response health state were derived from a vignette study. The description of the health states in the vignette study remains unclear. The utility values derived from the vignette study, and used for the response and non-response health state are very optimistic and may lack external validity. The utility difference between a response and non-response health state is a key driver of cost-effectiveness
What alternative approach has the EAG suggested?	The EAG has proposed using utility values from a similar appraisal (HST17- Odevixibat for treating progressive familial intrahepatic cholestasis) in place of the values used in this study.
What is the expected effect on the cost-effectiveness estimates?	The ICER significantly increased as seen in EAG05 of the EAG preferred assumptions
What additional evidence or analyses might help to resolve this key issue?	The ICONIC study collected quality of life data using the PedsQL. It is recommended to utilise an existing mapping algorithm to convert PedsQL scores to the EQ5D. This mapped data should be assessed, and if appropriate, employed in the model instead of the utility values obtained from the vignette study.

1.6 Other key issues: summary of the EAG's view

Issue 12: Inclusion of severity modifier

Report section	3.2.9
Description of issue and why the EAG has identified it as important	The inclusion of a severity modifier depends on the utility values used in the model. When alternative utility values are used, the use of a severity modifier is unjustified based on NICE threshold.
What alternative approach has the EAG suggested?	The ERG has recommended removing severity modifiers due to uncertainties around the utility values used in the model
What is the expected effect on the cost-effectiveness estimates?	The ICER increased significantly as seen in EAG07 of the EAG preferred assumptions.
What additional evidence or analyses might help to resolve this key issue?	Utility values from the PedsQL collected in the ICONIC study should be mapped to the EQ5D. These values should be used in place of the current estimates and the model re-evaluated to determine if the severity modifier threshold is met.

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case	[redacted]	[redacted]	[redacted]
EAG01: OS extrapolation changed from log-normal to exponential	[redacted]	[redacted]	[redacted]
EAG02: Probability of response changed for SoC	[redacted]	[redacted]	[redacted]
EAG03: Equivalent mortality risk between responders and non-responders	[redacted]	[redacted]	[redacted]
EAG04: Removal of caregiver utility	[redacted]	[redacted]	[redacted]
EAG05: Utility values for non-response and response health state changed to estimates to Kamath *et al* [1]	[redacted]	[redacted]	[redacted]
EAG 06: Mortality risk from GALA applied to non-responders from 2 years of age.	[redacted]	[redacted]	[redacted]
EAG07: Removal of severity modifier from ICER	[redacted]	[redacted]	[redacted]
EAG's preferred base case (combining all the above scenarios]) - deterministic	[redacted]	[redacted]	[redacted]
EAG's preferred base case (combining all the above scenarios]) – probabilistic	[redacted]	[redacted]	[redacted]

External Assessment Group Report

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

1.1.1 Remit of this assessment

To assess the clinical and cost effectiveness of maralixibat within its marketing authorisation to treat cholestatic pruritus in patients with Alagille Syndrome from two months of age and older.

1.1.2 Condition, symptoms, and economic burden

Alagille Syndrome (ALGS) is a genetic disease that can affect a range of organs in the body.[2] Mutations in the JAG1 gene usually cause this disease, but around 2% of those with ALGS will have mutations in the NOTCH2 gene. These mutations can be inherited or can occur spontaneously.[2]

ALGS can impact the liver, heart, skeleton, eyes, kidneys and vascular system, and the type and severity of symptoms can vary greatly between individuals.[3] People with ALGS may have only mild symptoms and have a normal life expectancy, but some have severe and even life-threatening complications. Cholestasis is the most common symptom, where bile flow is impaired due to a lack of bile ducts, and often develops during the first three months of life.[4] Bile is produced by the liver, stored in the gall bladder, and then released during digestion and helps the body absorb fats and fat-soluble vitamins and get rid of toxins. When bile flow is reduced or stops completely, it can lead to poor weight gain and growth deficiencies, and an excess of toxins in the body. Cholestasis causes jaundice, pruritus (itching), xanthomas (bumps on the skin from fat deposits), increased serum concentration of bile acids and growth failure.[4, 5] Pruritus is the most debilitating symptom, affecting all aspects of a child's life including sleep, appetite, education, relationships, and ability to take part in everyday activities. Severe and unremitting pruritus is present in approximately 80% of cases at 2 years.[6]

The reported incidence of ALGS at birth ranges from 1 in 30,000 to 1 in 70,000, which is due to the variable clinical presentations of the condition and the evolution of its diagnostic criteria.[7] ALGS was first recognised in the 1970s and was defined as

bile duct paucity associated with at least 3 of 5 major criteria (cholestasis, heart disease, dysmorphic facial features, vertebral anomalies, eye problems) and treated as a liver condition.[4] In the modern day, the condition is treated as a multi-system disorder. With an understanding that not all patients with the disorder will have hepatic abnormalities in the first months of birth, and diagnostic criteria now needing fewer positive findings from an expanded range of characteristics, especially in people with a positive family history,[8, 9] most recent reports suggest the true incidence is likely to be around 1 in 30,000.[3, 10]

Current treatment for ALGS focuses on alleviating symptoms. Treatments to reduce itching may include ursodeoxycholic acid, cholestyramine, rifampicin, naltrexone, ondansetron, and selective serotonin reuptake inhibitors (SSRIs). Antihistamines such as chlorphenamine may be used to aid sleep.[11] As cholestasis causes difficulties in absorbing fats and nutrients, nutritional supplements and high-calorie diets are important for many people with ALGS.[12] If ALGS does not respond to drug and dietary therapies, a partial biliary diversion may be carried out although this is rare in the UK.[5] For some people, symptoms may improve over time,[4] but between 15% and 50% of people with ALGS will have a liver transplant before 18 years of age.[7, 11] There is currently no reliable way to predict whether liver symptoms in infancy will resolve or progress.[6]

There is currently a lack of significant evidence concerning the economic burden of ALGS, and more research is needed to understand its economic consequences.[6]

1.2 Background

Maralixibat is licensed to treat cholestatic pruritus, the most common symptom of Alagille syndrome. This indication is the focus of this EAG report. The company has also submitted a marketing authorisation variation application to the European Medicines Agency for treatment of patients with progressive familial intrahepatic cholestasis (PFIC).[13] The latter indication is subject to a separate NICE technology appraisal in development.[14]

1.2.1 Mechanism of Action

Maralixibat is an oral, minimally absorbed selective inhibitor of the - ileal bile acid transporter (IBAT). IBAT is present in the small intestine and mediates the uptake of bile acids in the intestines, recycling them back to the liver.[12] By inhibiting IBAT, more bile acids are excreted in the faeces, leading to lower levels of bile acids systemically, thereby reducing bile acid mediated liver damage. This leads to improvements in liver function, pruritus, xanthomas (lipid accumulation in the skin), quality of life (QOL), growth and other symptoms of cholestatic liver diseases.[15]

1.2.2 Treatment Overview

There are currently no specific guidelines for the treatment of cholestatic pruritus in patients with ALGS in the UK. Similarly, there are no approved pharmacotherapies to treat patients with ALGS in the UK apart from MRX.

Instead, ALGS patients can be treated with off-label supportive pharmacotherapy which can provide symptomatic relief. Specifically for patients with cholestatic pruritus, treatment might often include ursodeoxycholic acid, which is a synthetic bile acid which aids bile flow, hepatobiliary secretion, and decreased bile toxicity.[16] Clinicians may also suggest bile acid binding resins, which have been approved in adults to manage cholestatic pruritus. This includes cholestyramine, which sequesters bile acids in a resin complex for excretion, thereby decreasing bile acid reuptake in the distal small bowel. However, tolerability may be an issue due to its taste and side effects such as bloating.[17] It can also cause further problems with absorption of fats and fat-soluble vitamins.[16] Despite these limitations and uncertainty in the magnitude of effect in relieving pruritus, it is still recommended in the European Association for the Study of the Liver guideline as a first-line treatment for cholestatic pruritus due to its safety profile.[18]

Another treatment option utilises hydroxylation of bile acids with the drug rifampicin, which is believed to make bile acids less pruritic, and more excretable by the kidneys. This has been shown to be effective in over half of patients suffering from pruritus, but there a range of side effects, including acute renal failure, vomiting, and hepatitis.[9] Additional treatment options include opioid antagonists, such as naltrexone, which blocks μ-opioid receptors, which are upregulated in cholestasis. Naltrexone has been shown to reduce pruritus in both adults and children with ALGS. However, patients may experience adverse effects, such as nausea, diarrhoea, abdominal pain, and irritability.

There are also adjunctive therapies that may be prescribed to a patient with ALGS. Antihistamines are a conventional initial therapy for pruritus, though the aetiology of cholestatic pruritis seems different to the origins of histaminergic itch. Nonetheless, antihistamines are used for mild cases, and side-effects of drowsiness can improve sleep.[9, 16] Similarly, selective serotonin reuptake inhibitors (SSRIs) can be used to relieve pruritus. Sertraline has been found to be an effective treatment in reducing itch, as well as improving skin scratching and sleep, suggesting that serotonergic pathways are implicated in the experience of itch.[19]

Some cases require surgical intervention. A partial external biliary diversion (PEBD) may be performed, which has been found to improve total serum cholesterol, severity of pruritus, and xanthomas in 20 ALGS patients.[20] Liver transplantation is often required in those with cholestasis, with ALGS making up 4% of liver transplants in paediatric patients, with added risk factors post-surgery.[21]

Emerging treatments include intestinal bile acid transport (IBAT) inhibitors. These act by blocking the reuptake of bile acids in the intestine and preventing them from returning to the liver. These include drugs such as MRX and odevixibat. Only MRX is currently approved in the UK for ALGS.[22] Odevixibat was recommended by NICE for treatment of PFIC (a rare genetic condition that reduces or stops the flow of bile acids and also causes various cholestasis related symptoms) in a previous highly specialised technologies guidance with a simple discount patient access scheme.[23]

1.2.3 Proposed place of the technology in the treatment pathway

MRX is licensed by the Medicines & Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA) for the treatment of cholestatic pruritus in patients with ALGS two months of age and older.[22, 24] The description of decision problem in Company Submission (CS) Document B suggested that MRX would be used in addition to established clinical management. Although this is broadly in line with how MRX was evaluated in its clinical studies included in the CS, patients in those studies were required to have not received, or to have stopped bile acid binding resins such as cholestyramine at least 28 days before study entry. The evidence presented in the CS, to some extent, deviates from the use of MRX in addition to established supportive therapy. This also raises an issue regarding the interpretation of effect estimates for MRX compared to SoC, which would typically have included bile acid resins as one of the treatments.

1.3 Critique of company's definition of decision problem

While the decision problem adopted by the company appears to align well with NICE's final scope, discrepancies exist between the population, intervention and comparator specified in the decision problem and those covered by the evidence presented and used in the CS and its model. These issues are highlighted in Table 3.

Table 3: Summary of the decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with cholestatic pruritus related to Alagille syndrome (ALGS)	People with cholestatic pruritus related to Alagille syndrome ALGS	NA	The target population is in line with the NICE scope. However, the evidence submitted in the CS covered patients with a narrower age range (age 1-18) than its license (age 2 months and older). In addition, enrolment into key MRX trials required persistent pruritus with an average daily ItchRO score >2 for two consecutive weeks. However ItchRO is not routinely used in UK clinical practice and this may lead to alternative criteria being used for selecting patients for treatment, leading to mismatch between trial evidence and patient population chosen to receive MRX in practice. The submitted evidence also includes a very small number of UK patients therefore is uncertainty in the generalisability of the submitted evidence to the UK setting.
Intervention	Maralixibat (in addition to established clinical management)	Maralixibat (in addition to established clinical management)	NA	The intervention mostly matches the NICE scope. However, there is a discrepancy between the target dose recommended in the marketing authorisation and the doses received by participants of

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				MRX clinical studies. Although the target dose of 380 µg/kg/day (could be reduced to 190 µg/kg/day in case of poor tolerability) is recommended in the marketing authorisation, various doses of MRX, including sub-licensed doses (140 µg/kg/day or lower) and above licensed doses (up to 760 µg/kg/day) were given to participants at different phases of maralixibat clinical studies (see Figure 2 in Section 2.3.2.5). As data from patients treated in maralixibat clinical studies (including their long-term extension) contributed to the GALA Cohort Comparison Study that provided estimate for treatment effect (hazard ratio) on event-free survival for liver-related events, the deviation from licensed doses may impact on the accuracy of estimated treatment effect. In addition, the established clinical management in the UK includes the use of the bile acid binding resin cholestyramine. Patients on such bile acids binding resins were excluded from pivotal ICONIC trial and therefore the effectiveness data that informed

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				the economic model deviates from a comparison of adding MRX to established clinical management versus established clinical management in the UK.
Comparator(s)	Established clinical management without maralixibat, which may include: • Off-label drug treatments such as ursodeoxycholic acid (UDCA), cholestyramine, rifampicin, ondansetron, naltrexone, selective serotonin reuptake inhibitor (SSRIs), and antihistamines • Dietary changes • Surgical interventions such as LTx	Established clinical management without maralixibat, including: • Off-label drug treatments such as UDCA, cholestyramine, and rifampicin • Surgical interventions such as LTx (with surgical biliary diversion (SBD) in a scenario)	A simplifying assumption was made, as there were no data available for the parametrisation of drug use beyond UDCA, rifampicin, and cholestyramine (i.e., ondansetron, naltrexone, SSRIs, and dietary changes). However, these were not expected to impact the economic analysis.	The EAG considers the comparators partially appropriate. However, as described above, participants in the MRX clinical studies were not allowed to receive bile acid binding resins as a pre-condition to enrolment. This raises questions about the generalisability of the estimated treatment effect for the SoC group in the economic model. The company did not include dietary changes, which the EAG agrees to be unlikely to be effective. The company included LTx but not SBD in their base case as it is rarely used in practice. The EAG agrees with the company's approach as the EAG's clinical adviser indicated that SBD does not seem to work well in ALGS.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Outcomes	The outcome measures to be considered include: • Change in symptoms of cholestasis including pruritus • Change in sBA level • Change in xanthomas • Change in sleep disturbance • Change in liver enzymes and bilirubin levels • Time to liver event (surgery, transplant, or liver cancer) • Measures of faltering growth and failure to thrive • Adverse events • Health-related quality of life (patient and carer-reported) • Overall survival • Transplant-free survival	The model includes: • Change in sBA levels and corresponding pruritus • Time to liver event and progression of liver disease (transplant, cirrhosis, ascites and portal hypertension (PHT)) • Adverse events • Health-related quality of life • Overall survival • Measures of faltering growth • Transplant-free survival • Number of patients requiring surgical interventions	The outcomes selected in the model were based on clinical opinion and the documented literature on possible outcomes for patients with ALGS. Change in xanthomas and bilirubin could not be directly linked to ALGS patient quality of life, survival, or costs incurred, and were therefore omitted. Survival is modelled indirectly using natural history data, as ICONIC did not collect long-term survival outcomes. Quality of life is included in the model using a vignette study, and time to surgery/pre-transplant survival is based on the literature.	The primary outcome of the ICONIC study was defined as changes of serum bile acid (sBA) levels. Patients were deemed responsive to treatment if they achieved a 50% reduction in sBA levels at week 12 or week 18 compared to baseline. Those who did not achieve 50% reduction were classed as non-responders. However, this definition of treatment success seems to lack clinical reasoning, and the use of biochemical markers neglects several patient-centred and clinically meaningful outcomes as suggested by NICE. Some patient-centred measures were included as secondary outcomes in the ICONIC study, such as the ItchRO scale as a measure of pruritus, which the EAG considered to be a more suitable measure of clinical response. The company did not include evidence on sleep disturbance, but its impact might be captured to some extent in utility measures.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	• Number of patients requiring surgical interventions			The company evaluated time to liver events, transplant-free survival and overall survival primarily based on data from the GALA Cohort Comparison Study. Eighty-four MRX-treated patients was included in the study with the longest follow-up of approximately six years. Given the small sample size and limited duration of long-term follow-up, data is still immature for liver events, transplant-free survival and overall survival.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be	The main outcome of the economic analysis is the incremental cost per quality-adjusted life year. The time horizon is a lifetime (100 years maximum), as ALGS is expected to impact patients and caregivers across their lifetimes. In the base-case, costs and outcomes are those that apply to the NHS and PSS only. A commercial agreement exists for maralixibat, which is included in the analysis.	–	The approach taken by the company is largely in line with the scope. The company included impact on the quality of life for caregivers. EAG has some reservation about the utility values used by the company. See section 3.2.7.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	Not applicable. No subgroups specified in scope.			No subgroups were specified in NICE scope.
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The company submission covers maralixibat within its marketing authorisation only.		As mentioned above, evidence included in the CS is mainly applicable to patients of 1 to 18 years old. As the treatment cost is based on body weight, the effectiveness and particularly cost-effectiveness of MRX for potentially continued use of the medication into adulthood has not been evaluated.

2 CLINICAL EFFECTIVENESS

2.1 Critique of the methods of review(s)

CS Appendix D, G, H, I (the 'Systematic Literature Review Technical Report') provides a detailed report of a systematic literature review (SLR) conducted to answer 7 different research questions, two of which address the efficacy and safety of treatment in patients with ALGS. The SLR was originally undertaken by one research consultancy in 2021, then updated by a different consultancy in May 2023, using the same review questions and selection criteria. The selection criteria in Tables 13-14 of the SLR in CS Appendix generally reflect the NICE scope but are not specific to pruritis, rather including any treatment for any aspect of ALGS. Non-English language publications are excluded from the reviews, which may risk missing useful studies, given the general lack of literature on ALGS acknowledged in CS Appendix D, G, H, I section 3.1.

The EAG has some concerns about screening methodology and reporting, due to discrepancies in numbers of results reported in the text in CS Appendix D, G, H, I sections 4.1 and 4.2, and the PRISMA diagrams (Figure 1 and Figure 2). The company clarification response (C2 and C3) provides a revised PRISMA diagram, however this appears to reflect the May 2023 SLR update only and the number of full text articles extracted reported here (n=32) does not match the number reported in the text of sections 4.1 and 4.2 (n=29).

2.1.1 Search strategies

A good range of sources were searched to identify clinical studies, including bibliographic databases as well as websites of HTA agencies, Google Scholar, reference lists, clinical trial registries and conference proceedings (CS Appendix D, G, H, I section 3.4). The search strategies for Embase and MEDLINE for the original October 2021 SLR reported in Appendix B, Tables 19 and 20 are not sufficiently comprehensive, as terms for population and intervention/comparators are only searched as subject headings. This means that records with key population or intervention terms in the title or abstract, but not in the subject (Emtree/MeSH) terms

would have been missed. Phrase searching is used for population and intervention/comparator terms in all databases, whereas use of Boolean AND or proximity operators to link terms would have been more sensitive.

The update searches run in May 2023 and reported in Appendix A, tables 24, 25 and 28 were undertaken by a different consultancy to the original October 2021 searches, using a different interface for the database searches (Ovid rather than Embase.com and Cochrane Library). This necessitated changes to the search syntax and means that the later searches are not a true update of the 2021 searches. Unfortunately, the update search strategies are limited to records added to databases since 11th October 2021; it would have been more thorough and systematic to retrieve all records from the update search, without a date limit, then deduplicate against results of the (less sensitive) 2021 searches.

Despite concerns about the literature search methodology, the EAG considers it unlikely that the company missed any relevant clinical studies due to their knowledge of the research on treatment of pruritus in ALGS.

2.1.2 Study selection and appraisal

A total of 21 publications of relevant clinical studies of MRX were identified, along with 2 unpublished studies. Identified publications predominantly reported data and analyses associated with MRX clinical studies, their long-term extensions and data from the GALA registry and GALA Cohort Comparison Study, which will be described and critiqued in sections 2.2 and 2.3 below. The company SLR also identified 62 epidemiological studies related to ALGS, which were used to inform the company's parameter inputs for cost-effectiveness analysis.

2.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company submission (CS) included one clinical trial (the ICONIC study; LUM001-304) that examined the safety and efficacy profile of maralixibat (MRX;

LUM001) within its marketing authorisation for treating cholestatic pruritus in patients with Alagille syndrome (ALGS). This is an exploratory phase-2b multicentre double-blind randomised placebo-controlled trial (RCT) with open-label extension in children aged 1-18 years diagnosed with ALGS. The ICONIC study is described in detail in the CS (Document B, B.2.2 section, pages 28-45). The study protocol (registration # NCT02160782) is published[25] and study related information is reported in additional sources.[26-30]

The CS (Document B) provides summary information about the trial design, intervention, population, patient numbers (e.g., how many were eligible, randomised, allocated and dropped out), outcomes and statistical analyses.

2.2.1 The ICONIC study: Design, methodology, and patient characteristics

The description of study design, endpoint definitions, methodology, study and patient characteristics of the ICONIC study are provided in Table 4 and Table 5.

The ICONIC study is an exploratory phase-2b multicentre double-blind randomised placebo-controlled trial (RCT) with open-label extension in children aged 1-18 years diagnosed with ALGS. The main objective was to evaluate short- and long-term safety/tolerability effects of MRX on serum bile acid (sBA) levels, pruritus, biochemical/clinical markers of cholestasis and liver disease in children with ALGS.

The primary efficacy endpoint in the ICONIC study was the mean change (expressed as the least square mean/LS Mean) in fasting sBA level from Week 18 to Week 22 in patients who previously responded to MRX treatment (MITT population: reduction in sBA ≥50% from baseline to Week 12 or Week 18), compared between MRX and Placebo (PBO) groups. Secondary/additional efficacy measures were mean changes in pruritus score (ItchRO), sBA, Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), cholesterol, PedsQL, Clinician Scratch Scores (CSS), Clinician Xanthoma Severity (CXS) score, and total/direct bilirubin levels in overall ITT population.

All safety analyses were done on the proportions (percentages) of participants with at least one adverse event (AE) in the overall treatment population (ITT) and without

inferential statistic tests. Clinical laboratory results, vital signs, physical exam findings, including body weight and height, concomitant medication usage, and serum alpha-fetoprotein (AFP) were monitored throughout the study.

Table 4: The ICONIC study: design and outcome definitions (as per the CS Document B)[£]

Study design: Exploratory international, multicentre phase-2b double-blind randomised placebo-controlled drug-withdrawal trial with open-label extension
Primary efficacy endpoints
Mean change from Week 18 to Week 22 (during DB-RWP) in fasting sBA levels in patients who previously responded to maralixibat treatment, as defined by a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (MITT Population)
Secondary efficacy endpoints
Mean change from Week 18 to Week 22 (during DB-RWP) in biochemical markers of cholestasis and liver disease (ALT, ALP), total bilirubin, direct bilirubin in overall patient population (ITT)
Mean change from Week 18 to Week 22 (during DB-RWP) in pruritus as measured by ItchRO(Obs)/ItchRO(Pt) in overall patient population (ITT)
Mean change from baseline (Week 0) to Week 18 (open-label run-in phase) in fasting sBA levels
Mean change from baseline (Week 0) to Week 18 (open-label run-in phase) in biochemical markers of cholestasis and liver disease (ALT, ALP, total bilirubin, direct bilirubin)
Mean change from baseline (Week 0) to Week 18 (open-label run-in phase) in pruritus as measured by ItchRO(Obs)/ItchRO(Pt)
Additional efficacy endpoints
Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 for pruritus response rates, and change from baseline (Week 0) to Weeks 18, 22, and 48, and then every 12 weeks for pruritus as measured by ItchRO(Obs)/ItchRO(Pt)
Change from baseline (Week 0) to Weeks 18, 22, 48, 60, 72, 84, 96 and 100, and change from Week 18 to Week 22 in Paediatric Quality of Life inventory (PedsQL) score in overall patient population (ITT)

Responder analysis for CSS at Weeks 18, 48, 60, 72, 84, 96, and 100
Change from baseline (Week 0) to Week 48 in xanthomas, as measured by Clinician Xanthoma Scale score
Change from baseline (Week 0) to Weeks 18, 22, and 48, and then every 12 weeks in fasting sBA levels
Change from baseline to Weeks 18, 22, and 48, and then every 12 weeks in biochemical markers of cholestasis and liver disease: ALT, ALP, total bilirubin, direct bilirubin, total cholesterol, low-density lipoprotein (LDL-C) and serum 7α-hydroxy-4-cholesten-3-one (7αC4)
Change from baseline (Week 0) in body height and weight at Weeks 3, 6, 12, 18, 18/LOCF, 22, 28, 38, 48, 48/LOCF, 60, 72, 84, 96, 100/LOCF, BID Day 0, BID Week 4, BID Week 8, and each 12-week repeating period
Plasma levels of MRX at baseline (pre-dose) and over time
Safety endpoints (adverse events):
Number of patients with at Least 1 AE at Weeks 18, 22, 48, and >48
Number of patients with at Least 1 Grade 3-5 AEs (Grades: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death) at Weeks 18, 22, 48, and >48
Number of patients with TRAEs at Weeks 18, 22, 48, and >48
Number of patients with SAEs at Weeks 18, 22, 48, and >48
Number of patients with AEs leading to discontinuations and/or dose modifications at Weeks 18, 22, 48, and >48
Change from baseline (Day 0) in clinical safety laboratory values, physical examination findings, and vital signs a at each clinic visit
DB-RWP=double-blind randomised withdrawal phase; MITT=modified intention-to-treat; AEs=adverse events; TRAEs=treatment related adverse events; SAEs=serious adverse events; LS= least square; ALP=alkaline phosphatase; ALT=alanine transaminase; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; PedsQL=Paediatric Quality of Life Inventory; sBA=serum bile acid; CSS=clinician scratch scores; LOCF=last observation carried forwards; BID=twice daily

£ Data compiled from CS Document B (Tables 5 and Tables 27-30)

Patients eligible for inclusion in the ICONIC study were children aged 12 months-18 years with ALGS and cholestasis, who experienced moderate to severe pruritus as measured by a mean daily score ItchRO[Obs] ≥2 for two consecutive weeks during the selection period.

The ICONIC study consisted of the following four phases: open-label (OL) run-in phase (Weeks 0-18: MRX dose escalation up to 380 µg/kg/day and stable dose), double-blind randomised withdrawal phase (DB-RWP; Weeks 18-22: MRX vs. placebo), long-term OL stable dosing phase (Weeks 22-48: MRX ≤ 380 µg/kg/day), and optional long-term follow-up phase (LTFP; Weeks 48-204: MRX ≤ 380 or 760 µg/kg/day).

Table 5: The description of the ICONIC study: eligibility of patient population and the trial methodology£

Study feature	***ICONIC (LUM001-304)***
Study location by country	Multicentre: 9 sites (Australia, Belgium, France, Spain, Poland, and the UK)
Study duration	Duration of treatment: 204 weeks
Method of randomisation	1:1 randomisation to either MRX or placebo. Randomisation used a permuted block algorithm stratified by predefined response criteria (≥50% sBA reduction from baseline to week 12 or week 18) and with entire blocks (size 4) assigned by study site using SAS software (version 9.4) by an unblinded statistician not involved in the conduct of the trial or analysis of the data. The randomisation code was assigned to each participant in sequence in the order of enrolment, and then the participants received the investigational products labelled with the same code. Both MRX and placebo were identical in appearance. All participants, investigators, and laboratory staff were masked to treatment allocation[27]
Study phases	Open-label (OL) run-in phase (Weeks 0 – 18) Dose escalation period (Weeks 0 – 6) Stable dosing period (Weeks 7 – 18) DB-RWP (Weeks 18 – 22) Open-label, stable dosing phase (Weeks 22 – 48) 1st LTFP (Weeks 48 – 101) 2nd LTFP (Weeks 101 – 204)
Method of blinding	According to the ICONIC study protocol: “All subjects, monitors, and study center personnel related to the study, except for the central pharmacist (or qualified designee) who prepares the study drug will be blinded to study treatment during the DB-RWP (Weeks 18-22)[25]

Population inclusion criteria	Australia, Europe, the UK. Children aged 12 months-18 years with ALGS and cholestasis, who experienced moderate to severe pruritus as measured by a mean daily score ItchRO[Obs]≥2 (0=none; 4=very severe pruritus) for two consecutive weeks during the selection period with at least one or more of the following: Levels of sBA >3 x ULN Conjugated bilirubin >1 mg/dl GGT levels >3 x UNL Otherwise unexplained deficiency of fat-soluble vitamins Resistant pruritus explainable only by liver disease
Population exclusion criteria	Surgical interruption of the enterohepatic circulation LTx Decompensated cirrhosis Clinically significant ascites Variceal haemorrhage and/or encephalopathy Other concomitant liver disease, or condition known to interfere with absorption, distribution, metabolism, or excretion of drug Administration of bile acids or lipid-binding resins during the 28 days prior to screening and throughout the duration of the study Patients who weighed >50 kg at screening or any other condition or abnormality that, in the opinion of the investigator or the supervising doctor, could compromise the safety of the participant or interfere with their participation
Intervention	Open-label run-in phase: ≤380 µg/kg/day MRX DB-RWP: ≤380 µg/kg/day MRX Open-label, stable dosing phase: ≤380 µg/kg/day MRX 1st long-term follow-up phase: ≤380 µg/kg/day MRX 2nd long-term follow-up phase: ≤380 or ≤760 µg/kg/day MRX (in participants with sBA levels > 8 µmol/L ULN or ItchRO(Obs) score ≥1.5))
Comparator	Placebo
Permitted concomitant medication	Patients had to stop bile acid chelating resins at least 28 days before initiation of the study and during the complete study period. The dosage and dosing regimen of concomitant drug therapy other than that specified by the protocol should not change during the first 22 weeks of study, with the exception of weight-based dose adjustments and vitamin supplementation. No new medications used to treat pruritus may be added during the first 22 weeks of the study. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the investigator or investigator's designee and sponsor to continue or discontinue the subject

Pre-specified subgroups of analyses	ItchRO(Obs) responders sBA responders ItchRO(Obs) weekly average morning severity scores across: Age group (up to 24 months, 2-12 years, >12 years) Baseline sBA (<275 µmol/L, ≥275 µmol/L) Baseline total bilirubin (<3.8 mg/dL, ≥3.8 mg/dL) Baseline ALT (<90 U/L, ≥90 U/L) Baseline ItchRO(Obs) weekly average morning severity score (<3 pts, ≥ 3 pts) sBA levels across: Age group (up to 24 months, 2-12 years, >12 years) Baseline sBA (<275 µmol/L, ≥275 µmol/L) Baseline total bilirubin (<3.8 mg/dL, ≥3.8 mg/dL) Baseline ALT (<90 U/L, ≥90 U/L) Baseline ItchRO(Obs) weekly average morning severity score (<3 pts, ≥3 pts)
RCT=randomised controlled trial; DB-RWP=double-blind randomised withdrawal phase; LTx=liver transplantation; GGT=Gamma-glutamyl transferase; ALGS=Alagille syndrome; DB-RWP=double-blind randomised withdrawal phase; MRX=maralixibat; sBA=serum bile acid; ULN= upper limit of normal; OL=open label; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; ALT=alanine transaminase; pts=points; LTFP=long-term follow-up phase	

£Data compiled from CS Document B (Table 7) and Clinical Study Report LUM001-304 (Table 4-2).[30]

Information on randomisation compiled from the trial publication[27] and the trial protocol.[25]

The EAG comment:

The EAG believes that the company provided a sufficiently detailed description of the objectives, design, as well as the definitions of endpoints of interest of ICONIC study (Document B).[25]

Regarding the study design, however, the company did not report a rationale for conducting the open-label (OL) run-in phase (Weeks 0-18) before the patients were entered in the 4-week double-blind randomised withdrawal phase (DB-RWP). There was no washout period allowed between the end of OL run-in phase treatment with MRX and the start of DB-RWP. It is uncertain if the lack of washout period influenced the efficacy endpoint results differentially across the randomised arms of MRX and placebo. For example, due to small sample size, randomization might not have been sufficiently successful in distributing the baseline characteristics (e.g., lingering effects of run-in phase medications) evenly between the study arms and could have confounded the efficacy results of the double-blind phase of the trial.

EAG acknowledges the fact that ALGS is a rare condition and it is difficult to accrue and enrol sufficient number of subjects into the study. In light of the rarity of the condition and ethical issues, the presence of methodological limitations in any given clinical trial is unavoidable. Since ICONIC study is a phase-2 trial, it is of exploratory rather than confirmatory nature. No sample size calculations were performed that would allow to specify the study power to detect the desired minimum magnitude of a clinical effect between MRX and placebo arms. Moreover, the length of DB-RWP follow-up was too short (4 weeks) to reliably document the effects of MRX in the treatment of patients with ALGS. The most parts of the study were designed as open-label one-arm follow-up without a comparator which leads to uncertainty in interpretation of the study results regarding the efficacy of MRX compared to standard treatment or placebo since it is difficult to separate the effect of MRX from other known or unknown confounding factors.

Note that the issues addressing the risk of bias of the ICONIC trial (i.e., randomisation, blinding, missing data, dropouts) are presented in the section 2.1 of the EAG report. In general, the methods of randomisation, allocation concealment, and blinding as described in the CS are deemed adequate.

The endpoints selected for the ICONIC study align with those specified in the NICE scope. However, it's important to note that a primary efficacy endpoint was specified *a priori* for a subgroup of previous MRX responders in the modified ITT population, comprising patients with a ≥50% reduction in sBA during the OL run-in phase of MRX treatment (Weeks 12-18). The EAG questions the arbitrary nature of this treatment response definition, as no evidence is presented to support the chosen threshold as demonstrating a clinically meaningful response to treatment. Despite the arbitrary definition, the subgroup of responders identified by this classification is relatively small, consisting of only 15 patients, raising concerns about the validity of using a modified ITT characterization. In appraisal of Odevixibat treatment in progressive familial intrahepatic Cholestasis, also a IBAT inhibitor with similar mechanism of action as MRX, a higher threshold of ≥70% reduction in sBA from baseline was used to define treatment response.[23]

In the clarification questions (CQ) file, the company provided the following rationale behind their choice of the primary efficacy endpoint (A3. Priority question: B.2.2, page 3):

"…*patients who did not respond in terms of an sBA reduction from baseline would not be expected to either continue to achieve a response if randomised to maralixibat or have their sBA increase if randomised to placebo. This approach is consistent with the SmPC for maralixibat that states patients should discontinue treatment if they have not experienced a treatment benefit after 3 months of continuous treatment. However, the randomised withdrawal period and long-term extension conclusively demonstrate that the benefit of treatment with maralixibat is sustained in those who achieve an initial response, and that benefits in terms of reductions in sBA and pruritis are superior to standard of care alone*."

The rationale presented by the company justifying this endpoint selection focuses on the sustained benefit in those who initially respond to maralixibat. The EAG team does not deem the company's rationale to be acceptable, since from a methodologic point of view, this endpoint is measured for the selected subsample of 'respondents' rather than for the total (ITT) population, which in turn might distort the MRX treatment effect point estimate due to selection bias.

The EAG reviewed the evidence contained in the published supplementary file accompanying the main ICONIC Gonzales 2021 paper.[26] Table 3 of this supplemental appendix presents individual patient-level sBA values at baseline and at week 18 for 29/31 participants in the ICONIC trial. The data is reproduced in Table 6 below for easy reference. The EAG was able to derive the change from baseline scores at week 18 and use this to define treatment response to treatment based on the 50% reduction in bile acids criteria. The estimated week 18 response rate was 38%. The EAG notes this value is very close to the company's estimate of the week 12 response of 37.6%, but the EAG was unable to calculate a 12-week response because this data was not presented in the supplementary material of the ICONIC trial. The ERG also calculated treatment response assuming a reduction in serum bile acids from baseline at week 18 of at least 70%, which was used in the HST17 appraisal of Odevixibat for PFIC[23] with a similar mechanism of action as maralixibat. The estimated treatment response rate at week 18 based on the 70% reduction in bile acids criteria reduced to 10.3%.

Table 6: Individual data within participants who completed the Week 48 study period of the ICONIC study (n=29)

sBA (µmol/L)			Reduction from baseline at week 18			
Baseline *n*=31	**Week 18 *n*=29**	**Change from baseline score**	**50%**	**70%**	**Achieved >=50%**	**Achieved >=70%**
79	64	15	39.5	55.3	No	No
380	245	135	190	266	No	No
142	68	74	71	99.4	Yes	No
115	99	16	57.5	80.5	No	No
520	267	253	260	364	No	No
440	412	28	220	308	No	No
20	22	2	10	14	No	No
41	9	32	20.5	28.7	Yes	Yes
72	34	38	36	50.4	Yes	No
657	183	474	328.5	459.9	Yes	Yes
479	239	240	239.5	335.3	Yes	No
499	213	286	249.5	349.3	Yes	No
239	98	141	119.5	167.3	Yes	No
152	209	57	76	106.4	No	No
50	14	36	25	35	Yes	Yes
298	166	132	149	208.6	No	No
412	310	102	206	288.4	No	No
503	454	49	251.5	352.1	No	No
329	288	41	164.5	230.3	No	No
371	254	117	185.5	259.7	No	No
583	416	167	291.5	408.1	No	No
748	679	69	374	523.6	No	No
276	190	86	138	193.2	No	No
44	56	12	22	30.8	No	No
23	7	16	11.5	16.1	Yes	No
31	18	13	15.5	21.7	No	No
335	131	204	167.5	234.5	Yes	No
85	100	15	42.5	59.5	No	No
204	337	133	102	142.8	No	No
Total number of responders					**10**	**3**
Treatment response					**10/31=32.23%**	**3/31=9.68%**

Data taken from Supplementary Table 3 of Gonzales 2021.[26]

In the ICONIC trial, all important efficacy endpoints, including serum sBA level, are continuous, thus surrogate measures and none of them is a dichotomous outcome measure based on a hard clinical outcome (i.e., liver transplantation, biliary diversion, mortality). For example, it would be informative to provide an analysis of the proportion of responders (≥50% reduction in sBA) compared between MRX vs. placebo arms at Week 22 (for DB-RWP). Turning a continuous biomarker into a binary classification leads to information loss.

Considering the absence of approved medications to treat ALGS (except for MRX), the company's choice of a comparator (placebo plus off-label treatment with ursodeoxycholic acid, cholestyramine, and rifampicin) was appropriate. Overall, the ICONIC trial's test intervention (MRX of indicated dosage) and the comparator matched those specified in the NICE scope's decision problem. Note that starting Week 102 (2nd long-term follow-up phase), some patients received a double dose of MRX (≤760 µg/kg/day). Since this dose was not a part of the approved indication (≤380 µg/kg/day), the efficacy/safety results of this study period would not be applicable to the NICE scope and decision problem.

The patient inclusion criteria for the ICONIC study were broadly aligned with that specified in the NICE scope's decision problem. The children aged 1-18 years diagnosed with ALGS with moderate to severe pruritus were eligible for inclusion, and patients who had undergone surgical intervention (e.g., liver transplantation, biliary diversion), had decompensated cirrhosis, weighed >50 kg at screening, encephalopathy, clinically significant ascites, or other liver disease or condition known to interfere with absorption, distribution, metabolism, or excretion of drug, were excluded from the trial. Patients receiving bile acids or lipid-binding resins during the 28 days prior to screening were also excluded from the trial.

2.2.2 The ICONIC study: statistical analysis

- A summary of the statistical analysis of the ICONIC study is provided in Document B (Tables 14-15, pages 41-45).
- Three population data sets were analysed:
    - Safety Population (SAF): all subjects who were enrolled and received at least one dose of the study drug.

- ITT Population: all subjects who were enrolled and received at least one dose of the study drug.
- MITT: all subjects who were enrolled, received study drug through Week 18, and had a reduction from baseline in sBA of ≥50% at the Week 12 or Week 18 measurement (sBA responder).

- The primary efficacy endpoint, the mean change (expressed as the least square mean/LS Mean) in fasting sBA level from Week 18 to Week 22 in patients who previously responded to MRX treatment (MITT population: reduction in sBA ≥50% from baseline to Week 12 or Week 18) compared between MRX and PBO was assessed using an ANCOVA model with treatment group as a factor, and sBA levels from Week 18 as covariates. The mean within-group change between weeks 18 and 22 was tested using two-sample Student's t-test.
- Secondary efficacy measures of continuous variables (LS mean change in ItchRO score for pruritus, fasting sBA level, ALP, ALT, total/direct bilirubin) in overall ITT population for DB-RWP (Week 18- Week 22) were analysed using ANCOVA model which included the baseline value of the variable of interest as a single covariate. For the OL run-in period (baseline to Week 18 and over time for all MRX recipients), one-sample Student's t-test was used.
- Additional efficacy measures of continuous variables (LS mean change) in fasting sBA level, ItchRO score for pruritus, PedsQL, CSS, Clinician Xanthoma Severity (CXS) score, ALT, ALP, total bilirubin, direct bilirubin, total cholesterol, low-density lipoprotein, and body height from Week 0 to Weeks 18, 22, 48, 60, 72, 84, 96, and 100 in overall ITT population were assessed using ANCOVA (Document B, page 43).
- Exploratory efficacy measures (healthcare utilisation, caregiver burden, and palatability of the MRX formulation over time) that are categorical were analyzed using the chi-square test or Fisher’s Exact test as appropriate based on sample sizes. Additionally, the Cochran-Mantel-Haenszel test was used to adjust for response group.[25]
- The primary and secondary effect estimates were expressed as the mean LS (within- or between-group difference in the LS mean change from baseline) and 95% confidence interval (95% CI).

- A planned unblinded interim analysis was conducted after all subjects completed the study through Week 48 or discontinued the study before the Week 48 clinic visit.
- The company conducted sensitivity analyses to explore the robustness of the ItchRO(Obs) difference (the mean LS change and 95% CIs) between the MRX and placebo groups (during DB-RWP: for Weeks 18-22) that is reported in Document B (page 72). The sensitivity analysis was done by the addition of the baseline value of various covariates (CSS, sBA level, total bilirubin, 7αC4 level, age, BMI, ALT, GGT, CXS Score) to the mixed ANCOVA model. Mixed-effects Model for Repeated measures (MMRM) in the sBA responder group (≥50% reduction in sBA level from baseline to Week 12 or 18), controlling for compliance (using minimum of 3 rather than 4 daily scores) and accounting for one participant (hospitalised during the DB-RWP for a SAE), baseline BMI score, sex, and age was conducted (Document B, pages 72-74).
- All safety analyses were done on the proportions (percentages) of participants with at least one adverse event (AE) in the overall treatment population (ITT) and without inferential statistic tests. Clinical laboratory results, vital signs, physical exam findings, including body weight and height, concomitant medication usage, and serum alpha-fetoprotein (AFP) were monitored throughout the study.

The EAG comment*:*

- The EAG agrees with the company's definitions for the ITT, Safety, and MITT population set definitions. In general, the company performed adequate statistical analyses for assessing the study efficacy and safety endpoints to compare MRX with placebo. From the CS although, it is not very clear what were the covariates adjusted for in the ANCOVA models for the secondary efficacy endpoints.
- The company indicated that given the rarity of the condition of interest, no power calculation was done. The EAG disagree with this justification as information from power calculation can inform interpretation of findings irrespective of the actual sample size achieved. The company sample of 30 ALGS subjects was based on practical considerations, rather than a desired

power for a pre-specified difference. Given this, the Type I error was not specifically controlled, as no *a priori* adjustment for multiple testing was done.

- The details of sensitivity analysis (as reported in Document B, section 2.7.1; pages 72-74) were not a priori defined in Statistical Analysis Plan (SAP)[31] or the ICONIC study protocol.[25].
- The study's statistical analysis should have accounted for the possibility of a significant placebo response, especially when using objective biomarkers like sBA levels. Strong methods to manage placebo effects, such as a placebo run-in phase or validated pruritus assessment tools, should have been employed. Additionally, the use of a randomised withdrawal design might have introduced bias, potentially underestimating the actual treatment effect. It was important for the statistical analysis to address these limitations in the study design and explore alternative analytical approaches that are less susceptible to bias.
- During clarification, the EAG requested the rationale for excluding data from non-responders to determine if calculating the treatment effect based on the ITT population was feasible. However, the company did not provide this data. Instead, they referred to Table 1 of the company's clarification response document (which we have reproduced below, Table 7), showcasing patient sBA measurements at different time points, stating that patients failing to meet sBA response criteria by week 12 did not continue contributing data to the trial. The company explained that their primary efficacy endpoint focused only on participants achieving an sBA reduction of ≥50% from baseline, aligning with the SmPC for maralixibat. They defended this approach, indicating that those who did not respond initially were not expected to continue responding or have improvements if assigned to maralixibat or placebo, respectively. Additionally, they emphasized that the randomised withdrawal period and long-term extension studies showed sustained benefits for those who initially responded to maralixibat, demonstrating superior sBA and pruritus reductions compared to standard care alone.
- The EAG disagrees with the company's approach to modelling the effectiveness of the maralixibat treatment in the economic model. The EAG's preferred approach would be to estimate the impact of maralixibat on sBA

levels relative to placebo/usual care based on the randomised withdrawal phase of the trial. Benefit or impact of treatment on sBA levels would then be mapped on the important and clinical meaningful events (pruritus, liver-related events, xanthoma) over the natural course of ALGS. The EAG acknowledges this approach but incorporation of trial data in the model would entail fundamental change to the structure of the company's economic model, something that is not feasible within the time available for completion of appraising maralixibat STA.

Table 7: Breakdown of patients meeting the sBA ≥50% from baseline to Week 12 or Week 18 criteria. Data provided by company at clarification

sBA level (µmol/L)	Baseline (week 0)	Week 12			Week 18			Week 22	
		Overall	MRX-MRX-MRX	MRX-PBO-MRX	Overall	MRX-MRX-MRX	MRX-PBO-MRX	MRX	PBO
Total									
n	31	29	N/A	N/A	29	N/A	N/A	13	16
Mean (SD)	283.43 (210.569)	172.32 (181.805)	N/A	N/A	192.50 (161.278)	N/A	N/A	216.23 (207.335)	253.19 (208.380)
sBA responder									
n	15	N/A	5	10	N/A	5	10	5	10
Mean (SD)	244.91 (197.16)	N/A	66.91 (20.08)	83.29 (14.135)	N/A	100.22 (24.714)	132.13 (17.397)	68.83 (49.589)	232.50 (34.908)
sBA non-responder									
n	14	Not collected or analysed							
Mean (SD)	318.07 (229.849)								
Patients excluded for reasons other than response									
n	2	0	0	0	0	0	0	0	0
Mean (SD)	329.88 (236.223)	N/A	N/A	N/A	N/A			N/A	N/A

Abbreviations: *MRX, maralixibat; PBO, placebo; sBA, serum bile acid; SD, standard deviation;*
Reproduced from data provided by company in response to EAG clarification question (CQ): A5., response document Table 1, page 4

Overall, the ICONIC trial addresses a crucial clinical question but suffers from methodological weaknesses in its trial design, small sample size, and the definition of the primary outcome. These concerns impact the reliability, applicability, and clinical relevance of the study's findings. While the inclusion of secondary outcomes such as the ItchRO is a positive aspect of the study, the definition of treatment success for the primary outcome remains arbitrary and potentially problematic. Future research

in this area should consider alternative trial designs (such as following up randomised patients in parallel over time), larger cohorts, and more clinically meaningful definitions of treatment success. This approach will enhance the credibility and usefulness of the study's results in the context of managing cholestatic pruritus in children with Alagille syndrome.

2.2.3 The ICONIC study: Study sample disposition

The ICONIC study sample disposition by study group/sample and study phase is presented in

Table 8 . In brief, 36 subjects were screened to participate in the ICONIC study of who 5 were excluded for being ineligible. The company specified in the questions clarification file the following (A16, page 13):

- "*Of the 5 children who were not enrolled in the ICONIC study following screening, 1 was excluded due to decompensated cirrhosis, and the other 4 were excluded as they failed to meet the minimum itch requirement of an average daily ItchRO score over 2 for 2 consecutive weeks in screening*"
- Of the remaining 31 participants enrolled in the 1st OL run-in phase, 29 completed it (2 participants discontinued due to AEs). Twenty-nine participants entered and completed the DB-RWP. Twenty-three of the 29 participants completed the OL stable dosing phase (6 participants dropped out: n=1 due to AE and n=5 did not provide consent to enroll in the optional LTFP). Of the remaining 23 participants were enrolled in LTFP, only 14 completed the study phase (9 participants dropped out: n=4 no consent, n=3 due to AE, physician's decision n=1, caregiver withdrawal n=1).

Table 8: Participant disposition by study phase (ICONIC study) £

Group/sample of participants	OL run-in phase (W0-W18) n (%)	DB-RWP (W18-W22)		OL stable dosing phase (W22-48)	Optional LTFP (W >48)
	MRX	MRX	PBO	MRX	MRX
Screened (n=36)	N/A	N/A	N/A	N/A	N/A
Enrolled/randomized/ continued	31	13	16	29	23
ITT Population	31	13	16	29	23
Safety population	31	13	16	29	23
MITT population	15	5	10	15	15
Completed study phase/period	29	13	16	23	14
Dropped or discontinued during the treatment phase	2	0	0	6	9

OL=open label; DB-RWP=double-blind randomised withdrawal phase; W=week; PBO=placebo; MRX=maralixibat; LTFP=long-term follow-up phase; N/A=not applicable; MITT=modified intention-to-treat

£Data compiled from the Clinical Study Report LUM001-304 (Table 4-1).[30]

***The EAG comment**:*

The CS provided sufficient data on study sample disposition during the ICONIC study treatment periods. It is important that there were no discontinuations or drop outs during the DB-RWP as this is the only phase of the trial (although only 4 weeks of duration) that provides relevant evidence for the assessment of comparative safety/efficacy profile of MRX. It should be noted that the rate of discontinuation was substantial after Week 23 into the OL stable dosing phase (Weeks 22-48: 6/29 [20.7%]) and the optional LTFP (Week 48 and onwards: 9/23 [39.1%]). Most frequent reason for the treatment discontinuation was the absence of consent to continue MRX treatment (17.0%), AEs (13.0%), and physician's decision/caregiver withdrawal (4.3%). The high rate of discontinuation may be indicative of the lack of long-term efficacy of MRX in this population.

2.2.4 The ICONIC study: Baseline characteristics of study population

This section focuses on the baseline patient characteristics relevant for the DB-RWP that covers the study period from Week 18 to Week 22. This study period included 29 participants randomised to receive either MRX (n=13) or PL (n=16) for 4 weeks (Table 9).

Table 9: Baseline characteristics of patients in the ICONIC study (ITT population): DB-RWP (Weeks 18-22)[b]

Baseline characteristics (at Week 18)	DB-RWP (Weeks 18-22)	
	MRX (n=13)	PBO (n=16)
Age [years]		
Mean (SD)	5.5 (5.03)	5.8 (3.75)
Median	4	5
Sex [n (%)]		
Male	9 (69.2)	10 (62.5)
Country [n (%)]		
Australia	5 (38.5)	4 (25.0)
The UK	2 (15.4)	1 (6.3)
France	3 (23.1)	6 (37.5)
Poland	0	2 (12.5)
Spain	2 (15.4)	1 (6.3)
Belgium	1 (7.7)	2 (12.5)
sBA, in µmol/L		
Mean (SD)	317.97 (233.67)	249.56 (196.80)
Median	335.41	195.81
ItchRO(Obs) weekly Morning Average Severity (Item I) score [a]		
Mean (SD)	2.879 (0.54)	2.930 (0.56)
Median	2.83	3.00
ItchRO(Obs) weekly Morning Average Frequency (Item 2) score [a]		
Mean (SD)	3.051 (0.62)	2.996 (0.52)
Median	3.00	3.00
Clinician Scratch Scale (CSS) Score		
Mean (SD)	3.0 (1.08)	3.5 (0.73)
Median	3.00	4.00
Cholesterol, in mg/dL		
Mean (SD)	557.3 (552.49)	461 (317.87)
Median	324.0	353.0
LDL Cholesterol, in mg/dL		
Mean (SD)	172.5 (54.56)	195.7 (64.48)
Median	178.00	194.50
Clinician Xanthoma Scale Score		
Mean (SD)	NR (1.29)	0.9 (1.31)
Median	1.00	0.00

Height z-score at baseline visit		
Mean (SD)	-1.54 (1.26)	-1,84 (1.48)
Median	-1.67	-1.54
History of receiving treatment for pruritus [n(%)]		
Any medication	12 (92%)	15 (94%)
Ursodeoxycholic acid	10 (77%)	13 (81%)
Rifampicin	10 (77%)	12 (75%)
Naltrexone	1 (8%)	0
Sertraline	0	1 (6%)
Alanine aminotransferase, U/L		
Mean (SD)	218 (150)	147 (55)
Median	196	144
Aspartate aminotransferase, U/L		
Mean (SD)	172 (76)	147 (61)
Median	183	135
Total bilirubin, µmol/L		
Mean (SD)	111.5 (112.4)	82.6 (72.9)
Median	78.7	48.7
Direct bilirubin, µmol/L		
Mean (SD)	80.2 (64.9)	69.0 (61.4)
Median	70.1	46.2
7α-C4, nmol/L		
Mean (SD)	36.9 (49.7)	16.3 (21.8)
Median	19.0	7.3
GGT score		
Mean (SD)	614 (482)	404 (300)
Median	463	311
FGF-19, pmol/L		
Mean (SD)	30.5 (69.4)	26.1 (55.5)
Median	9.4	7.7
PedsQL Total Scale Score (Parent)		
Mean (SD)	64.79 (13.77)	55.90 (17.80)
Median	NR	NR
Additional clinical criteria/features of ALGS [n (%)]		
Chronic cholestasis	13 (100.0%)	16 (100.0%)
Cardiac disease	12 (92.3%)	15 (93.8%)
Renal abnormalities	4 (30.8%)	8 (50.0%)
Vascular abnormalities	1 (7.7%)	3 (18.8%)
Skeletal abnormalities	7 (53.8%)	9 (56.3%)

Ocular abnormalities	7 (53.8%)	8 (50.0%)
Characteristic facial features	12 (92.3%)	15 (93.8%)
Concomitant medications to treat pruritus (>10% of participants) [n (%)]		
Rifampicin	10 (76.9%)	11 (68.8%)
Phenobarbital	[redacted]	[redacted]
Ursodeoxycholic acid	10 (76.9%)	13 (81.3%)
Other concomitant medications (>10% of participants) [n (%)]		
Phytomenadione	[redacted]	[redacted]
Vitamin K NOS	[redacted]	[redacted]
Vitamin D NOS	[redacted]	[redacted]
Tocofersolan	[redacted]	[redacted]
Tocopherol	[redacted]	[redacted]
Sodium bicarbonate	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]

DB-RWP=double-blind randomised withdrawal phase; W=week; PBO=placebo; MRX=maralixibat; sBA=serum bile acid; OL=open label; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; ALT=alanine transaminase; LTFP=long-term follow-up phase; GGT=gamma–glutamyl transferase; FGF-19=fibroblast growth factor-19; ALGS=Alagille syndrome; SD=standard deviation; NR=not reported

a ItchRO average scores are based on the 7 days prior to the baseline visit date.

b Data compiled from CS Document B (Tables 10-11), Clinical Study Report LUM001-304 (Table 4-3),[30] and the trial publication[27]

The study participants were from Australia (n=9), the UK (n=3), and countries of European Union (n=17). The mean age was 5.5 years (SD=4.2) and 19 (61.3%) of the study sample were males.

All or most of the subjects presented with chronic cholestasis (100%), cardiac disease (93.1%), and characteristic facial features (93.1%). At least half of the study participants had an ocular or skeletal abnormality.

The majority of study participants (94.0%) had received some treatment for pruritus before the study entry, of which ursodeoxycholic acid and rifampicin were the most frequently used, accounting for 79.1% and 76.0% of the subjects, respectively.

The most frequently reported use (>10% of participants) of concomitant medications to treat pruritus received during the DB-RWP was similar to those received prior the study entry (ursodeoxycholic acid: 79.3% and rifampicin: 72.4%). No additional concomitant pruritus medications with a frequency >10% were taken in any other

study phase.[30] This was corroborated by the company's response in the CQ file (A10. B.2.3.1.1 Baseline characteristics, Table 9, page 10).

[redacted]

Study participant baseline characteristics at different study phases (where all participants received MRX according to the study protocol) are provided in Table 10.

Table 10: Baseline characteristics of patients in the ICONIC study (ITT population) at different study phases (except for DB-RWP during Weeks 18-22)[b]

Baseline characteristics	OL run-in MRX phase (W0-W18) (n=31)	OL stable MRX dosing phase (W22-48) (n=29)	Optional LTFP MRX (W >48) (n=23)
Age [years]			
Mean (SD)	5.4 (4.25)	5.7 (4.29)	6.2 (4.26)
Median	5.00	5.00	5.00
Sex [n (%)]			
Male	19 (61.3)	19 (65.5)	14 (60.9)
Country [n (%)]			
Australia	9 (29.0)	9 (31.0)	9 (39.1)
Belgium	5 (16.1)	3 (10.3)	3 (13.0)
France	9 (29.0)	9 (31.0)	6 (26.1)
Spain	3 (9.7)	3 (10.3)	1 (4.3)
Poland	2 (6.5)	2 (6.9)	1 (4.3)
The UK	3 (9.7)	3 (10.3)	3 (13.0)
sBA, in µmol/L			
Mean (SD)	283.43 (210.57)	280.23 (212.95)	246.89 (203.32)
Median	275.64	275.64	203.66
ItchRO(Obs) weekly Morning Average Severity (Item I) score [a]			
Mean (SD)	2.909 (0.55)	2.907 (0.54)	2.895 (0.51)
Median	3.00	3.00	2.83
ItchRO(Obs) weekly Morning Average Frequency (Item 2) score [a]			
Mean (SD)	3.00 (0.60)	3.02 (0.55)	3.03 (0.55)
Median	3.00	3.00	3.00

Clinician Scratch Scale (CSS) Score			
Mean (SD)	3.3 (0.9)	3.3 (0.32)	3.3 (0.88)
Median	4.00	4.00	4.00
Cholesterol, in mg/dL			
Mean (SD)	512.1 (419.82)	504.2 (432.81)	417.3 (273.51)
Median	327.0	324.0	319.0
LDL Cholesterol, in mg/dL			
Mean (SD)	184.9 (58.37)	185.3 (60.34)	185.7 (62.63)
Median	178.0	178.0	178.0
Clinician Xanthoma Scale Score			
Mean (SD)	0.9 (1.26)	0.9 (1.28)	0.8 (1.17)
Median	0.0	0.0	0.0
Height z-score at baseline visit			
Mean (SD)	-1.67 (1.34)	-1.71 (1.37)	-1.68 (1.40)
Median	-1.58	-1.58	-1.48
History of receiving treatment for pruritus [n(%)]			
Any medication	29 (94%)	26 (89.6%)	20 (86.5%)
Ursodeoxycholic acid	25 (81%)	23 (79.3%)	17 (73.9%)
Rifampicin	23 (74%)	22 (75.9%)	18 (78.3%)
Phenobarbital	4 (12.9%)	3 (10.3%)	1 (4.3%)
Naltrexone	1 (3.0%)	1 (3.4%)	1 (4.3%)
Sertraline	1 (3.0%)	1 (3.4%)	1 (4.3%)
Alanine aminotransferase, U/L			
Mean (SD)	181.0 (109.0)	178.7 (111.8)	182.6 (123.5)
Median	171.0	164.0	164.0
Aspartate aminotransferase, U/L			
Mean (SD)	168.0 (76.0)	158.2 (68.32)	155.7 (72.38)
Median	161.0	158.0	158.0
Total bilirubin, µmol/L			
Mean (SD)	104.2 (98.9)	[redacted]	[redacted]
Median	78·7	[redacted]	[redacted]
Direct bilirubin, µmol/L			
Mean (SD)	78.2 (62.7)	[redacted]	[redacted]
Median	70.1	[redacted]	[redacted]
7α-C4, nmol/L			
Mean (SD)	10.32 (14.66)	10.22 (15.082)	7.05 (7.545)
Median	4.5	4.0	3.5

GGT score			
Mean (SD)	508.0 (389.0)	498.1 (399.1)	408.6 (278.6)
Median	419.0	386.0	354.0
FGF-19, pmol/L			
Mean (SD)	27.4 (60.1)	NR	NR
Median	8·4	NR	NR
PedsQL Total Scale Score (Parent)			
Mean (SD)	61.10 (16.98)	68.34 (15.49)	69.74 (17.43)
Median	62.22	72.78	71.43
Additional clinical criteria/features of ALGS [n (%)]			
Chronic cholestasis	31 (100.0%)	29 (100.0)	23 (100.0)
Cardiac disease	29 (93.5%)	27 (93.1)	21 (91.3)
Renal abnormalities	12 (38.7%)	12 (41.4)	10 (43.5)
Vascular abnormalities	5 (16.1%)	4 (13.8)	4 (17.4)
Skeletal abnormalities	17 (54.8%)	16 (55.2)	14 (60.9)
Ocular abnormalities	17 (54.8%)	15 (51.7)	13 (56.5)
Characteristic facial features	29 (93.5%)	27 (93.1)	22 (95.7)
Concomitant medications for pruritus (>10% of participants) [n (%)]			
Rifampicin	23 (74.2%)	21 (72.4%)	16 (69.6%)
Phenobarbital	[redacted]	[redacted]	[redacted]
Ursodeoxycholic acid	25 (80.6%)	23 (79.3%)	16 (69.6%)
Other concomitant medications (>10% of participants) [n (%)]			
Phytomenadione	[redacted]	[redacted]	[redacted]
Vitamin K NOS	[redacted]	[redacted]	[redacted]
Vitamin D NOS	[redacted]	[redacted]	[redacted]
Tocofersolan	[redacted]	[redacted]	[redacted]
Tocopherol	[redacted]	[redacted]	[redacted]
Sodium bicarbonate	[redacted]	[redacted]	[redacted]
Paracetamol	[redacted]	[redacted]	[redacted]

DB-RWP=double-blind randomised withdrawal phase; W=week; PL=placebo; MRX=maralixibat; sBA=serum bile acid; OL=open label; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; ALT=alanine transaminase; LTFP=long-term follow-up phase; GGT=gamma–glutamyl transferase; FGF-19=fibroblast growth factor-19; ALGS=Alagille syndrome; SD=standard deviation; NR=not reported

a ItchRO average scores are based on the 7 days prior to the baseline visit date.

b Data compiled from CS Document B (Tables 10-11), Clinical Study Report LUM001-304 (Table 4-3),[30] and the trial publication[27]

Data presented in Table 10 suggests that along the three MRX treatment periods (Weeks 0-18, 22-48, and >48), some of the baseline laboratory parameters had improved in the study participants. For example, serum levels of sBA, cholesterol,

total/direct bilirubin, and GGT tended to reduce during the prolonged treatment with MRX from Week 0 to Week 48. No differences were observed for ALT, AST, and LDL levels. Likewise, there was no trend regarding the ItchRo and CSS score change over time.

The EAG comment:

Overall, the EAG did not observe a gross baseline imbalance in age, sex, and the severity of pruritus between the MRX and placebo groups. However, several indicators of cholestasis (sBA), bile acid malabsorption (7α-C4), and hepatic function (ALT, AST, bilirubin) were higher in patients in the MRX group compared to those in placebo group. Moreover, fewer subjects in the MRX vs. placebo group had renal (30.8% vs. 50.0%) and vascular (7.7% vs. 18.1%) abnormalities. In the MRX compared to placebo group, more patients received [redacted]. Unless, the company adjusted for the baseline differences in sBA (the main efficacy variable), 7α-C4, ALT, AST, and bilirubin, the treatment effect of MRX relative to placebo would be overestimated, because mean changes of greater magnitude would be expected in the MRX compared to placebo group. Even if the company adjusted the above-mentioned baseline differences, there is still a possibility for a residual confounding biasing the benefit in favour of MRX.

Data presented in Table 10 suggested improvements in some of the baseline laboratory parameters during the prolonged treatment with MRX from Week 0 to Week 49. However, it is difficult to interpret these observations in the absence of the control group in these treatment phases.

2.2.5 The ICONIC study: primary and secondary efficacy endpoints (DB-RWP: Weeks 18-22) and long-term extension

The mean changes in the efficacy endpoints during the DB-RWP (weeks 18-22) are provided in Table 11.

Primary efficacy endpoint (MRX vs. placebo groups compared)

In the MITT subset of study participants (n=15 previous responders to MRX with a reduction in sBA ≥50% from baseline to Week 12 or Week 18), those who received MRX experienced statistically greater mean reduction in sBA compared to placebo from Week 18 to Week 22 [redacted]. From Week 18 to Week 22, the MITT population who received MRX had the mean sBA reduction of [redacted] whereas those who received placebo had the mean sBA increase of [redacted] µmol/L.

Table 11: Primary and secondary efficacy endpoints during DB-RWP (Weeks 18-22)[£]

Efficacy endpoint	Treatment arm	Control arm	Between-arm difference
Primary efficacy endpoint – MITT population*			
	MRX (n=5)	**Placebo** (n=10)	
LS mean (SE) change in sBA levels (µmol/L)	[redacted]	[redacted]	[redacted]
Secondary efficacy endpoint – ITT population**			
	MRX (**n**=13)	**Placebo** (**n**=16)	
LS mean (SE) change in sBA levels (µmol/L)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in ItchRO(Obs) score	[redacted]	[redacted]	[redacted]
LS mean (SE) change in ItchRO(Pt) score	[redacted]	[redacted]	[redacted]
LS mean (SE) change in ALT (U/L)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in ALP (U/L)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in total bilirubin (µmol/L)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in direct bilirubin (µmol/L)	[redacted]	[redacted]	[redacted]

LS mean (SE) change in CSS score	[redacted]	[redacted]	[redacted]
LS mean (SE) change in CXS score	NR	NR	NR
LS mean (SE) change in total cholesterol (mg/dl)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in LDL cholesterol (mg/dl)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in PedsQL fatigue scale score (parent)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in PedsQL total scale score (parent)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in 7α-C4 levels (nmol/L)	[redacted]	[redacted]	[redacted]
LS mean (SE) change in height z-Score	NR	NR	NR
LS mean (SE) change in weight z-score	NR	NR	NR

MITT=modified intention-to-treat; ITT= intention-to-treat; sBA=serum bile acid; MRX=maralixibat; SE=standard error; 95% CI=95 percent confidence interval; NR=not reported; LS= least square; ALP=alkaline phosphatase; ALT=alanine transaminase; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; PedsQL=Paediatric Quality of Life Inventory; CSS=clinician scratch scores; CXS=clinician xanthoma scale

*MITT population: Patients who previously responded to MRX treatment (a reduction in sBA ≥50% from baseline to Week 12 or Week 18)
**ITT population: All patients randomised to MRX or placebo
£ Data compiled from CS Document B (Tables 18-21), Clinical Study Report LUM001-304 (Appendix 8.1: Tables 14.2.1.1-14.2.41.3),[30] and the trial publication (Table 2).[27]

Secondary efficacy endpoints (MRX vs. placebo groups compared)

All secondary and additional efficacy endpoints were based on ITT population.

At the end of DB-RWP (at Week 22), there were statistically significant between-group differences in the mean changes (from Week 18) for sBA (-114), ItchRO(Obs) (-1.5), ItchRO(Pt) (-2.0), CSS (-0.90), and total cholesterol ([redacted]) in favour of MRX over placebo. The values of these parameters in the MRX group were either reduced

(i.e., improved) or maintained, whereas in the placebo group, they tended to increase (i.e., worsen) over time during the randomised phase of the study.

There were no significant differences in the mean changes of ALT, ALP, total/direct bilirubin, LDL cholesterol, and quality of life (PedsQL total and fatigue) scores between patients randomised to MRX and placebo during Weeks 18-22. At Week 22, the patients randomised to MRX had a significantly lower rise in the mean total cholesterol level compared with that in the placebo group ([redacted]).

Secondary and additional efficacy endpoints (MRX only group)

In ITT population remaining in the OL MRX only arm (run-in MRX phase, MRX stable dosing phase, and the optional LTFP), statistically significant mean reductions from the baseline (Week 0) in sBA levels and pruritus score (observer and patient-based) were observed over time. In Table 12, these data are provided for Weeks 18, 48, and 100. Likewise, statistically significant improvements in cholesterol (total and LDL), CSS, CXS, quality of life (PedsQL: total and fatigue), and growth (z-score for height) were maintained over prolonged MRX treatment time. The corresponding changes for ALT, ALP, bilirubin, and weight (z=score) at Week 18, 48, and 100 of MRX treatment were not statistically significant.

Table 12: Mean change from baseline (Week 0) in the efficacy endpoints over time in the overall ITT population who received OL MRX before and after DB-RWP[β]

Efficacy endpoint[£]	Mean change (SE) from baseline to Week 18 (end of run-in phase)	Mean change (SE) from baseline to Week 48 (end of stable dosing phase)	Mean change (SE) from baseline to Week 100 (end of 1st LTFP)
sBA (µmol/L)	[redacted]	[redacted]	[redacted]
ItchRO(Obs) score	[redacted]	[redacted]	[redacted]
ItchRO(Pt) score	[redacted]	[redacted]	[redacted]

ALT (U/L)	[redacted]	[redacted]	[redacted]
ALP (U/L)	[redacted]	[redacted]	[redacted]
Total bilirubin (µmol/L)	[redacted]	[redacted]	[redacted]
Direct bilirubin (µmol/L)	[redacted]	[redacted]	[redacted]
CXS	[redacted]	[redacted]	[redacted]
CSS	[redacted]	[redacted]	[redacted]
Total cholesterol (mg/dl)	[redacted]	[redacted]	[redacted]
LDL cholesterol (mg/dl)	[redacted]	[redacted]	[redacted]
PedsQL fatigue scale score	[redacted]	[redacted]	[redacted]
PedsQL total scale score	[redacted]	[redacted] (3.39)	[redacted] (2.74)
Height z-Score	[redacted]	[redacted]	[redacted]
Weight z-score	[redacted]	[redacted]	[redacted]

SE=standard error; MRX=maralixibat; sBA=serum bile acid; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; ALT=alanine transaminase; GGT=gamma–glutamyl transferase; FGF-19=fibroblast growth factor-19; ALP=alkaline phosphatase; LOCF=last observation carried forward; CSS=clinician scratch score; CXS=clinician xanthoma severity scale

£ Efficacy endpoint measurement is for LOCF-based sample size (n) at each point in time

β Data compiled from CS Document B (Tables 22-23), Clinical Study Report LUM001-304 (Appendix 8.1: Tables 14.2.1.1-14.2.41.3),[30] and the trial publication (Table 2).[27]

Sensitivity analysis

The results of sensitivity analysis for differences in the mean ItchRO(Obs) score changes between the maralixibat and placebo groups for DB-RWP (Weeks 18-22) are provided in Table 16.

There was a consistent trend in statistically significant effect estimates of MRX on pruritus present across various subgroups and methods of adjustment (e.g., controlling for sBA responder status, presence of bile duct paucity, baseline CSS, sBA, bilirubin, 7αC4, age, BMI, ALT, family history of ALGS, GGT, cholesterol, and CXS score).

Table 13: Subgroup and sensitivity analyses on ItchRO(Obs) differences between the MRX and placebo groups between Week 18 and Week 22[β]

Method or subgroup using ANCOVA controlling for	Study group[£]		LS mean difference estimate 95% CI	p value
	MRX n	Placebo n		
ANCOVA*	[redacted]	[redacted]	[redacted]	[redacted]
sBA responders	[redacted]	[redacted]	[redacted]	[redacted]
Presence of bile duct paucity	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CSS	[redacted]	[redacted]	[redacted]	[redacted]
Baseline sBA level	[redacted]	[redacted]	[redacted]	[redacted]
Baseline total bilirubin	[redacted]	[redacted]	[redacted]	[redacted]
Baseline 7αC4 level	[redacted]	[redacted]	[redacted]	[redacted]
Baseline age (months)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BMI	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ALT level	[redacted]	[redacted]	[redacted]	[redacted]
Family history of ALGS	[redacted]	[redacted]	[redacted]	[redacted]
Baseline cholesterol level	[redacted]	[redacted]	[redacted]	[redacted]
Baseline GGT level	[redacted]	[redacted]	[redacted]	[redacted]
Baseline CXS score	[redacted]	[redacted]	[redacted]	[redacted]
Baseline sex, age, and BMI at baseline (MMRM)	[redacted]	[redacted]	[redacted]	[redacted]

BMI=body mass index; MRX=maralixibat; GGT=Gamma-glutamyl transferase; LS=least square; ALGS=Alagille syndrome; ANCOVA=analysis of covariance; ALT=alanine transaminase; ItchRO(Obs)=Itch-observer-reported outcome; ItchRO(Pt)=Itch-patient-reported outcome; PedsQL=Paediatric Quality of Life Inventory; sBA=serum bile acid; CSS=clinician scratch scores; LOCF=last observation carried forwards; CXS=Clinician Xanthoma Severity; MMRM=mixed-effects model for repeated measures

* ANCOVA: mixed model with MRX as a fixed effect and baseline value as a covariate was used for LS means change from Week 18.

£ model-based effect estimate corresponds to LOCF-based sample size (n) at Week 22 (except for MMRM)

β Data compiled from CS Document B (Table 24),

The EAG comment:

The EAG would like to highlight important limitations in the evidence supporting the clinical effectiveness of MRX for treating cholestatic pruritus in Alagille syndrome.

The evidence of clinical effectiveness of MRX included in the CS is supported by a single small (n=29 participants) exploratory clinical study (ICONIC) that had a very short randomised placebo-controlled phase of 4 weeks duration. The most part of this trial was designed as an open-label uncontrolled study.

The ICONIC study employed a randomised withdrawal design, initially treating all participants with the active drug before randomising them to continue treatment or switch to a placebo. This design choice is problematic for several reasons. Firstly, it lacks real-world clinical relevance, as it does not reflect how treatment decisions are typically made at the outset. Additionally, it may introduce bias and lacks equipoise, potentially undermining the external validity of the findings. Furthermore, the study suffered from a small sample size, a consequence of the rarity of Alagille syndrome in children. Thirty-six patients were initially considered for inclusion but only 31 were included in the final ITT population, representing 14% of patients excluded during screening).

ALGS is a rare condition (1 in 30,000), and therefore, it is difficult to accrue an adequate sample size of patients for a clinical trial, which in turn leads to methodological shortcomings of any given clinical trial. Thus, no formal sample size calculations could be performed for this very small number of patients, something the company submission documents alluded to by saying the sample sizes were based on practical considerations rather than for statistical considerations. A limited sample size compromises statistical power, making it challenging to detect clinically significant differences and limiting the generalisability of results.

The ICONIC study demonstrated statistically significant clinical benefits of MRX in improving measures of cholestasis (serum sBA level) and pruritus (the itch reported outcome/ItchRO score) associated with ALGS at the end of the 4-week randomised period (Week 22). For the primary efficacy endpoint, MRX was associated with a greater and significantly reduced mean serum sBA compared to placebo in the MITT population (15 previous responders to MRX with a reduction in sBA ≥50% from baseline to Week 12 or Week 18). These results are not unequivocal due to several limitations in i) the study design (too short randomised placebo-controlled phase), ii)

small sample (n=29), iii) the subjective nature of the itch reported outcome, and iv) population subset-based (n=15) definition of the primary efficacy endpoint. These limitations lead to uncertainties sufficient to hinder the valid interpretation of the study results.

For example, it is uncertain if the significant clinical benefit of MRX over placebo seen during the 4-week interval of DB-RWP would be maintained beyond 4 weeks. Given the small sample of the ICONIC trial, it is uncertain how replicable are the observed results in the real world. Although the 50% reduction in sBA levels may be considered a clinically important change in the severity of ALGS, the EAG believes that the primary efficacy endpoint definition is problematic as it is subgroup- and not ITT-based. Furthermore, the size of this subgroup is even smaller than the size of ITT (n=15 vs. n=29).

Upon the EAG team's request, the company provided the response to clarification question (CQ) file that included the summary of baseline characteristics of patients in the ICONIC study stratified by the responder status defined as patients who previously met the sBA ≥50% response criteria or not at either week 12 or week 18 (CQ: A6. Priority question: B.2.3.1.1, Tables 4-5, pages 5-6). In Table 4, one can observe in the subsample of sBA ≥50% responders a notable disbalance in the baseline mean sBA scores between MRX vs. placebo groups (Table 4: 288.81 vs. 222.96, respectively [score difference=65.85]; favouring placebo), whereas in the sBA ≥50% non-responders population, this disbalance is much smaller (Table 5: 336.19 vs. 293.90, respectively [score difference=42.29]; favouring placebo). The greater baseline disbalance in the mean sBA levels (with higher values in MRX vs. placebo group) present in the sBA ≥50% responders could have led to an overestimate of the primary efficacy endpoint compared to that from the ITT based analysis.

There were some between-group imbalances that could have led to an overestimate of the beneficial effect of MRX over placebo. For example, patients in MRX arm had higher baseline levels of sBA, 7α-C4, and hepatic function parameters (ALT, AST, bilirubin) compared to those in placebo group. Moreover, fewer subjects in the MRX vs. placebo group had renal (30.8% vs. 50.0%) and vascular (7.7% vs. 18.1%) abnormalities. [redacted]

[redacted]

Additional uncertainty stems from the inconsistency of the study findings, as the mean changes (from Week 18 to Week 22) in several efficacy endpoints such as ALT, ALP, total/direct bilirubin, LDL cholesterol, and quality of life (PedsQL total and fatigue) scores did not significantly differ between MRX and placebo groups.

There is even more uncertainty in the uncontrolled MRX arm's open-label run-in and follow-up extension phases, as it is impossible to tease out the unique effect of MRX from those of extraneous known/unknown concurrent factors (e.g., naturally occurring phenomena like changes in growth, diet, subjective outcome assessment/reporting).

The company reported that treatment with MRX was associated with improved growth and statistically significant increase from baseline in mean height z score (CS Document B, Section B.2.6.2 and Figure 12; reproduced as Figure 1 below). Nevertheless, the EAG noted that the change in mean weight z score up to week 100 [redacted] compared with [redacted] in mean height z score) and not statistically significant (see Table 12 above). The reason for the discordant improvement between height and weight was unclear. The EAG also noticed that the increase in mean height z score seemed to have plateaued between around week 30 and week 100, but there appeared to be a further increase between week 100 and 204 (see Figure 1 below). This coincided with a potential increase of permitted dose of MRX to 760 µg/kg/day (doubling the current licensed dose) during this phase of long-term extension, although it is difficult to discern whether this was a dose-response relationship due to lack of a control group.

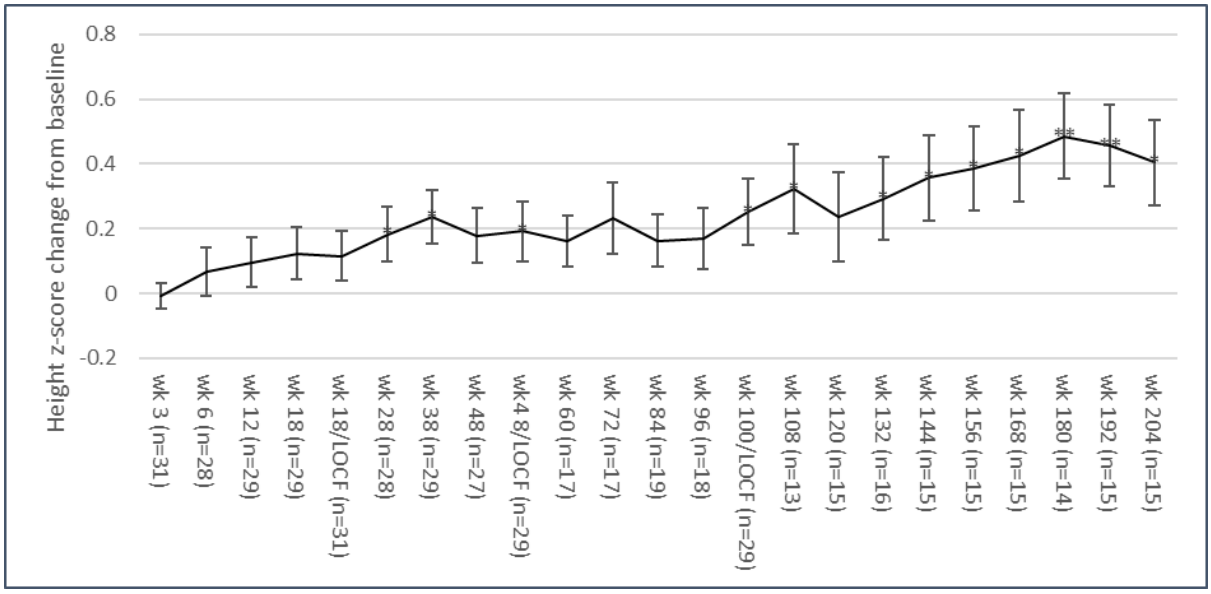


Figure 1: Mean change from baseline in height z-score over time in ICONIC overall population (ITT)
(Reproduced from CS Document B, Figure 12)

Although the sensitivity analysis suggested the robustness of the MRX effect on improving the severity of pruritus, the statistical significance levels in the analyses were not adjusted for multiple testing, which might have led to inflated type I error and spurious significant associations between the MRX and pruritus.

Given that the ICONIC study included only 3 (9.6%) UK patients, the representativeness of the ICONIC trial population in relation to the average UK patient with ALGS is questionable, thereby limiting the extent of generalisability of the trial's results to the UK's general clinical practice.

2.2.6 The ICONIC study: safety endpoints (adverse events)

The main focus of this section is the comparison of AEs between MRX and placebo arms during DB-RWP (from Week 18 to Week 22). The safety dataset for this study phase included 29 participants randomised to receive either MRX (n=13) or PBO (n=16). See Table 14.

AEs during DB-RWP

In general, fewer patients experienced at least one AE in the MRX arm vs. placebo arm (53.8% vs. 75%). However, infections and infestations occurred in 6 (46.2%) vs. 4 (25.0%) people on MRX vs. PBO respectively, among which upper respiratory infection occurred in 2 (15.4%) vs. 0 (0%) people on MRX vs. PBO respectively.

In contrast, ‘skin and subcutaneous tissue disorders’ and ‘pruritus’ were more frequent in participants receiving placebo, likely due to the underlying condition rather than MRX itself. Most AEs during the DB-RWP were mild-to-moderate severity, with moderate severity AEs being more prevalent among placebo vs. MRX recipients (50% vs. 7.7%).

Table 14: Summary of AEs in the ICONIC study during the DB-RWP (safety population n=29 patients)[β]

Adverse event	**MRX (n=13) n (%)**	**Placebo (n=16) n (%)**
AEs by SOC* and PT		
Patients with at least 1 AE	7 (53.8)	12 (75.0)
Gastrointestinal disorders	2 (15.4)	3 (18.8)
Diarrhoea	1 (7.7)	1 (6.3)
Abdominal pain	1 (7.7)	1 (6.3)
Vomiting	1 (7.7)	1 (6.3)
Nausea	1 (7.7)	0
Pyrexia	0	2 (12.5)
Infections and infestations	6 (46.2)	4 (25.0)^
Upper respiratory infection	2 (15.4)	0
Nasopharyngitis	1 (7.7)	0
Gastroenteritis	0	1 (6.3)
Influenza	1 (7.7)	0
Pharyngitis	0	1 (6.3)
Injury, poisoning, procedural complications	0	1 (6.3)
Metabolism and nutrition disorders	1 (7.7)	0
Nervous system disorders	0	1 (6.3)
Psychiatric disorders	0	1 (6.3)
Skin and subcutaneous tissue disorders	2 (15.4)	5 (31.3)
Pruritus	1 (7.7)	5 (31.3)
AEs by severity (Grade: 1-5)		
Grade 1 (mild)	6 (46.2)	3 (18.8)
Grade 2 (moderate)	1 (7.7)	8 (50.0)
Grade 3 (severe)	0	0
Grade 4 (life-threatening)	0	0
Grade 5 (fatal)	0	0
AE=adverse event; MRX=maralixibat; PT=preferred term; SOC=system organ class		

*SOC is bolded; ^Based on Table 5-14 of the CSR for ICONIC; incorrectly shown as “1 (25)” in CS Document B Table 27. [β] Data compiled from CS Document B (Tables 27-28)

During the DB-RWP, patients in the MRX arm had a lower incidence of treatment-related AEs compared with patients on placebo (pruritus n=1 [7.7%] vs. pruritus n=3 [18.8%]). Document B (Table 29, page 80).

One patient in each arm MRX and placebo had a SAE (7.7% vs. 6.3%). There were no discontinuations of MRX during the DB-RWP (Document B, page 80).

There were no discontinuations due to AEs during the DB-RWP between the MRX and placebo arms (Document B, Table 30, pages 80-81).

Post DB-RWP MRX-only study phases

In the post-randomised MRX-only study phases (stable MRX dosing [Weeks 23-48] and LTFU [Week 48 and onwards]), the most frequently reported AEs by PT (> 40% in total) were abdominal pain (52.2%), pyrexia (43.5%), and nasopharyngitis (40.0%). Document B (Table 27, pages 77-78).

Most AEs experienced by MRX-treated patients during stable MRX dosing [Weeks 23-48] ([redacted]) and LTFU [Week 48 and onwards] ([redacted]) were of mild to moderate severity (Grades 1-2). The Grade 3-4 (severe-to-life threatening) AEs were less frequent during the stable MRX dosing (Weeks 22-48) than in the LTFU phase (> Week 48) ([redacted]). No patients experienced a Grade 5 AE (i.e., there were no deaths associated with placebo or the study drug). Document B (Table 28, page 79).

The incidence of treatment-related AEs in the OL run-in [Weeks 0-18] and LTFU [Week 48 and onwards] periods were similar (38.7% vs. 34.8%, respectively), but it was lower in the stable dosing period [Weeks 23-48] (3.4%).

The occurrence of SAEs with MRX was low. In total, 14 patients experienced a total of 33 SAEs. None of the SAEs were considered by the investigator to be related to the study drug. Infections and infestations (n=7) and GI events (n=3) were the most frequently reported types of SAEs. The incidence of SAEs was similar during the OL run-in period and after the DB-RWP (12.9% vs. 17.2%) and it was slightly higher during the LTFU phase (26.1%). Document B (Table 28, page 80).

The discontinuations due to AEs occurred in 6 patients with comparable frequency across the MRX only phases: the OL run-in phase ([redacted]), post DB-RWP

stable MRX dosing phase ([redacted]), and LTFU phase ([redacted]). Document B (Table 30, page 81).

***The EAG comment**:*

The evidence on safety data obtained from the ICONIC trial indicates that MRX has an acceptable safety profile. The most frequent AEs were Grade 1-2 (mild-to-moderate) PTs such as abdominal pain, diarrhea, vomiting, pyrexia, and nasopharyngitis. These events resolved spontaneously without any change in MRX dose or other medical intervention. However, difficulties regarding teasing out the safety events (e.g., ALT, AST, pruritus, skin and subcutaneous tissue disorders) that are due to underlying condition (i.e., ALGS) from those that MRX may help to initiate or exacerbate already existing ones, still remains. Therefore, post-market long-term monitoring of hepatic function (ALT, AST levels) and other related events is warranted.

2.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS included the GALA cohort comparison study[32-34] that indirectly compared event free survival (EFS) duration between the aggregated MRX-treated cohort of patients with ALGS and the control group, i.e., standard of care-treated ALGS patients of the GALA study (clinical research registry).[10, 35, 36]

The MRX-treated aggregate cohort was comprised of 84 ALGS patients who participated in three randomised placebo-controlled trials (RCTs)/and their open-label uncontrolled MRX-only treatment extensions:

- ITCH/IMAGINE II study[37-41]
- IMAGO/IMAGINE study[42-45]
- ICONIC study[26-30]

The 84 patients were children aged 12 months-18 years with ALGS/cholestasis and moderate to severe pruritus as measured by a mean daily score ItchRO[Obs]≥2, recruited in the centres across North America, Australia, and Europe.

The Gala study cohort is a natural history external control group consisting of a selected subset of 469 ALGS patients, born after 1997 who also met the same inclusion/exclusion criteria as those used in the three MRX ALGS RCTs (these criteria are listed below in this section). This GALA control sample restriction was used to make the MRX and GALA control groups comparable in terms of the distribution of important baseline covariates (age, bilirubin, GGT, and ALT) that are thought to affect the efficacy endpoint(s) of interest. The balance of baseline covariates between the two cohorts was explored by inspecting the standardised differences plot for each covariate (Document B, page 33).

The primary efficacy endpoint of interest for this indirect comparison was PFS defined as the time to the first occurrence of any of the following four events: liver transplant (LTx), surgical biliary diversion (SBD), liver decompensation (variceal bleeding, ascites requiring therapy), or death.

Brief description of ITCH/IMAGINE II and IMAGO/IMAGINE studies is provided below (

Table 15). The ICONIC study is described in section 2.2 of the EAG report.

Since the results of ITCH/IMAGINE II and IMAGO/IMAGINE studies are applied to those of the GALA comparison study, they are provided in section 2.4 of the EAG report.

Table 15: Summary description of ITCH/IMAGINE II and IMAGO/IMAGINE studies*

*ITCH study [RCT] LUM001-301 n=37	IMAGINE II study [ITCH extension] LUM001-305 n=34	IMAGO study [RCT] LUM001-302 n=20	IMAGINE study [IMAGO extension] LUM001-303 n=19
Study design			
Multicentre phase-2 DB placebo-controlled randomised trial.	Multicentre phase-2 DB-extension study.	Multicentre phase-2 DB placebo-controlled randomised trial.	Multicentre phase-2 DB-extension study.
Study phases			
4-wk screening 5-wk dose-escalation 8-wk stable dose 4-wk follow-up	4-wk DB dose-escalation 8-wk dose optimization 36-wk stable dosing 48-wk safety monitoring 120-wk LTFU Tx	4-wk screening 5-wk dose-escalation 8-wk stable dose 4-wk follow-up	4-wk DB dose-escalation 8-wk dose optimization 60-wk stable dosing 52-wk follow-up Tx 128-wk LTFU Tx
Study objectives			
To evaluate the safety and efficacy of 13-wk Tx with MRX in pats with ALGS.	To evaluate the long-term safety and durability of MRX in pats with ALGS who completed ITCH study.	To evaluate the safety and tolerability of 13-wk Tx with MRX in pats with ALGS.	To evaluate the long-term efficacy, safety, and tolerability of MRX in pats with ALGS who completed IMAGO study.
Study inclusion criteria			
Male and female ALGS pats aged 1-18 yrs with cholestasis and daily ItchRO(Obs) score ≥2 for 2 consecutive weeks prior to randomization.	Participants who had completed ITCH study (LUM001-301).	Male and female ALGS pats aged 1-18 yrs with cholestasis (total sBA > 3 x ULN), and daily ItchRO(Obs) score ≥2 for 2 consecutive weeks prior to randomization.	Participants Who had completed IMAGO study (LUM001-302).
Study exclusion criteria			
Surgical interruption of the enterohepatic circulation, liver transplant, ALT >15×ULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhea requiring specific intravenous	AE/SAE related to MRX during ITCH study leading to Tx discontinuation; conditions or abnormalities believed to have compromised the safety of the participant, or interfered with the completing the	Surgical disruption of the enterohepatic circulation, liver transplant, ALT or AST > 15xULN, decompensated cirrhosis, INR > 1.5, albumin < 30 g/L, history or presence of clinically significant ascites, variceal	AE/SAE) related to the study drug during IMAGO study (LUM001-302) that led to the discontinuation from the study. Participants with a history or presence of gallstones or kidney stones; or with a history of

fluid or nutritional intervention.	study; history or presence of gallstones or kidney stones; non-adherence (dosing compliance of <80%) or were unlikely to comply with the study protocol.	hemorrhage, other concomitant liver disease, and/or encephalopathy. Chronic diarrhea requiring specific intravenous fluid or nutritional intervention for the diarrhea and/or its sequelae.	non-adherence during the LUM001-302 study were not eligible to participate.
Settings and locations			
13 centers in the US and Canada (1 site in Canada).	11 sites in 2 countries (the US and Canada).	3 sites in the UK	3 sites in the UK
Intervention (n) vs. comparator (n)			
<u>Intervention (n=25)</u> MRX (70 µg/kg/d) n=8 MRX (140 µg/kg/d) n=11 MRX (280 µg/kg/d) n=6 <u>Comparator (n=12)</u> Placebo n=12	<u>DB dose escalation (n=34)</u> Pats from PBO group of ITCH study received weekly dose increases of MRX up to 140 µg/kg/day. Pats randomized to MRX during ITCH study continued to receive the same dose of MRX (4 wks). <u>Dose optimization (n=34)</u> Pats received by dose adjustment either 35, 70, 140, or 280 µg/kg/day of MRX based on response in pruritus and sBA levels (8wks). <u>Stable dosing/safety monitoring (n=34)</u> Pats were dosed with the Week 12 dose of MRX, or the highest tolerated MRX dose below the Week 12 dose <u>LTFU Tx (n=34)</u> Pats that were willing and eligible to	<u>Intervention (n=14)</u> Cohort A MRX (140 µg/kg/d) n=6 Cohort B MRX (280 µg/kg/d) n=8 <u>Comparator (n=6)</u> Cohort A Placebo n=3 Cohort B Placebo n=3	<u>DB dose escalation (n=5)</u> Pats from PL group of IMAGO study (n=5) received weekly dose increases of MRX up to 140 µg/kg/day (or maximum tolerated lower dose). Pats randomized to MRX during IMAGO study (n=14) continued to receive the same dose of MRX as at Week 13 of IMAGO study (4 wks). <u>Dose optimization (n=19)</u> Pats received by dose adjustment either 35, 70, 140, or 280 µg/kg/day of MRX based on response in pruritus and sBA levels (8 wks). <u>Stable dosing (n=19)</u> Pats were dosed with the Week 12 dose of MRX, or the

	roll over into the LTFU Tx period were maintained at the same Week 96 MRX dose level (120 wks).		highest tolerated MRX dose below the Week 12 dose (60 wks). <u>Follow-up Tx (n=7)</u> Pats were maintained to receive MRX at the dose they were receiving at Week 72 (52 wks). <u>LTFU Tx (n=7)</u> During this period, pts had an option to enroll in this study portion and then they could have their dose of MRX increased up to 560 µg/kg/d (280 µg/kg twice daily [BID]), based on efficacy (sBA and ItchRO score) and safety assessment results.
Permitted concomitant medication			
Patients were expected to maintain a stable dose and administration schedule for all permitted concomitant medications in the course of the study. No new medications used to treat pruritus were permitted to be added during the course of the study.			
Study endpoints			
<u>Primary efficacy endpoints</u> The mean score change from baseline to Week 13: ItchRO(Obs) for pruritus <u>Secondary efficacy endpoints</u> The mean score changes from baseline to Week 13: Fasting sBA level Liver-related parameters (ALP, ALT, AST, GGT, and	<u>Primary efficacy endpoints</u> Mean change from baseline to Week 48 in fasting sBA level <u>Secondary efficacy endpoints</u> Mean change from baseline to Week 216/EOT and Week 220/EOS in fasting sBA level Mean change from baseline to Week 216/EOT and Week 220/EOS in pruritus, as measured by: ItchRO[Obs], caregiver	<u>Primary efficacy endpoints</u> The mean score changes from baseline to Week 13/ET: Fasting sBA level <u>Secondary efficacy endpoints</u> The mean score changes from baseline to Week 13/ET: Liver enzymes (ALT, AST, ALP).	<u>Primary efficacy endpoints</u> The mean score changes from baseline to Week 48: Fasting sBA level <u>Secondary efficacy endpoints</u> The mean score changes from baseline to Week 48: Liver enzymes (ALT, AST, ALP)

total and direct bilirubin). Biomarkers of disease and QOL <u>Safety endpoints</u> Occurrence of TEAEs, SAEs, and TEAEs leading to permanent discontinuation of study drug. Changes in clinical laboratory values Physical examination findings (e.g., vital signs, body weight, height, and BMI), 12-lead ECG results, concomitant medication usage AESP (GI events, events related to liver deterioration, thyroid function abnormality events, growth retardation events.	Clinician Scratch Scale <u>Safety endpoints</u> AEs and SAEs Clinical safety laboratory results Vital signs Physical exam findings Concomitant medication usage	ItchRO (Observer ItchRO/patient ItchRO) for pruritus PedsQL <u>Safety endpoints</u> AEs Clinical safety laboratory results Vital signs Physical exam findings Concomitant medication usage ECG results	ItchRO (Observer ItchRO/caregiver ItchRO) for pruritus GGT Total/direct bilirubin <u>Safety endpoints</u> AEs Clinical safety laboratory results Vital signs Physical exam findings Concomitant medication usage AFP
Statistical methods			
ALGS a rare disease. The planned sample size of 37 evaluable ALGS subjects was based on practical considerations. The proposed sample of 28 subjects for the primary efficacy analyses would give 80% power to detect an effect size of ≥1.12. The analysis was based on an ANCOVA model with treatment and baseline average daily ItchRO(Obs) score as covariates. LS mean change from baseline to Endpoint (Week 13/ET), with 95% CI and p-values.	Change from baseline was tabulated overall and by Tx group assigned in Study LUM001-301, using summary statistics including the number of observations, mean, median, SD, minimum, and maximum. Differences from baseline were calculated and summarized with a 95% CI for the mean. Safety data were summarized descriptively overall and individual participant listings were prepared z-	The primary analysis of the primary efficacy endpoint was based on an ANCOVA model with treatment and baseline sBA as a covariate. The difference between treatment groups (individual and combined MRX, and placebo) in change from baseline to Week 13/ET in sBA level was evaluated by ANCOVA using a PROC MIXED model. LS mean differences in change from baseline were presented along with	Change from baseline was tabulated overall and by Tx group assigned in Study LUM001-302, using summary statistics including the number of observations, mean, median, SD, minimum, and maximum. Differences from baseline were calculated and summarized with a 95% CI for the mean.

Efficacy analyses were based on the MITT defined as all participants randomized, receiving at least one dose of study drug, and having at least one post-baseline efficacy assessment.	scores for height, weight, and BMI were calculated.	95% CIs, and pair-wise treatment p-values. The primary efficacy analysis was based on the MITT population. The analysis of sBA was based on both MITT the PP population, as a sensitivity analysis. MITT included all subjects who were randomized, received at least 1 dose of treatment, and had at least 1 postbaseline efficacy assessment. ITT population included all subjects who were randomized and dosed. Subjects were analyzed by assigned treatment. The PP population consisted of all subjects in the Safety Population who did not have a major protocol violation.	

NR=not reported; ITT = intention-to-treat; RCT = randomized controlled trial; DB=double blind; ALGS=Alagille syndrome; Tx=treatment; pat=patients; MRX=maralixibat; yrs=years; ALT=alanine transaminase; ItchRO=Itch-reported outcome; ULN=upper limit of normal; ECG=electrocardiogram; 95% CI=95 percent confidence interval; PBO=placebo; d=day; MITT= modified intention-to-treat; PP=per protocol; AST=aspartate aminotransferase, GGT=gamma-glutamyltransferase; ET=early termination; ANCOVA=analysis of covariance; n=number of subjects; AESP=adverse events of special interest; AE=adverse event; SAE=serious adverse event; TEAE= treatment-emergent adverse event; BMI=body mass index; sBA=serum bile acid; QOL=quality of life; wk=week; CSS=clinician scratch score; INR=international normalized ratio; ALP=alkaline phosphatase; AFP=alpha-fetoprotein

* Data compiled from CS Document B (Table 9). ITCH Clinical Study Report (Study synopsis, page 12),[37] IMAGINE-II Clinical Study Report (Study synopsis, page 2),[41] IMAGO Clinical Study Report (Study synopsis, page 10),[42] and IMAGINE Clinical Study Report (Study synopsis, page 2).[44]

2.3.1 ITCH/IMAGINE II study

ITCH study (LUM001-301)

ITCH study was a multicentre phase-2 DB placebo-controlled randomised trial with 13 weeks of treatment in children (age: 1-18 years) with ALGS. The trial was conducted in 13 centres in the US and Canada (1 site in Canada).

The study objective was to assess the effects of escalated and stable doses of 13 weeks vs. placebo on pruritus, sBA, liver enzymes, and other biochemical markers associated with cholestatic liver disease.

The study enrolled ALGS patients 1-18 years of age with cholestasis and daily ItchRO(Obs) score ≥2 for 2 consecutive weeks prior to randomization.

The study included 4 periods: i) 4-week screening period, ii) 5-week dose-escalation period, iii) 8-week stable dose period, and iv) 4-week follow-up period. Randomization occurred during the screening period and before dose-escalation period. Thirty-seven subjects were randomly assigned to receive either 1 of 3 doses of MRX: low dose (70 µg/kg/day, n=8), mid dose (140 µg/kg/day, n=11), high dose (280 µg/kg/day, n=6) or placebo (n=12). The randomised treatment period lasted for 13 weeks (dose escalation and stable dosing periods). Randomization was performed by the central pharmacy using schedules prepared by a clinical research organization. The caregivers, participants, investigators, and the sponsor were unaware of treatment assignment.

After randomisation occurred, the dose-escalation period started during which MRX was administered once daily and was escalated over 5 weeks to enhance tolerability of MRX. During stable dosing, the final dose of MRX was maintained for 8 weeks.

The primary and secondary efficacy endpoints were the mean score changes from baseline to Week 13 for pruritus (ItchRO(Obs)), fasting sBA level, liver-related parameters and biomarkers of disease. The safety endpoints included the occurrence of AEs, SAEs, TEAEs, clinical/laboratory values, physical examination findings (e.g., vital signs, body weight, height, and BMI), and AEs of special interest (e.g., GI events, events related to liver deterioration, thyroid function abnormality events, growth retardation events).

Only 2 participants could not complete the 13-week treatment period; 1 participant on placebo was lost to follow-up and 1 participant who was randomized to MRX (70 µg/kg/day) withdrew because of a rash and elevated liver biochemistries after receiving one dose (14 µg/kg).

The primary efficacy endpoint (i.e., mean ItchRO(Obs) score change for pruritus from baseline to Week 13) compared between MRX and placebo was not met.

IMAGINE II study (LUM001-305)

All participants (n=34; 11 from placebo and 23 from MRX arms) who completed ITCH study (LUM001-301) were enrolled in its extension follow-up IMAGINE II study (LUM001-305) whose objective was to evaluate the long-term safety and durability of MRX in patients with ALGS. This study was conducted at 11 sites in 2 countries (US and Canada).

The study was divided into 5 periods: i) 4-week dose-escalation period, ii) 8-week dose-optimization period, iii) 36-week stable dosing period, iv) 48-week safety monitoring period, and v) 120-week long-term follow-up treatment (LTFU) period.

During the dose-escalation period of IMAGINE II study, patients who were assigned to placebo group in ITCH study (n=11) started receiving weekly dose increases of MRX up to 140 µg/kg/day. In IMAGINE II study, patients randomized to MRX (n=23) during ITCH study continued to receive the same dose of MRX as they received in Week 13 of the LUM001-301 study. For the dose optimization period, patients received either 35, 70, 140, or 280 µg/kg/day of MRX based on their response based on effect on pruritus and tolerability. Reductions in dose were based on tolerability. During the stable dosing and safety monitoring periods, participants were dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. Patients that were willing and eligible to roll over into the LTFU Tx period were maintained at the same Week 96 dose level.

The primary efficacy endpoint was the mean score changes from baseline to Week 48 in fasting sBA level and the secondary efficacy endpoints were the mean changes from MRX baseline through Week 216/end of treatment and Week 220/end of study in fasting sBA level and pruritus (ItchRO[Obs], caregiver and Clinician Scratch Scale). Safety was evaluated based on AEs, SAEs, clinical safety laboratory results, vital signs, physical exam findings, and concomitant medication usage.

Thirteen of the 34 patients discontinued the extension study treatment. The most frequent reason for the treatment disconsolation was an AE (n=6, 17.6%). None of the patients was lost to follow-up.

2.3.2 IMAGO/IMAGINE study

IMAGO study (LUM001-302)

IMAGO study was a multicentre phase-2 DB placebo-controlled randomised trial with 13 weeks of treatment in children (age: 1-18 years) with ALGS. The trial was conducted in 3 sites in the UK.

The study objective was to assess the effects of escalated and stable doses of MRX for 13 weeks vs. placebo on pruritus (Observer ItchRO/patient ItchRO score), sBA levels, QoL (PedsQL score), liver enzymes (AST, ALT, ALP), and other biochemical markers associated with cholestatic liver disease.

The study included ALGS patients 1-18 years of age with cholestasis (sBA > 3 x ULN for the subject's age) and daily ItchRO(Obs) score ≥2 for 2 consecutive weeks prior to randomization.

The study was comprised of 4 periods: i) 4-week screening period, ii) 5-week dose-escalation period, iii) 8 (up to 11)-week stable dose period, and iv) 4-week follow-up period. The longest period of study participation for any subject was 23 weeks.

After screening and before dose escalation period, eligible subjects were randomised in cohort A (MRX 140 µg/kg/day vs. placebo) and cohort B (MRX 280 µg/kg/day vs. placebo) in a ratio of 2:1. Overall, twenty subjects were randomly assigned to receive either MRX 140 µg/kg/day (n=6; cohort A), MRX 280 µg/kg/day (n=8; cohort B), or placebo (n=6; cohort A and B). The randomised treatment period lasted for 13 weeks (dose escalation and stable dosing periods).

The primary efficacy endpoint of IMAGO was change in fasting sBA level from baseline to Week 13/ET in MRX (140 µg/kg/day, 280 µg/kg/day, or combined) vs. placebo. The secondary efficacy endpoints were mean changes from baseline to Week 13 in ItchRO (for pruritus), PedsQL, ALT, AST, ALP. Safety was assessed by measuring the frequency of AEs, clinical laboratory tests, vital signs, ECG, physical exams, and concomitant medication use.

Of the 20 randomized patients, 19 completed the study and 1 patient discontinued early due to an AE.

The primary efficacy endpoint (i.e., mean sBA change from baseline to Week 13/ET) compared between MRX and placebo was not met.

IMAGINE study (LUM001-303)

IMAGINE study was the long-term extension study for patients enrolled in IMAGO (LUM001-302). The objective of the study was to evaluate the long-term efficacy, safety, and tolerability of MRX in patients with ALGS.

The study was divided into 5 parts: i) a dose-escalation period (4 weeks), ii) a dose-optimization period (8 weeks), iii) a stable dosing period (60 weeks), iv) follow-up treatment period (52 weeks), and v) LTFP Tx period for eligible participants who chose to stay on treatment with MRX (28 weeks).

For the dose escalation period, participants who were randomised to receive placebo during IMAGO study (n=5) started receiving weekly dose increases of MRX up to 140 µg/kg/day or to a maximum tolerated dose below 140 µg/kg/day (10 mg maximum total dose). Participants who received MRX in IMAGO remained on the same dose (n=14). For the dose optimization period, patients received either 35, 70, 140, or 280 µg/kg/day of MRX based on their response based on effect on pruritus and tolerability. Reductions in dose were based on tolerability. During the stable dosing, participants were dosed with the Week 12 dose, or the highest tolerated dose below the Week 12 dose. During the follow-up treatment period (52 weeks duration), participants continued to receive MRX at the dose they were receiving at Week 72. The LTFU Tx period (28 weeks duration) was for eligible participants who chose to stay on treatment with MRX. They could increase their MRX dose to a maximum of 560 µg/kg/day (280 µg/kg twice daily).

Participation in the LTFU Tx period continued until the first of the following occurred: i) the participants were eligible to enter another MRX study, (ii) MRX was available commercially, or (iii) the sponsor stopped the program or development in this indication.

Study primary endpoints included the mean change from MRX baseline to Week 48 in fasting sBA level; the secondary endpoints were the mean change in pruritus (ItchRO score), ALT, AST, ALP, GGT and total and direct bilirubin.

Of the 19 patients who enrolled in the extension, 12 (63.20%) prematurely discontinued the treatment, of who 8 (42.10%) did not consent to enroll in the 52-week FU treatment period. Of the remaining 4 patients, 1 withdrew due to AE and 3 were withdrawn by a caregiver.

The EAG comment:

In general, the populations, interventions, comparators, and the endpoints selected for the two randomised trials ITCH (LUM001-301) and IMAGO (LUM001-302) matched with those specified in the NICE scope.

The ITCH and IMAGO studies were comparable to the ICONIC study in terms of their design (phase-2, double-blind placebo-controlled trials, study phases), efficacy endpoints (cholestasis, pruritus, liver enzymes, quality of life, and adverse events), and study populations (children and adolescents with ALGS). IMAGO unlike ITCH and ICONIC studies was conducted in hospitals across the UK (3 sites), whereas ITCH and ICONIC studies were mostly conducted in North America (the US) and Europe.

The ITCH and IMAGO studies share their limitations and uncertainties with the ICONIC study. For example, both ITCH and IMAGO studies are of exploratory rather than confirmatory nature. No sample size calculations were performed that would allow to specify the study power to detect the desired minimum magnitude of a clinical effect between MRX and placebo arms. The most parts of the IMAGO/IMAGINE and ITCH/IMAGINE II studies were designed as open-label one-arm follow-up without a comparator which leads to uncertainty in interpretation of the study results in regard to the efficacy of MRX compared to standard treatment or placebo since it is difficult to separate the effect of MRX from other known or unknown confounding factors. Importantly, the length of DB-randomised treatment periods for both trials were too short (13 weeks) to reliably document the effects of MRX in the treatment of patients with ALGS.

Unlike the ICONIC study, neither ITCH nor IMAGO could demonstrate statistically significant results for the primary efficacy endpoint in favour of MRX compared to placebo (or standard of care). The lack of beneficial effect of MRX observed in the two trials could explain the company's not including ITCH and IMAGO studies as the key/main relevant evidence of the CS to NICE alongside with the ICONIC study for supporting clinical effectiveness of MRX in treating pruritus associated with ALGS. Another reason may be the lower dose of MRX (up to 280 µg/kg/day) used in these trials compared to the EMA-authorized indicated MRX dose of 380 µg/kg/day that was administered in the ICONIC study.

The higher dosing of MRX in the ICONIC (380 µg/kg/day) vs. ITCH and IMAGO studies (range: 70 µg/kg/day - 280 µg/kg/day) during the randomised treatment period is a possible factor that could explain the statistically significant efficacy endpoint estimates in favour of MRX over placebo, observed in the ICONIC trial.

In general, the methods of randomisation, allocation concealment, and blinding as described in the CS are deemed adequate for the ITCH and IMAGO trials.

Additional critique of the GALA study

The GALA cohort controlled study investigated the long-term efficacy of maralixibat treatment in Alagille Syndrome (ALGS) by comparing outcomes with a historical control from the GALA database. This study utilised data from the maralixibat-arm of three maralixibat controlled trials (ICONIC, ITCH, and IMAGO) involving 88 patients, 84 of whom received treatment were included in the analysis. Long-term follow-up data, inclusive of discontinued participants of a median follow-up of 6 years were gathered to assess clinical outcomes.

The primary outcome focused on liver-related events (such as transplantation, severe bile duct issues, decompensation events like variceal bleeding or ascites requiring therapy) and death. The GALA database, tracking information from over 1400 ALGS patients across 29 countries, served as the historical control. The analysis employed a composite measure called Event-Free Survival (EFS), which encompassed the ALGS-related clinical events mentioned above. The study used step-wise selection strategy to select 469 from a total of 1400 patients in the GALA database to form a GALA controlled group that aligns with the maralixibat-treated

cohort based on crucial criteria like patient characteristics and baseline variables (age, sex, bilirubin, GGT, ALT).
Comparing EFS between the Maralixibat-treated cohort and the GALA control group revealed a delayed occurrence of clinical events in the maralixibat cohort. Significantly, the maralixibat group exhibited a 70% improvement in EFS compared to the control, suggesting enhanced Event-Free Survival with maralixibat treatment. The EAG has concerns and critique of key issues in the GALA Cohort Control Study as described below.

2.3.2.1 Event-Free Survival (EFS) Maturity and Median Survival Time

The available six-year follow-up for the maralixibat arm leaves the median survival time unattained in the maralixibat cohort. This immaturity of the data limits our ability to precisely estimate the Event-Free Survival (EFS) hazard ratio, thereby affecting the reliability of conclusions drawn on the long-term effects of treatment. Consequently, extending survival curves beyond this limited follow-up duration presented significant methodological challenges. Such extrapolation was subject to greater uncertainty, jeopardising the accuracy of predicting long-term outcomes and subsequently rendering the estimations of the long-term treatment effect unreliable.

2.3.2.2 Hazard Ratio Interpretation and Proxy for Mortality

The hazard ratio for mortality associated with treatment response that was used in the economic model was taken from the hazard ratio for event free survival estimated from the GALA Cohort Comparison Study. The study's reliance on a composite EFS measure, encompassing Surgical Biliary Diversion (SBD), liver transplantation, decompensation events, or death, when comparing maralixibat-treated participants with the GALA control group, raises concerns due to the data's immaturity. The use of hazard ratio for EFS as a proxy for mortality becomes contentious considering the composite nature of the EFS outcome. While it incorporates significant events like liver transplant and decompensation, there exists uncertainty regarding whether these events adequately mirror mortality in ALGS patients. Seeking clarification from clinical experts, the EAG discovered that certain patients may achieve near-normal life expectancies post-liver transplant, challenging the assumption that these events adequately portray overall survival. The EAG clinical advise is supported by the fact

that the post-liver transplant survival used in the company's economic model is derived from a Pooled 2.5-year survival of 71% in the study by Hou et al.[46] In the absence of a transplant, the survival rates for individuals with ALGS decline significantly with age, with just 24% of those aged 18.5 years surviving without undergoing transplantation.[47] For patients who receive a transplant, the probability of survival stands at approximately 79% within one year following the transplantation procedure.[48] Therefore patients who undergo liver transplant have a good survival rate in this population, this implies a hazard ratio derived from liver-transplant events not a good proxy for mortality hazard ratio in the economic model.

2.3.2.3 Lack of Adjustment for Serum Bile Acids (sBA)

The primary analysis evaluating EFS did not include baseline serum bile acids (sBA) levels. This absence of adjustment for sBA, despite its critical role as a marker for treatment response, raises considerable concerns. sBA plays a pivotal role as a prognostic factor influencing event-free survival. Omitting sBA in the analysis might introduce bias, potentially compromising the accuracy of hazard ratio estimation.

2.3.2.4 Inconsistency in Baseline Definition

The inconsistency in defining baseline between the maralixibat and GALA control cohorts poses a fundamental issue concerning the starting point for measuring event free survival. The divergence in defining baseline dates between cohorts, particularly using the first maralixibat dose versus the criteria for inclusion in the maralixibat study, complicates comparative assessments. This inconsistency significantly impacts treatment effect estimation, resulting in varied hazard ratios and increased uncertainty when evaluating maralixibat's efficacy compared to no treatment. Considering date of birth instead of visit/treatment start for baseline measurement could have offered a more consistent starting point across cohorts. A scenario analysis conducted by the company in repeating the analysis using date of birth as the starting point for measuring survival, the hazard ratio for maralixibat versus placebo changed from 0.3 to 0.5, indicating that maralixibat is less efficacious on event-free survival when age is used as the starting point. The EAG prefers the method of counting survival from the date of birth as this approach aligns more with common baseline from which to measure survival, portraying longer survival times

and potentially reducing uncertainty in estimating the treatment effect for maralixibat versus no treatment.

2.3.2.5 Use of above-licensed doses during long-term follow-up for MRX treated patients

Patients enrolled in MRX clinical studies and hence included in the GALA Cohort Comparison Study received varied dose of treatment, as briefly shown in Figure 2 below. Some of the patients started to receive MRX in doses (significantly higher than the target dose (380 µg/kg/day) from approximately 100 weeks / two years since initial enrolment into the trial. As described earlier in Section 2.2.5, the EAG observed some improvement in various outcomes at around week 100 of MRX clinical studies, which might be attributed to the increased dose. This benefit would have contributed to any treatment effects observed in the GALA Cohort Comparison Study. Nevertheless costs related to the higher doses of MRX were not considered in the company's economic model.

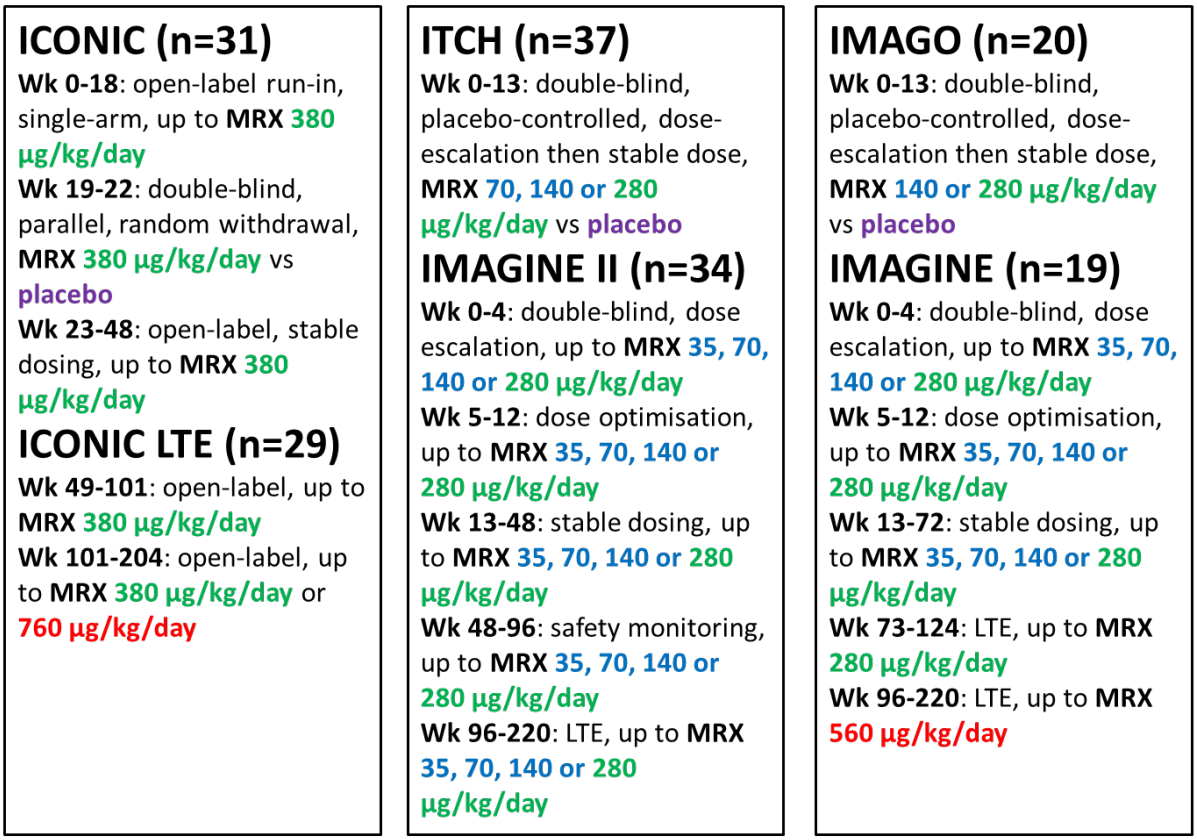


Figure 2: Different doses used in various phases of maralixibat clinical studies in patients with ALGS

2.4 Additional work on clinical effectiveness undertaken by the EAG

RISE study (MRX-801) for infants

In addition to the ICONIC study described earlier in section 2.2 and other MRX trials contributing to MRX-treated patients in the GALA Cohort Comparison Study described in section 2.3 of the EAG report, the company briefly mentioned the RISE (MRX-801) study in the Ongoing studies section in CS Document B (Section B.2.11, page 83-84). RISE is the only study which provided evidence for infants younger than 12 months. It is a single-arm, multicentre, open-label study of MRX for infants ≥2 months and <12 months of age with ALGS or progressive familial intrahepatic cholestasis. Interim findings presented in European Public Assessment Report

(EPAR),[24] based on 8 infants with ALGS showed that at week 13 the mean change from baseline in sBA was -88.9 µmol/L (SD 113.3; median -53.7, range -306.1 to 14.4) and the mean change in Clinician Scratch Scale (CSS) was -0.2 (SD 1.91, median -1.0, range -3.0 to 3.0). Rates of treatment response based on sBA or CSS were not presented, although the EPAR described that "two patients experienced improvement in both pruritus and sBA".

2.5 Conclusions of the clinical effectiveness section

- The clinical effectiveness evidence for MRX was primarily informed by the ICONIC study and the GALA Cohort Comparison Study. The double-blind random withdrawal phase (DB-RWP) of the ICONIC study demonstrated the effectiveness of MRX compared with placebo in reducing symptoms of cholestatic pruritus, sBA and other blood chemistry measures. However the short duration (4 weeks) of DB-RWP was insufficient for providing long-term data on comparative effectiveness, which was provided by the GALA Cohort Comparison Study.
- A reduction in sBA > 50% at 12 or 18 weeks was used as the criterion for treatment response, which was one of the main parameter input into the company's economic model. The reduction of sBA of this magnitude is clinically relevant but may not be as important as measurements of itching for symptomatic control of cholestatic pruritus from patient's perspective. The EAG is concerned that treatment response estimated from the run-in period of the ICONIC study might be biased due to the lack of a parallel control group and the prohibition of use of bile acid resins for study entry.
- Given the lack of parallel placebo or SoC control group in the ITCH study, the company assumed a response rate of 0% for the comparator in its economic model. The EAG questions this assumption and consider the response rate from ITCH trial, which was a double-blind trial with a parallel placebo group to be a more suitable source of response rate for the comparator (see Section 3.2.6.2), Long-term comparative effectiveness for MRX compared with SoC was provided by the GALA Cohort Comparison Study, which included MRX-treated patients from clinical studies of MRX in ALGS and a matched control

cohort of patients who did not receive MRX. The HR for liver-related events derived from this study was another key parameter input into the company's economic model. With a longest follow-up of around 6 years, the data was still very immature for long-term treatment outcomes. The EAG consider the HR of 0.305 being highly uncertain and potentially biased in favour of MRX due to the duration of follow-up and low number of events such as deaths; choice of baseline for the control group; and use of above-licensed doses for MRX treated patients in the long-term extension phases of MRX clinical studies,

3 COST EFFECTIVENESS

3.1 EAG comment on company's review of cost-effectiveness evidence

CS Appendix D, G, H, I (the 'Systematic Literature Review Technical Report') provides a detailed report of an SLR conducted to meet 7 different research objectives, including the identification of cost effectiveness analyses for ALGS treatment (n=0), health-related quality of life (HRQoL, n=6) evidence, costs and resource use studies (n=0) and clinical and economic burden evidence (n=0).

3.1.1 Search strategies

An appropriate range of sources were searched to identify economic and HRQoL studies, including bibliographic databases as well as websites of HTA agencies, Google Scholar, reference lists, and conference proceedings (CS Appendix D, G, H, I section 3.4). As the CRD HTA, NHS EED and ScHARRHUD databases are no longer updated, the EAG recommends also searching the INAHTA HTA database and using a web search engine such as Google to ensure comprehensiveness.

The search strategies for Embase and MEDLINE for the original October 2021 SLR reported in Appendix B, Tables 19 and 20 are not sufficiently comprehensive, as the terms for ALGS are only searched as subject headings. This means that records with key population terms in the title or abstract, but not in the subject (Emtree/MeSH) terms would have been missed. Phrase searching is also used for all ALGS (population) search terms, whereas use of Boolean AND or proximity operators to link terms would have been more sensitive.

Sensitive search filters for economic studies,[49] HRQoL[50] and resource use are used in both the 2021 and 2023 searches, however the filters developed for Embase are wrongly applied to both Embase and MEDLINE databases. As MEDLINE uses a different subject thesaurus (MeSH) to Embase (Emtree), the filters are not effective across both databases, as demonstrated by several search lines in Table 27 retrieving 0 results.

As the company's SLRs identified no cost-effectiveness evidence, the EAG ran brief, targeted Embase and internet (Google) searches and was also unable to find any

cost-effectiveness studies relating to ALGS treatments. Additional searches run by the EAG can be found in the Appendix (section 7). The EAG considers it possible that some potentially useful HRQoL or costs related studies may have been missed by the company's searches, however the key papers in these areas were identified and included in the SLRs.

3.1.2 Additional critique of company's review of cost-effectiveness evidence

The company reviews yielded no cost-effectiveness studies when performed in 2021 and during an update in May 2023. Supplementary searches by EAG for cost effectiveness evidence were similarly unsuccessful, suggesting a paucity of relevant economic evaluations in ALGS treatment. While the review appears reasonably comprehensive overall, improvements could be made to the search strategies to enhance retrieval of all relevant studies. However, the key studies seem to have been identified by the existing searches.

The company SLR also supports the development of the ALGS health state vignettes to be used in utility valuation study, which can be found in more detail in section 3.5. The company searched using appropriate bibliographic databases like Embase, MEDLINE and Embase Classic and supplementary searches of other resources like Cochrane Library were also carried out. However, some limitations were identified by EAG in the search strategies, including a lack of sensitivity in the ALGS population search terms and inappropriate use of study design filters across databases MEDLINE and Embase, as seen in Appendix B Table 20 of the company SLR.

3.2 Summary and critique of the company's submitted economic evaluation by the EAG

3.2.1 NICE reference case checklist

Table 16: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Estimate of initial treatment response was obtain from maralixibat treated patients in the ICONIC study but was simply assumed to be zero for the comparator arm. Estimated treatment effect was obtained from GALA Cohort Comparison Study. See EAG's critique in Section 3.2.6.

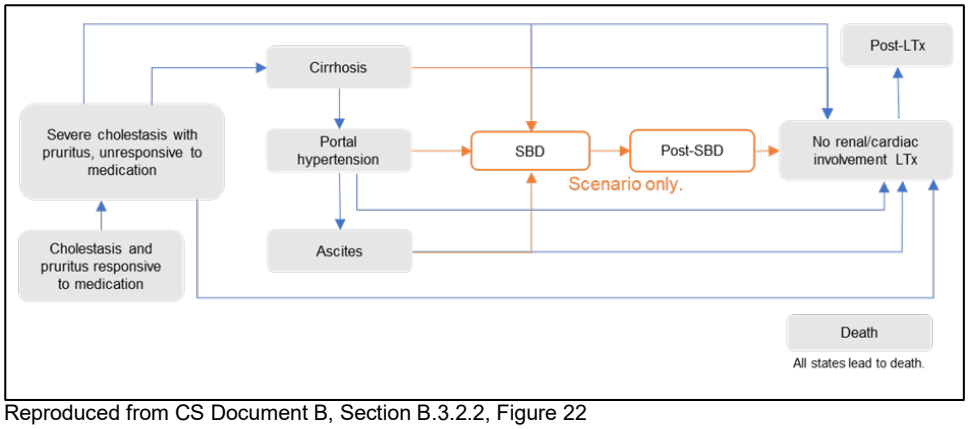
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ5D-5L data was reported directly by patients or carers. A vignette study was conducted to elicit utility values from patients and carers
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

3.2.2 Model structure

The company used a Markov model with a cycle length of 12 weeks. The model has 10 health states:

- Cholestasis and pruritus, with response to treatment
- Cholestasis and pruritus, with loss of response to treatment
- Cirrhosis
- Portal hypertension (PHT)
- Ascites
- Surgical biliary diversion (SBD) (scenario only)
- Post-SBD (scenario only)
- Liver transplant (without cardiac or renal involvement, with a proportion of patients remaining in cycle to capture re-transplant).
- Post-liver transplant
- Death (absorbing state)

All patients begin responsive to treatment, but patients in the SoC arm are unresponsive after the first cycle (i.e. treatment response in the SoC arm is set to zero). Response to MRX is derived from the proportion of patients with a 50% reduction in sBA levels from baseline to 12 weeks in the ICONIC study.[27] Following the first cycle, the probability of discontinuation, i.e., loss of response, is set equal to the proportion of patients in the ICONIC study who discontinued MRX after 18 weeks due to AEs. After patients become unresponsive, they progress through the various health states until death (absorbing health state) as shown in Figure 3 below.



Reproduced from CS Document B, Section B.3.2.2, Figure 22

Figure 3: Model schematic

Transition probabilities define the progression of patients from one health state to another. Transition probabilities were either assumed, derived from various literature sources, or digitised Kaplan-Meier curves. A summary of the transition probabilities used in the model is shown in

Table 17 below.

Table 17: Transition probabilities derived and used in cost-effectiveness model (CEM)

Transition	Reported value	Value (12-week cycle)	Source (Reference number in CS Document B)
Response to MRX	[redacted]	[redacted]	ICONIC (39)
Response to SoC	–	0%	Assumption
Discontinuation of MRX	[redacted]	[redacted]	ICONIC (39)
Discontinuation of SoC	[redacted]	[redacted]	Clinical opinion (Appendix M)
Unresponsive → Cirrhosis	41/94 at 10 years	1.31%	Lykavieris (12)
Cirrhosis → PHT	40% at 30 years	0.39%	Kamath (8)
PHT → ascites	36% at 30 years	0.34%	Kamath (8)
Unresponsive → LTx	47% at 4 years	3.58%	Quiros-Tejeira (92)
Cirrhosis → LTx	7.27% at 1 year	1.72%	Hagstrom (93)
PHT → LTx	23% at 1 year	5.9%	Krasinskas (94)

Ascites → LTx	–	5.9%	Assumed equal to PHT→ LTx
Post-SBD → LTx	0% in the base-case 36% at 18 years	0% or 0.6%	NAPPED (95)
LTx → LTx (re-transplantation)	22% at 1 year	5.55%	Adam (89)
Unresponsive → SBD Cirrhosis → SBD	0% in the base-case 50% at 29 months in a scenario	0% in the base-case 6.38% in a scenario	Foroutan (85)
PHT → SBD Ascites → SBD	50% at 29 months in scenario		

Reproduced from CS Document B, Section B.3.3.2, Table 34

EAG comment

The lifetime horizon was long enough to capture important differences in costs and clinical outcomes. The 12-week cycle length was adequate to capture relevant changes.

Although the health states modelled are relevant to the disease area, the EAG disagrees with the structural assumptions of the model, particularly, the modelling assumption that underpins transition from a responsive to an unresponsive health state. The company used a single biomarker (sBA levels) with an arbitrary threshold (reduction of ≥50% from baseline) as a proxy for response and delay disease progression. A similar appraisal (HST17) used a much higher threshold to define response[23] to treatment (defined as ≥ 70% reduction in sBA levels from baseline).

It is unclear whether patients who achieved the company-defined sBA response threshold also had a pruritus response. An alternative approach that precludes the use of arbitrary response thresholds would have estimated the impact of treatment or reduction in sBA levels, on the risk of clinically meaningful events such as cirrhosis, PHT, ascites and LTx. Estimated risks could then be used to derive transition probabilities from a responsive health state to other health states.

The model does not permit patients on MRX i.e., responsive to treatment, to develop ascites, PHT, cirrhosis and LTx despite evidence from the GALA study showing that patients in the MRX cohort had these events.

The assumption of 0% response in SoC is unsupported by the evidence presented. Treatment groups were not randomised per the model structure and the arbitrary mITT population studied does not reflect current indications for managing ALGS.

The model assumes the probability of a responsive patient maintaining a response is solely dependent on the risk of medication-related adverse event. This is a strong assumption for the following reasons. First, the sample size of the ICONIC study is too small to make such strong inferences. Second, it assumes that patients cannot become unresponsive to MRX due to treatment failure. Third, long term data from the ICONIC study showed that 6/31 people discontinued (19.35%) MRX due to AEs. Given the small sample size and the possibility of subsequent treatment failure, the risk of response loss after an initial response is likely to be higher in clinical practice.

3.2.3 Population

MRX has received marketing authorisation in the UK.[22] The patient population considered in the model is in line with its license: People with cholestatic pruritus related to Alagille syndrome (ALGS). This aligns with the scope issued by NICE. The company submission relies on data from the ICONIC and GALA study.

As described in section 2.2, the ICONIC study was a multicentre, phase 2b trial with an initial single arm, open label run-in phase (week 0-18), a double-blind, placebo-controlled random treatment withdrawal phase (week 18-22) and, open-label extensions. The open-label run-in phase of the ICONIC study provided data on response to MRX (0-12 weeks) and the probability of maintaining a response to MRX (0-18 weeks).

The GALA Cohort Comparison Study included aggregate data from three MRX clinical studies (ICONIC, ITCH and IMAGO) and their long-term extensions. Overall survival and the hazard ratio of mortality between responders and non-responders were derived from the GALA Cohort Comparison Study.

EAG comment

The GALA study was immature and median OS was not reached in the combined maralixibat cohort. Parametric extrapolation of digitised KM curves from the GALA study fit the data up to a 20-year span. Beyond 20-years, the curves diverge substantially with the most pessimistic extrapolation predicting a median OS of 77 years, which is in the region of the average life expectancy of the general UK population.

The hazard ratio (HR) of mortality between responders and non-responders derived from the GALA study is uncertain because its estimation relied on endpoints other than death. Liver decomposition events, SBD and LTx were also used to estimate the HR. Furthermore, the HR estimate is sensitive to the choice of baseline for the GALA control participants.

3.2.4 Interventions and comparators

The final scope issued by NICE as seen in Table 1 of the company submission includes the following additional comparators: dietary changes and off label drugs such as: ondansetron, naltrexone, selective serotonin reuptake inhibitor (SSRIs), and antihistamines. The company excluded dietary changes and the above listed drugs due to the absence of data. Surgical diversion was only included in a scenario analysis.

EAG comment

The EAG considers the comparators partially appropriate. Participants in the ICONIC study were not allowed to receive bile acid chelating resins as a pre-condition to enrolment. This raises questions about the generalisability of the treatment to the SoC group in the economic model.

3.2.5 Perspective, time horizon and discounting

The perspective is per the NICE reference case with benefits from an NHS and PSS perspective. The base case analysis discounted costs and benefits at an annual rate

of 3.5% in line with NICE reference case. The lifetime horizon is sufficient to capture all relevant costs and outcomes.

3.2.6 Treatment effectiveness and extrapolation

3.2.6.1 Summary of company treatment effectiveness and extrapolation

Treatment efficacy evidence was obtained from the ICONIC study. All patients begin the cycle in a responsive health state. While responsive, patients can either become unresponsive or die but cannot transition to other health states. All patients begin the cycle in a responsive health state. In the SoC arm, all patients become unresponsive after the first cycle. In the MRX arm, the transition from a responsive health state to an unresponsive health state after the first cycle is derived from the proportion of people ([redacted]) who achieved a ≥50% reduction in sBA levels in the ICONIC study at 12 weeks. This group of patients was classified as responders in a mITT analysis. A detailed discussion on the bias implicit in this approach can be found in Section 2.2. The probability of death in responders was adjusted using the HR of event-free survival from the GALA Cohort Comparison Study (see section 0). Transition probabilities between the various health states are shown in Table 17 above.

3.2.6.2 EAG Critique of treatment effectiveness and extrapolation

Response rate, treatment failure and discontinuation of treatment

The model estimates a [redacted] response rate in the MRX group and 0% in the SoC arm. The randomised withdrawal design of the ICONIC study lacks both internal and external validity, undermining its use for modelling response rate in the model. A similar appraisal (HST17) used a ≥70% reduction in sBA levels to define response[23] to treatment. When this threshold was applied to participants in the ICONIC study, only 3 of 31 participants met this threshold.

Regardless of the threshold used, the sample size was small, and no formal sample size calculation was undertaken. The decision to use sBA levels over other outcomes collected such as bilirubin levels and xanthoma scores was not justified. The EAG preference would be to derive response rate from a randomised

comparison of patients receiving MRX and usual care. Treatment outcomes could then be mapped onto the risk of developing important clinical events over the natural course of ALGS and explicitly modelled.

Treatment failure in responders was not accounted for in the economic model. There appeared to be a lower number of participants meeting the response threshold at week 18 compared to week 12 which could undermine the implicit assumption of no treatment failure in responders.

The model assumes equivalence between discontinuation of treatment and loss of response in responders. The probability of loss of response [redacted] is based on the side-effects profile of the patients in ICONIC study excluding treatment failure. Given the small number of patients in the iconic study (n=31), this estimate may be unreliable. This is also likely an underestimate given that only serious adverse events were considered and the implicit assumption of no treatment failure in responders who tolerate MRX.

This assumption of 0% response rate in the SoC arm is unjustified based on the evidence provided. Treatment groups were not randomised at baseline in the ICONIC study which makes it impossible to determine what a response would be in patients receiving SoC. Furthermore, participants were not given medication that could confound treatment effect even when such medication are prescribed for patients with cholestatic pruritis.

In Table 34 of the ITCH study,[37] [redacted] patients randomised to receive placebo achieved a 50% reduction in sBA levels between baseline and week 13 compared to [redacted] patients in the MRX arm. Although the medication dose administered to patients randomised to receive MRX differed from those used in the ICONIC study, patients on placebo who did not receive MRX achieved a response rate of [redacted] Using observer Itch reported outcomes (ItchRO) scores rather than sBA levels as a proxy for response, 8.3% of patients achieved a study-defined response threshold of a < 1.5 change from baseline in ItchRO scores compared to 40% of patients on MRX. When the threshold was increased to a change from baseline of < 2.0, 8.3% of patients in the placebo group met this threshold compared to 16.0% of patients in the MRX group.

Results from the ITCH study undermines the 0% assumption in patients receiving SoC and shows that response rates are sensitive to the outcome used to define response.

3.2.6.3 Modelling of OS is unrealistic, and the mortality hazard ratio estimate between responders and non-responders used in the economic model is flawed

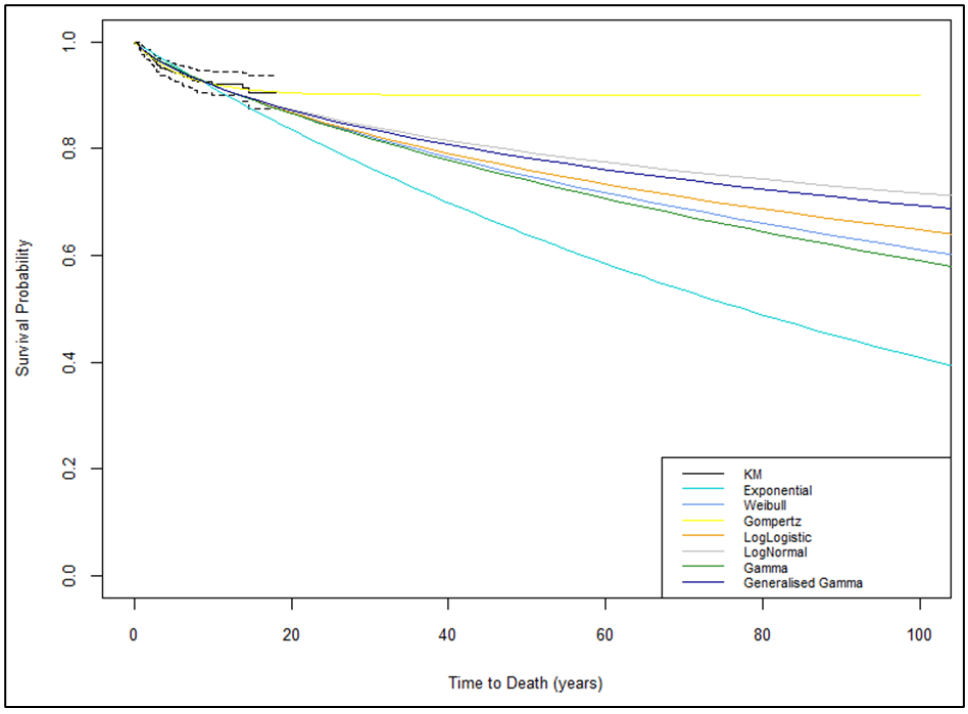
The company utilised digitised Kaplan-Meier curves from GALA[10] to reconstruct individual patient-level time-to-event data for the treatment-naïve population (mortality in the usual care arm). They employed an algorithm by Liu et al (2021)[51] for this reconstruction process. Parametric survival models were then applied to extrapolate this reconstructed data, aiming to predict the lifetime survival in treatment naïve ALGS patients. The parametric models fit the data satisfactorily up to a 20-year span, beyond which they diverged substantially and showed poor fit. Among these models, the exponential curve was the most pessimistic, predicting a median overall survival of 77 years, while the Gompertz model rendered the median survival inestimable as shown in Table 18 below. Due to the poor fit of all the parametric survival curves, the company chose the log-logistic curve, positioned midpoint between all survival curves, for the base-case. However, the EAG disputes this choice. The Log-logistic model chosen by the company implausibly estimated median survival at 216 years with 65% of patients alive at 100 years of age. Indeed, all curves fitted by the company predicted overtly optimistic survival times that are extremely unlikely (Figure 4).

Table 18: Survival probabilities at different ages

Distribution	Year 10	Year 18	Year 50	Year 100	Median survival (years)
Observed survival [a]	92.1%	90.5%	-	-	Not evaluable
Exponential	91.4%	85.1%	63.9%	40.9%	77.4

Weibull	92.0%	87.6%	74.9%	61.1%	156.0
Log-normal	91.8%	88.1%	79.3%	71.6%	497.4
Log-logistic	91.9%	87.7%	76.1%	64.8%	216.6
Gompertz	92.0%	90.6%	90.0%	90.0%	Not evaluable
Gamma	92.0%	87.6%	74.1%	59.0%	138.8
Generalised Gamma	91.8%	88.0%	78.3%	69.6%	339.0

Reproduced from CS Document B, Section B.3.3.3, Table 38



Reproduced form CS Document B, Section B.3.3.3, Figure 24

Figure 4: Parametric extrapolations of the survival of children with ALGS who presented with neonatal cholestasis

Considering the uncertainties predicting overall survival by all curves, the EAG contends that the exponential curve should be used in the base-case, in absence of better data. Despite its optimistic prediction of a median survival of 77 years which notably rivals the UK population's life expectancy, it falls within the expected range of human life expectancy and provides a more conservative estimate compared to

other models. The EAG conducted a scoping literature review to determine if there is additional published evidence on the survival of patients with ALGS that could be used to inform treatment-naive mortality extrapolations in this population. The review identified approximately 12 papers, all of which reported in various ways on native liver survival or transplant-free survival. However, one study (Hori 2010)[52] reported survival data, but this was in patients who had undergone a liver transplant rather than reporting overall survival in the treatment naive ALGS population; hence, it was not suitable for extrapolating overall survival in this population.

The company applies a HR of 0.305 to responders in the economic model reducing mortality in responders and boosting the already optimistic survival times predicted for the treatment naïve population. The HR estimate of 0.305 used in the model was obtained from the GALA study which in addition to death, included other events: LTx, biliary diversion and liver decomposition.

Excluding all other events, [redacted] of 469 ([redacted]%) patients in the GALA cohort died in the GALA cohort while [redacted] of 84 ([redacted]%) patients in the MRX cohort died.[32] The company justified their use of the estimate, arguing that 58.3% of deaths in the GALA control group occurred due to disease complications which could have been prevented by treatment with MRX. However, a similar cause of death was unavailable for the MRX cohort.

The HR estimate from the GALA study was also sensitive to the use of other baseline definitions. The baseline chosen for the GALA primary analysis was the time the MRX cohort entered the study. When other baseline definitions such as date of birth and first eligible visits were used, the HR was 0.504 and 0.618 respectively.

The EAG contends that the HR estimate is a composite estimate which makes it an inappropriate substitute for mortality. A crude examination of deaths in both groups shows that patients in the MRX cohort had a higher risk of death compared to patients in the GALA control group ([redacted]% vs [redacted]%). In the absence of data on the cause of death in the MRX cohort, we cannot make inferences on treatment-related risk of death.

Due to these substantial uncertainties in the HR estimate used by the company, the EAG assumes equivalent mortality risk between responders and non-responders.

The company assumes non-responder mortality risk is independent of age and set mortality risk from all non-responder health state equivalent to the GALA control group from the first cycle. This is a strong assumption as the baseline age from which the estimates were derived differ substantially from the model baseline age (e.g. the GALA study selection criteria excluded participants less than 1 year old). The company acknowledges the differences in baseline age between the model cohort and the target population but argues that mortality risk decreases over time and younger participants are at increased risk of death compared to older patients. This claim is unsupported as the OS data from the GALA study is immature as explained above. Furthermore, the median age of participants in the GALA control group was 4.3 years (IQR: 2.2 years, 9.6 years).

3.2.7 Health related quality of life

Health-related quality of life used in the economic model were derived from a vignette study conducted by the company, briefly described below.

Although the ICONIC study collected quality of life data using the Itch reported outcome (ItchRO), PedsQL, the company argued that the age of participants and the lack of mapping algorithms prevented their use in the economic model. A summary of all health state utility used in the model, including those derived from the vignette study can be found in Table 19 below.

3.2.7.1 Vignette study

The economic model used a vignette study (CS Appendix M) to establish HRQoL across health states in ALGS with 200 members of the UK general population. It employed EQ-5D-5L, time trade-off (TTO), and visual analog scale (VAS) valuation methods to determine caregiver and patient health-state utilities. Caregiver burden was also assessed. Development of the vignettes were informed by a SLR, clinical trial data, and clinician interviews. Four patient health state vignettes (progressive cholestasis, non-progressive cholestasis, successful liver transplant, chronic liver transplant rejection) and three caregiver health state vignettes were developed. The health states used in the study do not directly reflect those used in the economic model. The vignette study results showed that the TTO values were higher than EQ-5D-5L values for all states.

Table 19: Summary of health states used in the vignette study

State	Description
Progressive cholestasis	sBA levels of 280 mmol/L or total Bilirubin levels of 6 mg/dl
Non-progressive cholestasis	sBA levels of 140 mmol/L or total Bilirubin levels of 3 mg/dl
Successful LTx	Patient has had a successful LTx
Chronic LTx rejection	Rejection denotes the host immune system attacking the liver – in this state the liver may still be functioning, and full function may be restored through immunosuppressive therapies, however there is still the risk of graft failure.

Abbreviations: sBA, serum bile acid.

Reproduced from CS Document B, Section B.3.4.5.1, Table 40

EAG Comment

- NICE recommends the use of vignette studies can be considered when obtaining utility from the published literature or clinical trial data is challenging. Vignette studies are expected to be consistent with the NICE methodological guidelines.[53] The company did not offer a comprehensive description of the contents of the vignette, but Table 19 above briefly outlines the health states featured in the vignette. According to NICE guidance, vignette content should encompass all pertinent aspects of health-related quality of life and patient experience with the specific disease. The clarity of how the quantitative description of sBA levels (as indicated in Table 19) aligns with the patient experience of ALGS remains unclear.
- The difference between the responsive and unresponsive health state from the vignette study is remarkably high (0.315) and differ substantially from utility values used in other similar appraisals. For example, in HST17 - Odevixibat for treating progressive familial intrahepatic cholestasis, the utility difference between treatment response and non-response health states is 0.161).[23]
- The company collected quality-of-life data in the ICONIC trial using (PedsQL) tool but did not use the information to derive EQ5D utility despite the existence of a mapping algorithm by Khan et al. (2014). The company argued

that the model cohort baseline age of 2 months precludes the use of the PedsQL to derive utility. However, the ICONIC study which informed the estimated probability of response to MRX in the model had a mean age of 5.4 and a median age of 5. Indeed, 81% of patients in the ICONIC study were over 2 years old. Due to the normal age spread of the ICONIC study (mean age of 5.4 and median age of 5), mapping the PedsQL and EQ5D should have been feasible. Utility estimates from such mapping should have been used to inform the utility values for responder and non-responder health states in the model.

3.2.7.2 Other Health States

Utility values for other health states except the liver transplant state, were derived from the literature and summarised in Table 20 below.

Table 20: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Responsive to medication	[redacted]	[redacted]	CS Document B, Section B.3.4 Measurement and valuation of health effect, page 109	Vignette study (see CS Appendix M)
Unresponsive to medication	[redacted]	[redacted]		
Cirrhosis	[redacted]	Assumption (+/– 20%)		Sum of unresponsive utility and 'liver disease' disutility (–0.04) from Sullivan et al[54]
PHT	[redacted]	Assumption (+/– 20%)		Sum of cirrhosis utility and 'liver disease' disutility (–0.04) from Sullivan et al[54]

Ascites	[redacted]	Assumption (+/– 20%)		Sum of PHT utility and 'gastrointestinal disorder' disutility (–0.05) from Sullivan et al[54]
SBD	[redacted]	Assumption (+/– 20%)		Assumed equivalent to LTx utility
Post-SBD	[redacted]	Assumption (+/– 20%)		SBD utility multiplied by the stoma multiplier (0.72) used in HST17[23]
LTx	[redacted]	Assumption (+/– 20%)		Vignette study, weighted average of progressive cholestasis and LTx rejection (see CS Appendix M)
Post-LTx	[redacted]	[redacted]		Vignette study, successful LTx (see CS Appendix M)
Death	0	NA	–	–

Abbreviations: LTx, liver transplantation; NA, not applicable; PHT, portal hypertension; SBD, surgical biliary diversion.

Reproduced from CS Document B, Section B.3.4.5, Table 43

3.2.7.3 Carer disutility

Carer utility values were derived from a vignette study conducted by the company. Carer disutility was applied to patient caregivers (1.7 caregivers per patient) in all health states up until age 18. A disutility of [redacted] was applied to the treatment response health state while a disutility of [redacted] was applied to the loss of response health state. The main EAG critiques of the vignette study also apply to the methods used to elicit carer utilities. Carer disutility was too optimistic and lack may lack face validity. Carer disutility in the loss of response health state was about six times the value in the response state (-0.063 vs -0.357). In contrast, the estimates used in a similar appraisal[23] was more conservative (a disutility of –0.1 was applied to the loss of response health state and -0.05 was applied to the response health state).

The EAG also considers the use of a vignette study to elicit caregiver utility inappropriate because the pre-conditions that allow for the use of a vignette study to elicit utility do not apply to caregivers who are adults and could complete the EQ-5D-5L questionnaire. The company was asked to clarify its chosen methodology and argued that due to the possibility of caregivers adapting to their conditions, direct utility elicitation was inappropriate.

Response shifts in people with long-term conditions is recognised in the literature.[55] However, research show that while there may be evidence of response shifts in people with long-term conditions, this may not be reflected in their self-assessment of health and wellbeing.[56]

A departure from NICE methodological guidance due to the possibility of response shift in caregivers is inappropriate and unsupported by the evidence provided. The EAG considers the method used to elicit caregiver utility does not adhere to NICE guidelines for technology appraisal and should not be used in this appraisal.

3.2.8 Resources and costs

The costs of MRX for each cycle was made up the following categories: drug acquisition costs (Table 21 and Table 22) and NHS visits costs (Table 23), and adverse event costs (Table 24). MRX was administered based on patient weight. No administration costs were included, and vial sharing was assumed because MRX is administered at home.

A patient access scheme (PAS), incorporating discounted drug price [redacted] was applied to the MRX drug acquisition costs. The base case analysis is based on the PAS drug acquisition costs.

Drug costs for SoC included acquisition (Table 22) and NHS visits costs. No administration costs were included. The proportion of patients in receiving each regimen was determined by the proportion of patients on each drug in the ICONIC study. Drug acquisition costs in both arms were only applied to treatment responders.

Table 21: Drug costs applied in the cost-effectiveness model

Technologies	Price per pack	Units per pack
MRX – list price	£43,970	30mL vial (9.5mg/mL)
MRX – PAS price	[redacted] ([redacted]% discount)	
UDCA	£6.59	60 x 150mg
Rifampicin	£41.18	100 x 300mg
Phenobarbital	£1.24	28 x 60mg

Abbreviations: *PAS, patient access scheme; UDCA, ursodeoxycholic acid.*
Reproduced from CS Document B, Section B.3.5.1.1, Table 46

Table 22: Drug costs for the SoC treatment arm

Comparator	dose per day	% patients	Unit size (mg)	Cost per pack	Units per pack	cost/cycle
UDCA	10mg	80.60%	150	£6.59	60	£0.62
Rifampicin	10mg	72.40%	300	£41.18	100	£1.15
Phenobarbital	120mg	12.90%	60	£1.24	28	£7.44

Abbreviations: *SoC, Standard of Care; UDCA, ursodeoxycholic acid*.
Reproduced from CS Document B, Section B.3.5.1.1, Table 47

Table 23: Health-state costs included in the cost-effectiveness model

Resource	Unit cost	Source
Paediatrician visit	£113.00	PSSRU 2021/22 (112)
Hepatologist visit	£113.00	PSSRU 2021/22 (112)
Dietician visit	£100.00	PSSRU 2021/22 (112)
Endocrinologist visit	£113.00	PSSRU 2021/22 (112)
Lab tests	£43.81	NHS reference costs (DAPS02) (111)
Cardiologist visit	£113.00	PSSRU 2021/22 (112)

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Reproduced from CS Document B, Section B.3.5.2, Table 48

Adverse events costs were also included in each arm for patients responsive to treatment. These included abdominal pain and ALT as shown in Table 24 below. No costs were included for abdominal pain despite this being the most frequently reported TEAE. No other AE was explicitly modelled by the company.

Table 24: Adverse Event unit costs

Adverse event	Cost per event	Frequency (MRX arm)	Frequency (SoC arm)	Cost per cycle (MRX)	Cost per cycle (SoC)
Abdominal pain	£0	6.45%	0%	£0.00	£0.00
ALT increased	£1.55	6.45%	0%	£0.10	£0.00

Abbreviations: ALT, alanine transaminase; MRX, maralixibat; SoC, standard of care.

Reproduced from CS Document B, Section B.3.5.3, Table 51

A weighted average cost of £16,836 was applied to all patients undergoing SBD. A unit cost of £44,244.22 was applied to all patients undergoing LTx and a further £15,199 in the first year following transplant. In the second and third year following LTx, a per cycle cost of £1,180 and £539 were applied respectively. After the third year, a lifetime per cycle cost of £539 was applied to those undergoing LTx. A one-off cost of £1279 was applied to all patients entering the death state.

A summary of per cycle health state cost is shown in **Table 25** below.

Table 25: Summary health-state costs

Health-state	Cost per cycle
Responsive to medication	£96.26
Unresponsive to medication	£305.60
SBD	£18,179.82
Post-SBD	£16,835.63
Cirrhosis	£305.60
PHT	£305.60
Ascites	£305.60
LTx	£44,244.32
Death	£1,279.00

Abbreviations: LTx, liver transplantation; PHT, portal hypertension; SBD, surgical biliary diversion.
1Separate health-state costs are allocated post-LTx and described below.

Reproduced from CS Document B, Section B.3.6, Table 55

3.2.9 Severity

The company QALY shortfall analysis followed the NICE's health technology evaluations manual.[57] Absolute shortfall was evaluated as the difference between the expected future health lost by adults living with the condition and adults living without the condition over their remaining lifetimes. The undiscounted QALY accrued by adults with the condition was estimated to be 10.80 QALYs compared to 24.96 total QALYs in the general population. The EAG was able to replicate the results of the company. A summary of health state benefits and associated utility values for patients on SoC is shown in **Table 26** below. The estimated shortfall of 14.16 justified a severity weighting of 1.2 according to NICE guidance (**Table 27**)

Table 26: Summary of health state benefits and utility values for QALY shortfall analysis

State	Odevixibat for PFIC (HST17)	PedsQL scores mapped to EQ-5D-5L[1]	Utility value: mean (standard error)	Undiscounted life years
Treatment response	0.91	0.800	[redacted]	[redacted]
Loss of response	0.83	0.760	[redacted]	[redacted]
Cirrhosis	0.79	0.72	[redacted]	[redacted]
Portal hypertension	0.75	0.68	[redacted]	[redacted]
Ascites	0.70	0.63	[redacted]	[redacted]
LTx	0.81	0.784	[redacted]	[redacted]
Post-LTx	0.859	0.859	[redacted]	[redacted]

Abbreviations: LTx, liver transplantation

[1]PedsQL scores reported in Kamath et al [1]and mapping algorithm from Khan [58]

* Standard error assumed 10% of mean value

Adapted from CS Document B, Section B.3.6, Table 55

Table 27: QALY weightings for severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
X1.2	0.85 to 0.95	12 to 18
X1.7	At least 0.95	At least 18

The justification for applying severity weighting is based on the utility values used in the economic model which the EAG argues is too optimistic. Alternative utility values are presented in **Table 26** above. Using utility values from HST 17,[23] the undiscounted QALYs accrued by patients with ALGS was estimated to be 14.76 QALYs resulting in an estimated shortfall of 10.2. Using utility values from mapped

PedsQL scores reported by Kamath et al, [1] the undiscounted QALYs accrued by patients with ALGS was estimated to be 13.80 QALYs resulting in a shortfall of 11.16. Neither of these estimates would qualify for use of a severity weighting. Hence, a severity weighting is unlikely to apply for this appraisal.

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

The company base case assumed a log-logistic distribution to model mortality in the MRX population and a hazard ration was applied to responders. A summary of base case inputs and assumptions used in the model can be found in CS Document B, Section B.3.10, Table 56 and Table 57. A PAS discount of [redacted]% was applied to the drug list price.

The discounted and undiscounted costs and QALYs between MRX and SoC is shown below in Table 28 and Table 29 below.

Table 28: Undiscounted costs and QALYs

Health-state	SoC		MRX		Incremental	
Treatment response	£44	[redacted]	[redacted]	[redacted]	[redacted]	1.41
Loss of response	£10,309	[redacted]	£10,290	[redacted]	-£19	-0.01
Cirrhosis	£6,468	[redacted]	£6,455	[redacted]	-£13	-0.01
Portal hypertension	£567	[redacted]	£566	[redacted]	-£1	0.00
Ascites	£38	[redacted]	£38	[redacted]	£0	0.00
SBD	£0	[redacted]	£0	[redacted]	£0	0.00
Post-SBD	£0	[redacted]	£0	[redacted]	£0	0.00
LTx	£1,110	[redacted]	£701	[redacted]	-£409	0.00
Post-LTx	£979	[redacted]	£844	[redacted]	-£136	-0.01
Death	£1,276	[redacted]	£1,276	[redacted]	-£0	0.00
Caregiver	-	[redacted]	-	[redacted]	-	0.20
Total†	£20,792	[redacted]	[redacted]	[redacted]	[redacted]	1.58

†Please note, total QALYs reported in this table doesn't account for the severity modifier.

Abbreviations: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.

Adapted from CS Document B, Section B.3.10, Table 61 and Table 65

Table 29: Discounted costs and QALYs

Health-state	SoC		MRX		Incremental	
Treatment response	£44	[redacted]	[redacted]	[redacted]	[redacted]	1.24
Loss of response	£7,582	[redacted]	£7,189	[redacted]	-£394	-0.16
Cirrhosis	£3,230	[redacted]	£3,063	[redacted]	-£167	-0.07
Portal hypertension	£222	[redacted]	£211	[redacted]	-£11	0.00
Ascites	£12	[redacted]	£12	[redacted]	-£1	0.00
SBD	£0	[redacted]	£0	[redacted]	£0	0.00
Post-SBD	£0	[redacted]	£0	[redacted]	£0	0.00
LTx	£1,097	[redacted]	£693	[redacted]	-£404	0.00
Post-LTx	£861	[redacted]	£704	[redacted]	-£157	-0.13
Death	£773	[redacted]	£735	[redacted]	-£38	0.00
Caregiver	-	[redacted]	-	[redacted]	-	0.25
Total†	£13,820	[redacted]	[redacted]	[redacted]	[redacted]	1.13

†Please note, total QALYs reported in this table doesn't account for the severity modifier.

Abbreviations: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.

Adapted from CS Document B, Section B.3.10, Table 62 and Table 66

The results for the company's base case cost-effectiveness analysis are presented in **Table 30** below.

Table 30: Base-case results (PAS price)

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs†	
MRX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

†Please note, the severity modifier is applied to incremental QALYs, excluding those for caregivers. As a result, the subtraction of Total QALYs reported in this table don't align with the Incremental QALYs in this table.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.

Reproduced from CS Document B, Section B.3.10.1, Table 58.

4.2 Company's sensitivity analyses

The company conducted a range of deterministic and probabilistic sensitivity analyses (PSA) on the base case. PSA included 1000 Monte Carlo simulations. The result for the PSA is shown in **Table 31** below.

Table 31: Probabilistic results (PAS price)

	MRX	SoC	Incremental	ICER
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	

Abbreviations: LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SoC, standard of care.

Reproduced from CS Document B, Section B.3.11.1, Table 68

At a willingness-to-pay threshold (WTP) of £20,000, 0% of simulations are cost-effective. Simulations begin to become cost-effective at a WTP threshold of £145,000 where [redacted] of simulations are cost-effective at this threshold. All simulations are cost-effective at a WTP threshold of [redacted] as shown in **Table** 32 below.

Table 32: Proportion of simulations cost-effective

Threshold	% simulations cost-effective at PAS price
£145,000	[redacted]
£170,000	[redacted]
£195,000	[redacted]
£220,000	[redacted]
£235,000	[redacted]

Abbreviations: PAS, patient access scheme

Reproduced from CS Document B, Section B.3.11.1, Table 69

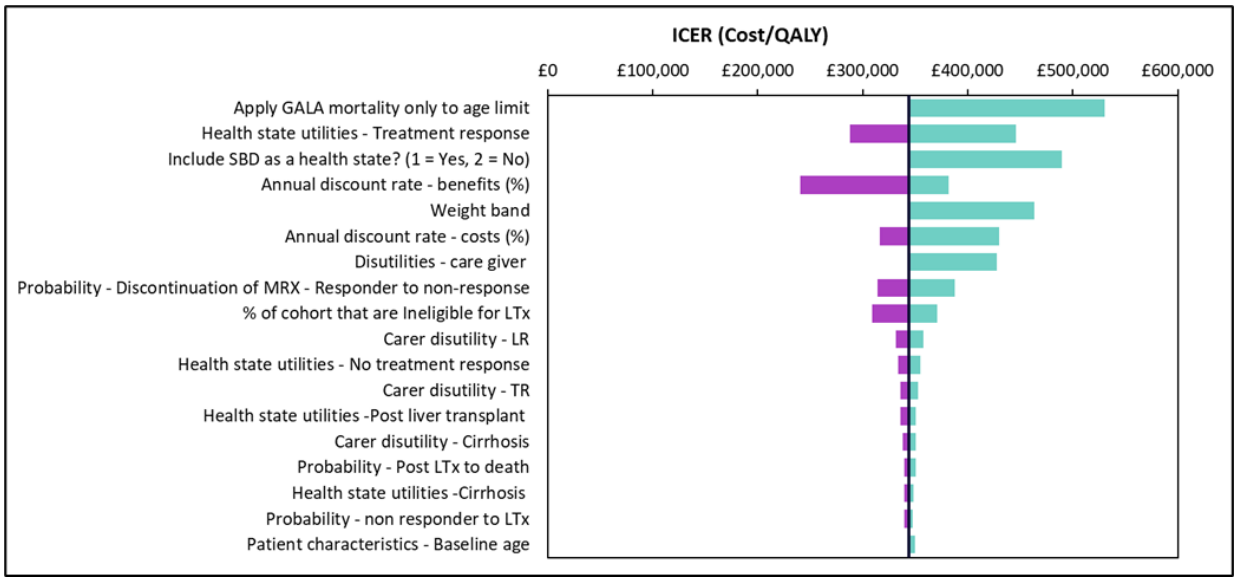
The cost-effectiveness acceptability curve and cost-effectiveness plane is shown in Figure 5 and Figure 6 below.

Reproduced from CS Document B, Section B.3.11.1, Figure 25

Figure 5: Cost-effectiveness plane from PSA (list price) (1,000 simulations) – PAS price

Reproduced from CS Document B, Section B.3.11.1, Figure 26
Figure 6: Cost-effectiveness acceptability curve from PSA (list price) (1,000 iterations) – PAS price

Deterministic sensitivity analysis was performed to explore the effect of uncertainty associated with each parameter. Parameters with the most impact on the ICER is shown in **Figure 7** below. The most influential parameters are utility values for responders, the age at which mortality from the GALA study is applied in the model, the weight band used, inclusion of carer disutility and inclusion of SBD health state. The results of the univariate sensitivity analysis are presented in the form of a tornado diagram as shown in **Figure 7** below.



Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LR, loss of response; LTx, liver transplantation; MRX, maralixibat; QALY, quality-adjusted life year; SBD, surgical biliary diversion; TR, treatment response
Reproduced from CS Document B, Section B.3.11.2, Figure 27

Figure 7: Tornado plot of DSA (most impactful parameters – List price)

4.3 Model validation and face validity check

Several validity checks on the results of the economic analyses were undertaken by the company. These include face, structural and external validity. The company reported that no issues were identified with the structural or computational accuracy of the model. The EAG considers that the model lacks face validity due to the implausible predicted survival as discussed in Section 3.2.6.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the EAG

The main issues highlighted by the EAG throughout this report that impacts the cost-effectiveness of MRX is summarised in Table 33.

It shows the expected direction of bias in the ICER and whether these are used in the EAG base case or examined in any exploratory analysis.

Table 33: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses
Model structure (Section 3.2.2)			
Structural assumptions of the model	NA	No	No
Treatment effectiveness and extrapolation (Section 3.2.6)			
SoC OS extrapolation changed from log-logistic to exponential	+	Base case Scenarios	Scenarios
Probability of response	+	Base-case Scenarios	No
Mortality risk between responders and non-responders	+	Base-case scenarios	No
Caregiver utility not applied	+	Base-case Scenarios	Scenarios
Include transition to SBD	+	Scenarios	Scenarios
Probability of response loss after first cycle	+	Scenarios	No
Weight band of cohort	+	Scenarios	Scenarios
Age which mortality risk from GALA is applied in non-responders	+	Base case Scenarios	Scenarios
Health-related quality of life (Section 3.2.7)			
Utility value for response and non-response health state	+	Base-case Scenarios	Scenarios

Footnotes: Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; '+/-' indicates that the bias introduced by the issue is unclear to the EAG; while '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator and '+and -' indicates the EAG believes the potential bias can be positive or negative depending on the assumptions used.

5.1.1 EAG revised base case

The assumptions made to the company model are described below. The impact of each EAG revision on the ICER is shown in Table 34.

EAG01: Due to the implausibility of the log-logistic model in estimating OS (median survival is predicted to be 216.6 years). The EAG prefers the exponential model for extrapolating SoC OS.

EAG02: Probability of response changed from 0% to [redacted]. Per cycle probability of response loss after initial response set to an annual rate of 5%.

EAG03: Mortality risk between responders and non-responders assumed to be equivalent due to considerable uncertainties around the HR estimate.

EAG04: Caregiver disutility not applied.

EAG05: Utility value for non-response and response health state changed from company value to those reported by Kamath *et al* [1]

EAG06: Mortality risk equivalent to GALA in all non-responder health states applied from 2 years to match lower quartile age of GALA study.

EAG07: Removal of severity modifier due to uncertain utility values for response and non-response health state

Table 34: Impact of individual EAG preferred model assumptions on ICER

Preferred assumption	**ICER**
Company base case	[redacted]
EAG01: OS extrapolation changed from log-normal to exponential	[redacted]
EAG02: Probability of response changed for SoC	[redacted]
EAG03: Equivalent mortality risk between responders and non-responders	[redacted]
EAG04: Removal of caregiver utility	[redacted]
EAG05: Utility values for non-response and response health state changed to estimates from Kamath *et al* [1]	[redacted]
EAG 06: Mortality risk from GALA applied to non-responders from 2 years of age.	[redacted]
EAG07: Removal of severity modifier from ICER	[redacted]

EAG deterministic base case results

The cumulative effect of EAG changes on the company deterministic base case is shown in Table 35.

Incremental net monetary benefit was calculated at a £20,000 threshold rather than the £30,000 threshold used in the company base case.

Deterministic incremental costs were [redacted] and incremental QALYs were [redacted]. The deterministic ICER for the EAG base case is [redacted] per QALY and the NMB at a £20,000 WTP threshold is [redacted]. The key drivers for the increased ICER were the response rate for SoC, utility values used for response and non-response health state, application of caregiver disutility, and removal of severity modifier (Table 35).

Table 35: Deterministic EAG Base Case Cost-effectiveness Results with PAS discount

Technology	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER	INMB
MRX	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG's probabilistic base case cost-effectiveness results

The EAG's base case was subject to a probabilistic sensitivity analysis using 1000 simulations drawn from the ERG parametric assumptions. The probabilistic incremental costs and QALYs were [redacted] and [redacted] respectively. The Probabilistic ICER was [redacted] and the incremental NMB was [redacted]. The probability of MRX being cost effective at a £20,000 and £30,000 per QALY threshold is [redacted]. [redacted] of simulations are cost-effective at a WTP threshold of [redacted] and [redacted] of simulations are cost-effective at a WTP threshold of [redacted]. The EAG probabilistic base case is summarised in Table 36 and the CEAC and cost-effectiveness plane is presented in Figure 8 and Figure 9 below.

Table 36: Probabilistic EAG Base Case Cost-effectiveness Results with PAS discount

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	INMB
MRX	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 8: Cost-effectiveness plane

Figure 9: Cost-effectiveness acceptability curve

5.1.2 EAG Scenario analysis

Given the uncertainties in the cost-effectiveness estimates, the EAG explored the following scenario analysis.

Scenario 1: Response to pruritus measured through ItchRO scores reported in Table 35 of the ITCH Clinical Study Report were used in place of sBA levels.[37] At a response threshold a reduction of ≥1.5 from baseline in ItchRO average daily scores, [redacted]% of patients randomised to placebo achieved a response compared to [redacted]% of patients on MRX. Increasing this threshold to a reduction of ≥2 from baseline, [redacted]% of patients randomised to placebo achieved a response compared to [redacted]% of patients on MRX. These values are used in place of sBA response rates from the ICONIC study. Other EAG base case assumptions were maintained.

Scenario 2: SBD health state was included. All EAG base case assumptions were maintained.

Scenario 3: Probability of response loss was increased by 10% and 30% in the MRX group to account for treatment failure independent of adverse events. All EAG base case assumptions was maintained.

Scenario 4: Weight band for model cohort increased to 25th percentile after two years to explore potential effects of treatment in boosting growth. All EAG base case assumptions were maintained.

Scenario 5: The age from which mortality risks from GALA were applied to non-responders set to 4 years to match the median age of the GALA cohort.

Scenario 6: Response to treatment was defined as a reduction of ≥70% sBA levels from baseline in line with HST17. Using this threshold, no patients receiving placebo were responsive in the ITCH study and only 3 of 31 participants in the ICONIC study were responsive based on data reported by Gonzales et al 2021.[27] A response rate of 9.68% was assumed in the MRX arm and a 0% response rate was assumed in the SoC arm. Other EAG base cases assumptions were maintained.

Scenario 7: Caregiver disutility was included but a disutility value of –0.05 and –0.1 was assumed for the response health state and loss of response health state respectively. Number of caregivers were changed from 1.7 caregivers per patient to 1 caregiver per patient. Other EAG base case assumptions were maintained.

The impact of each scenario on the ICER is presented in **Table 37.**

Table 37: EAG scenario analysis. Impact on ICER

	Incremental costs	**Incremental QALYs**	**ICER £/QALY**
Scenario 1 ≥ -1.5 ≥ -2.0	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
Scenario 2	[redacted]	[redacted]	[redacted]
Scenario 3 10% 30%	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]

Scenario 4	[redacted]	[redacted]	[redacted]
Scenario 5	[redacted]	[redacted]	[redacted]
Scenario 6	[redacted]	[redacted]	[redacted]
Scenario 7	[redacted]	[redacted]	[redacted]

5.2 Conclusions of the cost effectiveness section

The model structure used by the company appears to be logical. However, the EAG has the following concerns about the cost-effectiveness analysis as detailed in Section 0

- The use of an arbitrary biomarker threshold to model treatment response is inappropriate. Treatment response should be mapped to the risk of developing modelled clinical events and compared between treatment arms. The use of alternative response rates and biomarkers in the model had a significant impact on the cost-effectiveness.
- OS for the treatment naïve population were immature resulting in significant uncertainty in extrapolation. Under the most pessimistic parametric assumption (exponential model), 41% of the cohort were predicted to be alive at 100 years of age.
- The difference in utility values used for the response and loss of response health state were unreliable and unsupported by evidence from the literature. This utility difference also informed the decision to apply a severity modifier. Using alternative utility values precludes the use of severity modifier and significantly impacts the cost-effectiveness results.
- The source and methods used to estimate caregiver utility were inappropriate. Removing caregiver utility significantly affects the cost-effectiveness results.

Other important factors that also had an impact on the cost-effectiveness results include:

- Assumption of equivalent mortality risks between responders and non-responders due to uncertainties in the HR estimate used.

- Increasing the age mortality risks from the GALA cohort were applied to non-responders.
- Including the SBD health state significantly impacted the cost-effectiveness results.
- Increasing the weight band of the cohort responsive to treatment after two years on treatment.
- Increasing the probability of per cycle response loss to explore potential effects of treatment failure in responsive patients significantly affects the cost-effectiveness results

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7 APPENDIX Additional literature searches undertaken by the EAG

Searches for ALGS utilities literature Date: 30/11/23

CEA Registry (Tufts Medical Center) https://cear.tuftsmedicalcenter.org/

Basic search – Utilities
Alagille 0 results
algs 0 results
arteriohepatic dysplasia 0 results

Advanced search – utilities

Keyword is: cholestasis
OR cholestatic
OR biliary stasis 0 results

ScHARRHud
https://www.scharrhud.org/index.php?recordsN1&m=search&action=searchRecords

Alagille in Any Field 0 results
ALGS in Any Field 0 results
arteriohepatic dysplasia in Any Field 0 results

cholestasis
OR cholestatic
OR biliary stasis in Any Field 0 results

MEDLINE
Ovid MEDLINE(R) ALL <1946 to November 29, 2023>

1 Alagille Syndrome/ 752
2 exp Cholestasis, Intrahepatic/ 14148
3 (alagille* or algs or arteriohepatic dysplasia).kf,tw. 1211
4 1 or 3 [Alagille syndrome] 1314
5 (child* or paediatric* or pediatric* or baby or babies or infant* or neonat* or newborn* or hereditary or familial or congenital or genetic).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 5687932
6 ((cholesta* or biliary stas?s) adj5 (liver or intrahepatic or hepat*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary

concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 16279
7 (bile duct* adj2 paucity).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word] 163
8 6 or 7 16386
9 5 and 8 4963
10 2 or 4 or 9 [broader paediatric/hereditary cholestatic liver disease] 17487
11 Quality-Adjusted Life Years/ 15962
12 (quality adjusted or adjusted life year$).ti,ab,kf. 24319
13 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 15073
14 (illness state$1 or health state$1).ti,ab,kf. 8607
15 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2021
16 (multiattribute$ or multi attribute$).ti,ab,kf. 1368
17 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. 20716
18 utilities.ti,ab,kf. 9675
19 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. 18048
20 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. 6216
21 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. 27086
22 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 2426
23 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. 16008
24 quality of life/ and ec.fs. 10876
25 quality of life/ and (health adj3 status).ti,ab,kf. 12032
26 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ 7702
27 ((qol or hrqol or quality of life).ti,kf. or ∗quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. 47222
28 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. 5373
29 *quality of life/ and (quality of life or qol).ti. 64746
30 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. 42917
31 quality of life/ and health-related quality of life.ti,ab,kf. 46055
32 models,economic/ 11099
33 or/11-32 [Filter FSF - sensitivity maximizing filter to identify HSU studies, from Arber et al, 2017 http://dx.doi.org/10.1017/S0266462317000897] 224930
34 4 and 33 7
35 10 and 33 107

Embase
Embase <1974 to 2023 November 29>

1 exp Alagille syndrome/ 2314
2 (alagille* or algs or arteriohepatic dysplasia).kf,tw. 1910
3 1 or 2 [Alagille syndrome] 2629
4 socioeconomics/ 163633
5 exp Quality of Life/ 666040
6 quality of life.ti,kw. 176824
7 ((instrument or instruments) adj3 quality of life).ab. 5480
8 Quality-Adjusted Life Year/ 35837
9 quality adjusted life.ti,ab,kw. 26802
10 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. 45295
11 disability adjusted life.ti,ab,kw. 6666
12 daly*.ti,ab,kw. 6548
13 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw. 50727
14 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw. 3007
15 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw. 1040
16 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw. 12466
17 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 71
18 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 533
19 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 39998
20 (hye or hyes).ti,ab,kw. 185
21 (health* adj2 year* adj2 equivalent*).ti,ab,kw. 53
22 (pqol or qls).ti,ab,kw. 757
23 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. 617
24 nottingham health profile*.ti,ab,kw. 1681
25 nottingham health profile/ 659
26 sickness impact profile.ti,ab,kw. 1294
27 sickness impact profile/ 2398
28 health status indicator/ 3530
29 (health adj3 (utilit* or status)).ti,ab,kw. 120484
30 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw. 25915
31 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 19481
32 disutilit*.ti,ab,kw. 1281
33 rosser.ti,ab,kw. 141
34 willingness to pay.ti,ab,kw. 13369
35 standard gamble*.ti,ab,kw. 1223
36 (time trade off or time tradeoff).ti,ab,kw. 2414

37 tto.ti,ab,kw. 2265
38 (hui or hui1 or hui2 or hui3).ti,ab,kw. 3194
39 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 39114
40 duke health profile.ti,ab,kw. 120
41 functional status questionnaire.ti,ab,kw. 175
42 dartmouth coop functional health assessment*.ti,ab,kw. 14
43 or/4-42 [Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2022: https://searchfilters.cadth.ca/link/18.] 1011503
44 3 and 43 82
45 intrahepatic cholestasis/ 7745
46 (child* or paediatric* or pediatric* or baby or babies or infant* or neonat* or newborn* or hereditary or familial or congenital or genetic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 6927815
47 ((cholesta* or biliary stas?s) adj5 (liver or intrahepatic or hepat*)).kf,tw. 21464
48 (bile duct* adj2 paucity).kf,tw. 275
49 47 or 48 21638
50 46 and 49 7649
51 45 or 50 [broader childhood/hereditary cholestatic liver disease] 12395
52 43 and 51 258
53 52 not 44 220

Search for economic evaluations relating to ALGS Date: 14/12/23

Google

alagille syndrome cost effectiveness browsed first 20 results 0 found (identified several results relating to HRQoL / costs and resource use already in CS)

alagille syndrome economic evaluation browsed first 20 results 0 found

alagille syndrome technology assessment browsed first 20 results 0 found

checked FDA and EMA approval documents/reviews: no pharmacoeconomic data

Embase (Ovid interface)

Embase Classic+Embase <1947 to 2023 Week 49>

1 exp Alagille syndrome/ 2317

2 (alagille* or algs or arteriohepatic dysplasia).kf,tw. 1917

3 1 or 2 2636

4 Health Economics/ 41012

5 exp Economic Evaluation/ 360143

6 exp Health Care Cost/ 347846

7 pharmacoeconomics/ 9802

8 4 or 5 or 6 or 7 642233

9 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1444122

10 (expenditure$ not energy).ti,ab. 52322

11 (value adj2 money).ti,ab. 3072

12 budget$.ti,ab. 48761

13 9 or 10 or 11 or 12 1490774

14 8 or 13 1746801

15 letter.pt. 1299476

16 editorial.pt. 788654

17 note.pt. 967062

18 15 or 16 or 17 3055192

19 14 not 18 1628248

20 (metabolic adj cost).ti,ab. 1950

21 ((energy or oxygen) adj cost).ti,ab. 5433

22 ((energy or oxygen) adj expenditure).ti,ab. 38674

23 20 or 21 or 22 44779

24 19 not 23 1618950

25 animal/ 2140547

26 exp animal experiment/ 3123335

27 nonhuman/ 7545215

28 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. 7410571

29 25 or 26 or 27 or 28 11357421

30 exp human/ 27240299

31 human experiment/ 651904

32 30 or 31 27242908

33 29 not (29 and 32) 8116637

34 24 not 33 1459707

35 0959-8146.is. 69780

36 (1469-493X or 1366-5278).is. 19388

37 1756-1833.en. 43453

38 35 or 36 or 37 115392

39 34 not 38 1452740

40 conference abstract.pt. 4985976

41 39 not 40 [CRD NHS EED filter] 1181015

42 3 and 41 31

0 results were cost effectiveness analyses of ALGS treatments.

Search for ALGS overall survival, survival after liver transplant. Date: 10/01/24

Ovid MEDLINE(R) ALL <1946 to January 09, 2024>

1 exp Survival Analysis/ or Survival Rate/ or Survival/ 494825

2 survival.kf,tw. 1214619

3 Alagille Syndrome/ 758

4 (alagille* or algs or arteriohepatic dysplasia).kf,tw. 1220

5 (1 or 2) and (3 or 4) 86

6 from 5 keep 11,18-19,24-25,36-37,39,42-44,50,58-59,65,70-71,78,82 19

Google:

alagille syndrome overall survival browsed first 30 results – *no additional studies found*

alagille syndrome liver transplant survival browsed first 20 results – *1 additional study found*

Title: Maralixibat for treating cholestatic pruritus in Alagille Syndrome

Addendum report

Produced by	Warwick Evidence
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Date completed	20/06/2024 (Addendum report incorporating revised Patient Access Scheme price)

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Declared competing interests of the authors
None.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

The purpose of this addendum report is to update the EAG's base case and scenario analyses using the revised drug price for the patient access scheme (PAS) supplied by the company in June 2024. The addendum updates Executive Summary Section 1.7 and Section 3.2.8, Section 4.1, Section 4.2 and Section 5 of the EAG final report.

Executive Summary

1 Executive summary

1.7 Summary of EAG's preferred assumptions and resulting ICER

Table 1: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company base case	[redacted]	[redacted]	[redacted]
EAG01: OS extrapolation changed from log-normal to exponential	[redacted]	[redacted]	[redacted]
EAG02: Probability of response changed for SoC	[redacted]	[redacted]	[redacted]
EAG03: Equivalent mortality risk between responders and non-responders	[redacted]	[redacted]	[redacted]
EAG04: Removal of caregiver utility	[redacted]	[redacted]	[redacted]
EAG05: Utility values for non-response and response health state changed to estimates to Kamath *et al* [1]	[redacted]	[redacted]	[redacted]
EAG 06: Mortality risk from GALA applied to non-responders from 2 years of age.	[redacted]	[redacted]	[redacted]
EAG07: Removal of severity modifier from ICER	[redacted]	[redacted]	[redacted]
EAG's preferred base case (combining all the above scenarios]) - deterministic	[redacted]	[redacted]	[redacted]
EAG's preferred base case (combining all the above scenarios]) – probabilistic	[redacted]	[redacted]	[redacted]

External Assessment Group Report

3 COST EFFECTIVENESS

3.2.8 Resources and costs

The costs of MRX for each cycle was made up the following categories: drug acquisition costs (Table 21 and Table 22) and NHS visits costs (Table 23), and adverse event costs (Table 24). MRX was administered based on patient weight. No administration costs were included, and vial sharing was assumed because MRX is administered at home.

A patient access scheme (PAS), incorporating discounted drug price [redacted] was applied to the MRX drug acquisition costs. The base case analysis is based on the PAS drug acquisition costs.

Drug costs for SoC included acquisition (Table 22) and NHS visits costs. No administration costs were included. The proportion of patients in receiving each regimen was determined by the proportion of patients on each drug in the ICONIC study. Drug acquisition costs in both arms were only applied to treatment responders.

Table 2: Drug costs applied in the cost-effectiveness model

Technologies	Price per pack	Units per pack
MRX – list price	£43,970	30mL vial (9.5mg/mL)
MRX – PAS price	[redacted] ([redacted] discount)	
UDCA	£6.59	60 x 150mg
Rifampicin	£41.18	100 x 300mg
Phenobarbital	£1.24	28 x 60mg

Abbreviations: *PAS, patient access scheme; UDCA, ursodeoxycholic acid.*
Reproduced from CS Document B, Section B.3.5.1.1, Table 46

Table 3: Drug costs for the SoC treatment arm

Comparator	dose per day	% patients	Unit size (mg)	Cost per pack	Units per pack	cost/cycle
UDCA	10mg	80.60%	150	£6.59	60	£0.62
Rifampicin	10mg	72.40%	300	£41.18	100	£1.15
Phenobarbital	120mg	12.90%	60	£1.24	28	£7.44

Abbreviations: *SoC, Standard of Care; UDCA, ursodeoxycholic acid*.
Reproduced from CS Document B, Section B.3.5.1.1, Table 47

Table 4: Health-state costs included in the cost-effectiveness model

Resource	Unit cost	Source
Paediatrician visit	£113.00	PSSRU 2021/22 (112)
Hepatologist visit	£113.00	PSSRU 2021/22 (112)
Dietician visit	£100.00	PSSRU 2021/22 (112)
Endocrinologist visit	£113.00	PSSRU 2021/22 (112)
Lab tests	£43.81	NHS reference costs (DAPS02) (111)
Cardiologist visit	£113.00	PSSRU 2021/22 (112)

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Reproduced from CS Document B, Section B.3.5.2, Table 48

4 COST EFFECTIVENESS RESULTS

4.1 Company's cost effectiveness results

The company base case assumed a log-logistic distribution to model mortality in the MRX population and a hazard ration was applied to responders. A summary of base case inputs and assumptions used in the model can be found in CS Document B, Section B.3.10, Table 56 and Table 57. A PAS discount of [redacted]% was applied to the drug list price resulting in a list price of [redacted].

The discounted and undiscounted costs and QALYs between MRX and SoC is shown below in Table 28 and Table 29 below.

Table 5: Undiscounted costs and QALYs

Health-state	SoC		MRX		Incremental	
Treatment response	£44	[redacted]	[redacted]	[redacted]	[redacted]	1.41
Loss of response	£10,309	[redacted]	£10,290	[redacted]	-£19	-0.01
Cirrhosis	£6,468	[redacted]	£6,455	[redacted]	-£13	-0.01
Portal hypertension	£567	[redacted]	£566	[redacted]	-£1	0.00
Ascites	£38	[redacted]	£38	[redacted]	£0	0.00
SBD	£0	[redacted]	£0	[redacted]	£0	0.00
Post-SBD	£0	[redacted]	£0	[redacted]	£0	0.00
LTx	£1,110	[redacted]	£701	[redacted]	-£409	0.00
Post-LTx	£979	[redacted]	£844	[redacted]	-£136	-0.01
Death	£1,276	[redacted]	£1,276	[redacted]	-£0	0.00
Caregiver	-	[redacted]	-	[redacted]	-	0.20
Total†	£20,792	[redacted]	[redacted]	[redacted]	[redacted]	1.58

†Please note, total QALYs reported in this table doesn't account for the severity modifier.

Abbreviations: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.

Adapted from CS Addendum Table 5 and Table 9

Table 6: Discounted costs and QALYs

Health-state	SoC		MRX		Incremental	
Treatment response	£44	[redacted]	[redacted]	[redacted]	[redacted]	1.24
Loss of response	£7,582	[redacted]	£7,189	[redacted]	-£394	-0.16
Cirrhosis	£3,230	[redacted]	£3,063	[redacted]	-£167	-0.07
Portal hypertension	£222	[redacted]	£211	[redacted]	-£11	0.00
Ascites	£12	[redacted]	£12	[redacted]	-£1	0.00
SBD	£0	[redacted]	£0	[redacted]	£0	0.00
Post-SBD	£0	[redacted]	£0	[redacted]	£0	0.00
LTx	£1,097	[redacted]	£693	[redacted]	-£404	0.00
Post-LTx	£861	[redacted]	£704	[redacted]	-£157	-0.13
Death	£773	[redacted]	£735	[redacted]	-£38	0.00
Caregiver	-	[redacted]	-	[redacted]	-	0.25
Total†	£13,820	[redacted]	[redacted]	[redacted]	[redacted]	1.13

†Please note, total QALYs reported in this table doesn't account for the severity modifier.

Abbreviations: LTx, liver transplantation; MRX, maralixibat; SBD, surgical biliary diversion; SoC, standard of care.

Adapted from CS Addendum Table 6 and Table 10

The results for the company's base case cost-effectiveness analysis are presented in **Table 30** below.

Table 7: Base-case results (PAS price)

Technologies	Total			Incremental			ICER versus baseline (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs†	
MRX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

†Please note, the severity modifier is applied to incremental QALYs, excluding those for caregivers. As a result, the subtraction of Total QALYs reported in this table don't align with the Incremental QALYs in this table.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; MRX, maralixibat; QALYs, quality-adjusted life years; SoC, standard of care.

Reproduced from CS Addendum Table 3

4.2 Company's sensitivity analyses

The company conducted a range of deterministic and probabilistic sensitivity analyses (PSA) on the base case. PSA included 1000 Monte Carlo simulations. The result for the PSA is shown in **Table 31** below.

Table 8: Probabilistic results (PAS price)

	MRX	SoC	Incremental	ICER
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	

Abbreviations: LY: Life years; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; SoC, standard of care.

Reproduced from CS Addendum Table 12

The probabilistic analysis resulted in an ICER of [redacted] The probability of cost-effectiveness at a £20,000/QALY and £30,000/QALY WTP threshold is [redacted] and [redacted] respectively. Simulations begin to become cost-effective at £25,000 WTP threshold where [redacted] of simulations are cost-effective at this threshold. All simulations are cost-effective at a WTP threshold of [redacted] as shown in **Table** 32 below.

Table 9: Proportion of simulations cost-effective

Threshold	% simulations cost-effective at PAS price
£25,000	[redacted]
£30,000	[redacted]
£35000	[redacted]
£40,000	[redacted]
£45,000	[redacted]

Abbreviations: PAS, patient access scheme

Reproduced from CS Document B, Section B.3.11.1, Table 69

The cost-effectiveness acceptability curve and cost-effectiveness plane is shown in Figure 5 and Figure 6 below.

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

Reproduced from CS Addendum, Figure 1

Figure 1: Cost-effectiveness plane from PSA (list price) (1,000 simulations) – PAS price

Abbreviations: PSA, probabilistic sensitivity analysis.

Reproduced from CS Addendum, Figure 2

Figure 2: Cost-effectiveness acceptability curve from PSA (list price) (1,000 iterations) – PAS price

Deterministic sensitivity analysis was performed to explore the effect of uncertainty associated with each parameter. Parameters with the most impact on the ICER is shown in **Figure 7** below. The most influential parameters are utility values for responders, the age at which mortality from the GALA study is applied in the model, the weight band used, inclusion of carer disutility and inclusion of SBD health state. The results of the univariate sensitivity analysis are presented in the form of a tornado diagram as shown in **Figure 7** below.

Abbreviations: DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; LR, loss of response; LTx, liver transplantation; MRX, maralixibat; QALY, quality-adjusted life year; SBD, surgical biliary diversion; TR, treatment response

Reproduced from CS Addendum, Figure 3
Figure 3: Tornado plot of DSA (most impactful parameters – List price)

4.3 Model validation and face validity check

Several validity checks on the results of the economic analyses were undertaken by the company. These include face, structural and external validity. The company reported that no issues were identified with the structural or computational accuracy of the model. The EAG considers that the model lacks face validity due to the implausible predicted survival as discussed in Section 3.2.6.

5 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

5.1 Exploratory and sensitivity analyses undertaken by the EAG

The main issues highlighted by the EAG throughout this report that impacts the cost-effectiveness of MRX is summarised in Table 33.

It shows the expected direction of bias in the ICER and whether these are used in the EAG base case or examined in any exploratory analysis.

Table 10: Main EAG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER	EAG analyses	Addressed in company analyses

Model structure (Section 3.2.2)			
Structural assumptions of the model	NA	No	No
Treatment effectiveness and extrapolation (Section 3.2.6)			
SoC OS extrapolation changed from log-logistic to exponential	+	Base case Scenarios	Scenarios
Probability of response	+	Base-case Scenarios	No
Mortality risk between responders and non-responders	+	Base-case scenarios	No
Caregiver utility not applied	+	Base-case Scenarios	Scenarios
Include transition to SBD	+	Scenarios	Scenarios
Probability of response loss after first cycle	+	Scenarios	No
Weight band of cohort	+	Scenarios	Scenarios
Age which mortality risk from GALA is applied in non-responders	+	Base case Scenarios	Scenarios
Health-related quality of life (Section 3.2.7)			
Utility value for response and non-response health state	+	Base-case Scenarios	Scenarios
Footnotes: Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; '+/-' indicates that the bias introduced by the issue is unclear to the EAG; while '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator and '+and -' indicates the EAG believes the potential bias can be positive or negative depending on the assumptions used.			

5.1.1 EAG revised base case

The assumptions made to the company model are described below. The impact of each EAG revision on the ICER is shown in Table 34.

EAG01: Due to the implausibility of the log-logistic model in estimating OS (median survival is predicted to be 216.6 years). The EAG prefers the exponential model for extrapolating SoC OS.

EAG02: Probability of response changed from 0% to [redacted]. Per cycle probability of response loss after initial response set to an annual rate of 5%.

EAG03: Mortality risk between responders and non-responders assumed to be equivalent due to considerable uncertainties around the HR estimate.

EAG04: Caregiver disutility not applied.

EAG05: Utility value for non-response and response health state changed from company value to those reported by Kamath *et al* [1]

EAG06: Mortality risk equivalent to GALA in all non-responder health states applied from 2 years to match lower quartile age of GALA study.

EAG07: Removal of severity modifier due to uncertain utility values for response and non-response health state

Table 11: Impact of individual EAG preferred model assumptions on ICER

Preferred assumption	**ICER**
Company base case	[redacted]
EAG01: OS extrapolation changed from log-normal to exponential	[redacted]
EAG02: Probability of response changed for SoC	[redacted]
EAG03: Equivalent mortality risk between responders and non-responders	[redacted]
EAG04: Removal of caregiver utility	[redacted]
EAG05: Utility values for non-response and response health state changed to estimates from Kamath *et al* [1]	[redacted]
EAG 06: Mortality risk from GALA applied to non-responders from 2 years of age.	[redacted]
EAG07: Removal of severity modifier from ICER	[redacted]

EAG deterministic base case results

The cumulative effect of EAG changes on the company deterministic base case is shown in Table 35.

Incremental net monetary benefit was calculated at a £20,000/QALY threshold rather than the £30,000/QALY threshold used in the company base case.

Deterministic incremental costs were [redacted] and incremental QALYs were [redacted]. The deterministic ICER for the EAG base case is [redacted] per QALY and the NMB at a £20,000/QALY WTP threshold is [redacted]. The key drivers for the increased ICER were the response rate for SoC, utility values used for response and non-response health state, application of caregiver disutility, and removal of severity modifier (Table 35).

Table 12: Deterministic EAG Base Case Cost-effectiveness Results with PAS discount

Technology	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER	INMB
MRX	[redacted]	[redacted]	[redacted]					
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG's probabilistic base case cost-effectiveness results

The EAG's base case was subject to a probabilistic sensitivity analysis using 1000 simulations drawn from the ERG parametric assumptions. The probabilistic incremental costs and QALYs were [redacted] and [redacted] respectively. The Probabilistic ICER was [redacted] and the incremental NMB at £20,000/QALY WTP threshold was [redacted]. The probability of MRX being cost effective at a £20,000 and £30,000 per QALY threshold is [redacted]. [redacted] of simulations are cost-effective at a WTP threshold of [redacted] per QALY and [redacted] of simulations are cost-effective at a WTP threshold of [redacted] per QALY**.** The EAG probabilistic base case is summarised in Table 36 and the CEAC and cost-effectiveness plane is presented in Figure 8 and Figure 9 below.

Table 13: Probabilistic EAG Base Case Cost-effectiveness Results with PAS discount

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	INMB
MRX	[redacted]	[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 4: Cost-effectiveness plane

Figure 5: Cost-effectiveness acceptability curve

5.1.2 EAG Scenario analysis

Given the uncertainties in the cost-effectiveness estimates, the EAG explored the following scenario analysis.

Scenario 1: Response to pruritus measured through ItchRO scores reported in Table 35 of the ITCH Clinical Study Report were used in place of sBA levels.[37] At a response threshold a reduction of ≥1.5 from baseline in ItchRO average daily scores, [redacted]% of patients randomised to placebo achieved a response compared to [redacted]% of patients on MRX. Increasing this threshold to a reduction of ≥2 from baseline, [redacted]% of patients randomised to placebo achieved a response compared to [redacted]% of patients on MRX. These values are used in place of sBA response rates from the ICONIC study. Other EAG base case assumptions were maintained.

Scenario 2: SBD health state was included. All EAG base case assumptions were maintained.

Scenario 3: Probability of response loss was increased by 10% and 30% in the MRX group to account for treatment failure independent of adverse events. All EAG base case assumptions was maintained.

Scenario 4: Weight band for model cohort increased to 25th percentile after two years to explore potential effects of treatment in boosting growth. All EAG base case assumptions were maintained.

Scenario 5: The age from which mortality risks from GALA were applied to non-responders set to 4 years to match the median age of the GALA cohort.

Scenario 6: Response to treatment was defined as a reduction of ≥70% sBA levels from baseline in line with HST17. Using this threshold, no patients receiving placebo were responsive in the ITCH study and only 3 of 31 participants in the ICONIC study were responsive based on data reported by Gonzales et al 2021.[27] A response rate of 9.68% was assumed in the MRX arm and a 0% response rate was assumed in the SoC arm. Other EAG base cases assumptions were maintained.

Scenario 7: Caregiver disutility was included but a disutility value of –0.05 and –0.1 was assumed for the response health state and loss of response health state respectively. Number of caregivers were changed from 1.7 caregivers per patient to 1 caregiver per patient. Other EAG base case assumptions were maintained.

The impact of each scenario on the ICER is presented in **Table 37.**

Table 14: EAG scenario analysis. Impact on ICER

	Incremental costs	**Incremental QALYs**	**ICER £/QALY**
Scenario 1 ≥ -1.5 ≥ -2.0	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]
Scenario 2	[redacted]	[redacted]	[redacted]
Scenario 3 10% 30%	[redacted] [redacted]	[redacted] [redacted]	[redacted] [redacted]

Scenario 4	[redacted]	[redacted]	[redacted]
Scenario 5	[redacted]	[redacted]	[redacted]
Scenario 6	[redacted]	[redacted]	[redacted]
Scenario 7	[redacted]	[redacted]	[redacted]

5.2 Conclusions of the cost effectiveness section

The model structure used by the company appears to be logical. However, the EAG has the following concerns about the cost-effectiveness analysis as detailed in Section 3.2.

- The use of an arbitrary biomarker threshold to model treatment response is inappropriate. Treatment response should be mapped to the risk of developing modelled clinical events and compared between treatment arms. The use of alternative response rates and biomarkers in the model had a significant impact on the cost-effectiveness.
- OS for the treatment naïve population were immature resulting in significant uncertainty in extrapolation. Under the most pessimistic parametric assumption (exponential model), 41% of the cohort were predicted to be alive at 100 years of age.
- The difference in utility values used for the response and loss of response health state were unreliable and unsupported by evidence from the literature. This utility difference also informed the decision to apply a severity modifier. Using alternative utility values precludes the use of severity modifier and significantly impacts the cost-effectiveness results.
- The source and methods used to estimate caregiver utility were inappropriate. Removing caregiver utility significantly affects the cost-effectiveness results.

Other important factors that also had an impact on the cost-effectiveness results include:

- Assumption of equivalent mortality risks between responders and non-responders due to uncertainties in the HR estimate used.

- Increasing the age mortality risks from the GALA cohort were applied to non-responders.
- Including the SBD health state significantly impacted the cost-effectiveness results.
- Increasing the weight band of the cohort responsive to treatment after two years on treatment.
- Increasing the probability of per cycle response loss to explore potential effects of treatment failure in responsive patients significantly affects the cost-effectiveness results

Single Technology Appraisal

Maralixibat for treating cholestatic pruritus in Alagille Syndrome [ID3941]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 5 February 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Incorrect reporting of ICONIC study endpoints

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Endpoints listed for the ICONIC study on page 40-41 are incorrect: a. Mean change from Week 18 to Week 22 (during DB-RWP) in fasting sBA levels in overall patient population (ITT) **is NOT a secondary endpoint** b. Responder analysis at Weeks 18, 48, 60, 72, 84, 96, and 100 in Pruritus response rates as measured by ItchRO (ItchRO[Obs] and ItchRO[Pt]) was **missed from the additional endpoints** c. Change Week 18 to Week 22 for PedsQL was **missed from the additional endpoints** d. 7αC4 **was missed from the additional endpoint** Change from baseline to	The company propose that the incorrect secondary endpoint should be removed (a), and the missing additional endpoints should be included (b-d) in the list of endpoints.	Incorrectly reports the endpoints investigated in the ICONIC study.	Thank you. The EAG has now removed (a) and added (b-d) to Table 4 of the EAG report as suggested by the company.

Weeks 18, 22, and 48, and then every 12 weeks in biochemical markers of cholestasis and liver disease			

Issue 2 Error in the number of infection-related AEs listed for the MRX vs. placebo group

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report states 'In general, the occurrence of AEs by PT in MRX and placebo groups was comparable with the exception of 'infections and infestations' and 'upper respiratory infection' being more frequent in MRX vs. placebo group (n=8 [61.5%] vs. n=1 [6.3%])'. Also, for infection and infestations 1 (6.3%) is listed for PBO in table 14 on page 72. This is incorrect.	The company propose to replace 'being more frequent in MRX vs. placebo group (n=8 [61.5%] vs. n=1 [6.3%])' with the following: *Infections and infestations occurred in 6 (46.2%) and 4 (25.0%) of people on MTX vs. PBO in the ICONIC study respectively. Upper respiratory infection occurred in 2 (15.4%) vs. 0 (0%) of people on MTX vs. PBO in the ICONIC study respectively.* The company also propose replacing "1 (6.3%)" as the number/% of infection and infestations in the PBO group in table 14 with the following: *4 (25.5%)*	Suggests an incorrect level of AEs with MTX treatment vs. PBO.	The discrepancy arose from an error in CS Document B Table 27, in which the number (percentage) of patients experiencing infections and infestations for the placebo arm during RWP was shown as "1 (25)" rather than "4 (25)". The EAG has revised the text based on the company's suggestion to read: "However, infections and infestations occurred in 6 (46.2%) vs. 4 (25.0%) people on MRX vs. PBO

			respectively, among which upper respiratory infection occurred in 2 (15.4%) vs. 0 (0%) people on MRX vs. PBO respectively." The EAG has changed the number/percentage from 1 (6.3%) to 4 (25) in the text and in Table 14 of the EAG report (note that the percentage 4/16 should be exactly 25% rather than 25.5%). The EAG has added a footnote to Table 14 to explain the discrepancy between the data presented in CS Document B and the data presented in the EAG report: ^Based on Table 5-14 of the CSR for ICONIC; incorrectly shown as "1 (25)" in CS Document B Table 27. The EAG noted that data in CS Document B

			Tables 27 and 28 were no longer marked as confidential in the revised version of the CS Document B provided by the company in December 2023, and therefore has unmarked some of the data in Table 14 of the EAG report.

Issue 3 Incorrect description of MTX as an ASBT inhibitor

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 28 the mechanism of action of MTX is described as an ASBT inhibitor, when the SmPC describes MTX as an IBAT inhibitor.	The company propose to replace 'Maralixibat is an oral, minimally absorbed selective inhibitor of the apical sodium-dependent bile acid transporter (ASBT). ASBT is present in the small intestine and mediates the uptake of bile acids in the intestines, recycling them back to the liver.12 By inhibiting ASBT, more bile acids are excreted in the faeces, leading to lower levels of bile acids systemically,	Incorrectly describes the mechanism of action of MTX	Thank you for identifying this error. EAG has corrected the text based on the company's suggestion.

	thereby reducing bile acid mediated liver damage.' With the following wording: Maralixibat is an oral, minimally absorbed selective inhibitor of the **ileal bile acid transporter (IBAT). IBAT** is present in the small intestine and mediates the uptake of bile acids in the intestines, recycling them back to the liver.12 By inhibiting **IBAT**, more bile acids are excreted in the faeces, leading to lower levels of bile acids systemically, thereby reducing bile acid mediated liver damage.		

Issue 4 Error in the reporting of the estimated treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG report that "Surgical interventions were only included in scenario analysis." (Page 102)	The Company propose to replace the sentence with "Surgical diversion was only included in a scenario."	Only surgical biliary diversion (SBD) is excluded from the base-case. Liver transplant (LTx) is included in the base-case, and is also considered a surgical intervention.	EAG has revised the text as follows: "Surgical diversion was only included in a scenario analysis"

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Document: ID3941 Maralixibat Warwick Evidence EAG report v0.1 250124 [CON]			
Table provided at clarification of 'Breakdown of patients meeting the sBA ≥50% from baseline to Week 12 or Week 18 criteria' **on page 52,** and in paragraph **on page 69**	This should be marked as confidential as this data is not currently published and there are no plans to publish it.	Not reproducible (table).	The table in question (Table 7 in the EAG report) was reproduced from the company's response to EAG clarification questions (CQ) A5, presented as Table 1 in the company's response document. The content of the table was not marked as confidential in the document. EAG will not be able to mark it as confidential unless the confidential marking for the company response document is revised/updated.

			However the EAG has added a footnote to acknowledge that the table was reproduced from the company's response to the EAG CQ. The EAG is unclear what text on page 69 would be considered as CIC, but similarly wish to highlight that data included in Table 1 to Table 6 of the company response to the EAG CQ were not marked as confidential, and therefore the EAG will not be able to mark them as CIC unless the confidential marking for the company response document is revised.
Statement from clarification of 'Of the 5 children who were not enrolled in the ICONIC study following screening, 1 was excluded due to decompensated	This should be marked as confidential as this data is not currently published and there are no plans to publish it.	Not reproducible (table).	The text was reproduced from the company's response to the EAG CQ A16 and was not marked as confidential. EAG will not be able to mark it as

cirrhosis, and the other 4 were excluded as they failed to meet the minimum itch requirement of an average daily ItchRO score over 2 for 2 consecutive weeks in screening' **on page 54.**			confidential unless the confidential marking for the company's response document is revised accordingly.
Inclusion of baseline demographics regarding phenobarbital, and all listed Other concomitant medications in table 9 / subsequent paragraph **on page 56-58**, and table 10 on **page 61,** and paragraph on **page 69/70**	This should be marked as confidential as this data is not currently published and there are no plans to publish it.	Not reproducible (table).	EAG has now marked the data as CIC as requested by the company.
The reported proportion of responders in ICONIC ([redacted]) (Page 104 and Page 122)	The proportion of responders in ICONIC is confidential as it isn't published information. The Company propose to highlight the proportion of responders as confidential information.	Although the medication dose administered to patients randomised to receive MRX differed from those used in the ICONIC study, patients on placebo who did not receive MRX achieved a response rate of [redacted]. EAG02: Probability of response changed from 0% to [redacted]. Per cycle probability	EAG has now marked the data as CIC as requested by the company.

		of response loss after initial response set to an annual rate of 5%.	
The reported PAS ICER ([redacted]) is not adequately highlighted. (Page 112)	The PAS ICER is confidential as it isn't published information. The Company propose to highlight the PAS ICER as confidential information.	A patient access scheme (PAS), incorporating discounted drug price ([redacted] per pack) was applied to the MRX drug acquisition costs.	Thank you. The EAG has now marked it as CIC.
The CEAC (Figure 5 and Figure 9) and CE plane (Figure 6 and Figure 8) are not redacted. (Page 119 and Page 124-125)	The PAS ICER is confidential as it isn't published information. The Company propose to highlight the PAS ICER as confidential information.	Not reproducible (figures).	The EAG has now marked the figures as CIC (blue coloured border).