Medicinrådet

Bilag til Medicinrådets vurdering af maralixibat til behandling af kolestatisk pruritus med ALGS

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. maralixibat
2. Forhandlingsnotat fra Amgros vedr. maralixibat
3. Ansøgers endelige ansøgning vedr. maralixibat

28 May 2026

Danish Medicines Council (Medicinrådet)
Copenhagen, Denmark

Dear Members of the Danish Medicines Council,

While there is inherent uncertainty of health-economic modelling in an ultra-rare condition such as ALGS, we note that the Council has unequivocally recognized the profound unmet medical need faced by these children and their families. Critically, the DMC has itself documented that no Danish patient has to date accepted partial external biliary diversion (PEBD), the only surgical alternative available within the approved indication. This is not a matter of patient preference; it reflects the procedural burden and morbidity risk of PEBD in very young children, and it unambiguously confirms that, in the absence of an effective pharmacological option, no family has chosen the available surgical route.

The DMC has confirmed meaningful and clinically relevant benefits across multiple domains. On **cholestatic pruritus**, the primary and most burdensome symptom, the Council stated that "maralixibat has a relieving effect on pruritus", with reductions of −1.5 points on the ItchRO scale and −0.9 points on the CSS to 48 weeks, accepting both the clinical meaningfulness and durability of this effect. The observed reduction in **serum bile acids** was equated by the DMC to "medical bile diversion", an important mechanistic signal supporting the biological plausibility of the treatment's hepatoprotective potential. **Xanthoma reduction** was found statistically significant, reflecting a systemic improvement in bile acid homeostasis. On **transplantation-free survival**, the Council recognized the event-free survival signal, noting that maralixibat "possibly has a hepatoprotective effect" and "may prolong time to liver transplantation". The **safety profile** was assessed as "relatively safe", with no safety concern identified as a barrier to use and adverse event frequency comparable to placebo.

The possibility of delaying liver transplantation has implications for prognosis that extend well beyond the primary indication. In ALGS, approximately 60% of patients undergo liver transplantation before adulthood, with a median age of just 2.8 years. Critically, 69% of these transplants are performed due to intractable pruritus, not advanced liver failure. The dominant driver of surgical intervention is therefore the very symptom that maralixibat has demonstrated the ability to meaningfully relieve. Transplantation in infants and very young children carries substantially higher peri-operative risk and longer-term complications, including lifelong immunosuppression, growth effects and neurodevelopmental burden, compared with transplantation at an older age. If maralixibat enables even a proportion of these children to delay or avoid transplantation, the long-term clinical implications are real and substantial, even if they are not fully captured within a short modelling horizon.

For this very small group of patients, access to maralixibat may represent a fundamentally different clinical trajectory than what is available today. It offers the prospect of meaningful symptom relief, restored sleep, improved daily functioning and overall wellbeing in a setting where no fully effective pharmacological treatment currently exists and where the only surgical alternative has not been accepted by any Danish patient to date. The evidence base, while inherently constrained by the epidemiological reality of an ultra-rare pediatric disease, represents the largest and most rigorous prospective dataset ever generated for this condition. The EMA granted a full marketing authorization on 9 December 2022 on this basis. The DMC's

own assessment confirmed the model structure, patient population and comparator were accepted, and that no safety concern constitutes a barrier to use. The clinical debate concerns the magnitude of benefit under uncertainty, not whether a meaningful benefit exists.

We respectfully request that the Council weigh these clinical dimensions in full when reaching its final determination. The number of patients is very small. The clinical need is very high. And the potential for a meaningfully better life, for children and the families who care for them, is real.

Yours sincerely,

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18.08.2026

MBA/LSC

Forhandlingsnotat

Dato for vurdering i Medicinrådet	02.09.2026
Leverandør	Abacus Medicine på vegne af MIRUM PHARMACEUTICALS INTERNATIONAL B. V
Lægemiddel	Livmarli (maralixibat)
Ansøgt indikation	Behandling af kolestatisk pruritus hos patienter med Alagilles syndrom (ALGS) i alderen 2 måneder og ældre
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Livmarli:

*Tabel 1: Forhandlingsresultat – **betinget** af en positiv anbefaling fra Medicinrådet*

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Livmarli	9,5 mg/ml (30 ml, 1 stk.)	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Livmarli, indkøbes lægemidlet til den SAIP, som er angivet i tabel 2.

*Tabel 2: Forhandlingsresultat – **ikke betinget** af Medicinrådets anbefaling*

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Livmarli	9,5 mg/ml (30 ml, 1 stk.)	[redacted]	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Livmarli gives i tillæg til den nuværende standardbehandling, som er best supportive care (ingen aktiv sygdomsmodificerende behandling.

Tabel 3 viser de årlige lægemiddeludgifter ved behandling med Livmarli for en patient på henholdsvis;

- 2 måneder (minimumsalder for anvendelse af Livmarli, jævnfør EMA produktresume) svarende til en vægt på 5,0 kg
- 5,5 år (gennemsnitsalderen i ICONIC-studiet) svarende til en vægt på 15,4 kg.
- 18 år (maksimal doseringsalder hvorefter dosis fastholdes svarende til en vægt på 51,9 kg)

Udgifterne til best supportive care er minimale og derfor ikke medtaget i nedenstående tabel 3.

Tabel 3: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK) **
Livmarli	9,5 mg/ml (30 ml, 1 stk.)	Startdosis (første behandlingsuge): 190 µg/kg/dag, oral, og derefter vedligeholdelsesdosis: 380 µg/kg/dag, oral	[redacted]	Patient på 5,0 kg: [redacted] Patient på 15,4 kg: [redacted] Patient på 51,9 kg: [redacted]

*Medicinrådets vurderingsrapport

** Medicinrådet følger ansøgers antagelse om, at patienternes gennemsnitsvægt følger femte percentil af den køns-alderstilsvarende danske befolkning (reference 45 i Medicinrådets vurderingsrapport).

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
Sverige	Ikke ansøgt	
England	Under vurdering	Link til status

Opsummering

[redacted]

Application for the assessment of Livmarli (maralixibat) for the treatment of cholestatic pruritus in patients with Alagille syndrome

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
XXXXXXXXXXXXXXXXXX	**Confidential information – Version for publication on the DMC's website**

Contact information

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Executive summary

Alagille syndrome (ALGS) is a rare, autosomal dominant multisystem disorder caused by mutations in the JAG1 and NOTCH2 genes, with a birth prevalence of 1 in 30,000 to 1 in 100,000 live births [1]. In Denmark, this equates to approximately 1 to 2 new cases per year [2]. ALGS primarily affects the liver, with most patients (75%–100%) showing signs of paucity of intrahepatic bile ducts (PIBD) by three months of age, leading to cholestasis characterized by elevated serum bile acids (sBA) and bilirubin levels [3-5]. Cholestasis is the earliest and most severe manifestation, affecting 85% of children, with a median onset at 12 months [6-9]. It leads to complications such as pruritus (59–88% of patients) [10, 11], cirrhosis (46%), portal hypertension (40%), and ascites (57%) [7, 12]. Pruritus is the most debilitating symptom [13] affecting 59% to 88% of ALGS patients [3, 6, 8, 14], and it is severe in 15% and 45% of those patients [7]. It is highly distressing, significantly impacts quality of life, causing self-inflicted injuries, infections, and scarring [3]. Due to the lack of approved therapies for cholestatic pruritus, many patients ultimately require liver transplantation (LTx).

LTx in ALGS is primarily driven by complications from persistent cholestasis, with intractable pruritus accounting for 69% of transplants [3], even in the absence of cirrhosis or liver failure [6] [15]. Most ALGS patients undergo LTx before the age of five, with a median age of 2.8 years [6]. In this context, IBAT inhibitors that target cholestatic pruritus offer a promising alternative. Livmarli (maralixibat) addresses the underlying pathophysiology by blocking the enterohepatic circulation of bile acids, thereby increasing their fecal excretion and reducing sBA levels [6]. Clinical data from the ICONIC study show that maralixibat provides durable and clinically meaningful improvements in cholestasis and pruritus [16], as measured by validated scales such as ItchRO and CSS [17]. Beyond its impact on cholestatic pruritus, maralixibat has demonstrated benefits in reducing other cholestatic symptoms like xanthomas and growth impairment [17], both of which negatively affect survival [17] and psychosocial well-being [17] . The ICONIC trial also reported significant improvements in quality of life (QoL) for both patients and caregivers [3], including better outcomes in schooling, social and family life, and reduced fatigue. ALGS has a profound impact on families, with patients often experiencing sleep disturbances and psychological distress, while caregivers face disrupted routines and increased anxiety [13, 18-20].

Although LTx remains the only option for patients with uncontrolled cholestatic pruritus and related complications, it carries significant risks such as rejection, infections, graft failure, and the need for lifelong immunosuppression. Younger patients are particularly vulnerable to retransplantation. The GALA-MRX study suggests that maralixibat may improve event-free survival (EFS), suggesting that maralixibat has the potential to delay the need for surgical interventions such as LTx [17].

Currently, no drugs are reimbursed specifically for treating cholestatic pruritus in ALGS, and supportive care remains the standard of care, relying on off-label treatments with limited long-term efficacy. In this landscape, maralixibat stands out as a well-tolerated and effective pharmacological option that can be initiated early in life, potentially transforming the treatment paradigm and delaying the need for liver transplantation.

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Tables and Figures

Abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
AE	Adverse event	**LTE**	Long-term extension
aHR	Adjusted hazard ratio	**LY**	Life years
AIC	Akaike Information Criteria	**LYG**	Life year gained
ALGS	Alagille syndrome	**MAA**	Marketing authorization approval
ALP	Alkaline phosphatase	**MITT**	Modified intent-to-treat
ALT	Alanine aminotransferase	**MMRM**	Mixed-effects model for repeated measures
ANCOVA	Analysis of covariance	**MRX**	Maralixibat
AP	Alkaline phosphatase	**NAFLD**	Non-alcoholic fatty liver disease
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 signaling pathway
BIM	Budget impact model	**ODD**	Orphan drug designation
BMI	Body mass index	**OL**	Open label
BSEP	Bile salt export pump	**OS**	Overall survival
CEM	Cost-effectiveness model	**PBO**	Placebo
CHMP	Committee for Medicinal Products for Human Use	**PEBD**	Partial external biliary diversion
CI	Confidence interval	**PedsQL**	Pediatric Quality of Life Inventory
CIC	Caregiver Impression of Change	**PFIC**	Progressive familial intrahepatic cholestasis
CMH	Cochran-Mantel-Haenszel	**PHT**	Portal hypertension
CRD	Centre for reviews and dissemination	**PIC**	Patient Impression of Change

CSS	Clinician scratch scores	**PRO**	Patient reported outcome
CTCAE	Common terminology criteria for adverse events	**PSA**	Probabilistic sensitivity analysis
DKK	Danish Krone	**PSS**	Parent satisfaction survey
DMC	Danish Medicines Council	**PSSRU**	Personal Social Services Research Unit
DSA	Deterministic sensitivity analyses	**QALY**	Quality-adjusted life years
EFS	Event-free survival	**QoL**	Quality of Life
EMA	European Medicines Agency	**RCT**	Randomized controlled trial
EOT	End of treatment	**RMSE**	Root mean square error
FSV	Fat-Soluble Vitamin	**RWP**	Randomized withdrawal phase
GALA	Global ALagille Alliance	**SAE**	Serious adverse event
GD	Graft dysfunction	**sBA**	Serum bile acid
GGT	Gamma-glutamyl transferase	**SBD**	Surgical biliary diversion
GI	Gastrointestinal	**SD**	Standard deviation
HADS	Hospital Anxiety and Depression Scale	**SE**	Standard error
HCC	Hepatocellular carcinoma	**SLR**	Systematic literature review
HR	Hazard ratio	**SmPC**	Summary of product characteristics
HRQoL	Health-related quality of life	**SoC**	Standard of care
HST	Health-state transition	**SSRI**	Selective serotonin reuptake inhibitor
IBAT	Ileal bile acid transporter	**TEAE**	Treatment-emergent adverse event
ICER	Incremental cost-effectiveness ratio	**TFS**	Transplant free survival
IPTW	Inverse probability of treatment weights	**TR**	Transplantation rate
IQR	Interquartile range	**TTO**	Time trade off
ItchRO	Itch-reported outcome	**UDCA**	Ursodeoxycholic acid
ITT	Intent-to-treat	**ULN**	Upper limit of normal
KS	Kolmogorov-Smirnov	**US**	United States
LDL	Low-density lipoprotein	**VAS**	Visual analogue scale
LOCF	Last observation carried forwards	**WPAI**	Work productivity and activity impairment
LR	Likelihood ratio	**WTP**	Willingness to pay
LTx	Liver transplant		

1. Regulatory information

Overview of the medicine	
Proprietary name	LIVMARLI
Generic name	Maralixibat
Therapeutic indication as defined by EMA	LIVMARLI (maralixibat) is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) from 2 months of age.
Marketing authorization holder in Denmark	MIRUM PHARMACEUTICALS INTERNATIONAL B.V.
ATC code	A05AX04: Maralixibat chloride
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	9.5mg/mL oral solution of maralixibat was approved by the European Medicines Agency on 9th December 2022 (EMEA/H/C/005857) for the treatment of cholestatic pruritus in patients with ALGS 2 months of age and older, in accordance with advice from the Committee for Committee for Medicinal Products for Human Use (CHMP) in October 2022. [Accessed on August 14th, 2024]. URL: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-livmarli_en.pdf
Has the medicine received a conditional marketing authorization?	MAA under exceptional circumstances The MA is associated with a RMP and the conduct of a study evaluating the safety and long-term efficacy of maralixibat in the treatment of cholestatic pruritus in patients with Alagille Syndrome.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	The European Commission (EC) granted orphan drug status to maralixibat in the indication for Alagille Syndrome on 13/12/2013 (EU/3/13/1214) following the positive opinion issued by the Committee for Orphan Medicinal Products (COMP) on 6/11/2013. EU/3/13/1214: Orphan designation for the treatment of Alagille syndrome [online]. 2014. [Accessed on August 14th, 2024]. URL: https://www.ema.europa.eu/en/documents/orphan-designation/eu3131214-public-summary-opinion-orphan-designation-4r5r-1-4-4-33-dibutyl-7-dimethylamino-2345-tetrahydro-4-hydroxy-11-dioxido-1-benzothiepin-5-ylphenoxymethylphenylmethyl-4-aza-1-azoniabi_en.pdf. Orphan Maintenance Assessment Report - Livmarli (maralixibat chloride) Treatment of Alagille syndrome EU/3/13/1214 [online]. 2022. [Accessed on August 14th, 2024]. URL: https://www.ema.europa.eu/en/documents/orphan-maintenance-report/livmarli-orphan-maintenance-assessment-report-initial-authorisation_en.pdf
Other therapeutic indications approved by EMA	Progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older.

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Unfortunately, we could not use this reimbursement route due to slight differences in current treatment practices across the Nordic countries and variations in submission timelines among them.
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	LIVMARLI (maralixibat) 9.5 mg/mL oral solution. One 30 ml bottle supplied with three oral syringes (0.5 mL, 1 mL, 3 mL).

2. Summary table

Summary	
Indication relevant for the assessment	LIVMARLI (maralixibat) is indicated in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) from the age of 2 months (Please see summary of the product characteristics (SmPC [21]).
Dosage regiment and administration	Dosage regiment: The recommended target dose is 380 micrograms/kg once daily. The starting dose is 190 micrograms/kg once daily and the dose should be increased to 380 micrograms/kg once daily after one Week. The maximum recommended daily dose for patients weighing more than 70 kg is 3 mL (28.5 mg). Mode of administration: Livmarli should be administered orally by a caregiver or by the patient using an oral syringe, with or without food. The use of Livmarli oral solution mixed directly with food or drink prior to administration has not been studied. Oral syringes of three sizes (0.5 mL, 1 mL and 3 mL) are supplied with each vial of Livmarli.
Choice of comparator	Established clinical management without maralixibat, including off-label drug treatments such as ursodeoxycholic acid, cholestyramine, and rifampicin.
Prognosis with current treatment (comparator)	ALGS has a highly variable prognosis influenced by the severity of liver and heart involvement. While some patients experience mild symptoms and live relatively normal lives, others face progressive complications such as cholestasis and severe pruritus, often necessitating liver transplantation, which carries significant risks. Additionally, cardiac anomalies can contribute to increased morbidity and mortality.
Type of evidence for the clinical evaluation	ICONIC (LUM001-304): Multicenter, double-blind randomized Phase 2b study with open-label follow-up. Duration of treatment: 204 Weeks. GALA Cohort Comparison Study: 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.

Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	Mean change in sBA levels and other biomarkers of cholestasis and liver function, mean change in pruritus assessed by ItchRO and CSS scales, mean change in quality of life assessed by PedsQL score, and EFS.
Most important serious adverse events for the intervention and comparator	AEs recorded in the ICONIC study are abdominal pain and increase in ALT levels. Only abdominal pain was considered to have an impact on QoL, for which a disutility of –0.0512028 was taken from Sullivan et al (Sullivan, Slejko et al. 2011).
Impact on health-related quality of life	Clinical documentation: Refers to Vignette Study. Health economic model: Better than comparator.
Type of economic analysis that is submitted	A cost-utility analysis was conducted using a Danish adaptation of an Excel-based cost-effectiveness model originally developed for NICE in the UK. The Danish model is constructed as a multi-state Markov model.
Data sources used to model the clinical effects	The model includes: • Change in sBA levels and corresponding pruritus • Time to liver events and progression of liver disease (transplant, cirrhosis, ascites and PHT) • Adverse events • Health-related quality of life • Event free survival • Overall survival • Measures of faltering growth • Transplant-free survival • Number of patients requiring LTx The outcomes selected in the model were based on clinical opinion and the documented literature on possible outcomes for patients with ALGS. Changes 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 literature.
Data sources used to model the health-related quality of life	Vignette Study
Life years gained	XXXXXXX
QALYs gained	XXXXXXX
Incremental costs	XXXXXXXXXXXX
ICER (DKK/QALY)	XXXXXXXXXXXX
Uncertainty associated with the ICER estimate	This economic evaluation presents the cost-effectiveness of maralixibat in ALGS vs SoC and is the first attempt at parameterizing an economic model in this condition. In the base-case, the ICER for maralixibat vs SoC is XXXXXXXXXXXX.

Summary	
	The ICER in the probabilistic analysis resulted in an ICER of DKK [redacted], 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.
Number of eligible patients in Denmark	[redacted]
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Alagille Syndrome: definition and pathophysiology

Alagille syndrome (ALGS) is a rare, autosomal dominant genetic disorder with complex multisystem involvement and significant clinical variability. It affects between 1 in 30,000 and 1 in 100,000 live births [1] and is primarily caused by mutations in the JAG1 gene (94% of cases) [3, 22, 23] or, less commonly, the NOTCH2 gene (2–4%) [24]. These genes are part of the NOTCH signaling pathway, which plays a critical role in organ development. Most cases (60%) result from de novo mutations, while 40% are inherited [5-7]. ALGS affects multiple organs, including the liver, heart, kidneys, skeleton, and brain, with the liver and heart being the most significantly impacted. The hepatic manifestations of ALGS stem from disrupted bile duct development due to impaired Jagged1 and Notch2 signaling. This leads to a condition known as paucity of interlobular bile ducts (PIBD) [25], where bile ducts are malformed, narrowed, and reduced in number [3, 26]. PIBD is present in 75% to 100% of ALGS patients [3], with at least 65% showing signs before three months of age [6]. These defects also contribute to vascular anomalies and congenital heart defects due to their roles in angiogenesis and cardiac development. The resulting liver dysfunction causes cholestasis, a condition marked by the accumulation of toxic bile acids in the liver due to impaired bile flow [27].

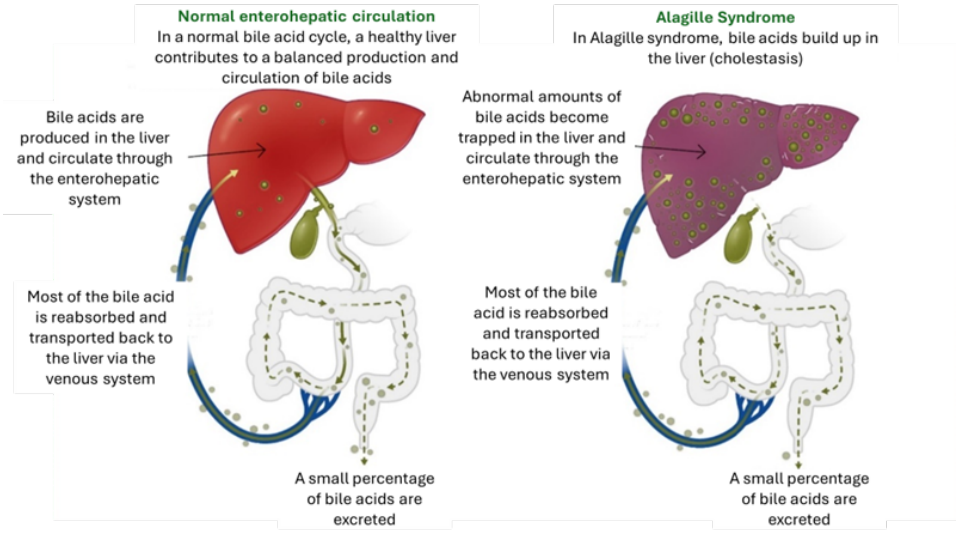
Cholestasis in ALGS is marked by elevated serum bile acids (sBA) and bilirubin, leading to jaundice [5]. A common and particularly distressing symptom is pruritus, affecting 59% to 88% of patients, with up to 45% experiencing it in severe form[3]. This intense itching significantly impairs sleep and quality of life and is a leading reason for liver

transplantation (LTx) in ALGS [9]. The condition also places a heavy emotional and practical burden on families, disrupting daily routines and overall well-being [23].

3.1.2 Clinical symptoms

Cholestasis is the most common and severe liver-related feature of ALGS, affecting approximately 85% of children, first appearing within the first months of life and at a mean age of 12 months [6-9, 28]. It results from impaired bile flow, causing bile acids to accumulate in the liver and bloodstream, leading to elevated serum bile acids (sBA) and jaundice, both hallmark signs of ALGS [3-5]. This buildup contributes to serious complications including pruritus (59–88%) [10, 11], cirrhosis (46%), portal hypertension (40%), and ascites (57%) [7, 12]. Cholestatic pruritus is a primary clinical manifestation of cholestasis in ALGS, which begins between 6 to 14 months of age [3], affects 59–88% of patients [3, 6, 8, 14], with 15–45% experiencing severe cases [7] [29]. It can lead to skin damage, infections, and significantly reduced quality of life [3], and is the leading cause of liver transplantation (69% of cases), even without cirrhosis [4]. The cholestatic pruritus associated with ALGS is among the most severe in any chronic liver disease [30].

Figure 1 Summary of liver changes in ALGS



Source: Mirum Pharmaceuticals' own illustration.

Extra-hepatic manifestations include hypercholesterolemia (>80%), xanthomas (up to 42%), growth failure (up to 87%), chronic fatigue (65–85%), sleep disturbances (23–54%), neurocognitive deficits (>50%), vitamin deficiencies (A, D, E, K), bone fractures (28%), and dental damage (50%) [3, 16] [23] [31] [32] [33] [34] [35] [36] [37]. ALGS also affects multiple organ systems: cardiac abnormalities occur in 91% of patients, bone anomalies in nearly 50%, eye anomalies in 50%, distinctive facial features in 90%, and renal/vascular complications in 39% [6, 15, 28, 34]. Cardiovascular disease affects 36% and can limit eligibility for liver transplantation, further complicating disease management [6, 28].

3.1.3 Diagnosis of Alagille Syndrome

ALGS is typically diagnosed in infancy or early childhood, based on a combination of clinical features and genetic testing [3]. While identification of a pathogenic variant in the *JAG1* or *NOTCH2* gene supports diagnosis [5, 13], genetic confirmation alone is not always possible, about 3% of patients show no detectable mutation despite clinical signs [38]. Therefore, clinical criteria remain essential.

The revised diagnostic criteria for ALGS include major manifestations across multiple organ systems [5, 9, 13]:

- Hepatic (75–100%): Cholestasis and bile duct paucity
- Cardiac (85–98%): Pulmonary artery stenosis, atrial septal defect (ASD), ventricular septal defect (VSD) and Tetralogy of Fallot (TOF)
- Skeletal (33–87%): Butterfly vertebrae and other spinal anomalies
- Renal (19–73%): Ureteropelvic junction anomalies, renal tubular acidosis
- Ocular (56–88%): Posterior embryotoxon, optic drusen, retinal abnormalities
- Facial features (70–98%): Triangular facies with distinct features
- Vascular anomalies (4–38%): Intracranial or intra-abdominal aneurysms

Diagnosis is confirmed based on the following rules [5, 9, 13]:

1) Four or more major criteria are required for diagnosis.
2) In the presence of family history, a confirmed JAG1 mutation is sufficient for diagnosis, even without clinical criteria.
3) If either a genetic mutation or family history is present, at least one major clinical criterion is needed.

In Denmark, ALGS is usually identified in newborns showing prolonged jaundice and congenital heart defects [2]. Diagnosis is supported by additional signs like eye anomalies and butterfly vertebrae, and confirmed through genetic testing for mutations in *JAG1* or *NOTCH2* [2]. Danish guidelines stress the importance of distinguishing ALGS from biliary atresia, as misdiagnosis and performing the Kasai procedure can worsen liver function in ALGS patients [2].

3.1.4 Natural course of the disease and prognosis with current treatment options

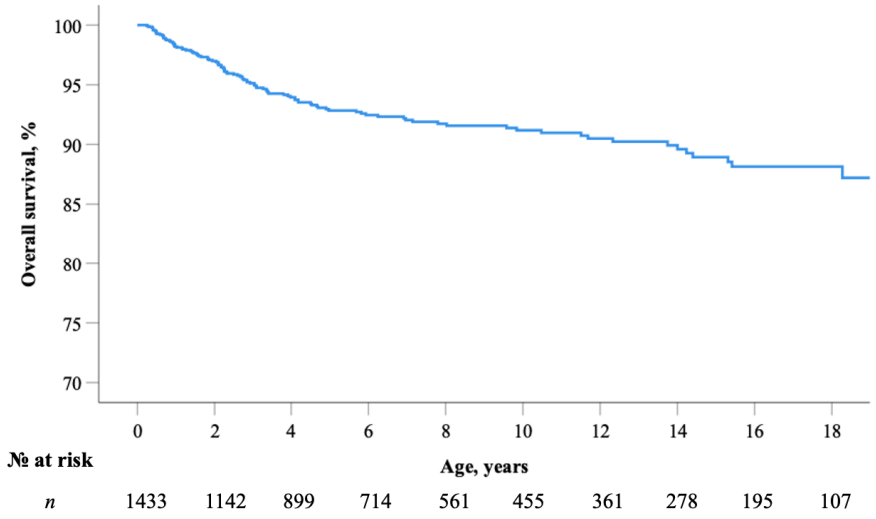
The natural progression of ALGS is marked by cholestasis, which leads to serious hepatic complications including cirrhosis, portal hypertension (PHT), and ascites, as well as secondary complications such as cholestatic pruritus, xanthomas, growth failure, and hepatic osteopathy [13]. Liver transplant (LTx) is the standard treatment for progressive cholestasis with approximately 60% of children undergoing LTx before adulthood, typically at a median age of 2.8 years [6, 28]. Persistent cholestasis is the leading indication for LTx (72%), with intractable pruritus affecting 69% of cases [6, 28]. Severe pruritus significantly impacts physical, psychosocial, and quality of life (QoL) outcomes [20], often necessitating LTx even in the absence of end-stage liver disease [18] [8, 31]. Other indications for LTx include growth failure (54%), xanthomas (49%), and PHT-

related complications (30%), such as ascites and variceal hemorrhages, which are more prevalent in older transplant recipients (median age 4.1 years vs. 2.5 years) [6, 28].

Mortality in ALGS is primarily driven by liver-related complications (22%, median age 2.8 years, IQR 1.6 – 6.7), followed by cardiac complications (18%, median age 1.1 years, IQR 0.5 – 4.5) [6, 28]. Cardiovascular deterioration can render patients ineligible for LTx, limiting treatment options [39]. Additional causes of death include multiorgan failure and non-cardiac vascular complications, each accounting for 15% of deaths. The Global Alagille Alliance (GALA) study reported an all-cause mortality rate of 8.5%, with mortality rates of 7.2% at age 5 and nearly 12% at age 18 (see the Figure below), and a median age of death of 2.6 years [6].

Survival outcomes in ALGS are consistent across epidemiological studies. Vandriel et al. (2019) reported 10- and 18-year overall survival (OS) rates of 92.9% and 90.7%, respectively [40]. Kasahara et al. (2003) found 1- and 5-year OS rates of 87.7% and 80.4% [41]. Vandriel et al. (2020) showed OS rates ≥88% in both JAG1 and NOTCH2 mutation carriers, with 10- and 18-year OS rates of 90.9% and 88.6% [42] [43]. Kohaut et al. (2015) reported 1-, 5-, and 10-year OS rates of 90.9%, 87.9%, and 84.8%, respectively, [44] highlighting consistency across studies.

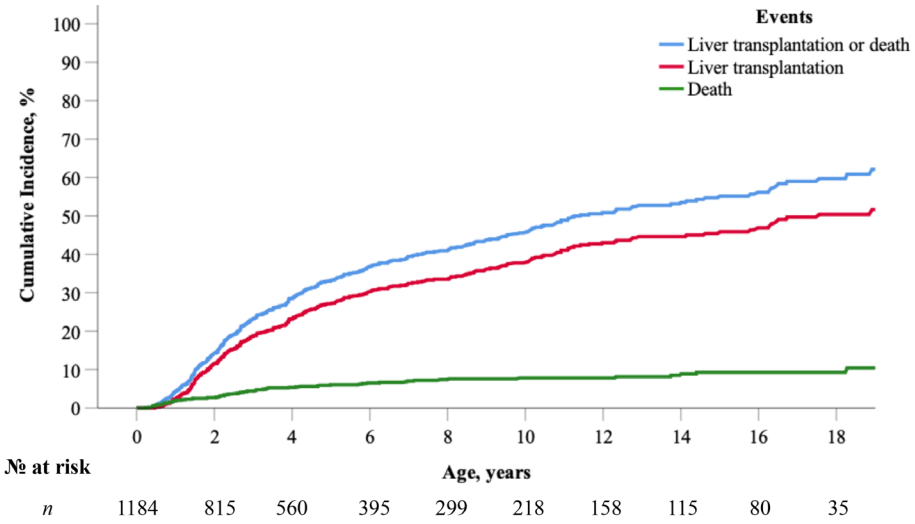
Figure 2 Kaplan–Meier survival analysis for all-cause mortality in ALGS patients



Source: Vandriel et al. 2023 [6].

In addition, the GALA study reported a competing risk analysis in children with neonatal cholestasis (n=1,184) assessed native liver survival (NLS), LTx, and death without LTx. At 5, 10, and 18 years, NLS rates were 66.8%, 54.4%, and 40.3%, respectively. The cumulative incidence of LTx was 27.1%, 37.8%, and 50.4%, while the risk of death without LTx was 6.1%, 7.8%, and 9.3%. These findings underscore the high burden of cholestasis and the urgent need for targeted therapies to reduce disease severity and delay or avoid LTx, especially in young children [6].

Figure 3 Cumulative incidence of NLS in the presence of competing events (LTx or risk of death without LTx) in children with ALGS who presented with neonatal cholestasis



Source: Vandriel et al. 2023 [6].

Currently, the standard of care for cholestatic pruritus in ALGS is largely supportive and does not alter the disease course [3]. As a result, many patients require LTx even in non-end-stage cases [8, 31] [6] [12]. While LTx can be effective, it carries significant risks, including increased mortality, surgical complications, lifelong immunosuppression, and limited eligibility due to extra-hepatic comorbidities [3, 17, 45] [13, 39]. Given these limitations—and the absence of approved treatments for cholestatic pruritus in Denmark—there remains a critical unmet need for safe and effective pharmacological therapies to improve prognosis and reduce reliance on transplantation.

3.1.5 Patients' quality of life and impact on caregivers

Patients with ALGS face significant QoL challenges due to severe hepatic symptoms and associated complications, particularly cholestatic pruritus, which disrupts sleep and negatively affects cognitive and psychosocial development [46], leading to reduced school engagement and social participation. Many patients also experience chronic fatigue (65-85%) [47] and sleep disturbances (23-54%) [3], which hinder development and daily functioning [13, 18-20]. Physical features such as growth retardation, xanthomas, and facial dysmorphism contribute to social exclusion and psychological distress [48], often resulting in diminished self-esteem and increased risk of depression [46]. Caregivers are also heavily impacted, reporting reduced QoL due to chronic sleep disruption, limited time for daily activities, and heightened anxiety [46]. On average, they spend over 85 hours per week managing the disease, with employed caregivers losing about 8 hours weekly to absenteeism, highlighting the substantial emotional, physical, and financial burden ALGS imposes on families [46].

3.2 Patient population

Incidence and prevalence of ALGS in Denmark

ALGS is estimated to affect between approximately 1/30,000 to 1/100,000 children born worldwide [1]. Early estimates based on clinical criteria (presence of 3 out of 5 major criteria) placed incidence at approximately 1 in 70,000 [49], but with the integration of genetic testing for *JAG1* and *NOTCH2* mutations, more recent studies suggest a refined incidence of between 1 in 30,000 and 1 in 50,000 live births [50] [51]. [redacted]. In Denmark, according to Sundhed [2] the incidence is estimated to be 1 per 30,000–50,000 live births, equating to roughly 1–2 new ALGS cases annually. For modeling purposes, a midpoint estimate of [redacted] live births is used.

To project annual ALGS births in Denmark, Eurostat data on live births from 2012 to 2023 were analyzed. The number of births in 2024 was estimated using the average from the previous five years (2019–2023), and projections for 2025–2029 assume a 0.12% annual increase, based on historical trends.

Table 1 Live births per year in Denmark from 2019 to 2023 and estimated live births from years 2024 to 2029

Year	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Live births (Nb)	61,167	60,937	63,473	58,430	57,469	60,295	60,368	60,440	60,513	60,585	60,658

As of 2023, [redacted] were identified in Denmark, including [redacted]. Specialized care is provided at centers in Aarhus and Copenhagen, with approximately [redacted] currently managed at Rigshospitalet in Copenhagen (Appendix L). Prevalence estimates for 2020–2024 were adjusted using the midpoint incidence rate [redacted] and documented cases, accounting for annual incident cases to reflect a realistic patient population.

Table 2 ALGS Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
ALGS incidence in Denmark	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALGS prevalence in Denmark	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALGS global prevalence*	Between 1 in 30,000 to 1 in 100,000 births	Between 1 in 30,000 to 1 in 100,000 births	Between 1 in 30,000 to 1 in 100,000 births	Between 1 in 30,000 to 1 in 100,000 births	Between 1 in 30,000 to 1 in 100,000 births

*Source for global prevalence for ALGS from Diaz-Frias et al 2024 [1].

Estimation of ALGS patients eligible for maralixibat treatment in Denmark

[redacted]. Based on literature indicating [redacted].

Table 3 Estimated number of ALGS patient with cholestatic pruritus in Denmark

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*In this Table, "Year 1" represents the year 2025. Abbreviations: ALGS: Alagille syndrome; MRX: maralixibat.

3.3 Current treatment options

The European Association for the Study of the Liver (EASL) recommends a comprehensive management approach, including the use of ileal bile acid transporter (IBAT) inhibitors where available [52]. However, in Denmark, no pharmacotherapies for ALGS are currently reimbursed, and treatment is limited to supportive care and off-label therapies. ALGS care in Denmark is centralized at two specialist pediatric hepatology centers: Rigshospitalet in Copenhagen and Aarhus University Hospital in Aarhus. Patients from across the country are referred to these institutions, which serve as national hubs for diagnosis, treatment, and long-term management of ALGS. Transition to adult care occurs at age 18, and follow-up frequency is determined by disease severity, with stable patients typically reviewed every 3 to 6 months (Appendix L). Danish clinicians adhere to both international and national guidelines [2].

In Denmark, supportive care includes nutritional management with medium-chain triglycerides (MCTs), glucose polymers, and supplementation of fat-soluble vitamins (A, D, E, K) to prevent deficiency states (Appendix L) [3] [13] [53]. Moreover, pharmacological treatment options are limited and primarily off-label (Appendix L) [3, 54, 55]:

- Ursodeoxycholic acid (UDCA) is widely used despite lacking efficacy in pruritus management.
- Rifampicin is prescribed for pruritus but carries risks of hepatotoxicity [56] and is discontinued if ineffective.
- Cholestyramine and other bile acid sequestrants are rarely used due to poor tolerability and limited efficacy in children.
- Antihistamines are not routinely used in Denmark due to lack of effectiveness.

Clinical experts from Rigshospitalet confirm that these treatments offer only

symptomatic relief and do not address the underlying disease pathology. Consequently, pruritus often remains refractory, contributing to the high rate of LTx in severe cases [3] [8, 31].

[redacted] LTx carries significant risks, including postoperative complications (infection, allograft failure, rejection), long-term immunosuppression [3, 17, 45], and increased mortality from liver-related causes (22%; median age 2.8 years, IQR, 1.6–6.7) and cardiac complications (median age 1.1 years) [6]. Consequently, [redacted].

Surgical biliary diversion (SBD) is an alternative option for severe, medication-resistant pruritus [6]. It aims to interrupt the enterohepatic circulation of bile acids but is less effective in ALGS than in other cholestatic diseases. SBD is rarely performed in Denmark due to its limited efficacy in ALGS and high complication rates, including permanent stoma and increased mortality (HR: 1.9; 95% CI: 1.4–2.6; $p < 0.001$) [6] [57, 58]. Only 5% of pediatric ALGS patients undergo SBD, and [redacted].

3.4 The intervention

LIVMARLI (maralixibat) is the first IBAT inhibitor with long-term clinical data in ALGS, offering a targeted approach to treatment. By blocking bile acid reabsorption in the intestine, it reduces circulating bile acids, which directly alleviates cholestatic pruritus. Additionally, it lowers serum cholesterol levels, improving xanthomas. This dual action addresses both symptoms and underlying disease mechanisms, making maralixibat a promising therapy for ALGS.

Table 4 Overview of Livmarli (maralixibat)

Overview of intervention	
Indication relevant for the assessment	LIVMARLI (maralixibat) is indicated in the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) from the age of 2 months (Please see summary of the product characteristics (SmPC [21]).
ATMP	No
Method of administration	Maralixibat is administered orally and comes in the form of an oral solution suitable for the pediatric population.
Dosing	Maralixibat is provided as an oral solution. The recommended target dose is 380 µg/kg once daily. The starting dose is 190 µg/kg once daily and should be increased to 380 µg/kg once daily after one Week. In case of poor tolerability, dose reduction from 380 µg/kg/day to 190 µg/kg/day, or treatment interruption can be considered. Renewed dose escalation can be attempted as tolerated. The maximum recommended daily dose for patients above 70 kg is 3 mL (28.5 mg). Alternative treatment should be considered in patients for whom no treatment benefit can be

Overview of intervention	
	established following 3 months of continuous daily treatment with maralixibat. Note: The SmPC [21] lists doses in free form i.e., 380 µg free maralixibat chloride equals 400 µg maralixibat chloride.
Dosing in the health economic model (including relative dose intensity)	LIVMARLI (maralixibat): Maximum dose: 28.50 mL Vial size: 30ml vial (9.5mg/mL) Dose cap (ml/day): 3.00 SoC and Dose (mg): Ursodeoxycholic acid: 10mg Rifampicin: 10mg Cholestyramine: 15mg
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Lifetime / Alternative treatment should be considered in patients for whom no treatment benefit can be established following 3 months of continuous daily treatment with maralixibat.
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Diagnostic test not included in the model. Lab tests included in the model.
Package size(s)	Each pack contains one 30 mL bottle and is co-packaged with three oral repeated-use syringes (0.5 mL, 1 mL and 3 mL) with the following graduations: • 0.5 mL polypropylene syringe with a white plunger: numbers for each 0.1 mL, major hash marks for 0.05 mL increments, and minor hash marks for 0.01 mL increments. • 1 mL polypropylene syringe with a white plunger: numbers for each 0.1 mL increment. 3 mL polypropylene syringe with a white plunger: numbers for each 0.5 mL increment, and hash marks for each 0.25 mL increment between 0.5 mL and 3 mL.

3.4.1 Description of ATMP

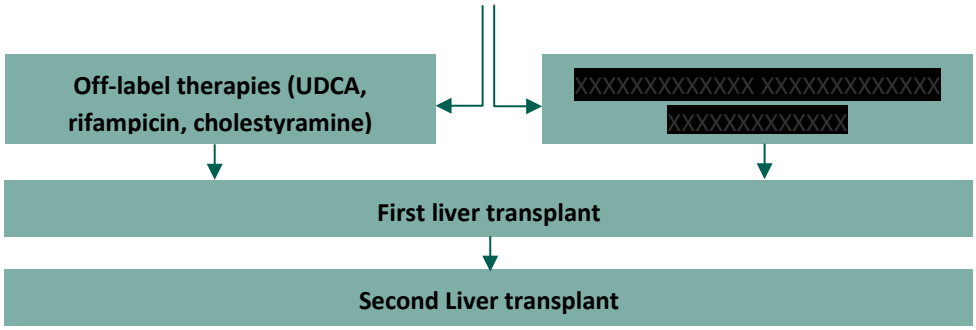
Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

[redacted] These off-label medications may include UDCA, rifampicin, and cholestyramine.

Figure 4 Proposed positioning of maralixibat in the treatment pathway for cholestatic pruritus in ALGS patients

Cholestatic pruritus in ALGS



3.5 Choice of comparator(s)

In Denmark, ALGS-related cholestatic pruritus is currently managed with off-label oral therapies such as UDCA, rifampicin, and cholestyramine, which together form the standard of care (SoC). These treatments offer limited symptomatic relief and do not modify disease progression [3]. XXXXXXXXX Given the lack of approved pharmacological options, these off-label therapies are considered the most relevant comparators for LIVMARLI (maralixibat) in the Danish context.

Table 5 Overview of the comparators

Overview of comparators			
Generic name	Ursodeoxycholic acid or UDCA	Rifampicin	Cholestyramine
ATC code	A05AA02	J04AB02	C10AC01
Mechanism of action	Ursodeoxycholic acid is a choleretic that stimulates bile flow.	Rifampicin inhibits the uptake of bile acids by hepatocytes.	Cholestyramine is an anion exchange resin that sequesters bile salts and is used for pruritus associated with elevated bile acids.
Method of administration	(blister) hard capsule	(blister) hard capsule	Oral/suspension form
Dosing	10-15mg/kg/day divided into 2-3 doses	5-10mg/kg/day divided into 1-2 doses	240mg/kg/day divided into 2-4 doses – Max dose 8g/day or 8000mg/day
Dosing in the health economic model (including relative dose intensity)	10mg	10mg	4000mg
Should the medicine be administered with other medicines?	No	No	No
Treatment duration/ criteria for end of treatment	Long term to improve bile flow & manage cholestasis. Continued as long as clinical improvement in liver function or reduction in symptoms. Ended if no improvement after 6-12months, side effects, and in cases of severe liver disease where it is no longer effective. The end-of-treatment criteria in the model for the drug are adverse events, loss of response i.e. progression to liver disease states (cirrhosis, PHT, ascites), SBD, LTx, or death.	Typically used for weeks to months, maybe long term if well tolerated. Ended if resolution or significant reduction of pruritus. Intolerance due to side effects or transfer to alternative therapies e.g., MRX or LTx if pruritus remains severe. The end-of-treatment criteria in the model for the drug are adverse events, loss of response i.e. progression to liver disease states (cirrhosis, PHT, ascites), SBD, LTx, or death.	Continued as long as it provides relief for symptomatic treatment of pruritus. Ended if inefficient in reducing pruritus after a trial period, development of side effects, or improvement in symptoms or replacement with alternative therapies. The end-of-treatment criteria in the model for the drug are adverse events, loss of response i.e. progression to liver disease states (cirrhosis, PHT, ascites), SBD, LTx, or death.
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No	No
Package size(s)	100 units	100 units	50 units

3.6 Cost-effectiveness of the comparator(s)

Since the comparators (UDCA, rifampicin, and cholestyramine) are old off-label medications, none of them have undergone assessment by the DMC.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The most relevant efficacy outcomes necessary to evaluate the effect of the Livmarli (maralixibat) are included in the Table below.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change in Serum Bile Acid from Week 18 to Week 22 in Serum Bile Acid Responders [ICONIC study]	Weeks: 18 and 22	The change from Week 18 to Week 22 in fasting sBA levels in participants who had a reduction in sBA ≥50% from baseline to Week 12 or Week 18 (MITT Population)	Evaluated by investigator
Change in Serum Bile Acid from baseline to Weeks: 18, 48 and 204 in Serum Bile Acid Responders [ICONIC study]	Baseline; week 18; week 48; week 204	The change from baseline to Weeks 18, 48 and 204 in levels of fasting total sBA measured in the ITT population.	Evaluated by investigator
Itch Reported Outcomes (ItchRO) [ICONIC study]	At several timepoints	Pruritus was assessed each day, in the morning and evening, using the ItchRO scales. Average daily ItchRO score was calculated as the mean of the morning and the evening ItchRO scores.	The ItchRO assessment was completed using an electronic diary (eDiary). Caregivers and participants (where age appropriate) were required to complete ≥10 eDiary reports during each of the 2 Weeks of the screening period. The patient-rated ItchRO (ItchRO [Pt]) was completed independently by participants aged ≥9 years and with caregiver assistance for participants aged 5–8 years. ItchRO (Pt) was not assessed in participants below 5 years of age.
Clinician Scratch Scale (CSS) [ICONIC study]	At several timepoints	Pruritus assessment is focused on scratching and visible damage to the skin as a result of scratching as observed by the physician.	Evaluated by investigator
Change in pruritus levels measured by ItchRO [Obs] Weekly Average Morning Severity Score [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change from baseline to Weeks 18, 48 and 204, and from Week 18 to Week 22 in pruritus as measured by ItchRO (Obs) in the ITT population.	See details under ItchRO outcome measure

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change in pruritus levels measured by ItchRO [Pt] Weekly Average Morning Severity Score [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change from baseline to Weeks 18, 48 and 204, and from Week 18 to Week 22 in pruritus as measured by ItchRO (Pt) in the ITT population.	See details under ItchRO outcome measure
Change in pruritus levels measured by CSS Score [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change from baseline to Weeks 18, 48 and 204, and from Week 18 to Week 22 in pruritus as measured by CSS in the ITT population.	Evaluated by investigator
Clinician Xanthoma Scale (CXS)		Used to assess the number of xanthomas present and the degree to which xanthomas interfere or limit activities [59].	Evaluated by investigator
Change in xanthomas, as measured by CXS score [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change from baseline to Weeks 18, 48 and 204, and from Week 18 to Week 22 in pruritus as measured by CXS in the ITT population.	Evaluated by investigator
Change in PedsQL Core [Parent] scale [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	The PedsQL is a questionnaire representing up to 45 items designed to assess health-HRQoL in infants, children, and adolescents across four functional domains: physical, emotional, social, and educational [60]. Each item has five levels (ranging from 0 to 4), with a higher PedsQL score indicating a better quality of life than a lower score. The change in the quality of life is measured at different time points in the ITT population using the PedsQL Core (Parent) scale.	The PedsQL can be completed by children and young people, with versions available for those aged 5-7, 8-12, and 13-18. However, in the ICONIC study, a parent-rated version was used. Per tool instructions, items were reverse scored and linearly transformed to a 0–100 scale, so that higher scores indicate better HRQoL. To reverse the score, the 0–4 scale items are transformed to 0–100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0. Scale scores were computed as the sum of the total number of items divided by the number of items answered.
Change in PedsQL Multidimensional Fatigue Scale [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	The PedsQL Multidimensional Fatigue Scale was used for fatigue assessment [61] and is composed of items across three subscales: general fatigue, sleep/rest	A parent-rated version of the PedsQL Multidimensional Fatigue Scale was employed in the ICONIC study.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		fatigue, and mental fatigue. In the ICONIC trial, the Multidimensional Fatigue Scale score was determined using all items of the PedsQL Multidimensional Fatigue Scale. The change in fatigue is measured at different time points in the ITT population using the PedsQL Multidimensional Fatigue scale.	
Change in body height and weight [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change in growth was measured at different time points in the ITT population by height and weight Z-scores.	Evaluated by investigator
Change in other biochemical markers of cholestasis [ICONIC study]	Baseline; weeks: 18, 22, 48, 204	Change in the total cholesterol levels and LDL cholesterol, and healthy bile acid synthesis i.e., 7α-C4 (a marker of healthy/non-cholestatic bile acid synthesis [62] and FGF-19. The biochemical markers of cholestasis were measured at different time points in the ITT population.	Evaluated by investigator
Event-free survival (EFS) [GALA cohort comparison study]	Time to event Follow-up time: 6 years	Event free survival or EFS is calculated as the number of days from baseline to the date of the first clinical event (with an event being defined as LTx, liver decompensation event i.e., variceal bleeding or ascites, SBD, or all-cause death).	Evaluated by investigator

3.7.2 Validity of outcomes

Elevated sBA levels are a key biological marker in ALGS and play a central role in cholestasis and related symptoms. Although the exact link between sBA levels and pruritus is not fully understood [63], clinicians use sBA as a pharmacodynamic biomarker to monitor treatment response. In the ICONIC trial, sBA levels were measured using validated liquid chromatography–mass spectrometry in a certified lab. A reduction of ≥50% in sBA was used to define treatment responders, while a ≥20% reduction was considered the minimal clinically relevant improvement.

The ItchRO scale was specifically developed and validated for use in pediatric cholestatic conditions, including Alagille syndrome, through cognitive debriefing with affected families [64]. ItchRO includes both observer-reported (ItchRO[Obs]) and patient-reported (ItchRO[Pt]) components, each using a 5-point ordinal scale ranging from 0 (“not itchy at all”) to 4 (“extremely itchy”) [65]. Validation of the ItchRO scale was supported by its consistent correlation with clinician-rated measures such as the CSS, and its responsiveness to treatment effects in clinical trials. Further psychometric validation was conducted using pooled data from three studies (IMAGO, INDIGO, and an observational study), as presented in the [66]Shire EASL poster. This analysis confirmed the scale’s test–retest reliability, known-groups validity, and responsiveness. ItchRO scores were shown to significantly differentiate between clinical severity groups and were consistent over time, with intraclass correlation coefficients supporting reliability. A ≥1-point reduction in ItchRO score was defined as the minimal clinically relevant difference, reflecting meaningful improvement in pruritus severity.

The CSS was validated for use in ALGS through its consistent application in the ICONIC study and related trials, where it demonstrated strong clinical relevance and alignment with patient-reported outcomes. The CSS is a clinician-rated, 5-point ordinal scale used to assess pruritus severity based on observable scratching behavior and skin damage. The scale ranges from 0 (no scratching), 1 (rubbing or mild scratching when undistracted), 2 (active scratching without abrasions), 3 (abrasions evident), to 4 (cutaneous mutilation, hemorrhage, and scarring) [17, 67].

The CXS was validated for use in ALGS through its application in the ICONIC study, where it demonstrated clinical relevance and sensitivity to treatment-related changes. The CXS is a clinician-rated, 5-point ordinal scale used to assess both the number and functional impact of xanthomas. The scale ranges from 0 (no xanthomas), 1 (fewer than 20 scattered lesions), 2 (more than 20 lesions not interfering with activity), 3 (lesions causing distortion of face or extremities), to 4 (xanthomas interfering with function, such as hand use or walking) [17]. Scores of 1 to 4 are categorized as minimal, moderate, disfiguring, and disabling, respectively [59]. A ≥1-point reduction in CXS was considered the minimal clinically relevant difference, reflecting meaningful improvement in disease burden.

HRQoL is assessed using the PedsQL, a validated tool that assesses physical, emotional, social, and educational domains in children, along with the PedsQL Multidimensional Fatigue Scale, which measures general, sleep/rest, and mental fatigue [60, 61]. The Scores are linearly transformed to a 0–100 scale, with higher scores indicating better

HRQoL. Improvements of +9 to +20 points were observed in total and fatigue scores, exceeding the threshold for clinical relevance.

The EFS endpoint was specifically validated for the ALGS population through a robust process that combined clinical consensus, harmonized real-world data, and advanced statistical modeling. EFS was defined as the time to the first occurrence of one of the following clinically significant events: liver transplantation, biliary diversion surgery, a decompensation event (such as ascites requiring treatment or variceal bleeding), or death – clinical important outcomes based on natural history. This composite endpoint was selected by the GALA Study Group to capture the most critical markers of disease progression in ALGS [12] [43]. A multidisciplinary team led the validation effort: biostatisticians, under the leadership of Dr. Bettina Hansen, developed and executed the statistical framework, while clinicians and hepatologists from the GALA consortium defined the endpoint and ensured its clinical relevance. A formal minimal clinically important difference was not predefined.

4. Health economic analysis

A cost-utility analysis was conducted using a Danish adaptation of an Excel-based cost-effectiveness model originally developed for NICE in the UK. This analysis focused on maralixibat in ALGS, utilizing clinically meaningful health states that capture the progressive and debilitating nature of the condition. The primary benefit of maralixibat is reflected in the delayed time to progression to progressive stages of liver disease and liver transplantation, which are associated with long-term costs and an increased risk of acute mortality. The comparator for the analysis is the standard of care, consisting of off-label anti-pruritic medication, which is linked to low rates of response. Maralixibat is indicated for the treatment of cholestatic pruritus in ALGS in patients two months or older. 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 authorization.

4.1 Model structure

The chosen cycle length is 12 Weeks, a decision supported by insights from a clinical expert (refer Appendix M) and the discontinuation recommendation outlined in the SmPC [21] for cases of non-response. The SmPC for MRX states that 'alternative treatment should be considered in patients for whom no treatment benefit can be established following 3 months of continuous daily treatment with maralixibat'. The probability of discontinuing treatment with MRX is equivalent to the proportion of people who had stopped maralixibat because of adverse events in the initial 18-Week pre-randomized phase of ICONIC. Although the ICONIC study provided clinical data over a longer duration, 12-Week results were utilized to prevent bias in estimating maralixibat's efficacy, given the study's design involving a RWP preceding long-term exposure. However, a scenario incorporating long-term data was developed based on guidance from a clinical expert (Appendix K). This 12-Week cycle length was selected to comprehensively capture the 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. Please refer to Figure 5 for an illustration of the model's structure.

Figure 5 Model schematic

Abbreviations: LTx: liver transplantation

The model was constructed using Microsoft Excel and aims to delineate the variances in costs and health outcomes between maralixibat and SoC. Disease progression is driven by patients' sBA response. Treatment with maralixibat is postulated to halt the progression of ALGS to severe stages of liver disease, such as cirrhosis, PHT, and ascites, potentially preventing the need for LTx. This outcome is expected as long as maralixibat effectively manages cholestatic pruritus or achieves a 50% reduction in sBA within 3 months, with patients continuing the treatment. Cholestasis, characterized by decreased bile flow leading to hepatocyte bile acid retention, is central to the disease mechanism. Protective adaptive transport mechanisms enable the elimination of bile acids from hepatocytes, subsequently elevating sBA levels in the systemic circulation [3-5]. An sBA response was therefore assumed to lead to a corresponding response in pruritus, [68, 69] as supported by the clinical expert in the Nordics (Appendix M). This approach is commonly used in the Nordics, whereas scales measuring ITCH are less common in clinical practice. sBA levels are considered a key measure of the physiological response to treatment, alongside feedback on the quality of life for patients and caregivers. Once progressed to 'unresponsive to medication', patients' liver disease progresses until indicated for a LTx. 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 (Appendix M) [8, 12]. Progression to these states is well-documented in the literature [12], with associated deteriorating health outcomes culminating in LTx, as ascites and PHT are complications of cirrhosis and are major contributors to mortality in end-stage liver disease [70, 71].

While HCC is mentioned in the literature as a potential outcome of ALGS, limited documentation exists, and insufficient data were found to parameterize this transition [72]. A portion of patients may require re-transplantation, assumed to occur once in the subsequent cycle following their initial liver transplantation [73].

4.2 Model features

The Table below summarizes the key inputs and assumptions used in the economic model. The approach adopted adheres to DMC guidelines, with a Danish restricted societal perspective considered, and dynamic discount rates applied.

Table 7 Features of the Economic Model

Model features	Description	Justification
Patient population	ALGS patients [redacted]	In line with MRX marketing authorization
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	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. [redacted]

Model features	Description	Justification
		[redacted]
Cycle length	84 days	[redacted]
Half-cycle correction	Yes	
Discount rate	dynamic discount rates are applied. Time Rate 1-35 3,5% per year 36-70 2,5% per year 71+ 1,5% per year	Method handbook section 6.9 who reference fm.dk https://fm.dk/nyheder/nyhedsarkiv/2023/juni/ny-vejledning-i-samfundsoekonomiske-konsekvensvurderinger/
Intervention	MRX	
Comparator(s)	SoC	[redacted]
Outcomes	OS, PFS	The model includes: • Change in sBA levels and corresponding pruritus • Time to liver event and progression of liver disease (transplant, cirrhosis, ascites and PHT) • Adverse events • Health-related quality of life • Overall survival • Measures of faltering growth • Number of patients requiring LTx 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 [74], and time to surgery/pre-transplant survival is based on the literature.

5. Overview of literature

5.1 Literature used for clinical assessment

The Clinical SLR reviewed published studies on the efficacy and safety of maralixibat and relevant comparators in ALGS, including both randomized and non-randomized trials (RCTs). While a full description is available in Appendix H, the key literature identified through this review is summarized in the table below and was used to inform the assessment of clinical outcomes.

Table 8 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Gonzales et al. 2021 [17] Full paper: ICONIC (LUM001-304) study evaluating maralixibat in children with ALGS.	ICONIC	NCT02160782	Start: 30/06/2014 Completion: 23/06/2021	Maralixibat
Hansen et al 2024 Hansen [48] Full paper: Event-free survival of maralixibat-treated patients with Alagille syndrome compared to a real-world cohort from GALA	GALA comparison study	NA	Start: NA Completion: NA	Maralixibat vs no treatment (natural history) (Concomitant medications used) for ALGS

Abbreviations: NA: Not applicable.

5.2 Literature used for the assessment of health-related quality of life

The HRQoL SLR aimed to identify utility values for use in the economic model for ALGS treatments. While it summarized existing evidence, it did not yield sufficient or relevant data for key model inputs. Therefore, utility values and other health economic inputs were sourced from a broader, targeted literature search that identified high-quality studies specific to the ALGS population and treatment context. The relevant literature used for HRQoL assessment is listed in the accompanying table.

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10 "Documentation of health-related quality of life [HRQOL]")

Reference (Full citation incl. reference number)	Health state/Disutility	Utility value	Reference to where in the application the data is described/applied
Vignette, 2022 [75] [74]	Responsive to medication	XXXXXXXXXXXX	The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.
	Unresponsive to medication	XXXXXXXXXXXX	
Sullivan, 2011 [76] (Sullivan, P.W., et al., Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making, 2011. 31(6): p. 800-4.)	Cirrhosis	XXXXXXXXXXXX	Sum of unresponsive utility and 'liver disease' disutility (–0.04) from Sullivan et al [76]. The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.
Sullivan, 2011 [76] (Sullivan, P.W., et al., Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making, 2011. 31(6): p. 800-4.)	PHT	XXXXXXXXXXXX	Sum of cirrhosis utility and 'liver disease' disutility (–0.04) from Sullivan et al [76]. The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.
Sullivan, 2011 [76] (Sullivan, P.W., et al., Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making, 2011. 31(6): p. 800-4.)	Ascites	XXXXXXXXXXXX	Sum of PHT utility and 'gastrointestinal disorder' disutility (–0.05) from Sullivan et al [76]. The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.

NICE, 2021 [75] (NICE, HST evaluation report: Odevixibat for progressive familial intrahepatic cholestasis [ID1570] 2021.)	Post-SBD	XXXXXXXXXXXX	SBD utility multiplied by the stoma multiplier (0.72) used in HST17 [75]. The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.
Vignette, 2022 [75] [74]	LTx	XXXXXXXXXXXX	Vignette study, weighted average of progressive cholestasis and LTx rejection (see Vignette, 2022 [75] [74]) . The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.
Vignette, 2022 [75] [74]	Post-LTx	XXXXXXXXXXXX	Vignette study, successful LTx (see Vignette, 2022 [75] [74]). The data is described in Section 10, "Documentation of health-related quality of life (HRQoL)," of the document.

5.3 Literature used for inputs for the health economic model

The SLR explored additional topics beyond clinical and HRQoL aspects, including cost-effectiveness, resource use, epidemiology, and the broader burden of ALGS. From this, three relevant studies were included in the health economic model. A targeted search also identified six high-quality publications specific to the ALGS population and treatment context, which were added as model inputs. Together, these nine references form the evidence base for the health economic analysis, summarized in Table 12.

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Variable	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Kamath et al [12] (Kamath, B.M., et al., Outcomes of Childhood Cholestasis in Alagille Syndrome: Results of a Multicenter Observational Study. Hepatol Commun, 2020. 4(3): p. 387-398.)	Responsive to medication	XXXXXXXXXXXX	SLR	Section 8
Vandriel et al [6] (Vandriel, S.M., et al., Natural history of liver disease in a large international cohort of children with Alagille syndrome: Results from the GALA study. Hepatology, 2023. 77(2): p. 512-529.)	Unresponsive to medication	XXXXXXXXXXXX	SLR	Section 8

Reference (Full citation incl. reference number)	Variable	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Emerick et al [7](Emerick, K.M., et al., Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. Hepatology, 1999. 29(3): p. 822-9.)	LTx	XXXXXXXXXXXX	SLR	Section 8
GALA cohort comparison study [28] (Mirum, Long-Term Outcomes of Long-Term Maralixibat Treatment in Patients with Alagille Syndrome Compared with an External Control Cohort from the Global ALagille Alliance (GALA) Clinical Research Database. 2021.)	Responsive to medication	XXXXXXXXXXXX	Targeted literature review	Section 8
D'Amico et al [77] (D'Amico, G., G. Garcia-Tsao, and L. Pagliaro, Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol, 2006. 44(1): p. 217-31.)	Cirrhosis (compensated)	XXXXXXXXXXXX	Targeted literature review	Section 8
Santambrogio et al [78] (Santambrogio, R., et al., Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford), 2013. 15(1): p. 78-84.)	PHT	XXXXXXXXXXXX	Targeted literature review	Section 8
Tonon et al [79](Tonon, M., et al., Outcomes and Mortality of Grade 1 Ascites and Recurrent Ascites in Patients With Cirrhosis. Clin Gastroenterol Hepatol, 2021. 19(2): p. 358-366 e8.)	Ascites	XXXXXXXXXXXX	Targeted literature review	Section 8
Hou et al [80](Hou, Y., et al., Survival and Complication of Liver Transplantation in Infants: A Systematic Review and Meta-Analysis. Front Pediatr, 2021. 9: p. 628771.)	Post-LTx (0-18 years)	XXXXXXXXXXXX XXXXXXXXXXXX	Targeted literature review	Section 8

Reference (Full citation incl. reference number)	Variable	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Baumann [81] (Baumann, U., et al., Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study. Pediatrics, 2022. 150(4).)	Post-LTx (18 years +)	XXXXXXXXXXXX	Targeted literature review	Section 8

6. Efficacy

6.1 Efficacy of maralixibat compared to placebo for patients with ALGS

6.1.1 Relevant studies

To support this reimbursement submission, key efficacy data come from the pivotal Phase II ICONIC trial (LUM001-304), published in The Lancet [17], which evaluated maralixibat in ALGS patients with cholestatic pruritus up to Week 204. Additional evidence includes a natural history comparison from the GALA database, published in Hepatology [48], showing improved event-free survival in maralixibat-treated patients. While interim data from the MRX-801 infant study were submitted to EMA, they are not included here. Supporting studies LUM001-301, LUM001-302, LUM001-303, and LUM001-305 are also referenced in Appendix O.

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (ref)	**Study design**	**Study duration**	**Patient population**	**Intervention**	Comparator	**Outcomes and follow-up time**
ICONIC, NCT02160782 Gonzales et al. 2021 [17]	Phase 2b RCT + OLE	204 weeks	ALGS patients naïve to maralixibat treatment	Maralixibat (≥380 µg/kg/day, ≥760 µg/kg/day)	Placebo	Change in sBA levels, change in pruritus and xanthomas, change in heigh and weight, and evaluation of other biomarkers for hepatic function and cholestasis.
GALA Cohort Comparison Study Hansen et al. 2022 [48]	ITC	6 years	ALGS patients treated with MRX vs an harmonized, aligned, natural history external control cohort from the GALA registry.	Maralixibat (≥380 µg/kg/day, ≥760 µg/kg/day)	SoC (off label therapies)	Liver-related event-free survival (SBD, LTx, decompensation event, or death).

Abbreviations: RCT: randomized controlled trial; OLE: Open label extension; ITC: Indirect treatment comparison; ALGS: Alagille syndrome; sBA: serum bile acids; QoL: quality of life; SBD: surgical biliary diversion; LTx: liver transplantation.

6.1.2 Comparability of studies

The GALA-MRX comparative analysis included two different sources of data: the maralixibat clinical trials (including ITCH/IMAGINE II, IMAGO/IMAGINE, and ICONIC with open-label follow-up) and the GALA registry. These sources differed in study design, patient selection, outcome measures, and data quality. In terms of study design, the maralixibat studies were prospective, interventional clinical trials with tightly controlled protocols and standardized follow-up schedules. They included short-term placebo-controlled periods and long-term open-label extensions of up to six years. Conversely, the GALA registry was a retrospective, observational study reflecting real-world practice [6]. It captured long-term clinical outcomes (i.e., NLS rates, global patients and graft survival following LTx) from a total of 1,543 children with ALGS between the ages of 12 months to 18 years across 29 countries, but with variable timing and consistency in data collection.

Regarding population selection, the maralixibat trials enrolled children aged 1–18 years who had significant cholestasis and pruritus, defined by elevated serum bile acids (sBA >3× upper limit of normal) and ItchRO(Obs) scores greater than 2. In contrast, GALA participants were included based on clinical diagnosis and standard of care. To make the cohorts comparable, a subset of 469 GALA patients was selected to match the maralixibat trial inclusion criteria as closely as possible.

6.1.2.1 Comparability of patients across studies

6.1.2.1.1 ICONIC study

The ICONIC study included children aged 1 to 15 years with ALGS, with a median age of 5 years and 61% male participants [17] [82]. Conducted across 10 clinical sites in 7 countries, most patients were recruited from the EU, with around 60% enrolled in Australia and France. All participants had confirmed *JAGGED1* mutations and chronic cholestasis, and 25.8% had a family history of ALGS. Growth delays were evident, with mean height and weight z-scores of -1.7 [82]. Baseline sBA and liver function markers were elevated, and pruritus severity was high, with mean ItchRO(Obs) scores of 2.91 and Clinician Scratch Scale scores of 3.3. Nearly half of the patients (n=14) presented with xanthomas [17] [82]. Overall, baseline demographics and clinical characteristics were comparable between randomized groups.

Table 12 Patient demographics and baseline disease characteristics in the ICONIC study

Parameter/ Category	Baseline all participants MRX (n=31)	Baseline MRX-MRX-MRX group MRX (n=13)	Baseline MRX-PBO-MRX group Placebo (n=16)
Age, in years [a]			
Mean (SD)	5.4 (4.2)	5.5 (5.0)	5.8 (3.7)
Median (IQR)	5 (2.0 – 7.0)	4 (2.0 – 7.0)	5 (3.5 – 8.0)
Sex, n (%)			

Male	19 (61)	9 (69)	10 (63)
Genotyped mutation within JAGGED1	31 (100)	13 (100)	16 (100)
Yes	31 (100)	13 (100)	16 (100)
ALGS Family History, n (%)			
Yes	8 (26)	1 (8)	7 (44)
Presence of bile duct paucity, n (%)			
Yes	18 (58)	4 (31)	12 (75)
Additional criteria/features of ALGS[a], n (%)			
Chronic cholestasis	31 (100)	13 (100)	16 (100)
Heart disease	29 (94)	12 (92)	15 (94)
Renal abnormalities	12 (39)	4 (31)	8 (50)
Vascular abnormalities	5 (16)	1 (8)	3 (19)
Bone abnormalities	17 (55)	7 (54)	9 (56)
Ocular abnormalities	17 (55)	7 (54)	8 (50)
Characteristic facial features	29 (94)	12 (92)	15 (94)
ItchRO (Obs)[b] Weekly Morning Average Severity score			
Mean (SD)	2.9 (0.5)	2.9 (0.5)	2.9 (0.6)
Median (IQR)	3.0 (2.4–3.3)	2.8 (2.4–3.3)	3.0 (2.5–3.3)
Clinician Scratch Scale Score[c]			
Mean (SD)	3.3 (0.9)	0.3 (1.1)	3.5 (0.7)
Median (IQR)	4.0 (3.0–4.0)	3.0 (3.0–4.0)	4.0 (3.0–4.0)
Clinician Xanthoma Scale Scored			
Mean (SD)	0.9 (1.3)	1. 0 (1.3)	0.9 (1.3)
Participants presenting with xanthomas, n (%)			
Yes	14 (45)	7 (54)	7 (44)
Total PedsQL Parent Scale score			
Mean (SD)	61 (17.0)	65 (13.8)	56 (17.8)
Serum bile acids (µmol/L)			
Mean (SD)	283 (211)	318 (234)	250 (197)
Median (IQR)	276 (79–479)	335 (79–412)	196 (79–460)
Alkaline phosphatase (U/L)			

Mean (SD)	601 (275)	638 (386)	585 (169)
Alanine Aminotransferase (U/L)			
Mean (SD)	181 (109)	218 (150)	147 (55)
Aspartate Aminotransferase (U/L)			
Mean (SD)	168 (76)	172 (76)	147 (61)
Gamma Glutamyl Transferase (U/L)			
Mean (SD)	508 (389)	614 (482)	404 (300)
Total bilirubin (µmol/L)			
Mean (SD)	104.2 (98.9);	111.5 (112.4)	82.6 (72.9)
Median (IQR)	78.7 (23.9–148.8)	78.7 (13.7–152.2)	48.7 (26.5–135.9)
Direct bilirubin (µmol/L)			
Mean (SD)	78.2 (62.7)	80.2 (64.9)	69.0 (61.4)
Median (IQR)	70.1 (13.7–138.5)	70.1 (13.7–138.5)	46.2 (12.8–123.1)
Cholesterol (mmol/L)			
Mean (SD)	13.3 (10.9)	14.4 (14.3)	11.9 (8.2)
Median (IQR)	8.5 (7.3–14.1)	8.4 (7.6–11.6)	9.1 (7.3–12.6)
7Ac4 (nmol/L)			
Mean (SD)	25.8 (36.6)	36.9 (49.7)	16.3 (21.8)
Median (IQR)	11.3 (4.5–31.5)	19.0 (10.0–31.5)	7.3 (3.5–19.3)
FGF-19 (pmol/L)			
Mean (SD)	27.4 (60.1)	30.5 (69.4)	26.1 (55.5)
Median (IQR)	8.4 (4.0–17.3)	9.4 (4.0–17.3)	7.7 (4.3–21.4)

a Subjects reporting more than one clinical criteria/feature for ALGS are counted in each category reported. b ItchRO average scores are based on the 7 days prior to the baseline visit date. Caregivers for all participants complete the ItchRO (Obs). c The clinician scratch scale uses a 5-point scale, where 0 = none, 1 = rubbing or mild scratching when undistracted, 2 = active scratching without evident skin abrasions, 3 = abrasion evident, 4 = cutaneous mutilation, hemorrhage, and scarring evident. d The clinician xanthoma scale uses a 5-point scale, where 0 = none, 1 = minimal, 2 = moderate, 3 = disfiguring, 4 = disabling. Abbreviations: MRX: maralixibat; SD: standard deviation; CSS: Clinician Scratch Scale; FGF-19: fibroblast growth factor-19; GGT: gamma–glutamyl transferase; IQR: Interquartile range, ItchRO(Obs): Itch Reported Outcome (Observer); sBA: serum bile acid; 7α-C4: 7α-hydroxy-4-cholesten-3-one. Source: Gonzales et al. 2021 [17], Livmarli (maralixibat) EPAR [82]

Baseline characteristics generally demonstrated balance between the maralixibat cohort and GALA control group, with no statistically significant imbalance in the baseline covariates. Importantly, bilirubin, GGT, and ALT were well balanced. Median sBA was higher in the maralixibat cohort; however, sBA data were limited in the GALA clinical research database (approximately 85% do not have sBA measures) since sBA are not sampled regularly on a clinical basis, often only at a single time point in some patients (at entry into the database), and not longitudinally.

6.1.2.1.2 GALA cohort comparison study

The GALA Cohort Comparison Study [48] showed that baseline characteristics were well-balanced between the maralixibat and GALA control groups, with no statistically significant differences in key covariates. While median sBA levels were higher in the maralixibat group, sBA data were limited in the GALA registry due to inconsistent clinical sampling, often recorded only once per patient and not longitudinally. Importantly, bilirubin, GGT, and ALT were well balanced. Median sBA was higher in the maralixibat cohort; however, sBA data were limited in the GALA clinical research database (approximately 85% do not have sBA measures) since sBA are not sampled regularly on a clinical basis, often only at a single time point in some patients (at entry into the database), and not longitudinally.

Table 13 Patient baseline demographics and characteristics in the maralixibat and GALA control groups of the GALA Cohort Comparison Study

Parameter/ Category	Maralixibat cohort (N=84)	GALA control group (N=469)	p-value
Sex, n (%)			
Male	49 (58.3)	274 (58.4)	0.99
Female	35 (41.7)	195 (41.6)	
Age at baseline, in years			
Median (Q1–Q3)	5.6 (2.7–9.9)	4.3 (2.2–9.6)	0.078
Year of Birth			
Median (Q1–Q3)	2009 (2005–2012)	2009 (2004–2013)	0.25
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)	
Mutation, n (%)			
JAGGED1	81 (97.6)	330 (95.1)	0.55a
NOTCH2	2 (24)	17 (4.9)	
Other/unknown	1 (0.2)	37 (9.6)	
Total bilirubin, mg/dL			
Median (Q1–Q3)	3.15 (1.00–8.15)	1.99 (0.60–11.52)	0.39
< 2	37 (44.0)	235 (50.1)	0.31
≥ 2	47 (56.0)	234 (49.9)	
GGT, log10×ULN			
Median (Q1–Q3)	1.25 (0.93–1.44)	1.24 (0.93–1.52)	0.58
GGT, ×ULN			
< 3	3 (3.6)	6 (1.3)	0.14[a]
≥ 3	81 (96.4)	463 (98.7)	

ALT, U/L			
Median (Q1–Q3)	145 (94–207)	130 (75–203)	0.12
sBA[b] in µmol/L			
Median (Q1–Q3)	200 (81–371)	125 (39–260)	0.003

All data are n (%) unless otherwise stated. a-Due to >20% of the cells having expected counts <5, chi-square results may be invalid, and the Fisher exact test was used instead. b-Baseline sBA data were available for 73 patients in the GALA control cohort. Approximately 85% of the sBA values were not available in the GALA clinical research database as frequent sBA measurement is not part of clinical practice. Abbreviations: ALT: alanine aminotransferase; GALA: Global ALagille Alliance; GGT: gamma-glutamyl transferase; Q1: first quartile; Q3: third quartile; sBA: serum bile acid; ULN: upper limit of normal. Adapted from Hansen BE et al. Hepatology 2024 [48].

Table 14 Distribution of First Event in the Maralixibat Cohort and GALA Control Group

	Maralixibat cohort (N=84)	GALA Control Group (N=469)
Number of Events	21	163
Liver transplantation	10	110
Surgical Biliary diversion	4	33 [a]
Liver decompensation	3	5
Death	4 [b]	15

a Includes 1 patients with an event of Kasai procedure. b Death information was collected from public records (deaths occurred at 2, 7, 9 months and 3.5 years after study discontinuation), no further information was available. Source: Livmarli (maralixibat) EPAR [82].

6.1.3 Comparability of the study population with Danish patients eligible for treatment

No known data exists which would give reason to distinguish between expected efficacy of MRX amongst newly diagnosed ALGS patients in Denmark vs. the available clinical efficacy data from the ICONIC trial and the GALA-MRX comparison study [redacted], however no gender ratio has been provided by the expert. The patients' characteristics in the relevant Danish population and in the health economic model are presented in Table below.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age at treatment initiation	[redacted]	[redacted]
Age	8.5 years (Appendix L)	
Gender	% Female: 50%; % Male: 50% (Appendix L)	% Female: 38.7% [17]

Patient weight	ALGS patients have considerably lower body weight compared with the general population, with real-world data indicating ALGS patients are typically around the 5th percentile for weight [83].	5th percentile weight band has been used – (Danish Weight curves - vækstkurver.dk) as it accounts for low weight typical in ALGS, ensures accurate treatment modeling, and captures cost-effectiveness for these patients while improving predictions for this population.

6.1.4 Efficacy – results per ICONIC study

The ICONIC trial was an international, multicenter, phase 2b placebo-controlled, double-blind, randomized drug-withdrawal study with a long-term open-label (OL) extension in children with ALGS designed to evaluate the safety and efficacy of maralixibat [17]. The objectives of the study are to evaluate the long-term efficacy and safety and tolerability of maralixibat, its effects on sBA levels, on biochemical markers of cholestasis and liver disease, and on pruritus [17].

6.1.4.1 Summary of the main efficacy outcomes

The primary analysis included 15 patients (mITT; 5 on MRX and 10 on PBO). The rest of the efficacy analysis was conducted in 29 patients during the RWP (ITT; 13 on MRX and 16 on PBO), and 23 patients during the long-term extension phase (ITT, 23 on MRX). However, analyses at Week 204 included 15 patients (ITT; 15 on MRX). The safety set included 31 patients.

Concomitant treatments used for pruritus

Most patients (94%) were using concomitant pruritus treatment at baseline. The most common anti-pruritus treatments used by patients were ursodeoxycholic acid (81%) and rifampicin (74%).

Table 16 Concomitant treatments used for pruritus in the ICONIC trial

Parameter/ Category	Baseline all participants MRX (n=31)	Baseline MRX-MRX-MRX group MRX (n=13)	Baseline MRX-PBO-MRX group Placebo (n=16)
History of receiving treatment for pruritus, n (%)			
Any medication, n (%)	29 (94)	12 (92)	15 (94)
Ursodeoxycholic acid	25 (81)	10 (77)	13 (81)
Rifampicin	23 (74)	10 (77)	13 (81)
Naltrexone	1 (3)	1 (8)	0
Sertraline	1 (3)	0	1 (6)

Abbreviations: W: Week; RWP: randomized withdrawal phase. Source: Gonzales et al 2021[17], Livmarli (maralixibat) EPAR [82].

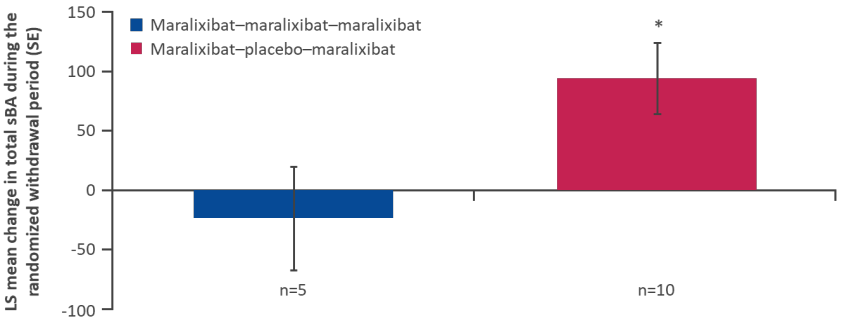
Please refer to Appendix A "ICONIC Study" for further details on patient flow, overview of the trial design and statistical analysis.

6.1.4.1.1 Serum bile acid endpoints

Change in serum bile acid levels (Primary Efficacy Endpoint – mITT Population)

The primary endpoint was evaluated per protocol in the mITT population i.e. participants achieving an sBA reduction of at least 50% from baseline to Week 12 or Week 18, i.e., 15 patients out of the 31 patients enrolled. In this primary endpoint assessed in the mITT population, randomization blocks assigned by the study site led to more sBA responders being assigned to placebo (n=10) than maralixibat (n=5). In the randomization phase (RWP), placebo-treated patients (N=10) experienced significant increases in sBA from Week 18 to Week 22 (mean increase 95.55 µmol/L, p=0.0086) while patients treated with maralixibat (N=5) had no change (mean decrease of 21.73 (43.125) µmol/L, p = 0.6234) (Appendix B). Thus, the primary endpoint was met with a statistically significant LS (SE) mean difference in sBA between maralixibat and placebo groups during the RWP (–117.28 µmol/L [52.828],p=0.0464; Appendix B; Figure below) [82].

Figure 6 Change in sBA (µmol/L) during the RWP (from Week 18 to Week 22) in the primary endpoint responder analysis (mITT)



LS Means and 95% Confidence Intervals from ANCOVA. Abbreviations: LS, least squares; PBO, placebo; sBA, serum bile acid; SE, standard error. Adapted from Gonzales E, et al. 2021 [17].

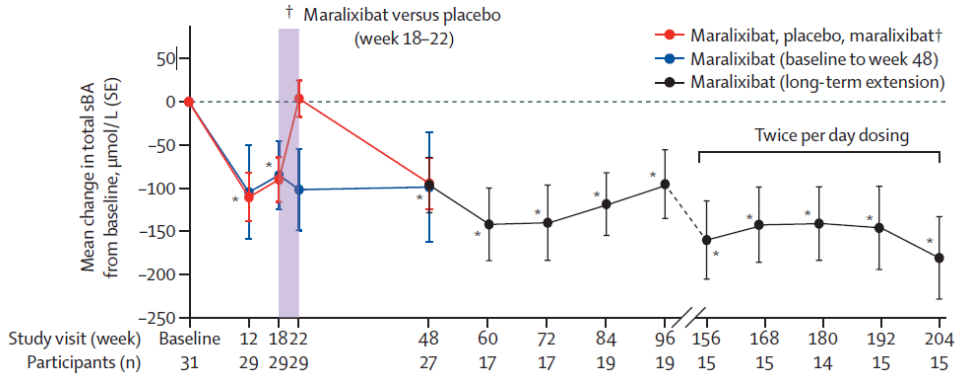
Change in serum bile acids over time (Prespecified Endpoint – ITT Population)

In the overall ITT Population (N=31 participants) there was a significant decrease in sBA levels from baseline up to Week 18 (-87.73 [22.280] µmol/L, p=0.0005, N=29). During the RWP, with all participants randomized to either placebo (N=16) or maralixibat (N=13), a significant reduction in sBA levels compared with placebo was also seen in the overall ITT population. At the end of the RWP, the participants receiving maralixibat (N=13) maintained the mean (SE) sBA reductions observed in the first 18 Weeks (-16.73 [30.412] µmol/L; p=0.5923, N=13), whereas those randomly assigned to placebo (N=16) had significant sBA increases to levels similar to that of baseline (mean increase 93.58 [33.219] µmol/L; p=0.0130, N=16) (see Appendix B). The LS mean difference between the two treatment groups was statistically significant (mean difference –113.95 µmol/L, 95%

CI –212.68 to –15.21, p=0.0254, Appendix B) [82]. Moreover, a significant reduction in sBA levels was also observed from baseline up to Week 48, after all patients had resumed maralixibat, (-96.44 [32.068] µmol/L, p=0.0058, N=27). Indeed, when the placebo group resumed treatment with maralixibat, at the end of the RWP, sBA levels fell back to the level previously observed with maralixibat [82].

These reductions were maintained in the 15 participants at Week 204 (vs baseline, –181, 95% CI –283 to –79; Figure below). After Week 100, 14 of 16 participants remaining in the study, who had sBA levels above the ULN (8 µmol/L) or pruritus (ItchRO (Obs) ≥1.5) increased maralixibat doses of 800 µg/kg/day (400µg/kg BID). Five of these patients had an additional reduction in sBA on the twice per day dosing [17].

Figure 7 Mean change from baseline in sBA from over time in the overall population (ITT)



*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 (red-shaded area), and the maralixibat treatment group (n=13) continued to receive maralixibat. Abbreviations: sBA, serum bile acid; SE, standard error. Adapted from Gonzales E, et al. 2021 [17].

6.1.4.1.2 Pruritus endpoints

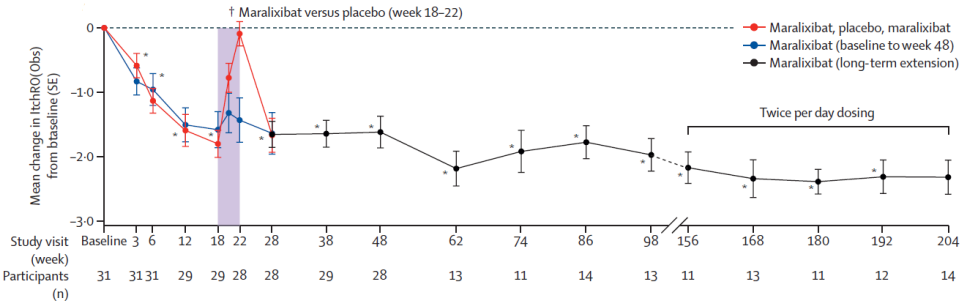
In the ICONIC trial, pruritus severity was assessed using ItchRO [Obs], ItchRO [Pt], and CSS scales.

Pruritus measured by ItchRO [Obs] Weekly Average Morning Severity Score (ITT Population)

At Week 18, a statistically significantly mean decrease (improvement) from baseline in ItchRO (Obs) was seen in the ITT population (–1.7, 95% CI –2.1 to –1.4; see Appendix B) reflecting an improvement in pruritus severity. At Week 22, in the ITT population, a statistically significant mean (SE) increase (worsening) from Week 18 in ItchRO (Obs) was seen in the placebo group (1.712 [0.2513], p-value <0.0001, N=16) with scores similar to those recorded at baseline, whereas the pruritus treatment effect was maintained in the group under maralixibat (0.201 [0.2180], p-value = 0.3754, N=12). The LS mean (SE) change in weakly mean morning ItchRO (Obs) score from Week 18 to Week 22 (RWP) differed significantly between the maralixibat and placebo groups (-1.483 [0.3103], p < 0.0001, prespecified pruritus endpoint – ITT population) [82].

After the RWP, all participants received maralixibat, and pruritus benefit was observed for participants including the ones who had been previously treated with placebo [17]. ItchRO (Obs) also improved significantly from baseline to Week 48 in the overall ITT population (–1·6, 95% CI –2·1 to –1·1) [17]. Moreover, maintenance of treatment effect on pruritus was also demonstrated in the 15 participants who continued to Week 204 (change from BL to Week 204: –2.3, 95% CI –2.9 to –1.7) [17].

Figure 8 Mean change from baseline in ItchRO [Obs] scores over time (up to Week 204) in the ITT population



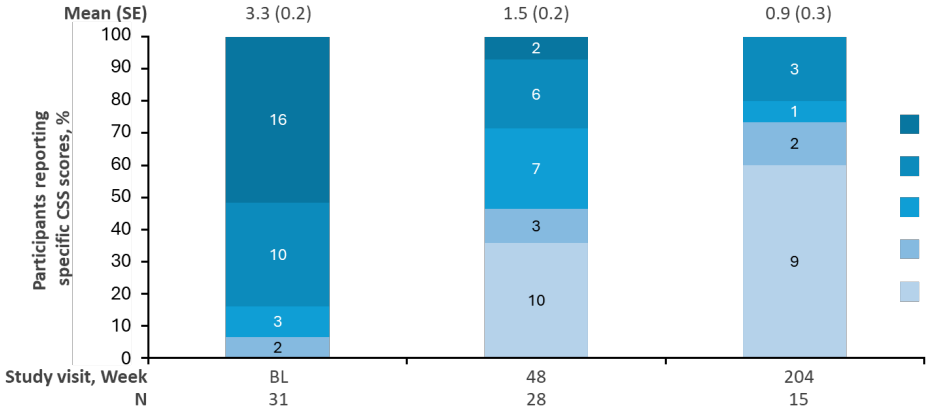
*95% CI excludes zero (compared with baseline, overall population (ITT)). †The maralixibat, placebo, maralixibat group (n=16) received placebo during the RWP (purple-shaded area), whereas the maralixibat treatment group (n=13) continued to receive maralixibat. Abbreviations: ItchRO: itch-reported outcome; SE: standard error. Adapted from Gonzales E, et al. 2021 [17].

In the patients (N=15) who continued to Week 204, the ItchRO(Obs) significantly decreased in the twice-per-day dosing compared to the once-per-day dosing period (–0·4, 95% CI –0·7 to –0·1) [17].

Pruritus measured by CSS scale

Changes in the Clinician Scratch Scale (CSS) score were in line with the changes in the ItchRO (Obs), with a significant improvement from baseline to Week 18 and Week 48 that was maintained to Week 204, and a clear separation between maralixibat-treated and placebo-treated groups during the RWP. At Week 18, a statistically significant mean decrease (improvement) from baseline in CSS scores was identified in the ITT population (–1.8, 95% CI –2.3; 1.2). At Week 22, a statistically significant increase (worsening) in mean change from Week 18 was identified in the placebo group (1.6, 95% CI 0.7; 2.4), whereas no difference at Week 22 from Week 18 in mean CSS was observed in the maralixibat group (0.4, 95% CI –0.4; 1.1). At the end of the RWP, CSS was significantly different between maralixibat and placebo group (mean difference –0·9 (–1·8 to –0·1)) (see Appendix B) [17]. Moreover, significant mean reductions from baseline in CSS were also maintained over time in the ITT population up to Week 204, indicating a sustained improvement in pruritus (Appendix B)[17].

Figure 9 CSS score over time (at baseline, and Weeks 48 and 204) in the ITT population



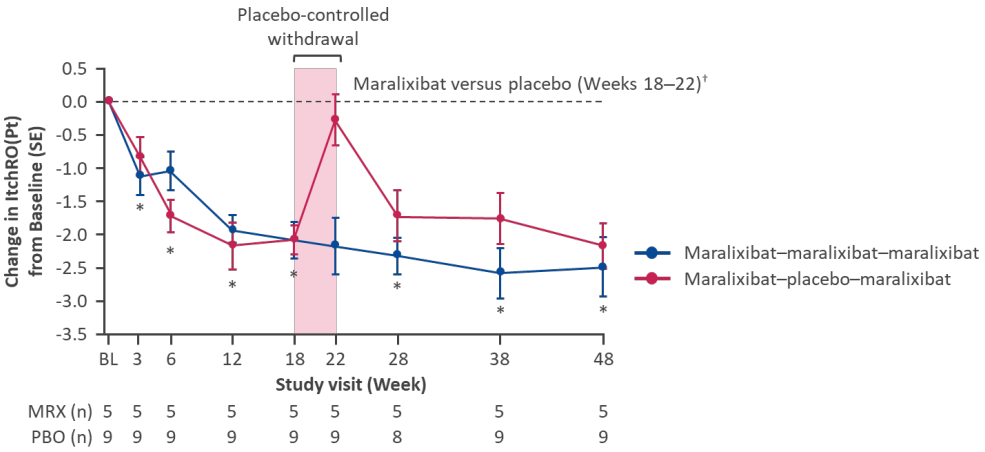
Numbers in the graph represent the numbers of participants reporting each CSS score. Abbreviations: CSS: clinician scratch scale; BL: baseline; SE: standard error. Adapted from Gonzales E, et al. 2021 [17].

At Week 18, 20 (69%) of 29 participants had low-rated to moderate-rated scores (0–2); this was also the case for 20 (71%) of 28 participants at Week 48, and 12 (80%) of 15 participants at Week 204.

Pruritus measured by ItchRO [Pt] Weekly morning average severity score

ItchRO (Pt) results were consistent with both ItchRO (Obs) and CSS, with significant improvement in pruritus severity from baseline to Week 18, during the RWP, from baseline to Week 48, and during the long-term extension phase. At Week 18, a statistically significant mean decrease (improvement) from baseline in ItchRO(Pt) Weekly average morning severity scores was identified in the ITT population (–2·1, 95% CI –2·6 to –1·5) [17].

Figure 10 Reductions in pruritus using patient-rated scores (ItchRO [Pt]) from Baseline to Week 48



*95% CI excludes zero (compared with BL, overall population). Pink shaded area indicated the RWP. †The MRX-PBO-MRX treatment group (n=16) received PBO during the RWP, whereas the MRX-MRX-MRX treatment group (n=13) continued to receive MRX. Abbreviations: BL: Baseline; ItchRO (Pt), Itch Reported outcomes (Patient);

MRX: maralixibat; PBO: placebo; RWP, SE: standard error. Adapted from Gonzales E, et al. 2021 (Supplemental) [17].

At the end of the RWP, a statistically significant increase (worsening) in mean change from Week 18 was identified in the placebo group (1.8, 95% CI 0.9 to 2.7), whereas no difference from Week 18 was observed in the maralixibat group (-0.1, 95% CI -1.4 to 1.2). The mean difference in ItchRO (Pt) score was significantly different between the two groups (mean difference –2·0, 95% CI –3·0 to –1·0) [17]. Moreover, at Week 48, when all participants were administered maralixibat, a statistically significant mean decrease (improvement) from baseline in ItchRO (Pt) scores was also observed (-2.3, 95% CI -2.8 to -1.7). Similar trends were observed over the long-term extension period (Appendix B) [17].

6.1.4.1.3 Evaluation of other biomarkers for hepatic function

Total and direct bilirubin levels over time

No clearly positive mean changes were observed for total and direct bilirubin from baseline to Weeks 18 and 48. However, in the 15 participants who continued to the long-term extension phase, mean levels of total and direct bilirubin decreased (improved) from baseline to Week 204, with direct bilirubin changing significantly (–19·6, 95% CI –37·6 to –1·7, see Appendix B) [17].

Alanine aminotransferase levels change over time

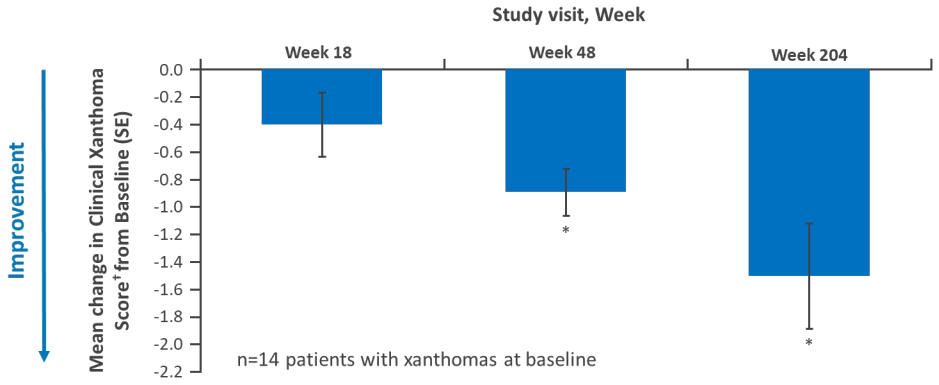
Overall, no clinically relevant changes were observed in alanine aminotransferase (ALT) levels [17]. During the RWP, mean ALT increased in the maralixibat-treated group (43, 95% CI 8 to 78; see Appendix B), however, participants with ALT elevations during the RWP experienced later ALT reductions while continuing maralixibat treatment. Over the whole cohort, there was little change in ALT for approximately the first 120 Weeks [17].

6.1.4.1.4 Evaluation of other clinical manifestations of cholestasis

Change in xanthomas as measured by CXS

In ICONIC, CXS score improved significantly from baseline to Weeks 18, 48 and 204 in patients who presented with xanthomas at baseline (N = 14) (Figure below). Reduction from baseline in xanthoma score mean (95% CI) of -0.4 (-0.9, 0.1) was reported at Week 18, -0.9 (-1.3, -0.5) at Week 48 and –1·5 (–2·4, –0·6) at Week 204 [82].

Figure 11 Changes in Clinical Xanthoma Score over time in patient with xanthomas at baseline



*95% confidence interval excludes zero. †In participants presenting with xanthoma at Baseline. Abbreviations: SE: standard error. Adapted from Gonzales E, et al. 2021(Supplemental) [17].

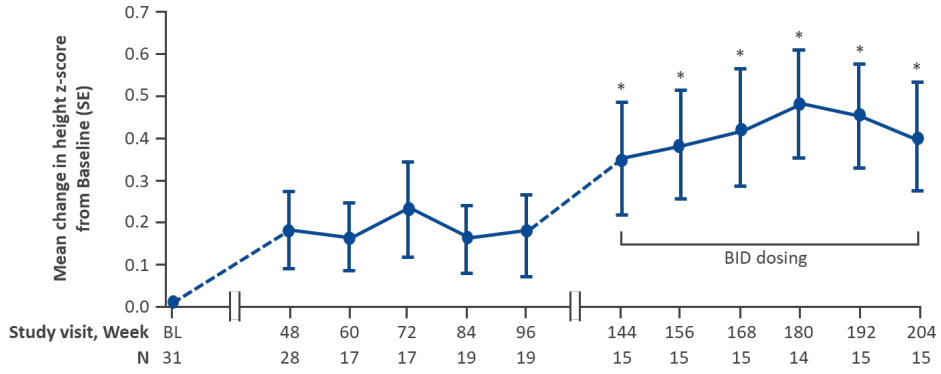
Other biochemical markers of cholestasis and bile acid synthesis

Durable control of cholestasis under maralixibat was further supported by data from the ICONIC study [17] on markers for cholestasis i.e., cholesterol levels and LDL cholesterol, and healthy bile acid synthesis i.e., 7α-C4 (a marker of healthy/non-cholestatic bile acid synthesis [62]) and FGF-19. Over the course of the study, a downward trend was observed in the total cholesterol levels of the overall population. During the RWP, maralixibat-treated patients had an LS mean change from Week 18 to Week 22 of 0.3 mmol/L (95% CI -0.5 to 1.0) in cholesterol, whereas those who received placebo had an increase of 2 mmol/L (95% CI 0.3 to 3.4) [17]. Similar effects were observed with LDL cholesterol [82]. Overall, the decrease in the total cholesterol levels were maintained from baseline to Weeks 48 and 204 in the ITT population [17]. Moreover, significant increases in mean 7αC4 levels and decreases in mean FGF-19 levels from baseline to Weeks 18, 48 and 204 were also observed in the ITT population, which were in line with the mechanism of action of maralixibat (see Appendix B) [17].

Change in growth as measured by height and weight Z-scores

Improvement in Z-scores of height was reported. Although the mean height Z-score was not significant from baseline to Week 48 (0.18, 95% CI -0.02 to 0.37; p=0.0704)[82] [17], for the 15 participants who remained on treatment through Week 204, height Z scores improved significantly from baseline (0.40, 95% CI 0.12 to 0.69) (Appendix B) [82] [17]. Moreover, improvement in the Z-score of weight was also reported from baseline to Weeks 18, 48, and 204, but it was not statistically significant (Appendix B) [82] [17].

Figure 12 Change in height z score from baseline to Week 204



*95% CI excludes zero (compared with baseline, overall population). Abbreviations: SE: standard error; BID: twice daily. Adapted from Gonzales E, et al. 2021; [17].

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

There were no differences in the definition of the outcomes used in the maralixibat trials and the MRX-GALA comparison study, the difference is in the selection of endpoints used in each study. The maralixibat trials focused on biochemical and symptomatic endpoints, including changes in sBA, validated pruritus scores (ItchRO[Obs], ItchRO[Pt], and CSS), and secondary outcomes like growth and quality of life. By contrast, the GALA registry lacked standardized pruritus assessments and relied on hard clinical outcomes such as liver transplantation, SBD, manifestations of portal hypertension, and death as proxies for disease progression. These endpoints were used to define the primary outcome EFS, the primary outcome in the GALA-MRX comparison, and other secondary outcomes like TFS, secondary endpoint of the trial (defined as the absence of liver transplant or death).

7.1.2 Method of synthesis

The GALA Cohort Comparison Study employed a non-randomized, indirect comparative design to evaluate long-term outcomes in ALGS patients treated with maralixibat (from IMAGINE, ICONIC, and IMAGINE II trials) [48] versus a real-world cohort from the GALA registry [6], the largest international ALGS database, comprising 1,543 children aged 12 months to 18 years. The primary endpoint was EFS, defined as time to LTx, SBD, hepatic decompensation (e.g., ascites or variceal bleeding requiring treatment), or death. Due to ethical and logistical constraints in conducting long-term placebo-controlled trials in pediatric ALGS populations, a direct head-to-head comparison was not feasible. Instead, this indirect approach enabled robust evaluation of clinically meaningful outcomes using real-world evidence. Two analyses were conducted: an interim analysis (data cut-off: 8 February 2021) and a final analysis upon completion of follow-up, with all eligible patients included and no formal sample size calculation performed. To ensure

comparability, GALA patients were filtered post hoc using eligibility criteria aligned with the maralixibat trials (age, total bilirubin, ALT, and GGT), excluding serum bile acid (sBA) levels due to inconsistent availability, resulting in a comparator cohort of 469 GALA patients matched against 84 maralixibat-treated patients.

Statistical methods and adjustments were rigorously applied to account for baseline differences and ensure valid comparisons. Index time alignment was achieved by defining the first dose as the index time for maralixibat patients, while for GALA patients, logistic regression was used to estimate the visit most similar in disease severity (based on age, sex, ALT, and bilirubin) to trial entry. To adjust for baseline imbalances, stabilized inverse probability of treatment weighting (IPTW) and average treatment effect in the treated (ATT) weights were applied, with propensity scores derived from logistic regression using age, sex, bilirubin, and ALT. Covariate balance was assessed using standardized mean differences, with a threshold of ±0.25. EFS was analyzed using Kaplan–Meier survival curves and Cox proportional hazards regression, adjusting for age, sex, bilirubin, ALT, and treatment group, with proportional hazards assumptions verified via log-minus-log plots. Multiple sensitivity analyses were conducted to test the robustness of findings, including alternative index time definitions, landmark analyses excluding early events at 3, 6, and 12 months, and subgroup analyses by region, site overlap, and sBA data availability. These consistently supported the treatment effect of maralixibat. Effective sample sizes remained stable after weighting, and no extreme weights compromised the analysis. Weighted Kaplan–Meier curves were included in supplementary materials. The composite EFS endpoint was justified by expert consensus as clinically meaningful, with harmonized definitions across data sources. Results were reported with hazard ratios (HRs), 95% confidence intervals, p-values, and graphical outputs, and no meta-analysis or network meta-analysis was conducted.

7.1.3 Results from the comparative analysis

Table 17 Results from the comparative analysis of maralixibat treated patient's cohort vs. GALA historical control cohort for ALGS

Results of GALA Cohort Comparison Study												
				Estimated absolute difference in effect				Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95 % CI	*P* value		Difference	95% CI	*P* value		
Event-free survival with an event being defined as LTx, liver decompensation event i.e., variceal bleeding or ascites, SBD, or all-cause death	MRX GALA control group MRX	84 469					Adjusted Unadjusted	HR: 0.305 HR: 0.380	0.189-0.491 0.238-0.604	<0.0001 <0.0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment Adjusted for age, sex, bilirubin, and ALT.	[48]
Transplant-free survival defined as the time to liver transplantation or death	MRX GALA control group MRX	84 469					Adjusted	HR: 0.332	0.197-0.559	<0.0001	Cox regression adjusted for age, sex, total bilirubin, and ALT.	[48]

Sensitivity analysis for EFS using different index times:	MRX	84				All based on adjusted Cox regression models.	[48]
	GALA control group	469					
First eligible visit:			HR:0.618	0.369–1.036	0.068		
Last eligible visit:	MRX		HR: 0.241	0.148–0.392	<0.0001		
Date of birth:			HR: 0.504	0.320–0.795	0.0032		
Random visit 1:			HR: 0.457	0.284–0.734	0.0012		
Random visit 2:			HR: 0.486	0.304–0.777	0.0026		
Random visit 3:			HR: 0.439	0.274–0.703	0.0006		
Landmark analysis to avoid immortal time bias. Landmark time:	MRX					Adjusted Cox regression; events within first 3, 6, or 12 months excluded.	[48]
	GALA control group						
3 months	MRX	83/456	HR:0.376	0.230–0.616	0.0001		
6 months		81/441	HR: 0.432	0.256–0.729	0.0017		
12 months		74/406	HR: 0.503	0.273–0.930	0.0284		
Propensity score weighted analysis. Weighting method:	MRX	84				Cox regression using weighted cohorts by estimated propensity scores.	
	GALA control group	469					
IPTW			HR:0.379	0.237–0.605	<0.0001		
ATT	MRX		HR: 0.297	0.165–0.535	<0.0001		

Subgroup analysis by region or subgroup:	MRX GALA control group MRX					Adjusted Cox models stratified by region or subgroup.
North America:		50/212	HR:0.249	0.114–0.542	0.0005	
Europe:		24/182	HR:0.360	0.187–0.693	0.0022	
Australia:		10/38	HR:0.140	0.024–0.832	0.0306	
Sites overlapping with GALA & trials:		62/214	HR:0.359	0.219–0.587	<0.0001	
GALA patients with sBA data:		84/73	HR:0.245	0.124–0.483	<0.0001	

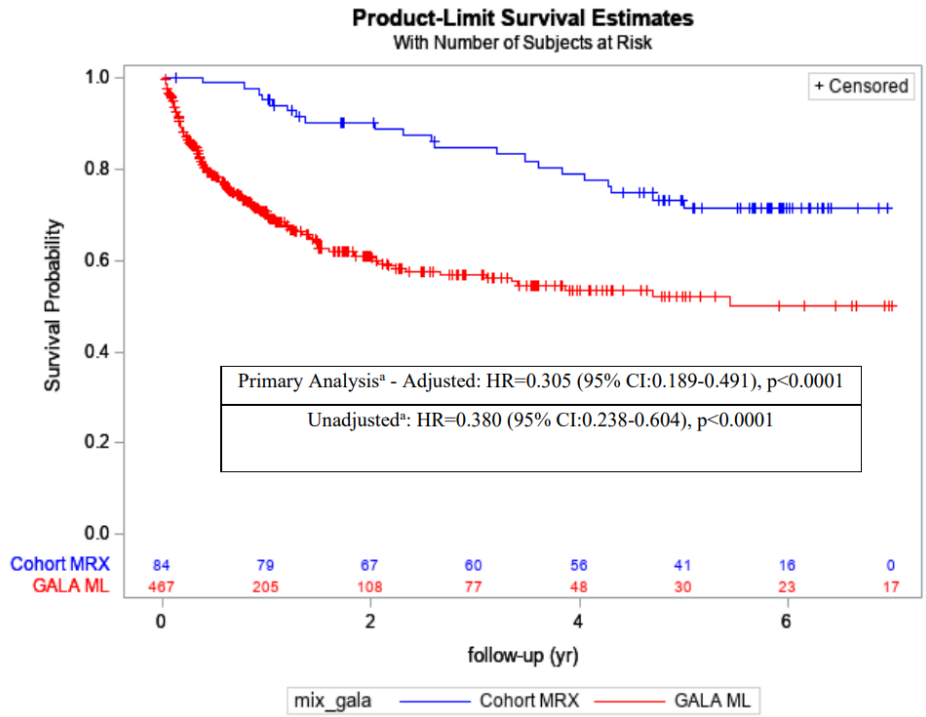
7.1.4 Efficacy – results per GALA cohort comparison study

The GALA Cohort Comparison Study assessed the long-term clinical impact of maralixibat in ALGS patients by comparing outcomes from maralixibat-treated cohorts (IMAGINE, ICONIC, IMAGINE II) with a historical control group from the GALA registry [48]. The analysis included 84 maralixibat-treated patients and 469 individuals from the GALA control cohort. Safety data showed five deaths in the maralixibat group: one was attributed to liver disease following decompensation events (ascites and hepatic encephalopathy), while the remaining four were of unknown cause, as those patients had discontinued the study and investigators could not confirm the reasons. Additionally, not all liver transplant cases in the maralixibat group were directly linked to cholestasis or liver disease. Further details on study design, patient flow, and statistical methods are available in Appendix A.

7.1.4.1 Primary analysis: Event-Free Survival

The GALA Cohort Comparison Study demonstrated that maralixibat significantly improves long-term outcomes in ALGS patients [48]. At six years of follow-up, EFS; defined as time to liver transplantation, surgical biliary diversion, hepatic decompensation, or death, was significantly higher in the maralixibat group compared to the GALA control group (see the Figure below). The adjusted analysis showed a 70% reduction in risk (HR: 0.305; 95% CI: 0.189–0.491; p < 0.0001), while the unadjusted model indicated a 62% improvement (HR: 0.380; 95% CI: 0.238–0.604; p < 0.0001) [48].

Figure 13 Kaplan-Meier plot for EFS – maralixibat cohort versus GALA control group



The number at risk is the original number of participants (at time 0) minus those who had an event or were censored (e.g., lost to follow-up) before the start of the given period. Shaded areas represent 95% CIs. *Cox regression models for the primary analysis: primary prespecified (adjusted), where the effect of maralixibat versus GALA log-likelihood test was adjusted for age, sex, bilirubin, and alanine aminotransferase (according to the statistical analysis plan), and primary unadjusted. Source: Livmarli (maralixibat) EPAR [82].

7.1.4.2 Sensitivity analysis from the GALA cohort comparison study

Sensitivity analyses in the GALA Cohort Comparison Study confirmed the robustness of the primary findings, showing that maralixibat significantly prolonged EFS compared to the GALA control group across various baseline definitions. Hazard ratios ranged from 0.241 to 0.618, with most analyses reaching statistical significance (see Table below) [48]. An additional analysis focusing on transplant-free survival (TFS), defined as time to liver transplantation or death, also showed a significant benefit for maralixibat (HR: 0.332; 95% CI: 0.197–0.559; p < 0.0001) [48]. To address potential immortal time bias, landmark analyses at 3, 6, and 12 months were conducted, all of which continued to support improved EFS in the maralixibat-treated cohort (see Figure below) [48].

Table 18 Sensitivity analysis on EFS HR by baseline visit definition

Baseline visit definition	EFS HR (95% CI)	p-value
First Eligible Visita	0.618 (0.369-1.036)	p=0.068
Last Eligible Visit	0.241 (0.148-0.392)	p<0.0001
Date of Birth [a]	0.504 (0.320-0.795)	p=0.0032
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

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. Adapted from Hansen BE, et al. 2024 [48].

Please refer to Appendix B "Results per GALA Cohort Comparison Study" for further details on the sensitivity and subgroup analysis from the GALA cohort comparison study.

8. Modelling of efficacy in the health economic analysis

This section describes how efficacy data from clinical trials and observational sources were used to inform the health economic model for maralixibat in children with Alagille syndrome (ALGS). Where relevant, extrapolation beyond the trial follow-up period was undertaken using validated modelling techniques and supported by external literature and clinical expert input.

8.1 Presentation of efficacy data from the clinical documentation used in the model

Efficacy data used in the model were derived from the ICONIC trial (LUM001-304), the long-term IMAGINE and IMAGINE II studies, and real-world data from the GALA natural history cohort. The model incorporates:

- Short-term treatment response (Week 12) and treatment discontinuation rates from ICONIC;
- Long-term event-free survival (EFS), extrapolated from GALA data;
- Transition probabilities related to disease progression, including progression to and from cirrhosis, portal hypertension (PHT), and ascites, informed by published literature;
- Transitions to and from liver transplantation (LTx);
- Mortality inputs, modelled both indirectly, by proxy of reduced serum bile acids (sBA), and directly, using comparisons between outcomes observed in maralixibat-treated patients and the GALA cohort.

Baseline patient characteristics and relevant general population comparators were primarily informed by ICONIC and GALA.

The baseline age incorporated into the model is set at [redacted], consistent with the approved indication for maralixibat. A weight distribution is applied within the model to inform drug dosing, based on growth curve data (Region Hovedstaden, Vaekstkurver.dk), with parameters corresponding to the 5th percentile of the general population. Patients enrolled in ICONIC had stature and weight below normal population averages, typical of ALGS due to impaired fat absorption; the average baseline z-score was -1.7 [82]. The model also reflects sex distribution from ICONIC (39.7% female), and includes an extreme scenario based on the 75th percentile weight band. Additionally, based on Nordic clinical expert input (Appendix M), the model accounts for the increased risk of retransplantation among pediatric patients. Different transition probabilities are applied depending on whether the patient is aged 0–18 or over 18 years, to reflect clinical emphasis on delaying LTx in smaller children. These inputs underpin both transition probabilities and extrapolated model outcomes. The structure ensures alignment between observed efficacy, disease progression, and the modeled long-term impact of treatment. While the model captures a broad range of clinical inputs, it is important to acknowledge that some aspects of disease burden are not fully reflected. These include caregiver burden, long-term educational and occupational impacts, and the emotional and psychological toll on patients and their families [84].

8.1.1 Extrapolation of efficacy data

This section describes how data from the clinical studies were used to estimate transition probabilities in the model and how transitions for health states beyond the observed follow-up period were extrapolated. The model incorporates both short-term data from the ICONIC study and long-term progression using real-world data from the GALA cohort and published literature. Where trial data were not available for certain transitions, external literature and clinical expert input were used to inform assumptions.

8.1.1.1 Extrapolation of Event-Free Survival (EFS)

EFS for the SoC comparator arm was derived from the GALA natural history cohort (N=469), which captured time to the first event: LTx, SBD, liver decompensation (ascites or variceal bleeding), or death. The MRX arm (N=84) used pooled long-term data from IMAGINE, ICONIC, and IMAGINE II trials (see Appendix A). To extrapolate EFS beyond the follow-up period:

- Parametric survival models (exponential, Weibull, Gompertz, log-logistic, log-normal, generalized gamma) were fitted to the GALA EFS data.
- Model selection was based on statistical fit (AIC, BIC in Table 27), visual inspection of survival curves (Figure 18), hazard function behavior, and plausibility.
- Although the Gompertz and log-normal distributions had the best statistical fit, the exponential distribution was selected for both the maralixibat and SoC arms to provide a conservative estimate of survival and avoid implausible long-term projections (see Appendix D.1.5–D.1.7).

This choice aligns with recommendations from Nordic clinical experts (Appendix M) and is consistent with observed outcomes in the GALA cohort (e.g. 92.1% survival at 10 years; 90.5% at 18 years).

8.1.1.2 Extrapolation of Health State Transitions

In addition to EFS, the model captures transitions across intermediate liver disease health states: cirrhosis, portal hypertension (PHT), ascites, LTx, and post-LTx. As the ICONIC and GALA studies do not follow patients through all these transitions, mortality and progression risks were obtained from high-quality published literature, as summarized in the Table below. The applied annual mortality estimates were:

Table 19. Annual mortality estimates

Health State	Annual Mortality	Source
Cirrhosis	[redacted]	D'Amico et al., 2006
Portal hypertension	[redacted]	Santambrogio et al., 2013
Ascites	[redacted]	Tonon et al., 2021
Post-LTx (0–18 years)	[redacted]	Hou et al., 2021
Post-LTx (18+ years)	[redacted]	Baumann et al., 2022

Transitions between health states were derived based on clinical pathway logic (e.g. cirrhosis → PHT → ascites → LTx), calibrated to replicate the natural history of ALGS as observed in GALA (median age at LTx = 2.8 years). Where intermediate transition probabilities were not directly available, they were informed by expert input and constrained to maintain internal model consistency (Appendix M).

Mortality transitions are summarized in the Table below.

Table 20: Summary of mortality transitions

Mortality from state:	Reported value	Per-cycle value	Source(s)	Description
Responsive to medication	[redacted]	[redacted]	Kamath et al 2020 l [12] and Hansen et al. 2023 [28]	[redacted]
Unresponsive to medication	[redacted]	[redacted]	Vandriel et al 2023 [6]	[redacted]
Cirrhosis (compensated)	[redacted]	[redacted]	D'Amico et al 2006 [77]	[redacted]
PHT	[redacted]	[redacted]	Santambrogio et al 2013 [78]	[redacted]

Ascites	[redacted]	[redacted]	Tonon et al 2021 [79]	[redacted]
LTx	[redacted]	[redacted]	Emerick et al. 1999 [7]	[redacted]
Post-LTx (0-18 years)	[redacted]	[redacted]	Hou et al 2021 [80]	[redacted]
Post-LTx (18 years +)	[redacted]	[redacted]	Baumann et al. 2022 [81]	[redacted]

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

Mortality from disease health states was derived from published survival studies. From the cirrhosis health state, mortality is based on a natural history study of survival in compensated cirrhosis [77]. The Kaplan-Meier curve from this study was digitized, and an exponential rate was applied to extrapolate survival across the model time horizon. This yielded a 10-year survival probability of 60% (i.e., a 40% probability of death), equivalent to a per-cycle probability of 1.2%. Mortality in portal hypertension (PHT) was derived from a study in patients with hepatocellular carcinoma (HCC) [78], which reported survival differences based on the presence of PHT. Although the study population was not ALGS-specific, it was considered appropriate for modelling mortality in patients with advanced portal hypertension, an expected complication in ALGS. As ALGS-specific data on HCC progression are limited, HCC-based mortality estimates were used as proxies. A midpoint 5-year survival of 47.7%, derived from a systematic review and meta-analysis [85], was used to calculate a per-cycle probability of 3.3%. Mortality in ascites was derived from a study of cirrhotic patients with Grade 1 ascites [79]. The published survival curve was digitized, and an exponential rate was applied to the 60-month data point, resulting in a per-cycle mortality probability of 4.5%. Mortality from liver transplantation (LTx) was divided into short-term and long-term phases. Short-term LTx mortality (i.e., during the transplant cycle) was derived from an ALGS-specific study [7], which reported a 1-year survival of 21%, corresponding to a per-cycle probability of 5.3%. Long-term post-LTx mortality was modelled separately for pediatric and adult patients. For those aged 0 to 18 years, estimates were based on a systematic review and meta-analysis of infant LTx outcomes [80], with a 1-year survival of 85% (per-cycle probability: 3.67%). For patients aged over 18 years, post-transplant mortality was based on a European Liver Transplant Registry study [81], reporting a 1-year survival of 93% (per-cycle probability: 0.33%). Although several of the source studies were conducted in adult populations, no pediatric-specific mortality data for these health states were identified. Where required, assumptions were validated and adjusted with input from Nordic clinical experts (Appendix M).

8.1.2 Calculation of Transition Probabilities

Transition probabilities were derived from trial data, extrapolated survival curves, and natural history literature. A 12-week cycle length was applied to align with the SmPC recommendation for evaluating treatment response after 3 months. An exponential model was used to estimate event probabilities, with the rate parameter derived from the overall number of events and follow-up time reported in relevant studies. A half-cycle correction was applied using the life-table method. All transitions were validated by clinical experts (Appendices L and M).

The transition probabilities between health states were derived as follows:

Treatment response:

- Response to maralixibat is derived from the ICONIC 12-week results. In this study, [redacted] of patients [redacted] achieved a [redacted] reduction in serum bile acids (sBA) and were classified as “responders”.

- All individuals enter the model in the “response” state in the first cycle. Responders remained on treatment in the “responsive” health state.
- Non-responders were assumed to discontinue maralixibat after 3 months, consistent with the SmPC [21], and transitioned to the standard of care (SoC) pathway.
- SoC was assumed to confer no disease-modifying effect. As described in the literature, off-label drugs used for symptomatic management (e.g. rifampicin, cholestyramine) do not alter disease progression [3]. In Denmark, maralixibat may be used in addition to SoC to manage cholestatic pruritus. The relevant comparator population is therefore patients with inadequate response to SoC.

Scenario analyses were conducted using alternative response definitions:

- ItchRO(Obs) response (≥1.0 point reduction) at Week 18: XXXXXXXXXXXX
- Long-term response (≥50% sBA reduction at 48 weeks): XXXXXXXXXXXX patients XXXXXXXXXXXX

Treatment discontinuation:

- Based on ICONIC Week 23–48 data (the ARW phase), XXXXXXXXXXXX patients discontinued treatment, corresponding to an annual discontinuation rate of 21%.
- This was converted to a per-cycle probability of XXXXXXXXXXXX using the formula:
- XXXXXXXXXXXX XXXXXXXXXXXX The ARW phase represents long-term treatment and was used to inform discontinuation beyond the initial response assessment.

Disease progression:

- Transition probabilities between disease health states (e.g. unresponsive to cirrhosis; cirrhosis to PHT; PHT to ascites) were derived from published natural history studies in ALGS or, where unavailable, from relevant non-ALGS liver disease populations.
- Transitions to LTx from cirrhosis, PHT, and ascites were based on a combination of ALGS-specific and broader hepatology literature [86] [87].
- Progression probabilities were modelled using exponential distributions and applied on a per-cycle basis. Rates are reported in Table 25.

Background mortality:

- Background mortality was modelled using age- and sex-specific life table data from Statistics Denmark (see Section 4.2).
- To avoid double-counting, disease-specific mortality derived from natural history data was combined with general mortality rates only when appropriate. This adjustment is further detailed in Appendix D.1.8.

Re-transplant:

- A fixed proportion of patients were assumed to require re-transplantation following initial LTx. For patients aged 0–18 years, estimates were based on a European cohort study [73]. For adults, data were taken from a cross-sectional study in transplant recipients [88].

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

Table 21: Transition probabilities derived and used in the cost-effectiveness model (CEM)

Transition	Reported value	Value (12-Week cycle)	Source	Description
Response to MRX	[redacted]	[redacted]	ICONIC trial [89]	[redacted]
Response to Standard of care (SoC)	[redacted]	[redacted]	Assumption based clinical expert opinion (Appendix M)	[redacted]
Discontinuation of MRX	[redacted]	[redacted]	ICONIC [82]	[redacted]
Discontinuation of SoC	[redacted]	[redacted]	Clinical opinion	[redacted]

			(Appendix M)	
Unresponsive → Cirrhosis	[redacted]	[redacted]	Lykavieris et al. 2001 [8]	[redacted]
Cirrhosis → Portal hypertension (PHT)	[redacted]	[redacted]	Kamath et al. 2020 [12]	[redacted]
PHT → ascites	[redacted]	[redacted]	Kamath et al. 2020 [12]	[redacted]

Unresponsive → LTx	[redacted]	[redacted]	Quiros-Tejeira et al. 1999 [90]	[redacted]
Cirrhosis → LTx	[redacted]	[redacted]	Hagström et al. 2021 [86]	[redacted]
PHT → LTx	[redacted]	[redacted]	Krasinskas et al. 2005 [87]	[redacted]

Ascites → LTx	[redacted]	[redacted]	Assumed equal to PHT→ LTx	[redacted]
LTx → LTx (re-transplantation) (0-18 years)	[redacted]	[redacted]	Adam et al. 2012 [73]	[redacted]
LTx → LTx (re-transplantation) (18 years +)	[redacted]	[redacted]	Broschewitz et al. 2017 [88]	[redacted]

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

8.2 Presentation of efficacy data from additional documentation

Not applicable. No additional efficacy data outside of ICONIC, IMAGINE, and GALA were used.

8.3 Modelling effects of subsequent treatments

Not applicable. Maralixibat does not alter sequencing or access to subsequent treatments. No post-discontinuation treatment effect is modelled.

8.4 Other assumptions regarding efficacy in the model

- Patients who respond to maralixibat (≥50% sBA reduction) remain stable unless they discontinue or lose response.
- No waning effect was assumed, consistent with long-term open-label follow-up data.
- No "cure point" was assumed.
- Patients who do not respond or discontinue revert to the SoC disease progression pathway.
- Assumptions supported by SmPC and clinical expert input (Appendix M).

8.5 Overview of modelled average treatment length and time in model health state

See Table below for:

- Modelled average and median duration of response
- Time spent in each health state (responsive, unresponsive, cirrhosis, etc.)
- Treatment duration estimates (maralixibat) prior to progression or discontinuation

The values are undiscounted and not half-cycle corrected. The background mortality has been applied using Statistics Denmark life tables. The observed median survival from ICONIC was provided where available; otherwise stated as "not reached".

Table 22 Estimates in the model

	Modelled average [year]	Modelled median [year]	Observed median from relevant study
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	

[redacted]

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Treatment response [months]	Loss of response [months]	Cirrhosis		PHT	Ascites	SBD	Post SBD	LTx		Post LTx
MRX	[redacted]											
SoC	[redacted]											

9. Safety

9.1 Safety data from the clinical documentation

9.1.1 ICONIC study

General safety profile

The mean duration of treatment was 2·6 years (135 Weeks [range 5–228, IQR 49–218]). Overall, data from the ICONIC study [17] demonstrates that maralixibat treatment was well tolerated throughout, with a low frequency of high-grade or treatment-related AEs as well as SAEs (see Table 33 under Appendix E) [17].

During the RWP, patients who 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). From baseline to Week 48 nine participants experienced serious adverse events; none were deemed related to maralixibat by the investigator. During the long-term extension, 6 participants reported SAEs, all deemed unrelated to maralixibat [17]. No deaths occurred during this study.

Frequency and severity of AEs

Most adverse events were self-limiting in nature and mild to moderate in severity. Diarrhea and abdominal pain were the most frequent adverse events and occurred with a similar incidence between the maralixibat-treated and placebo-treated groups during the RWP. The incidence of AEs in each study phase is presented in the Table 35 under Appendix E [17].

Discontinuations and/or dose modifications due to adverse events

Five participants had adverse events that led to study discontinuation from baseline to Week 204. Two of these events were considered possibly related to study drug (one staphylococcal hand infection and one alanine aminotransferase elevation without raised serum bilirubin). The other three events were not considered related to study drug (acute renal failure, raised serum bilirubin, and combined extradural and subdural bleeding). The key treatment emergent adverse events were gastrointestinal disorders (see Table "Incidence of AEs in two or more patients in any phase for the safety population") [17].

Over 204 Weeks, dose reductions were made for two participants. One participant had elevations in alanine aminotransferase (at dose 380 µg/kg twice per day; deemed possibly related to maralixibat treatment) with no concomitant change in bilirubin, and one participant experienced intermittent diarrhea (at dose 513 µg/kg per day split out into 380 µg/kg in the morning and 133 µg/kg in the afternoon). Neither participant experienced further complications or clinical sequelae, and each was able to continue maralixibat treatment [17].

There were no study discontinuations for gastrointestinal-related events.

Adverse events used in the health economic model

AEs recorded in the ICONIC study have been detailed in Table 36 under Appendix E 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 [76].

9.2 Safety data from external literature applied in the health economic model

Not applicable.

10. Documentation of health-related quality of life (HRQoL)

Ten publications in the May 2023 SLR reported HRQoL outcomes, mostly using PedsQL (one used CHQ-PF50), with none mapping PedsQL to EQ-5D. Three reported ICONIC trial outcomes: two showed significant improvements in QoL and fatigue with maralixibat at Weeks 18 and 48, aligned with sBA reductions; two others reported improved PedsQL scores in the long-term extension. Kamath et al. (2022) [91] further showed that ItchRO responders experienced significant HRQoL gains from baseline to Week 48. Several studies also documented the heavy QoL burden in ALGS, especially pruritus, on both patients and carers, affecting daily activities, work, social life, relationships, emotional health, and sleep.

In the model, QoL is mainly derived from a Vignette Study [74] on ALGS and supporting literature. Trial PedsQL data could not be mapped to EQ-5D due to participant age, so a

literature-based scenario was applied. The base case excludes caregiver disutilities from the Vignette Study [74], though the substantial caregiver burden is acknowledged. Given ICONIC findings, maralixibat is expected to deliver significant QoL improvements for both patients and caregivers.

10.1 Presentation of the health-related quality of life

In the economic model, HRQoL was populated using a vignette study [74], as ICONIC trial PedsQL data could not be mapped to EQ-5D due to participant age. Nevertheless, ICONIC QoL data are presented for completeness. HRQoL was assessed using the PedsQL Core [Parent] scale and the PedsQL Multidimensional Fatigue Scale, with outcomes reported as mean changes from baseline in PedsQL QoL and fatigue scores over time (ITT).

ICONIC secondary efficacy endpoints included mean change from baseline in ItchRO (Obs) [89], while exploratory endpoints evaluated PedsQL Total Score (Parent) from Weeks 18–100. Statistically significant improvements were observed in QoL and fatigue at most time points. Reported scales included Psychosocial Health Summary, Physical Health Summary, Multidimensional Fatigue, and Family Impact Total Scores. School Functioning was not collected due to participant age, preventing mapping to EQ-5D using published algorithms (e.g., Khan et al. [92]).

The PedsQL is a validated, modular instrument (up to 45 items across physical, emotional, social, and educational domains). In ICONIC, the parent-rated version was used, with items reverse scored and linearly transformed to a 0–100 scale (higher scores = better HRQoL).

In the ITT population, PedsQL Core [Parent] scores improved significantly from baseline at Weeks 18 and 48 and in the long-term extension, though not versus placebo in the RWP [82] [17]. Fatigue, assessed via the PedsQL Multidimensional Fatigue Scale (Parent), also improved significantly: mean changes from baseline were +20 (95% CI 9–32) at Week 18, +20 (9–32) at Week 48, and +17 (6–29) at Week 204 [17]. No placebo difference was seen during the RWP. Detailed results are presented in Appendix F.

10.1.1 Study design and measuring instruments

10.1.1.1 Vignette study [74]

In the economic model, a Vignette Study [74] was used to populate HRQoL throughout the health states. Given PedsQL collected as part of ICONIC did not report scales that could be mapped to EQ-5D, a vignette study was carried out to describe caregiver and patient health-state utilities using EQ-5D-5L and time trade off (TTO) valuation methods, as well as describing caregiver burden in ALGS. Initial vignettes were informed by an SLR, a review of clinical trial data and interviews with clinicians. The health states identified are summarized in the table in Appendix F.

10.1.2 Data collection

The vignette study health states were designed to be broad enough for patients and caregivers to understand and provide meaningful valuations, and therefore do not directly align with the more granular health states in the economic model. Descriptive statistics for patient health-state EQ-5D-5L evaluations are shown in Appendix F: successful LTx had the highest index value XXXXX, while chronic liver rejection had the lowest XXXXX. Greater variability in responses was observed in the more severe states (progressive cholestasis and chronic rejection) compared with the milder states. Caregiver health-state EQ-5D-5L results (Appendix F) showed the highest index value for non-progressive cholestasis/successful LTx XXXXX, while chronic rejection XXXXX and progressive cholestasis XXXXX were rated similarly.

Table 24 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	NA	NA	NA	NA
Time point 1	NA	NA	NA	NA

10.1.3 HRQoL results

10.1.3.1 Methods and key conclusions of the vignette study:

Four patient and three caregiver health-state vignettes were developed for ALGS, based on trial data, literature, and interviews with caregivers and clinicians. These described patients with pruritus, progressive cholestasis, non-progressive cholestasis, successful LTx, and chronic liver rejection. Utility values were estimated using TTO, EQ-5D-5L, and VAS in 200 UK general population interviews. HRQoL was rated highest for successful LTx and non-progressive cholestasis, with very similar values; TTO values were slightly higher than EQ-5D-5L. Vignette valuation with EQ-5D-5L aligns with approaches recently advocated in NICE's *Case for Change* [93]. In the absence of trial-based utilities, this study was considered an adequate proxy for modeling health-state utilities in ALGS.

An online caregiver survey (seven countries) collected demographic and clinical data, and assessed caregiver burden using EQ-5D-5L, HADS, WPAI:CG, and condition-specific questions. Caregivers spent on average 85 hours/week (~12 hours/day) caring, and WPAI results confirmed significant negative impacts on productivity. Comparisons with published data in Dravet syndrome and PFIC [94, 95] suggest caregiver burden in ALGS is similar. Strengths of the survey include its relatively large multinational sample and use of multiple data sources (including trial PROs) to inform vignettes. Limitations include

potential oversimplification of heterogeneous ALGS manifestations and small regression samples, particularly for WPAI outcomes limited to employed caregivers.

For additional health states (cirrhosis, PHT, ascites, SBD), utilities were derived from composite estimates (Sullivan et al. [76], HST17 [75]). The stoma disutility multiplier was derived from ulcerative colitis (2006), using TTO utility ratios (0.57 ÷ 0.79 = 0.72). Caregiver utilities were calculated as the utility decrement between vignette study results and age-matched UK population EQ-5D values (Ara & Brazier [96]); mean caregiver age was 40.3 years, with age-matched utility 0.8995. These caregiver utilities were used in sensitivity analyses. A summary table of caregiver utilities is presented in Appendix F.

Example of figure displaying the mean change from baseline through the different data collection time points for both the intervention and comparator:

Not applicable, as health-state utilities were derived from vignette-based valuations rather than longitudinal trial data.

10.1.3.2 Literature

A scenario was performed using the PedsQL outcomes reported in Kamath et al. [20] in ALGS. A mapping algorithm was used [92], for which the individual scales and calculated EQ-5D utilities are reported in Table 43. 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 44 in Appendix F, 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 [redacted] Health state utility values (HSUVs) used in the health economic model

10.1.4 HSUV calculation

In the economic model, a vignette study was used to populate HRQoL throughout the health states and has been described in Section 10.3.3 HRQoL results and the summary for disutility for AEs are provided below in Section 10.4.2. The full report is provided in Appendix L.

10.1.4.1 Mapping

Not Applicable. See Vignette Study [74].

10.1.4.2 Disutility calculation

AEs recorded in the ICONIC study have been detailed in the Table 45 in Appendix F 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 [76].

10.1.5 HSUV results

The overview of health state utility values for the cost effectiveness analysis is provided in Appendix F

The summary of utility values for cost effectiveness analysis is provided in Appendix F.

10.2 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not Applicable. See Vignette Study [74].

10.2.1 Study design

Not applicable.

10.2.2 Data collection

Not applicable.

10.2.3 HRQoL Results

Not applicable.

10.2.4 HSUV and disutility results

Not applicable.

11. Resource use and associated costs

The costs included in the analysis include drug, healthcare resource, surgery and mortality costs which are incurred by the Danish healthcare system and the Medicinpriser.dk database 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.

11.1 Medicine costs - intervention and comparator

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 (Appendix M), whereas costs were sourced from the different Danish healthcare

system sources including the DRG takster 2024, læger.dk, labportal.rh.dk (Appendix N) and the Medicinpriser.dk database.

11.1.1 Medicine acquisition costs

The acquisition cost of drugs included in the SoC arm are reported in the Table below. Drug costs were sourced from the Medicinpriser.dk Database. 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.

Table 25: Medicine costs included in the cost-effectiveness model

Technologies	Price per pack (AIP)	Units per pack
MRX	XXXXX	30mL vial (9.5mg/mL)
UDCA	DKK 139.45	100 x 250mg
Rifampicin	DKK 516.67	100 x 150mg
Cholestyramine	DKK 311	50 x 4000mg

Abbreviations: UDCA, ursodeoxycholic acid.

Maralixibat dosing is weight-based, with cost per cycle calculated using SmPC weight bands [21]. For each weight band, the daily dose (mL) was multiplied by the cost/mL to derive a weekly cost, which was then converted into a cycle cost. Cycle 1 and subsequent cycles differ due to the lower dose applied in Week 1 versus Weeks 2 onwards. As maralixibat is administered at home, vial sharing was applied in the base case.

Patients with ALGS are typically shorter and lighter than the general population due to fat malabsorption and malnutrition. The 5th percentile weight band was applied in the base case (consistent with ICONIC trial [82] baseline z-score of –1.7). Within the model, weights were sampled from normal distributions (mean and SD per cycle) rather than cohort means, to more accurately estimate average dosing and cost over time. Maralixibat cycle costs were applied only to the treatment response health state (maralixibat arm).

SoC costs were applied within the treatment response health state, using weighted average cycle costs for UDCA, rifampicin, and cholestyramine. The proportions of patients on UDCA and rifampicin were based on ICONIC baseline data, while cholestyramine use was informed by Nordic clinical expert opinion [Appendix M]. Unit costs were sourced from Medicinpriser.dk, and comparator costs were derived from unit costs and dosing data (cost per mg, cost per day, cost per cycle). As with maralixibat, SoC costs were applied only to treatment responders.

Table 26: Medicine costs used in the model

Comparator	dose per day	% patients	Unit size (mg)	Cost per pack (AIP)	Units per pack	cost/cycle
UDCA	10mg	XXXX%	250	DKK 625.10	100	DKK 4.69

Rifampicin	10mg	XXxX%	400	DKK 1048.40	100	DKK 10.85
Cholestyramine	4000mg	XXxX%	4000	DKK 311	50	DKK 522.48

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

11.2 Medicine costs – co-administration

Not applicable.

11.3 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.

11.4 Disease management costs

11.4.1 Health-state unit costs and resource use

A summary of health-state costs included in the cost-effectiveness model is presented in the table “Health-state costs included in the cost-effectiveness model,” with corresponding units per health state provided in the subsequent table. These costs were sourced from the latest reference costs on læger.dk, reflecting the average unit reimbursement rates paid by the Danish healthcare system to hospitals within each specialty.

Healthcare resource use costs per cycle are also summarized in a separate table. As no direct Danish evidence for post-LTx follow-up costs was identified, estimates were adapted from Swedish data reported by the Public Health Agency of Sweden (Folkhälsomyndigheten, 2016)) [97]. The report indicated a liver transplantation event cost of ~SEK 70,000 in the first post-transplant year and ~SEK 40,000 annually thereafter. These were adjusted for inflation to 2024 values using the SEK Inflation Calculator (1955–2024, inflationtool.com), giving SEK 91,680.29 (first year) and SEK 52,388.74 (subsequent years). Applying an exchange rate of 0.66 (SEK to DKK) resulted in DKK 60,685.71 (first year) and DKK 34,677.55 (subsequent years). This source has precedent, having been accepted by the DMC in its assessment of patisiran for hereditary transthyretin-mediated amyloidosis (hATTR) [98].

Final cycle costs (“Summary health-state costs” table) were calculated by multiplying unit resource costs by the number of units per health state, and summing across units to derive a total cost per cycle for each health state.

Table 27 Health-state costs included in the cost-effectiveness model

Resource	Unit cost	Source	DRG Code

Pediatrician visit	DKK 796.98	Læger.dk (Takstkort 19A Pædiatri) [99]	-
Hepatologist visit	DKK 2,665	DRG Takster 2024 [100]	The DRG code "MDC07 1-dagsgruppe, pat. 0-6 år" is specifically related to Major Diagnostic Category (MDC) 07, which covers diseases of the hepatobiliary system and pancreas. It applies to one-day hospital stays for patients aged 0-6 years. This code applies if the child sees a hepatologist for a condition related to MDC07 (liver, gallbladder, bile ducts, or pancreas)
Dietician visit	DKK 622.87	DMC Document Værdisætning af enhedsomkostninger Version 1.7 process: assumed as Kliniske diætister average total pay 2024 (samlet løn) 530.062,8 / average number of working hours (i.e. 1,924 -222 holiday hours = 1702) x 2 (for overheads) [101] [102]	-
Endocrinologist visit	DKK 2,818	DRG Takster 2024 [100]	MDC10 1-dagsgruppe, pat. 0-6 år. this applies to endocrinology (such as visits to an endocrinologist).
Lab tests	DKK 1947	Labportal.rh.dk/LabPortal	-
Cardiologist visit	DKK 2,280	DRG Takster 2024 [100]	MDC05 1-dagsgruppe, pat. 0-6 år Applies to: Cardiology services, including pediatric cardiology (for heart conditions in children).

Abbreviations: DKK: Danish krone; DMC: Danish Medicine Council.

Table 28: Health-state units per cycle included in the cost-effectiveness model

Resource	Response	Loss of response	Cirrhosis	PHT	Ascites
Pediatrician visit	0.23	0.12	0.12	0.12	0.12
Hepatologist visit	0.23	0.69	0.69	0.69	0.69
Dietician visit	0.23	1.38	1.38	1.38	1.38
Endocrinologist	0.00	0.23	0.23	0.23	0.23
Lab tests	0.23	0.69	0.69	0.69	0.69

Cardiologist visit	0.00	0.23	0.23	0.23	0.23

Source: Appendix K.

Table 29: Summary health-state costs

Health-state	Cost per cycle
Responsive to medication	[redacted]
Unresponsive to medication	[redacted]
Cirrhosis	[redacted]
PHT	[redacted]
Ascites	[redacted]
LTx	[redacted]
Post-LTx	[redacted]
Death	[redacted]

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

Table 30 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Liver transplant	One off cost	DKK 837,119	26MP06	DRG 2024 [100]

11.5 Costs associated with management of adverse events

AEs are considered in the model base-case. The unit costs reported in Table 53 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 Livmarli (maralixibat) SmPC [21] and Table 53). These values were then applied to the treatment response health-state in each treatment arm as a final cost per cycle.

Table 31: 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	DKK 0	6.45%	0%	DKK 0.00	DKK 0.00
ALT increased	DKK 13.6	6.45%	0%	DKK 0.88	DKK 0.00

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

Table 32 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
[Adverse event]	Not applicable	Not applicable

11.6 Subsequent treatment costs

Not applicable.

11.7 Patient costs

Not applicable.

11.8 Other costs

11.8.1 Cost of surgery

A unit cost of DKK 837,119 is applied to patients undergoing LTx. Post-LTx, patients incur a per-cycle cost of DKK 13,956 (DKK 60,685.71 annual) in Year 1 following their LTx, and DKK 7,975 per cycle from Year 2 onwards. These costs were taken from the DRG Takster 2024 for LTx [100], and the Public Health Agency of Sweden for the post-LTx cost [97]. All costs associated with LTx are displayed within the Table 55.

Table 33: Breakdown of costs associated with LTx

Procedure/resource use	Unit cost	Source
One-off cost of LTx	DKK 837,119	DRG Takster 2024 (26MP06) DRG [100]
Post-LTx (1st year) per cycle	DKK 60,685.71	2016 Folkhalsomyndigheten (Swedish) report: Hepatit B vaccination som ett särskilt vaccinationsprogram [97]. The cost estimates have been adjusted for inflation to 2024 values using SEK Inflation Calculator - Swedish Krona (1955-2024) (inflationtool.com) and adjusted to DKK using the spot rate 0,66 (Sept. 30, 2024).
Post-LTx (2nd year onwards) per cycle	DKK 34,677.55	

Abbreviations: LTx, liver transplantation.

11.8.2 Cost of mortality

A one-off cost of DKK 51,050.85 per patient per cycle was applied to all patients entering the Death health state, reflecting additional care needs at end of life. This estimate was sourced from a study of supportive and palliative care in end-stage liver disease, which reported mean costs of £18,458 per patient in the 12 months prior to death [103]. The value was adjusted for inflation to July 2024 using the Bank of England inflation calculator, and then converted to Danish kroner (GBP→DKK = 8.95), giving DKK 221,080.

While the model applies a lifetime horizon (so all patients eventually incur these costs), differences in survival between maralixibat and SoC—driven by slowed disease

progression—result in variation in the overall mortality costs due to discounting in the base case.

It should be noted that the analysis does not capture all ALGS-related costs. Substantial additional costs are likely, including those for specialist nutritional needs, frequent medical appointments, and the financial burden on caregivers (e.g., lost work, mental health support). Consequently, the long-term costs included in the model are likely underestimated.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in the Table below.

Table 34 Base case overview

Feature	Description
Comparator	SoC: UDCA, rifampicin and cholestyramine
Type of model	Markov model
Time horizon	Lifetime (up to age 100)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Vignette Study [74]
Costs included	Pharmaceutical costs Healthcare resources Adverse events
Dosage of medicine	Based on weight
Average time on treatment	XXX XXX
Avg. time in model health state (MRX) years	
Treatment response	XX
Loss of response	XX
Cirrhosis	XX
PHT	X
Ascites	X
SBD	X
Post SBD	X
LTx	XX
Post LTx	XX
Death	XX

Feature	Description
Avg. time in model health state (SoC) years	
Treatment response	[redacted]
Loss of response	[redacted]
Cirrhosis	[redacted]
PHT	[redacted]
Ascites	[redacted]
SBD	[redacted]
Post SBD	[redacted]
LTx	[redacted]
Post LTx	[redacted]
Death	[redacted]
Discontinuation	Patients with insufficient effect will stop treatment, and treatment will be discontinued after LTx. Physicians will not continue a treatment if the patient does not experience a clinically relevant effect
Mortality in responders	[redacted]
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
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 [82] 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.

Abbreviations: HR, Hazard ratio; LTx, liver transplantation; MRX, maralixibat; QoL, Quality of Life.

12.2 Base-case analysis inputs and assumptions

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, utilities and weight bands.

12.2.1 Summary of base-case analysis inputs

Not applicable.

12.2.2 Base case results

In the base case, the incremental cost-effectiveness ratio (ICER) for maralixibat vs SoC is DKK [redacted] which represents [redacted] incremental QALYs and DKK [redacted] incremental costs.

A summary of the base-case results including a summary of the disaggregated costs and outcomes is provided in the Table below.

It is important to note that, given the heavy burden of ALGS, not all impacts are captured in these results, 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).

Table 35 Base case results

Per patient	Maralixibat (MRX)	Standard Of Care (SoC)	Difference
Medicine costs (DKK)	[redacted]	295.73	[redacted]
Medicine costs – co-administration (DKK)	[redacted]	[redacted]	[redacted]
Administration (DKK)	[redacted]	[redacted]	[redacted]
Disease management costs (DKK)	[redacted]	[redacted]	0
Costs associated with management of adverse events (DKK)	[redacted]	[redacted]	[redacted]
Subsequent treatment costs (DKK)	[redacted]	Not applicable	Not applicable
Patient costs (DKK)	[redacted]	Not applicable	Not applicable
Palliative care costs (cost of surgery and cost of mortality in DKK)	[redacted]	[redacted]	-
Discounted Costs (DKK – kr.)			
Treatment response	[redacted]	[redacted]	[redacted]
Loss of response	[redacted]	[redacted]	[redacted]
Cirrhosis	[redacted]	[redacted]	[redacted]
Portal hypertension	[redacted]	[redacted]	[redacted]
Ascites	[redacted]	[redacted]	[redacted]
LTx	[redacted]	[redacted]	[redacted]

Post-LTx	XXXXXX	XXXXXX	XXXXXX
Death	XXXXXX	XXXXXX	XXXXXX
Total	XXXXXX	XXXXXX	XXXXXX
Discounted Life Years (LYs)			
Treatment response	XXXXXX	XXXXXX	XXXXXX
Loss of response	XXXXXX	XXXXXX	XXXXXX
Cirrhosis	XXXXXX	XXXXXX	XXXXXX
Portal hypertension	XXXXXX	XXXXXX	XXXXXX
Ascites	XXXXXXX	XXXXXXX	XXXXXXX
LTx	XXXXXX	XXXXXX	XXXXXX
Post-LTx	XXXXXX	XXXXXX	XXXXXX
Death	XXXXXX	XXXXXX	XXXXXX
Total	XXXXXX	XXXXXX	XXXXXX
Discounted QALYs			
Treatment response	XXXXXX	XXXXXX	XXXXXX
Loss of response	XXXXXX	XXXXXX	XXXXXX
Cirrhosis	XXXXXX	XXXXXX	XXXXXX
Portal hypertension	XXXXXX	XXXXXX	XXXXXX
Ascites	XXXXXXX	XXXXXXX	XXXXXXX
LTx	XXXXXX	XXXXXX	XXXXXX
Post-LTx	XXXXXX	XXXXXX	XXXXXX
Death	XXXXXX	XXXXXX	XXXXXX
Caregiver	XXXXXX	XXXXXX	XXXXXX
Total	XXX	XXXX	XXX
Incremental costs per life year gained (DKK)	XXXX		
Incremental cost per QALY gained (ICER) DKK	XXXXX		

Abbreviations: LTx, liver transplantation; MRX, maralixibat; SoC, standard of care.

12.3 Sensitivity analyses

12.3.1 Exploring uncertainty

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 DKK XXXX.

12.3.2 Deterministic sensitivity analyses

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 Section 11 using the list price for maralixibat. Results were also displayed in descending order in as a tornado plot in Figure below “Cost-effectiveness plane from PSA (1,000 simulations)”. The cost-effectiveness of maralixibat is most sensitive to changes in the health state utilities, 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 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.

Table 36 One-way sensitivity analyses results

Parameters	Lower bound ICER (DKK/QALY)	Upper bound ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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

12.3.3 Probabilistic sensitivity analyses

PSA results and figures can be found in Appendix G.

12.3.4 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 analyses undertaken and the results of the scenario analyses, presented as the ICER of maralixibat compared to SoC are shown in the Tables below.

Table 37 Summary of scenario analysis with ICER results

Scenario	Incremental cost (DKK)	Incremental benefit (QALYS)	ICER (DKK/QALY)	% change
[redacted]				

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

[redacted] However, the source selected in the analysis was deemed more appropriate given the design and population of the study (meta-analysis in infants) [80].

[redacted]

12.4 Validation

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 (Appendix M).

12.4.1 Validation of cost-effectiveness analysis

Quality assurance measures were internally conducted throughout the development of the model. To ensure the reliability of model estimates, validation procedures were carried out, which included scrutinizing extreme values and performing formula audits. Additionally, the model structure and inputs underwent thorough critique and validation by a clinician and a health economics consultant. Any identified errors were promptly rectified. Overall, the validation process revealed no issues concerning the structural or computational accuracy of the model.

12.5 Interpretation and conclusions of economic evidence

The current model has several strengths, including use of trial data and long-term outcomes from GALA. However, the analysis may underestimate the true benefit of maralixibat given the rarity and debilitating nature of ALGS, which profoundly affects many aspects of patients' and caregivers' lives. This is especially relevant as many patients are children, and caregivers are typically their parents.

This evaluation is the first attempt to parameterize an economic model in ALGS, presenting the cost-effectiveness of maralixibat versus SoC. In the base case, maralixibat yielded an ICER of DKK[redacted], corresponding to [redacted] incremental QALYs and DKK [redacted] incremental costs. The probabilistic analysis produced a similar ICER (DKK [redacted]), consistent with the deterministic analysis and reflecting limited uncertainty. Extreme scenarios—such as post-LTx mortality, maralixibat discontinuation, and varying weight bands—were tested and showed significant effects on the ICER.

Treatment efficacy was based on ICONIC, which demonstrated improvements in sBA levels and pruritus outcomes. Incorporating the 12-week sBA responder analysis in the base case added robustness. The model further benefits from extensive sensitivity testing, particularly regarding maralixibat discontinuation and post-LTx mortality.

Limitations remain due to data scarcity, as ALGS-specific evidence is constrained by small patient numbers and few long-term studies, leading to uncertainty around outcomes in states such as cirrhosis, PHT, and ascites. HRQoL was informed by a vignette study, the most appropriate source in the absence of mappable trial utilities. Cost inputs were sourced from Danish references and the literature.

Maralixibat is expected to significantly improve QoL by maintaining patients in the *treatment response* state, delaying progression, and reducing surgical needs through sBA control and pruritus relief. ICONIC findings support these assumptions, which are incorporated into the model. Beyond direct health gains, maralixibat is anticipated to have broader impacts: alleviation of severe pruritus improves sleep, growth (height and weight z-scores), and mental well-being, while reducing risks of PTSD, impulse control issues, and other social-emotional impairments. By delaying disease progression and need for LTx, maralixibat is also expected to improve educational and employment opportunities, as well as overall quality of life for patients and caregivers.

13. Budget impact analysis

13.1 Number of patients (including assumptions of market share)

The incidence and prevalence of ALGS in Denmark, as well as the estimated number of eligible patients for maralixibat over the next five years, are detailed under “Patient Population” in Section 3. Assumptions regarding the expected market share of Livmarli (maralixibat), both in scenarios of recommendation and non-recommendation, are described below.

Market share projections for subsequent years following Livmarli’s commercialization were based on the percentage change in its sales observed in Germany between 2023 and 2024. To estimate market share accurately, the number of eligible ALGS patients in Germany was determined, followed by an assessment of how many were treated after Livmarli entered the market. This estimation assumes that eligible patients have an average age of XXX years, as reported in the ICONIC study, corresponding to a mean weight of XXX kg. By analyzing the number of German ALGS patients treated with Livmarli in 2023 and 2024, the percentage market share relative to the total eligible German ALGS population was calculated. The market share of Livmarli in Germany was then used as a reference point to estimate its anticipated market share in Denmark, forming the basis for our budget impact analysis. Using the estimated number of eligible patients over the next five years, as described in Section 3.2, along with market share, the total expected number of patients in both scenarios (one where Livmarli is recommended and another where it is not) are presented in the Table below.

Table 38 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
SoC (including UDCA, rifampicin & cholestyramine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Livmarli (maralixibat)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
SoC (including UDCA, rifampicin & cholestyramine)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Livmarli (maralixibat)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

13.2 Budget impact

The cost input in the budget impact analysis originates from the cost utility analysis described in section 11 of this application but discounting and patient costs have been excluded. The Table below shows the budget consequences for the regional hospital budgets in both scenarios; when Livmarli is recommended and when Livmarli is not recommended. The Table below also includes the total budget impact of recommending Livmarli.

Table 39 Expected budget impact of recommending Livmarli

	Year 1	Year 2	Year 3	Year 4	Year 5
Livmarli is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Livmarli is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*No additional costs are expected with the introduction of maralixibat, as routine patient monitoring is already established for those on SoC and is not anticipated to change substantially with Livmarli (maralixibat).

14. List of experts

Clinical experts consulted by Abacus Medicine Pharma Services in connection with the development of this submission include:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

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Appendix A. Main characteristics of studies included

A.1 ICONIC study

The ICONIC trial was an international, multicenter, phase 2b placebo-controlled, double-blind, randomized drug-withdrawal study with a long-term open-label (OL) extension in children with ALGS designed to evaluate the safety and efficacy of maralixibat [17]. The objectives of the study are to evaluate the long-term efficacy and safety and tolerability of maralixibat, its effects on sBA levels, on biochemical markers of cholestasis and liver disease, and on pruritus [17].

Patient flow

36 participants were screened between October 2014 and August 2015 to participate in the ICONIC study. 31 participants were enrolled into the open-label period of the study, during which two discontinued due to serious adverse events not related to maralixibat. 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 (> Week 48) [17] [82].

Analyses at Week 204 included 15 patients. Indeed, during the long-term extension phase:

- At Week 104, 7 patients had discontinued the study (2 patients due to adverse events, 1 patient due to physician decision, 1 patient due to caregiver decision and 3 patients due to no renewal of consent),
- At Week 156, 1 patient had discontinued the study without renewal of consent.

Table 40 Analysis population and reasons for stopping the study

	Open phase (W1-W18)	Randomized withdrawal phase (W19 – W22)		Post-randomization phase (W23 – W48)	Long-term extension phase (>W48 and up to W204)
	Maralixibat	Maralixibat	Placebo	Maralixibat	Maralixibat
Population ITT	31	13	16	28	23
Modified TTI population (mITT)	15	5	10		
Safety population	31	13	16	29	23
Stopping the study during the	2	0	0	6	8

treatment period:						
-	No consent to enter the extension phases	0	0	0	5	4
-	Unwanted event	2	0	0	1 (increased serum bilirubin*)	2 (1 acute renal failure* and 1 alanine aminotransferase increase†)
-	Physician's decision	0	0	0	0	1
-	Caregiver's decision	0	0	0	0	1

*Deemed unrelated to maralixibat by the investigator. †Deemed possibly related to maralixibat by the investigator.

Abbreviations: W: Week, RWP: randomized withdrawal phase.

Source: Gonzales et al 2021[17], Livmarli (maralixibat) EPAR [82].

Concomitant treatments used for pruritus

Most patients (94%) were using concomitant pruritus treatment at baseline. The most common anti-pruritus treatments used by patients were ursodeoxycholic acid (81%) and rifampicin (74%).

Table 41 Concomitant treatments used for pruritus in the ICONIC trial

Parameter/ Category	Baseline all participants MRX (n=31)	Baseline MRX-MRX-MRX group MRX (n=13)	Baseline MRX-PBO-MRX group Placebo (n=16)
History of receiving treatment for pruritus, n (%)			
Any medication, n (%)	29 (94)	12 (92)	15 (94)
Ursodeoxycholic acid	25 (81)	10 (77)	13 (81)
Rifampicin	23 (74)	10 (77)	13 (81)
Naltrexone	1 (3)	1 (8)	0
Sertraline	1 (3)	0	1 (6)

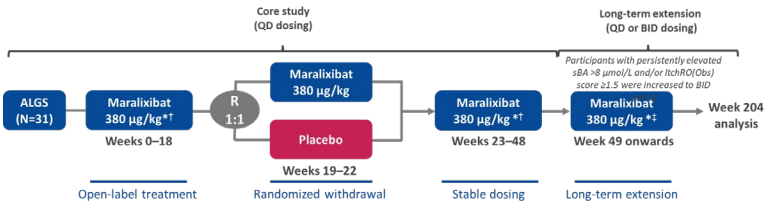
Abbreviations: W: Week; RWP: randomized withdrawal phase.

Source: Gonzales et al 2021[17], Livmarli (maralixibat) EPAR [82].

Overview of trial design

Table 42 Summary of methodology of the ICONIC study

ICONIC (LUM001-304)

Objective	The objectives of the study to evaluable the long-term efficacy and safety and tolerability of maralixibat, its effects on sBA levels, on biochemical markers of cholestasis and liver disease, and on pruritus.
Study title and identifier	Long-Term, Open-Label Study with a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients with Alagille Syndrome (ICONIC). LUM001-304 EudraCT number: 2013-005373-43 ClinicalTrials.gov ID: NCT02160782
Study type and design	The ICONIC study consisted of for phases (see Figure below): - Open-label run-in phase (OL phase): from baseline to Week 18, all patients received ≥380 µg/kg/day of maralixibat. - Randomized, double-blind, placebo-controlled drug-withdrawal period (Randomized withdrawal phase; RWP): from Weeks 19-22, patients were randomized 1:1 to receive either ≤380 µg/kg/day of maralixibat, or placebo. - Open-label stable dosing phase (after RWP – ARW phase): from Weeks 23-48, all patients received ≤380 µg/kg/day of maralixibat. - Optional long-term treatment period (long-term extension phase; LTE). The first long-term follow-up phase was from Weeks 49-101, and all patients received ≤380 µg/kg/day of maralixibat. The second long-term follow-up phase was from Weeks 101-204, all eligible patients received ≤380 µg/kg once per day or twice per day. **Figure 14: Trial design of pivotal ICONIC study for maralixibat in ALGS**  *380 µg/kg/day of maralixibat is equivalent to maralixibat chloride 400 µg/kg. †Included a 6-Week dose escalation period for all participants during the first 6 Wee of the open-label treatment period and for participants who received placebo duri the randomized withdrawal period. ‡Twice per day dosing (started after Week 100) was equivalent to maralixibat chlori 800 µg/kg.
Sample size (n)	36 participants were screened between October 2014 and August 2015 to participa in the ICONIC study. 31 participants were enrolled into the open-label period of t study, during which two discontinued due to serious adverse events not related maralixibat. 29 (maralixibat n=13, placebo n=16) entered the RWP and completed t open-label stable dosing phase, and 23 entered the long-term extension phase Week 48).
Study population	Safety population (SAF): All patients who were enrolled received at least one dose of the study drug.

	Intention-to-treat (ITT): All patients who were enrolled received at least one dose of the study drug. Modified Intent-To-Treat Population (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. For each treatment phase, the following subjects were included in each respective analysis population: - OL Phase: Subjects dosed during the OL phase. - RW Phase: Subjects randomized and dosed during the RW phase. - ARW Phase: Subjects dosed after the RW phase.

Main inclusion and exclusion 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/intractable pruritus explainable only by liver disease
	- 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 hemorrhage 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 (Australia, Belgium, France, Spain, Poland and the United Kingdom).

Intervention	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 randomized 1:1 to receive either ≥380 µg/kg/day of maralixibat, or placebo. During the second (optional) 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.
Comparator	Placebo arm was included in the RWP phase.
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.
Is the study used in the health economic model?	Yes
Reported outcomes	Primary efficacy endpoint (mITT) 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 (ITT) - Change from Week 18 to Week 22 in fasting sBA levels. - 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 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 baseline to Week 18 in fasting sBA levels. - Change from baseline to Week 18 in pruritus as measured by ItchRO (Obs)/ItchRO (Pt). - Change from baseline to Week 18 in biochemical markers of cholestasis and liver disease (ALT, ALP, total bilirubin, direct bilirubin). Additional efficacy endpoints (ITT)

	- 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 Pediatric 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.
Endpoints included in this application	sBA levels mean change, change in pruritus assessed by ItchRO (Obs), ItchRO (Pt) and CSS scales, change in biochemical markers of cholestasis including ALT and total and direct bilirubin levels, change in CXS, change in other biochemical markers of cholestasis and bile acid synthesis (e.g., cholesterol), change in growth as measured by weight and height Z-scores, and QoL assessed by PedSQL scales.

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)
	  ○ 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)
Statistical methods	The primary analysis population for efficacy was the MITT Population. Analyses for the primary and secondary efficacy outcome variables were also performed on the ITT Population. The difference between treatment groups in change from Week 18 to Week 22 in serum bile acid were evaluated using an ANCOVA model with treatment group as a factor, and Week 18 serum bile acid as a covariate. An ANCOVA model that includes the stratification variable sBA responder indicator as an additional covariate was also performed on the ITT Population. This model also included the sBA responder covariate by treatment sequence interaction term. The LS mean difference between treatment groups (MRX minus PBO) with standard error, 95% CI for the LS mean difference, and *p* value for testing if the treatment group LS means are equal were calculated to determine if the change in sBA levels between the treatment groups are statistically significant. Secondary, exploratory, and other efficacy variables that are continuous measures were analyzed similarly to the primary efficacy analyses, using summary statistics and, with the exception of PIC, CIC, and CGTB, by ANCOVA. Efficacy measures that are categorical binary responder outcomes were analyzed using the chi-square or Fisher's Exact test, as appropriate based on sample sizes. No adjustments were made for multiple comparisons. For subjects who early terminated from the study prior to Week 100 or are otherwise missing Week 18, Week 22, Week 48, and/or Week 100 data were imputed in a LOCF approach.
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.
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).

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; GGT: gamma-glutamyl transferase; EOT: end of treatment; ET: early termination; ItchRO: Itch-reported outcome; ITT, intent-to-treat; LDL-C: low-density lipoprotein cholesterol; LOCF: last observation carried forward; mITT: modified intention-to-treat; PedsQL: Pediatric Quality of Life Inventory; PIC: Patient Impression of Change; RCT: randomized controlled trial; sBA: serum bile acid; ULN: upper limit of normal.

The ItchRO score (Itch reported Outcome) is a pruritus score (between 0 and 4). Caregivers of all patients will complete the observer questionnaire: ItchRO (Obs). Children aged 9 years and older will fill out only the patient questionnaire: ItchRO (Pt). Children aged 5 to 8 years will complete the patient questionnaire with the help of

their caregiver if necessary: ItchRO (Pt). The daily score considered is the highest of the morning and evening ItchRO scores. The average daily score is calculated by summing all daily scores and dividing by the number of days for which the ItchRO score has been recorded.
The Clinician-Measured Xanthoma Scale (CXS) is an observation-based scale used by clinicians to assess xanthomas. This scale ranges from 0 to 4, with 4 indicating the most severe clinical expression resulting in a major impact on quality of life.
Clinician-Measured Pruritus Scale (CSS) is observation-based, by the clinician, of the itch and/or physical evidence of the itch, such as excoriations. This scale varies between 0 and 4 (4 representing the highest level of pruritus).
Source: ICONIC study [17] [82]

A.2 GALA cohort comparison study

The GALA Cohort Comparison Study [48] was a cohort comparison conducted between the maralixibat-treated patient cohort from IMAGINE, ICONIC, and IMAGINE II, vs. a historical international cohort of standard-care treated patients (ASBTi naïve) 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 [6]. 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.

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), specifically the time it took for the first occurrence of any event including LTx, SBD, liver decompensation and death.

Patient flow

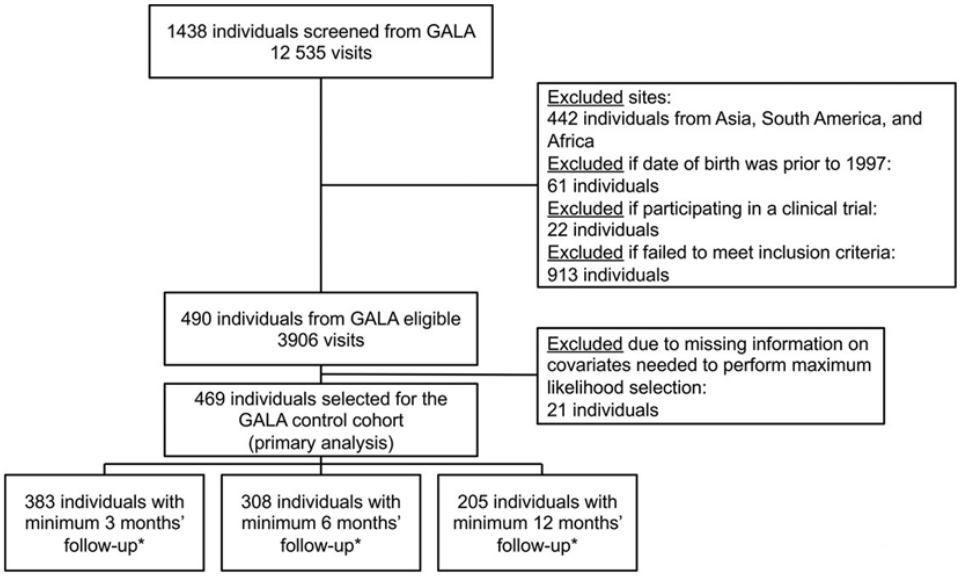
The analysis included 469 individuals from the GALA control cohort and 84 individuals treated with maralixibat.

GALA Control Group

The control group for the current analysis was selected from GALA and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The GALA control group included ALGS patients without death or surgical treatment (SBD, LTx) or liver decompensation, and the key inclusion and exclusion criteria were aligned with maralixibat ALGS studies' entry criteria.

This cohort consisted of individuals who received standard-of-care treatment for ALGS but were not treated with maralixibat or another ileal bile acid transporter inhibitor. Standard-of-care in GALA represents the standard management of cholestasis, including treatments for pruritus such as antihistamines, rifampicin, cholestyramine, and nutritional support, including fat-soluble vitamins. A total of 490 patients, with 3,906 visits, were included in the analyses in the GALA Cohort Comparison Study control group [48] (Figure below).

Figure 15 Patient disposition in the GALA Cohort Comparison Study



Adapted from Hansen BE, et al. 2024 [48].

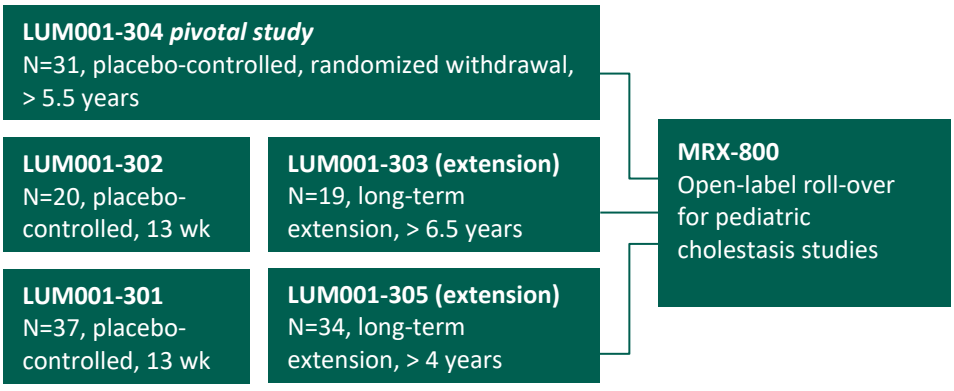
*A minimum amount of follow-up time was considered to avoid immortal time bias (i.e., an early observed effect due to survivor treatment selection bias).

Abbreviations: GALA, Global ALagille Alliance.

Maralixibat treated participants

In total, 86 participants with ALGS have been treated with maralixibat across 3 clinical studies (ICONIC/LUM001-304, ITCH/LUM001-301, IMAGO/LUM001-302) and their LTE studies (LUM001-304 was extended, IMAGINE II/LUM001-305 was the LTE for LUM001-301, and IMAGINE I/LUM001-303 was the LTE for LUM001-302), as well as 1 ongoing rollover study (MERGE/MRX-800). A total of 84 patients were included in the maralixibat cohort from across LTE Studies IMAGINE I/LUM001-303, ICONIC/LUM001-304, and IMAGINE II/LUM001-305 [104-107].

Figure 16 Maralixibat Alagille Clinical Studies



There were 5 deaths reported in the maralixibat cohort; 1 related to liver disease (decompensation events of ascites and hepatic encephalopathy preceded death); the other 4 remain unknown as these participants had discontinued the study and the investigators were not able to obtain/provide the reason for death. Also, among the reasons for transplantation, some cases might not have been triggered by cholestasis/liver disease.

Overview of the study design

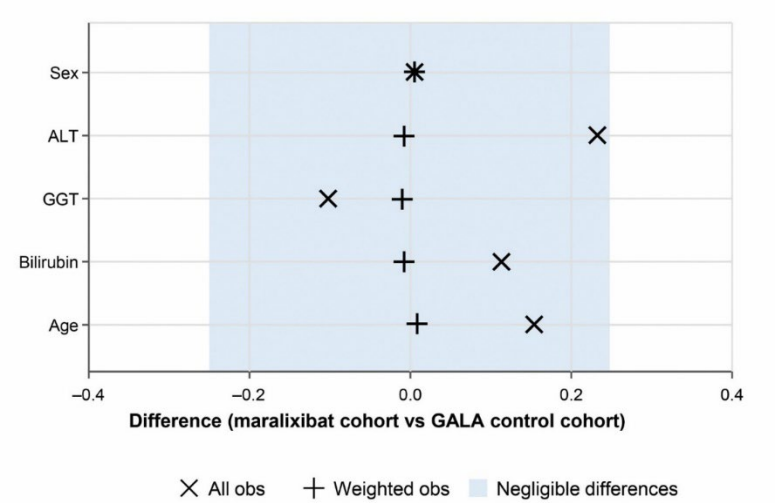
Please see the Table below for more details of the GALA comparison study.

Table 43 Summary of methodology of the GALA Cohort Comparison Study

	GALA Cohort Comparison Study
Objective	The comparison study aimed to assess the impact of long-term maralixibat treatment on clinical outcomes (i.e., EFS) in patients with ALGS.
Study title	Long-Term Outcomes of Long-Term Maralixibat Treatment in Patients with Alagille Syndrome Compared with an External Control Cohort from the Global ALagille Alliance (GALA) Clinical Research Database.
Study design	The GALA Cohort Comparison Study [48] 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 [108]. Distribution between the two cohorts was assessed for critical factors, including age, bilirubin, GGT, and ALT. Balance was assessed by examining a standardized differences plot summarizing differences between the treated and control groups. Standardized mean differences within the prespecified boundary of ±0.25 were considered balanced. In instances when balance was not achieved using standardized mean differences, two approaches were applied in the time-to-event analysis: (1) Cox regression adjusting for these covariates; and (2) assigning weights using either stabilized inverse probability of treatment weights (stabilized IPTWs) estimated by the propensity scores of the logistic regression: maralixibat yes/no or average treatment effect in the treated (ATT) weights.

None of the standardized mean differences exceeded the upper limit of 0.25 for critical factors, meaning that the two cohorts were appropriately matched in the study.

Figure 17: Standardized mean differences for critical factors



The symbol at the intersection of sex and 0.0 is not a separate symbol, but the "plus" and "x" symbols overlapping.

Sample size (n)	The analysis included 469 individuals from the GALA control cohort and 84 individuals treated with maralixibat.
Study population	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.
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 Section 6.1 for details on the eligibility criteria from the ICONIC study, and Section 6.6 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 (Supplemental Methods from Bettina E. Hansen et al 2024, http://links.lww.com/HEP/I186), which was aligned with the maralixibat clinical trials: - Age at inclusion: >12 months and <18 years - Cholestasis, defined by one or more of the following: o Total SBA >3 x ULN o Conjugated or direct bilirubin >1 mg/dL o Total bilirubin >2 mg/dL o GGT >3 x ULN - Residence in North America, Europe, or Australia, where the maralixibat trials were conducted 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 (Supplemental Methods from Bettina E. Hansen et al 2024, http://links.lww.com/HEP/I186):

	- 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) - Participation in any interventional clinical study at any time
Settings and locations	Please see Section 6.1 for details on the settings and locations from the ICONIC study, and Section 6.6 for details on the settings and locations from the IMAGO/IMAGINE and ITCH/IMAGINE studies. 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.
Intervention	Please see Section 6.1 for details on the trial drugs from the ICONIC study, and Section 6.6 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.
Comparator	Patients in the GALA control group who were under standard of care were considered to be the external control group.
Permitted concomitant medication	Please see Section 6.2 for details on the permitted concomitant medication from the ICONIC study and see Section 6.6 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.
Is the study used in the health economic model?	Yes
Index time	For the primary analysis the patient-specific index time was selected applying a maximum likelihood approach to align the disease severity between the two cohorts with the initiation of maralixibat. This approach fits the logistic regression model where outcome is maralixibat yes/no – each subject from the maralixibat data has one row corresponding to maralixibat=yes, and those from GALA have possibly multiple rows all corresponding to maralixibat=no and all identified as eligible visits. The model adjusts for the confounders: age, sex, total bilirubin, and alanine aminotransferase (ALT). After fitting the logistic regression model, each subject from GALA has the row and corresponding date selected as index where predicted probability of maralixibat is greatest. This index time will be referred to as the “best fit”.
Reported outcomes	Primary outcome: Time from baseline to the date of the first clinical event that comprise EFS, i.e., - LTx - SBD - Liver decompensation (variceal bleeding, ascites requiring therapy) - Death The primary endpoint is EFS, which was defined as the absence of these events. Thus, the primary endpoint is a composite endpoint of the first event of liver decompensation (ascites, variceal bleeding), SBD, liver transplantation, or death.

	TFS was defined as the absence of a transplant or death. Hepatocellular carcinoma was prespecified to be excluded as an event. For participants who were still actively receiving maralixibat, events were identified by on-study adverse event report forms. For the maralixibat cohort, patients were followed until the date of event or date of last contact, and data were censored on March 31, 2021. For the GALA control cohort, patients were followed until date of event (if within 7 years of follow-up) or until 7 years of follow-up with data administratively censored on April 21, 2021.
Endpoints included in this application	EFS
Sensitivity and Pre-planned subgroup analysis	A series of prespecified sensitivity analyses were performed to determine the robustness of the findings: - Different index times including (1) first visit; (2) last visit; (3) a set of three random visits; (4) day of birth for both cohorts (i.e., maralixibat and GALA control cohort) - TFS as a secondary endpoint - The impact of landmarking from follow-up for the first 3, 6, and 12 months to avoid selection biases that may occur in individuals who are potentially too sick to be included in a trial setting (immortal time bias) - Different approaches to propensity score weighting (i.e., IPTW and ATT) Subgroup analysis was planned for: - Different geographic regions (Europe, Australia, North America) - Overlapping GALA and maralixibat study sites - Individuals for whom sBA data were available
Missing data	For the maralixibat cohort, the date of the clinical event was used in the time-to-event analysis. For those without an event but still under observation (i.e., participated in long-term follow-up study NCT04168385) at the time of administrative censoring (March 31, 2021), this date was used. For those individuals not under observation at the time of administrative censoring (e.g., lost to follow-up or refusal to consent for data collection), the date of last contact was used.
Statistical methods	This comparison study followed a prespecified SAP, and its primary analysis was the comparison of the time to first clinical event between the maralixibat-treated participants (maralixibat cohort) and the 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. Pre-specified sensitivity analyses of the primary analysis and subgroup analyses were conducted.
Sample size, power calculation	No formal sample size calculations were performed. Available patients meeting the selection criteria were analyzed.
Data management, patient withdrawals	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-

	toevent 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; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; HCC: hepatocellular carcinoma; EFS: event-free survival; LTx: liver transplantation; sBA: serum bile acid; SBD: surgical biliary diversion; ULN: upper limits of normal.

Source: MRX-GALA comparison study [48]

Appendix B. Efficacy results per study

B.1 Results per ICONIC study

Table 44 Results per ICONIC study [17]

Results of ICONIC (NCT02160782)												
Outcome	**Outcome (specific)**	**Study arm**	**N**	**Result (CI)**	**Estimated absolute difference in effect**			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
	Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	**P value**	**Difference**	**95% CI**	**P value**		
sBA	Change in sBA (fasting) mITT population	Randomized Withdrawal Period: MRX	5	-21.73 (43.125)	-117.28	232.38 to 2.18	0.0464 *				The difference between treatment groups in change from Week 18 to Week 22 in fasting sBA levels was evaluated using an analysis of covariance (ANCOVA) model with treatment group as a factor, and Week 18 sBA as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the MITT population, which included all participants who were	Clinical gov.
		Randomized Withdrawal Period: Placebo	10	95.55 (30.488)								

							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. The P-value for testing if the treatment group least squares (LS) means were equal was calculated to determine if the change in sBA levels between the treatment groups was statistically significant. Clinical gov.	
Mean change during RWP in fasting sBA (ITT)	Randomized Withdrawal Period: MRX	13	-16.73 (-83 to 50)	-113.958	-212.68 to -15.21	0.0254 *	Student's t-test used to test if mean change is statistically significant. Difference was calculated through an ANCOVA model. The least square mean difference in sBA between the maralixibat and placebo groups in the 15 participants who achieved an sBA reduction of at least 50% from baseline to week 12 or 18 (the primary endpoint) was –117 µmol/L (SE 53; 95% CI –232 to –2). Clinical gov.	Clinical .gov
	Randomized Withdrawal Period: Placebo	16	93.58 (23 to 164))					
Mean change from baseline to Week 18 in	Open-label Period: MRX Baseline	31	283.43 (210.569)	Estimated Value -87.73	-133.37	0.0005 *	The null hypothesis that the mean change was equal to zero was tested using the Student's t-test	Clinical .gov

	fasting sBA levels					to -42.09		to determine if the mean change in sBA levels between baseline and Week 18 (the open-label period) was statistically significant. Clinical gov.	
	Pruritus measured by ItchRO[Obs] Weekly Average Morning Severity Score (ITT Population)	Open-label Period: MRX Week 18	29	192.50 (161.278)					
	Mean change from baseline to week 48 in sBA	Baseline	31	NA	-96	-162 to -31	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27	NA					
	Mean change from baseline to week 204	Baseline	31	NA	-181	-283 to 79	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 204 weeks	15	NA					
ItchRO(Obs)	change from baseline to Week 18 in pruritus as	Open-label Period: MRX Baseline	31	2.909 (0.5480)	Estimated value -1.704	-2.051 to -1.357	< 0.0001 *	The null hypothesis that the mean change was equal to zero was tested using the Student's t-test to determine if the mean change in ItchRO(Obs) scores between	Clinical .gov and

measured by ItchRO(Obs)							baseline and Week 18 (the open-label period) was statistically significant. Clinical gov.	ICONIC table
	Open-label Period: MRX Week 18	29	1.203 (0.8446)					
Mean change during RWP in ItchRO(Obs) week 19-22	Randomized Withdrawal Period: MRX	13	0.2 (0.3 to 0.7)	-1.5	-2.1 to –0.8	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
	Randomized Withdrawal Period: Placebo	16	1.7 (1.2 to 2.2)					
Change from baseline to week 48	Baseline	31	NA	–1·6	–2·1 to –1·1	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.

	Maralixibat 48 weeks	27	NA					
Change from baseline to week 204	Baseline	31	NA	-2.3	-2.9 to –1.7	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
	Maralixibat 204 weeks	15	NA					
Change in ItchRO (Obs) Weekly morning average score within participants who completed the long-term extension (Week=204; N=15)	Baseline	NA	NA	2.8 (0.5)		NA		Table Change in ItchRO (Obs) Weekly morning average score within participants who completed the long-term extensi
	MRX week 204	15		0.5 (0.7)		NA		
	MRX End of QD	NA		-0.4	(-0.7 to -0.1	Sig*	*Significant 95% CIs (that exclude 0)	

								on (Week =204; N=15)	
								ICONIC table 3.	
								ICONIC table 3.	
ItchRO(Pt) ‡Numbers for this row are as follows: change from baseline at week 18 (n=14), change during the randomised withdrawal window period (weeks 19–22; n=5), maralixibat–placebo comparison (week 22; n=9), change from baseline to week 48 (n=14), change from baseline to week 204 (n=6).									Clinical gov.
ItchRO(Pt)	Change from baseline at week 18	Baseline	31	NA	-2.1	-2.6 to –1.5	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat week 18	14	NA					
	Mean change from Week 18 to Week 22 in pruritus as measured by ItchRO(Pt)	Randomized Withdrawal Period: MRX	5	-0.149(0.3719)	Estimated Value -1.988	-3.009 to -0.967	Sig *	The difference between treatment groups in change from Week 18 to Week 22 in ItchRO (Pt) was evaluated using an ANCOVA model with treatment group as a factor, and Week 18 ItchRO(Pt) as a covariate. The analysis used a tabulation of fitted summary statistics from ANCOVA in the intent-to-treat	ICONIC table 3. And Clinical gov.
		Randomized Withdrawal Period: Placebo	9	1.839(0.2771)					

								population, which included all participants who were enrolled, and received at least one dose of study drug. Clinical gov.	
	Change from baseline to week 48 in itchRO(Pt)	Baseline	NA	NA	-2.3	-2.8 to 1.7	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	14						
	Change from baseline to week 204 in itchRO(Pt)	Maralixibat 204 weeks	6	NA	-2.4	-3.5 to –1.3	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
Aspartate aminotransferase, U/L AST	Mean change from baseline to Week 18	Open-label Period: MRX Week 18	29	NA	–7	–24 to 9	Not sig.	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Open-label Period: MRX Baseline	NA	NA					
	Change during the randomized	MRX RWP	13	NA	42	(11 to 73)	Sig*	*Significant 95% CIs (that exclude 0)	ICONIC table 3.

	withdrawal window phase (RWP	Placebo RWP	16	NA	37	5 to 70	Sig*		
	Change from baseline to Week 48	MRX 48 weeks	27	NA	14	-7 to 35	Not sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
	Change from Baseline to Week 204	Maralixibat 204 weeks	15	NA	43	–3 to 88	Not Sig.	Not Significant 95% CIs (that exclude 0)	
		Baseline	NA						ICONIC table 3.
Alanine transaminase U/L	Mean change from baseline to Week 18	MRX Week 18	29	NA	-1.3	-33.4 to 30.9	Not Sig.	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
ALT	Change during the	MRX RWP	13	NA	43	8.0 to 78.0	Sig*	Not Significant 95% CIs (that exclude 0)	

	randomized withdrawal window phase (RWP	Placebo RWP	16	NA	13	–12 to 37	Not sig.		ICONIC table 3.
	Change from baseline to Week 48	MRX	27	NA	18	-15.0 to 50.1	Not Sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
	Change from Baseline to Week 204	MRX	15	NA	71	–4 to 147	Not Sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
Gammaglutamyl transferase, U/L	Mean change from baseline to Week 18	MRX Week 18	29	NA	29	–36 to 93	Not sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
GGT	Change during the randomized withdrawal window phase (RWP	MRX RWP	13	NA	32	–46 to 109	Not sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Placebo RWP	16	NA	–34	–146 to 78	Not sig.	*Significant 95% CIs (that exclude 0)	
		MRX	27	NA	25	-42 to 92	Not sig.	*Significant 95% CIs (that exclude 0)	

	Change from baseline to Week 48	Baseline	NA	NA					ICONIC table 3.
	Change from Baseline to Week 204	MRX	15	NA	–7	–123 to 109	Not sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
Total bilirubin µmol/L	Mean change from baseline to Week 18	MRX Week 18	29	NA	–8·0	–17·2 to 1·3	Not. Sig.	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
	Change during the randomized withdrawal window phase (RWP	MRX RWP	13	NA	7·5	–5·4 to 20·4	Not. Sig.	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Placebo RWP	16	NA	6·1	–1·4 to 13·6	Not sig.		
	Change from baseline to Week 48	MRX	27	NA	0·5	–11·9 to 13·0	Not sig.	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					

	Change from Baseline to Week 204	MRX	15	NA	–18·1	–37·9 to 1·6	Not sig.	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
Direct bilirubin	Mean change from baseline to Week 18	MRX Week 18	29	NA	–8·6	–15·3 to –1·9	Sig*	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA						
	Change during the randomized withdrawal window phase (RWP	MRX RWP	13	NA	1·9	–5·9 to 9·6	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Placebo RWP	16	NA	2·7	–3·1 to 8·6	Not sig		
	Change from baseline to Week 48	MRX	27	NA	–4·1	–9·7 to 1·5	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					
	Change from Baseline to Week 204	MRX	15	NA	–19·6	–37·6 to –1·7	Sig*	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Baseline	NA	NA					

	Safety set	31	211	−1.5 (-3.1 to 0.1)	4.5	−8.97 to −0.03	0.04	The absolute difference in effect is estimated using a two-sided t-test.	ICONIC table 3.
		NA	209	−6.0 (−10.2 to −1.8)					
CSS Score	Change from baseline at week 18	Baseline	NA	NA	-1.8	-2.3 to –1.2	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	NA	NA					
	Change during the randomised withdrawal window period (weeks 19–22)	Maralixibat	13	0.4 (-0.4 to 1.1)	-0.9	1-8 to –0.1	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat placebo	16	1.6 (0.7 to 2.4)					
	Change from baseline to week 48	Baseline	NA	NA	-1.8	-2.3 to -1.3	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27	NA					

	Change from baseline to week 204	Baseline	NA	NA	-2.3	-3.0 to -1.7	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 204 weeks	15	NA					
CXS score, with xanthoma at baseline (n=14)	Change from baseline at week 18	Baseline	NA	NA	-0.4	-0.9 to 0.1	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	14	NA					
	Change during the randomised withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: MRX	NA	NA	NA			The duration of the time window was insufficient to generate clinically meaningful data. Values shown are for the overall study population, including but not limited to the 15 participants who achieved prespecified criteria for inclusion in the primary endpoint analyses. All analyses, with exception of the maralixibat–placebo comparison, were made based on within group comparisons. Mean difference and 95% CI are the least square mean difference from a repeated measures ANCOVA model that includes treatment group as a fixed effect and baseline value as	Clinical gov.
		Randomized Withdrawal Period: Placebo							

							a covariate. As a result, the least square mean difference is not equal to the difference of the individual treatment groups in the two columns to the left. Clinical gov.	
	Change from baseline to week 48	Baseline	NA	NA	-0.9	-1.3 to -0.5	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27	NA					
	Change from baseline to week 204	Baseline	NA	NA	-1.5	-2.4 to –0.6	<0.005	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 204 weeks	25	NA					
Quality of Life, PedsQL Core (parent)	Change from baseline at week 18	Baseline	NA	NA	11	4 to 17	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29	NA					
	C hange during the randomised	Randomized Withdrawal Period: MRX	13	-8 (-17 to 1)	2	-10 to 15	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.

	withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: Placebo	16	-8 (-17 to 0)					
	Change from baseline to week 48	Baseline	NA	NA	9	2 to 16	Sig*	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat	27	NA					
	Change from baseline to week 204	Baseline	NA	NA	9	-2 to 21	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat	15	NA					
Fatigue, PedsQL Multidimensional Fatigue Scale	Change from baseline at week 18	Baseline	NA	NA	20	9 to 32	Sig*	Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29	NA					
	Change during the randomised withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: MRX	13	-4	14	-3 to 31	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Randomized Withdrawal Period: Placebo	16	-17					
		Baseline	NA	NA	20	9 to 32	Sig *		

	Change from baseline to week 48	Maralixibat 48 weeks	27					*Significant 95% CIs (that exclude 0)	ICONIC table 3.
	Change from baseline to week 204	Baseline	NA	NA	17	6 to 29	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat weeks 204	15						
Growth (height), Z score	Change from baseline at week 18	Baseline	NA	NA	0.12	-0.04 to 0.29	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29	NA					
	Change during the randomised withdrawal window period (weeks 19–22)	NA	NA	NA	NA			The duration of the time window was insufficient to generate clinically meaningful data. Values shown are for the overall study population, including but not limited to the 15 participants who achieved prespecified criteria for inclusion in the primary endpoint analyses. All analyses, with exception of the maralixibat– placebo comparison, were made based on within group comparisons. Mean difference and 95% CI are the least square mean difference from a repeated measures ANCOVA model that includes treatment group as a fixed effect and baseline value as a covariate. As a result, the least square mean difference is not equal to the	

								difference of the individual treatment groups in the two columns to the left	
	Change from baseline to week 48	Baseline	NA	NA	0.18	-0.02 to 0.37	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27						
	Change from baseline to week 204	Baseline	NA	NA	0.40	0.12 to 69	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat weeks 204	15						
Growth (weight), Z score	Change from baseline at week 18	Baseline	NA	NA	0.02	-0.10 to0.14	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29						
	Change during the randomised withdrawal window period (weeks 19–22)	NA	NA	NA	NA			The duration of the time window was insufficient to generate clinically meaningful data. Values shown are for the overall study population, including but not limited to the 15 participants who achieved prespecified criteria for inclusion in the primary endpoint analyses. All analyses, with exception of the maralixibat– placebo comparison, were made based on within	

								group comparisons. Mean difference and 95% CI are the least square mean difference from a repeated measures ANCOVA model that includes treatment group as a fixed effect and baseline value as a covariate. As a result, the least square mean difference is not equal to the difference of the individual treatment groups in the two columns to the left.Clinical gov.	
	Change from baseline to week 48	Baseline	NA	NA	0.02	-0.15 to 0.18	Not sig	Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27						
	Change from baseline to week 204	Baseline	NA	NA	0.16	-0.25 to 0.58	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat weeks 204	15						
Cholesterol, mmol/L	Change from baseline at week 18	Baseline	NA	NA	-2.3	-3.6 to –0.9	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29						

	Change during the randomised withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: MRX	13	0.3 (-0.5 to 1.0)	-1.9	-3.5 to –0.4	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Randomized Withdrawal Period: Placebo	16	2 (0.3 to 3.4)					
	Change from baseline to week 48	Baseline	NA	NA	-1.6	2.7 to 0.5	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27						
	Change from baseline to week 204	Baseline	NA	NA	-3.7	-5.7 to –1.6	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat weeks 204	15						
7α-C4, nmol/L	Change from baseline at week 18	Baseline	NA	NA	35.1	12.1 to 58.1	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29						

	C hange during the randomised withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: MRX	13	-16.5 (-55.3 to 22.3)	31.1	1.9 to 61.3	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Randomized Withdrawal Period: Placebo	16	-20.4 (-48.2 to 7.4)					
	Change from baseline to week 48	Baseline	NA	NA	21.3	-2.0 to 44.7	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 48 weeks	27	NA					
	Change from baseline to week 204	Baseline	NA	NA	40.9	15.5 to 66.2	Sig *	*Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat weeks 204	15	NA					
FGF-19, pmol/L	Change from baseline at week 18	Baseline	NA	NA	-19.9	-40.2 to 0.4	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
		Maralixibat 18 weeks	29	NA					

C hange during the randomised withdrawal window period (weeks 19–22)	Randomized Withdrawal Period: MRX	NA	NA	NA			The duration of the time window was insufficient to generate clinically meaningful data. Values shown are for the overall study population, including but not limited to the 15 participants who achieved prespecified criteria for inclusion in the primary endpoint analyses. All analyses, with exception of the maralixibat– placebo comparison, were made based on within group comparisons. Mean difference and 95% CI are the least square mean difference from a repeated measures ANCOVA model that includes treatment group as a fixed effect and baseline value as a covariate. As a result, the least square mean difference is not equal to the difference of the individual treatment groups in the two columns to the left. Clinical gov.	
	Randomized Withdrawal Period: Placebo	NA	NA					
Change from baseline to week 48	Baseline	NA	NA	-16.1	-38.7 to 6.6	Not sig	Not Significant 95% CIs (that exclude 0)	ICONIC table 3.
	Maralixibat 48 weeks	27	NA					
	Baseline	NA	NA	-9.5	2 to -1.8	Sig *	*Significant 95% CIs (that exclude 0)	

Change from baseline to week 204	Maralixibat weeks 204	15	NA	ICONIC table 3.

B.2 Results per GALA cohort comparison study

Table 45 Results per GALA cohort comparison study

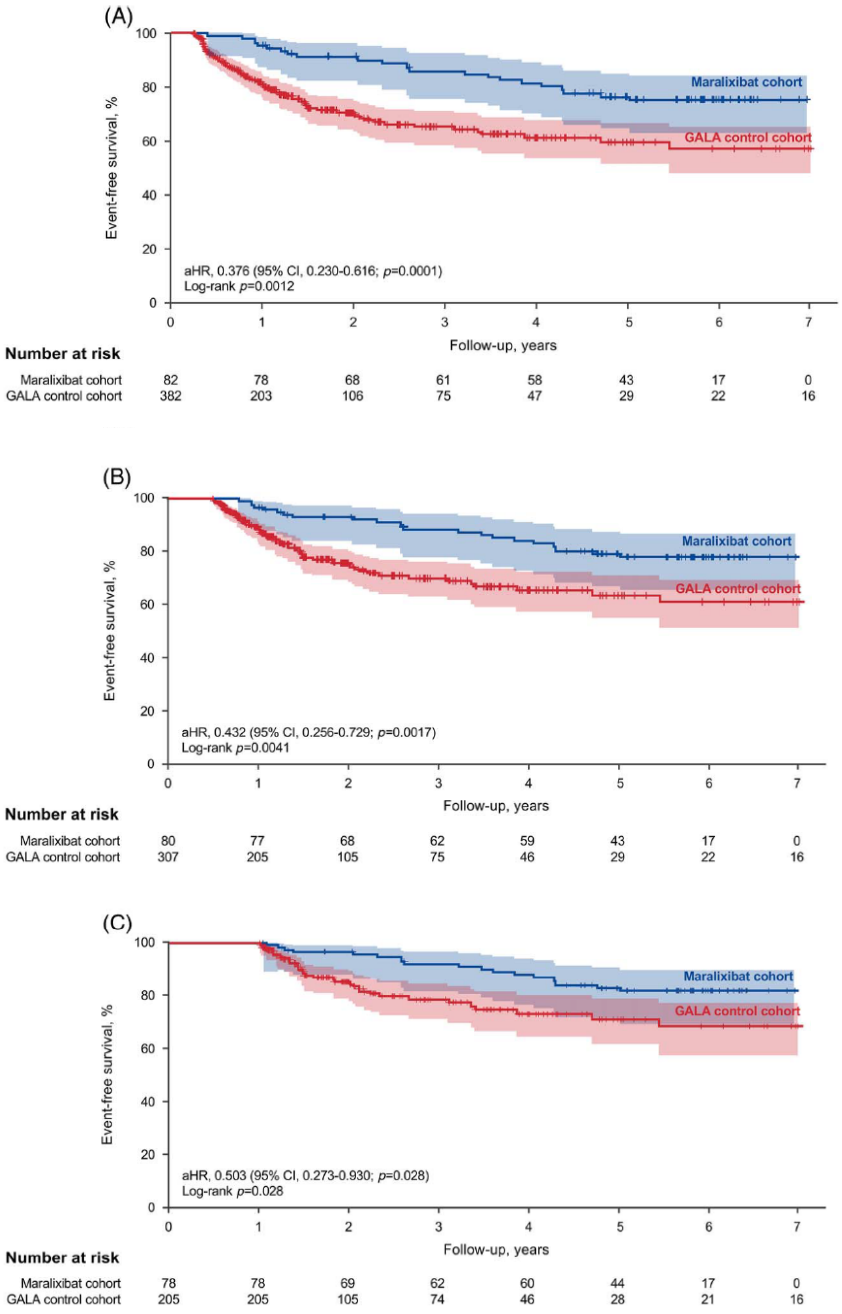
Results of GALA Cohort Comparison Study												
				Estimated absolute difference in effect				Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95 % CI**	***P* value**		**Difference**	**95% CI**	***P* value**		
Event-free survival with an event being defined as LTx, liver decompensation event i.e., variceal bleeding or	MRX	84					Adjusted	HR: 0.305	0.189-0.491	<0.0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment Adjusted for age, sex, bilirubin, and ALT.	[48]
								HR: 0.380	0.238-0.604	<0.0001		
	GALA control group MRX	469					Unadjusted					

ascites, SBD, or all-cause death								
Transplant-free survival defined as the time to liver transplantation or death	MRX GALA control group MRX	84 469		Adjusted	HR: 0.332	0.197-0.559	<0.0001	Cox regression adjusted for age, sex, total bilirubin, and ALT.	[48]
Sensitivity analysis for EFS using different index times:	MRX GALA control group MRX	84 469						All based on adjusted Cox regression models.	[48]
First eligible visit:					HR:0.618	0.369–1.036	0.068		
Last eligible visit:					HR: 0.241	0.148–0.392	<0.0001		
Date of birth:					HR: 0.504	0.320–0.795	0.0032		
Random visit 1:					HR: 0.457	0.284–0.734	0.0012		
Random visit 2:					HR: 0.486	0.304–0.777	0.0026		
Random visit 3:					HR: 0.439	0.274–0.703	0.0006		

Landmark analysis to avoid immortal time bias. Landmark time:	MRX GALA control group					Adjusted Cox regression; events within first 3, 6, or 12 months excluded.	[48]
3 months	MRX	83/456		HR:0.376	0.230–0.616	0.0001	
6 months		81/441		HR: 0.432	0.256–0.729	0.0017	
12 months		74/406		HR: 0.503	0.273–0.930	0.0284	
Propensity score weighted analysis. Weighting method:	MRX GALA control group	84 469				Cox regression using weighted cohorts by estimated propensity scores.	
IPTW				HR:0.379	0.237–0.605	<0.0001	
ATT	MRX			HR: 0.297	0.165–0.535	<0.0001	
Subgroup analysis by region or subgroup:	MRX GALA control group					Adjusted Cox models stratified by region or subgroup.	
North America:	MRX	50/212		HR:0.249	0.114–0.542	0.0005	
Europe:		24/182		HR:0.360	0.187–0.693	0.0022	
Australia:		10/38		HR:0.140	0.024–0.832	0.0306	
Sites overlapping with GALA & trials:		62/214		HR:0.359	0.219–0.587	<0.0001	
GALA patients with sBA data:		84/73		HR:0.245	0.124–0.483	<0.0001	

B.2.1 Sensitivity analysis from the GALA cohort comparison study

Figure 18 Kaplan-Meier estimates of EFS in the maralixibat and GALA control cohorts with landmark time points for events occurring in the first (A) 3 months, (B) 6 months, and (C) 12 months



The number at risk is the original number of participants (at time 0) minus those who had an event or were censored (e.g., lost to follow-up) before the start of the given period. Participants who had events within the first 3, 6, or 12 months were excluded from the analysis (thus, there are no events within these respective periods). This was done to avoid immortal time bias. Shaded areas represent 95% CIs. Abbreviations: aHR:

adjusted hazard ratio; EFS: event-free survival; GALA: Global ALagille Alliance. Adapted from Hansen BE, et al. 2024 [48].

B.2.2 Subgroup analysis from the GALA cohort comparison study

Due to potential differences in SoC between the various regions and centers from which participants originated, a subgroup analysis was conducted to address such disparities in EFS between maralixibat and GALA control groups. The results demonstrated consistency with the primary outcome; EFS between the maralixibat and GALA control groups were also statistically significant across regional subgroups. This implies that variations in SoC did not influence the observed improvement in EFS with maralixibat (see Table below) [48].

Table 46 Subgroup analysis on EFS HR by region

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

Adapted from Hansen BE, et al. 2024 [48].

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 centers in the analyses): HR=0.350; 95% CI: 0.219, 0.587; p<0.0001 [48]. 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 [48].

Appendix C. Comparative analysis of efficacy

Not applicable.

Appendix D. Extrapolation

D.1 Extrapolation of Event-Free Survival (EFS)

EFS for the SoC comparator arm was derived from the GALA natural history cohort (N=469) from the GALA cohort comparison study, which captured time to the first event: LTx, SBD, liver decompensation (ascites or variceal bleeding), or death. The MRX arm (N=84) used pooled long-term data from IMAGINE, ICONIC, and IMAGINE II trials (see Section 6 and Appendix A).

D.1.1 Data input

Patient-level data were reconstructed based on a digitization 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 [109], 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 [109]. The Kolmogorov-Smirnov test statistic was also calculated.

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 [6]. 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.

Table 47: 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)

D.1.2 Model

Parametric survival models (exponential, Weibull, Gompertz, log-logistic, log-normal, generalised gamma) were fitted to the GALA EFS data. 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 [110], the following standard parametric functions were considered: exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalized gamma.

D.1.3 Proportional hazards

Not applicable.

D.1.4 Evaluation of statistical fit (AIC and BIC)

The 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. These results are presented in Table 51.

Table 48: 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**
Generalized gamma	658.0	3	673.2	**7**

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

D.1.5 Evaluation of visual fit

Model fit was also assessed via visual inspection against the Kaplan-Meier plot. Figure 15 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, 87.4–93.7), 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 both 0.001.

Parametric extrapolations of the reconstructed patient-level data are shown in Figure 22. 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.

[redacted]

[redacted]

[redacted]

D.1.6 Evaluation of hazard functions

While formal plots of the hazard functions were not generated, differences in hazard behaviour across the fitted parametric models were inferred from the extrapolated survival curves presented in Figure 16 and from additional survival projections embedded in the economic model. Each parametric distribution assumes a distinct hazard profile: for example, the exponential distribution implies a constant hazard over time, while Weibull and Gompertz allow for monotonic changes in hazard, and log-logistic, log-normal, and gamma distributions accommodate non-monotonic hazards. These differences were indirectly assessed through the shape and divergence of survival trajectories over the extrapolation horizon.

The visual inspection of these curves highlighted considerable variation in long-term survival estimates, reflecting the impact of differing hazard assumptions. The exponential curve consistently projected lower survival across the model time horizon, indicative of its constant and relatively higher hazard assumption. In contrast, distributions such as Gompertz and log-normal produced longer survival estimates, driven by hazard functions that decline or decelerate over time. These observations are supported by the fitted parameter values and covariance matrices extracted from the model's survival bank.

Given this divergence and the tendency of more flexible distributions to produce optimistic survival projections, a conservative approach was taken. The exponential distribution was selected for the base case as it implies a constant hazard and yielded the most cautious long-term survival estimate. This decision was further validated by clinical expert opinion, who confirmed that the conservative trajectory better reflected expected outcomes in this population, and avoided implausible extrapolations beyond the observed data.

D.1.7 Validation and discussion of extrapolated curves

Although the Gompertz and log-normal distributions had the best statistical fit, the exponential distribution was selected for both the maralixibat and SoC arms to provide a conservative estimate of survival and avoid implausible long-term projections. This choice aligns with recommendations from Nordic clinical experts (Appendix M) and is consistent with observed outcomes in the GALA cohort (e.g. 92.1% survival at 10 years; 90.5% at 18 years).

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 (Appendix M) confirmed the range was broadly representative of expected outcomes. As such, the conservative curve was selected in the base case (exponential).

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 Denmark (84 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.

The outputs of the parametric extrapolations are summarised in Table 52, which shows survival probabilities at 10, 18, 50, and 100 years, as well as median survival estimates. While all models aligned closely with observed survival at 10 and 18 years, the long-term projections diverged substantially. Distributions such as the log-normal and generalized gamma predicted median survival exceeding 300 years, which is clearly implausible. In contrast, the exponential model produced a conservative and more clinically realistic estimate of 77.4 years, supporting its selection for the base case.

Table 49: Survival probabilities at different ages

Distribution	Year 10	Year 18	Year 50	Year 100	Median survival (years)
Observed survival a	[redacted]				
Exponential	[redacted]				
Weibull	[redacted]				
Log-normal	[redacted]				
Log-logistic	[redacted]				
Gompertz	[redacted]				
Gamma	[redacted]				
Generalized Gamma	[redacted]				

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

D.1.8 Adjustment of background mortality

These models were used to predict disease-specific mortality, which was combined with life-table 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.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Waning of treatment effect was not explicitly modelled. The exponential distribution, selected for its conservative long-term projections, assumes a constant hazard rate over time and thus implicitly incorporates a conservative approach to long-term treatment benefit.

D.1.11 Cure-point

No explicit cure-point was modelled. The exponential distribution implies a constant hazard across time, which is a conservative assumption and was preferred by clinical experts.

D.2 Extrapolation of [effect measure 2]

Not applicable.

Appendix E. Serious adverse events

Safety results, including serious adverse events from the ICONIC trial, are already described in Section 9.1. The tables from that section are presented here

Table 50 Overview of safety events from baseline to Week 48

	Open-label period (baseline to Week 18)	Randomized withdrawal window phase (RWP)		Stable-dosing period (Weeks 23 to 48)
	MRX (N=31)	MRX (N = 13)	Placebo (n = 16)	MRX (N=29)
Participants with 1 or more treatment emergent adverse event	30 (97%)	7 (54%)	12 (75%)	25 (86%)
Treatment emergent adverse events potentially related to study drug*	12 (39%)	1 (8%)	3 (19)	1 (3%)
Treatment emergent adverse events leading to study drug discontinuation†	2 (7%)	0	0	1 (3%)
Serious adverse events	4 (13%)	1 (8%)	1 (6%)	5 (17%)
Serious adverse events potentially related to study drug*	0	0	0	0

Adapted from Gonzales E, et al. 2021 [17].

Data are n (%).

*Any treatment emergent or serious adverse event that was determined by an investigator as related or possibly related to the study drug is considered as potentially related to the study drug.

†There were two discontinuations due to treatment emergent adverse events during the open-label period of the study; one participant discontinued for a serious adverse event deemed unrelated to maralixibat by the investigator (post-traumatic epidural and subdural hematomas), one participant discontinued for a treatment emergent adverse event deemed possibly related to maralixibat by the investigator (staphylococcal hand

infection). During the stable dosing period, one participant discontinued due to a treatment emergent adverse event deemed unrelated to maralixibat by the investigator (increased serum bilirubin levels).

Table 51 Overview of safety events from Week 48 to Week 204

	Long-term extension (Weeks 48 to 204) MRX (N=23)
Participants with ≥1 TEAE	23 (100)
TEAEs potentially related to study drug[a]	8 (35)
SAEs	6 (26)
SAEs potentially related to study drug[a]	0 (0)
TEAEs leading to study drug discontinuation[b]	2 (9)
TEAEs leading to death	0 (0)

Adapted from Gonzales E, et al. Lancet 2021; 398:1581–1592 (Supplemental).
a Any TEAE or SAE that was determined by a clinical investigator as related or possibly related to the study drugs, or is missing any associated data, is considered as potentially related to the study drug;
b There were discontinuations due to TEAEs during the long-term extension; 1 participant discontinued due to a TEAE deemed unrelated to maralixibat by the investigator (acute renal failure), and 1 participant discontinued due to ALT elevations considered possibly related to study medication by the investigator. A third discontinuation occurred after the period reported here (Week 213) due to an ALT elevation considered related to study drug.

Frequency and severity of AEs

The incidence of AEs in each study phase is presented in the Table below [17].

Table 52 Serious adverse events (time point)

n (%)	Open-label phase (≤a 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
Number of patients with at least 1 AE	30 (97)	7 (53.8)	12 (75.0)	25 (86.2)	23 (100.0)
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)

Diarrhea	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)
General disorders and administration site conditions	7 (22.6)	0	3 (19)	10 (34.5)	12 (52.2)
Pyrexia	6 (19.4)	0	2 (12.5)	7 (24.1)	10 (43.5)
Infections and infestations	21 (68)	6 (46.2)	4 (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)
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)	
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)
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)
Oropharyngeal pain	1 (3.2)	0	0	3 (10.3)	3 (13.0)

Adapted from Gonzales E et al. 2021 (Supplemental) [17].

a Any TEAE or SAE that was determined by an investigator to be related or possibly related to the study drug or is missing any associated data is considered as potentially related to the study drug;

b occurring in ≥10% of participants in any treatment group during any period of the study, or in ≥2 participants

Abbreviations: MRX: maralixibat; RWP: randomized withdrawal window period.

Adverse events used in the health economic model

AEs recorded in the ICONIC study have been detailed in the Table below.

Table 53 Adverse events used in the health economic model

Adverse events	Disutility	MRX	SoC		
		Frequency used in economic model for MRX (probability per cycle)	**Frequency used in economic model for SoC (probability per cycle)**	**Source**	**Justification**
Abdominal pain, n (%)	-0.051	6.45%	0%	Sullivan et al. 2011 [76]	Disutilities for AEs are included to capture their impact on quality of life, enhance model realism, and provide a balanced assessment of treatment benefits and risks.
ALT increase	0.00	6.45%	0%	Sullivan et al. 2011 [76]	
Disutility per cycle		-0.0033		0.00	

Appendix F. Health-related quality of life

Table 54 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Used in the vignette study [74] to assess health-related quality of life (HRQoL) for patients with ALGS and their caregivers. The tool was utilized during: - Time trade-off (TTO) valuation interviews with the UK general population (n=200). - Online caregiver burden survey (n=105 caregivers).	To assess HRQoL changes across different patient and caregiver health states. To generate preference-based utility values for economic evaluations. To capture decrements in HRQoL for more severe health states.
Time Trade Off (TTO)	In the vignette study [74], the TTO was conducted with a representative sample of the UK general population.	To estimate the preference-weighted utility values of different health states, including progressive cholestasis and liver transplant outcomes. Supporting cost-effectiveness evaluations of treatments.
Hospital Anxiety and Depression Scale (HADS)	In the vignette study [74], HADS was administered as part of the caregiver burden survey.	To assess the psychological impact (anxiety and depression) on caregivers, highlighting mental health burdens associated with caregiving.
Work Productivity and Activity Impairment: Caregiving (WPAI:CG)	In the vignette study [74] it was included in the caregiver survey.	To quantify impacts on work productivity and daily activity due to caregiving responsibilities.
Visual Analogue Scale (VAS)	Part of the EQ-5D-5L assessment and standalone in the TTO interviews in the vignette study [74].	Clinical effectiveness: To evaluate subjective perceptions of health states, ranking them from 0 (worst health) to 100 (best health).

Table 55 Mean change from baseline in QoL PedsQL scores over time (ITT) [82] [17]

Quality of Life, PedsQL Core (Parent)	Change from baseline at Week 18 MRX (n=29)	Change during the randomized withdrawal phase (RWP) MRX (n=13)	 PBO (n=16)	Maralixibat-placebo comparison (Week 22)	Change from baseline to Week 48 MRX (n=27)	Change from baseline to Week 204 MRX (n=15)
Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Gonzales E, et al. Lancet 2021; 398:1581–1592.

Student's t-test was used to test if mean change was statistically significant.

Data are mean (95% CI). *Significant 95% CIs (that exclude 0).

Abbreviations: ITT, intent-to-treat; PedsQL, Pediatric Quality of Life Inventory; BL: baseline; MRX: maralixibat; PBO: placebo.

Table 56 Mean change from baseline in PedsQL fatigue scores over time (ITT) [17] [82]

Fatigue, PedsQL Multidimensional Fatigue Scale	Change from baseline at Week 18 MRX (n=29)	Change during the randomized withdrawal phase (RWP) MRX (n=13)	 PBO (n=16)	Maralixibat-placebo comparison (Week 22)	Change from baseline to Week 48 MRX (n=27)	Change from baseline to Week 204 MRX (n=15)
Mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adapted from Gonzales E, et al. Lancet 2021; 398:1581–1592.

Student's t-test was used to test if mean change was statistically significant.

Data are mean (95% CI). *Significant 95% CIs (that exclude 0).

Abbreviations: ITT, intent-to-treat; PedsQL, Pediatric Quality of Life Inventory; BL: baseline; MRX: maralixibat; PBO: placebo.

Table 57: 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.

Table 58: 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 59: 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.

Table 60: Summary of PedsQL scores reported in Kamath et al [20] and mapping algorithm from Khan [92]

Scale	PedsQL		Mapped EQ-5D	
	ALGS	Healthy	ALGS	Healthy
Total score	[redacted]	[redacted]	[redacted]	[redacted]

Physical functioning	[redacted]	[redacted]
Emotional functioning	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]
School functioning	[redacted]	[redacted]
Age	[redacted]	
Gender	[redacted]	

Abbreviations: PedsQL, Pediatric Quality of Life Inventory TM.

Table 61: Summary of adverse events used in the model

Adverse event	Disutility value: mean (standard error)	95% confidence interval	Reference
Abdominal Pain	–0.0512028 (0.005311)	–0.0616124 – 0.0407931	Sullivan et al. [76].
ALT Increased	0	–	

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

Table 62 Overview of health state utility values for cost-effectiveness analysis

State	Utility value	Reference	Description
Responsive to medication	[redacted]	Vignette study [74]	The vignette study reported mean EQ-5D-5L utility values for cholestasis health states. For the model, the mean score of [redacted] from patients with non-progressive cholestasis was used to represent the responsive to medication state, while the mean score of 0.539 from patients with progressive cholestasis was applied to the unresponsive to medication state.
Unresponsive to medication	[redacted]	Vignette study [74]	
Cirrhosis	[redacted]	Vignette study [74]	The utility for cirrhosis has been calculated as the sum of the unresponsive to medication utility

			[redacted] from the vignette study and the 'liver disease' disutility [redacted] reported by Sullivan et al. 2011 [76]
PHT	[redacted]	Vignette study [74]	The utility for PHT has been calculated as the sum of the cirrhosis utility (0.501) from the vignette study and the 'liver disease' disutility (–0.038) reported by Sullivan et al. 2011 [76]
Ascites	[redacted]	Vignette study [74]	The utility for ascites has been calculated as the sum of the PHT utility (0.462) from the vignette study and the 'gastrointestinal disorder' disutility (–0.051) from Sullivan et al. 2011 [76]
SBD	[redacted]	Vignette study [74]	Assumed equivalent to LTx utility
Post-SBD	[redacted]	Vignette study [74]	The response to medication [redacted] utility multiplied by the stoma multiplier [redacted] used in HST17 [75]
LTx	[redacted]	Vignette study [74]	The utility for the LTx health state was calculated as a weighted average of two EQ-5D-5L mean index scores from the vignette study: The utility for progressive cholestasis (0.539) was used to represent patients with a functioning transplant and no rejection, weighted by the probability of not requiring a retransplant in a given cycle (i.e., 1 minus the retransplant probability). The utility for rejection to LTx [redacted] was used to represent patients who experience graft rejection and require a retransplant, weighted by the

			cycle probability of retransplantation.
Post-LTx	[redacted]	Vignette study [74]	The utility for the post-LTx health state was taken from the "successful liver transplant" EQ-5D-5L mean index score of [redacted], as derived from the vignette study.
Death	0	-	–

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

Table 63: 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]
LTx	[redacted]	[redacted]
Post-LTx	[redacted]	[redacted]
Death	[redacted]	[redacted]

Abbreviations: LTx, liver transplantation; NA, not applicable; PHT, portal hypertension.

Appendix G. Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed to explore the effect of uncertainty associated with key model inputs. 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 DKK [redacted], respectively, compared to [redacted] and DKK [redacted] in the deterministic analysis results. A scatterplot presents the total number of simulations (Figure 17). The ICER in the probabilistic analysis resulted in an ICER of [redacted] DKK /QALY.

Table 64 Probabilistic results

	MRX	SoC	Incremental (DKK)	ICER (DKK/QALY)
Total costs (DKK)	[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]

Table 65 Overview of parameters in the PSA

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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.

Appendix H. Literature searches for the clinical assessment

A global SLR was performed to identify existing epidemiological, burden, efficacy and safety, economic, cost and resource use, health-related quality of life (HRQoL) studies conducted in ALGS. The systematic literature review (SLR) was first developed to support the development of the NICE submission and health state vignettes to be used in the utility valuation study (Vignette Study).

Pre-defined search strategies and eligibility criteria were used to identify all relevant literature for the review questions. A pre-selected number of databases, including Embase and Medline were searched. Grey literature searches were performed including the proceedings of relevant conferences. The retrieved papers were reviewed at a first and second pass stage by two independent reviewers prior to extraction. The Original SLR was performed in October 2021 by FIECON. Moreover, an update to the SLR was performed in May 2023 by Initiate Consultancy Limited. Additionally, an update in September 2024 was conducted by Abacus Medicine Pharma Services.

In this submission, we included the combined results of both the Original systematic literature review (SLR) and its subsequent updates for the clinical and health-related quality of life (HRQoL) cost effectiveness, cost and resource use, epidemiology and humanistic and economic burden review question searches.

H.1 Efficacy and safety of the intervention and comparator(s)

A Clinical SLR was conducted to answer the following research questions which follow the PICOS (population, interventions, comparators, outcomes and study type) principle [111]:

> *What randomized controlled trials (RCTs) have measured the efficacy and safety of treatment in patients with ALGS? (review question number 1)*
>
> *What non-RCTs have measured the efficacy and safety of treatment in patients with ALGS? (review question number 2)*

Searches to identify evidence for the two review questions written above were conducted in the following databases for the Clinical SLR:

- Embase (covers biomedical literature from 1974 to present)
- MEDLINE (covers journals from 1966 to present)
- Embase Classic (the Embase back file covering citations between 1947 and 1973)

In addition to the databases listed above, searches to identify clinical studies were conducted in:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)

- Cochrane Clinical Answers

The May 2023 SLR update included the following databases via OVID:

- Embase (covers biomedical literature from 1974 to present)
- MEDLINE (covers journals from 1966 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)
- Cochrane Clinical Answers

The September 2024 update included the following databases for the clinical search strategy.

- Embase (Medline) (from the 18th of May 2023 to the 1st of September 2024)
- Cochrane Library Interface (CENTRAL and Cochrane Clinical Answers)

Table 66 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Medline	Medline; NLM	1966 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Embase classic	Ovid	between 1947 and 1973 for the Original SLR	Original SLR: 11.10.2021
CENTRAL	Cochrane Library Interface	1996 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Database	Platform/source	Relevant period for the search	Date of search completion
Cochrane Clinical Answers	Cochrane Library Interface	2012 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Supplementary searches of "grey" literature were performed in Google Scholar and through the NICE, Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH) and Scottish Medicines Consortium (SMC) websites. Only completed HTA submissions were considered.

Searches included clinicaltrials.gov, searches of the manufacturer's repository of evidence, websites of manufacturers of comparator products, bibliographic searching of any SLRs identified during screening, and the following relevant congresses over the last two years:

- European Association for the Study of the Liver (EASL)
- Federation of International Societies of Pediatric, Gastroenterology, Hepatology and Nutrition (FISPGHAN) – includes European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN), North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN), and Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN)
- American Association for the Study of Liver Disease (AASLD)

The grey searches described above were searched again during the May 2023 SLR update and the September 2024 update, respectively.

Table 67 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Source name	Location/source	Search strategy	Date of search
PBAC	PBS.com	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
CADTH	CDA-AMC.ca	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
SMC	scottishmedicines.org.uk	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
clinicaltrials.gov	clinicaltrials.gov	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
MAH repository	Internal repository	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
EASL	EASL.eu	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question,	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Source name	Location/source	Search strategy	Date of search
		epidemiological/pathogenesis question	
FISPGHAN	FISPGHAN.org	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
AASLD	AASLD.org	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Abbreviations: MAH: Marketing Authorization Holder

Table 68 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

H.1.1 Search strategies

The Tables below present the search strategies for Embase, MEDLINE and Embase Classic, CENTRAL and Cochrane Clinical Answers during the first SLR search. These strategies included terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review questions. Only publications available in English were included in the searches and no date restrictions were applied.

Table 69 of search strategy table for Embase, MEDLINE and Embase Classic (Embase interface)

No.	Query	Results
#1	'alagille* syndrome'/exp OR 'alagille syndrome'/exp OR 'ALGS'/exp OR 'Alagille-watson syndrome'/exp OR 'Watson Alagille syndrome'/exp OR 'arteriohepatic dysplasia'/exp OR 'cardiovertebral syndrome'/exp OR 'cholestasis with peripheral pulmonary stenosis'/exp OR 'hepatic ductular hypoplasia'/exp OR 'hepatofacioneurocardiovertebral syndrome'/exp OR	3,528

No.	Query	Results
	‘paucity of interlobular bile ducts’/exp OR ‘syndromic bile duct paucity’/exp OR ‘watson-miller syndrome’/exp OR ‘JAG1’/exp	
#2	‘maralixibat’/exp OR ‘inhibitor* of the apical sodium-dependent bile acid transporter’/exp OR ‘apical sodium-dependent bile acid transporter inhibitor*’/exp OR ‘ASBT inhibitor*’/exp OR ‘ASBTi’/exp OR ‘inhibitor* of the ASBT’/exp OR ‘ileal bile acid transport*’/exp OR ‘IBA transport*’/exp OR ‘IBAT’/exp OR ‘ileal bile acid transporter inhibitor’/exp OR ‘IBAT inhibit*’/exp OR 'ursodeoxycholic acid'/exp OR 'ursodiol'/exp OR ‘liver transplantation’/exp OR ‘liver transplant*’/exp OR ‘LT’/exp OR ‘partial biliary diversion’/exp OR ‘partial external biliary diversion’/exp OR ‘PEBD’/exp OR ‘rifampin’/exp OR ‘naltrexone’/exp OR ‘cholestyramine’/exp	314,921
#3	('clinical trial'/de OR 'randomized controlled trial'/de OR ‘controlled clinical trial’/de OR ‘multicenter study’/de OR ‘Phase 3 clinical trial’/de OR ‘Phase 4 clinical trial’/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR ‘editorial’/de OR ‘note’/de)	2,456,073
#4	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)	3,907,539
#5	#1 AND #2 AND (#3 OR #4) AND [humans]/lim	182

Table 70 of search strategy table for CENTRAL and Cochrane Clinical Answers (Cochrane Library interface)

No.	Query	Results
#1	‘alagille syndrome’ OR ‘ALGS’ OR ‘Alagille-watson syndrome’ OR ‘Watson Alagille syndrome’ OR ‘arteriohepatic dysplasia’ OR ‘cardiovertebral syndrome’ OR ‘cholestasis with peripheral pulmonary stenosis’ OR ‘hepatic ductular hypoplasia’ OR ‘hepatofacioneurocardiovertebral syndrome’ OR ‘paucity of interlobular bile ducts’ OR ‘syndromic bile duct paucity’ OR ‘watson-miller syndrome’ OR ‘JAG1’	227

No.	Query	Results
#2	'maralixibat' OR 'inhibitor* of the apical sodium-dependent bile acid transporter' OR 'apical sodium-dependent bile acid transporter inhibitor*' OR 'ASBT inhibitor*' OR 'ASBTi' OR 'inhibitor* of the ASBT' OR 'ileal bile acid transport*' OR 'IBA transport*' OR 'IBAT' OR 'ileal bile acid transporter inhibitor' OR 'IBAT inhibit*' OR 'ursodeoxycholic acid' OR 'ursodiol' OR 'liver transplantation' OR 'liver transplant*' OR 'LT' OR 'partial biliary diversion' OR 'partial external biliary diversion' OR 'PEBD' OR 'rifampin' OR 'naltrexone' OR 'cholestyramine'	14244
#3	#1 and #2 in trials	35

Tables below include the search strategies via OVID utilized during the May 2023 SLR update (18th of May 2023).

Table 71 of search strategy table for Embase database (via OVID platform)

Index	Description	No.	Query	Results
#1	Population	1	exp Alagille Syndrome/	2,950
		2	Alagille Syndrome.mp.	3,425
		3	ALGS.mp.	455
		4	exp Alagille-Watson Syndrome/	2,950
		5	Alagille-Watson Syndrome.mp.	15
		6	exp Watson Alagille Syndrome/	2,950
		7	Watson-Alagille Syndrome.mp.	7
		8	exp arteriohepatic dysplasia/	2,950
		9	arteriohepatic dysplasia.mp.	252
		10	exp Cardiovertebral Syndrome/	740
		11	Cardiovertebral Syndrome.mp.	0
		12	exp cholestasis with peripheral pulmonary stenosis/	740

		13	cholestasis with peripheral pulmonary stenosis.mp.	0
		14	exp hepatic ductular hypoplasia/	740
		15	hepatic ductular hypoplasia.mp.	19
		16	exp hepatofacioneurocardiovertebral syndrome/	740
		17	hepatofacioneurocardiovertebral syndrome.mp.	0
		18	exp paucity of interlobular bile ducts/	740
		19	paucity of interlobular bile ducts.mp.	190
		20	syndromic bile duct paucity.mp.	17
		21	exp watson-miller syndrome/	740
		22	watson-miller syndrome.mp.	1
		23	JAG1.mp.	3,648
		24	or/1-23	6,706
#2	Interventions/comparators	25	exp maralixibat/ or maralixibat.mp.	146
		26	inhibitor* of the apical sodium dependent bile acid transporter.mp.	27
		27	apical sodium-dependent bile acid transporter inhibitor*.mp.	60
		28	ASBT inhibitor*.mp.	184
		29	ASBTi.mp.	27
		30	inhibitor* of the ASBT.mp.	43
		31	ileal bile acid transport*.mp.	443

		32	IBA transport*.mp.	22
		33	IBAT.mp.	1,501
		34	ileal bile acid transporter inhibitor.mp.	130
		35	IBAT inhibit*.mp.	107
		36	ursodeoxycholic acid.mp.	24,608
		37	exp ursodiol/	21,455
		38	ursodiol.mp.	853
		39	exp liver transplantation/	202,963
		40	liver transplantation.mp.	215,078
		41	exp liver transplant/	98,117
		42	liver transplant.mp.	62,959
		43	partial biliary diversion.mp.	57
		44	PEBD.mp.	126
		45	exp rifampin/	119,371
		46	rifampin.mp.	36,642
		47	exp naltrexone/	25,610
		48	naltrexone.mp.	29,959
		49	exp cholestyramine/	13,532
		50	cholestyramine.mp.	6,781
		51	or/25-50	425,145
#3	Study types: RCT Filter	52	Clinical Trial/	1,613,992
		53	Randomized Controlled Trial/	1,377,821
		54	controlled clinical trial/	564,553

55	multicenter study/	711,362
56	Phase 3 clinical trial/	69,626
57	Phase 4 clinical trial/	5,457
58	exp RANDOMIZATION/	206,405
59	Single Blind Procedure/	51,785
60	Double Blind Procedure/	210,413
61	Crossover Procedure/	75,192
62	PLACEBO/	403,213
63	..nlp randomi?ed controlled trial$. Including Related Terms	97,679
64	rct.tw.	84,487
65	(random$ adj2 allocat$).tw.	98,065
66	single blind$.tw.	54,612
67	double blind$.tw.	414,947
68	((treble or triple) adj blind$).tw.	3,359
69	placebo$.tw.	614,028
70	Prospective Study/	1,535,034
71	or/52-70	4,701,513
72	Case Study/	2,434,225
73	abstract report/ or letter/	2,532,877
74	Conference proceeding.pt.	0
75	Conference abstract.pt.	4,766,727
76	Editorial.pt.	1,424,832
77	Letter.pt.	2,520,123

		78	Note.pt.	939,980
		79	72 or 73 or 74 or 75 or 76 or 77 or 78	11,900,256
		80	71 not 79	3,864,349
#4	Observation study filter	81	'clinical trial'/	1,076,033
		82	'case control study'.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]	364,935
		83	'family study'/	25,768
		84	'longitudinal study'/	193,370
		85	'retrospective study'/	1,466,713
		86	'prospective study'/ not 'randomized controlled trial'/	780,346
		87	'cohort analysis'/	1,035,202
		88	(cohort adj (study or studies)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, bt, nm, ox, px, rx, an, ui, sy, ux, mx]	1,005,386
		89	('case control' adj (study or studies)).ti,ab.	295,811
		90	('follow up' adj (study or studies)).ti,ab.	129,738
		91	(observational adj (study or studies)).ti,ab.	412,574
		92	(epidemiologic* adj (study or studies)).ti,ab.	217,300
		93	('cross sectional' adj (study or studies)).ti,ab.	590,523
		94	or/81-93	5,795,741

#5	Population AND Intervention/Comparator	95	24 and 51	1,222
#6	Population AND Intervention/Comparator AND RCT filter	96	80 and 95	70
#7	Population AND Intervention/Comparator AND Observational study filter	97	94 and 95	230
#8	Population AND Intervention/Comparator AND RCT filter AND Observational study filter	98	96 or 97	255
#9	Restrict results to humans	99	limit 98 to humans	249
#10	Restrict result for update period 11th Oct 2021 to 18th May 2023	100	limit 99 to dd=20211011-20230518	44

Table 72 of search strategy table for Medline database (via OVID platform)

Index	Description	No.	Query	Results
#1	Population	1	exp Alagille Syndrome/	740
		2	Alagille Syndrome.mp.	1,087
		3	ALGS.mp.	160
		4	exp Alagille-Watson Syndrome/	740
		5	Alagille-Watson Syndrome.mp.	7
		6	exp Watson Alagille Syndrome/	740
		7	Watson-Alagille Syndrome.mp.	3
		8	exp arteriohepatic dysplasia/	740
		9	arteriohepatic dysplasia.mp.	116
		10	exp Cardiovertebral Syndrome/	740

		11	Cardiovertebral Syndrome.mp.	0
		12	exp cholestasis with peripheral pulmonary stenosis/	740
		13	cholestasis with peripheral pulmonary stenosis.mp.	0
		14	exp hepatic ductular hypoplasia/	740
		15	hepatic ductular hypoplasia.mp.	8
		16	exp hepatofacioneurocardiovertebral syndrome/	740
		17	hepatofacioneurocardiovertebral syndrome.mp.	0
		18	exp paucity of interlobular bile ducts/	740
		19	paucity of interlobular bile ducts.mp.	84
		20	syndromic bile duct paucity.mp.	7
		21	exp watson-miller syndrome/	740
		22	watson-miller syndrome.mp.	1
		23	JAG1.mp.	1,781
		24	or/1-23	2,742
#2	Interventions/ comparators	25	exp maralixibat/ or maralixibat.mp.	20
		26	inhibitor* of the apical sodium dependent bile acid transporter.mp.	9
		27	apical sodium-dependent bile acid transporter inhibitor*.mp.	12
		28	ASBT inhibitor*.mp.	59
		29	ASBTi.mp.	5
		30	inhibitor* of the ASBT.mp.	18

		31	ileal bile acid transport*.mp.	155
		32	IBA transport*.mp.	11
		33	IBAT.mp.	663
		34	ileal bile acid transporter inhibitor.mp.	28
		35	IBAT inhibit*.mp.	38
		36	ursodeoxycholic acid.mp.	6,664
		37	exp ursodiol/	4,516
		38	ursodiol.mp.	221
		39	exp liver transplantation/	64,131
		40	liver transplantation.mp.	81,251
		41	exp liver transplant/	64,131
		42	liver transplant.mp.	21,087
		43	partial biliary diversion.mp.	20
		44	PEBD.mp.	47
		45	exp rifampin/	19,693
		46	rifampin.mp.	24,281
		47	exp naltrexone/	8,650
		48	naltrexone.mp.	11,153
		49	exp cholestyramine/	2,666
		50	cholestyramine.mp.	3,631
		51	or/25-50	130,186
#3	Study types: RCT Filter	52	Clinical Trial/	538,010
		53	Randomized Controlled Trial/	593,127

54	controlled clinical trial/	95,308
55	multicenter study/	333,950
56	Phase 3 clinical trial/	0
57	Phase 4 clinical trial/	0
58	exp RANDOMIZATION/	106,929
59	Single Blind Procedure/	0
60	Double Blind Procedure/	0
61	Crossover Procedure/	0
62	PLACEBO/	0
63	..nlp randomi?ed controlled trial$. Including Related Terms	22,168
64	rct.tw.	30,943
65	(random$ adj2 allocat$).tw.	43,453
66	single blind$.tw.	22,918
67	double blind$.tw.	169,763
68	((treble or triple) adj blind$).tw.	1,472
69	placebo$.tw.	246,023
70	Prospective Study/	659,009
71	or/52-70	1,850,146
72	Case Study/	2,336,813
73	abstract report/ or letter/	1,217,493
74	Conference proceeding.pt.	0
75	Conference abstract.pt.	0
76	Editorial.pt.	650,118

		77	Letter.pt.	1,217,493
		78	Note.pt.	0
		79	72 or 73 or 74 or 75 or 76 or 77 or 78	3,977,163
		80	71 not 79	1,807,748
#4	Observation study filter	81	'clinical trial'/	0
		82	'case control study'.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]	108,911
		83	'family study'/	0
		84	'longitudinal study'/	0
		85	'retrospective study'/	0
		86	'prospective study'/ not 'randomized controlled trial'/	0
		87	'cohort analysis'/	0
		88	(cohort adj (study or studies)).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]	528,254
		89	('case control' adj (study or studies)).ti,ab.	127,029
		90	('follow up' adj (study or studies)).ti,ab.	56,007

		91	(observational adj (study or studies)).ti,ab.	158,957
		92	(epidemiologic* adj (study or studies)).ti,ab.	94,794
		93	('cross sectional' adj (study or studies)).ti,ab.	253,209
		94	or/81-93	1,159,372
#1+#2	Population AND Intervention/Comparator	95	24 and 51	305
#1+#2+#3	Population AND Intervention/Comparator AND RCT filter	96	80 and 95	12
#1+#2+#4	Population AND Intervention/Comparator AND Observational study filter	97	94 and 95	12
#1+#2+#3+#4	Population AND Intervention/Comparator AND RCT filter AND Observational study filter	98	96 or 97	22
Limit	Restrict results to humans	99	limit 98 to humans	17
Limit date	Restrict result for update period 11th Oct 2021 to 18th May 2023	100	limit 99 to dt=20211011-20230518	4

Table 73 of search strategy table for CENTRAL and Cochrane Clinical Answers (Cochrane Library interface)

No.	Query	Results from 18 May 2023
#1	exp Alagille Syndrome/	12
#2	Alagille Syndrome.mp.	47
#3	ALGS.mp.	25
#4	exp Alagille-Watson Syndrome/	12
#5	Alagille-Watson Syndrome.mp.	0
#6	exp Watson Alagille Syndrome/	12
#7	Watson-Alagille Syndrome.mp.	0
#8	exp arteriohepatic dysplasia/	12
#9	arteriohepatic dysplasia.mp.	2
#10	exp Cardiovertebral Syndrome/	12
#11	Cardiovertebral Syndrome.mp.	2
#12	exp cholestasis with peripheral pulmonary stenosis/	12
#13	cholestasis with peripheral pulmonary stenosis.mp.	0
#14	exp hepatic ductular hypoplasia/	12
#15	hepatic ductular hypoplasia.mp.	1
#16	exp hepatofacioneurocardiovertebral syndrome/	12
#17	hepatofacioneurocardiovertebral syndrome.mp.	0
#18	exp paucity of interlobular bile ducts/	12
#19	paucity of interlobular bile ducts.mp.	0
#20	syndromic bile duct paucity.mp.	0

#21	exp watson-miller syndrome/	12
#22	watson-miller syndrome.mp.	0
#23	JAG1.mp.	8
#24	or/1-23	56
#25	exp maralixibat/ or maralixibat.mp.	30
#26	inhibitor* of the apical sodium dependent bile acid transporter.mp.	5
#27	apical sodium-dependent bile acid transporter inhibitor*.mp.	17
#28	ASBT inhibitor*.mp.	7
#29	ASBTi.mp.	9
#30	inhibitor* of the ASBT.mp.	0
#31	ileal bile acid transport*.mp.	61
#32	IBA transport*.mp.	0
#33	IBAT.mp.	22
#34	ileal bile acid transporter inhibitor.mp.	49
#35	IBAT inhibit*.mp.	14
#36	ursodeoxycholic acid.mp.	1496
#37	exp ursodiol/	615
#38	ursodiol.mp.	87
#39	exp liver transplantation/	1727
#40	liver transplantation.mp.	4383
#41	exp liver transplant/	1727
#42	liver transplant.mp.	1977

#43	partial biliary diversion.mp.	2
#44	PEBD.mp.	6
#45	exp rifampin/	1345
#46	rifampin.mp.	1829
#47	exp naltrexone/	1553
#48	naltrexone.mp.	2847
#49	exp cholestyramine/	287
#50	cholestyramine.mp.	513
#51	or/25-50	11735
#52	24 and 51	36
#53	limit 52 to yr="2021 -Current"	8

Tables below include the search strategies utilized during the September 2024 SLR update (from 18th May 2023 to 1st September 2024).

Table 74 of search strategy table for Embase, MEDLINE and Embase Classic (Embase interface)

No.	Query	Results
#1	('alagille* syndrome' OR 'alagille syndrome'/exp OR 'algs' OR 'alagille-watson syndrome'/exp OR 'watson alagille syndrome'/exp OR 'arteriohepatic dysplasia'/exp OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'jag1') AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	426
#2	('maralixibat'/exp OR 'inhibitor* of the apical sodium-dependent bile acid transporter' OR 'apical sodium-dependent bile acid transporter inhibitor*' OR 'asbt inhibitor*' OR 'asbti' OR 'inhibitor* of the asbt' OR 'ileal bile acid transport*' OR 'iba transport*' OR 'ibat' OR 'ileal bile acid transporter inhibitor'/exp OR 'ibat inhibit*' OR 'ursodeoxycholic acid'/exp OR 'ursodiol'/exp OR 'liver transplantation'/exp OR 'liver transplant*' OR 'lt' OR 'partial biliary diversion' OR 'partial external biliary diversion'/exp OR 'pebd' OR 'rifampin'/exp OR 'naltrexone'/exp OR 'cholestyramine'/exp) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	27,299

No.	Query	Results
#3	('clinical trial'/de OR 'randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR ((allocated NEXT/2 random):ti,ab) OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR (((treble OR triple) NEXT/1 blind*):ti,ab) OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	241,954
#4	('clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	565,188
#5	#1 AND #2 AND (#3 OR #4) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	68

Table 75 of search strategy table for CENTRAL and Cochrane Clinical Answers (Cochrane Library interface)

No.	Query	Results
#1	'Alagille syndrome' OR 'ALGS' OR 'Alagille-watson syndrome' OR 'Watson Alagille syndrome' OR 'arteriohepatic dysplasia' OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'JAG1'	12
#2	'maralixibat' OR 'inhibitor* of the apical sodium-dependent bile acid transporter' OR 'apical sodium-dependent bile acid transporter inhibitor*' OR 'ASBT inhibitor*' OR 'ASBTi' OR 'inhibitor* of the ASBT' OR 'ileal bile acid transport*' OR 'IBA transport*' OR 'IBAT' OR 'ileal bile acid transporter inhibitor' OR 'IBAT inhibit*' OR 'ursodeoxycholic acid' OR 'ursodiol' OR 'liver transplantation' OR 'liver transplant*' OR 'LT' OR 'partial biliary diversion' OR 'partial external biliary diversion' OR 'PEBD' OR 'rifampin' OR 'naltrexone' OR 'cholestyramine'	1325
#3	#1 and #2 in trials	7

H.1.2 Systematic selection of studies

H.1.2.1 Selection criteria

The selection criteria specified in the Tables below was used to inform the inclusion of studies at first and second pass stages of the reviews. Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided in line with the inclusion criteria.

Table 76 Inclusion and exclusion criteria used for assessment of studies - Review Question 1 (RCTs)

Selection criteria	Inclusion criteria	Exclusion criteria	Changes local adaptation
Population	Patients with ALGS	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest	No further changes
Interventions/ comparators	Intervention • Maralixibat Comparators or combinations of: • Odevixibat • Ursodiol • Rifampicin • Antihistamines • Bile salt binding agents • Ursodeoxycholic acid • Cholestyramine • Naltrexone • Sertraline	No intervention / comparators of interest	No further changes

Outcomes	Liver-related outcomes • Change in serum bile acid (sBA) • Incidence of jaundice • Change in pruritus (e.g. ItchRO, Clinician Scratch Scale (CSS)) • Change in alkaline phosphatase • Cholestasis measured by change in bile flow • Liver transplantation • Transplant-free survival (native liver survival) / event-free survival (EFS) • Time to liver event • Surgical biliary diversion (SBD) • Hepatocellular carcinoma (HCC) • Progressive liver disease leading to liver failure • Change in fecal bile acid (fBA) • Change in 7α-Hydroxy-4-cholesten-3-one (7αC4) • Change in liver biomarkers / enzymes (ALT, AST and bilirubin) • Cirrhosis • Hepatomegaly • Change in height and weight (growth) • Xanthomas	No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes	No further changes

	• Renal disease measured by the gradual loss of kidney function Mortality Deaths Adverse events • Treatment emergent adverse events (TEAE) • Serious adverse events		
Study type	RCTs	Non-RCTs Observational studies (including patient registries) Cross-sectional studies Animal studies In vitro/ex vivo studies Individual case study reports	No further changes
Publication type	Article Conference abstract Conference paper Article in press	Short survey Reviews Letters Comment articles	No further changes
Language	English	Non-English publications without an official English translation	No further changes

Abbreviations: ALGS – Alagille Syndrome; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; CSS – Clinical scratch scale; EFS – Event-free survival; fBA – Faecal bile acid; HCC – Hepatocellular carcinoma; RCT – Randomised controlled trials; SLR – Systematic literature review; sBA – Serum bile acid; SBD - Surgical biliary diversion; TEAE – Treatment emergent adverse events

Table 77 Selection criteria used for Review Question 2 (non-RCTs)

Selection criteria	Inclusion criteria	Exclusion criteria	Changes local adaptation
Population	Patients with ALGS	Studies that do not include patients of interest to the SLR Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest	No further changes
Interventions/ comparators	Intervention • Maralixibat Comparators or combinations of: • Odevixibat • Ursodiol • Rifampicin • Antihistamines • Bile salt binding agents • Ursodeoxycholic acid • Cholestyramine • Naltrexone • Sertraline	No intervention / comparators of interest	No further changes
Outcomes	Liver-related outcomes • Change in serum bile acid (sBA) • Incidence of jaundice • Change in pruritus (e.g. ItchRO, Clinician Scratch Scale (CSS)) • Change in alkaline phosphatase	No reported outcomes of interest, i.e., only reporting pharmacodynamics, pharmacokinetics, genetic, cellular, or molecular outcomes	No further changes

	• Cholestasis measured by change in bile flow • Liver transplantation • Transplant-free survival (native liver survival) / event-free survival (EFS) • Time to liver event • Surgical biliary diversion (SBD) • Hepatocellular carcinoma (HCC) • Progressive liver disease leading to liver failure • Change in fecal bile acid (fBA) • Change in 7α-Hydroxy-4-cholesten-3-one (7αC4) • Change in liver biomarkers / enzymes (ALT, AST and bilirubin) • Cirrhosis • Hepatomegaly • Change in height and weight (growth) • Xanthomas • Renal disease measured by the gradual loss of kidney function Mortality • Deaths Adverse events • Treatment emergent adverse events (TEAE) • Serious adverse events		
Study type	Non-RCTs	RCTs	No further changes

	Observational studies (including patient registries) Cross-sectional studies	Animal studies In vitro/ex vivo studies Individual case study reports	
Publication type	Article Conference abstract Conference paper Article in press	Short survey Reviews Letters Comment articles	No further changes
Language	English	Non-English publications without an official English translation	No further changes

Abbreviations: ALGS – Alagille Syndrome; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; CSS – Clinical scratch scale; EFS – Event-free survival; fBA – Faecal bile acid; HCC – Hepatocellular carcinoma; RCT – Randomised controlled trials; SLR – Systematic literature review; sBA – Serum bile acid; SBD - Surgical biliary diversion; TEAE – Treatment emergent adverse events.

H.1.2.2 Systematic selection of studies

Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the review question and selection criteria. A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required.

Full text copies of all potentially relevant records were obtained following the completion of first pass and subsequently evaluated in more detail (second pass) against the pre-defined selection criteria. A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required. A reason for exclusion was provided for studies excluded following the full text review during the second pass in section H.1.3.

The same study selection process was employed in the May 2023 SLR update and the September 2024 update.

H.1.2.3 Search results

The database searches identified all literature published in each database prior to 11th October 2021, retrieving 1,722 references, of which 178 were duplicates, leaving 1,544 unique references for first pass screening. Of the 243 full texts assessed at second pass, 168 individual studies (over 181 review questions) did not meet the inclusion criteria.

Out of the 78 extracted individual studies, six were RCTs, 7 non-RCTs, 6 health-related quality of life (3 studies overlap with RCT/ non-RCT studies) and 62 were epidemiological studies.

The database searches retrieved 1,722 publications, of which 178 were duplicates. Of the 1,544 titles and abstracts reviewed at first pass, 1,301 did not meet the inclusion criteria. Of the 243 publications assessed at second pass, 75 were deemed to be suitable for extraction. A further three publications were identified during 'grey literature' searches. The final number of publications extracted was 78.

Of the 78 publications that were extracted:

- Six were extracted for the RCT question.
- Seven were extracted for the non-RCT question.
- Zero were extracted for the cost-effectiveness question.
- Zero were extracted for the cost and resource use question.
- Six were extracted for the HRQoL question.
- Zero were extracted for the burden question.
- 62 were extracted for the epidemiological/ pathogenesis question.

Several publications met the inclusion criteria for more than one review question. As such, the sum of the publications extracted for each review question exceeds the total of 78 publications.

The database searches identified all literature published in each database from 11th October 2021 to 18th May 2023, retrieving 192 references. Out of these, 44 were duplicates, leaving 148 unique references for the first pass screening. Following first pass screening, 64 full texts were assessed at second pass, 35 individual studies did not meet the inclusion criteria.

No further publications were identified during 'grey literature' searches. The final number of publications extracted was 29.

Of the 29 publications that were included:

- Three were extracted for the RCT question.
- Five were extracted for the non-RCT question.
- Zero were extracted for the cost-effectiveness question.
- Two were extracted for the cost and resource use question.
- Four were extracted for the HRQoL question.
- Zero were extracted for the burden question.

- 15 were extracted for the epidemiological/pathogenesis question.

The Original SLR combined with the May 2023 update presents evidence for a total of 107 publications (mark in red in the data grid extraction).

The database searches identified all literature published in each database from 18th May 2023 to 1st September 2024, retrieving 306 references (68 from the Embase clinical search strategy, 7 from the Cochrane clinical search strategy, and 231 from the cost-effectiveness, health-related quality of life, and cost and resource use studies search strategy). Of these, 79 were duplicates, leaving 227 unique references for the first-pass screening. Following the first-pass screening, 42 full texts (articles, abstracts, or posters) were assessed during the second pass, and 23 individual studies did not meet the inclusion criteria.

No further publications were identified during 'grey literature' searches. The final number of publications extracted was 19.

Of the 19 publications that were included:

- Zero were extracted for the RCT question.
- 10 were extracted for the non-RCT question.
- Zero were extracted for the cost-effectiveness question.
- Zero were extracted for the cost and resource use question.
- Zero were extracted for the HRQoL question.
- Zero were extracted for the burden question.
- 9 were extracted for the epidemiological/pathogenesis question.

The Original SLR combined with the May 2023 update and the September 2024 update presents evidence for a total of 126 publications (marked in blue in the grid extraction).

Figure 19 Original SLR PRISMA Flow Chart

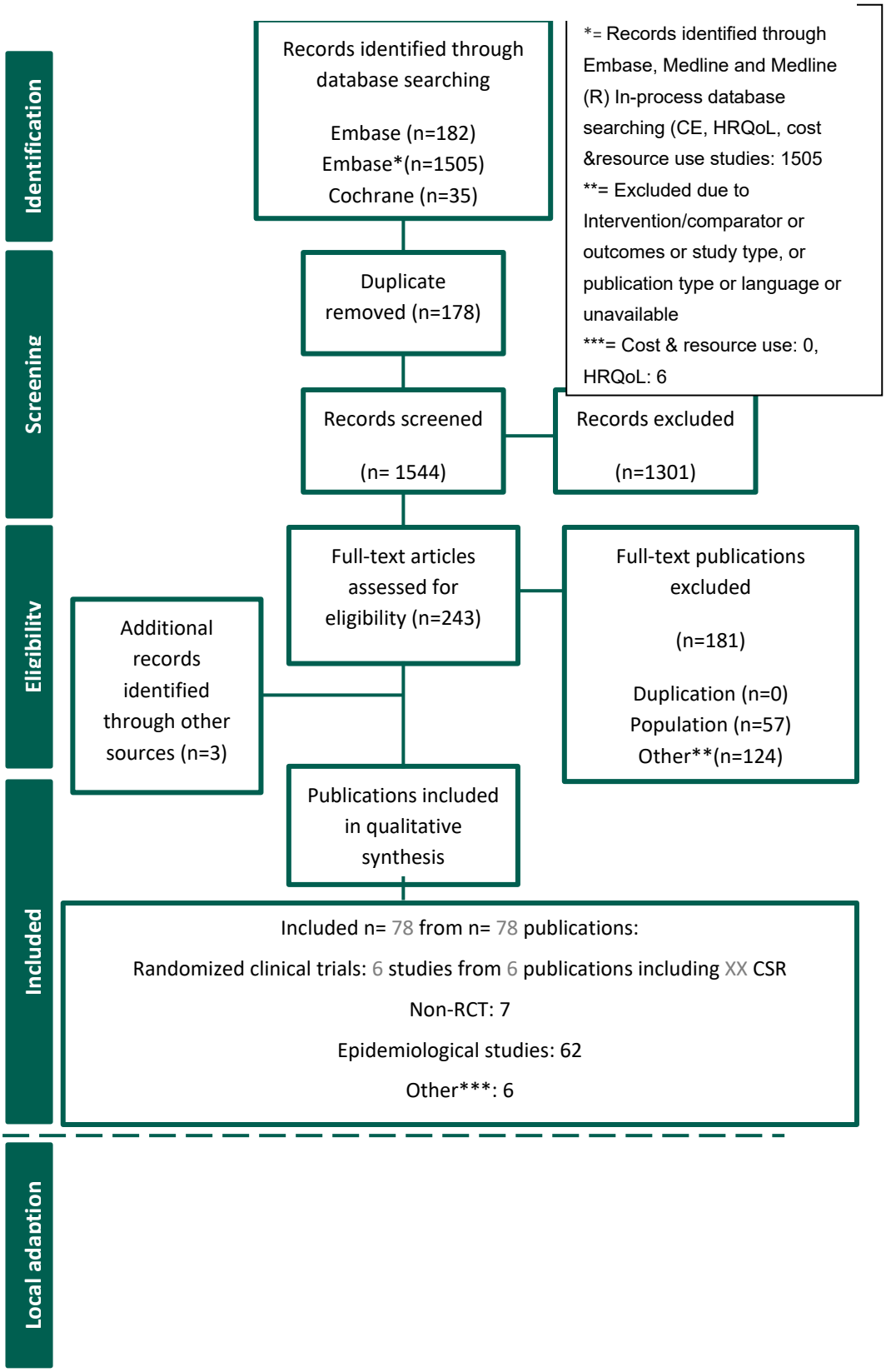


Figure 20 May 2023 SLR update PRISMA Flow Chart

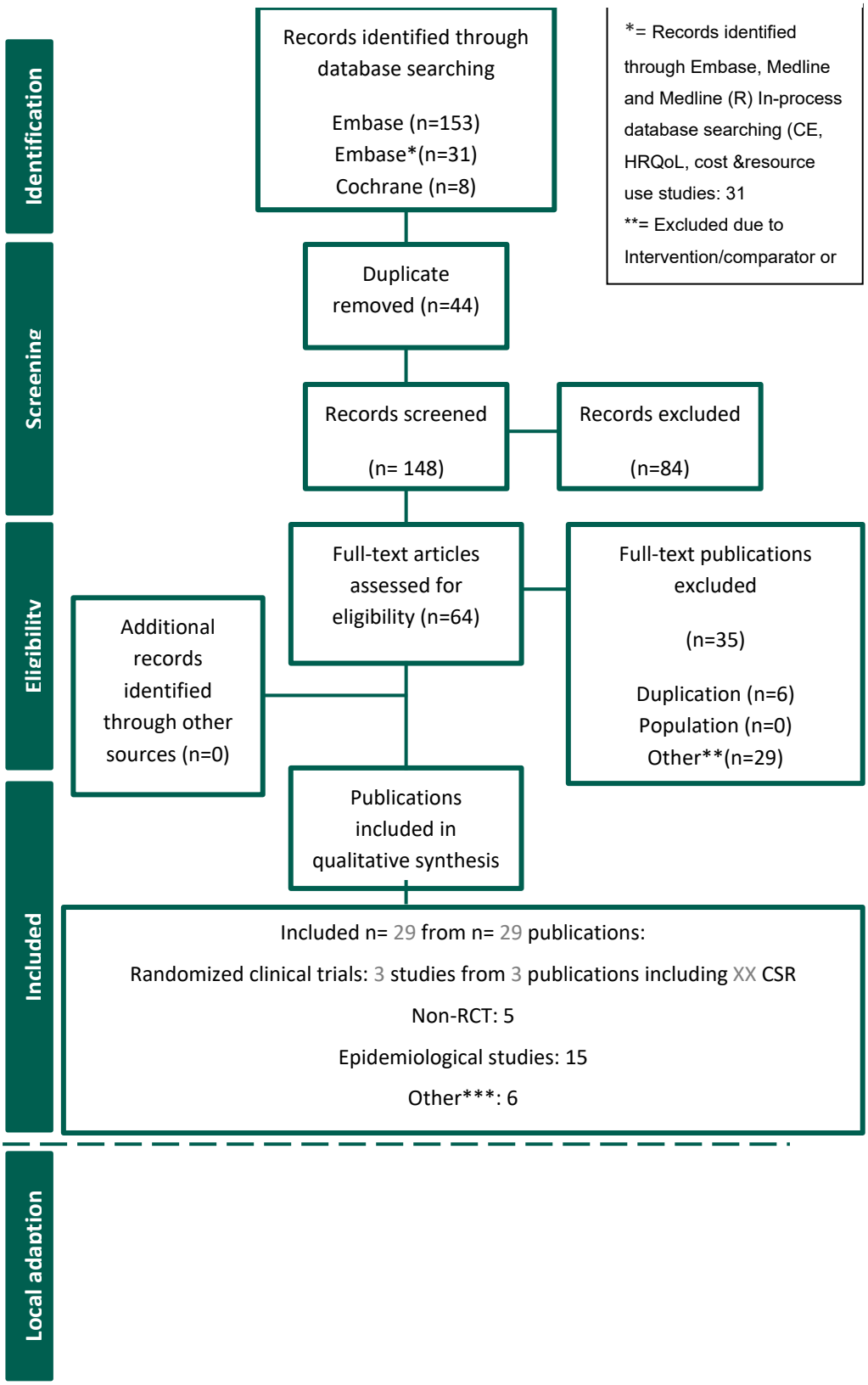
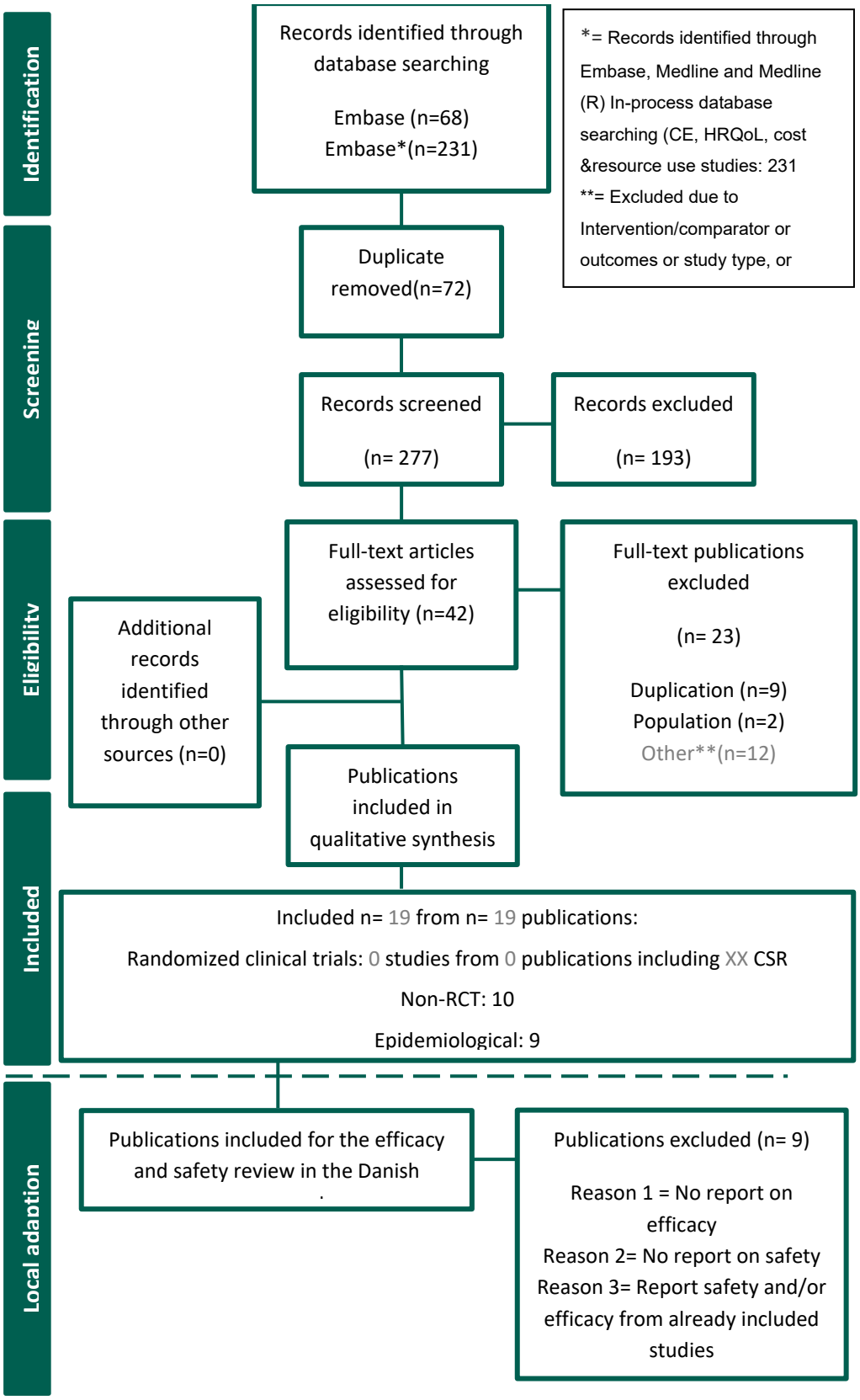


Figure 21 September 2024 SLR update PRISMA Flow Chart



H.1.2.4 List of publications retrieved for the Clinical SLR

Since Appendix H is only for the literature searches for the clinical assessment, we only focus here on the publications retrieved from the Original and updates of the SLR for the Clinical research questions, questions number 1 and 2 only.

Of the 48 references that met the selection criteria for review questions 1 and 2 during the title and abstract screening from the first search, 24 were considered for full text review of RCTs and 24 were considered for full text review of non-RCTs. A total of 13 clinical references (six RCT and seven non-RCT) were identified as part of this SLR.

Moreover, eight clinical references were identified in the May 2023 update and ten clinical references were identified in the September 2024 update.

The Tables below include the list of publications retrieved from the Original and the SLR updates for the Clinical research questions.

Table 78 Overview of study design for studies included in the analysis (Original SLR)

Clinical publications from Original SLR (n=13)							
Study	**Reference**	**Publication type**	**RCT or non-RCT**	**Intervention(s)**	**Study design**	**Endpoints**	**Sub-groups**
NCT02047318 - IMAGINE	Baker et al. 2017[112]	Abstract	Non-RCT	Maralixibat 280 µg/kg/day.	This was an ad hoc 48- and 96-week analysis of IMAGINE, a long-term Phase II extension study of maralixibat in children with ALGS who had previously completed the IMAGO 13-week randomized placebo-controlled study.	• sBA levels • ItchRO • CSS • Safety	NR
ICONIC long-term extension	Gonzales et al. 2019[113]	Abstract	Non-RCT	Maralixibat 400 µg/kg/day following reaching week 48 in ICONIC.	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	• sBA levels • ItchRO • Clinician Xanthoma Severity Scale • CSS • Safety	NR
ICONIC long-term extension	Gonzales et al. 2019[114]	Abstract	Non-RCT	After an 18-week maralixibat run-in period (6 weeks ascending doses up to 400 µg/kg daily and 12 weeks of stable dosing), subjects were randomized to placebo or continued maralixibat treatment for 4	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	• sBA levels • ItchRO • Clinician Xanthoma Severity Scale • PedsQL	NR

			weeks. After this all subjects were treated with maralixibat.				
NR	Kamath et al. Abstract 2021[115]	Non-RCT	Patients received doses of maralixibat from 66.5 µg/kg to 380 µg/kg once daily up to 380 µg/kg twice daily.	Five Phase II clinical trials	•	Safety	A sub-analysis was performed based on 13-week placebo-controlled data from two of the five studies in the integrated population.
NR	Kronsten et al. Abstract 2011[116]	Non-RCT	Ursodeoxycholic acid was the most prescribed anti-pruritic. Others included rifampicin, cholestyramine, naltrexone, sedative antihistamines, nonsedating antihistamines, ondansetron and phenobarbitone. Combination therapy was required in 70%.	NR	•	NR	NR
NR	Kronsten et al. Full paper 2013 KRONSTEN [19]	Non-RCT	98% of patients received antipruritic medication. Ursodeoxycholic acid was the most prescribed drug with. Other drugs prescribed were	A retrospective review of antipruritic medication in patients with ALGS	•	Antipruritic drug efficacy measured using a 5-point scale based on patient, family and physician opinion	NR

				rifampicin, cholestyramine, naltrexone, alimemazine, nonsedating antihistamine agents, ondansetron, and phenobarbitone.			
NR	Thebaut et al. 2017[117]	Full paper	Non-RCT	Oral treatment with sertraline (Zoloft) was started at a dose of around 1mg.kg-1 once daily (using 25 or 50 mg tablets available). Doses were thereafter increased by increments of 0.5 mg/kg every 2 weeks, up to 4 mg/kg/day, according to clinical response and at the physician's discretion. Dosages of other antipruritic medications (ursodeoxycholic acid, rifampicin) were maintained constant.	A prospective, multicenter study to assess efficiency and safety of the serotonin reuptake inhibitor sertraline in treating children with refractory cholestatic pruritus	• Pruritus quantification • Liver biomarkers • sBA levels • Sertraline concentration • Safety	• Patients were considered as responders if they had improvement of ≥3 points on the itching scale, associated with improvement in skin scratch marks score and/or in sleep impairment score.
NCT02160782 - ICONIC	Foster et al. 2020[118]	Abstract	RCT	This study evaluated the psychometric properties of the	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-	• ItchRO	NR

			ItchRO (Obs) in the ICONIC study.	withdrawal study with open-label extension of maralixibat in children with ALGS.			
NCT02160782 - ICONIC	Gonzales et al. Poster 2020[119]	RCT	Participants received doses of 400 µg/kg/day of maralixibat chloride (equivalent to 380 µg/kg/day of maralixibat, and hereafter referred to as 380 µg/kg/day maralixibat) for 18 weeks.	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	•	ItchRO • CSS • sBA levels	NR
NCT02160782 - ICONIC	Gonzales et al. Full paper 2021[120]	RCT	After 18 weeks of maralixibat 380 µg/kg once per day, participants were randomly assigned (1:1) to continue maralixibat or receive placebo for 4 weeks.	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	•	sBA levels • height z-score	NR
NCT02160782 - ICONIC	Gonzales et al. Full paper 2021	RCT	Baseline to Week 18 with maralixibat doses up to 380 µg/kg once daily. Weeks 19 to 22 remain on maralixibat 380 µg/kg or receive placebo once daily. Weeks 23 to 48, open-label	ICONIC (LUM001-304) was an international, multicenter, Phase IIb, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	•	sBA levels	NR

				maralixibat 380 µg/kg once daily for all study participants (including an initial 6-week dose escalation for participants previously receiving placebo).			
NCT02057692 - ITCH	Shneider et al.2017[121]	Abstract	RCT	Once daily placebo, 70, 140 or 280 µg/kg of maralixibat for 13 weeks.	This trial tested the hypothesis that pharmacologic interruption of the enterohepatic circulation of bile acids, using the ASBT inhibitor maralixibat (previously LUM001; SHP625), would reduce pruritus in ALGS.	• ItchRO	NR
NCT02057692 - ITCH	Shneider et al. 2018[122]	Full paper	RCT	Approximately 1 year after the start of the study (after 9 participants had begun investigational drug administration), an additional higher dose arm (280 µg/kg/day, n = 8) was added to the study based on preliminary results from a similar but smaller study conducted in the United Kingdom (Safety and efficacy study of LUM001 in the treatment of cholestatic liver	This was a double-blind, randomized, placebo-controlled Phase IIb trial. Originally, participants were randomized to one of three treatment arms in a 2:1 randomization ratio between maralixibat and placebo (n = 8 each in placebo, 70 µg/kg/day, or 140 µg/kg/day), with the primary comparison between the pooled maralixibat groups and placebo.	• ItchRO • sBA levels • ALT • GGT • Cholesterol	NR

					disease in patients with Alagille syndrome [IMAGO]; design and preliminary results reported [NCT01903460]).		

Abbreviations: ALGS – Alagille syndrome; ALT – Alanine transaminase; ASBT – apical sodium-dependent bile acid transporter; CSS – Clinician Scratch Score; GGT – gamma-glutamyl transferase; ItchRO – itch reported outcome; sBA – serum bile acid; RCT – randomised clinical trial

Table 79 Overview of study design for studies included in the analysis (2023 SLR update)

Clinical publications from May 2023 SLR update (n=8)							
Study	**Reference**	**Publication Type**	**RCT or Non RCT**	**Intervention(s)**	**Study design**	**Endpoints**	**Subgroups**
Shneider et al 2022	Shneider et al 2022[123]	Full paper	Non-RCT	Drug: LUM001 (maralixibat) Drug: Placebo	Prospective longitudinal cohort comparison	The current investigation sought to determine the feasibility of assessing the outcome of a natural history cohort derived from a prospective longitudinal clinical	NR

						database study focused in part on ALGS that could potentially serve as a control arm for a single-arm clinical trial.	
Hansen et al 2023	Hansen et al 2023[124]	Abstract	Non-RCT	Maralixibat	A prespecified analysis plan applied novel analytical technique to compare real world evidence (RWE) from GALA with a MRX cohort with the aim to compare event-free survival (EFS) in patients with ALGS.	Event free survival	sBA sub-group
Gonzalez-Peralta et al 2022 (MRX-EAP)	Gonzalez-Peralta et al 2022 (MRX-EAP)[125]	Poster	Non-RCT	Maralixibat	RWE evidence - three children were enrolled in the MRX EAP presenting with a variety of clinical manifestations. Clinicians rated pruritus using the Clinician Scratch Scale on a scale of 0-4 (0= none - 4=cutaneous mutilation, hemorrhage and scarring evident). Laboratory parameters including total bilirubin, alanine aminotransferase and alkaline phosphatase were monitored at varying time intervals in the months prior to and after starting MRX treatment.	Pruritus - Clinician scratch scores	NR
Hansen et al 2021	Hansen et al 2021[126]	Abstract	Non-RCT	Maralixibat	A prespecified analysis plan applied novel analytical technique to compare RWE from GALA with a MRX cohort	Event Free Survival	sBA sub-group

					with the aim to compare event-free survival (EFS) in patients with ALGS.		
Kamath et al 2022	Kamath et al 2022[91]	Poster	RCT	Maralixibat	To evaluate the impact of long term maralixibat treatment on the growth and nutritional status of patients with ALGS.	Statistical analysis using Spearman and Pearson correlation coefficients and t-tests to evaluate the association between height and other parameters known to correlate with growth from three clinical studies (and their open label extensions) of maralixibat for the treatment of pruritus in ALGS.	Patients were divided into four subgroups based on baseline height or weight Z-score quartiles (Q1, Q2, Q3 and Q4)
Hansen et al 2022	Hansen et al 2022[127]	Abstract	Non-RCT	Maralixibat	A prespecified analysis plan applied novel analytical technique to compare RWE from GALA with a MRX cohort with the aim to compare event-free survival (EFS) in patients with ALGS.	Event free survival	sBA sub-group
Ramen et al 2021	Ramen et al 2021[128]	Poster	RCT	Maralixibat Placebo	To evaluate the overall clinical safety of MRX in an integrated population of patients with ALGS who received MR. To conduct a sub-analysis of safety data in the 13-week placebo-controlled studies, LUM001-301 and LUM001-302.	Clinical safety of MRX in an integrated population of patients with ALGS.	Sub-analysis of 13-week placebo-controlled studies – 13-week MRX / 13-week placebo

Shneider et al 2022b	Shneider et al 2022b[129]	Full paper	RCT	Pooled analysis of: NCT01903460 IMAGO Experimental: LUM001 LUM001 administered orally once each day Intervention: Drug: LUM001 Placebo Comparator: Placebo Placebo administered orally once each day Intervention: Drug: Placebo NCT02057692 ITCH Experimental: LUM001 LUM001 for oral administration Intervention: Drug: LUM001 Placebo Comparator: Placebo	Fat-soluble vitamin insufficiency at baseline and Week 48: Vitamin A insufficiency Vitamin D insufficiency Vitamin E insufficiency Vitamin K insufficiency Any vitamin insufficiency Change from baseline to Week 48 in key outcomes (combined studies and multiple imputation): ItchRO (Obs) CSS Serum bile acid (µmol/L) PedsQL total, parent Multidimensional fatigue scale TB (mg/dl) Total cholesterol (mg/dl) ALT (U/L) Albumin (g/dl) Platelet (103/ul) Height z-score Weight z-score Treatment-emergent serious adverse events and adverse events by	NR

	Placebo administered orally once each day Intervention: Drug: Placebo NCT02047318 (IMAGINE) Experimental: LUM001 (Maralixibat) LUM001 also known as Maralixibat (MRX) administered orally up to twice each day Intervention : Drug : LUM001 (Maralixibat) NCT02117713 (IMAGINE II) Experimental: LUM001 (Maralixibat) Participant will receive LUM001 also known as Maralixibat (MRX)	treatment (combined studies)

				administered orally once per day. Intervention: Drug: LUM001 (Maralixibat)			

Abbreviations: ALGS – Alagille syndrome; ALT – Alanine transaminase; ASBT – apical sodium-dependent bile acid transporter; CSS – Clinician Scratch Score; GGT – gamma-glutamyl transferase; ItchRO – itch reported outcome; sBA – serum bile acid; RCT – randomised clinical trial

Table 80 Overview of study design for studies included in the analysis (2024 SLR update)

Clinical publications from September 2024 n=10 (10 non-RCT and 0 RCT)							
Study	**Reference**	**Publication Type**	**RCT or Non RCT**	**Intervention(s)**	**Study design**	**Endpoints**	**Subgroups**
GALA cohort comparison study	Hansen et al 2024 Hansen [48]	Full paper	Non-RCT	Maralixibat vs Control group received standard of care for ALGS, including antipruritic agents such as antihistamines, cholestyramine, and nutritional support. N (randomized): 84 in the maralixibat group and 469 in the GALA group.	Participants from the GALA cohort were included based on matching key eligibility criteria of maralixibat trials	Event-Free Survival (EFS), defined as the absence of key clinical events such as portal hypertension (PHT), surgical biliary diversion (SBD), liver transplant, or death Transplant-Free Survival (TFS), defined as the absence of liver transplant or death	Subgroup analyses were conducted based on geographic regions: North America, Europe, and Australia

			Dose and duration: Specific doses for maralixibat are not provided. Treatment duration extended up to 6 years.			
NR	Howard et al Abstract 2023 [130]	Non-RCT	The study focused on maralixibat without any comparator. A total of 116 US patients with Alagille syndrome (ALGS) and cholestatic pruritus were included. The median duration of maralixibat therapy was 480 days.	This was a real-world data analysis based on pharmacy data from the Mirum Access Plus (MAP) program in the US, capturing concomitant medication trends over time. The analysis included patients who received their first commercial shipment of maralixibat by April 1, 2022, and continued therapy to observe at least one year of	Reduction of concomitant medications rather than specific efficacy outcomes, including choleretics, PXR agonists, antihistamines, bile acid sequestrants, opioid antagonists, SSRIs, and nutritional or vitamin supplements.	NR

					potential maralixibat use.		
NR	Himes et al 2023 [131]	Abstract	Non-RCT	Maralixibat (MRX) was provided to 37 patients with Alagille syndrome (ALGS) through an Expanded Access Program (EAP) at a target dose of 380 µg/kg taken orally once daily. There was no comparator drug involved in this real-world safety analysis.	This was a real-world safety analysis based on data from the Expanded Access Program (EAP), designed to facilitate access to Maralixibat for ALGS patients who could not participate in clinical trials. It did not follow a formal randomized control trial (RCT) design.	Safety profile of Maralixibat, specifically the occurrence of treatment-emergent adverse events (TEAEs). Adverse events were regularly reported to a central database, with the median duration of exposure being 243 days, ranging from 52 to 385 days	NR
NR	Hoskins et al 2023 [132]	Full paper	Non-RCT	Maralixibat was administered to children with Alagille syndrome (ALGS) to evaluate its impact on xanthomas and hypercholesterolemia. A total of 63 patients were	This was a non-randomized, integrated analysis of two clinical trials focused on assessing the effects of	Xanthoma reduction and improvements in lipid profiles over a 96-week period. Xanthoma severity was scored using the CXS scale, and cholesterol levels were tracked. Quality of life (QoL) was	Responders and non-responders for xanthoma reduction

			initially enrolled, with 35 having data available up to Week 96	Maralixibat in children with ALGS. The study evaluated real-world outcomes without a randomized control trial structure.	assessed using the PedsQL social functioning (SF) and physical functioning (PF) scales	
NR	Hirschfield et al 2024 [133] Abstract	Non-RCT	Maralixibat was administered to 14, aged 16 years and > with ALGS who were transitioning to adult care. The treatment included various dosing schedules, either beginning before age 16 or at/after age 16, with pruritus and serum bile acids assessed over the course of the study.	Observational study within a clinical development program, focusing on the efficacy and safety of MRX in young adults with ALGS.	Changes in pruritus and serum bile acids. The mean baseline pruritus score was 2.5, which significantly decreased to 0.8 before age 16. Serum bile acid (sBA) levels also decreased from a baseline mean of 130 µmol/L to 52 µmol/L before age 16, with stable levels observed across the transition to adult care.	NR
NR	Vandriel et al 2023 [134] Abstract	Non-RCT	Surgical biliary diversion (SBD) was performed on 62 children with Alagille syndrome (ALGS) across 26 centers. The types of SBD included Partial External Biliary	This was a multicenter retrospective observational analysis assessing the impact of SBD on native liver	The study focused on native liver survival (NLS), with total bilirubin levels <4.0 mg/dL post-SBD significantly associated with extended NLS. Serum bile acids (SBA) were also	NR

			Diversion (54.8%), Partial Internal Biliary Diversion (19.4%), and Ileal Exclusion (12.9%).	survival (NLS), risk of liver transplantation (LT), and mortality in ALGS patients. No randomization or blinding was conducted.	evaluated, showing a significant reduction post-SBD. Pruritus and xanthomas were assessed, showing limited improvement post-SBD.
NR	Thebaut et al Abstract 2023 [135]	Non-RCT	Maralixibat. Dose: Starting daily dose of 400 µg/kg.d. Duration: Median exposure was 12 months (range 3–24 months).	Prospective cohort analysis of French real-life data.	Reduction in pruritus as measured by the Visual Analog Itching Scale (VAIS), scored from 0 to 10, and Clinical Skin Scratch Scale (CSS), scored from 0 to 4. Assessments occurred at baseline, 3 months, 6 months, and every 6 months thereafter. A clinically meaningful decrease was defined as ≥1-point decrease in CSS and ≥3-point decrease in VAIS. Changes in serum bile acid levels and total serum bilirubin levels, measured at the same intervals as primary efficacy assessments.

NR	Matarazzo et al 2023 [136]	Abstract	Non-RCT	Maralixibat, oral administration, 400 µg/kg once daily (QD).	Prospective study, Italian multicenter study	Reduction in serum bile acid (sBA) levels. Measured as a ≥25% decrease in sBA levels. Evaluated at 3 months. Improvement in pruritus. ItchRO scale (1-to-4), with improvement measured by at least a 1-point decrease on the scale. Assessed at 3 months. Frequency and severity of treatment-emergent adverse events (AEs)	NR
RISE	Gonzales et al. 2023 [137]	Abstract	Non-RCT	Maralixibat (MRX) administered over a 13-week core study period	Safety and tolerability of Maralixibat in infants with Alagille syndrome (ALGS) starting from 2 months of age. An interim analysis for the ALGS cohort is reported here.	Change from baseline (CFB) in serum bile acids (sBA) at 13 weeks. TEAEs	NR

RISE	Gonzales et alAbstract 2023b [138]	Non-RCT	Maralixibat (MRX) administered over a 13-week core study period	Open-label, Phase 2 trial. Infants under 1 year of age with ALGS or PFIC, gestational age ≥36 weeks, body weight ≥2.5 kg 13-weeks period and with a long-term extension planned	Change from baseline (CFB) in serum bile acids (sBA) at 13 weeks. TEAEs	NR

Abbreviations: ALGS – Alagille syndrome; ALT – Alanine transaminase; ASBT – apical sodium-dependent bile acid transporter; CSS – Clinician Scratch Score; GGT – gamma-glutamyl transferase; ItchRO – itch reported outcome; sBA – serum bile acid; RCT – randomised clinical trial

H.1.3 Excluded full text references

The Table below includes the studies which were excluded at second pass with the reason for exclusion in the Original SLR and the SLR updates.

Table 81 List of publications excluded at second pass (n=168)

	Author (s)	Title	Publication source	Reason for exclusion (PICOS)
1	Serradilla J., Bueno A., Andres A.M., Sanchez-Galan A., Encinas J.L., Nuno J., Hierro L., Hernandez-Oliveros F., Lopez-Santamaria M.	200 living donor liver transplantation in children: Outcomes and results according to indication for transplantation and graft type	Transplantation (2020) 104:SUPPL 3 (S506). Date of Publication: 1 Sep 2020	Outcomes
2	Baker, A; Kelly, DA; Gu, J; Jaecklin, T; McClean, P; Kamath, BM; Shneider, BL; Thompson, RJ	A long-term phase 2 safety and efficacy study of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with alagille syndrome: preliminary results from the imagine study	Hepatology, 2017, 66(6), 1255A-1256A	Duplicate
3	EUCTR2013-003832-54-GB,	A multicentre clinical study to evaluate the safety and efficacy of lum001, an agent that inhibits bile acid reuptake from the intestine, in the treatment of cholestatic liver disease in paediatric patients with alagille syndrome	http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2013-003832-54-GB	Outcomes
4	Baker A., Kelly D., McClean P., Karthikeyan P., McKiernan P., Dorenbaum A., Kamath B.M., Shneider B., Barbat S., Medendorp S., Raychaudhuri A., Kennedy C.A., Thompson R.J.	A phase 2, randomized, placebo-controlled study (IMAGO) of LUM001, a novel inhibitor of the apical sodium-dependent bile acid transporter (ASBT), in paediatric patients with alagille syndrome (ALGS)	Journal of Hepatology (2015) 62 SUPPL. 2 (S259). Date of Publication: April 2015	Outcomes
5	NCT02963077,	A Safety and Pharmakokinetic Study of A4250 Alone or in Combination With A3384	https://clinicaltrials.gov/show/NCT02963077	Outcomes
6	Davit-Spraul A., Pourci M.L., Atger V., Cambillau M., Hadchouel M., Moatti N., Legrand A.	Abnormal lipoprotein pattern in patients with Alagille syndrome depends on icterus severity	Gastroenterology (1996) 111:4 (1023-1032). Date of Publication: 1996	Outcomes

7	Anooshiravani M., Tempia M., Rougemont A.-L., Hanquinet S.	Acoustic radiation force impulse (ARFI): A preliminary study of liver elastography in children	Pediatric Radiology (2011) 41 SUPPL. 1 (S260). Date of Publication: May 2011	Outcomes
8	Hayashi N., Okuyama H., Matsui Y., Yamaya H., Kinoshita E., Minato H., Niida Y., Yokoyama H.	Adult-onset renal failure in a family with Alagille syndrome with proteinuria and a novel JAG1 mutation	Clinical Kidney Journal (2013) 6:3 (295-299). Date of Publication: June 2013	Study type
9	Ciocca M., Álvarez F.	Alagille syndrome	Archivos Argentinos de Pediatria (2012) 110:6 (509-515). Date of Publication: December 2012	Language
10	Benmiloud S., Lakhssassi Z., Lafram I., Atmani S., Bouharrou A., Hida M.	Alagille syndrome	Journal de Pediatrie et de Puericulture (2009) 22:6 (278-285). Date of Publication: September 2009	Language
11	Krantz I.D., Piccoli D.A., Spinner N.B.	Alagille syndrome	Journal of Medical Genetics (1997) 34:2 (152-157). Date of Publication: 1997	Publication type
12	Kamath B.M., Schwarz K.B., Hadĩć N.	Alagille syndrome and liver transplantation	Journal of Pediatric Gastroenterology and Nutrition (2010) 50:1 (11-15). Date of Publication: January 2010	Publication type
13	Gilbert M.A., Loomes K.M.	Alagille syndrome and non-syndromic paucity of the intrahepatic bile ducts	Translational Gastroenterology and Hepatology (2021) 6 Article Number: 22. Date of Publication: 1 Apr 2021	Publication type
14	Hwang S.M., Jeon T.Y., Yoo S.-Y., Kim J.H., Kang B., Choe Y.H., Cho H., Kim J.S.	Alagille syndrome candidates for liver transplantation: Differentiation from end-stage biliary atresia using preoperative CT	PLoS ONE (2016) 11:2 Article Number: e0149681. Date of Publication: 1 Feb 2016	Population
15	Moog U., Engelen J., Albrechts J., Hoorntje T., Hendrikse F., Schrander-Stumpel C.	Alagille syndrome in a family with duplication 20p11	Clinical Dysmorphology (1996) 5:4 (279-288). Date of Publication: 1996	Study type
16	Volynets G.V., Nikitin A.V., Skvortsova T.A.	Alagille syndrome in children	Rossiyskiy Vestnik Perinatologii i Pediatrii (2020) 65:2 (108-116). Date of Publication: 2020	Language

17	Kurtz W., Strohm W.D., Lambrecht E., Leuschner U.	Alagille syndrome, a rare differential diagnosis of intrahepatic cholestasis	Zeitschrift für Gastroenterologie (1987) 25:10 (668-672). Date of Publication: Oct 1987	Language
18	Castañeda C., Fragoso T., Gra B., Guerra L., Castellanos O., Trujillo M.E.	Alagille's syndrome in Cuba. A report of 9 cases	G.E.N (1992) 46:4 (341-346). Date of Publication: 1992 Oct-Dec	Language
19	Shrivastava R., Williams A., Mikhail A., Roberts D., Richards M., Aithal V.	An unusual cause of hypertension and renal failure: A case series of a family with Alagille syndrome	Nephrology Dialysis Transplantation (2010) 25:5 (1501-1506). Date of Publication: May 2010	Study type
20	McElhinney D.B., Krantz I.D., Bason L., Piccoli D.A., Emerick K.M., Spinner N.B., Goldmuntz E.	Analysis of cardiovascular phenotype and genotype-phenotype correlation in individuals with a JAG1 mutation and/or Alagille syndrome	Circulation (2002) 106:20 (2567-2574). Date of Publication: 12 Nov 2002	Population
21	Socha P., Nowicka G., Jankowska I., Rujner J., Pawłowska J., Socha J.	Apolipoprotein E polymorphism in Alagille syndrome and progressive familial intrahepatic cholestasis	Digestive Diseases and Sciences (2000) 45:4 (675-679). Date of Publication: 2000	Outcomes
22	Lebensztejn D.M.	Application of ursodeoxycholic acid (UDCA) in the therapy of liver and biliary duct diseases in children	Medical Science Monitor (2000) 6:3 (632-636). Date of Publication: 2000	Outcomes
23	Kahn E., Daum F.	Arteriohepatic dysplasia (Alagille's syndrome): A common cause of conjugated hyperbilirubinemia	Annals of Clinical and Laboratory Science (1984) 14:6 (480-486). Date of Publication: 1984	Outcomes
24	Kahn E.I., Daum F., Markowitz J.	Arteriohepatic dysplasia. II. Hepatobiliary morphology	Hepatology (1983) 3:1 (77-83). Date of Publication: 1983	Outcomes
25	Shiau H., Guffey D., Minard C.G., Leung D.H.	Biopsy paired study of APRI and FIB-4 as prospective biomarkers of liver fibrosis in inherited pediatric cholestatic liver disease	Gastroenterology (2016) 150:4 SUPPL. 1 (S1171). Date of Publication: April 2016	Outcomes
26	Sondheimer J.M.	Bleeding is a risk in Alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2003) 36:4 (509). Date of Publication: April 2003	Publication type
27	Urganci N., Kurtaraner T., Kalyoncu D., Usta A.M., Ozguven B.Y.	Blind liver biopsy: A 17-year experience	Revista de Gastroenterologia del Peru (2020) 40:4 (322-328). Date of Publication: 2020	Population

28	Gautier S., Kurabekova R., Tsiroulnikova O., Pashkova I., Gichkun O., Mozheiko N., Monakhov A., Shevchenko O.	Blood levels of insulin like growth factor-1 (IGF-1) and growth hormone associate with liver function and 6 month survival after pediatric liver transplantation	Transplantation (2020) 104:SUPPL 3 (S555). Date of Publication: 1 Sep 2020	Outcomes
29	Kindler J.M., Mitchell E.L., Piccoli D.A., Grimberg A., Leonard M.B., Loomes K.M., Zemel B.S.	Bone geometry and microarchitecture deficits in children with Alagille syndrome	Bone (2020) 141 Article Number: 115576. Date of Publication: 1 Dec 2020	Outcomes
30	Özçay F., Tokel K., Varan B., Saygili A.	Cardiac evaluation of pediatric liver transplantation candidates	Transplantation Proceedings (2002) 34:6 (2150-2152). Date of Publication: September 2002	Population
31	Bordin G., Valverde I., Cernat E., Baker A., Miller O.	Cardiovascular assessment of children with alagille syndrome prior to liver transplantation: Should hybrid MRI-catheter have the last word	Cardiology in the Young (2018) 28 Supplement 1 (S116). Date of Publication: 1 Apr 2018	Outcomes
32	Janowski K., Obrycki L., Czubkowski P., Litwin M., Wierzbicka A., Gliwicz D., Kostewicz K., Socha P.	Cardiovascular risk assessment in childrem with biliary atresia and Alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2017) 64 Supplement 1 (673). Date of Publication: 1 Apr 2017	Outcomes
33	Andre M., Day A.S.	Causes of prolonged jaundice in infancy: 3-year experience in a tertiary paediatric centre	New Zealand Medical Journal (2016) 129:1429 (14-21). Date of Publication: 29 Jan 2016	Population
34	Xu X., Rahbar A., Omarsdottir S., Teng J., Németh A., Fischler B., Söderberg-Nauclér C.	CD13 autoantibodies are elevated in sera from mothers of infants with neonatal cholestasis of different causes	Journal of Pediatric Gastroenterology and Nutrition (2017) 64:1 (76-82). Date of Publication: 2017	Population
35	Roberts P., Trout A., Dillman J., Gupta A., Sheridan R., Towbin A.	Central macroregenerative nodules in obstructive cholangiopathies and biliary cirrhosis: Not limited to alagille syndrome	Pediatric Radiology (2017) 47 Supplement 1 (S100-S101). Date of Publication: 1 May 2017	Outcomes
36	Landis B.J., Cooper D.S., Hinton R.B.	CHD associated with syndromic diagnoses: Peri-operative risk factors and early outcomes	Cardiology in the Young (2014) 26:1 (30-52). Date of Publication: 22 Dec 2014	Publication type
37	Dhole S.D., Kher A.S., Ghildiyal R.G., Tambse M.P.	Chronic liver diseases in children: Clinical profile and histology	Journal of Clinical and Diagnostic Research (2015) 9:7 (SC04-SC07). Date of Publication: 1 Jul 2015	Population

38	Kelly D.A., Wilson D.C.	Chronic liver failure	Current Paediatrics (2006) 16:1 (51-58). Date of Publication: Feb 2006	Publication type
39	Chiang C.-M., Jeng Y.-M., Ho M.-C., Lai M.-W., Li H.-Y., Chen P.-L., Lee N.-C., Wu J.-F., Chiu Y.-C., Liou B.-Y., Ni Y.-H., Hsu H.-Y., Chang M.-H., Chen H.-L.	Clinical and genetic features of Alagille Syndrome: Comparisons between patients with progressive disease versus jaundice-free course	Journal of Pediatric Gastroenterology and Nutrition (2021) 72:SUPPL 1 (912). Date of Publication: 1 May 2021	Outcomes
40	Wang M.-J., Zhong X.-M., Ma X., Ning H.-J., Zhu D., Gong Y.-Z., Jin M.	Clinical characteristics and gene variants of patients with infantile intrahepatic cholestasis	Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics (2021) 23:1 (91-97). Date of Publication: 1 Jan 2021	Outcomes
41	Mohan P., Lemoine J., Trotter C., Rakova I., Billings P., Peacock S., Kao C.-Y., Wang Y., Xia F., Eng C.M., Benn P.	Clinical experience with non-invasive prenatal screening for single-gene disorders (NIPT-SGD)	Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology (2021). Date of Publication: 6 Aug 2021	Population
42	Liu X., Wei H., Liu P., Liu X., Tang L., Yang Y., Li Y.	Clinical features and gene mutation analysis of patients with Alagille syndrome	National Medical Journal of China (2021) 101:31 (2454-2459). Date of Publication: 17 Aug 2021	Language
43	EUCTR2020-004628-40-BE,	Clinical study to Evaluate the Safety and Tolerability of Maralixibat in the Treatment of Infants with Progressive Familial Intrahepatic Cholestasis and Alagille Syndrome	http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2020-004628-40-BE	Outcomes
44	Leonard L.D., Chao G., Baker A., Loomes K., Spinner N.B.	Clinical utility gene card for: Alagille Syndrome (ALGS)	European Journal of Human Genetics (2014) 22:3 (436). Date of Publication: March 2014	Outcomes
45	Rauch R., Hofbeck M., Zweier C., Koch A., Zink S., Trautmann U., Hoyer J., Kaulitz R., Singer H., Rauch A.	Comprehensive genotype-phenotype analysis in 230 patients with tetralogy of Fallot	Journal of Medical Genetics (2010) 47:5 (321-331). Date of Publication: May 2010	Population
46	Volynets G.V., Khavkin A.I., Nikitin A.V., Skvortsova T.A.	Congenital cholestatic diseases in children of early age: Step-by-step differential diagnosis	Voprosy Prakticheskoi Pediatrii (2019) 14:5 (26-33). Date of Publication: 2019	Population

47	Gauthier F., Hadchouel M.	Congenital disorders of the bile ducts	Revue du Praticien (2000) 50:19 (2142-2145). Date of Publication: 1 Dec 2000	Language
48	Kamath B.M., Bason L., Piccoli D.A., Krantz I.D., Spinner N.B.	Consequences of JAG1 mutations	Journal of Medical Genetics (2003) 40:12 (891-895). Date of Publication: December 2003	Population
49	Humphreys R., Zheng W., Prince L.S., Qu X., Brown C., Loomes K., Huppert S.S., Baldwin S., Goudy S.	Cranial neural crest ablation of Jagged1 recapitulates the craniofacial phenotype of Alagille syndrome patients	Human Molecular Genetics (2012) 21:6 (1374-1383) Article Number: ddr575. Date of Publication: March 2012	Study type
50	Krantz I.D., Rand E.B., Genin A., Hunt P., Jones M., Louis A.A., Graham Jr. J.M., Bhatt S., Piccoli D.A., Spinner N.B.	Deletions of 20p12 in alagille syndrome: Frequency and molecular characterization	American Journal of Medical Genetics (1997) 70:1 (80-86). Date of Publication: 2 May 1997	Outcomes
51	Kamath B.M., Abetz-Webb L., Kennedy C., Hepburn B., Gauthier M., Johnson N., Medendorp S., Dorenbaum A., Todorova L., Shneider B.L.	Development of a Novel Tool to Assess the Impact of Itching in Pediatric Cholestasis	Patient (2018) 11:1 (69-82). Date of Publication: 1 Feb 2018	Outcomes
52	Stalke A., Baumann U., Illig T., Skawran B., Schlegelberger B., Von Neuhoff N., Pfister E.-D.	Diagnosis of monogenetic metabolic hepatopathies in children by next generation sequencing	Journal of Pediatric Gastroenterology and Nutrition (2016) 62 SUPPL. 1 (498). Date of Publication: May 2016	Population
53	Quiros-Tejeira R.E., Ament M.E., Heyman M.B., Martin M.G., Rosenthal P., Gornbein J.A., McDiarmid S.V., Vargas J.H.	Does liver transplantation affect growth pattern in alagille syndrome?	Liver Transplantation (2000) 6:5 (582-587). Date of Publication: 2000	Outcomes
54	Loomes K.M., Spino C., Goodrich N.P., Hangartner T.N., Marker A.E., Heubi J.E., Kamath B.M., Shneider B.L., Rosenthal P., Hertel P.M., Karpen S.J., Kerkar N., Molleston J.P., Murray K.F., Teckman J., Whitington P., Sherker A., Magee J.C., Sokol R.J.	DXA bone density deficits differ in alagille syndrome and chronic intrahepatic cholestasis	Journal of Pediatric Gastroenterology and Nutrition (2016) 63 Supplement 2 (S337-S338). Date of Publication: 1 Oct 2016	Intervention/ comparator
55	Loomes K.M., Spino C., Goodrich N.P., Hangartner T.N., Marker A.E., Heubi J.E., Kamath B.M., Shneider B., Rosenthal P.,	DXA bone density in alagille syndrome correlates with fracture history and degree of cholestasis	Hepatology (2015) 62 SUPPL. 1 (1034A-1035A). Date of Publication: October 2015	Outcomes

	Hertel P.M., Karpen S.J., Kerkar N., Molleston J.P., Murray K.F., Schwarz K.B., Teckman J., Turmelle Y.P., Whitington P.F., Sherker A.H., Magee J.C., Sokol R.J.			
56	Balli F., Rigo G.P., Gatti G.	Endoscopic retrograde cholangiopancreatography in the diagnosis of Alagille's syndrome	Pediatria Medica e Chirurgica (1984) 6:6 (831-834). Date of Publication: 1984	Language
57	Pawlowska J., Socha P., Jankowska I.	Factors affecting catch-up growth after liver transplantation in children with cholestatic liver disaeses	Annals of Transplantation (2010) 15:1 (72-76). Date of Publication: 2010	Population
58	Thompson R.	Familial cholestatic syndromes	Annales Nestle (2008) 66:3 (121-126). Date of Publication: October 2008	Publication type
59	Libbrecht L., Cassiman D.	Frequency and pathogenesis of central liver nodules in Alagille syndrome patients	Pediatric Radiology (2017) 47:8 (1023-1024). Date of Publication: 1 Jul 2017	Publication type
60	Baussan C., Cresteil D., Gonzales E., Raynaud N., Dumont M., Bernard O., Hadchoue M., Jacquemin E.	Genetic cholestatic liver diseases: The example of progressive familial intrahepatic cholestasis and related disorders	Acta Gastro-Enterologica Belgica (2004) 67:2 (179-183). Date of Publication: April/June 2004	Publication type
61	Rajagopalan R., Gilbert M.A., McEldrew D.A., Nassur J.A., Loomes K.M., Piccoli D.A., Krantz I.D., Conlin L.K., Spinner N.B.	Genome sequencing increases diagnostic yield in clinically diagnosed Alagille syndrome patients with previously negative test results	Genetics in Medicine (2021) 23:2 (323-330). Date of Publication: 1 Feb 2021	Population
62	Rapp J.B., Bellah R.D., Maya C., Pawel B.R., Anupindi S.A.	Giant hepatic regenerative nodules in Alagille syndrome	Pediatric Radiology (2017) 47:2 (197-204). Date of Publication: 1 Feb 2017	Outcomes
63	Tanikawa K., Kage M., Yano H.	Histopathological study of interlobular bile ducts in Alagille syndrome	Hepatology International (2013) 7 SUPPL. 1 (S100-S101). Date of Publication: June 2013	Outcomes
64	Salem J.-E., Bruguiere E., Iserin L., Guiochon-Mantel A., Plouin P.-F.	Hypertension and aortorenal disease in Alagille syndrome	Journal of Hypertension (2012) 30:7 (1300-1306). Date of Publication: July 2012	Publication type
65	Herman H.K., Abramowsky C.R., Caltharp S., Metry D., Cundiff C.A., Romero R., Gillespie S.E., Shehata B.M.	Identification of bile duct paucity in alagille syndrome: Using CK7 and EMA immunohistochemistry as a reliable panel for accurate diagnosis	Pediatric and Developmental Pathology (2016) 19:1 (47-50). Date of Publication: 1 Jan 2016	Outcomes

66	Han S., Jeon T.Y., Hwang S.M., Yoo S.-Y., Choe Y.H., Lee S.-K., Kim J.H.	Imaging findings of Alagille syndrome in young infants: Differentiation from biliary atresia	British Journal of Radiology (2017) 90:1077 Article Number: 20170406. Date of Publication: 2017	Population
67	Huang T., Yang G., Dang X., Ao F., Li J., He Y., Tang Q., He Q.	Implementing targeted region capture sequencing for the clinical detection of Alagille syndrome: An efficient and cost-effective method	Molecular Medicine Reports (2017) 16:5 (6876-6881). Date of Publication: 1 Nov 2017	Publication type
68	Stephens M.C., Boardman L.A., Lazaridis K.N.	Individualized Medicine in Gastroenterology and Hepatology	Mayo Clinic Proceedings (2017) 92:5 (810-825). Date of Publication: 1 May 2017	Publication type
69	Bass L.M., Kamath B.M.	Inherited disorders of cholestasis in adulthood	Clinical Liver Disease (2013) 2:5 (200-203). Date of Publication: October 2013	Publication type
70	Berard E., Triolo V., Sokol R.J.	Intracranial hemorrhages in Alagille syndrome [3] (multiple letters)	Journal of Pediatrics (2000) 136:5 (708-710). Date of Publication: 2000	Publication type
71	Rock N., Demaret T., Stephenne X., Scheers I., Smets F., McLin V., Boschi A., Sokal E.	Intracranial hypertension and papilledema in a large cohort of pediatric Alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2019) 68 Supplement 1 (878). Date of Publication: 1 May 2019	Outcomes
72	Balistreri W.F.	Intrahepatic cholestasis	Journal of Pediatric Gastroenterology and Nutrition (2002) 35:SUPPL. 1 (S17-S23). Date of Publication: 2002	Publication type
73	Obinata K., Nakatsu N., Watanabe T.	Investigation of serum bile acids; seven patients with Alagille syndrome	European Journal of Pediatrics (1985) 144:3 (236-239). Date of Publication: 1985	Outcomes
74	Li L., Dong J., Wang X., Guo H., Wang H., Zhao J., Qiu Y., Abuduxikuer K., Wang J.	JAG1 mutation spectrum and origin in Chinese children with clinical features of alagille syndrome	PLoS ONE (2015) 10:6 Article Number: e0130355. Date of Publication: 15 Jun 2015	Population
75	Guegan K., Stals K., Day M., Turnpenny P., Ellard S.	JAG1 mutations are found in approximately one third of patients presenting with only one or two clinical features of Alagille syndrome	Clinical Genetics (2012) 82:1 (33-40). Date of Publication: July 2012	Population

76	Warthen D.M., Moore E.C., Kamath B.M., Morrissette J.J.D., Sanchez P., Piccoli D.A., Krantz I.D., Spinner N.B.	Jagged1 (JAG1) mutations in Alagille syndrome: Increasing the mutation detection rate	Human Mutation (2006) 27:5 (436-443). Date of Publication: May 2006	Population
77	Grochowski C.M., Loomes K.M., Spinner N.B.	Jagged1 (JAG1): Structure, expression, and disease associations	Gene (2016) 576:1 (381-384). Date of Publication: 15 Jan 2016	Study type
78	Crosnier C., Attié-Bitach T., Encha-Razavi F., Audollent S., Soudy F., Hadchouel M., Meunier-Rotival M., Vekemans M.	JAGGED1 gene expression during human embryogenesis elucidates the wide phenotypic spectrum of Alagille syndrome	Hepatology (2000) 32:3 (574-581). Date of Publication: 2000	Study type
79	Chen H.-L., Wu S.-H., Hsu S.-H., Liou B.-Y., Chen H.-L., Chang M.-H.	Jaundice revisited: Recent advances in the diagnosis and treatment of inherited cholestatic liver diseases	Journal of Biomedical Science (2018) 25:1 Article Number: 75. Date of Publication: 26 Oct 2018	Population
80	Degtyareva A., Filippova E., Goutie M., Viktoria R.	Kidneys malformations in Alagille syndrome patients	Journal of Pediatric Gastroenterology and Nutrition (2018) 66 Supplement 2 (734). Date of Publication: 1 Apr 2018	Outcomes
81	Larrosa-Haro A., Sáenz-Rivera C., González-Ortiz M., Coello-Ramírez P., Vázquez-Camacho G.	Lack of cholesterol-lowering effect of graded doses of cholestyramine in children with Alagille syndrome: A pilot study	Journal of Pediatric Gastroenterology and Nutrition (2003) 36:1 (50-53). Date of Publication: January 2003	Outcomes
82	Gottrand, F; Clavey, V; Fruchart, JC; Farriaux, JP	Lipoprotein pattern and plasma lecithin cholesterol acyl transferase activity in children with Alagille syndrome	Atherosclerosis	Outcomes
83	Otero Durán L., Bermúdez De Castro López E., Navarro Torres M., Fernández Camblor C., Hierro Llanillo L.	Liver transplant and renal function in patients with Alagille syndrome	Pediatric Nephrology (2011) 26:8 (1362). Date of Publication: August 2011	Outcomes
84	Demaret T., Varma S., Vainilovich Y., Halac U., El Bizri D., Ambroise J., Scheers I., Stephenne X., Smets F., Sokal E.	Liver transplantation does not impact the renal function outcome in Alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2017) 64 Supplement 1 (720). Date of Publication: 1 Apr 2017	Population
85	Shneider B.L.	Liver transplantation for alagille syndrome: The jagged edge	Liver Transplantation (2012) 18:8 (878-880). Date of Publication: August 2012	Publication type

86	Finotti M., Auricchio P., Vitale A., Gringeri E., Cillo U.	Liver transplantation for rare liver diseases and rare indications for liver transplant	Translational Gastroenterology and Hepatology (2021) 6. Date of Publication: 1 Apr 2021	Population
87	Cordero M.R., Campos M.A., Rivera G.L., Cavalieri S.B., Ribal M.L., Larraguibel C., Benavides S., Santis M.A., Muñoz M.	Liver transplants in pediatric patients: The experience at hospital luis calvo mackenna, Santiago, Chile	Liver Transplantation (2012) 18 SUPPL. 1 (S108). Date of Publication: May 2012	Population
88	Hol F.A., Hamel B.J.C., Geurds M.P.A., Hansmann I., Nabben F.A.E., Daniels O., Mariman E.C.M.	Localization of Alagille syndrome to 20p11.2-p12 by linkage analysis of a three-generation family	Human Genetics (1995) 95:6 (687-690). Date of Publication: 1995	Outcomes
89	Ee L.C., Beale K., Fawcett J., Cleghorn G.J.	Long-term growth and anthropometry after childhood liver transplantation	Journal of Pediatrics (2013) 163:2 (537-542). Date of Publication: August 2013	Population
90	Hori T., Egawaa H., Takadaa Y., Oikea F., Kasaharaa M., Oguraa Y., Sakamotoa S., Ogawaa K., Yonekawaa Y., Nguyenb J.H., Doi H., Uenod M., Uemoto S.	Long-term outcomes after living donor liver transplantation for alagille syndrome: A single center 20-year experience in Japan	American Journal of Transplantation (2010) 10:8 (1951-1952). Date of Publication: August 2010	Publication type
91	Kasahara M., Umeshita K., Inomata Y., Uemoto S.	Long-term outcomes of pediatric living donor liver transplantation in Japan: An analysis of more than 2200 cases listed in the registry of the japanese liver transplantation society	American Journal of Transplantation (2013) 13:7 (1830-1839). Date of Publication: July 2013	Population
92	Leiskau C., Samuel S., Pfister E.-D., Junge N., Laue T., Mutschler F., Goldschmidt I., Beneke J., Stupak J., Schrem H., Baumann U.	Low dose steroids do make a difference-failure to thrive after pediatric liver Transplantation	Journal of Pediatric Gastroenterology and Nutrition (2019) 68 Supplement 1 (949). Date of Publication: 1 May 2019	Outcomes
93	Kamath B.M., Loomes K.M., Piccoli D.A.	Medical management of alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2010) 50:6 (580-586). Date of Publication: June 2010	Publication type
94	Mouzaki M., Bass L.M., Piccoli D.A., Heubi J.E., Rosenthal P., Miller H., Baker A.J., Spinner N.B., Beyene J., Kamath B.M.	Modeling liver disease outcome in an international multi-center cohort of alagille syndrome patients	Hepatology (2011) 54 SUPPL. 1 (470A). Date of Publication: October 2011	Outcomes
95	Cosme Á., Cobo A.M., Meunier-Rotival M., Hadchouel M., Jara P., Ojeda E., Bujanda L., Orbegozo J.	Molecular and clinical characteristics of a family with Alagille syndrome	Medicina Clinica (2008) 130:1 (17-19). Date of Publication: 19 Jan 2008	Language

96	Wang N.-L., Lu Y., Gong J.-Y., Xie X.-B., Lin J., Abuduxikuer K., Zhang M.-H., Wang J.-S.	Molecular findings in children with inherited intrahepatic cholestasis	Pediatric Research (2020) 87:1 (112-117). Date of Publication: 1 Jan 2020	Population
97	Ong E., Williams S.M., Anderson J.C., Kaplan P.A.	MR imaging of a hepatoma associated with Alagille syndrome	Journal of Computer Assisted Tomography (1986) 10:6 (1047-1049). Date of Publication: 1986	Study type
98	Shiau H., Guffey D., Loomes K.M., Seidman C., Ragozzino E., Molleston J.P., Schady D., Leung D.H.	Multi-center liver biopsy validation study of APRI and FIB-4 as biomarkers of liver fibrosis severity and predictors for transplant in inherited cholestatic liver diseases	Hepatology v70 suppl.1 2019 (2019) 70 Supplement 1 (202A-203A). Date of Publication: 1 Oct 2019	Outcomes
99	Ayyala R., Prabhu S., Sena L.	Multi-modality imaging of vascular anomalies in alagille syndrome in children: A pictorial review	Pediatric Radiology (2014) 44 SUPPL. 1 (S176). Date of Publication: May 2014	Outcomes
100	Crosnier C., Driancourt C., Raynaud N., Dhorne-Pollet S., Pollet N., Bernard O., Hadchouel M., Meunier-Rotival M.	Mutations in JAGGED1 gene are predominantly sporadic in Alagille syndrome	Gastroenterology (1999) 116:5 (1141-1148). Date of Publication: 1999	Outcomes
101	Foster, B; Gauthier, M; Vig, P; Jaecklin, T; Kamath, BM; Andrae, DA	Natural variability of pruritus in alagille syndrome; an analysis from the iconic study utilising the itch reported outcome observer (ITCHRO [OBS]) tool	Hepatology (Baltimore, Md.)	Outcomes
102	Leung D., Sorensen L., Ye W., Hawthorne K., Kamath B., Ng V., Loomes K., Fredericks E., Sokol R., Squires J., Karpen S., Molleston J., Heubi J., Murray K., Wang K., Rosenthal P., Teckman J., Sherker A., Magee J.	Neurocognitive status in alagille syndrome: Results of a multi-center prospective observational study	Journal of Pediatric Gastroenterology and Nutrition (2017) 65 Supplement 2 (S289-S290). Date of Publication: 1 Nov 2017	Outcomes
103	Alvarez L., Hierro L., García-Miñaur S., Aroeira L.S., Martínez P., Andueza S., Camarena C., De La Vega A., Díaz C., Jara P.	Next generation sequencing: Identifying atypical Alagille syndrome and NOTCH2 variants	Journal of Pediatric Gastroenterology and Nutrition (2017) 64 Supplement 1 (608-609). Date of Publication: 1 Apr 2017	Population
104	Aamann L., Ørntoft N., Becher N., Grønbæk H., Vilstrup H., Ott P., Vogel I., Lildballe D.	NGS-panel consisting of genes with cholestatic potential identified pathogenic and predisposing variants in 10 of 33 patients with unexplained cholestatic liver disease	European Journal of Human Genetics (2019) 26 Supplement 1 (198). Date of Publication: 2019	Outcomes

105	Shneider B.L., Goodrich N.P., Ye W., Sawyers C., Molleston J.P., Merion R.M., Leung D.H., Karpen S.J., Kamath B.M., Cavallo L., Wang K., Teckman J.H., Squires J.E., Sundaram S.S., Rosenthal P., Romero R., Murray K.F., Loomes K.M., Jensen M.K., Bezerra J.A., Bass L.M., Sokol R.J., Magee J.C.	Nonfasted Liver Stiffness Correlates with Liver Disease Parameters and Portal Hypertension in Pediatric Cholestatic Liver Disease	Hepatology Communications (2020) 4:11 (1694-1707). Date of Publication: 1 Nov 2020	Population
106	Chin K., Uemoto S., Takahashi K.-I., Egawa H., Kasahara M., Fujimoto Y., Sumi K., Mishima M., Sullivan C.E., Tanaka K.	Noninvasive ventilation for pediatric patients including those under 1-year-old undergoing liver transplantation	Liver Transplantation (2005) 11:2 (188-195). Date of Publication: February 2005	Population
107	Kamath B.M., Bauer R.C., Loomes K.M., Chao G., Gerfen J., Hutchinson A., Hardikar W., Hirschfield G., Jara P., Krantz I.D., Lapunzina P., Leonard L., Ling S., Ng V.L., Le Hoang P., Piccoli D.A., Spinner N.B.	NOTCH2 mutations in Alagille syndrome	Journal of Medical Genetics (2012) 49:2 (138-144). Date of Publication: February 2012	Population
108	Bettocchi S., Fiorica L., Paolella G., Agostoni C.V., Farallo M., Nebbia G.	Nutritional status in alagille syndrome	Digestive and Liver Disease (2015) 47 SUPPL. 4 (e246). Date of Publication: 8 Oct 2015	Outcomes
109	Fahnehjelm K.T., Fischler B., Martin L., Nemeth A.	Occurrence and pattern of ocular disease in children with cholestatic disorders	Acta Ophthalmologica (2011) 89:2 (143-150). Date of Publication: March 2011	Population
110	Hingorani M., Nischal K.K., Davies A., Bentley C., Vivian A., Baker A.J., Mieli-Vergani G., Bird A.C., Aclimandos W.A.	Ocular abnormalities in Alagille syndrome	Ophthalmology (1999) 106:2 (330-337). Date of Publication: 1 Feb 1999	Outcomes
111	Brodsky M.C., Cunniff C.	Ocular anomalies in the Alagille syndrome (arteriohepatic dysplasia)	Ophthalmology (1993) 100:12 (1767-1774). Date of Publication: 1993	Outcomes
112	El-Karaksy H., Hamed D., Fouad H., Mogahed E., Helmy H., Hasanain F.	Ocular findings in patients with cholestatic disorders of infancy: A single-centre experience	Arab Journal of Gastroenterology (2017) 18:2 (108-113). Date of Publication: 1 Jun 2017	Population
113	Nischal K.K., Hingorani M., Bentley C.R., Vivian A.J., Bird A.C., Baker A.J., Mowat A.P., Mieli-Vergani G., Aclimandos W.A.	Ocular ultrasound in Alagille syndrome: A new sign	Ophthalmology (1997) 104:1 (79-85). Date of Publication: 1997	Outcomes

114	Libbrecht L., Cassiman D.	On the Pathogenesis of Central Liver Nodules in Alagille Syndrome	Journal of Pediatric Gastroenterology and Nutrition (2017) 64:3 (e80). Date of Publication: 1 Mar 2017	Publication type
115	Arnon R., Annunziato R., Schiano T., Miloh T., Baisley M., Sogawa H., Contreras A.G., Lee S., Kerkar N.	Orthotopic liver transplantation for adults with Alagille syndrome	Clinical Transplantation (2012) 26:2 (E94-E100). Date of Publication: March/April 2012	Population
116	Maldini G., Torri E., Lucianetti A., Guizzetti M., Pinelli D., Bertani A., Corno V., Giovanelli M., Zambelli M., Stroppa P., Alberti D., Torre G., Spada M., Gridelli B., Colledan M.	Orthotopic liver transplantation for alagille syndrome	Transplantation Proceedings (2005) 37:2 (1174-1176). Date of Publication: March 2005	Outcomes
117	Bauser-Heaton H., Ma M., Wise-Faberowski L., Asija R., Shek J., Zhang Y., Peng L.F., Sidell D.R., Hanley F.L., McElhinney D.B.	Outcomes After Initial Unifocalization to a Shunt in Complex Tetralogy of Fallot With MAPCAs	Annals of Thoracic Surgery (2019) 107:6 (1807-1815). Date of Publication: 1 Jun 2019	Population
118	Gunadi, Kaneshiro M., Okamoto T., Sonoda M., Ogawa E., Okajima H., Uemoto S.	Outcomes of liver transplantation for Alagille syndrome after Kasai portoenterostomy; Alagille syndrome with agenesis of extrahepatic bile ducts at porta hepatis	Transplantation (2019) 103:8 Supplement 1 (246-247). Date of Publication: 1 Aug 2019	Outcomes
119	Gunadi, Kaneshiro M., Okamoto T., Sonoda M., Ogawa E., Okajima H., Uemoto S.	Outcomes of liver transplantation for Alagille syndrome after Kasai portoenterostomy: Alagille Syndrome with agenesis of extrahepatic bile ducts at porta hepatis	Journal of Pediatric Surgery (2019) 54:11 (2387-2391). Date of Publication: 1 Nov 2019	Outcomes
120	Kamath B., Yin W., Mouzaki M., Miller H., Anand R., Rand E., Alonso E., Bucuvalas J.	Outcomes of liver transplantation in alagille syndrome	Journal of Hepatology (2012) 56 SUPPL. 2 (S58). Date of Publication: April 2012	Outcomes
121	Giannakudis J., Röpke A., Kujat A., Krajewska-Walasek M., Hughes H., Fryns J.-P., Bankier A., Amor D., Schlicker M., Hansmann I.	Parental mosaicism of JAG1 mutations in families with Alagille syndrome	European Journal of Human Genetics (2001) 9:3 (209-216). Date of Publication: 2001	Outcomes
122	Emerick K.M., Whitington P.F.	Partial external biliary diversion for intractable pruritus and xanthomas in Alagille syndrome	Hepatology (2002) 35:6 (1501-1506). Date of Publication: June 2002	Outcomes

123	Zahmatkeshan M., Geramizadeh B., Haghighat M., Enteshari H.	Paucity of intrahepatic bile ducts in neonates: The first case series from Iran	Iranian Journal of Pediatrics (2013) 23:1 (65-70). Date of Publication: February 2013	Population
124	Karpen S.J.	Pediatric Cholestasis: Epidemiology, Genetics, Diagnosis, and Current Management	Clinical Liver Disease (2020) 15:3 (119-115). Date of Publication: 1 Mar 2020	Publication type
125	Black K., Ziogas I., Thurm C., Hall M., Hafberg E.T., Alexopoulos S., Godown J., Gillis L.A.	Pediatric liver transplant outcomes in alagille syndrome: A linked database analysis	Hepatology (2020) 72:1 SUPPL (1095A-1096A). Date of Publication: 1 Nov 2020	Outcomes
126	Mizuta K., Urahashi T., Ihara Y., Sanada Y., Okada N., Yamada N., Hirata Y., Katano T., Ushijima K., Otomo S.	Pediatric liver transplantation using segmental grafts in Japan: A single-center experience with 270 patients	Transplantation (2016) 100:7 Supplement 1 (S135). Date of Publication: 1 Jul 2016	Population
127	Cicak Novak M., Babic K., Maric A., Saratlija M., Novak M., Vukovic J.	Pediatric liver transplantation: Present state in Croatia	Intensive Care Medicine (2011) 37 SUPPL. 2 (S440). Date of Publication: November 2011	Population
128	Vázquez-Martínez E.R., Varela-Fascinetto G., García-Delgado C., Rodríguez-Espino B.A., Sánchez-Boiso A., Valencia-Mayoral P., Heller-Rosseau S., Pelcastre-Luna E.L., Zenteno J.C., Cerbón M., Morán-Barroso V.F.	Polymorphism analysis and new JAG1 gene mutations of Alagille syndrome in Mexican population	Meta Gene (2014) 2:1 (32-40). Date of Publication: 2014	Outcomes
129	Huysentruyt K., Vandriel S., Piccoli D.A., Lin H.C., Hulst J.M., Roelants M., Kamath B.M.	Predictors of growth in children with Alagille syndrome: Towards condition-specific growth charts	Hepatology v70 suppl.1 2019 (2019) 70 Supplement 1 (1024A-1025A). Date of Publication: 1 Oct 2019	Outcomes
130	Witt H., Neumann L.M., Grollmuß O., Luck W., Becker M.	Prenatal diagnosis of Alagille syndrome	Journal of Pediatric Gastroenterology and Nutrition (2004) 38:1 (105-106). Date of Publication: January 2004	Study type
131	Shevchenko O., Kurabekova R., Tsirulnikova I., Olefirenko G., Gichkun O., Tsirulnikova O., Gautier S.	Prognostic value of TGF-b1 plasma level at pediatric living donor liver transplantation	Clinical Chemistry and Laboratory Medicine (2017) 55 Supplement 1 (S377). Date of Publication: 1 Jun 2017	Population

132	Serrano D., Gauthier M., Harrington M., Acevedo L.	Psychometric validation of the Itch Reported Outcome (ItchRO™) assessment in pediatric patients with Alagille syndrome or progressive familial intrahepatic cholestasis	Hepatology (2016) 64:1 Supplement 1 (284A-285A). Date of Publication: 1 Oct 2016	Population
133	Ohkohchi N., Orii T., Kawagishi N., Satomi S.	Quality of life of pediatric patients receiving living donor liver transplantation in long-term follow-up period	Transplantation Proceedings (2001) 33:7-8 (3610-3613). Date of Publication: 2001	Population
134	Akdur A., Kirnap M., Karakayalý F.Y., Yildirim S., Moray G., Haberal M.	Rare indications for liver transplantation: Single center experience	Transplant International (2013) 26 SUPPL. 2 (304). Date of Publication: November 2013	Population
135	van Ta T., Nguyen T.A., Nguyen T.V.	Ratio of JAG1 and NOTCH2 gene mutation characteristics in children with alagille syndrome at Children's hospital 1 in Ho Chi Minn city, Vietnam	Systematic Reviews in Pharmacy (2019) 10:1 (173-178). Date of Publication: 1 Dec 2019	Outcomes
136	El-Rifai N., Gottrand F.	Role of ursodeoxycholic acid in pediatric cholestatic disease	Gastroenterologie Clinique et Biologique (2004) 28:10 I (852-859). Date of Publication: October 2004	Language
137	Alhammad A., Kamath B.M., Chami R., Ng V.L., Chavhan G.B.	Solitary hepatic nodule adjacent to the right portal vein: A common finding of Alagille syndrome?	Journal of Pediatric Gastroenterology and Nutrition (2016) 62:2 (226-232). Date of Publication: 1 Feb 2016	Outcomes
138	Krantz I.D., Colliton R.P., Genin A., Rand E.B., Li L., Piccoli D.A., Spinner N.B.	Spectrum and frequency of jagged1 (JAG1) mutations in Alagille syndrome patients and their families	American Journal of Human Genetics (1998) 62:6 (1361-1369). Date of Publication: June 1998	Outcomes
139	Jurkiewicz D., Gliwicz D., Ciara E., Gerfen J., Pelc M., Piekutowska-Abramczuk D., Kugaudo M., Chrzanowska K., Spinner N.B., Krajewska-Walasek M.	Spectrum of JAG1 gene mutations in Polish patients with Alagille syndrome	Journal of Applied Genetics (2014) 55:3 (329-336). Date of Publication: August 2014	Population
140	Gridelli B., Spada M., Petz W., Bertani A., Lucianetti A., Colledan M., Altobelli M., Alberti D., Guizzetti M., Riva S., Melzi M.L., Stroppa P., Torre G.	Split-liver transplantation eliminates the need for living donor liver transplantation in children with end-stage cholestatic liver disease	Transplantation (2003) 75:8 (1197-1203). Date of Publication: 27 Apr 2003	Population
141	Yancey P.G., Asztalos B.F., Stettler N., Piccoli D., Williams D.L., Connelly M.A., Rothblat G.H.	SR-BI- and ABCA1-mediated cholesterol efflux to serum from patients with Alagille syndrome	Journal of Lipid Research (2004) 45:9 (1724-1732). Date of Publication: September 2004	Study type

142	Davit-Spraul A., Cosson C., Couturier M., Hadchouel M., Legrand A., Lemonnier F., Therond P.	Standard treatment of α-tocopherol in Alagille patients with severe cholestasis is insufficient	Pediatric Research (2001) 49:2 (232-236). Date of Publication: 2001	Outcomes
143	Kamath B.M., Loomes K.M., Oakey R.J., Krantz I.D.	Supernumerary digital flexion creases: An additional clinical manifestation of alagille syndrome	American Journal of Medical Genetics (2002) 112:2 (171-175). Date of Publication: 1 Oct 2002	Outcomes
144	Mainwaring R.D., Sheikh A.Y., Punn R., Reddy V.M., Hanley F.L.	Surgical outcomes for patients with pulmonary atresia/major aortopulmonary collaterals and alagille syndrome	European Journal of Cardio-thoracic Surgery (2012) 42:2 (235-241) Article Number: ezr310. Date of Publication: August 2012	Outcomes
145	Mainwaring R.D., Sheikh A.Y., Punn R., Reddy V.M., Hanley F.L.	Surgical outcomes for patients with pulmonary atresia/major aortopulmonary collaterals and alagille syndrome	Interactive Cardiovascular and Thoracic Surgery (2011) 13 SUPPL. 2 (S94). Date of Publication: September 2011	Outcomes
146	Flores C.D., Yu Y.R., Miloh T.A., Goss J., Brandt M.L.	Surgical outcomes in Alagille syndrome and PFIC: A single institution's 20-year experience	Journal of Pediatric Surgery (2018) 53:5 (976-979). Date of Publication: 1 May 2018	Outcomes
147	Monge M.C., Mainwaring R.D., Sheikh A.Y., Punn R., Reddy V.M., Hanley F.L.	Surgical reconstruction of peripheral pulmonary artery stenosis in Williams and Alagille syndromes	Journal of Thoracic and Cardiovascular Surgery (2013) 145:2 (476-481). Date of Publication: February 2013	Outcomes
148	Torfgard K., Gwaltney C., Paty J., Mattsson J., Soni P.	Symptoms and daily impacts associated with progressive familial intrahepatic cholestasis and other pediatric cholestatic liver diseases: A qualitative study with patients and caregivers	Journal of Pediatric Gastroenterology and Nutrition (2018) 67 Supplement 1 (S208-S209). Date of Publication: 1 Nov 2018	Population
149	Berrocal T., Gamo E., Navalón J., Prieto C., Al-Assir I., Cortés P., Pastor I., Hierro L.	Syndrome of Alagille: radiological and sonographic findings. A review of 37 cases.	European radiology (1997) 7:1 (115-118). Date of Publication: 1997	Outcomes
150	Almes M., Rohmer B., Ruiz M., Thébaut A., Lachaux A., Gottrand F., Mention K., Debray D., Lacaille F., Lamireau T., Roquelaure B., Fabre A., Broué P., Dabadie	Targeted-capture next-generation sequencing in the diagnosis of pediatric cholestasis	Journal of Pediatric Gastroenterology and Nutrition (2019) 68 Supplement 1 (761-762). Date of Publication: 1 May 2019	Population

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151	Mueller R.F.	The Alagille syndrome (arteriohepatic dysplasia)	Journal of Medical Genetics (1987) 24:10 (621-626). Date of Publication: 1987	Publication type
152	Abetz-Webb L., Kennedy C., Hepburn B., Gauthier M., Johnson N., Medendorp S., Dorenbaum A., Shneider B.L., Kamath B.M.	The burden of pruritus on patients with alagille syndrome: Results from a qualitative study with pediatric patients and their caregivers	Hepatology (2014) 60 SUPPL. 1 (526A-527A). Date of Publication: October 2014	Outcomes
153	Loomes K.M., Underkoffler L.A., Morabito J., Gottlieb S., Piccoli D.A., Spinner N.B., Baldwin H.S., Oakey R.J.	The expression of Jagged1 in the developing mammalian heart correlates with cardiovascular disease in Alagille syndrome	Human Molecular Genetics (1999) 8:13 (2443-2449). Date of Publication: 1999	Study type
154	Takeda M., Sakamoto S., Uchida H., Shimizu S., Yanagi Y., Fukuda A., Yoshioka T., Kasahara M.	The morphological and histopathological assessment of Alagille syndrome with extrahepatic bile duct obstruction: the importance of the differential diagnosis with subgroup “o” biliary atresia	Pediatric Surgery International (2021). Date of Publication: 2021	Outcomes
155	Fattouh A.M., Mogahed E.M., AbdelHamid N., Sobhy R., Saber N., El-Karaksy H.	The prevalence of congenital heart defects in infants with cholestatic disorders of infancy: A single center study	Cardiology in the Young (2016) 26 Supplement 1 (S89). Date of Publication: 1 May 2016	Population
156	Fattouh A.M., Mogahed E.A., Hamid N.A., Sobhy R., Saber N., El-Karaksy H.	The prevalence of congenital heart defects in infants with cholestatic disorders of infancy: A single-centre study	Archives of Disease in Childhood (2016) 101:9 (803-807). Date of Publication: 1 Sep 2016	Population
157	Taylor S.A., Chen S.-Y., Gadhvi G., Feng L., Gromer K.D., Abdala-Valencia H., Nam K., Dominguez S.T., Montgomery A.B., Reyfman P.A., Ostilla L., Wechsler J.B., Cuda C.M., Green R.M., Perlman H., Winter D.R.	Transcriptional profiling of pediatric cholestatic livers identifies three distinct macrophage populations	PLoS ONE (2021) 16:1 January Article Number: e0244743. Date of Publication: 1 Jan 2021	Population
158	Elli L., Maieron R., Martelossi S., Guariso G., Buscarini E., Conte D., di Giulio E., Staiano A., Barp J., Bassotti G., Bianco M.A., Buri L., Carrara M., Ghidini B.,	Transition of gastroenterological patients from paediatric to adult care: A position statement by the Italian Societies of Gastroenterology	Digestive and Liver Disease (2015) 47:9 (734-740). Date of Publication: 1 Sep 2015	Population

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159	Mitchell T., Gooding H., Mews C., Adams L., Macquillan G., Garas G., Ravikumara M., Collins M., Lopez A., Jeffrey G.	Transition to adult care for paediatric liver transplant recipients	Journal of Gastroenterology and Hepatology (Australia) (2015) 30 SUPPL. 3 (110). Date of Publication: September 2015	Population
160	Alvarez F.	Treatments in chronic cholestasis in children	Annales Nestle (2008) 66:3 (127-135). Date of Publication: October 2008	Population
161	Akdur A., Kirnap M., Soy E.H.A., Ozcay F., Moray G., Arslan G., Haberal M.	Unusual indications for a liver transplant: A single-center experience	Experimental and Clinical Transplantation (2017) 15 Supplement 1 (128-132). Date of Publication: 1 Feb 2017	Population
162	Akdur A., Kirnap M., Ayvazoglu Soy E.H., Ozcay F., Moray G., Arslan G., Haberal M.	Unusual indications for a liver transplant: A single-center experience	Transplantation (2016) 100:7 Supplement 1 (S554). Date of Publication: 1 Jul 2016	Population
163	Akdur A., Kirnap M., Ozcay F., Selcuk H., Yildirim S., Moray G., Haberal M.	Unusual indications for liver transplantation; single center experience	Transplant International (2015) 28 SUPPL. 4 (618). Date of Publication: November 2015	Population
164	Karpen S., Kamath B., Alexander J., Ichetovkin I., Rosenthal P., Soliman W., Thompson R., Heubi J.	Use of a comprehensive 66 gene panel to diagnose the causes of cholestasis in >700 individuals	Journal of Pediatric Gastroenterology and Nutrition (2017) 65 Supplement 2 (S299-S300). Date of Publication: 1 Nov 2017	Population
165	Yerushalmi, B; Sokol, RJ; Narkewicz, MR; Smith, D; Karrer, FM	Use of rifampin for severe pruritus in children with chronic cholestasis	Journal of pediatric gastroenterology and nutrition	Population
166	Kay M.H., Wyllie R., Steffen R.M.	Use of ursodeoxycholic acid in the treatment of arteriohepatic dysplasia	Clinical Pediatrics (1996) 35:11 (593-596). Date of Publication: November 1996	Study type
167	Santamaria R., Lopez-Aguilera J., Gonzalez De Caldas R., Sanchez-Frias M., Garcia-Rios A., Buendia P., Aljama P.	Vascular abnormalities as predominant feature in alagille syndrome patients with a novel mutation in JAG1 gene	Journal of Hypertension (2016) 34 Supplement 2 (e180). Date of Publication: 1 Sep 2016	Outcomes

168	Sanada Y., Naya I., Katano T., Hirata Y., Yamada N., Okada N., Ihara Y., Onishi Y., Mizuta K.	Visceral artery anomalies in patients with Alagille syndrome	Pediatric Transplantation (2019) 23:2 Article Number: e13352. Date of Publication: 1 Mar 2019	Outcomes
May 2023 update exclusions (n=32):				
169	Gonzales E; Vig P; Tucker E; Garner W; Jaecklin T; Jacquemin E; Kamath B	Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome	Journal of pediatric gastroenterology and nutrition	Duplicate
170	Kamath B.; Raman R.; Garner W.; Tucker E.; Vig P.; Gonzales E.	Gastrointestinal tolerability of maralixibat in patients with Alagille syndrome: An integrated analysis of short- and long-term treatment	J. Pediatr. Gastroenterol. Nutr.	Duplicate
171	Khendek L.; Alvarez F.; Beaunoyer M.; Drouin E.; Lallier M.; Paganelli M.	EARLY PREDICTORS OF UNFAVORABLE OUTCOME IN NORTH AMERICAN INDIAN CHILDHOOD CIRRHOSIS	J. Can. Ass. Gastroenterol.	Outcomes
172	Newton K.; Schwarz K.; Gonzalez K.; Boyd N.; Parker J.; Huang J.	Electronic health record module to standardize transition services in pediatric liver transplant	J. Pediatr. Gastroenterol. Nutr.	OUtcomes
173	Roldan-Montijo M.; Zarate-Mondragon F.; Hernandez A.O.; Cervantes-Bustamante R.; Montijo-Barrios E.; Toro-Monjaraz E.M.; Cadena-Leon J.F.; Arellano K.R.I.; Ramirez-Mayans J.A.	EPIDEMIOLOGICAL TENDENCY OF PROLONGED NEONATAL CHOLESTATIC SYNDROME IN A TERTIARY CENTER IN MEXICO CITY	J. Pediatr. Gastroenterol. Nutr.	Unavailable

174	Miloh T.A.; Goldstein A.; Howard R.; Marden J.; Gaburo K.; Rosenthal P.	Cost of pediatric liver transplant among commercial and medicaid insured patients	Hepatology	Duplicate
175	Herceg S.; Dilber D.; Saric D.; Bartonicek D.; Mihalec M.; Frkovic S.H.; Belina D.; Duric Z.; Planinc M.	Alagille syndrome in infant with fallot tetralogy	Arch. Dis. Child.	Publication Type
176	Gan W.; Li J.; Chen S.; Li X.	Alagille syndrome in adult: Clinical or genetic diagnosis?	Hepatology	Unavailable
177	Shneider B.L.; Kamath B.; Ye W.; Goodrich N.P.; Magee J.C.; Loomes K.M.; Jones K.; Spino C.; Wang K.S.; Squires R.H.; Rosenthal P.; Molleston J.P.; Karpen S.J.; Jensen M.K.; Horslen S.P.; Bezerra J.A.; Alonso E.M.; Sokol R.J.	Utilization of multi-center prospective longitudinal databases to inform clinical trials in rare diseases - Examination of cholestatic liver disease in alagille syndrome (algs)	Hepatology	Unavailable
178	Crnkoviccuk M.; Perse B.; Matijevic P.; Zaja O.	A longterm follow-up of two siblings with alagille syndrome	Arch. Dis. Child.	Publication Type
179	Ovchinsky N.; Savage J.; Kjems L.; Horn P.	The assert study: A phase 3 double-blind, randomized, placebo-controlled study of the safety and efficacy of odevixibat in patients with Alagille syndrome	J. Pediatr. Gastroenterol. Nutr.	Unavailable

180	Singh, Satender Pal; Mondia, Nitisha	Letter to the Editor: Much more needed in natural history of Alagille syndrome.	Hepatology	Publication type
181	Himes R.W.; Mogul D.; Baek M.; Gonzalez-Peralta R.P.	REAL-WORLD SAFETY EXPERIENCE IN PATIENTS WITH ALAGILLE SYNDROME TREATED WITH MARALIXIBAT	Hepatology	Unavailable
182	Boster J.M.; Goodrich N.P.; Spino C.; Loomes K.M.; Alonso E.M.; Kamath B.M.; Sokol R.J.; Sundaram S.S.	SEVERE SARCOPENIA IN CHILDREN WITH CHRONIC INTRAHEPATIC CHOLESTATIC LIVER DISEASE DOES NOT CORRELATE WITH CHOLESTASIS	Hepatology	Unavailable
183	Umemura K.; Fujita K.; Kamei M.	Three-year Follow-up of Progressive Chorioretinal Atrophy in Atypical Alagille Syndrome: a Case Report	Retin Cases Brief Rep	Publication type
184	Sokol R.J.; Friederich M.W.; Strode D.K.; Van Hove R.A.; Miller K.; Gabel L.; Horslen S.P.; Kohli R.; Lovell M.A.; Miethke A.; Molleston J.P.; Romero R.; Squires J.E.; Squires R.H.; Sundaram S.S.; Magee J.C.; Van Hove J.L.K.	ACCURACY OF GDF15 AND FGF21 TO DIFFERENTIATE MITOCHONDRIAL HEPATOPATHIES FROM OTHER PEDIATRIC LIVER DISEASES	Hepatology	Outcomes
185	Anonymous.	25th Annual Meeting of the Society of Pediatric Liver Transplantation	Transplantation	Outcomes

186	Celik N.; Emiroglu R.	Pediatric Liver Transplantation For Hereditary Metabolic Disorders With Structural Liver Damage	Turkish J. Pediatr. Dis.	Outcomes
187	Nobile E.; De Filippis A.; Circhetta S.; Bernardini F.; Viscusi M.; Gallo P.; Ussia G.P.	ALAGILLE SYNDROME, A CASE REPORT	Eur. Heart J. Suppl.	Publication type
188	Chichelnitskiy E.; Ruhl L.; Goldschmidt I.; Rubsamen N.; Kelly D.; D'Antiga L.; Nicastro E.; McLin V.; Debray D.; Hierro L.; Pawlowska J.; Czubkowski P.; Baumann U.; Falk C.	Characterization of the longitudinal dynamics of soluble and cellular immune mediators in pediatric liver transplantation (pLTx) identified cytokine/chemokine signatures potentially linked to beneficial immunosuppressive regimes (IS) and recovery	J. Pediatr. Gastroenterol. Nutr.	Outcomes
189	Chan A.P.; Venick R.S.	Childhood Cholestatic Liver Diseases that Persist Into Adulthood: Lessons for the Adult Gastroenterologist	J Clin Gastroenterol	Publication type
190	Kawahara S.; Imagawa K.; Takeuchi S.; Iwasaki T.; Okada Y.; Nakamura Y.; Saito S.; Sasaki T.; Masumoto K.; Takada H.	Differential diagnosis of neonatal cholestasis by genetic testing: A case report	J. Pediatr. Surg. Case Rep.	Publication type
191	Hahn J.W.; Moon S.Y.; Shin M.; Seong M.W.; Park S.S.; Moon J.S.; Ko J.S.	The etiology of genetic neonatal/infantile cholestasis and usefulness of the molecular genetic testing	J. Pediatr. Gastroenterol. Nutr.	Unavailable

192	Sokol R.J.; Gonzales E.; Kamath B.; Baker A.; Vig P.; Garner W.; Hansen B.E.; Jacquemin E.; Thompson R.J.	Predictors of 6-year event-free survival in patients with Alagille syndrome treated with maralixibat, an IBAT inhibitor	J. Pediatr. Gastroenterol. Nutr.	Unavailable
193	Karun A.; Prasanth K.S.; Bindu S.; Sankar V.H.; Ajith Krishnan A.S.	Clinical and Genetic Spectrum of Monogenic Cholestatic Chronic Liver Diseases in Children - A Single Centre Experience From Kerala	J. Clin. Exp. Hepatol.	Outcomes
194	Ebel N.H.; Goldstein A.; Howard R.; Marden J.; Anderson A.; Rosenthal P.	Healthcare resource utilization in patients with alagille syndrome	Hepatology	Duplicate
195	Beneville B.; Maloney L.; Lin H.	The role and timing of nutritional interventions in children with alagille syndrome and progressive familial intrahepatic cholestasis	J. Pediatr. Gastroenterol. Nutr.	Unavailable
196	Psychogios A.; Pelstring K.; Robie D.; Amr S.	A novel deleterious NOTCH2 mutation (c.5422dup) on a female with premature ovarian insufficiency without symptoms of Alagille syndrome 2	Mol. Genet. Metab.	Publication type
197	Patterson, Catherine; So, Stephanie; Rogers, Alaine; Ng, Vicky L	Motor outcomes in young children pre-and one-year post-liver transplant.	PEDIATR TRANSPLANT	Outcomes
198	Gwaltney, Chad; Ivanescu, Cristina; Karlsson, Lisa; Warholic, Natalie; Kjems, Lise; Horn, Patrick	Validation of the PRUCISION Instruments in Pediatric Patients with Progressive Familial Intrahepatic Cholestasis.	Adv Ther	Outcomes

199	Sahoo B.; Agrawal S.; Kumar K.; Malhotra S.; Sibal A.	Hepatoblastoma in Alagille Syndrome	J. Clin. Exp. Hepatol.	Study type
200	Kamath, Binita M; Goldstein, Andrea; Howard, Robin; Garner, Will; Vig, Pamela; Marden, Jessica R; Billmyer, Emma; Anderson, Annika; Kirson, Noam; Jacquemin, Emmanuel; Gonzales, Emmanuel	Maralixibat Treatment Response in Alagille Syndrome is Associated with Improved Health-Related Quality of Life.	J Pediatr	Duplicate
201	Wehrman, Andrew; Lee, Christine K	The cholestatic infant: updates on diagnosis and genetics.	Curr Opin Pediatr	Publication type - review
202	Ayoub, Mohammed D; Kamath, Binita M	Alagille Syndrome: Current Understanding of Pathogenesis, and Challenges in Diagnosis and Management.	Clin Liver Dis	Publication type - review
203	Gonzales, Emmanuel; Hardikar, Winita; Stormon, Michael; Baker, Alastair; Hierro, Loreto; Gliwicz, Dorota; Lacaille, Florence; Lachaux, Alain; Sturm, Ekkehard; Setchell, Kenneth D R; Kennedy, Ciara; Dorenbaum, Alejandro; Steinmetz, Jana; Desai, Nirav K; Wardle, Andrew J; Garner, Will; Vig, Pamela; Jaecklin, Thomas; Sokal, Etienne M; Jacquemin, Emmanuel	Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study.	Lancet	Duplicate

H.1.4 Quality assessment

Data were extracted by one reviewer and checked for accuracy and consistency by a second reviewer. Discrepancies were resolved through discussion between the two reviewers. For each publication, data were extracted into a data collection form (Excel sheet) and developed in line with the University of York CRD and NICE reporting requirements [111, 139].

Each RCT identified in the clinical SLR has undergone a comprehensive quality assessment using NICE guidelines. This assessment consists of the following questions: [111, 139]

- Was the method used to generate random allocations adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors, e.g., severity of disease?
- Was the treatment allocation sequence adequately concealed?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data.

In addition non-RCTs and RCTs were quality assessed according to CRD guidance in order to answer the questions of whether the studies are robust enough to guide treatment, prevention, diagnostic or policy decisions [111]. Full details of the data extraction and quality assessments are provided as part of section H.1.11.

The same process was followed in May 2023 SLR update and the September 2024 update.

H.1.5 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The HRQoL SLR was conducted as part of the Original SLR to answer the following research questions which follow the PICOS (population, interventions, comparators, outcomes and study type) principle[111]:

> *What is the health-related quality of life impact of ALGS on patients and their caregivers? (review question number 4)*

Searches to identify evidence for the review question listed above were conducted in the following databases for the Original SLR:

- Embase (covers biomedical literature from 1974 to present)
- MEDLINE (covers journals from 1966 to present)
- Embase Classic (the Embase back file covering citations between 1947 and 1973)

In addition to the databases listed above, searches to identify clinical studies were conducted in:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)
- Cochrane Clinical Answers

In addition to the databases listed above the following databases were searched to identify economic and HRQoL studies:

- CRD HTA Database
- CRD National Health Service (NHS) Economic Evaluation Database (EED) (from 1994 and March 2015)
- ScHARRHUD (from 2010 to present)
- EuroQol database

The May 2023 SLR update included the following databases via OVID:

- Embase (covers biomedical literature from 1974 to present)
- MEDLINE (covers journals from 1966 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)

- Cochrane Clinical Answers
- CRD HTA Database
- CRD National Health Service (NHS) Economic Evaluation Database (EED) (from 1994 and March 2015)

The following databases were searched directly (not via OVID):

- ScHARRHUD (from 2010 to present)
- EuroQol database

Table 82 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Medline	Medline; NLM	1966 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Embase classic	Ovid	between 1947 and 1973 for the Original SLR	Original SLR: 11.10.2021
CENTRAL	Cochrane Library Interface	1996 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Cochrane Clinical Answers	Cochrane Library Interface	2012 until October 2021 for the Original SLR, from October 2021 to May 2023 for	Original SLR: 11.10.2021;

Database	Platform/source	Relevant period for the search	Date of search completion
		the first SLR update, and from May 2023 until September 2024 for the second update	1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
CRD HTA Database	crd.york.ac.uk/CRDWeb	1989 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
CRD National Health Service (NHS) Economic Evaluation Database (EED)	crd.york.ac.uk/CRDWeb	1994 and 2015 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
ScHARRHUD	ScHARR-outcomes.sites.sheffield.ac.uk	2010 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
EuroQol database	EuroQol.org	1970 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Supplementary searches of “grey” literature were performed in Google Scholar and through the NICE, Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH) and Scottish Medicines Consortium (SMC) websites. Only completed HTA submissions were considered.

Searches included clinicaltrials.gov, searches of the manufacturer’s repository of evidence, websites of manufacturers of comparator products, bibliographic searching of

any SLRs identified during screening, and the following relevant congresses over the last two years:

- European Association for the Study of the Liver (EASL)
- Federation of International Societies of Pediatric, Gastroenterology, Hepatology and Nutrition (FISPGHAN) – includes European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN), North American Society for Pediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN), and Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN)
- American Association for the Study of Liver Disease (AASLD)

The grey searches described above were searched again during the May 2023 SLR update and the September 2024 update, respectively.

Table 83 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
PBAC	PBS.com	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
CADTH	CDA-AMC.ca	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
SMC	scottishmedicines.org.uk	Clinical review question, cost effectiveness question, cost and resource use question,	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023;

Source name	Location/source	Search strategy	Date of search
		HRQoL question, disease burden question, epidemiological/pathogenesis question	2nd SLR update: 01.09.2024
clinicaltrials.gov	clinicaltrials.gov	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
MAH repository	Internal repository	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
EASL	EASL.eu	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
FISPGHAN	FISPGHAN.org	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
AASLD	AASLD.org	Clinical review question, cost effectiveness question, cost and resource use question, HRQoL question, disease burden question, epidemiological/pathogenesis question	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

Abbreviations: MAH: Marketing Authorization Holder

Table 84 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

I.1.1 Search strategies

The Tables below present the search strategies for ScHARRHUD and EuroQol databases during the first SLR search. These strategies included terms for free text and keywords (Medical Subject Heading (MESH) and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review questions. Only publications available in English were included in the searches and no date restrictions were applied.

Table 85 Search strategy for Embase, MEDLINE and Embase Classic databases used for cost-effectiveness, cost and resource use and HRQoL studies (Embase interface ([11/10/2021])

No.	Query	Results
#6	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,030,214
#7	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR	1,074,201

No.	Query	Results
	(sf20 OR ‘sf 20’ OR ‘sf twenty’ OR sftwenty):ab,ti OR (15D OR 15-D OR ‘15 dimension’):ab,ti OR (‘standard gamble*’ OR sg):ab,ti OR (‘time trade off*’ OR ‘time tradeoff*’ OR tto OR timetradeoff*):ab,ti	
#8	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti)	1,898,591
#9	'natural history'/de OR 'natural history':ti,ab OR ('natural':ab,ti AND histor*:ab,ti) OR 'current management':ab,ti OR (('current*' NEXT/3 'manage*'):ab,ti) OR (('disease' NEXT/3 'manage*'):ab,ti) OR 'guideline'/de OR (('treatment' NEXT/3 'guideline*'):ti,ab) OR 'pathogenesis'/de OR 'pathogenesis':ti,ab OR 'diagnosis'/de OR 'diagnosis':ti,ab OR 'onset:ab,ti' OR (('disease' NEXT/3 'presentation'):ab,ti) OR 'epidemiology'/de OR 'prevalence'/de OR 'incidence'/de OR 'mortality'/de OR epidemiol*:ti,ab OR 'prevalence':ti,ab OR 'incidence':ti,ab OR 'mortality*':ti,ab OR survival:ab,ti OR 'burden':ti,ab OR 'disease burden'/de OR 'unmet need':ab,ti OR 'demography'/de OR demograph*:ab,ti OR morbid*:ab,ti OR 'morbidity'/de OR risk:ab,ti OR 'risk'/de OR 'etiology'/de OR etiology:ab,ti OR aetiology:ab,ti OR distribution:ab,ti OR frequency:ab,ti OR pattern:ab,ti	12,969,588
#10	#1 AND (#6 OR #7 OR #8 OR #9) AND [humans]/lim	1,505

Table 86 Search strategy for ScHARRHUD search strategy used for the QoL search ([11/10/2021])

No.	Query	Results
#1	‘alagille syndrome’ OR ‘ALGS’ OR ‘Alagille-watson syndrome’ OR ‘Watson Alagille syndrome’ OR ‘arteriohepatic dysplasia’ OR ‘cardiovertebral syndrome’ OR ‘cholestasis with peripheral pulmonary stenosis’ OR ‘hepatic ductular hypoplasia’ OR ‘hepatofacioneurocardiovertebral syndrome’ OR ‘paucity of interlobular bile ducts’ OR ‘syndromic bile duct paucity’ OR ‘watson-miller syndrome’ OR ‘JAG1’	0

Table 87 Search strategy for EuroQol database search strategy used for the QoL search ([11/10/2021])

No.	Query	Results
#1	'alagille syndrome' OR 'ALGS' OR 'Alagille-watson syndrome' OR 'Watson Alagille syndrome' OR 'arteriohepatic dysplasia' OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'JAG1'	0

Table 88 Search strategy for NHS HTA and EED used for cost-effectiveness, cost and resource use and HRQoL studies (via University of York website) ([11/10/2021])

No.	Query	Results
#1	alagille syndrome OR ALGS OR Alagille-watson syndrome OR Watson Alagille syndrome OR arteriohepatic dysplasia OR cardiovertebral syndrome OR cholestasis with peripheral pulmonary stenosis OR hepatic ductular hypoplasia OR hepatofacioneurocardiovertebral syndrome OR paucity of interlobular bile ducts OR syndromic bile duct paucity OR watson-miller syndrome OR JAG1	0
#2	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	25,720
#3	#1 AND #2 in NHSEED, HTA	0
#4	qol OR quality of life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	13,074
#5	#1 AND #4 in NHSEED, HTA	0

The Tables below include the search strategies via OVID utilized during the May 2023 SLR update.

Table 89 Search strategy for Embase (via OVID platform) used for cost-effectiveness, cost and resource use and HRQoL studies

		N	Query	Results
# 1	Population	1	exp Alagille Syndrome/	2224
		2	Alagille Syndrome.mp.	2353

3	ALGS.mp.	298
4	exp Alagille-Watson Syndrome/	2224
5	Alagille-Watson Syndrome.mp.	8
6	exp Watson Alagille Syndrome/	2224
7	Watson-Alagille Syndrome.mp.	4
8	exp arteriohepatic dysplasia/	2224
9	arteriohepatic dysplasia.mp.	136
10	exp Cardiovertebral Syndrome/	0
11	Cardiovertebral Syndrome.mp.	0
12	exp cholestasis with peripheral pulmonary stenosis/	0
13	cholestasis with peripheral pulmonary stenosis.mp.	0
14	exp hepatic ductular hypoplasia/	0
15	hepatic ductular hypoplasia.mp.	11
16	exp hepatofacioneurocardiovertebral syndrome/	0
17	hepatofacioneurocardiovertebral syndrome.mp.	0
18	exp paucity of interlobular bile ducts/	0
19	paucity of interlobular bile ducts.mp.	106
20	syndromic bile duct paucity.mp.	10
21	exp watson-miller syndrome/	0
22	watson-miller syndrome.mp.	0
23	JAG1.mp.	1873

		24	or/1-23	3983
# 2	Interventions/comparators	25	exp maralixibat/ or maralixibat.mp.	131
		26	inhibitor* of the apical sodium dependent bile acid transporter.mp.	18
		27	apical sodium-dependent bile acid transporter inhibitor*.mp.	48
		28	ASBT inhibitor*.mp.	125
		29	ASBTi.mp.	22
		30	inhibitor* of the ASBT.mp.	25
		31	ileal bile acid transport*.mp.	295
		32	IBA transport*.mp.	11
		33	IBAT.mp.	845
		34	ileal bile acid transporter inhibitor.mp.	104
		35	IBAT inhibit*.mp.	71
		36	ursodeoxycholic acid.mp.	18003
		37	exp ursodiol/	16994
		38	ursodiol.mp.	633
		39	exp liver transplantation/	139463
		40	liver transplantation.mp.	134477
		41	exp liver transplant/	34205
		42	liver transplant.mp.	42101
		43	partial biliary diversion.mp.	37
		44	PEBD.mp.	79
		45	exp rifampin/	99871

		46 rifampin.mp.	12377
		47 exp naltrexone/	16984
		48 naltrexone.mp.	18839
		49 exp cholestyramine/	10874
		50 cholestyramine.mp.	3154
		51 or/25-50	295969
# 6	Economic Filter	52 'socioeconomics'/	160074
		53 'cost benefit analysis'/	94013
		54 'cost effectiveness analysis'/	180547
		55 'cost of illness'/	21177
		56 'economic evaluation'/	19847
		57 'cost utility analysis'/	12246
		58 'cost control'/	76076
		59 'economic aspect'/	124084
		60 'financial management'/	120974
		61 'health care cost'/	223347
		62 'health care financing'/	13866
		63 'health economics'/	35621
		64 'hospital cost'/	25316
		65 fiscal.ab,ti.	12214
		66 financial.ab,ti.	156411
		67 finance.ab,ti.	8586
		68 funding.ab,ti.	127236

		69	'cost minimization analysis'/	3983
		70	(cost adj estimate*).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]	4201
		71	(cost adj variable*).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]	323
		72	(unit adj cost*).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]	5544
		73	or/52-72	1121797
# 7	Quality of life filter	74	'quality adjusted life year'/	35267
		75	'Value of life'.ab,ti.	669
		76	socioeconomics/	160074
		77	(qaly* or qald* or qale* or qtime*).ab,ti.	26828
		78	(quality adjusted or adjusted life year*).ab,ti.	34039
		79	'Disability adjusted life'.ab,ti.	6348
		80	daly*.ab,ti.	6069
		81	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ab,ti.	1787
		82	(multiattribute* or multi attribute*).ab,ti.	1495
		83	(utility adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit	66787

	or units or health* or life or estimate* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculate* or range* or increment* or state or states or status)).ab,ti.	
84	utility.ab,ti.	364203
85	utilities.ab,ti.	14966
86	disutili*.ab,ti.	1234
87	(hsuv or hsuvs).ab,ti.	194
88	'health* year* equivalent*'.ab,ti.	41
89	(hye or hyes).ab,ti.	167
90	(hui or hui1 or hui2 or hui3).ab,ti.	3072
91	('illness state*' or health state*).ab,ti.	14754
92	('euro qual' or 'euro qual5d' or 'euro qol5d' or eq 5d or eq5 d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ab,ti.	29976
93	(eq sdq or eqsdq).ab,ti.	1
94	(short form* or shortform*).ab,ti.	60233
95	(sf36* or 'sf 36*' or 'sf thirtysix' or 'sf thirty-six').ab,ti.	45444
96	(sf6 or 'sf 6' or sf6d or 'sf 6d' or 'sf six' or sfsix or sf8 or 'sf 8' or 'sf eight' or sfeight).ab,ti.	5403
97	(sf12 or 'sf 12' or 'sf twelve' or sftwelve).ab,ti.	10550
98	(sf16 or 'sf 16' or 'sf sixteen' or sfsixteen).ab,ti.	63
99	(sf20 or 'sf 20' or 'sf twenty' or sftwenty).ab,ti.	379

	100	(15d or 15 d or '15 dimension').ab,ti.	7657
	101	('standard gamble*' or sg).ab,ti.	21108
	102	('time trade off*' or 'time tradeoff*' or tto or timetradeoff*).ab,ti.	3500
	103	or/74-102	714111
# 8 Resource use filter	104	burden.ti.	63535
	105	resource*.ti.	68641
	106	(burden* adj3 (illness* or disease* or sickness* or treatment* or therap*)).ab,ti.	88231
	107	(resource* adj4 (use* or usage or utilit*)).ab,ti.	64627
	108	'Office visits'.ab,ti.	7040
	109	'ambulatory care'/	41574
	110	visit.ab,ti.	229602
	111	visits.ab,ti.	242032
	112	visited.ab,ti.	55493
	113	appointment*.ab,ti.	58529
	114	'hospitalization'/	524833
	115	hospitalization*.ab,ti.	334690
	116	hospitalisation*.ab,ti.	41362
	117	hospitalised.ab,ti.	25243
	118	hospitalized.ab,ti.	216061
	119	admission*.ab,ti.	502451
	120	readmission*.ab,ti.	75963

		121	admitted.ab,ti.	466063
		122	readmitted.ab,ti.	19317
		123	'length of stay'/ or 'hospital stay*'.ab,ti.	386146
		124	(bed adj3 day*).ab,ti.	7206
		125	((days or time or length or duration*) adj3 hospital*).ab,ti.	206455
		126	(((days or time or length or duration*) adj3 (stay or stays or stayed)) or ((days or time or length or duration*) adj3 (discharge or discharged or home or homes))).ab,ti.	293451
		127	or/104-126	2312173
# 9	Epidemiological, burden, disease background and guidelines filter	128	'natural history'/	264712
		129	'natural history'.ti,ab.	77114
		130	('natural' and histor*).ab,ti.	104995
		131	'current management'.ab,ti.	11486
		132	('current*' adj3 'manage*').ab,ti.	28088
		133	('disease' adj3 'manage*').ab,ti.	73445
		134	'guideline'/ or ('treatment' adj3 'guideline*').ti,ab.	45382
		135	'pathogenesis'/	405042
		136	'pathogenesis'.ti,ab.	640402
		137	'diagnosis'/	1412588
		138	'diagnosis'.ti,ab.	2700411
		139	onset.ab,ti.	865329
		140	('disease' adj3 'presentation').ab,ti.	20666

141	'epidemiology'/	241650
142	'prevalence'/	942990
143	'incidence'/	575336
144	'mortality'/	900393
145	epidemiol*.ti,ab.	576192
146	'prevalence'.ti,ab.	1134010
147	'incidence'.ti,ab.	1327368
148	'mortality*'.ti,ab.	1453914
149	survival.ab,ti.	1756106
150	'burden'.ti,ab.	455254
151	'disease burden'/	44442
152	'unmet need'.ab,ti.	22816
153	'demography'/	357315
154	demograph*.ab,ti.	742431
155	morbid*.ab,ti.	782346
156	'morbidity'/	411339
157	risk.ab,ti.	3993040
158	'risk'/	509341
159	'etiology'/	339534
160	etiology.ab,ti.	316491
161	aetiology.ab,ti.	76851
162	distribution.ab,ti.	1146778
163	frequency.ab,ti.	1276513

		164	pattern.ab,ti.	986756
		165	or/128-164	14669318
	Population + Economic filter	166	24 and 73	32
	Population + Quality of life filter	167	24 and 103	53
	Population + Resource use filter	168	24 and 127	186
	Population + Epidemiological, burden, disease background and guidelines filter	169	24 and 165	1991
	Population + all of above	170	166 or 167 or 168 or 169	2042
	Limit	171	limit 170 to humans	1774
	Date limit	172	limit 171 to dd=20211011-20230518	94

Table 90 Search strategy used for Medline Search (via OVID platform)

		N	Query	Results
# 1	Population	1	exp Alagille Syndrome/	740
		2	Alagille Syndrome.mp.	1089
		3	ALGS.mp.	161
		4	exp Alagille-Watson Syndrome/	740
		5	Alagille-Watson Syndrome.mp.	7
		6	exp Watson Alagille Syndrome/	740
		7	Watson-Alagille Syndrome.mp.	3
		8	exp arteriohepatic dysplasia/	740

		9	arteriohepatic dysplasia.mp.	116
		10	exp Cardiovertebral Syndrome/	740
		11	Cardiovertebral Syndrome.mp.	0
		12	exp cholestasis with peripheral pulmonary stenosis/	740
		13	cholestasis with peripheral pulmonary stenosis.mp.	0
		14	exp hepatic ductular hypoplasia/	740
		15	hepatic ductular hypoplasia.mp.	8
		16	exp hepatofacioneurocardiovertebral syndrome/	740
		17	hepatofacioneurocardiovertebral syndrome.mp.	0
		18	exp paucity of interlobular bile ducts/	740
		19	paucity of interlobular bile ducts.mp.	84
		20	syndromic bile duct paucity.mp.	7
		21	exp watson-miller syndrome/	740
		22	watson-miller syndrome.mp.	1
		23	JAG1.mp.	1783
		24	or/1-23	2745
# 2	Intervention/comparator	25	exp maralixibat/ or maralixibat.mp.	20

26	inhibitor* of the apical sodium dependent bile acid transporter.mp.	9
27	apical sodium-dependent bile acid transporter inhibitor*.mp.	12
28	ASBT inhibitor*.mp.	59
29	ASBTi.mp.	5
30	inhibitor* of the ASBT.mp.	18
31	ileal bile acid transport*.mp.	156
32	IBA transport*.mp.	11
33	IBAT.mp.	663
34	ileal bile acid transporter inhibitor.mp.	28
35	IBAT inhibit*.mp.	38
36	ursodeoxycholic acid.mp.	6669
37	exp ursodiol/	4521
38	ursodiol.mp.	221
39	exp liver transplantation/	64167
40	liver transplantation.mp.	81321
41	exp liver transplant/	64167
42	liver transplant.mp.	21112
43	partial biliary diversion.mp.	20
44	PEBD.mp.	47
45	exp rifampin/	19700
46	rifampin.mp.	24296

	47	exp naltrexone/	8652
	48	naltrexone.mp.	11161
	49	exp cholestyramine/	2666
	50	cholestyramine.mp.	3632
	51	or/25-50	130284
# 3 Economic filter	52	'socioeconomics'/	0
	53	'cost benefit analysis'/	0
	54	'cost effectiveness analysis'/	0
	55	'cost of illness'/	0
	56	'economic evaluation'/	0
	57	'cost utility analysis'/	0
	58	'cost control'/	0
	59	'economic aspect'/	0
	60	'financial management'/	0
	61	'health care cost'/	0
	62	'health care financing'/	0
	63	'health economics'/	0
	64	'hospital cost'/	0
	65	fiscal.ab,ti.	9838
	66	financial.ab,ti.	110509
	67	finance.ab,ti.	7250
	68	funding.ab,ti.	77809
	69	'cost minimization analysis'/	0

	70	(cost adj estimate*).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]	2725
	71	(cost adj variable*).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]	194
	72	(unit adj cost*).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]	3102
	73	or/52-72	201362
Quality of life filter	74	'quality adjusted life year'/	0

#			
4	75	'value of life'.ab,ti.	535
	76	socioeconomics/	0
	77	(qaly* or qald* or qale* or qtime*).ab,ti.	14193
	78	(quality adjusted or adjusted life year*).ab,ti.	22800
	79	'disability adjusted life'.ab,ti.	5142
	80	daly*.ab,ti.	4615
	81	((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ab,ti.	1155
	82	(multiattribute* or multi attribute*).ab,ti.	1245
	83	(utility adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimate* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculate* or range* or increment* or state or states or status)).ab,ti.	42717
	84	utility.ab,ti.	256026
	85	utilities.ab,ti.	9185
	86	disutili*.ab,ti.	611
	87	(hsuv or hsuvs).ab,ti.	106
	88	'health* year* equivalent*'.ab,ti.	40

	89	(hye or hyes).ab,ti.	75
	90	(hui or hui1 or hui2 or hui3).ab,ti.	1941
	91	('illness state*' or health state*).ab,ti.	8372
	92	('euro qual' or 'euro qual5d' or 'euro qol5d' or eq 5d or eq5 d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ab,ti.	16203
	93	(eq sdq or eqsdq).ab,ti.	1
	94	(short form* or shortform*).ab,ti.	43402
	95	(sf36* or 'sf 36*' or 'sf thirtysix' or 'sf thirty six').ab,ti.	26134
	96	(sf6 or 'sf 6' or sf6d or 'sf 6d' or 'sf six' or sfsix or sf8 or 'sf 8' or 'sf eight' or sfeight).ab,ti.	3919
	97	(sf12 or 'sf 12' or 'sf twelve' or sftwelve).ab,ti.	6118
	98	(sf16 or 'sf 16' or 'sf sixteen' or sfsixteen).ab,ti.	34
	99	(sf20 or 'sf 20' or 'sf twenty' or sftwenty).ab,ti.	358
	100	(15d or 15 d or '15 dimension').ab,ti.	6061
	101	('standard gamble*' or sg).ab,ti.	13962
	102	('time trade off*' or 'time tradeoff*' or tto or timetradeoff*).ab,ti.	2328
	103	or/74-102	377208
Resource use filter	104	burden.ti.	40634

#			
5	105	resource*.ti.	55116
	106	(burden* adj3 (illness* or disease* or sickness* or treatment* or therap*)).ab,ti.	55558
	107	(resource* adj4 (use* or usage or utilit*)).ab,ti.	46622
	108	'office visits'.ab,ti.	4070
	109	'ambulatory care'/	0
	110	visit.ab,ti.	127465
	111	visits.ab,ti.	144169
	112	visited.ab,ti.	37168
	113	appointment*.ab,ti.	32189
	114	'hospitalization'/	0
	115	hospitalization*.ab,ti.	191674
	116	hospitalisation*.ab,ti.	24308
	117	hospitalised.ab,ti.	15709
	118	hospitalized.ab,ti.	133949
	119	admission*.ab,ti.	282091
	120	readmission*.ab,ti.	40187
	121	admitted.ab,ti.	258578
	122	readmitted.ab,ti.	9029
	123	'length of stay'/ or 'hospital stay*'.ab,ti.	106422
	124	(bed adj3 day*).ab,ti.	4232

		125	((days or time or length or duration*) adj3 hospital*).ab,ti.	119762
		126	(((days or time or length or duration*) adj3 (stay or stays or stayed)) or ((days or time or length or duration*) adj3 (discharge or discharged or home or homes))).ab,ti.	160937
		127	or/104-126	1284937
# 6	Epidemiological, burden, disease background and guidelines filter	128	'natural history'/	0
		129	'natural history'.ti,ab.	54219
		130	('natural' and histor*).ab,ti.	76778
		131	'current management'.ab,ti.	8456
		132	('current*' adj3 'manage*').ab,ti.	19991
		133	('disease' adj3 'manage*').ab,ti.	50957
		134	'guideline'/ or ('treatment' adj3 'guideline*').ti,ab.	28005
		135	'pathogenesis'/	0
		136	'pathogenesis'.ti,ab.	485901
		137	'diagnosis'/	0
		138	'diagnosis'.ti,ab.	1821197
		139	onset.ab,ti.	586345
		140	('disease' adj3 'presentation').ab,ti.	11631
		141	'epidemiology'/	0
		142	'prevalence'/	0
		143	'incidence'/	0

	144	'mortality'/	0
	145	epidemiol*.ti,ab.	446225
	146	'prevalence'.ti,ab.	781092
	147	'incidence'.ti,ab.	902529
	148	'mortality*'.ti,ab.	963117
	149	survival.ab,ti.	1161643
	150	'burden'.ti,ab.	286459
	151	'disease burden'/	0
	152	'unmet need'.ab,ti.	12538
	153	'demography'/	0
	154	demograph*.ab,ti.	436797
	155	morbid*.ab,ti.	499930
	156	'morbidity'/	0
	157	risk.ab,ti.	2691841
	158	'risk'/	0
	159	'etiology'/	0
	160	etiology.ab,ti.	217723
	161	aetiology.ab,ti.	54029
	162	distribution.ab,ti.	955515
	163	frequency.ab,ti.	966232
	164	pattern.ab,ti.	785395
	165	or/128-164	9638917
Population + Economic filter	166	24 and 73	2

Population + Quality of life filter	167	24 and 103	16
Population + Resource use filter	168	24 and 127	50
Population + Epidemiological, burden, disease background and guidelines filter	169	24 and 165	996
Population + all of above	170	166 or 167 or 168 or 169	1013
Limit	171	limit 170 to humans	783
Date limit	172	limit 171 to dt=20211011-20230518	53

Table 91 Search strategy for ScHARRHUD search used for the QoL search strategy ([18/05/2023])

No.	Query	Results
#1	'alagille syndrome' OR 'ALGS' OR 'Alagille-watson syndrome' OR 'Watson Alagille syndrome' OR 'arteriohepatic dysplasia' OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'JAG1'	0

Table 92 Search strategy for EuroQol database search used for the QoL search strategy ([18/05/2023])

No.	Query	Results
#1	'alagille syndrome' OR 'ALGS' OR 'Alagille-watson syndrome' OR 'Watson Alagille syndrome' OR 'arteriohepatic dysplasia' OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'JAG1'	0

The Tables below show the searches for Cost-effectiveness, health-related quality of life, and cost and resource use studies search strategy from the last SLR update conducted the 16/10/2024 for the period between 18th May 2023 to 1st September 2024.

Table 93 Search strategy for Embase search ([16/10/2024] (From 18th May 2023 to 1st September 2024) for cost-effectiveness, health-related quality of life, and cost and resource use studies search

No.	Query	Results
#6	('socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR (cost NEXT/1 estimate*) OR (cost NEXT/1 variable*) OR (unit NEXT/1 cost*)) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	104,772
#7	('quality adjusted life year'/de OR 'value of life':ab,ti OR 'socioeconomics'/de OR qaly*:ab,ti OR qald*:ab,ti OR qale*:ab,ti OR qtime*:ab,ti OR ((quality:ab,ti AND adjusted:ab,ti OR adjusted:ab,ti) AND life:ab,ti AND year*:ab,ti) OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing):ab,ti) OR ((quality NEXT/3 wellbeing):ab,ti) OR qwb:ab,ti OR ((multiattribute*:ab,ti OR multi:ab,ti) AND attribute*:ab,ti) OR ((utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti) OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR hsuv:ab,ti OR hsuvs:ab,ti OR 'health* year* equivalent*':ab,ti OR hye:ab,ti OR hyes:ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR (('illness state*':ab,ti OR health:ab,ti) AND state*:ab,ti) OR 'euro qual':ab,ti OR 'euro qual5d':ab,ti	130,909

No.	Query	Results
	OR 'euro qol5d':ab,ti OR 'eq 5d':ab,ti OR 'eq5 d':ab,ti OR eq5d:ab,ti OR euroqual:ab,ti OR euroqol:ab,ti OR euroqual5d:ab,ti OR euroqol5d:ab,ti OR 'eq sdq':ab,ti OR eqsdq:ab,ti OR (short:ab,ti AND form*:ab,ti) OR shortform*:ab,ti OR sf36*:ab,ti OR 'sf 36*':ab,ti OR 'sf thirtysix':ab,ti OR 'sf thirty six':ab,ti OR sf6:ab,ti OR 'sf 6':ab,ti OR sf6d:ab,ti OR 'sf 6d':ab,ti OR 'sf six':ab,ti OR sfsix:ab,ti OR sf8:ab,ti OR 'sf 8':ab,ti OR 'sf eight':ab,ti OR sfeight:ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'sf twelve':ab,ti OR sftwelve:ab,ti OR sf16:ab,ti OR 'sf 16':ab,ti OR 'sf sixteen':ab,ti OR sfsixteen:ab,ti OR sf20:ab,ti OR 'sf 20':ab,ti OR 'sf twenty':ab,ti OR sftwenty:ab,ti OR 15d:ab,ti OR '15 d':ab,ti OR '15 dimension':ab,ti OR 'standard gamble*':ab,ti OR sg:ab,ti OR 'time trade off*':ab,ti OR 'time tradeoff*':ab,ti OR tto:ab,ti OR timetradeoff*:ab,ti) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	
#8	(burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti)) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	252,240
#9	('natural history'/de OR 'natural history':ti,ab OR ('natural':ab,ti AND histor*:ab,ti) OR 'current management':ab,ti OR (('current*' NEXT/3 'manage*'):ab,ti) OR (('disease' NEXT/3 'manage*'):ab,ti) OR 'guideline'/de OR (('treatment' NEXT/3 'guideline*'):ti,ab) OR 'pathogenesis'/de OR 'pathogenesis':ti,ab OR 'diagnosis'/de OR 'diagnosis':ti,ab OR 'onset:ab,ti' OR (('disease' NEXT/3 'presentation'):ab,ti) OR 'epidemiology'/de OR 'prevalence'/de OR 'incidence'/de OR 'mortality'/de OR epidemiol*:ti,ab OR 'prevalence':ti,ab OR 'incidence':ti,ab OR 'mortality*':ti,ab OR survival:ab,ti OR 'burden':ti,ab OR 'disease burden'/de OR 'unmet need':ab,ti OR 'demography'/de OR demograph*:ab,ti OR morbid*:ab,ti OR 'morbidity'/de OR risk:ab,ti OR 'risk'/de OR 'etiology'/de OR etiology:ab,ti OR aetiology:ab,ti OR distribution:ab,ti OR frequency:ab,ti OR pattern:ab,ti) AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	1,205,471
#10	#1 AND (#6 OR #7 OR #8 OR #9) AND [humans]/lim AND [english]/lim AND ([embase]/lim OR [medline]/lim) AND [18-05-2023]/sd NOT [02-09-2024]/sd	231

Table 94 Search strategy for EuroQol database search (update 2024 from 18th May 2023 to 1st September 2024) for the QoL search strategy

No.	Query	Results
#1	'alagille syndrome' OR 'ALGS' OR 'Alagille-watson syndrome' OR 'Watson Alagille syndrome' OR 'arteriohepatic dysplasia' OR 'cardiovertebral syndrome' OR 'cholestasis with peripheral pulmonary stenosis' OR 'hepatic ductular hypoplasia' OR 'hepatofacioneurocardiovertebral syndrome' OR 'paucity of interlobular bile ducts' OR 'syndromic bile duct paucity' OR 'watson-miller syndrome' OR 'JAG1'	0

Table 95 Search strategy for NHS HTA and EED search (via University of York website) (update 2024 from 18th May 2023 to 1st September 2024) for the cost-effectiveness, cost and resource use and quality of life search strategy

No.	Query	Results
#1	alagille syndrome OR ALGS OR Alagille-watson syndrome OR Watson Alagille syndrome OR arteriohepatic dysplasia OR cardiovertebral syndrome OR cholestasis with peripheral pulmonary stenosis OR hepatic ductular hypoplasia OR hepatofacioneurocardiovertebral syndrome OR paucity of interlobular bile ducts OR syndromic bile duct paucity OR watson-miller syndrome OR JAG1	0
#2	economics OR cost OR burden OR econ* OR health care cost OR indirect cost OR productivity	0
#3	#1 AND #2 in NHSEED, HTA	0
#4	qol OR quality of life OR patient satisfaction OR utility OR patient reported outcome OR time tradeoff OR TTO OR activities of daily living OR ADL OR social impact	0
#5	#1 AND #4 in NHSEED, HTA	0

I.1.2 Systematic selection of studies

I.1.2.1 Selection criteria

The selection criteria specified in the Table below was used to inform the inclusion of studies at first and second pass stages of the reviews. Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided in line with the inclusion criteria.

Table 96 Inclusion and exclusion criteria used for assessment of studies - Review Question 4 (HRQoL studies)

Selection criteria	Inclusion criteria	Exclusion criteria
Population	• Patients with ALGS	• Studies that do not include patients of interest to the SLR • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest, with only a minority of patients being of interest
Interventions/ comparators	• No restriction by intervention or comparator	

Outcomes	• Utility scores
	• Disutilities
	• Patient-reported outcomes:
	  ○ European Quality of Life Five Dimension (EQ-5D)
	  ○ PedsQL
	  ○ SF-5D
	  ○ Multidimensional Fatigue Scale
	  ○ SF-36
	  ○ HUI
	  ○ PGWB
	  ○ SIP
	  ○ QWB
	• Patient-Reported Outcomes Measurement Information System (PROMIS) (PROMIS Item Bank – Mood and Sleep; PROMIS Item Bank – Itch-Activity and Clothing; PROMIS Item Bank – Itch-interference; PROMIS Itch-Scratching Behavior scale only)
	• CHQ-PF50
	• Infant Dermatitis Scale
		• No reported outcomes of interest

Study type	• RCTs
	• Non-RCTs
	• Cross-sectional studies
	• Retrospective observational review
	• Observational studies
	• HRQoL elicitation studies
	• HRQoL validation studies
	• Economic evaluations:
	  • Cost-utility analysis
	  • EEACT
		• Individual case study reports

Publication type	• Article • Conference abstract • Conference paper • Article in press	• Short survey • Reviews • Letters • Comment articles
Language	• English	• Non-English publications without an official English translation

Abbreviations: ALGS – Alagille Syndrome; CHQ-PF50 – Child health questionnaire parent form 50; EEACT – Economic evaluation alongside a clinical trial; HRQoL – Health-related quality of life; PedsQL – Pediatric quality of life inventory; PROMIS – Patient reported outcomes measurement information system; RCT – Randomized-controlled trial

I.1.2.2 Systematic selection of studies

Please refer to section "H.1.2.2 Systematic selection of studies" since the same process was used for the review question number 4 (HRQoL SLR).

I.1.2.3 Search results

Please refer to section "H.1.2.3 Search results" since that section gives an overview of all the publications retrieved from the Original SLR and the updates for all review questions, including the review question number 4 (HRQoL SLR).

I.1.2.4 List of publications retrieved from the HRQoL SLR

Since Appendix I is only for the literature searches for the HRQoL, we only focus here on the publications retrieved from the Original and updates of the SLR for review question number 4 (HRQoL data).

During the Original SLR, 10 references met the selection criteria across review question 4 during the title and abstract screening, and six were considered for full text review. After full text review, these six references met the selection and were extracted.

A total of these six HRQoL references were identified as part of the Original SLR, and a summary of the extracted references is presented in the Table below:

Table 97 Summary of HRQoL publications (n= [6])

Study	Reference	N	Intervention	Elicitation method	Valuation method
NR	Gonzales et al. 2019[114]	31	Maralixibat	NR	PedsQL
NCT02160782 - **ICONIC**	Kamath et al. 2021[140]	27	Maralixibat	NR	PedsQL, MF, FI
NR	Elisofon et al. 2021[18]	88	Liver transplant	CHQ-PF50	CHQ-PF50 Pruritus was measured on a 1 to 5 scale
NR	Kamath et al. 2017[141]	37	Maralixibat	NR	PedsQL (parent)
NCT02160782 - **ICONIC**	Gonzales et al. 2021[120]	31	Maralixibat	NR	PedsQL score PedsQL Multidimensional fatigue scale
NCT02160782 - **ICONIC**	Gonzales et al. 2021[142]	31	Maralixibat	NR	PedsQL score PedsQL Multidimensional fatigue scale

Abbreviations: CHQ-PF50 – Child Health Questionare – Parent Form 50; FI – Family Impact; MF – Multidimensional Fatigue; PedsQL – Pediatric Quality of Life Inventory

During the May 2023 SLR update, seven references met the selection criteria across review question 4 during the title and abstract screening. These seven references were considered for full text review. Overall, four references met the selection criteria following the first and second pass of the HRQoL studies review and were extracted.

A summary of the extracted references is presented in the Table below:

Table 98 Summary of HRQoL publications (May 2023) (n=4)

Study	Reference	N	Intervention	Elicitation method	Valuation method
NCT02160782 (ICONIC)	Kamath et al 2022[91]	N=31	Maralixibat	NR	Quality of life was assessed using the Pediatric Quality of Life Inventory (PedsQL) Core (Parent) scale and fatigue using the PedsQL Multidimensional Fatigue Scale
Quadrado et al 2023	Quadrado et al 2023 Jahrestagung der GPGE. Pädiatrie 35, 65–95 (2023)[143]	N=95	Any	Online survey	Caregiver sleep, work and productivity impact, relationships and family, HRQoL, and emotional health were assessed and reviewed by caregivers and patient association groups (PAGs) to ensure the questions adequately captured caregiver burden. A separate survey was developed for a matched control group of parents from the UK general population.
Quadrado et al 2022	Quadrado et al 2022[144]	HCPs n=4, caregivers n=5	Any	Qualitative interviews	Vignettes
Gwaltney et al 2022	Gwaltney et al 2022[145]	N=36	Any	Qualitative interviews	The ObsRO and PRO instruments called PRUCISION

During September 2024 SLR update, 3 references met the selection criteria across review question 4 during the title and abstract screening, and 1 was considered for full text review. Overall, zero references met the selection criteria following the first and second pass of the HRQoL studies review.

I.1.3 Excluded full text references

Please refer to section “H.1.3 Excluded full text references” since all the excluded references from the Original and SLR updates are included in that section.

I.1.4 Quality assessment

Please refer to section “H.1.4 Quality assessment” since the same quality assessment process was used for the review question number 4 (HRQoL SLR).

I.1.5 Unpublished data

Not applicable.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

As mentioned above in Section 5.3, three publications used as input in the economic model were retrieved from the SLR that was conducted, more specifically, from the epidemiological part of the SLR.

This section will focus on the Epidemiological SLR.

The Epidemiological SLR was conducted as part of the Original SLR to answer the following research questions which follow the PICOS (population, interventions, comparators, outcomes and study type) principle [125]:

What is the pathogenesis and disease presentation, diagnosis, epidemiology, natural history, and management of ALGS? (review question number 7)

Please refer to Appendix H and Appendix I to understand how the searches to identify evidence for the review question listed above were conducted.

Table 99 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Medline	Medline; NLM	1966 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Embase classic	Ovid	between 1947 and 1973 for the Original SLR	Original SLR: 11.10.2021

Database	Platform/source	Relevant period for the search	Date of search completion
CENTRAL	Cochrane Library Interface	1996 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024
Cochrane Clinical Answers	Cochrane Library Interface	2012 until October 2021 for the Original SLR, from October 2021 to May 2023 for the first SLR update, and from May 2023 until September 2024 for the second update	Original SLR: 11.10.2021; 1st SLR update: 18.05.2023; 2nd SLR update: 01.09.2024

J.1.1 Search strategies

Please refer to the search strategies section in Appendix H and Appendix I, as these sections present all the search strategies used for the Original SLR search and its updates.

J.1.2 Systematic selection of studies

J.1.2.1 Selection criteria

The selection criteria specified in the Table below was used to inform the inclusion of studies at first and second pass stages of the reviews. Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided in line with the inclusion criteria.

J.1.2.2 Systematic selection of studies

Please refer to section “H.1.2.2 Systematic selection of studies” since the same process was used for the review question number 4 (HRQoL SLR).

J.1.2.3 Search results

Please refer to section “H.1.2.3 Search results” since that section gives an overview of all the publications retrieved from the Original SLR and the updates for all review questions, including the review question number 7 (Epidemiological SLR).

J.1.2.4 List of publications retrieved from the HRQoL SLR

Since Appendix J is only for the literature searches for the Epidemiological studies, we only focus here on the publications retrieved from the Original and updates of the SLR for review question number 7 (Epidemiological SLR).

Of the 217 references that met the selection criteria across review question 7 during the title and abstract screening, 62 were considered for full text review.

No studies were identified in this SLR that investigated or reported national prevalence and incidence rates for ALGS. Molina et al 2022[146] identified during the May 2023 update describes that according to the National Organization for Rare Disorders, the incidence of ALGS is estimated at 1 in 30,000 to 1 in 45,000 births.

There are several publications that reported various epidemiological outcomes, which are summarized below.

From the May 2023 update, 15 further papers were identified as part of the epidemiological review.

Moreover, from the September 2024 update, 9 papers were identified as part of the epidemiological review.

The first Table below summarizes the region of enrolment, and the second Table below provides a summary of the studies included for review question 7. The Tables have been updated to include the results from the May 2023 update and the September 2024 update, respectively.

Table 100 Region of enrolment of studies included for review question 7

Region of enrolment	Number of publications (original)	Number of publications (May 2023)	Number of publications (September 2024)	Number of publications (total original + 2023)	Number of publications (total original + 2023 + 2024)
France	4	0	1	4	5
South Korea	2	0	2	2	4
Egypt	1	0	0	1	1
Vietnam	1	0	0	1	1
Argentina	1	0	0	1	1
United Kingdom	3	0	0	3	3
United States of America / Canada	15	6	1	21	22
India	2	0	0	2	2
China	3	2	1	5	6
New Zealand	1	0	0	1	1
Poland	3	0	1	3	4
Japan	2	0	0	2	2

Taiwan	1	0	0	1	1
Italy	1	2	0	3	3
Malaysia	1	0	0	1	1
Australia	1	0	0	1	1
Russia	0	0	1		1
Multinational	4	3	1	7	8
Nor reported	0	2	1	2	3

Table 101 Summary of epidemiological studies (n= 86])

Reference	Country of study	Patient population	Mortality	Pathogenesis/ natural history	Native liver survival	Diagnosis
Kohaut et al. 2015[44]	France	During the study period, 242 children with ALGS were referred to our institution, of which 55 of underwent LT during childhood (22.7%). The mean age at transplantation was 6 years old, with the main indication for OLT being secondary to refractory pruritus. All of the children had at least 3 disease-specific features and almost half of them (26/55) had all the clinical features	Overall survival: 1 year: 90.9% 5 years: 87.9% 10 years: 84.8% Graft survival 1 year: 87.7% 5 years: 87.7% 10 years: 81.7%	Pretransplantation findings among 25 children: Celiac stenosis 12/25 (48%) Hepatic artery stenosis 1/25 (4%) Small caliber HA (<3 mm) 10/25 (40%) Superior mesenteric artery stenosis 2/25 (8%) Renal artery stenosis 2/25 (8%)	Age at liver transplantation: 6 years old [1–17] (mean [dispersion])	Extrahepatic features % (n): Dysmorphic face=92.7 (51/55) Eyes anomalies=61.8 (34/55) Vertebral anomalies=65.4 (36/55) Cardiac murmur=90.9 (50/55) Mutation % (n): JAGGED 1=85.4 (47/55) NOTCH 2=1.8 (1/55) Unavailable=12.7 (7/55)

Hahn et al. 2015[147]	South Korea	Investigated 49 patients who visited Seoul National University Hospital for evaluation of murmur/cyanosis or cholestasis, between 1983 and 2013. We excluded 8 cases; 7 suspected ALGS patients who were lost to follow-up until diagnosis, and 1 suspected ALGS patient who died before the diagnosis was confirmed. Finally, 41 patients who were diagnosed with ALGS were included in the study. The inclusion criteria were as follows: (1) positive for ≥3 clinical criteria (chronic cholestasis, congenital heart disease, butterfly vertebrae, posterior embryotoxon, and peculiar face); and (2) positive for ≥1 clinical	The mortality rate of the patients who underwent cardiac operations was 16.7%, and the mean follow-up duration was 4.64± 4.89 years (range, 0.02–16.5 years). Eight patients died at a median age of 4 years (range, 3 months to 15 years). The 5-year survival was 75% with severe liver disease, and 16.7% with combined severities of liver and heart.	34 patients (82.9%) displayed chronic cholestasis, 36 (87.8%) displayed congenital heart disease, 37 (92.5%; except for one, which was undetermined) displayed a peculiar face, 13 (31.7%) displayed butterfly vertebrae, and 12 (30.0%; except for one, which was undetermined) posterior embryotoxon. jaundice (58.5%), murmur (7.3%), cyanosis (4.9%). Jaundice with murmur (12.2%), jaundice with small bowel obstruction (2.4%), and cardiac anomaly detected during the prenatal period via foetal echocardiography (14.6%).	Overall, 37 of the 41 patients underwent liver biopsy via ultra-sonography guidance or wedge resection. Thirty-two patients (78 %) had findings compatible with a paucity of intrahepatic bile ducts. Moreover, one of them had documented biliary atresia. The median level of maximum total bilirubin was 7.15 mg/dL (range, 0.5–70.4 mg/dL). The severe liver disease group consisted of 19 patients (46.3%), and 9 of them (47.7%) received liver transplantation at the median ages of 1.92 years (range, 1.25–23.08 years).	An analysis of the JAG1 gene was performed in 28 patients, with 27 subjects showing the JAG1 gene mutation, and one subject showing several polymorphisms but no mutations. Cardiovascular anomaly/ Total No. (%)/ No. of peripheral PS/ Other combined anomaly/ Intervention/ JAG1 mutation (+)

		criteria with a proven JAG1 mutation				
Ferrara et al. 2020[148]	France, USA, Netherlands, Italy	The total number of patients with JIA followed in these 7 centres was approximately 4,000, and the total number of patients with Alagille followed by the hepatology department of these centres was 195. We collected 10 cases of Alagille syndrome associated with chronic arthritis, 6 female and 4 male children, with a median age of 11 years (range 4-18 years) at last follow-up.	NR	The median age at the onset of arthritis was 6.5 years (range 2-10 years), and the median number of active joints was 3 (range 1-8). The most common sites of arthritis were the knees (9 of 10) followed by ankles (7 of 10), small joints of hands or feet (5 of 10), elbows (4 of 10), wrists (3 of 10), cervical spine (2 of 10), temporomandibular joint (2 of 10), shoulders (1 of 10), and hips (1 of 10). Two patients also had uveitis, 1 with other signs of sarcoidosis.	Two patients underwent liver transplantation with arthritis resolution in 1 patient and partial remission in the other patient. One patient died before transplantation.	Patients were diagnosed with ALGS if they showed the following conditions: Cholestasis, pulmonary arterial stenosis, osteoporosis, strabismus, renal disease, butterfly vertebra, embryotoxon, typical facies, renal disease, pulmonary arterial hypoplasia, embryotoxon + Axenfeld anomaly, pulmonary arterial stenosis +atrial septal defect, retinopathy.

				Four patients had skin manifestations (3 psoriasis and 1 with porphyria tarda-like lesions).		
Koofy et al. 2011[149]	Egypt	Thirty-two cholestatic children were included in the study after informed consent was obtained from the parents or guardians. Their ages ranged from 1 month to 15 years with a mean age of 3.8 years. The children were divided into 2 groups. Group 1 included 13 children with PILBD and 3 or more criteria of ALGS. Group 2 included 19 cholestatic children with histologically proven NH.	NR	Group 1: ALGS (n=13): facies/ 8 (61.5) Audible murmur/ 5 (38.5) Renal anomalies by ultrasound/ 0 (0) Vertebral anomalies/ 0 (0) Posterior embryotoxon/ 9 (69.2) Jaundice/ 7 (53.8) Pruritis/ 7 (53.8) Xanthomata/ 1 (7.7) Hepatomegaly/ 7 (53.8) Splenomegaly/ 5 (38.5)	NR	Emerick and associates (8) established the diagnostic criteria of ALGS. These criteria included the presence of PILBD in collaboration with 3 of the 5 major features of the syndrome. These features included chronic cholestasis, cardiac disease, skeletal abnormalities, the characteristic facial features, and the ocular manifestations (PE and ON drusen). Using this classification, 13 of our patients were diagnosed with ALGS.
Kohaut et al. 2017[44]	France	Age 6 years old: Mean [dispersion]= [1–17] Weight 16 kg: Mean [dispersion]= [8–47]	NR	Extrahepatic features: Dysmorphic face=92.7 (51/55) Eyes anomalies=61.8	Surgical complications following liver transplantation in	All of the children had at least 3 disease-specific features and almost half of them (26/55) had all the

		Height 102 cm: Mean [dispersion]= [74–163] Sex: % (n) Male=60 (33/55) Female=40 (22/54)		(34/55) Vertebral anomalies=65.4 (36/55) Cardiac murmur=90.9 (50/55) Celiac stenosis=12/25 (48%) Hepatic artery stenosis=1/25 (4%) Small caliber HA (<3 mm) =10/25 (40%) Superior mesenteric artery stenosis=2/25 (8%) Renal artery stenosis=2/25 (8%)	children with Alagille syndrome Classical'' hepatic arterial revascularization: Acute hemoperitoneum, Bowel obstruction, Hepaticojejunostomy stenosis, Biliary leakage, Arterial reconstruction with aortic/iliac anastomosis, Acute hemoperitoneum, Bowel obstruction, Hepaticojejunostomy stenosis, Biliary leakage	clinical features. Genetic evaluation demonstrated a JAG 1 gene mutation in 47 patients and a NOTCH 2 mutation in 1. Three families declined genetic testing. Four patients without JAG 1 mutations were not further evaluated for NOTCH 2 mutations.
Ferrara et al. 2020[148]	France, United states, Netherlands, Italy	The total number of patients with JIA followed in these 7 centres was approximately 4,000, and the total number of patients with Alagille followed by the hepatology department of these centres was 195.	NR	Patient number/ Country/ Age at study (y)/ Sex Alagille syndrome main clinical manifestations/ Gene mutations/ Other features included	NR	All patients were diagnosed with Alagille syndrome in the first year of life because of neonatal cholestasis. All patients had cardiac involvement (9 of 10 pulmonary arterial stenosis, 1 pulmonary arterial hypoplasia, 1 tetralogy of

		We collected 10 cases of Alagille syndrome associated with chronic arthritis, 6 female and 4 male children, with a median age of 11 years (range 4-18 years) at last follow-up				Fallot, 1 atrial septal defect); 9 of 10 had characteristic facies; 8 of 10 had an ocular abnormality (3 embryotoxon, 2 strabismus, 2 pigmentary retinal anomalies, 1 Axenfeld anomaly); 7 out of 10 had ..kidney disease; 3 of 10 had osteoporosis; and 3 had butterfly vertebra.
Lin et al. 2012[150]	Vietnam	Twenty-one unrelated probands were referred from the Department of Gastroenterology at Children's Hospital in Ho Chi Minh City, Vietnam under a protocol of informed consent and enrolled into our IRB approved study at The Children's Hospital of Philadelphia.	NR	In comparing the clinical phenotype of the Vietnamese cohort with JAG1 mutations to our existing ALGS cohort, the liver and cardiac phenotypes occur in over 94% in both populations. Notably, bile duct paucity was found in all four children who had liver biopsies. Renal involvement occurs with a similar frequency of 27.3% in the Vietnamese cohort	NR	Mutations in JAG1 or NOTCH2 were found in 19 out of the 21 individuals (90%) with the clinical diagnosis of ALGS. A total of 18 JAG1 mutations (86%) and 1 NOTCH2 mutation (5%) were found, 17 of which are novel.

				compared to 30.5% in our cohort.		
Gilbert et al. 2019[151]	NR	Single centre study, which includes 401 probands and 111 affected family members amassed over a 27-year period	NR	NR	NR	JAG1 (94.3%; n = 377 out of 401), NOTCH2 (2.5%; n = 10 of 401), and mutation negative cases (3.2%; n = 13 of 401) of ALGS. In addition, we report 86 novel JAG1 pathogenic variants and three novel NOTCH2 pathogenic variants. 94.3% of individuals with clinically diagnosed ALGS have a pathogenic variant in the JAG1 gene, 2.5% have a pathogenic variant in the NOTCH2 gene, and 3.2% are molecularly uncharacterized.

Garcia et al. 2005[152]	Argentina	Thirty-eight patients with Alagille syndrome were studied for IO year (1990-1999) at the Posadas Hospital, Pediatric Hepatology and Pediatric Dennatology Area, and at the Garraham Pediatric Hospital Hepatology Service, fourteen girls and 24 boys between 2 months and 15 years of age (average 29 months) were observed.	NR	Major features Peculiar facies/ 85% Embryotoxon butterfly-like vertebral arch/ 57% Defects/ 63% Cardiovascular (pulmonary artery/ hypoplaia stenosis/cardiopathy)/ 84% chronic Cholestasis and pruritus / 100% cholestasis / 92% (during neonatal period) jaundice / 78% xanthomas / 28% Minor features Growth retardation/ 76% Mental retardation/ 12.5% Delayed puberty/ 12.5% Renal disturbances/ 21% Bone abnormalities/ 0%	Liver transplant was performed in 18.4% of the patients - two of them died after this operation.	The average age of diagnosis was 29 months old (range of between 2 months and 15 years). Cholestasis was evident in 92% of patients during the neonatal period. Family antecedents related to the syndrome were found in 18.5% of the patients. Peculiar facies developed in 85% of patients. Chronic cholestasis and pruritus were observed in all the patients and jaundice was evident in 78%. Eighty-four percent of the patients had heart disease (pulmonary stenosis, intraauricular communication, intraventricular communication), 76% of them showed growth retardation, and vertebrae abnormalities were found in 63%. Embryotoxon appeared in 76% of patients, and renal disturbances in 21%. Eleven

				High-pitched voice/ 62.5%		children (28%) had xanthomas, in the neck, elbows, palms, helixes, inguinal area, gluteus, and knees.
Elmslie et al. 1995[153]	United Kingdom	Index cases were included in the study if they had a definite diagnosis of Alagille syndrome based on the criteria of Mueller.'0 All 14 index cases, 24 parents, and four sibs were examined at The Hospital for Sick Children.	10-20% mortality	NR	NR	Major criteria History of prolonged jaundice in infancy requiring investigation Pulmonary murmur Posterior embryotoxon Vertebral end plate notches First degree relative with Alagille syndrome (omit if proband)
Halvorsen et al. 1995[154]	United States	NR	NR	In five of eight patients (63%) either the sonogram, CT, MRI, or scintigram revealed an abnormal external shape to the liver. In each of these five cases, the predominant abnormality was a	NR	A spherical liver or lobe distorted lobar architecture, displaced portal and hepatic veins, and delayed hepatocyte function can be seen with Alagille's syndrome. When these findings are encountered either alone

				globular mass either residing in or replacing one lobe of the liver. These masses were well-circumscribed and caused displacement of the normal intrahepatic vascular anatomy. In three of the six cases in which the spleen was imaged, splenomegaly was noted; however, cirrhosis was not identified in the liver biopsies of any of these three patients.		or in combination, especially in a patient with any of the associated clinical findings, the diagnosis of arteriohepatic dysplasia should be considered.
Srivastava et al. 2014[155]	India	Nine patients [six boys, median age of diagnosis 5 months (1 month to 9 years)] were diagnosed to have ALGS. Majority (eight out of nine) of cases had neonatal cholestasis; six were diagnosed in the first year of life, and three cases, between the ages of 7–9 years. In the three older	NR	NR	NR	Age at diagnosis/ gender/ Cholestasis (jaundice/pruritus)/ Facies Posterior/ embryotoxon/ Heart defect on echocardiography/ Vertebral anomaly/ Liver biopsy/ PILBD included

		children, two cases presented with intractable pruritus after resolution of NC, and one case, without history of NC with persistent jaundice and pruritus from 2 years of age. The median age appearance of jaundice was 1 month (range 0–2). Eight cases had pruritus, with the median age of onset of pruritus being 4 months (range 4–24).				
Lykavieris et al. 2003[156]	France	The records of 174 patients with Alagille syndrome were reviewed, and 38 (22%) patients without liver failure who experienced haemorrhage that led to a drop in haemoglobin level of at least 3 g/dL or to blood transfusion were identified (27/38 were boys)	NR	The 38 patients reported in this series experienced 49 bleeding episodes at a median age of 3.75 years (range: 1 month–27 years). Twenty of the 38 children displayed all clinical features of ALGS; 13 and 5 displayed 4 and 3 features, respectively.	NR	Neonatal cholestasis was the initial clinical sign of the disease in all but 5 children who presented with jaundice after the age of 6 months. Median age at diagnosis was 10 months (range: 1 month–6 years). Paucity of interlobular bile ducts was present in all liver specimens of 32 patients who underwent liver biopsy. Severe

						cholestasis existed in 33 patients. One patient has a deletion of the 20p12 region, and 13 of 17 patients studied have a JAGGED1 mutation
Kamath et al 2017[157]	NR	272 cholestatic ALGS subjects (2 months-25 years) with a median follow-up of 2.3 years (0-8.5yrs) were included.	NR	Mean (SD) total bilirubin, ALT and GGT at baseline were 5.7mg/dL (6.6), 175U/L (136), and 526U/L (606) respectively. Growth at baseline was significantly delayed compared to norms, with median height Z-score -1.9 (interquartile range [IQR] -2.7, -1.0) and weight Z-scores -1.8 (IQR -2.9, -0.8). Amongst cholestatic ALGS subjects, 50% reported ascites and almost 25% had one or more episode of variceal bleeding by the age of 25 years. 38%	70% of cholestatic ALGS children had undergone liver transplantation by 17 years of age and 10% had died (multiple causes, only 3 clearly liver-related). Survival to early adulthood with native liver is only 20% with a high rate of liver-related complications.	86% had JAG1 mutations, 3% had NOTCH2 mutations and 17/157 had no mutations detected in either JAGGED1 or NOTCH2.

				experienced bone fractures with the majority of these occurring before the age of 13 years.		
Wang et al. 2008[158]	China	157 children including 111 males and 46 females, who presented with conjugated jaundice from less than 3 months of age were admitted to the Department of Infectious Diseases, Children's Hospital of Fudan University, a tertiary hospital in Shanghai for further investigation of their aetiology.	NR	Jaundice resolution along with growth was noticed in all the 6 cases. However, various degrees of pruritus appeared before the age of 1 year in all of them. In cases 4 and 5, icterus was not observed macroscopically at the age of 9 months and 11 months respectively, and the serum total bilirubin level decreased to the normal range at the age of 2 years and 3 months and 1 year and 7 months, respectively. In the other cases,	NR	Diagnosis was made by histological findings of interlobular bile ducts paucity with involvement of at least 3 of the 5 major abnormalities: cardiac murmur, eye abnormalities (posterior embryotoxon), butterfly y-like vertebral anomalies, renal abnormalities and characteristic faces; or at least 4 of the 5 features if liver biopsy was not performed.

				jaundice was persistent, and the serum total bilirubin level was above the upper normal limit all the time. High levels of total serum bile acid and gamma glutamyl transpeptidase were seen in all the cases.		
Roberts et al. 2021[159]	New Zealand	26 children (11 male) were diagnosed with ALGS over 33 years. 16/26 (62%) were European, 5/26 (8%) Māori, 3/26 (12%) Pasifika, 2/26 (8%) Asian (both Indian).	3 children died as a result of congenital heart disease (CHD).	17/20 children who developed neonatal cholestasis underwent liver biopsy. Findings included bile duct paucity (15/17, 88%), fibrosis (9/17, 53%) and giant cell hepatitis (6/17, 35%). Extrahepatic manifestations included CHD (25/26, 96%), characteristic facies (22/26, 85%), skeletal anomalies (14/26, 54%), ocular findings (12/26, 46%), renal anomalies (11/26, 42%), and	7/26 (27%) underwent LT for ESLD; 1 died post LT. 16 patients (62%) are still alive with their native livers.	Genetic testing was undertaken in 16 (62%) of which 14 (88%) and 0 were JAG1 and NOTCH2 mutation-positive respectively.

				vascular anomalies (both cerebral and systemic; 4/26, 15%). Peripheral pulmonary stenosis was the commonest CHD (18/26, 72%).		
Liu et al. 2018[160]	China	16 infants who were diagnosed as having ALGS in the Department of Pediatrics, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between 2009 and 2015. Further, to identify the characteristics of serum biochemical parameters in ALGS, 16 biliary atresia (BA) patients who were confirmed by surgery in recent two years were compared.	NR	Patient level data for No./ Cholestasis/ Heart disease/ Butterfly vertebrae/ Facies Eye/ Renal anomalies/ Mutation position included	NR	The age of onset was 3 days to 8 months. The mean age at the time of diagnosis was 4.9 months (range: 1.5 months to 16 months). We identified 14 different JAGI gene variations and I NOTCH2 gene mutation in I6 Chinese ALGS patients. Our study suggested clinical features of ALGS are highly variable and not all patients meet the classical diagnostic criteria. It was suggested that hypercholesterolaemia and significantly elevated GGT, TBA and ALT may be helpful to diagnose ALGS. Genetic

						testing is integral in the diagnosis of ALGS.
Vandriel et al. 2020[161]	NR	1154 ALGS (58% male) patients from 25 countries were included (median follow-up 5.6 years, IQR 2.3–11.3). Of the 75% genetically confirmed patients, 93% have a mutation in JAG1 and 4% in NOTCH2 (69% de novo).	Overall, 10-and 18-year survival rates were 90.9% and 88.6%, respectively.	Any cardiac anomaly was the most common extrahepatic manifestation (89%), followed by characteristic facies (88%), posterior embryotoxon (49%), butterfly vertebrae (44%), and renal anomalies (35%). MRI and CT reports revealed cerebral and intra-abdominal vascular anomalies in 34% and 31% of patients, respectively Increasing frequency of bile duct paucity with age (p = 0.01) and features of biliary	NR	NR

				obstruction in 20% of biopsies <6-months. 10-and-18-year TFS rates in 911 ALGS patients presenting with neonatal cholestasis was 57% and 41%, respectively.		
Cho et al. 2015[162]	South Korea	19 children (10 female, nine male) were diagnosed with ALGS at Asan Medical Centre, Seoul, Korea. The diagnosis of ALGS was based on the presence of three or more of the following major clinical features: chronic cholestasis, cardiovascular abnormalities, vertebral anomalies, ocular anomalies, and characteristic facial dysmorphias.12 One patient who had two major clinical features and	NR	Most patients (89%, 17/19) presented with neonatal cholestasis within 6 months after birth. The median age at presentation was 2 months (range, 7 days–6 months). At age 1 year, cholestasis improved in nine of 17 patients. Those who had cholestasis at 1 year of age had a complication, such as liver cirrhosis (n = 5), liver transplantation (LT; n = 2), or had died (n = 1).	NR	The diagnosis of ALGS was based on the presence of three or more of the following major clinical features: chronic cholestasis, cardiovascular abnormalities, vertebral anomalies, ocular anomalies, and characteristic facial dysmorphias. Fourteen patients (74%, 14/19) had JAG1 mutations. No mutations in NOTCH2 were found. Five patients (26%, 5/19) did not have mutations in JAG1 or NOTCH2 but met standard clinical diagnostic criteria for ALGS.

		a JAG1 mutation was diagnosed with ALGS.				
Subramaniam et al. 2011[163]	UK	128 children with suspected Alagille syndrome referred to our tertiary centre between 1980 and 2005. In 29 children, the diagnosis of ALGS had been proposed before referral to us. Our diagnostic criteria for this study required the presence of bile duct paucity and at least 3 of 5 classical criteria or 4 of 5 classical criteria in the absence of paucity	NR	117 children (62 boys), age at diagnosis was younger than 16 weeks in 80, between 16 weeks and 1 year in 14, and older than 1 year in 23. Of 107 children (91.4%) with heart disease, 77 (72%) had peripheral pulmonary stenosis; 11 (10%) Fallot tetralogy or pulmonary atresia; 4 (3.7%) atrial septal defect, ventricular septal defect, or patent ductus arteriosus; 8 (7.4%) pulmonary valve or infundibular stenosis; and 7 (6.5%) mitral incompetence or aortic	Eleven patients had biopsies repeated at a median age of 6 months (range 1–24 months), and 9 of them (81.8%) showed development of bile duct paucity. Of the 35 children who underwent hepatobiliary iminodiacetic scan or diisopropyl iminodiacetic acid scan, 21 (60%) showed no excretion of the isotope after 24 hours, representing a potential false-positive result for	NR

				valve abnormalities. Of the 27 patients (23%) with clinical signs of renal disease, 16 had renal tubular acidosis, 6 dysplastic or non-functioning kidneys, 2 hydronephrosis, 3 hypoplastic kidneys, 1 renal agenesis, and 1 renal stone. Hepatomegaly was seen in 83 patients (70.9%) and splenomegaly in 41 patients (35%). One child aged 3 years had normal liver histology.	biliary atresia. In 29 of 104 children (27.8%), small, contracted, or no gallbladder was seen on ultrasound (US), findings often associated with biliary atresia.	
Vandriel et al. 2020[43]	NR	NR	OS rates at 10- and 18-years were ≥88% (log-rank, P=0.08). JAG1-and-NOTCH2 ALGS patients were similar in terms of history of NC (90% vs. 82%, P=0.55), bile duct paucity (54% (n=7/13) vs. 64% (n=202/317, P=0.56), renal anomalies (28% vs. 36%, P=0.50) and vascular anomalies (27% vs. 32%, P=0.79). NOTCH2 OS rates at 10- and 18-	Among 845 genotyped ALGS patients, a pathogenic or LP variant in JAG1 was identified in 97.5% (n=824) and a pathogenic or LP NOTCH2 variant in 2.5 (n=21). Of JAG1 variants, truncating was identified in 73% (n=604), non-truncating	NR	Among 845 genotyped ALGS patients, a pathogenic or LP variant in JAG1 was identified in 97.5% (n=824) and a pathogenic or LP NOTCH2 variant in 2.5% (n=21). Of JAG1 variants, truncating was identified in 73% (n=604), non-truncating in 17% (n=137),

			years were ≥88% in both groups (log-rank P =0.73).	in 17% (n=137), and structural variants in 10% (n=83). Those with a NOTCH2 variant were significantly less likely to have characteristic facies (52% vs. 89%, P<0.001), an ECHO confirmed cardiac anomaly (38% vs. 92%, P<0.001), posterior embryotoxon (13% vs. 52%, P=0.002), or butterfly vertebrae (0% vs. 43%, P<0.001).		and structural variants in 10% (n=83).
Emerick et al. 1999[164]	United States	The 92 patients in this series include 83 unrelated probands and 9 significantly affected family members. The 9 family members included here presented with infantile cholestasis (n 5 5), heart murmur (n 5 3), and adult-onset renal failure and abnormal liver function tests (n 5 1).	The presence of intracardiac congenital heart disease was the only clinical feature statistically associated with increased mortality (P< .001) The factors that contributed significantly to mortality were complex congenital heart disease (15%), intracranial bleeding (25%), and hepatic disease or hepatic transplantation	At some point during the clinical course, hepatomegaly was present in 93% and splenomegaly in 70% of patients. Severe pruritus was a cause of significant morbidity (approximately 45% of children) during the first decade of life, but typically improved with	The 20-year predicted life expectancy is 75% for all patients, 80% for those not requiring liver transplantation, and 60% for those who required liver transplantation.	NR

		There was a positive family history of features associated with ALGS in 30 of 71 families (42%).	(25%). Only major structural congenital heart disease in infancy was specifically associated with increased mortality (P < .001).	time thereafter. Xanthomas were present in 39 of 92 patients (42%) and were most prevalent in the early school age years with gradual improvement thereafter in a moderate number of cases.		
Huysentruyt et al. 2019[165]	NR	We identified 400 children with ALGS (US 318, Canada 82); 258 were excluded due to missing data (no measurements 41; sex 40; GA 134), prematurity (41) or concurrent mutation (2), leaving 142 ALGS for data analysis (461 weight and 407 height measurements). Of those 44% were female, with similar sex distribution across centres (p=0.512)	NR	Median (Q1; Q3) BWZ and BLZ were -1.47 (-1.9; -0.7) and -1.07 (-1.6;0.0) respectively, with similar sex and centre distribution (p-values ≥0.111); 56.9% were born SGA. Postnatal weight decreased to a minimum at age 3 months (median (Q1; Q3) WAZ -3.13 (-3.9; -2.1); compared to t0: p< 0.001), followed by an increase between age 9-24 months (median	NR	NR

(Q1;Q3) WAZ -1.84 (-2.6;-1.0) at t8; compared to t7: p=0.002 and to t0: p=0.058) and a plateau phase thereafter. A similar decrease was seen for height, with a nadir at 6-12 months (median (Q1; Q3) HAZ at t6 -2.41 (-3.5; -1.7); compared to t0, p< 0.001), followed by less pronounced catch-up growth. WAZ was significantly lower in patients pre/without liver transplant (p=0.042), with neonatal cholestasis, intracardiac, renal or skeletal abnormalities, history of nutritional support (p-values ≤0.006) and correlated with conjugated bilirubin (r=-0.168, p=0.023), platelets (r=-0.369, p< 0.001) and BWZ (r=-0.277, p<

				0.001). HAZ was significantly lower in patients with neonatal cholestasis, intracardiac, pulmonary tree, renal, or skeletal abnormalities and a history of nutritional support (all p-values ≤0.002) and correlated with conjugated bilirubin		
Nagasaka et al. 2005[166]	Japan	Five patients with ALGS (patients 1 through 5) and 5 patients with PFIC (patients 6 through 10) with ages ranging from 3 to 4 years were enrolled in the current study.	NR	Disease–Patient No./ Age (y)/ Sex/ B/P/ Extrahepatic anomalies ALGS–1/ 3/ Female/ 0.25/ PPS, BV, POET ALGS–2/ 3/ Female/ 0.12/ PPS, BV ALGS–3/ 3/ Male/ 0.21/ PPS, BV, POET ALGS–4/ 4/ Male/ 0.18/ PPS, BV ALGS–5/ 3/ Male/ 0.25/ PPS, BV, POET	NR	The diagnosis of ALGS was made by clinical manifestations and liver histology showing a paucity of interlobular bile ducts.

Olsen et al. 2005[167]	United States of America	Subjects were participants of two previously reported studies of prepubertal (Tanner Stage 1 or 2) children with ALGS. The first study (ALGS Study 1) included children diagnosed with ALGS, without end-stage liver disease and treated at The Children's Hospital of Philadelphia (CHOP). The second study (ALGS Study 2) included children with ALGS from paediatric care centres throughout North and Central America. Thirty-one (14 female) prepubertal children with ALGS with a mean age of 8.4 6 2.7 years (range, 4.1–13.7 yrs) met the study criteria.	NR	Children with ALGS have smaller bones (lower BA) and less bone mass (lower BMC) compared to same age peers. SIn our study, children with ALGS had significant deficits in WB BA and BMC adjusted for stature, indicating they have ''narrow'' bones (low BA-for-HT), low bone mass for their HT (low BMC-for-HT) and, therefore, less cortical bone strength than their peers. For the spine, the smaller bone size and less bone mass in the children with ALGS was explained by differences in stature. However, there was a high degree of variability in spine z-scores, and 39% of subjects had spine BMC-for-HT z-scores	NR	NR

				less than 22.0. In a healthy population, 3% of subjects have z-scores less than -2.0. The results of our study support the importance of examining bone status of chronically ill children in relation to their size and demonstrate the significant deficits in regions of cortical and trabecular bone in children with ALGS.		
Rodriguez et al. 2016[168]	United States of America	NR	NR	The proximal LPA and RPA, but not the MPA, were significantly smaller than those of the control subjects (P<0.01). The proximal LPA was significantly smaller than the proximal RPA (P<0.01) in the Alagille group (0.55 LPA:RPA ratio). Within the Alagille group,	NR	The diagnosis of Alagille syndrome was made on the basis of a combination of genetic testing for JAG 1 mutation, liver biopsy confirming paucity of interlobular bile ducts and/or characteristic clinical findings. Once patients were identified, the families of the patients were contacted and informed consent was

		75% of the lobar and segmental branches showed mild or no stenoses (Grade 1), 17% showed moderate stenosis (Grade2) and 8% showed severe stenosis (Grade 3). While not statistically significant, the right lung demonstrated a greater percentage of Grades 2 and 3 stenoses (28%, right vs. 20% left, P=0.1). The right middle and lingula lobes of both lungs showed more Grade 2 and 3 stenoses (33% upper/middle vs. 18% lower, P<0.01). Study ID/ Age at time of scan (years)/ Sex/ Weight (kg)/ Body surface area/ Other cardiac diagnoses included	obtained prior to official enrolment in the study. The consent signed was a broader consent investigating cardiovascular illness in the Alagille population. The medical records were then reviewed and a database of patients with cardiac involvement compiled.

LOGIC[169]	United States of America	Participants had ALGS (n = 49), CIC (n = 41), A1AT (n = 44), or BASD (n = 14).	NR	In ALGS, height-adjusted and weight-adjusted subtotal BMD and BMC Z-scores were negatively correlated with TB (P < 0.001) and SBA (P = 0.02). Mean height-adjusted and weight-adjusted subtotal BMC Z-scores were lower in ALGS participants with a history of bone fractures.	NR	NR
Shiau et al. 2020[170]	NR	This study included 64 individual participants with either ALGS (n = 40) or PFIC subtypes 1-3 (n = 24) with liver biopsies performed between January 2003 to December 2015.	NR	Variable/n/F0-F2 (n = 27)/n/F3-F4 (n = 13)/P Value Genetic confirmation (%)/ 27/ 11 (40.7)/ 13/ 7 (53.8)/0.509	Variable/ Yes LT, n = 13 (%) LT indications: Chronic cholestasis/ 13 (100.0) Intractable pruritus/ 10 (76.9) Malnutrition/ 9 (69.2) Deforming xanthomas/ 4 (30.8) Pathological fractures/ 3 (23.1) Variable/n/ Median (IQR)/	The diagnosis of ALGS or PFIC was first confirmed by documented genetic mutation (JAG-1 or NOTCH-2 for ALGS). If no records of genetic mutation were available, clinical criteria were used to confirm the diagnosis. Clinical criteria for ALGS included any combination of three or more of the following: (1) peripheral pulmonary stenosis (or tetralogy of

					Age at LT (years)/ 13/ 3.5 (2.4, 4.3)	Fallot), (2) posterior embryotoxon, (3) butterfly vertebrae, (4) renal manifestations, (5) vascular anomalies, (6) facial features historically described in ALGS, (4) or (7) or bile duct paucity (per pathologic reports).
Janowski et al. 2020[171]	Poland	Children with BA and ALGS,>4 years old and who did not require liver transplantation (LTx) and preserved normal liver function, and who were under the care of The Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics of the Children's Memorial Health Institute in Warsaw, Poland, from 2014 to 2019.	NR	Although patients with ALGS had frequently abnormal lipid profile (higher levels of TC, LDL C, APO B, TC/ HDL ratio, and LDL/HDL ratio), they did not present with arterial hypertension and abnormal IMT or PWV. Moreover, lipid parameters were not directly related to vascular parameters—cIMT and PWV.	NR	The diagnosis of ALGS was confirmed by typical liver histopathological features (paucity of bile ducts) and clinical manifestations (the fulfilment of at least 3 of 5 the following features: cholestasis, posterior embryotoxon, cardiac defects, skeletal abnormalities, classic syndromic facies), and genotyping of the JAG1 gene (13/17 cases analysed, pathogenic mutations in the JAG1 gene were identified in 11 cases) (20).

Rock et al. 2020[172]	Switzerland and Belgium	Eighty-five paediatric patients with clinically or genetically defined ALGS were identified. Ten were followed-up at University Hospitals Geneva and 75 at the Cliniques Universitaires Saint-Luc in Brussels. Among the 85 patients with clinically proven ALGS, 50 patients underwent genetic testing. Fourteen patients were excluded because of lack of ophthalmic data before or after LT. Two other patients, who received transplants at beginning of the LT program, died within a month of LT. Data for 69 patients were available for inclusion in the analysis.	NR	Papilledema tended to be more common in the patients who had undergone LT than in those who had not (P<0.07). There was a statistically significant difference in the follow-up duration between the patients who underwent LT (median 109 months; interquartile range 51–145 months) and the 29 patients who did not (median 75 months; interquartile range 5–63 months; P<0.001).	/Papilledema, n=9/ Nonpapilledema, n=60/ P LT/ 8 (89)/ 32 (53)/ 0.07 Age at LT, mo/ 42 (32;51)/ 32 (21;51)/- Follow-up time, mo/ 64 (44;109)/ 60 (12,138)/ 0.42	Thirty-eight of the 50 (74%) were positive for a pathogenic variant in JAG1, 3 were positive for a deletion in JAG1 and none for NOTCH2.
Rock et al. 2018[173]	NR	Ophthalmologic examination data from 85 paediatric patients with clinically (n=48) and/or	NR	41 patients (41/69, 59%) of this group had LT of whom 2 developed true	NR	NR

		genetically (n=37) proven AS followed in two referring hospitals (UCL St Luc Brussels, n=75; HUG Geneva n=10). Patients were included if data were available before and after liver transplantation (LT).		papilloedema before LT and 6 after LT (6/41,14%). In all patient's normal neurological exam and cerebral MRI were reported (4/69, 6%).		
Sokol et al. 1983[174]	United States of America and Canada	NR	NR	NR	NR	Of the five subjects identified as having characteristic facies by more than 75% of the US/Canadian examiners (patients 4, 8, 9, 11, and 15), only two actually had Alagille syndrome. In addition, two of the four subjects judged as not having characteristic facies by 100% of the French examiners (patients 3, 7, 10, and 14) actually did have Alagille syndrome. The calculated sensitivity of the characteristic facies for

						Alagille syndrome was 54% and 32%, the specificity 44% and 68%, and the predictive value 46% and 47%, based on the results from the US/Canadian group and the French group, respectively.
Tzakis et al. 1993[175]	United States of America	475 children underwent orthotopic liver transplantation at the Children's Hospital of Pittsburgh. In 23 (5%) of these patients the underlying primary disease was Alagille's syndrome.	Eight children (35%) required re-transplantation. One received three grafts and was alive 4 years later. The overall mortality after re-transplantation was 75% (six of eight patients died). The cause of graft failure was hepatic artery thrombosis in eight cases, viral hepatitis in two cases, portal vein thrombosis in one case, and rejection in one case.	NR	Finding/ No. (%) of Patients (N=23) Intrahepatic bile duct paucity and cholestasis/ 23 (100) Cardiovascular anomalies with pulmonary artery stenosis as the main component/ 23 (100) Dysmorphic facies/ 15 (65) Psychomotor retardation/ 14 (61) Skeletal malformations/ 11 (48) Ocular abnormalities (posterior	NR

					embryotoxon)/ 10 (43.5)	
Marino et al. 1992[176]	United States of America	In the period from March 1980 to September 1986, 268 children underwent OLT at the Children's Hospital of Pittsburgh of these patients, 13 (10 male and 3 female) had advanced liver disease secondary to AHD.	Only two out of seven patients who had extensive hilar dissection at the time of the initial exploration are alive (28.6%), compared to five out of six patients who had no dissection of the porta hepatis (83.3%). This survival rate of 28.6% in the AHD patients with previous hilar dissection was worse than that of liver transplant recipients for extra hepatic biliary atresia (EHBA) and previous portoenterostomy (63%) transplanted during the same period. Contributing factor/ Cause of death/ No. of patients Hepatic artery thrombosis/ 1 – Bacterial septicaemia (Citrobacter	-/Present/ Absent/ Not stated Abnormal face/ 9/ 2/ 2 Xanthomas/ 3/ 4/ 6 Growth retardation/ 13/ –/ – Pulmonary artery stenosis/ 13/ –/ – Vertebral anomalies/ 3/ 3/ 7 Paucity of interlobular bile ductules/ 13/ –/ – Posterior embryotoxon/ 3/ 1/ 9	NR	The diagnosis was based on liver histology, showing paucity of interlobular bile ductules, and the presence of peripheral pulmonary artery stenosis, based on clinical data or findings at autopsy.

			freundii)			
Rapp et al. 2016[177]	US	3 males and 3 females, mean age of 8.8 years (range 1.4 - 25.9 years).	NR	All patients had imaging findings showing varying degrees of chronic liver disease and portal hypertension. In the setting of cirrhosis, large hepatic masses, which ranged from 6.4 cm to 11.8 cm in size, were also identified.	NR	Patients with AS can develop cirrhosis which puts them at high risk of developing primary hepatic neoplasms. Among our group of AS patients from over a 12-year period, GHRN were the only hepatic masses we identified. Strikingly large in size, with distinct US and MRI features, recognition and discrimination of these lesions from malignant tumours, such as hepatocellular carcinoma, is important to avoid unnecessary intervention.

Gliwicz-Miedzinska et al. [178]	Poland	Out of 55 patients with Alagille syndrome treated in our department over the period 1983-2011, twelve patients underwent Ltx (22%). A retrospective review of their clinical data was performed. All of them developed severe cholestasis in the first months of life. In eight children numerous surgical interventions took place before Ltx: six of the qualified children had Kasai operation and one – cholecystoduodenostomy performed for suspected biliary atresia; additionally, two of them underwent partial external biliary diversion and one – ileal bypass, as an unsuccessful attempt to treat severe pruritus and xanthomas.	Patient survival one year after Ltx was 83.3%. Two patients died in the early postoperative period; the 1.5-year-old boy died due to infectious complications, and the 1.5-year-old girl died of intra-abdominal haemorrhage.	Children were qualified to Ltx on the basis of following indications: malnutrition and/or growth retardation (8 patients), severe pruritus (8), portal hypertension (1), synthetic liver failure (3). Mean PELD value was 14.8 (range 10-37). Eight patients had cardiovascular anomalies: peripheral pulmonary stenosis in all eight cases and ASD II in two cases.	Mean age at Ltx was 5.6 years (range 1$_7$.5-12).	NR

Valamparampil et al. 2019[179]	India	Eight children with ALGS	100% patient and graft survival at a mean follow-up of 26 months (range 3–62 months)	Jaundice was noted after a median duration of 20 days after birth (range, 7–60 days). Three patients had undergone Kasai porto-enterostomy for misdiagnosis of biliary atresia. The most common indication for transplantation was severe pruritus with poor quality of life. Explant livers in two children showed cirrhosis with early well differentiated hepatocellular carcinoma. The median z-score for weight and height at LT were -2.7 (range: -0.9 to -6.44)/-3.6 (range: -0.93 to -7.96) while at follow-up were -1.7 (range: -0.35 to -3.4) and -2.1 (range: -1.4 to -3.9) respectively. The	Eight children with ALGS underwent living donor liver transplantation at a median age of 4 years (range, 1–7 years).	NR

				estimated glomerular filtration rate was normal pre-LT and follow-up.		
Ganschow et al. 2001[180]	NR	A total of 23 children (aged 2 to 16 years) were included in this study	Patient and graft survival was 85.7%. One patient died due to multiorgan failure, and a second one died after a severe intrathoracic bleeding caused by a vascular malformation.	The following manifestations were found in the study subjects: liver cirrhosis, n =12; stenosis of the pulmonary artery, n=15; xanthomas, n=8; other vascular malformations, n=6; vertebral defects, n=4; nephropathy, n=4; ventricular septal defect, n=4; intracranial bleeding, n=3; and posterior embryotoxon, n=3; 14 of the 23 children underwent Ltx because of symptomatic cholestasis (n= 9) and chronic end-stage liver disease (n=5).	NR	NR

Englert et al. 2006[181]	NR	A total of 37 children were included in our retrospective study. The manifestations of ALGS in our study population. Twenty-four of the 37 patients underwent OLT for chronic end-stage liver failure (n=8) or symptomatic liver disease (n=16). The median age at transplantation was 3.6 yr (Range 7 months to 13.3 yr); there were five female, and 19 male patients.	Patient survival was 91.7% after 1 yr.	There was no significant catch-up growth in 11 of the 16 children transplanted without underlying liver cirrhosis. However, five children did actually show significant catch-up growth in the follow-up period from 2 to 5 yr. Patient growth was at or below the third percentile preoperatively and reached in three cases the 10th percentile afterwards. In two cases, it even reached the 20th percentile. The eight children with preoperative end-stage liver disease showed severe growth failure (patients' growth was below the third percentile in all cases) and had catch-up	Graft survival was 87.5%. One patient died of a septic complication, another one after having severe intrathoracic bleeding (suspected vascular malformation). The reason for re-transplantation was primary non-function in all patients.	We performed genetics in 11 patients; in seven patients' mutations in JAG1 were found.

				growth post-operatively.		
Tiao et al. 2012[182]	Taiwan	Patients diagnosed as ALGS and underwent LT between 1987 and 2010. Nine patients underwent living donor LT.	5-year overall survival rate after living donor LT was 88.9%.	Cholestasis and characteristic faces were seen in all patients. Posterior embryotoxon was seen in 4/9 (44.4%), butterfly vertebrae in 3/9 (33.3%), heart defect (pulmonary stenosis in 2) in 3/9 (33.3%), and renal disease in 2/9 (22.2%) patients. Iminodiacetic acid scans showed no excretion of isotope into the bowel after 24 hours in 4/9 (44.4%). A small gallbladder on ultrasonography was noted in 3/9 (33.3%) and suggested a false diagnosis of biliary atresia.	The mean age at time of LT was 4.6 years.	All underwent diagnostic laparotomy and liver biopsy. Liver biopsy showed characteristic features of paucity of interlobular bile ducts in all patients.

Valamparampil et al. 2019[183]	NR	LT was done for 10 children (5 boys) with ALGS (out of total 354 paediatric liver transplants) during the study period	We have 100% patient and graft survival at a median follow-up of 32 months (range 3-72 months). All patients have good graft function with normal aminotransferase levels and eGFR within normal ranges. The median z-score for weight and height at follow-up was −1.7 (range: −3.4 to −0.35) and −2.1 (range: −3.9 to −1.4), respectively	Jaundice was the most common initial symptom and was detected in all children after a median duration of 20 days after birth (range, 7-60 days). All except patient 1 had cardiac anomalies with PA stenosis being the commonest. There was no history of fractures or history of affected family members in any of the patients.	Ten LDLT were performed with all receiving left lateral segment grafts. The median age at LT was 28 months (range, 12-84 months). The median GRWR was 2.9 (range 1.3-4.2). Intraoperatively, no intra-abdominal vascular malformations were identified. All patients had suitable recipient hepatic artery for arterial anastomosis, and no child needed additional procedures such as vascular conduits. Roux-en-Y hepaticojejunostomy was used for biliary drainage of the graft in all the children. The median duration of hospital stay after LT was 18 days (range	The diagnosis was based on modified criteria for ALGS; the presence of mutation in JAG1 or NOTCH2, family history of ALGS, or clinical signs were considered.4 Clinical criteria for diagnosis included consistent liver histology (bile duct paucity and/or cholestasis on explant histopathology), cardiac, renal, ocular, or skeletal involvement, structural vascular anomalies, and presence of characteristic facies.4,6 Bile duct paucity is defined as absence or marked reduction in the number of bile ducts in the portal triads (<0.5 interlobular bile ducts per triad) in the presence of normal-sized branches of the portal vein and hepatic artery.

					15-21 days). There were no post-transplant vascular or biliary complications in the cohort.	
Lykavieris et al. 2001[184]	NR	One hundred and seventy-four children with ALGS (106 boys) were investigated at Bicêtre Hospital between 1960 and 2000. Twenty-four had a sibling affected by ALGS; seven of these siblings are included in this series as well as two offspring of affected mothers. All patients had at least three of the five major clinical features. Thirteen children with severe neonatal jaundice underwent Kasai operation for suspected biliary atresia before the diagnosis of ALGS was established. Cholecystostomies with	Overall survival of the 163 patients was 68 (4) % at 10 years and 62 (4) % at 20 years. Fifty-seven patients died at a median age of four years (range 2 months to 26 years).	Pruritus was present in 24 patients and noted for the first time at a median age of 14 months (range 4 months to 6 years); it disappeared spontaneously in seven patients at ages ranging from six to 20 years (median 13 years). In the remaining 17 patients, pruritus was controlled by medical treatment. Xanthomas were found in one patient at age two years and disappeared one year later. Liver enlargement was present in 20 patients. Hepatomegaly	Survival with native liver was 51 (4) % at 10 years and 38.5 (4.5) % at 20 years. In the univariate analysis, 10 year survival with native liver was worse in patients with neonatal cholestatic jaundice than in those with late onset of cholestasis (45 (5)% v 79 (8)%; p=0.0004), in patients with xanthomas than in those without xanthomas (43 (6)% v 60 (6)%; p=0.017), and in patients who underwent a Kasai	Of the 174 patients studied, 81 displayed all five major clinical features of the syndrome, 68 displayed four major features, and 25 three major features. In 132 children, 38 being small for gestational age (with a weight below the 10th percentile for gestational age), the presenting symptom was neonatal cholestatic jaundice. In 42 children, two being small for gestational age (significantly less than in the other group, p<0.01), there was no history of clinically evident neonatal jaundice and presenting symptoms occurred at a median age of

		external bile drainage and cholecystojejunal anastomoses were performed in 24 and six patients, respectively.		persisted in nine of the 10 patients who died and regressed progressively in eight of 10 who survived after age 15. Splenomegaly was present in six patients. Of the four patients with oesophageal varices, one presented with gastrointestinal bleeding. Two patients died from end-stage liver disease at age 10 and 13.5 years, respectively, before the era of LT. Cholelithiasis was found in one patient at age three years. Another patient presented with hepatocellular carcinoma at age 44 years.	operation than in those who did not (38 (13)% v 54 (4)%; p=0.048). In the multivariate analysis, neonatal cholestatic jaundice was the only independent prognostic factor (RR 2.52; 95% CI 1.25–5.88; p=0.012) whereas xanthomas and Kasai operation were not (no xanthomas: RR 0.78, 95% CI 0.49–1.23, NS; no Kasai operation: RR 0.65, 95% CI 0.35–1.21, NS)	33 months (range 4 months to 10 years) consisting of hepatomegaly (n=12), cardiac murmur (n=9), failure to thrive (n=8), pruritus (n=4), jaundice (n=3), and fortuitous finding of abnormal liver function tests (n=6). Eleven of these 42 patients did not present with any clinical or biochemical signs of cholestasis and are not included in the study. Therefore, 163 children with ALGS and chronic cholestasis form the basis of this report.
Kamath et al. 2020 (LOGIC)[12]	NR	At the time of data analysis, the total number of patients with ALGS in	Fifty-eight participants had liver transplant and 11 died with native liver during the study follow-up.	Regression analysis revealed that every 10 mg/dL increase in total	Estimated transplant-free survival at the age of 18.5 years was	Participants were confirmed as ALGS by standard clinical criteria

LOGIC was 377. Participants with a liver transplant prior to enrolment were excluded (n = 74) from this analysis of pretransplant natural history, and an additional 10 participants were excluded for having a non-ALGS gene mutation (ABCB4, ABCB11, or HNF1beta), resulting in a sample of 293 participants with ALGS.

bilirubin was associated with a decrease in height z-score by 0.10 (P = 0.03) and weight z-score by 0.15 (P = 0.007).

Total bilirubin was higher for younger participants (P = 0.03) with a median of 6.9 mg/dL for those less than 1 year old compared with a median of 1.3 mg/dL for participants 13 years or older. The median gamma-glutamyl transferase also dropped from 612 to 268 in the same age groups.

24% (95% CI: 16%, 36%).

Among the 11 participants who died with native liver during the study, only three deaths were directly attributable to liver disease. The remainder were due to cardiac involvement, pulmonary haemorrhage, and “other”.

and/or the presence of a disease-causing mutation in JAG1 or NOTCH2. The clinical criteria were at least three of the following: bile duct paucity on liver biopsy, heart murmur, or cardiac anomaly; posterior embryotoxon or other anterior chamber defect; butterfly vertebrae; and/or characteristic facial features and renal anomalies.

Czubkowski et al. 2021[185]	Poland	Out of 89 patients with ALGS treated in our department over the period 1995-2019, 18 patients (13 males) underwent LTx (20%) and 2 are currently on the waiting list	One patient was deceased as a result of intra-abdominal haemorrhage. Median post-transplant follow-up was 9.2 years (1.9-13.4), and overall patient survival was 94%.	All transplanted patients developed severe cholestasis in the first months of life. Cardiovascular anomalies were present in 13 (72%) of patients, the most common pulmonary stenosis (55%) but no complex heart defects. There was significant catch-up growth and weight gain in presented group. Protocol biopsies 3-8 years post-transplant were performed in 13 patients and showed normal or mild fibrosis in 77% and moderate fibrosis in 23%.	Median age at LTx was 5.8 years (range 1.5-11.8).	NR

Bales et al. 2010[186]	USA	Four hundred ninety-five surveys were mailed, and 93 were returned undelivered due to inaccurate address listing. Of the remaining 402 surveys, 42 were completed and returned with associated parental consent, yielding a completion rate of 10%. The study group comprised 24 males and 18 females, ranging in age from 1 to 35 years (mean 10 years) at the time of survey completion.	NR	Twelve patients (28%) had a history of bone fracture, with a total of 27 fractures reported. Moreover, the 2 groups did not differ with respect to the presence of cardiac anomalies, renal disease, vertebral anomalies, or surrogate markers of liver disease severity, including a history of biliary diversion or transplantation.	NR	JAG1 mutation data were available on 29 patients (11 patients with fractures and 18 patients without fractures). Within the fracture group, 1 patient had a chromosomal deletion, and 5 patients had nucleotide(s) deletions and/or insertions, which resulted in frameshift and premature protein truncation. Three patients had nonsense mutations, and 2 others had splice site mutations. The distribution of mutations was similar in both fracture and no-fracture groups. Overall, within the fracture group, 73% (8/11) of the mutations were predicted to be protein truncating.
Vandriel et al. 2020[42]	USA	Nineteen (79% male) NOTCH2 patients and 755 (57% male, p=0 05) JAG1 patients were identified.	Overall survival rates at 10-and 18-years were ≥90% in both groups (log-rank p=0 71)	NOTCH2 patients were significantly less likely to have characteristic facies (53% vs. 88%, p<0.001), an ECHO	NR	Pathogenic NOTCH2 variants included frameshift (32%), missense (26%), splice site (21%) and nonsense (21%) NOTCH2-

				confirmed cardiac anomaly (58% vs 93%, p=0 001), posterior embryotoxon (14% vs 53%, p=0.004), or butterfly vertebrae (0% vs. 44%, p=0.001). 10- and 18-year NLS in patients presenting with neonatal cholestasis were comparable between the two groups (59%		and JAG1-ALGS patients were similar in terms of neonatal cholestasis (89% vs 82% respectively, p=0 55), histological evidence of bile duct paucity (42% (n=5/12) vs 60% (n=186/308), p=0 24), and presence of renal anomalies (26% vs 34%, p=0 46)
Tornincasa et al. 2019[187]	Italy	Among 31 children with ALGS, 13 neurologically asymptomatic patients (median age 10.5 years, range 2-24) were enrolled according to inclusion criteria	NR	Typical ALGS abnormalities showed the following prevalence: moyamoya like arteriopathy 7.7%, internal carotid arteries stenosis 30.8%, and artery aneurysm 15.4%. As uncommon ALGS alterations, we found scaphocephaly in 15.4% of cases, cerebellar tonsils herniation in 23%, and venous anomalies in 7.7% of	NR	NR

				patients. Never described ALGS-associated malformations such as corpus callosum thinning (15.4%), increased volume of the lateral ventricles (30.8%), gliotic outbreaks (30.8%) macrocerebellum (15.4%), perioptic cerebrospinal fluid spaces expansion (7.7%), medulla oblongata dysmorphism (7.7%), reduced volume of IV ventricle and cisterns of the base (30.8%) were observed.		
Narula et al. 2006[188]	United Kingdom	Forty-one children met the inclusion criteria for the study. Four patients were excluded because they did not fulfil the clinical criteria for ALGS diagnosis. Another 10 children without a	NR	Feature/ n = 41 Typical facies/ 98% congenital heart disease/ 93% (73% PPS* 20% other) Cholestasis/ 93%	NR	Confirmed ALGS syndrome (3 out of 5 diagnostic features). The clinical criteria included 3 of the following 5 features: chronic cholestasis, skeletal abnormalities, cardiac disease, characteristic facial

	documented ophthalmic examination were excluded because they had no obvious visual loss. Of the children who were included, 22 were male and 19 females. Six children had received a liver transplant. Three children had molecular adsorbent recirculating system therapy for treatment of intractable pruritus. Five children died of ALGS-related pretransplant complications. JAG1 mutation results were available in 16 children, and 10 (62%) children had a JAG1 mutation detected.	Posterior embryotoxon/ 70% Butterfly vertebrae/ 24% Failure to thrive 83%	features and ocular abnormalities. The clinical criteria for diagnosis of ALGS were present in those children included in the study who did not have a liver biopsy

Schwarzenberg et al. 1992[189]	United States	Over the last 33 years, the paediatric gastroenterologists at the University of Minnesota have followed 16 children with syndromic paucity, six of whom are now beyond age 18 years.	Of the 16 patients, four died in childhood (one of cardiac complications, two from liver failure associated with Kasai procedures at another institution, and one of unknown causes). toms. Out of six patients who reached adulthood, two died (one at age 31, one at age 34)	Out of 16 patients, six patients are still in childhood (less than 14 years old). One has predominantly cardiac complications, one has had a liver transplant (for liver failure associated with a Kasai procedure at another institution), one has type IV renal tubular acidosis, but is otherwise healthy, and the other three are doing well with few clinical symptoms. Six patients have reached adulthood, and five of those six patients had complications of arteriohepatic dysplasia after age 16 years that resulted in severe morbidity (three) or death (two). These complications included hepatic failure (two), renal failure (one),	NR	Diagnosis was made on the basis of clinical documentation of the stigmata of arteriohepatic dysplasia, combined with a liver biopsy demonstrating paucity of the interlobular bile ducts

				cerebellar herniation (one), and hepatocellular carcinoma (one).		
Kasahara et al. 2003[41]	Japan	529 children underwent LRLT at Kyoto University Hospital. Of these, 20 (3.8%) were performed for ALGS.	Of the 20 recipients, 17 are currently alive with good graft function at a median follow-up of 5.2 years (range: 0.5–10). The overall 1- and 5-year patient actual survival rates were 87.7% and 80.4% (Three patients died as the result of the following: complications related to surgery, heart failure caused by progressive pulmonary artery stenosis, and a graft with unsuspected bile duct paucity), respectively.	Manifestations/ No. of patients Chronic cholestasis/ 20 Pulmonary artery stenosis/ 17 Peculiar facies/ 15 Butterfly-like vertebral arch defect/ 10 Posterior embryotoxon/ 4 Other Pruritus/ 18 Failure to thrive/ 14 Hypercholesterolemia/ 11 Renal hypoplasia/ 3 Renal insufficiency/ 1 Intracranial haemorrhage and stroke/ 2	LRLT was performed at a median age of 1.3 years (range: 0.6–5.7) for eight patients who had undergone Kasai procedure and 5.2 years (range: 1.4–12.9) for the other patients (P-0.002).	The diagnosis of ALGS was made based on physical, radiologic, and histopathologic findings. Thirty-six donor candidates were evaluated by standard liver function tests, blood group combination, anatomic variation, and graft size matching. Among the 36 potential donors, 11 donors underwent magnetic resonance cholangiopancreatography, and four underwent preoperative liver biopsy.

				Pathologic bone fracture/ 1		
Lim et al. 2003[190]	Malaysia	A total of 6 patients were identified as ALGS. There were 2 males and 4 females; the male to female ratio is 1:2. All were Malays except for one Indian girl (patient 4). Ages ranged from 2 months to 5 years at presentation. 4/6 patients (66%) had a positive family history (with a pair of brother-sister i.e. patient 2 and 3). In fact, there were 13 individuals (6 patients and 7 relatives) diagnosed with ALGS in these 5 families. Only 6/13 (46%) of them	1 patient died.	All 6 patients presented with typical ALGS facies and cholestasis (100%). Other symptoms that patients presented were: portal hypertension (PHT), synthetic liver dysfunction, biochemical evidence of hepatitis and hepatomegaly, congenital structural cardiac abnormality, posterior embryotoxic, butterfly vertebrae, hyperlipidaemia, failure to thrive, hypertriglyceridemia and	NR	A proband with the absence of family history requires presence of 3-4 major features for diagnosis unless the gene defect is detected when only 1 or more features are required. With the presence of family history, 1 or more features will make the diagnosis, unless the gene defect is detected when no or any (minor) features are required.

		presented with liver involvement.		hypercholesterolaemia. None of them have renal anomalies. Five patients are still alive.		
Kamath et al. 2012[45]	NR	The study cohort of 91 ALGS patients had an almost equal sex distribution and an age range of 6 months to 17 years.	The 1-year patient survival rates were 87% for the ALGS patients	Although cardiac involvement in general and structural intracardiac disease (including pulmonary stenosis and septal defects) were prevalent in the SPLIT patients with ALGS who underwent LT, complex cardiac anomalies were rarely seen in these children. Only 3 children in the SPLIT ALGS cohort had significant cardiac anomalies (tetralogy of Fallot, hypoplastic tricuspid valve and atrial septal defects, and subaortic and aortic	The majority of the ALGS children who underwent LT were in the toddler and school age years, with 57% undergoing transplantation between the ages of 1 and 4 years and 29% undergoing transplantation between the ages of 5 and 12 years. Reports of liver transplantation (LT) for patients with ALGS have come largely from single centres, which have	NR

				valve stenosis and mitral valve replacement). Extrahepatic Features of the ALGS Patients / Number of patients Heart murmur / 88 Structural intracardiac involvement / 23 Complex cardiac anomalies / 5 Facial features /86 Eye anomalies / 47 Skeletal anomalies / 43 Renal anomalies / 40	reported survival rates of 57% to 79%.	
Blue et al. 2007[191]	Australia	Identified 26 patients with ALGS and 505 patients with PA. Five cases of ALGS with PA were identified. 4 with PA and ventricular septal defect (VSD), 1 with PA and intact ventricular septum	Four of 5 patients (80%) have died as a result of cardiac disease. One individual is receiving palliative management.	The most striking feature is the failure of small pulmonary arteries to grow following systemic-to-pulmonary arterial shunts.	NR	NR

Alagille et al. 1987[192]	France	Eighty patients were found to have several abnormalities, classified as syndromic PILBD. Thirty-one patients with nonsyndromic PILBD were excluded from this study; none had peculiar facies, cardiovascular abnormalities, vertebral arch defects, or embryotoxon. Among these 31 patients, seven had a 1-antitrypsin deficiency or congenital rubella.	Twenty-one of our 80 patients died. Liver complications were responsible for death in only four (5 %) patients; severe cardiac or vascular abnormalities were responsible for six (7.5 %) of these deaths	The clinical course was characterized by recurrent episodes of cholestasis, often associated with common respiratory tract infections, especially during the first years of life. In 28 patients, cholestasis was severe and permanent in the 3 or 4 first years of life, leading to more or less severe malnutrition. In 11 of these 28 patients, portal fibrosis was well developed. However, in the oldest patients, cholestasis progressively decreased after about 5 years of age, with the persistence of only biochemical signs of cholestasis.	The results of liver function tests were normal, but total bile acids, gamma-glutamyl transferase, and alkaline phosphatase blood levels were always very high. In a few patients with early or later progressive cirrhosis, liver function was disturbed, as in any cirrhosis. In general, however, the long-term prognosis was not related to liver failure.	In general, we accept the diagnosis of incomplete syndromic PILBD if at least three of the five main features are present (including cholestasis). We believe that these patients must be observed closely; as they mature, the clinical diagnosis is easier to make.

Yang et al. 2020[193]	China	One hundred and seventy-nine children underwent LT between September 2017 and April 2019 at the Beijing Friendship Hospital, Capital Medical University in Beijing, China. The research was approved by the Ethics Committee of Capital Medical University Affiliated Beijing Friendship Hospital (approval number: 2020-P2-044-01). Eleven patients (6.1%) were indicated for ALGS, based on either genetic diagnosis or clinical diagnosis.	a 100% patient and graft survival in 11 ALGS patients	All 11 patients were complicated by cholestasis, of whom 9 were misdiagnosed as biliary atresia (BA) and received exploratory laparotomy, laparoscopic exploration, or Kasai portoenterostomy. Nine patients (81.8%) were complicated with cardiovascular malformations identified by echocardiography, with pulmonary artery stenosis (44.4%) as the most common form.	At the time of surgery, the median (range) age of the patients (8 males and 3 females) was 23.5 (12.0–149.0) months.	Traditionally, the classical diagnosis of ALGS requires interlobular bile duct paucity together with at least 3 of the 5 major clinical features, including chronic cholestasis, cardiopulmonary defects, craniofacial abnormalities, posterior embryotoxon, and butterfly vertebrae. Using revised diagnostic criteria, namely a JAG1 mutation or family history of ALGS, diagnosis can be done with only 2 of the 5 clinical manifestations
Rovner et al. 2002[194]	United States	Children with ALGS evaluated at The Children's Hospital of Philadelphia, as well as from other paediatric gastroenterology centres throughout North and Central America, were	NR	Children (mean age 6.7 ± 3.6 years) with ALGS (n=26) had low height-for-age z-scores (HAZ), weight-for-age z-scores (WAZ) (−1.9 ± 1.3 and −1.7 ± 1.1, respectively), and	NR	ALGS was defined as the presence of bile duct paucity in addition to three of five diagnostic criteria (chronic cholestasis, cardiac disease, skeletal abnormalities, ocular abnormalities,

invited to participate in this study. Exclusion criteria included: use of pancreatic enzyme supplementation, use of any medication known to affect growth and any significant illness unrelated to ALGS. After exclusions, there were 26 prepubertal subjects (14M, 12F) with a mean age of 6.7 ± 3.6 years (range, 1.8–12.4 years). Fifteen subjects had cardiac defects, most commonly pulmonic stenosis. Information about cardiac defects was not available for four subjects.

delayed skeletal maturation (−1.4 ± 1.8 years). Fifty-eight percent of the subjects were less than the 5th percentile for height and 54% were less than the 5th percentile for weight. At least 20% of children with ALGS had low dietary intake for several nutrients including: calories, fat, calcium, vitamin D, and vitamin E. There were no statistically significant differences between males and females for HAZ (−1.9 ± 1.4, −1.8 ± 1.2), WAZ (−1.7 ± 1.0, −1.6 ± 1.3) and BMIZ (−0.3 ± 1.2, −0.4 ± 1.4). Males and females did not differ in the magnitude of the skeletal delay (−1.4 ± 1.5 vs. −1.2 ± 1.8 years).

characteristic facies) or the presence of Jag1 mutation.

Kamath et al. 2004[195]	United States	From 1992 to 2002, 268 probands and family members with ALGS have been enrolled in our database at The Children's Hospital of Philadelphia. Those individuals included in the database either met clinical criteria for ALGS, carried a mutation in or a deletion of JAG1, or were obligate carriers of a mutation.	29 individuals from the original cohort have died. Ten of these 29 died of complications of noncardiac vascular disease, thereby accounting for 34% of the mortality in this population.	Retrospective review of the records of 268 individuals in our database determined that 9% have documented vessel abnormalities or a history of a vascular event. We report 25 individuals who had vascular complications. Fourteen of these had mutations in JAG1, and 2 have had mutations identified in the family but the individuals themselves were not tested (these individuals were obligate carriers). Four patients did not have a mutation in JAG1 but met clinical criteria for ALGS. Samples were not available for mutational analysis in another 4 patients; however, they also met clinical criteria for ALGS. The age range	Two children had complicated courses in the post-liver transplant period and intracranial bleeding episodes during this time	The main clinical manifestations of ALGS have been well characterised (cholestasis caused by intrahepatic bile duct paucity, congenital heart defects involving primarily the pulmonary arteries, butterfly vertebrae, anterior chamber defects of the eye, typically posterior embryoxton, and facial dysmorphism) and are the basis for the clinical diagnosis

of affected individuals in this study was 4 months to 44 years. Of the 25 individuals reported, 16 had documented structural abnormalities of the vascular system. These included intracranial vessel, aortic, and renal artery anomalies. Of note, we report the first mutation-proven case of moyamoya in ALGS. In 12 individuals, the results of a cardiac evaluation were known, and in these, 10 of 12 (83%) had stenosis at some level in the pulmonary tree. The remaining 9 individuals (8 children, 1 adult) had significant intracranial vascular events with no documented vessel abnormality. Two children had complicated courses in

the post–liver transplant period and intracranial bleeding episodes during this time. Two individuals had a clear history of trauma preceding the bleeding event. Another infant developed seizures, was found to have a left subdural hematoma, and died during attempted evacuation. One child suffered multiple areas of infarcts in the right parietal and left frontal lobes after cardiac catheterization, although no vessel anomalies were seen. Finally, 1 mutation-positive infant developed respiratory failure and suffered an ischemic event while intubated and ventilated

Quiros-Tejeira et al. 2004[196]	United States	Forty-three patients were identified after 810 records were reviewed of children identified with cholestasis. Twenty-five patients were identified in the University of California at Los Angeles Medical Center and 18 in the University of California at San Francisco Medical Center. Referrals or consultations were requested because of cholestatic liver disease in 37 patients and LTx evaluation in 6. Twenty-five subjects were male (58%). Thirty-five percent of the probands had a positive family history for cholestatic liver disease. Family history of heart disease was not regularly available.	Twelve patients died (28%) at a median age of 2.3 years (range, 0.6-20.5 years). Five deaths occurred after LTx (median age, 2.7 years; range, 2.1-8.7 years). All deaths were secondary to complications of LTx	NR	Twenty patients (47%) underwent LTx at a median age of 4 years (range, 1.3-15.4 years). The patients who underwent Kasai procedure underwent transplantation at the median age of 2 years (range, 1.4-2.6 years).	NR

Kamath et al. 2012[197]	NR	466 JAG1 mutation-positive individuals, 329 (70.6%) were probands and 137 (29.4%) were relatives of the probands. All individuals met classic clinical criteria for ALGS except for seven patients, who had subtle or atypical features, but all carried typical JAG1 mutations.	NR	NR	NR	Renal involvement in JAG1 mutation-positive ALGS is common and has a prevalence of at least 39% in our evaluable patients. The most common renal anomalies are renal dysplasia, renal tubular acidosis, vesico-ureteric reflux and urinary obstruction. A targeted renal evaluation consisting of serum biochemistry, renal ultrasound and urinalysis should be considered standard of care in ALGS.
Carpenter et al. 2018[198]	United States	A total of 52 Alagille patients were identified in the 14-year period, ranging from 11 months to 27 years of age (mean: 8 years). Nineteen patients (37%) had neurovascular imaging.	NR	NR	NR	The majority (68–80%) of Alagille patients carry haploinsufficiency to the Jagged-1 (Jag1) mutation. Jagged-1 is a ligand that interacts with receptors in the Notch signalling pathway. Biochemical studies have shown that the Jagged-1/Notch signalling pathway plays an

						important role in modulation of the vascular smooth muscle phenotype. The high prevalence of clinically significant cerebral arterial disease supports non-invasive screening of Alagille patients with MRI and MR angiography for early detection and treatment of potentially debilitating and life-threatening conditions.
Vandriel et al. 2019[40]	NR	731 ALGS (41% female) subjects from 32 centres were included (median follow-up 4.75 yrs, IQR 2.0-10.2). Among the 76% (n=554/731) genetically confirmed patients, 95% had a JAG1 mutation and 4% a NOTCH2 mutation (70% de novo)	10- and 18-years overall survival rates were 92.9% and 90.7% respectively	Presence of any cardiac anomaly and characteristic facies were the most common clinical manifestations, 87% (each), followed by posterior embryotoxon, 45%, butterfly vertebrae, 43% and renal anomalies, 38%. Available MRI and CT reports revealed cerebral and intra-abdominal vascular	10 and 18 years NLS were 69.7% and 56.5% respectively	NR

				anomalies in 36% (n=57/159) and 26% (n=27/105) of the subjects. 79% of the ALGS subjects presented with neonatal cholestasis. 299 liver biopsies reports were reviewed and revealed an increasing frequency of bile duct paucity with age and bile duct plugs in <6% of biopsies <6 months.		
Paez-Escamilla et al 2021[199]	USA	n=3	NR	Three patients with molecularly confirmed Alagille syndrome demonstrated unusual retinal and macular findings, with two showing progressive vision loss. Due to the rarity of retinal findings in AS and the observed progression of disease in our patients,	NR	NR

				clinical genetic testing for retinal dystrophies could be completed in two cases. These investigations failed to reveal a separate molecular cause for the observed retinal dystrophy, helping to confirm the association with JAG1-related AS		
Gill 2021[200]	NR	NR	NR	Identification of a butterfly vertebral anomaly, for example, can help the neonatologist come to the diagnosis of Alagille syndrome sooner rather than later in an infant who goes on to develop jaundice. Alagille syndrome classically involves the triad of intrahepatic cholestasis, pulmonary stenosis with or without	NR	Identification of a butterfly vertebral anomaly, for example, can help the neonatologist come to the diagnosis of Alagille syndrome sooner rather than later in an infant who goes on to develop jaundice. Alagille syndrome classically involves the triad of intrahepatic cholestasis, pulmonary stenosis with or without complex congenital heart disease, and butterfly

				complex congenital heart disease, and butterfly vertebrae. Less common musculoskeletal findings include phalangeal shortening, short ulna, absent 12th rib, and pelvic anomalies		vertebrae. Less common musculoskeletal findings include phalangeal shortening, short ulna, absent 12th rib, and pelvic anomalies
Leung et al 2022[201]	Canada, USA	Between November 2007 and April 2018, 647 of 809 LOGIC participants with native liver were eligible for IQ testing. Two hundred and fifteen children (33.2% of eligible patients) completed testing (ALGS n = 70, PFIC n = 43, A1AT n = 102) at a mean age of 8.2 years (SD 3.8) (Table 1).	NR	In this prospective multi-center study, IQ deficits in children ages 3–16 years with inherited cholestatic liver disorders and native liver were greatest among participants with ALGS. Participants with ALGS scored significantly lower than test norms on the WPPSI-III/WISC-IV in FSIQ, VIQ/VCI, WMI, and PSI, but not PIQ/PRI. In contrast,	NR	NR

			PFIC and A1AT showed fewer IQ deficits.
Molina et al 2022[146]	NR		According to the National Organization for Rare Disorders, the incidence of ALGS is estimated at 1 in 30,000 to 1 in 45,000 births
Li et al 2022[202]	China	n=8 (3f/5m)	The clinical manifestations were adult-onset (62.5%, 5/8), cholestasis (50%, 4/8), butterfly vertebrae (62.5%, 5/8), systolic murmurs (12.5%, 1/8), typical facies (12.5%, 1/8), posterior embryotoxon, and renal abnormalities (0/8). Genetic sequencing showed that all patients had mutations, with four occurring in the JAG1 gene and four in the NOTCH2 gene. Six were

			substitution mutations, one was a deletion mutation, and one was a splicing mutation. Five had been previously reported; but the others, one JAG1 mutation and two NOTCH2 mutations were unique and are reported here for the first time.	
Gopal et al 2022[203]	Various (Systematic review)	135 articles, including 785 patients	Posterior embryotoxon was the most common presenting pathology, followed by disc drusen. Com- mon posterior pathologies include optic drusen, pigmented retinopathy, angulated retina vessels and chorioretinal atrophy. Uncommon findings include moya moya, intra-cranial haemorrhages and idiopathic intracranial hypertension. Ocular	Alagille syndrome is a complex genetic disorder with variable manifestations. Ocular pathologies should be taken in context with systematic pathologies for diagnosis

				pathologies are unlikely related to fat soluble vitamin deficiency. Diagnosis can be carried out by Jag1 and notch2 gene testing, with ultrasound detection of optic drusen a sensitive modality. Medical management includes ursodeoxycholic acid, fat soluble vitamin supplementation and cholestyramine, with surgical management including liver transplantation	
Vandriel et al 2023[204]	29 Countries	a total of 1543 children with ALGS were reported in the GALA database. Of these subjects, 110 (7%) did not meet the study eligibility criteria and were excluded from further analysis. The study cohort consisted of 1433 (57%	A survival analysis was performed to compare overall survival in ALGS with (n = 1184) and without (n = 203) a history of neonatal cholestasis. A Kaplan–Meier analysis showed the cumulative rate of survival at 10 and 18 years was significantly lower in children	This analysis of the GALA data set provides insights into the natural history of liver disease and outcomes of this complex disorder. In this real-world global view, 40% of children with ALGS-cholestasis reached adulthood with	To determine the rate of NLS, LT, or risk of death without LT in those with a history of neonatal cholestasis (n = 1184), a competing risk analysis was performed to

male) clinically and/or genetically confirmed children with ALGS, with a median follow-up of 6.0 years (IQR, 2.5–12.2). The largest number of patients were ascertained from Europe, 34% (n = 487), followed by North America, 29% (n = 420), and Asia, 23% (n = 333). Evaluable results of molecular genetic testing were available in 62% (n = 892/1433) of patients with ALGS and a pathogenic variant in JAG1 or NOTCH2 was identified in 98% (n = 878/892). Among genotyped patients, 2% (n = 14) were negative for a pathogenic variant in JAG1 or NOTCH2, despite meeting clinical criteria for ALGS (≥3 with ALGS who presented with neonatal cholestasis in comparison with those who did not (log-rank p < 0.001). The 10 and 18-year patient survival rates in patients with ALGS presenting with cholestasis were 89% and 86% compared with 100% and 97%, respectively their native liver. A competing risk analysis revealed that this rate of NLS is largely driven by LT and, perhaps surprisingly, not death, despite the multisystem nature of this disorder with substantial cardiac involvement. As expected, heterogeneity in rates of NLS was observed across geographic regions and likely represents differences in allocation policies and clinical resources. The burden of liver disease is greatest among young children, with the median age of LT being only 2.8 years and almost three-quarters of all LTs occurring in the first 5 years of life. The majority of early LTs occur because of complications evaluate the risk of each of these three independent outcomes. At 5, 10, and 18 years, the rate of NLS was 66.8%, 54.4%, and 40.3%. The cumulative incidence of LT at 5, 10, and 18 years was 27.1% (95% CI, 24.3–30.1), 37.8% (95% CI, 34.2–41.3), and 50.4% (95% CI, 45.4–55.2). The 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). There were no significant differences between male and female patients in terms of

clinical characteristics). The majority of ALGS cases were de novo (56%).

associated with cholestasis, including pruritus, with a smaller number occurring later in childhood due to the onset of PHT. The NLS of 40% at 18 years is higher than the 24% rate recently reported by the Childhood Liver Disease Research Network (ChiLDReN), which is composed of North American tertiary referral centers and therefore may select a more severely affected group of patients.[6] In addition to LT, a time to first adverse liver-related event analysis demonstrates the extent of clinically significant liver comorbidities occurring during childhood, with more than 60% of children experiencing

NLS rates (log-rank, p = 0.35). Rates of NLS were significantly different across the seven geographic regions (log-rank, p < 0.001; A surgical BD was reported in 5% (n = 56/1184) of children with ALGS, at a median age of 2.4 years (IQR, 1.9–4.4; n = 53). NLS rates in patients with ALGS who underwent a surgical BD, revealed a 1.9-fold greater risk of LT/death (95% CI, 1.3–3.0; p < 0.001).

					an adverse liver event during the study period	
Yongguang et al 2022[205]	China	NR				Mutations in Notch ligands, Notch receptors, and upstream and downstream genes of Notch are closely associated with many metabolic bone diseases, such as Alagille syndrome. The Notch signaling pathway forms a precise molecular regulatory network around upstream proteolytic enzymes and downstream NICD molecules, which plays an important role in regulating bone metabolism and maintaining normal physiological functions of bone. Some important gene mutations in the Notch signaling pathway can promote the metabolic imbalance of osteoblasts, osteoclasts, chondrocytes

				and other cells, and ultimately lead to the occurrence of metabolic bone diseases
Lan et al 2022[206]	USA	n=4 (ALGS)	In patients with Williams and Alagille syndromes, extensive transcatheter intervention is required to sufficiently reduce PA pressures and right ventricular stroke work. Transcatheter therapy was shown to be ineffective for long-segment stenosis and pales hemodynamically in comparison with published outcomes of surgical reconstruction. Regardless of the chosen strategy, a virtual treatment planning platform could identify lesions most critical for optimizing	

				right ventricular afterload.
Black et al 2022[207]	USA	156 LT recipients with ALGS were age-matched with 312 LT recipients with BA	Despite increased rate of congenital heart defects, higher creatinine, and higher MELD/PELD scores at time of transplant, this study demonstrates that there is no difference in either patient or graft survival between patients with ALGS and BA	Children with ALGS had higher laboratory model MELD/ PELD scores (median: 14.0 vs. 8.0; $p < 0.001$) and were more likely to have a diagnosis of congenital heart disease (80.7% vs. 16.4%; $p < 0.001$). Forty (25.6%) children with ALGS required some type of cardiac intervention (catheter or surgical) either before or after LT, with 19 (12.2%) of them receiving more than one intervention. Serum creatinine at the time of transplant was higher in patients with ALGS (0.37 vs. 0.30mg/dL; p= <0.001). No difference was

				observed regarding patient or graft survival between children with ALGS and children with BA (log-rank test, p = 0.08 and p = 0.27, respectively). The post-LT length of stay was longer for children with ALGS compared to children with BA (median: 16.0 days vs. 13.0 days; p = 0.006)
Habash et al 2023[208]	29 countries (GALA)	1433 pediatric patients from the GALA study with clinical or genetically confirmed ALGS diagnoses born between 1997 and 2019 were enrolled,	Graft survival rate was 83% at 18 years, and patient survival rate was 88% at 20 years following liver transplant. This rate of long-term graft survival was achieved through careful selection of liver graft recipients and a multidisciplinary approach. Despite that, the long-term posttransplant survival rates continue to be lower than other common indications of liver transplantation	The authors report a previously unrecognized significant liver disease burden with 95% of all the patients having liver involvement at any given time, 85% having neonatal cholestasis, and 24% having xanthomas. Previous studies indicated that between 20% and 75%

in the pediatric population (e.g., biliary atresia)	of patients with ALGS require liver transplantation.[3,5] In contrast, in this study, 40% of the patients reached adulthood with their native liver, which is higher than the previously reported native liver survival rate.[3] The median age of liver transplantation was 2.8 years, and 72% of liver transplantation occurred in patients younger than 5 years of age. Cholestasis and its sequelae (pruritus, xanthomas, and fat-soluble vitamin deficiency) were the leading indication of liver transplantation followed by clinically evident portal hypertension

Leonardi et al 2023[209]	Italy	232 patients underwent PLT; excluding patients with combined transplantation, intra-operative death and incomplete follow-up, 130 patients were regularly followed.	At the end of follow-up, 90 patients were alive. Among the remaining 40 patients 13 died within 3 months from LT. Excluding perioperative deaths, patient-survival rates at 1, 5, 10 and 20 years after LT, were 91.7%, 84.3%, 80.2% and 74.4% respectively.	
Ranucci et al 2022[210]	Italy	Position statement		Alagille syndrome - laboratory hallmarks and biomarkers: High GGT, sBA, cholesterol and triglycerides. Gene JAG1, NOTCH 2. Physical examination findings of an infant with cholestatis jaundice and Alagilles: Dysmorphic features (rarely exhibits characteristic facial anomalies before age of 6 months). Cardiac examination: murmur/congenital cardiac malformations; a systolic murmur audibles from the back. Acholic stools, totally decoloured with clay-like

aspect are the strongest argument to suspect a biliary obstructive disease but can be observed in only a few other diseases, notably Alagille syndrome (AGS), alpha-1-antitrypsin deficiency (A1ATD), and cystic fibrosis. Testing of CPK, BUN, creatine, Ca/P, AFP∗, lipid profile (C, C-LDL, C–HDL, triglycerides) To analyse systemic involvement and suspect the presence of a metabolic conditions; high levels of C in Alagille syndrome. Skeletal xray - spinal abnormalities (such as butterfly vertebrae). some conditions such as Alagille syndrome and cystic fibrosis is reported causes of false positive intraoperative cholangiogram, and should be excluded before surgical exploration, as mistakenly

			performed HPE may worsen their condition
Mainwaring 2023[211]	USA	This study was to evaluate the impact of liver dysfunction in children with Alagille syndrome undergoing congenital heart surgery. The data indicate that patients with significant liver dysfunction had a four-fold higher relative risk of mortality	Ten patients have subsequently undergone liver transplantation following repair of their congenital heart defect. All 10 patients had moderate or severe liver dysfunction. Since there were 26 patients in this category and a total of 8 operative or late deaths (leaving 18 mid-term survivors), 55% of survivors underwent liver transplantation. There have been no late deaths in patients following liver transplantation. Three additional patients have

				undergone biliary drainage procedures for the palliation of symptoms.	
Black et al 2022b[207]	USA	156 LT recipients with ALGS were identified and matched to a control group of 312 recipients with BA	No difference was observed regarding patient or graft survival between children with ALGS and children with BA (log-rank test, P = 0.08 and P = 0.27, respectively; Fig. 1). The benchmark point estimates of unadjusted cumulative 1-, 3-, and 5-year patient survival is 95.2%, 94.2%, and 94.2% in ALGS and 97.9%, 97.5%, and 97.5% in BA. When comparing patient and graft survival based on type of graft (living donor, deceased donor whole liver, deceased donor partial/split liver), there was no difference between children with ALGS and BA (log-rank test, P = 0.11 and P = 0.20, respectively; Fig. 1). There was no difference in survival when stratified on sex (P = 0.1). There was no difference seen in patient or graft survival between the linked database ALGS		

			population compared to those patients only in the SRTR ALGS population (log-rank test, P = 0.25 and P = 0.19, respectively; Digital Content 3, http://links.lww.com/MPG/C854). Eight patients with BA and 9 patients with ALGS died during the observed period. Four patients (1.3%) with BA and four patients (2.6%) with ALGS died within 30 days post-LT. Cause of death for 1 patient with ALGS and 1 with BA was coded for as “cardiac: other specify” and “cardiac arrest,” respectively. There were 3 ALGS and 1 BA patients that did not have a specific cause of death with the assigned code of “other specify.” In the other patients (5 ALGS and 6 BA patients), cardiac disease was not the cause of death.	
Hahn et al 2024	South Korea	N= 148 with neonatal cholestasis. Of the total 148 patients examined, 49 (33.1%) were received a confirmed		First, patients suspected of having neonatal intrahe-patic cholestasis are examined to rule out any abnormalities usingthe

		geneticdiagnosis, including 14 (9,5%) with Alagille syndrome.			following evaluations: medical history, vital signs, NST, C-reactive protein level, thyroid function test, infection, and meta-bolic disease. Consequently, single-gene testing is consideredwhen clinical symptoms suggest specific diseases such as DJS, NICCD, ALGS, and ARC syndrome. ALGS and NICCD are identified as the primary genetic causes of neonatal intrahepatic cholestasis in the Korean cohort. ALGS diagnosis heavily relies on JAG1 and occasionally NOTCH2 mutations, which can present variably, underscoring the importance of a tailored diagnostic approach
Lemoine et al 2023	USA	N=13 with a diagnosis of ALGS.	One and 5-year, and overall patient survival were 92%, 92%, and 85%: one death occurred in the patient with pulmonary hypertension while	Overall graft survival was 79%, with 2 graft losses to primary non function and one to	

			the second occurred in a patient 6.9 years after LT (graft functional at time of death). Overall graft survival was 79%, with 2 graft losses to primary non function and one to patient death. The 1-year, 5-year, and overall graft survival for first LT were 92%, 92%, and 85% respectively. Donor hepatic artery to recipient aorta anastomosis provides reliable arterial inflow, but unlike previous reports, direct hepatic artery to hepatic artery anastomosis including live donor transplants appear to be reliable in our experience.	patient death. The 1-year, 5-year, and overall graft survival for first LT were 92%, 92%, and 85% respectively. Outcomes after liver transplant for Alagille's syndrome have improved: 1- and 5-year patient and graft survival exceed 90% for first transplants.
Sokol et al 2023	Multinational	Pediatric patients with ALGS and cholestatic pruritus, with a median age of 70 months and weight z-score of −1.41	Two deaths were reported among 76 participants over six years, contributing to a 3% mortality rate	At six years, the EFS rate was 76%, and the TFS rate was 79% for patients treated with maralixibat. Lower bilirubin and sBA levels at week 48 correlated with better native liver survival rates

Semenova et al 2023	Russia	The study included 18 patients (12 boys and 6 girls) diagnosed with cholestatic liver disease associated with ALGS. The median age at diagnosis was 21 months, with a range from 2 months to 142 months. The age of onset varied from 5 days to 24 months, primarily occurring in the first month of life	ALGS is caused by pathogenic variants in the JAG1 or NOTCH2 genes, leading to cholestatic liver disease characterized by bile duct paucity. The disease presentation can be variable, and not all patients meet the classical diagnostic criteria. A high frequency of cholestatic liver disorder (89-100%) was observed in the cohort	Diagnosis of ALGS typically involves identification of bile duct paucity alongside at least three of the following five criteria: cholestasis, cardiac defects, skeletal abnormalities, ophthalmologic abnormalities, and characteristic facial features. In this study, only six out of 18 patients met the diagnostic criteria without genetic analysis
Joung et al 2023	South Korea	21 pediatric patients with Alagille syndrome (ALGS) under 18 years old.	Renal involvement in ALGS includes renal dysplasia, nephrocalcinosis, nephrolithiasis, vesicoureteral reflux, and renal tubular acidosis. The study found a progression to CKD in 50% of patients with renal involvement.	Diagnosed by clinical manifestations, targeted JAG1 sequencing, and/or liver biopsy.

Murillo Perez et al 2023	NR	The study focuses on patients with Alagille Syndrome (ALGS), specifically those experiencing neonatal cholestasis and who have at least one recorded serum bile acid (SBA) measurement during follow-up. The initial cohort (GALA) included 1,525 patients, with 570 meeting the study's inclusion criteria (348 males and others with missing data on gender).		The study reports native liver survival (NLS) rates among patients, showing a gradual decline over time: 97.2% at 1 year, 81.8% at 5 years, 67.3% at 10 years, 59.3% at 15 years, and 53.6% at 18 years.
Czubkowski et al 2023	Poland	Total of 20 children, predominantly male (15 males, 5 females). All diagnosed with Alagille syndrome (AGS) and experienced severe cholestasis from infancy, necessitating liver transplantation due to progressive disease.	The study reported a mortality rate of 5%, with one patient dying from intra-abdominal haemorrhage in the early post-transplant period.	The median age at transplantation was 6.2 years, with a range of 1.5 to 11.8 years. Post-transplant complications included portal vein stenosis in three patients and hepatic artery thrombosis in two patients. Despite early complications,

					the study reported a long-term patient survival rate of 94%, with significant improvements in growth and weight gain post-transplant. Long-term outcomes indicated that all surviving patients maintained normal graft function and experienced no significant extrahepatic complications, underscoring the effectiveness of transplantation in managing AGS.	
Wang et al 2023	China	Genetically confirmed Alagille syndrome (ALGS) patients with JAG1 mutations. Patients included were diagnosed > one year of age	Mortality data includes the death of two patients under one year of age in the discovery cohort and two more in the validation cohort at nine months and two years and ten months, respectively. Patients with GHCA levels below 607.69 nmol/L	ALGS is caused by mutations in JAG1 or NOTCH2, with JAG1 mutations accounting for around 95% of cases. The condition is autosomal dominant	Good prognosis was associated with native liver survival, with GHCA concentrations above 607.69 nmol/L linked to an increased	Diagnosis of ALGS was based on genetic confirmation of JAG1 variants and standard clinical criteria, including bile duct paucity and the presence of three major

			had a higher rate of death or need for liver transplantation compared to those above this threshold	and impacts multiple organs, with a variable clinical presentation, often including liver disease requiring transplantation. Prognosis is influenced by bile acid composition, with enhanced hydroxylation processes potentially leading to better outcomes	likelihood of surviving with the native liver. This biomarker's predictive accuracy reached 88.00% in the validation cohort	clinical features or at least four out of six features (e.g., cholestasis, cardiac murmur, skeletal abnormalities)
Yan et al. 2024	China	17 children diagnosed with ALGS	Reported mortality rate can reach up to 10%, but none of the patients in this study died during follow-up	Cholestasis was the most common symptom (94%), followed by characteristic facies (88%) and heart disease (75%). Butterfly vertebrae appeared in 71%, and posterior embryotoxon was found in 58% of patients examined. Growth retardation was observed in 53% of patients. Genetic	though two cases required liver transplantation	NR

testing showed pathogenic variants in the JAG1 gene for most patients

J.1.3 Excluded full text references

Please refer to section “H.1.3 Excluded full text references” since all the excluded references from the Original and SLR updates are included in that section.

J.1.4 Quality assessment

Please refer to section “H.1.4 Quality assessment” since the same quality assessment process was used for the review question number 7 (Epidemiological SLR).

J.1.5 Unpublished data

Not applicable.

J.1.6 Targeted literature search for [estimates]

Not applicable.

Table 102 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
D’Amico et al [77] (D'Amico, G., G. Garcia-Tsao, and L. Pagliaro, Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol, 2006. 44(1): p. 217-31.)	Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies - PubMed	Retrieved through a targeted literature search in PubMed using the following search terms: ("cirrhosis" AND "natural history" AND "prognostic indicators") with filters applied for systematic reviews and studies published in high-impact hepatology journals.	05.11.2024
Santambrogio et al [78] (Santambrogio, R., et al., Hepatic resection for hepatocellular carcinoma in	Hepatic resection for hepatocellular carcinoma in patients with Child–Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? - PMC	Identified through a targeted literature search focusing on hepatic resection outcomes in cirrhotic patients. Search terms included ("hepatic resection" AND "portal	07.09.2024

Source name/ database	Location/source	Search strategy	Date of search
patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindicatio n? HPB (Oxford), 2013. 15(1): p. 78-84.)		hypertension" AND "Child-Pugh A"), with results refined to studies in indexed hepatobiliary journals.	
Tonon et al [79](Tonon, M., et al., Outcomes and Mortality of Grade 1 Ascites and Recurrent Ascites in Patients With Cirrhosis. Clin Gastroenterol Hepatol, 2021. 19(2): p. 358-366 e8.)	Outcomes and Mortality of Grade 1 Ascites and Recurrent Ascites in Patients With Cirrhosis - PubMed	Selected through a focused literature search on ascites-related outcomes in cirrhosis. Search terms included ("ascites" AND "cirrhosis" AND "mortality"), with filters applied for studies published in hepatology and gastroenterology journals within the past five years.	12.10.2024
Hou et al [80](Hou, Y., et al., Survival and Complication of Liver Transplantation in Infants: A Systematic Review and Meta-Analysis. Front Pediatr, 2021. 9: p. 628771.)	Frontiers | Survival and Complication of Liver Transplantation in Infants: A Systematic Review and Meta-Analysis	Identified through a targeted search for systematic reviews on liver transplantation in infants. Search terms included ("infant liver transplantation" AND "survival" AND "meta-analysis"), with results prioritized from pediatric and transplant-focused journals.	07.08.2024
Baumann [81] (Baumann, U., et al., Prognosis of Children Undergoing Liver Transplantation : A 30-Year European Study.	Prognosis of Children Undergoing Liver Transplantation: A 30-Year European Study - PubMed	Retrieved from a structured search in pediatric transplant literature. Search terms included ("pediatric liver transplantation" AND "long-term prognosis" AND "30 years"), with results screened from	07.08.2024

Source name/ database	Location/source	Search strategy	Date of search
Pediatrics, 2022. 150(4).)		high-impact pediatric journals.	

Below is a Table presenting the clinical publications identified in the Clinical SLR. Additionally, the rationale for the use or non-use of these clinical publications in the CUA model is explained.

Table 103 Summary of clinical publications identified in the SLR (N=25) and the rationale for their use or non-use in the CUA model

Trial name	Reference	Publication type	Intervention(s)	Study design	Included in model	Rationale for use/non-use in model
ICONIC with open-label follow-up	Gonzales et al. 2019 [113]	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 [17] (e.g. the impact on biochemical markers of cholestasis, growth, xanthoma severity, and QoL) is explored in Section 6, as this provides a holistic
	Gonzales et al. 2019 [114]	Abstract				
	Foster et al. 2020 [118]	Abstract				
	Gonzales et al. 2020 [119]	Poster				
	Gonzales et al. 2021 [120]	Full paper				
	Gonzales et al. 2021 [17]	Full paper				

						overview of the patient-impact of maralixibat treatment. However, this data is 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.
GALA Cohort Comparison Study	Hansen et al 2024 [48]	Full paper	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.
IMAGINE	Baker et al. 2017 [112]	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 was omitted. A scenario is provided with safety data collected across all MRX dose groups.
ITCH	Shneider et al.2017 [121]	Abstract	Maralixibat (70	Phase 2 RCT		ICONIC was used as the primary source of input

	Shneider et al. 2018 [122]	Full paper	µg/kg/day, 140 µg/kg/day, 280 µg/kg/day) Placebo		Yes (scenario)	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.
N/A	Kronsten et al. 2011 [116]	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 program, and as such cannot be used to inform comparative effectiveness.
	Kronsten et al. 2013 [19]	Full paper				
N/A	Thebaut et al. 2017 [117]	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 uses 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 [115]	Abstract	Maralixibat (66.5 µg/kg/day to 380	Pooled analysis of ITCH/IMAGINE II,	No	There were no major differences between safety outcomes of ICONIC and this pooled

			µg/kg/day, 380 µg/kg twice daily) Placebo	IMAGO/IMAGINE, and ICONIC with open-label follow-up		analysis – as a result, ICONIC was selected in the base-case and no additional scenario was provided.
N/A	Raman et al 2021 [128]	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 [125]	Poster	Maralixibat	Outcomes of patients in the maralixibat Expanded Access Program	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 [91]	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 [123]	Full paper	N/A	Application of eligibility criteria from ITCH to a prospective	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.

				longitudinal cohort study of children with cholestasis (LOGIC)		
N/A	Shneider et al 2022b [129]	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.
MRX-EAP	Himes et al 2023	Full paper	Maralixibat	Outcomes of patients in maralixibat EAP and commercial programs	No	This study provides case reports for eight patients only, and as such is not robust enough to be relevant to this submission.
Non-RCT	Sokol RJ et al 2023	Full paper	Maralixibat	Predictors of event-free survival (EFS) in patients from ITCH, IMAGINE II and IMAGO with up to 6 years of follow-up.	No	Only predictors of EFS were assessed thus it was not incorporated in the model.

Appendix K. Clinical expert opinion letter

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Appendix L. Danish clinical expert feedback

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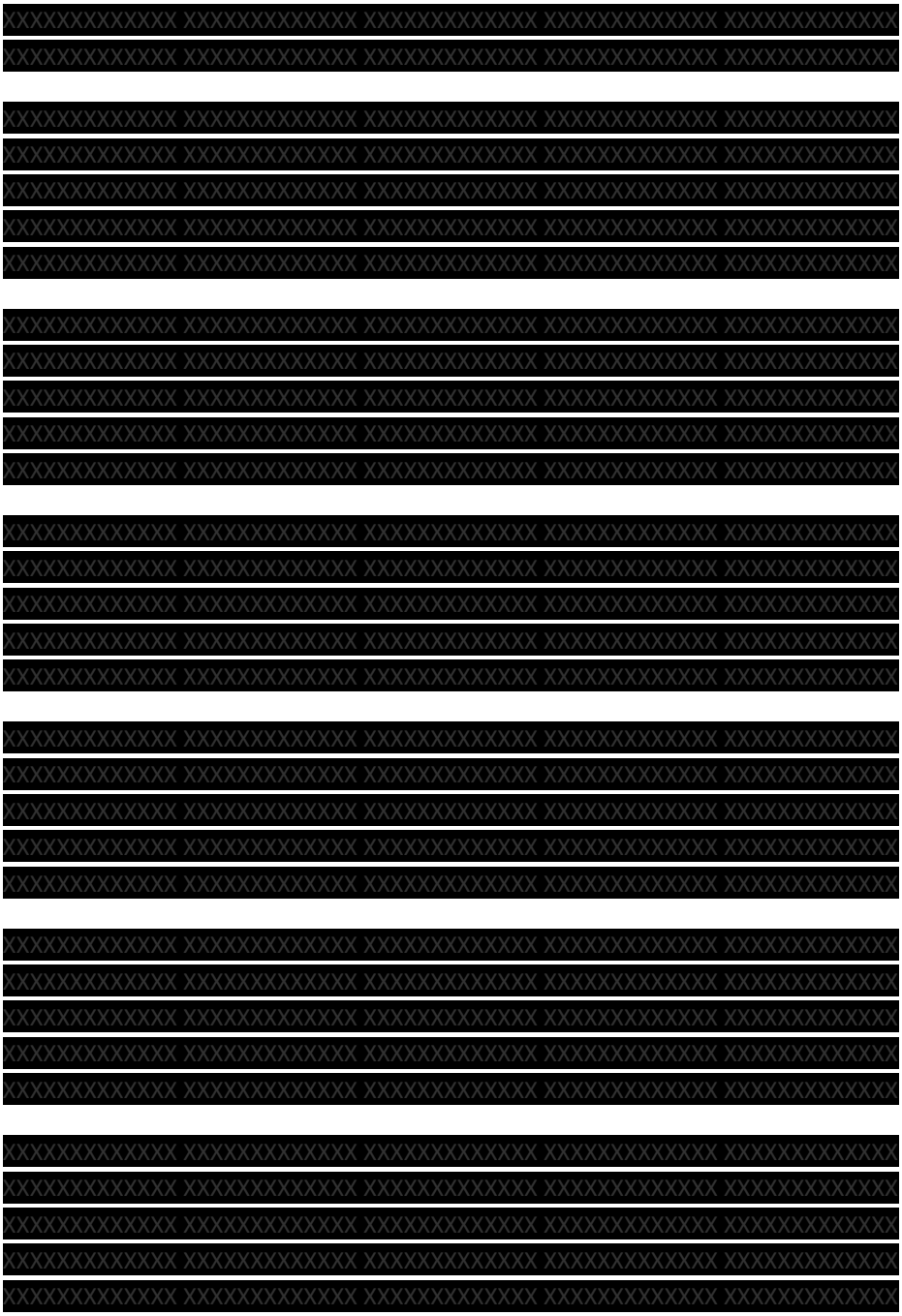

Table 104 XXXXXXXXXXXXX

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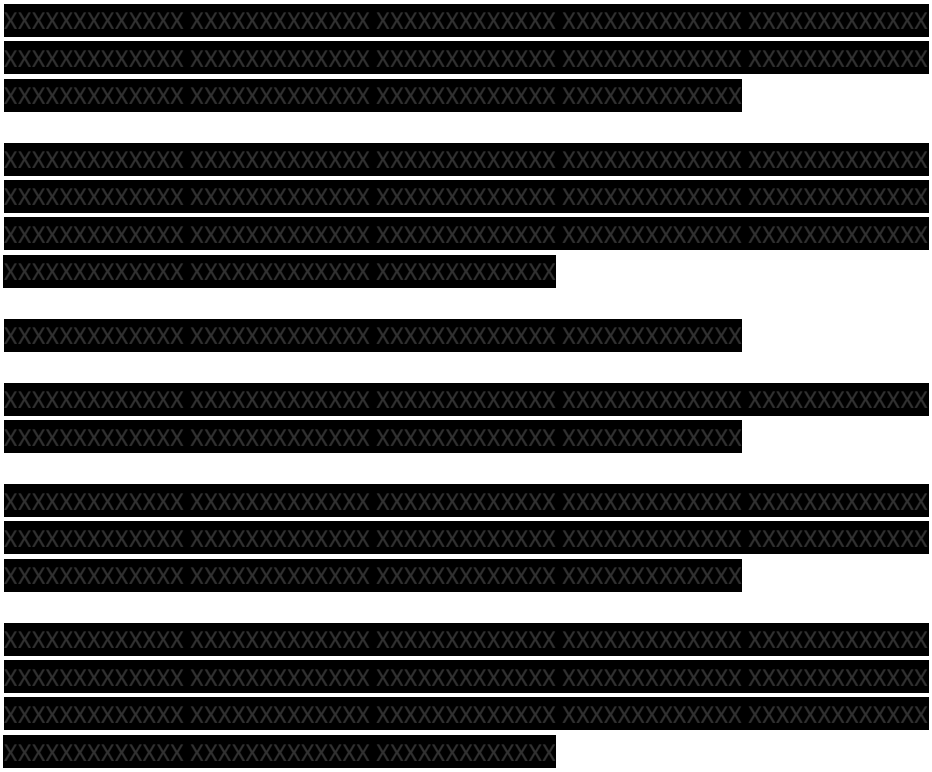

Appendix M. Swedish clinical expert feedback

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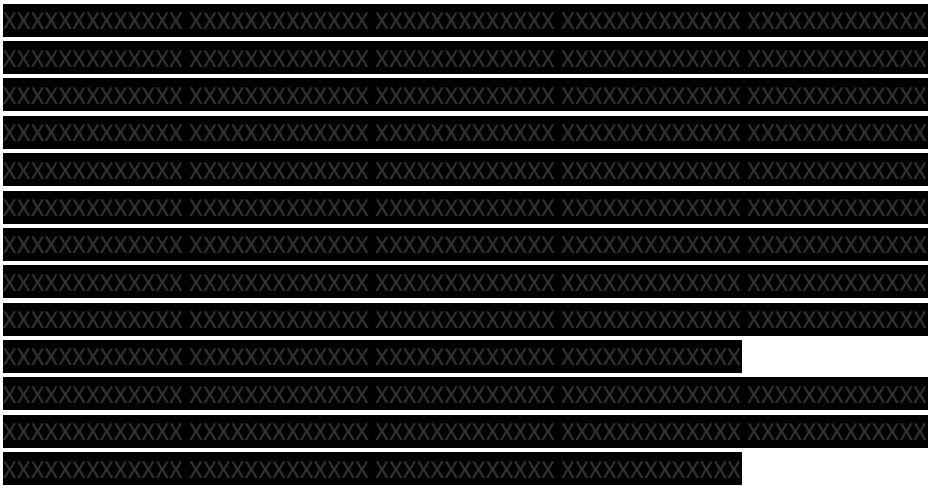

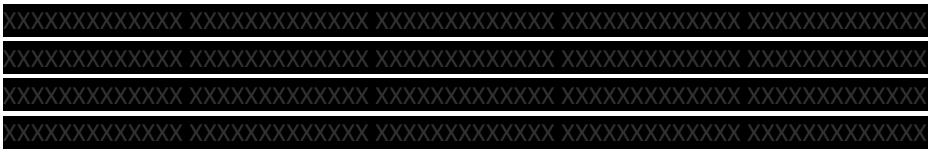

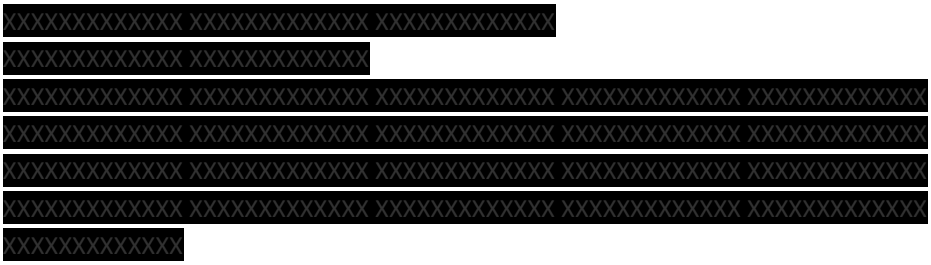

Appendix N. Lab tests included in the model

Table 105 Costs of lab tests related to ALGS included in cost effectiveness model

Lab test	Unit cost (DKK)	Source
Serum bilirubin cv	14	RH Laboratorieundersøgelse
Serum Bile acid	14	RH Laboratorieundersøgelse
complete blood count	18	RH Laboratorieundersøgelse
Alanine aminotransferase (ALT)	14	RH Laboratorieundersøgelse
Alpha fetoprotein (AFP)	45	RH Laboratorieundersøgelse
Gamma glutamyl transpeptidase	16	RH Laboratorieundersøgelse
Aspartate aminotransferase (AST)	16	RH Laboratorieundersøgelse
Prothrombin	1.157	RH Laboratorieundersøgelse
Glucose	14	RH Laboratorieundersøgelse
Albumin	14	RH Laboratorieundersøgelse
Vitamin A, E, D, K status	592	RH Laboratorieundersøgelse
TSH	33	RH Laboratorieundersøgelse

Appendix O. Supporting evidence

O.1 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, support the use of maralixibat as an efficacious and well-tolerated treatment for ALGS.

Please see Table below for more details about the methodology together with a summary of the efficacy and safety of the IMAGO/IMAGINE and ITCH/IMAGINE II studies.

Table 106 Summary of methodology of the IMAGO/IMAGINE and ITCH/IMAGINE II studies

	IMAGO [104]	IMAGINE [105]	ITCH [106]	IMAGINE II [107]
Trial design	Randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of 13 Weeks of treatment with maralixibat in pediatric patients with ALGS	Multicenter, double-blind study of maralixibat in children >12 months of age diagnosed with ALGS who have completed participation in IMAGO	Randomized, 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 consecutive	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.	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 consecutive Weeks in the screening	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 experienced an AE

	Weeks in the screening period prior to randomization. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15× ULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhea requiring specific intravenous fluid or nutritional intervention, were excluded.	Participants must not have 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.	period prior to randomization. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15× ULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhea requiring specific intravenous fluid or nutritional intervention, were excluded.	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 centers in the United States and Canada.	This study was conducted in 11 centers 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	Daily dosing of maralixibat occurred over up to 252 Weeks of treatment and consisted of an initial dose escalation period followed by a dose optimization period, stable dosing period, and long-term follow-up treatment period.	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 optimization period, stable dosing period, and long-term follow-up treatment period. Subjects received either 35 µg/kg/day, 70

	randomly assigned to receive 70 µg/kg/day, 280 µg/kg/day, or placebo.	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.		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 score of the ItchRO (Obs), and PedsQL.	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.
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.

O.1.1 ITCH (LUM001-301) and IMAGINE II (LUM001-305)

ITCH (LUM001-301) [106] is a Phase 2, randomized, double-blind, placebo-controlled, parallel group, multicenter 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 randomization. Subjects with surgical interruption of the enterohepatic circulation, LTx, ALT >15xULN, decompensated cirrhosis, history or presence of other concomitant liver disease, or chronic diarrhea 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) [107] was a long-term extension study based on the participants enrolled in ITCH (LUM001-301). In ITCH, participants were randomized 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 optimization period, a stable dosing period, a safety monitoring period, and 2 long-term optional follow-up treatment periods. Participants randomized 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 optimization 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 pediatric 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: -2.257; SD=0.7519; p-value=0.0026). 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 -0.976 (Week 2) to -2.257 (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.

O.1.2 IMAGO (LUM001-302) and IMAGINE (LUM001-303)

ITCH IMAGO (LUM001-302) [104] is a Phase 2, randomized, 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 randomization. Two dose cohorts were considered, with eligible subjects 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) [105] 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 pediatric 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 randomized 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 optimization 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 randomized 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 ($p \leq 0.05$) 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.

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