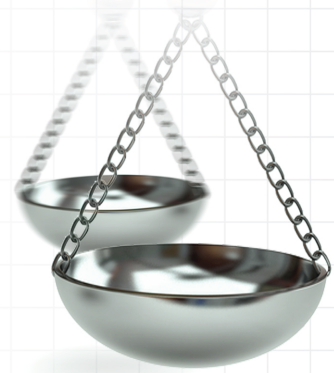
Systematic Review

For reprint orders, please contact: info@becaris.com



Journal of **Comparative Effectiveness Research**

The burden of Alagille syndrome: uncovering the potential of emerging therapeutics – a comprehensive systematic literature review

Philip Bufler[1,2], Robin Howard[3], Lucia Quadrado[3], Guy Lacey[3], Jolan Terner-Rosenthal[3], Andrea Goldstein[3], Pamela Vig[3] & Deirdre Kelly*[,4,5]

[1]Department of Pediatric Gastroenterology, Nephrology & Metabolic Diseases, Charité – Universitätsmedizin Berlin, Berlin, Germany

[2]German Center for Child & Adolescent Health (DZKJ), partner site Berlin, Berlin, Germany

[3]Mirum Pharmaceuticals, Inc., Foster City, CA, USA

[4]Guy's & St Thomas' NHS Foundation Trust, London, UK

[5]Evelina London Women's & Children's Clinical Group, Evelina London Children's Hospital, London, UK

*Author for correspondence: Tel.: +44 121 454 0507; deirdrekelly@nhs.net

Aim: Alagille syndrome (ALGS) is a rare, cholestatic multiorgan disease associated with bile duct paucity, leading to cholestasis. Clinical symptoms of cholestasis include debilitating pruritus, xanthomas, fat-soluble vitamin deficiencies, growth failure, renal disease and impaired health-related quality of life (HRQoL). The main objective was to review the current literature on the epidemiological, clinical, psychosocial and economic burden of ALGS in view of the development of ileal bile acid transporter (IBAT) inhibitors. **Methods:** Electronic literature databases were searched in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. **Results:** 330 publications were screened, 119 were relevant: 11 randomized controlled trials (RCTs), 21 non-RCTs, 10 HRQoL studies, two studies assessing cost/resource use and 77 epidemiological studies across several databases through 31 July 2024. Studies confirm that patients with ALGS experience cardiac anomalies, impaired growth, renal disease, poor HRQoL, fat-soluble vitamin deficiencies and debilitating pruritus; until the approval of IBAT inhibitors for the treatment of cholestatic pruritus in patients with ALGS, supportive management was the standard of care. **Conclusion:** This review confirms the substantial clinical, economic and HRQoL burden associated with ALGS and consolidates current treatment evidence. Data from recent trials in ALGS demonstrate the potential impact of IBAT inhibitors to transform lives by improving cholestatic pruritus symptoms, HRQoL and native liver survival.

Plain language summary: understanding the impact of Alagille syndrome and the promise of new treatments

What is this article about? This article is about Alagille syndrome (ALGS), a rare disease that affects multiple organs and leads to bile duct problems, causing symptoms like severe itching, poor growth, kidney disease, vitamin deficiencies and low quality of life. The main goal of the review was to examine the impact of ALGS on patients' health and well-being and consider how a new treatment class, called ileal bile acid transporter (IBAT) inhibitors, could help.

What were the results? The researchers reviewed 330 publications, which were narrowed down to 119 relevant studies. These included clinical trials, quality of life studies and cost/resource studies. The findings confirm that people with ALGS experience a range of serious issues, including heart problems, poor growth, kidney disease and debilitating itching. Before the approval of IBAT inhibitors, treatment mainly focused on managing symptoms.

What do the results of the study mean? The review concludes that ALGS causes significant health, economic and quality of life challenges for patients. However, recent research shows that IBAT inhibitors could dramatically improve symptoms like itching, overall quality of life and liver health in these patients, offering hope for better management of the disease.

First draft submitted: 30 September 2024; Accepted for publication: 17 December 2024; Published online: 14 January 2025

Keywords: Alagille syndrome • ALGS • cholestasis • health-related quality of life • pruritus

Alagille syndrome (ALGS) is a rare, life-threatening, multisystem disease that typically presents in the first three months of life with a range of clinical manifestations, including cardiac, renal, liver, neurological and vascular disorders. The reported incidence of ALGS is 1 in 30,000 to 50,000 live births [1,2,3]. Liver-related manifestations, including cholestasis, pruritus, growth deficits, xanthomas and progressive liver disease, present in infancy and may lead to liver transplantation or death in childhood [4,5,6]. ALGS occurs due to variants/deletions in two genes, *JAG1* and *NOTCH2*, associated with the Notch signaling pathway [1,2,3]. Due to the diverse roles of Notch signaling, disruption of either gene results in a broad range of clinical manifestations as described above [7].

ALGS-associated cholestatic liver disease often presents with debilitating and intractable pruritus requiring liver transplantation, even in the absence of liver failure [8]. Cholestasis is defined as "*an acute or chronic hepatobiliary condition in which the formation, secretion or flow of bile is impaired*" [9]. Pruritus, a common and severe symptom of cholestasis and the leading indication for liver transplantation, affects up to 88% of children with ALGS, with the first recognizable symptoms occurring as early as 6 months after birth [10]. It is also possible that pruritic symptoms develop before 6 months of age, but this time frame is the earliest that infants begin to demonstrate behaviors consistent with pruritus (e.g., scratching and rubbing). Xanthomas are a uniquely burdensome presentation of ALGS, occurring in 24–42% of patients with ALGS; the presence of xanthomas is an indication for liver transplantation in approximately half of the liver transplant recipients with ALGS [1,10,11]. Cardiac manifestations range from heart murmurs to structural defects, occurring in almost all individuals with ALGS (97%) [12]. Complex congenital heart disease can be the most significant indicator of early mortality [3]. Ophthalmic features affecting the cornea, iris and retina are also present, with posterior embryotoxon being the most common. Renal complications are also common in ALGS, with renal dysplasia being the most prominent anomaly [8]. This, in addition to characteristic facies and butterfly vertebrae, constitutes a wide range of features that are frequently present, however not required for diagnosis [1].

There are a limited number of peer-reviewed published clinical studies in ALGS due to the rarity of the disease. Since the publication of the only available systematic literature review back in 2018 [1], results of several new clinical trials have become available as has new information on the economic and societal burden of ALGS [13,14,15,16]. The purpose of this literature review is to provide a comprehensive summary of the epidemiology, health-related quality of life (HRQoL) burden of ALGS, current standard of care and impact of new therapies (i.e., ileal bile acid transporter [IBAT] inhibitors) for the treatment of cholestatic pruritus in ALGS.

Materials & methods

A literature review was conducted to identify the epidemiological, clinical, psychosocial and economic burden of ALGS. The full list of research questions to be answered is presented in Appendix A.

Searches to identify evidence for all seven review questions were conducted on 13 April 2022, in the following databases: Embase, MEDLINE, Embase Classic, Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library), Cochrane Clinical Answers, Centre for Reviews and Dissemination (CRD) Health Technology Assessment (HTA) Database, CRD National Health Service (NHS) Economic Evaluation Database (EED), School of Health and Related Research Health Utilities Database (ScHARRHUD) and EuroQol database. Supplementary searches of any publications not produced by commercial publishers ('grey' literature) were also performed. An update to the search was performed and included additional references published up to 16 May 2023. A final update to the search was performed on 31 July 2024 and included additional references published up to this date. The full search strategy is presented in Appendix B.

All references identified were deduplicated and assessed by two independent reviewers. An initial review of search results was performed to identify relevant literature based on assessment of title and abstract. A second review of the relevant search results involved a review of the full publication. Any discrepancies between the reviewers were discussed and resolved with a third independent reviewer. Full details of the data extraction are included in Appendix C.

The studies were selected during the first and second review by applying eligibility criteria, which defined our review question according to the PICOS (population, intervention, comparison, outcomes and study type)

principle [17]. The full selection criteria can be found in Appendix D. Studies published as abstracts, conference presentations, or press releases were eligible if adequate data were provided in line with the inclusion criteria.

Results

The database searches identified all relevant literature published in each database prior to 31 July 2024, retrieving 1959 references, of which 233 were duplicates, leaving 1726 unique references for first review screening. Of the 330 full texts assessed in the second review, 212 individual studies did not meet the inclusion criteria (Appendix D).

Of the 119 extracted individual studies, there were 11 randomized controlled trials (RCTs), 21 non-RCTs, 10 HRQoL studies, 2 cost and resource use studies and 77 epidemiological studies. 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 118 publications. Appendix F reports the number of studies excluded in the form of a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

Epidemiology

Seventy-seven epidemiology studies were considered for full text review. Throughout these studies, themes associated with patient population, mortality, pathogenesis and natural history, native liver survival and diagnosis were explored. No studies that reported prevalence or incidence rates met the inclusion criteria for the literature review.

Genetics & clinical findings

The clinical diagnostic criteria for ALGS include bile duct paucity on liver histology (classed as a bile duct to hepatic artery ratio of <0.5) as well as at least three out of the seven typical clinical symptoms: cholestasis, characteristic facial features, vertebral abnormalities, eye abnormalities, heart defects, skeletal abnormalities, kidney abnormalities and vascular abnormalities [2]. Genotyping can be used as confirmatory testing for the diagnosis; a *JAG1* variant has been shown to be present in 86% to 98% of cases and a *NOTCH2* variant present in 2–5% of cases [18,19,20,21]. In an analysis by Vandriel *et al.* [21] using the Global Alagille Alliance (GALA) registry, the largest natural history registry assessing outcomes in >1600 patients with ALGS, 755 *JAG1* and 19 *NOTCH2* patients were identified. Patients with the *NOTCH2* variant were significantly less likely to have ALGS characteristic facies, a cardiac anomaly confirmed by echocardiography, or butterfly vertebrae. However, the incidence of neonatal cholestasis, bile duct paucity and renal anomalies, as well as overall survival rates, were similar between *JAG1* and *NOTCH2* patients with ALGS.

Cholestasis is a hallmark symptom of ALGS [9]. In a retrospective study evaluating the symptomology of patients with ALGS, 82.9% of patients had chronic cholestasis identified between birth and 24 months of age [22]. Furthermore, of the 37 patients undergoing liver biopsy, 32 had a paucity of intrahepatic bile ducts [22]. Another study included 32 children with cholestasis (median age: 8 years), 13 of whom had paucity of interlobular bile ducts as well as three or more criteria of ALGS [23].

Cardiovascular, ophthalmologic, renal, skeletal anomalies and dysmorphic anomalies are the major diagnostic criteria outside of liver manifestations, with peripheral pulmonic stenosis, butterfly vertebrae and ocular posterior embryotoxon noted as other diagnostic features [24]. Synonymous syndromic features of ALGS were also reported in other studies, together with cholestasis and systolic cardiac murmurs [25,26]. Kohaut *et al.* [27] observed in their cohort of patients with ALGS who received a liver transplant that all of the children had at least three disease-specific features, and almost half of them (26 of 55) presented with all clinical features. Genetic testing was also performed in these patients; however, it is unclear whether the genetic testing predated the observation of the clinical features of ALGS or *vice versa*.

Natural history, morbidity & mortality in ALGS

ALGS is a heterogeneous condition, characterized by a variety of clinical manifestations, which inform diagnosis but also define progression of disease. Ninety-five percent of children will develop issues with the liver, of which 85% will have neonatal onset of cholestasis [10]. Debilitating pruritus secondary to cholestatic liver disease manifests in 74% of patients at a median age of 12 months. Cardiovascular abnormalities are quite common in patients with ALGS [28,29]. Structural cardiac abnormalities, like tetralogy of Fallot, are associated with significant morbidity and mortality in patients with ALGS, with the highest mortality rate (75%) reported in patients presenting with both tetralogy of Fallot and pulmonary atresia; the mortality rate in patients with tetralogy of Fallot alone is

34% [12]. Renal abnormalities have been reported to occur in 19–74% of patients with ALGS [1]. Importantly, a study evaluating patients from a North American liver transplantation database indicated that patients with ALGS who have preexisting renal insufficiency may potentially worsen following liver transplantation [8]. Children are often born with clear skeletal abnormalities, which are the typical clinical manifestations clinicians will diagnose at birth. Patients with ALGS are predisposed to poor bone heath, including osteoporosis and metabolic bone disease, which is related to malabsorption and fat-soluble vitamin deficiencies [30,31] and is associated with increased fracture risk [32]. Thus, it is not surprising that children with ALGS have smaller bones and lower bone mass compared with their age group peers, which might explain the observed differences in stature [33].

As children with ALGS age, morbidity develops beyond liver manifestations, with 28% of patients experiencing xanthomas, macular atrophy and progressive vision loss [34,35,36]. Development of neurodevelopmental disorders may affect IQ, and 84% of patients will experience significant cardiac disease, some of which may restrict their ability to be able to receive a liver transplant [37].

Lack of physical development further impacts a child's ability to thrive and keep up with peers. Failure to thrive issues fundamentally impact a child's growth, characterized by smaller bones, weaker joints and reduced growth and height compared with their peers that does not necessarily catch up after liver transplant [33,38,39]. Children with ALGS may continue to experience these growth disparities even after liver transplant.

Extensive disease burden, characterized by the wide variety of clinical manifestations, leads to collateral mortality issues. Patients who had liver dysfunction and received congenital heart surgery before or instead of liver transplantation reportedly had a fourfold higher relative risk of mortality compared with those without liver dysfunction [40]. The risk of death for those who did not receive a liver transplant at 5, 10 and 18 years was 6.1, 7.8 and 9.3%, respectively. Patients who underwent surgical biliary diversion experienced a 1.9-fold increase in risk of liver transplant/death. Overall, native liver survival to early adulthood ranges between 20 and 40% [10,19]. Patients can also develop manifestations in adulthood. Li *et al.* reported diagnosis in adults of cholestasis, butterfly vertebrae, systolic murmurs and typical facies in 50, 62, 12.5 and 12.5% of patients, respectively [26]. In 5 epidemiology studies, the reported overall survival (OS) rates were between 80.4 and 92.9% among patients with ALGS, regardless of liver transplantation status [21,27,41,42,43]. The reported 10-year and 18-year OS rates were 92.9 and 90.7%, respectively, whereas reported native liver survival rates were substantially lower than OS – 69.7 and 56.5%, respectively [21,43].

Current standard of care for the management of ALGS

Management of liver disease in ALGS focuses on controlling the symptoms of pruritus and providing nutrition to help alleviate fat-soluble vitamin deficiencies [1]. While several clinical management approaches have been employed for pruritus associated with ALGS, they are often insufficient [44]. Prior to the development and approval of IBAT inhibitors for the treatment of cholestatic pruritus in ALGS, the management of pruritus has been largely supportive, with choleretic agents (ursodeoxycholic acid [UDCA]) and other medications (cholestyramine, rifampicin, naltrexone) used to address the itch [2,44,45]. However, the efficacy of these agents is limited, and many have intolerable adverse event (AE) profiles [46]. Pruritus is often refractory to treatment with established therapies and is a leading indication for liver transplantation as indicated previously [12,44,45,47,48].

Cholestatic pruritus in ALGS is sometimes managed by surgically interrupting the enterohepatic circulation of bile acids through partial biliary diversion [44,49,50]. The long-term efficacy of such interventions is a matter of debate, and the risk associated with surgery, as well as the medical and psychosocial burden related to a permanent stoma, warrants careful consideration [1,51,52,53]. Due to disease management shortcomings for ALGS, liver transplantation is often performed and associated with complications.

Main indications for liver transplantation in patients with ALGS are persistent cholestasis including intractable pruritus, growth failure, xanthomas, metabolic bone disease, and/or fat- soluble vitamin deficiency [10]. Native liver function may deteriorate due to cholestasis-induced cirrhosis in patients with ALGS, leading to liver failure [24]. It has been reported that by 5 years of age, 15–30% of children with ALGS will progress to advanced liver disease requiring liver transplant [15].

Liver transplantation brings substantial mortality risk to children. Between 20 and 75% of patients will require a liver transplant by 18 years of age, with the median age of liver transplant reported at 2.8 years [10]. Of those, 72% of transplantations are expected to occur in patients below the age of 6 years [54]. Most patients will expect a longer hospital stay due to complications associated with ALGS, compared with similar liver indications [39,55]. Survival rates post-liver transplant at 5, 10 and 20 years were reported as 92, 91 and 88%, respectively [10].

The LOGIC study, a longitudinal study of liver disease progression in patients, including those with ALGS (n = 293), reported that only 24% of patients with ALGS survive to early adulthood (95% CI: 16–36%) with their native liver, reflecting the high rate of liver-related complications [30]. Among 11 patients who died with native liver during the study, only three of these deaths were directly attributable to liver disease.

These data are supported by findings from the GALA study, indicating survival with native liver was 40.3% at 18 years of age [34]. The probability of survival to 20 years of age has been reported as 80% in patients with ALGS who did not require liver transplant and the predicted probability of survival to 20 years of age in all patients is 75%, indicating that liver involvement has a major impact on long-term morbidity and mortality [25]. Another analysis of the GALA data by Habash *et al.* [56] reported a previously unrecognized substantial liver disease burden, with 95% of all the patients having liver involvement at any given time and 85% having neonatal cholestasis. Furthermore, survival with native liver was reported as 51% at 10 years and 38.5% at 20 years [11]. Overall, the impact on native liver survival depends on the degree of cholestasis in infancy, as demonstrated by data from GALA.

Black *et al.* reported that children with ALGS were more likely to receive a diagnosis of congenital heart disease (80.7 vs 16.4%; $p < 0.001$) as compared with children with other forms of liver disease, which increases potential complications with liver transplantation [55]. Forty (25.6%) children with ALGS required some type of cardiac intervention (catheter or surgical) either before or after successful liver transplantation, with 19 (12.2%) of them receiving more than one intervention.

Kamath *et al.* 2reported that 70% of children with ALGS required liver transplantation by 17 years of age, of which 10% died (3 deaths were liver related) [19]. The mean age of patients receiving liver transplantation was between 5 and 6 years of age (range: 1–17 years) [12,27,57]. Another study reported that death occurred after liver transplantation in 5 of 12 patients, of which all 5 deaths were caused by transplant complications [29]. In the LOGIC trial, 58 participants received liver transplants and 11 died with native liver in the study follow-up [30]. Data from the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) 2022 Annual Report indicated that posttransplant mortality among all pediatric liver transplant recipients irrespective of indication was 4% at 6 months, 6% at 1 year, 8.2% at 3 years, 9.8% at 5 years and 13.9% at 10 years [58].

HRQoL & burden

A total of 10 HRQoL publications were identified in the literature review reporting outcomes using the Pediatric Quality of Life Inventory (PedsQL), Family Impact Scale (FIS), Multidimensional Fatigue (MF) Scale Score and Child Health Questionnaire – Parent Form 50 (CHQ-PF50) in patients with ALGS (Table 1). There were no studies that reported utilities or disutilities associated with ALGS management. Burden is defined as the impact of living with ALGS, measured by cost, mortality and other factors. A single publication reported on financial burden.

Elisofon *et al.* [47] reported CHQ-PF50 outcomes; children with ALGS who did not undergo a liver transplant had significantly lower HRQoL, as measured by physical summary scores, than patients who received liver transplants due to any liver disease (43.06 vs 48.1, respectively; $p < 0.05$). While there have been no comparisons of the CHQ-PF50 between children with ALGS and healthy children, variations of this questionnaire have been studied in healthy children in Europe and the US and have demonstrated markedly higher HRQoL values than what are observed in the aforementioned study in children with ALGS either with or without a liver transplant [59,60,61].

Kamath *et al.* [62] demonstrated significant impairments in HRQoL in patients with ALGS compared with healthy patients (determination of 'healthy' was based on parent/caregiver reporting [63]) using the PedsQL, which is a 0 to 100 scale with higher values associated with improved HRQoL. In this study, lower scores were reported in the ALGS cohort compared with healthy patients: 69.86 ± 16.09 versus 83.91 ± 12.47, respectively.

Quadrado *et al.* [64] examined changes in PedsQL items over time by using mixed-methods approach to create vignettes using ALGS clinical trial data. The utility scores obtained in this study demonstrate the wide-ranging negative impact of ALGS symptoms on patients' and caregivers' quality of life (QoL) for each of four different health states–progressive cholestasis, non-progressive cholestasis, after a successful liver transplant and chronic transplant failure.

Quadrado *et al.* [65] highlighted the significant HRQoL burden faced by caregivers of children with ALGS, with a focus specifically on work, economic burden, sleep quality and emotional well-being, with liver transplant status having an effect on each parameter. All children who did not receive a liver transplant reported debilitating pruritus. Compared with caregivers of children with moderate or severe pruritus, caregivers of children with no pruritus or mild pruritus had significantly better sleep quality ($p = 0.008$). Most caregivers (79%) reported a negative

Table 1. Summary of the key studies exploring QoL in patients with ALGS.

Author	n	Countries/centers	Intervention	Valuation method	Race/ethnicity	Results			Ref.
						PedsQL change from baseline	FIS change from baseline	MF scale change from baseline	
Kamath *et al.* (2023)	27	Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center	Maralixibat	PedsQL core FIS MF scale	NR	HRQoL change from baseline to Week 48: Responders (n = 20): 11.6 ± 20.3 Nonresponders (n = 7): 1.2 ± 11.1 p = 0.21	HRQoL change from baseline to Week 48: Responders (n = 20): 17.8 ± 23.4 Nonresponders (n = 7): 3.9 ± 7.8 p = 0.14	HRQoL change from baseline to Week 48: Responders (n = 20): 25.8 ± 23.0 Nonresponders (n = 7): -3.1 ± 19.8 p = 0.03	[13,14,67]
Gonzales *et al.* (2019b)	31		Maralixibat	PedsQL		9.5-point increase from baseline to Week 48	NR	NR	[13,67,68]
Elisofon *et al.* (2010)	88	ALGS Alliance mailing list US: 1 hospital	Liver transplant	CHQ-PF50	NR	NR	NR	NR	[47]
Kamath *et al.* (2017)	37	ITCH Canada: 1 hospital US: 11 hospitals	Maralixibat	PedsQL (parent)	Race: Asian: 3% Black or African–American: 14% White: 78% More than 1 race: 3% NR: 3% Ethnicity: Hispanic or Latino: 19% Not Hispanic or Latino: 81%	QoL markedly reduced	NR	NR	[19,52]
Gonzales *et al.* (2021b)	31	Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center	Maralixibat	PedsQL core PedsQL MF scale	NR	PedsQL core: 9-point increase from baseline to Week 48 ($p < 0.05$)	NR	PedsQL MF scale: 20-point increase from baseline to Week 48 ($p < 0.05$)	[13,67,69]
Gonzales *et al.* (2021a)	31		Maralixibat	PedsQL core PedsQL MF scale		PedsQL core: 9-point increase from baseline to Week 48 (p = 0.02)	NR	PedsQL MF scale: 20-point increase from baseline to Week 48 (p = 0.0013)	[13,67,69]

ALGS: Alagille syndrome; CHQ-PF50: Child Health Questionnaire – Parent Form 50; FIS: Family Impact Scale; HRQoL: Health-related quality of life; MF: Multidimensional fatigue; NR: Not reported; PedsQL: Pediatric Quality of Life Inventory; QoL: Quality of life.

Table 2. Summary of cost and resource use study findings.

Study	Annualized mean total medical costs		Annualized mean number of medical visits		Population inclusion	Ref.
	Commercially insured population	Medicaid-insured population	Commercially insured population	Medicaid-insured population		
Miloh *et al.* (2023)	$512,124 (range: $1066–$1,638,008)	$211,863 (range: $176–$1,020,575)	65.3 (range: 9.5–256.1)	52.8 (range: 5.5–240.7)	Patients receiving liver transplant	[16]
Ebel *et al.* (2023)	$57,029 (range: $0–$1,336,236)	$24,820 (range: $0–$1,006,499)	31.0 (range: 1.5–237.1)	47.9 (range: 0.7–689.9)	Patients with ALGS	[70]

ALGS: Alagille syndrome.

financial impact from caregiving. Fifty-nine percent changed employment due to their caregiving role and 18% of all caregivers had stopped working entirely. Caregivers of individuals who had not received a liver transplant had markedly higher anxiety scores compared with those who had received a liver transplant and marginally higher depression scores, as measured by the Hospital Anxiety and Depression Scale (HADS). Posttraumatic stress has been reported in caregivers of children following liver transplantation in similar indications. Changes in work productivity, leading to economic issues, as well as an impact on sleep and relationships, were also reported [66].

Menon *et al.* [15] demonstrated the burden of ALGS-associated pruritus, which interrupts sleep, resulting in poor scholastic performance and causes lichenification of skin and secondary infections.

Elisofon *et al.* [47] reported the one study to date that has explored the impact on caregivers for patients with ALGS. In a comparison of proxy Child Health Questionnaire scores between parents of children with ALGS versus those with attention-deficit/hyperactivity disorder and juvenile rheumatoid arthritis, ALGS caregivers had significantly increased impairment ($p \leq 0.5$) in psychosocial subdomain scales, including limited parental time, stress and worry and interruption of family activities.

Taken together, these studies highlight the significant impairment in HRQoL, physical health and psychosocial functioning of patients with ALGS and the negative emotional impact and burden this has on their caregivers and family.

Cost & resource use

Two publications reported cost and resource use in patients with ALGS.

Miloh *et al.* [16] reported the cost and resource use in 53 commercially insured and 100 Medicaid-insured children who received a liver transplant, noting that for both populations, the majority of costs incurred were due to inpatient visits. Ebel *et al.* [70] reported similar findings in their cost and resource use publication, which assessed 171 commercially insured and 215 Medicaid-insured patients with ALGS. Costs reported in Miloh *et al.* [16] were higher (commercial: $512,124 vs $57,029; Medicaid: $211,863 vs $24,820), as reported amounts were for high-cost liver transplants, whereas Ebel *et al.* [70] reported cost and resource use for general healthcare visits in the ALGS population. While the costs were higher in the Miloh *et al.* study due to the focus on patients who received a liver transplant, in the Ebel *et al.* analysis, a total of 14 patients (11 Medicaid-insured and 3 commercially insured) also received a liver transplant during the follow-up period. The annualized mean total medical costs for patients with liver transplants were markedly higher compared with those without a liver transplant, irrespective of commercial or Medicaid insurance (commercial: $387,197 [liver transplant] vs $51,097 [no liver transplant]; Medicaid: $92,226 [liver transplant] vs $21,185 [no liver transplant]). The wide ranges of costs and resource uses among patients with ALGS suggest a lack of standardized treatment regimens for patients and highlight the impact of liver transplants on medical costs.

Table 2 captures annualized costs from both studies and demonstrates the economic burden of cholestatic liver disease. With such high per-patient costs, it could be suggested that future treatment mitigating some of the key complications for patients could be cost-effective in addition to improving QoL.

Clinical efficacy & safety of therapy

A total of 27 clinical references were identified as having measured the efficacy and safety of treatments for cholestatic pruritus associated with ALGS. Table 3 summarizes the key clinical studies identified in the literature review and Table 4 summarizes the results of the outcomes of these papers. Appendix E contains the additional clinical studies identified and their outcomes.

Table 3. Summary of key clinical studies included in the literature review.

Author	Intervention(s)	Countries/centers	Study design	Race/ethnicity	End point(s)	Refs.
Gonzales *et al.* (2021a) – ICONIC†	Participants received doses of 380 μg/kg/d of maralixibat for 18 weeks. Following this, a double-blind, randomized withdrawal period occurred where participants were randomized to receive either maralixibat or placebo for four weeks. Then, all participants received open-label maralixibat to 48 weeks, and were then allowed to enter the long-term extension study where doses could be increased to up to 380 μg/kg twice per day dependent on sBA levels and pruritus.	Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center	ICONIC (LUM001–304) was an international, multicenter, phase 2b, double-blind, placebo-controlled drug-withdrawal study with open-label extension of maralixibat in children with ALGS.	NR	• sBA levels	[13,67,69]
Foster *et al.* (2020) – ICONIC	This study evaluated the psychometric properties of the ItchRO(Obs) in the ICONIC study.				• ItchRO	[13,67,92]
Gonzales *et al.* (2019a) – ICONIC	Participants reaching Week 48 of ICONIC were eligible to continue maralixibat chloride 400 μg/kg once daily in this open-label extension. From the end of year two, participants could receive up to 400 μg/kg twice daily if sBA was >ULN and/or pruritus was persisting.				• sBA levels • ItchRO • Clinician Xanthoma Severity Scale • CSS • Safety	[13,67,93]
Gonzales *et al.* (2019b) – ICONIC	After an 18-week maralixibat run-in period (6 weeks of ascending doses up to 400 μg/kg [maralixibat chloride] daily and 12 weeks of stable dosing), participants were randomized to placebo or continued maralixibat treatment for 4 weeks. After this, all participants were treated with maralixibat.				• sBA levels • ItchRO • Clinician Xanthoma Severity Scale • PedsQL	[13,67,68]
Gonzales *et al.* (2020) – ICONIC	Participants received doses of 380 μg/kg/day of maralixibat for 18 weeks. Following this, a double-blind, randomized withdrawal period occurred where participants were randomized to receive either maralixibat or placebo for 4 weeks. Then, all participants received open-label maralixibat to 48 weeks, and were allowed to enter the long-term extension study after.				• ItchRO • CSS • sBA levels	[13,67,81]
Gonzales *et al.* (2021b) – ICONIC	Participants received doses of 380 μg/kg/day of maralixibat for 18 weeks. Following this, a double-blind, randomized withdrawal period occurred where participants were randomized to receive either maralixibat or placebo for 4 weeks. Then, all participants received open-label maralixibat to 48 weeks, and were allowed to enter the long-term extension study after where doses could be increased to up to 380 μg/kg twice per day dependent on sBA levels and pruritus.				• sBA levels • Height Z-score	[13,67,69]
Kamath *et al.* (2021) – ICONIC	Six-week dose escalation period (maralixibat doses up to 380 μg/kg/d), a 4-week randomized withdrawal period (Weeks 18 to 22) and long-term stable dosing.		International, multicenter, long-term, phase 2b, placebo-controlled, randomized drug withdrawal study with an OLE in children with ALGS experiencing moderate to severe pruritus.		• ItchRO	[94]

† Please note that other studies relating to ICONIC are previous and/or subanalyses of the primary ICONIC manuscript (Gonzales *et al.*, 2021a [13] that were presented or published separately.

ALGS: Alagille syndrome; CSS: Clinician scratch scale; EFS: Event-free survival; GALA: Global Alagille Alliance; ItchRO(Obs): Itch-Reported Outcome (Observer); ObsRO: Observer-reported outcome; OLE: Open-label extension; PedsQL: Pediatric Quality of Life Inventory; QoL: Quality of life; sBA: Serum bile acid; ULN: Upper limit of normal.

10.57264/cer-2024-0188

Table 3. Summary of key clinical studies included in the literature review (cont.).

Author	Intervention(s)	Countries/centers	Study design	Race/ethnicity	End point(s)	Refs.
Hansen *et al.* (2023)	Maralixibat	ICONIC Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center ITCH Canada: 1 hospital US: 11 hospitals IMAGO UK: 2 hospitals 1 liver center IMAGINE I Included participants rollover from IMAGO IMAGINE II Included participants rollover from ITCH MERGE Canada: 1 hospital Australia: 2 hospitals Europe: Belgium: 1 hospital France: 2 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center 2 hospitals US: 6 hospitals GALA cohort Asia: 7 hospitals Australia/New Zealand: 3 hospitals Europe: 32 hospitals Canada: 7 hospitals South America: 5 hospitals US: 22 hospitals Others: 8 hospitals	The GALA control cohort in this study aligned with key maralixibat eligibility criteria from the clinical trials. The clinical trials included ICONIC (LUM001–304), ITCH (LUM001–301), IMAGINE II (LUM001–305), IMAGO (LUM001–302), IMAGINE I (LUM001–303), and ongoing study MERGE (MRX-800).	ICONIC NR ITCH Race: Black or African–American: 13.5% White: 78.4% Other (including missing): 8.1% Ethnicity: Hispanic/Latino: 18.9% IMAGO Race: Black or African–American: 5.0% White: 85.0% Other (including missing): 10.0% Ethnicity: Hispanic or Latino: 0% IMAGINE I Included participants rolled over from IMAGO IMAGINE II Included participants rolled over from ITCH MERGE Included participants rolled over from ICONIC, IMAGINE I, and IMAGINE II GALA cohort NR	• EFS	[13,52,67,81, 82,84,95,96,97,98]
Rosenthal *et al.* (2023) – RISE	Maralixibat	Europe: Belgium: 1 hospital France: 2 hospitals Poland: 1 hospital UK: 1 Liver Center South America: Brazil: 1 hospital North America: Mexico: 1 hospital US: 7 hospitals	Open-label, single group assignment, phase 2 trial	NR	• sBA levels • Biochemical markers of liver function	[85,99]

† Please note that other studies relating to ICONIC are previous and/or subanalyses of the primary ICONIC manuscript (Gonzales *et al.*, 2021a [13] that were presented or published separately.

ALGS: Alagille syndrome; CSS: Clinician scratch scale; EFS: Event-free survival; GALA: Global Alagille Alliance; ItchRO(Obs): Itch-Reported Outcome (Observer); ObsRO: Observer-reported outcome; OLE: Open-label extension; PedsQL: Pediatric Quality of Life Inventory; QoL: Quality of life; sBA: Serum bile acid; ULN: Upper limit of normal.

10.57264/cer-2024-0188

Table 3. Summary of key clinical studies included in the literature review (cont.).

Author	Intervention(s)	Countries/centers	Study design	Race/ethnicity	End point(s)	Refs.
Gonzales *et al.* (2023) – RISE	Maralixibat		Open-label, single group assignment, phase 2 trial		• sBA levels • Biochemical markers of liver function	[99,100]
Ovchinsky *et al.* (2021) – ASSERT	Eligible patients were randomized 2:1 to receive either odevixibat 120 μg/kg/d or placebo capsules for oral administration once daily for 24 weeks.	Asia: Malaysia: 1 hospital Europe: Belgium: 1 hospital France: 3 hospitals Germany: 3 hospitals Italy: 3 Hospitals The Netherlands: 2 hospitals Poland: 1 hospital UK: 1 liver center US: 5 hospitals Other: Turkey: 1 hospital	Double-blind, randomized, placebo-controlled, multicenter phase III trial.	Race: White: 82.7% Black or African–American: 7.7% Asian: 5.8% Other: 3.8% Ethnicity: Hispanic or Latino: 3.8% Not Hispanic or Latino: 84.6% NR: 11.5%	• Scratching score • sBA • Pruritus • Xanthomatosis • Sleep parameters • QoL • Biochemical markers of liver function	[90]
Ovchinsky *et al.* (2022) – ASSERT	Participants were randomized (2:1) to receive doses of 120 μg/kg/d of odevixibat or placebo for 24 weeks.		Phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[88]
Ovchinsky *et al.* (2023) – ASSERT	Eligible patients were randomized 2:1 to receive either odevixibat 120 μg/kg/day or placebo capsules for oral administration once daily for 24 weeks.		Phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[91]
Ovchinsky *et al.* (2023) – ASSERT	Eligible patients were randomized 2:1 to receive either odevixibat 120 μg/kg/day or placebo capsules for oral administration once daily for 24 weeks.		Phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[101]
Ovchinsky *et al.* (2024) – ASSERT	Eligible patients were randomized 2:1 to receive either odevixibat 120 μg/kg/day or placebo capsules for oral administration once daily for 24 weeks.		Phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[89]

† Please note that other studies relating to ICONIC are previous and/or subanalyses of the primary ICONIC manuscript (Gonzales *et al.*, 2021a [13] that were presented or published separately.

ALGS: Alagille syndrome; CSS: Clinician scratch scale; EFS: Event-free survival; GALA: Global Alagille Alliance; ItchRO(Obs): Itch-Reported Outcome (Observer); ObsRO: Observer-reported outcome; OLE: Open-label extension; PedsQL: Pediatric Quality of Life Inventory; QoL: Quality of life; sBA: Serum bile acid; ULN: Upper limit of normal.

Table 3. Summary of key clinical studies included in the literature review (cont.).

Author	Intervention(s)	Countries/centers	Study design	Race/ethnicity	End point(s)	Refs.
Ovchinsky *et al.* (2023) – ASSERT and ASSERT-EXT	ASSERT: Eligible patients were randomized 2:1 to receive either odevixibat 120 μg/kg/day or placebo capsules for oral administration once daily for 24 weeks. ASSERT-EXT: Eligible patients receive odevixibat 120 μg/kg/day for 72 weeks.		Open-label extension of phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[102]
Ovchinsky *et al.* (2023) – ASSERT-EXT	ASSERT-EXT: Eligible patients receive odevixibat 120 μg/kg/day for 72 weeks.		Open-label extension of phase III, double-blind, randomized, placebo-controlled study of odevixibat in patients with ALGS (ASSERT, NCT04674761).		• Scratching score PRUCISION ObsRO • sBA • Sleep parameters • QoL • Biochemical markers of liver function	[91]

† Please note that other studies relating to ICONIC are previous and/or subanalyses of the primary ICONIC manuscript (Gonzales *et al.*, 2021a [13] that were presented or published separately.

ALGS: Alagille syndrome; CSS: Clinician scratch scale; EFS: Event-free survival; GALA: Global Alagille Alliance; ItchRO(Obs): Itch-Reported Outcome (Observer); ObsRO: Observer-reported outcome; OLE: Open-label extension; PedsQL: Pediatric Quality of Life Inventory; QoL: Quality of life; sBA: Serum bile acid; ULN: Upper limit of normal.

10.57264/cer-2024-0188

Table 4. End point results in key clinical studies.

Study	Countries/centers	Race/ethnicity	sBA levels	ItchRO	CSS	Xanthoma severity scale	Safety	ALT	GGT	Bilirubin	Ref.
Foster *et al.* (2020) ICONIC – end point results	Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center	NR	NR	Positive correlations between ItchRO and CSS indicated convergent validity: r = 0.63 to 0.78 Negative correlations between ItchRO and PedsQL scores indicated divergent validity, with correlations ranging from r = -0.1 to -0.96	NR	NR	NR	NR	NR	NR	[13,92]
Gonzales *et al.* (2019a) ICONIC – mean change from baseline to Week 48 – maralixibat population			-158.5 μmol/l (95% CI: -260.1 to -56.9) p = 0.0048	-2.3 (-2.8, -1.8) p < 0.0001	-2.2 (-2.9, -1.5) p < 0.0001	-0.7 (-1.3, -0.02) p = 0.0453	NR	NR	NR	NR	[13,67,93]
Gonzales *et al.* (2019b) – ICONIC – mean change from baseline to Week 48 – overall population			-101 μmol/l (36% reduction) p = 0.003	-1.6 (72% experienced reduction from baseline of ≥1 pts)	NR	44% decrease	Maralixibat was generally safe; most frequent AEs were diarrhea, abdominal pain, vomiting and upper respiratory tract infections	18 U/l increase	NR	Total bilirubin unchanged	[13,67,68]
Gonzales *et al.* (2020) ICONIC – end point – overall population			Reduction in sBA correlated with reduction in ItchRO score (p = 0.0123) at Week 48	-1.6 reduction at Week 48	Reduction in CSS correlated with reduction in ItchRO score (p = 0.0002) at Week 48	NR	NR	NR	NR	NR	[13,67,81]
Gonzales *et al.* (2021a) ICONIC – mean change from baseline to Week 48 – overall population			-96 μmol/l (95% CI: -162 to -31)	-1.6 pts (2.1 to -1.1)	-1.8 (-2.3 to -1.3)	-0.9 (-1.3 to -0.5)	Stable dosing period from Weeks 23–48; 86% of participants had 1 or more TEAEs and 17% had SAEs	18 U/l (-15 to 50)	25 U/l (-42 to 92)	Total: 0.5 μmol/l (-11.9 to 13) Direct: -4.1 μmol/l (-9.7 to 1.5)	[13,67]
Gonzales *et al.*, 2021b ICONIC – mean change from baseline to Week 48 – overall population			-96 μmol/l (p = 0.0058)	-1.6 pts (p < 0.0001)	-1.8 pts (p < 0.0001)	-0.9 pts (p = 0.0006)	NR	18 U/l (p = 0.2787)	25 U/l (p = 0.4562)	Total: 0.5 μmol/l (p = 0.9285) Direct: -4.1 μmol/l (p = 0.1489)	[13,67,69]

AE: Adverse event; ALT: Alanine aminotransferase; CSS: Clinician Scratch Scale; GGT: γ-glutamyltransferase; ItchRO: Itch-reported outcome; NR: Not reported; ObsRO: Observer-reported outcome; PedsQL: Pediatric quality of life inventory; pts: Point; SAE: Serious adverse event; sBA: Serum bile acid; TEAE: Treatment-emergent adverse event.

Table 4. End point results in key clinical studies (cont.).

Study	Countries/centers	Race/ethnicity	sBA levels	ItchRO	CSS	Xanthoma severity scale	Safety	ALT	GGT	Bilirubin	Ref.
Hansen *et al.* (2023)	ICONIC Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center ITCH Canada: 1 hospital US: 11 hospitals IMAGO UK: 1 liver center 2 hospitals IMAGINE I Included participants rolled over from IMAGO IMAGINE II Included participants rolled over from ITCH MERGE Canada: 1 hospital Australia: 2 hospitals Europe: Belgium: 1 hospital France: 2 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center 2 hospitals US: 6 hospitals GALA cohort Asia: 7 hospitals Australia/New Zealand: 3 hospitals Europe: 32 hospitals Canada: 7 hospitals South America: 5 hospitals US: 22 hospitals Others: 8 hospitals	ICONIC NR ITCH Race: Black or African–American: 13.5% White: 78.4% Other (including missing): 8.1% Ethnicity: Hispanic/Latino: 18.9% IMAGO Race: Black or African–American: 5.0% White: 85.0% Other (including missing): 10.0% Ethnicity: Hispanic or Latino: 0% IMAGINE I Included participants rolled over from IMAGO IMAGINE II Included participants rolled over from ITCH MERGE Included participants rolled over from ICONIC, IMAGINE I and IMAGINE II GALA cohort NR	NR	NR	NR	NR	NR	NR	NR	NR	[13,52,67,81, 82,84,95,96,97,98]

AE: Adverse event; ALT: Alanine aminotransferase; CSS: Clinician Scratch Scale; GGT: γ-glutamyltransferase; ItchRO: Itch-reported outcome; NR: Not reported; ObsRO: Observer-reported outcome; PedsQL: Pediatric quality of life inventory; pts: Point; SAE: Serious adverse event; sBA: Serum bile acid; TEAE: Treatment-emergent adverse event.

10.57264/cer-2024-0188

Table 4. End point results in key clinical studies (cont.).

Study	Countries/centers	Race/ethnicity	sBA levels	ItchRO	CSS	Xanthoma severity scale	Safety	ALT	GGT	Bilirubin	Ref.
Kamath *et al.* (2021) – ICONIC	Australia: 2 hospitals Europe: Belgium: 1 hospital France: 3 hospitals Poland: 1 hospital Spain: 1 hospital UK: 1 liver center	NR	NR	At Week 48, 74% of patients had achieved ItchRO response (≥1-point reduction)	NR	NR	NR	NR	NR	NR	[13,67,94]
Rosenthal *et al.* (2023) – RISE	Europe: Belgium: 1 hospital France: 2 hospitals Poland: 1 hospital UK: 1 liver center South America: Brazil: 1 hospital North America: Mexico: 1 hospital US: 7 hospitals	NR	-89 μmol/l	NR	NR	NR	90% of patients had ≥1 TEAE and 50% of patients had a Grade ≥3 TEAE	Mean change from baseline to Week 13: 148 U/l	NR	>50% of participants with Week 13 data had a reduction in total bilirubin >30%	[85,99]
Gonzales *et al.* (2023) – RISE			-89 (113.3) μmol/l	NR	NR	NR	87.5% of patients had ≥1 TEAE and 50% of patients had a Grade ≥3 TEAE	NR	NR	NR	[99,103]
Ovchinsky (2021) – ASSERT	Asia: Malaysia: 1 hospital Europe: Belgium: 1 hospital France: 3 hospitals Germany: 3 hospitals Italy: 3 Hospitals The Netherlands: 2 hospitals Poland: 1 hospital UK: 1 liver center US: 5 hospitals Other: Turkey: 1 hospital	Race: White: 82.7% Black or African–American: 7.7% Asian: 5.8% Other: 3.8% Ethnicity: Hispanic or Latino: 3.8% Not Hispanic or Latino: 84.6% NR: 11.5%	NR	NR	NR	NR	NR	NR	NR	NR	[90]
Ovchinsky (2022) – ASSERT			Odevixibat: -90 μmol/l vs placebo: 22 μmol/l (p = 0.0012)	PRUCISION ObsRO change from baseline: Odevixibat: -1.7 vs placebo: -0.8 (p = 0.0024)	NR	NR	Overall incidence of TEAEs was similar across the placebo and odevixibat-treated groups; incidence of treatment-emergent diarrhea was 29% with odevixibat and 6% with placebo	Odevixibat: 243 U/l vs placebo: 146 U/l	NR	Total: Odevixibat: 3.041 mg/dL vs placebo: 3.77 mg/dL	[88]

AE: Adverse event; ALT: Alanine aminotransferase; CSS: Clinician Scratch Scale; GGT: γ-glutamyltransferase; ItchRO: Itch-reported outcome; NR: Not reported; ObsRO: Observer-reported outcome; PedsQL: Pediatric quality of life inventory; pts: Point; SAE: Serious adverse event; sBA: Serum bile acid; TEAE: Treatment-emergent adverse event.

10.57264/cer-2024-0188

Table 4. End point results in key clinical studies (cont.).

Study	Countries/centers	Race/ethnicity	sBA levels	ItchRO	CSS	Xanthoma severity scale	Safety	ALT	GGT	Bilirubin	Ref.
Ovchinsky *et al.* (2023) – ASSERT			Odevixibat: -90 μmol/l vs placebo: 22 μmol/l (p = 0.0012)	PRUCISION ObsRO change from baseline: Odevixibat: -1.7 vs placebo: -0.8 (p = 0.0024)	NR	NR	Overall incidence of TEAEs was similar across the placebo and odevixibat-treated groups; incidence of treatment-emergent diarrhea was 11% with odevixibat and 6% with placebo	Mean (SD) change from baseline to Week 24 – Odevixibat: 57 (84) U/l vs placebo: -2.8 (48) U/l	NR	Mean (SD) at Week 24 – Odevixibat: 52.0 (43.4) μmol/l vs placebo: 61.6 (57.0) μmol/l Mean (SD) change from baseline to Week 24 – Odevixibat: 0.01 (19.0) μmol/l vs placebo: 2.8 (15.0) μmol/l	[104]
Ovchinsky *et al.* (2023) – ASSERT			Odevixibat-treated patients with a pruritus response, mean (SE) at baseline: 243 (23) μmol/l Change from baseline to the average of weeks 20 and 24: -107 (23) μmol/l	Odevixibat-treated patients with a pruritus response, mean (SE) at baseline: 2.8 (0.1) Change from baseline to weeks 21–24: -2.0 (0.1)	NR	NR	75% of odevixibat-treated pruritus responders had at least one TEAE	NR	NR	NR	[101]
Ovchinsky *et al.* (2024) – ASSERT			Odevixibat: -90 μmol/l vs placebo: 22 μmol/l (p = 0.0012)	PRUCISION ObsRO change from baseline: Odevixibat: -1.7 vs placebo: -0.8 (p = 0.0024)	NR	Odevixibat: 27 (77%) of 35 patients had no change from baseline to week 24 in xanthomas, including 25 patients who had no xanthomas at any timepoint during the study. Seven (20%) of 35 patients showed improvements in xanthomas with odevixibat and one (3%) patient had an increase from 0 to 1 in the Clinician Xanthoma Scale score. Placebo: 14 (82%) of 17 patients had no change from baseline to week 24 in xanthomas, with all 14 having no xanthomas at any timepoint. Two (12%) of 17 patients in the placebo group showed improvements in xanthomas (the score decreased from 2 to 1 in one patient and 3 to 1 in another patient) and one (6%) patient showed worsening (the score increased from 0 to 3).	Overall incidence of TEAEs was similar across the placebo and odevixibat-treated groups	Mean (SD) at Week 24 - Odevixibat: 245 (121) U/l vs placebo: 146 (66) U/l Mean (SD) change from baseline to week 24 – Odevixibat: 57 (84) U/l vs placebo: -3 (48) U/l	Mean (SD) at Week 24 - Odevixibat: 460 (270) U/l vs placebo: 594 (461) U/l Mean (SD) change from baseline to week 24 – Odevixibat: 100 (166) U/l vs placebo: 59 (354) U/l	Mean (SD) at Week 24 - Odevixibat: 52.64 (42.27) μmol/l vs placebo: 64.44 (59.70) μmol/l Mean (SD) change from baseline to week 24 – Odevixibat: 0.01 (18.98) μmol/l vs placebo: 2.82 (15.04) μmol/l	[89]

AE: Adverse event; ALT: Alanine aminotransferase; CSS: Clinician Scratch Scale; GGT: γ-glutamyltransferase; ItchRO: Itch-reported outcome; NR: Not reported; ObsRO: Observer-reported outcome; PedsQL: Pediatric quality of life inventory; pts: Point; SAE: Serious adverse event; sBA: Serum bile acid; TEAE: Treatment-emergent adverse event.

10.57264/cer-2024-0188

Table 4. End point results in key clinical studies (cont.).

Study	Countries/centers	Race/ethnicity	sBA levels	ItchRO	CSS	Xanthoma severity scale	Safety	ALT	GGT	Bilirubin	Ref.
Ovchinsky *et al.* (2023) – ASSERT and ASSERT-EXT			NR	NR	NR	NR	NR	Change from baseline in patients treated with odevixibat for up to 48 weeks: 64 (102) U/l	Change from baseline in patients treated with odevixibat for up to 48 weeks: 2 (238) U/l	Change from baseline in patients treated with odevixibat for up to 48 weeks: -0.1 (0.9) mg/dL	[102]
Ovchinsky *et al.* (2023) – ASSERT-EXT			Odevixibat-odevixibat at Week 12: 122 (22), $p < 0.01$ vs ASSERT baseline Placebo-odevixibat at Week 12: 76 (15), $p < 0.05$ vs ASSERT-EXT baseline	Odevixibat-odevixibat at Week 12: 0.7 (0.1), $p < 0.001$ vs ASSERT baseline Placebo-odevixibat at Week 12: 0.9 (0.1), $p < 0.001$ vs ASSERT-EXT baseline	NR	NR	59% of patients treated with odevixibat had TEAEs at cut-off date (09 September 2022)	NR	NR	NR	[102]

AE: Adverse event; ALT: Alanine aminotransferase; CSS: Clinician Scratch Scale; GGT: γ-glutamyltransferase; ItchRO: Itch-reported outcome; NR: Not reported; ObsRO: Observer-reported outcome; PedsQL: Pediatric quality of life inventory; pts: Point; SAE: Serious adverse event; sBA: Serum bile acid; TEAE: Treatment-emergent adverse event.

As mentioned, prior to September 2021, treatment options available for patients with ALGS were mainly used for supportive or symptomatic relief. They included off-label use of UDCA to increase bile flow and other medications to help manage pruritus [71]. However, the evidence clearly indicated that these interventions are not very effective, and the majority of patients do not respond or combination therapy is required, which is associated with a number of issues as well [46]. Given that patients with ALGS have intrahepatic accumulations of bile acids that damage the liver and have additional deleterious multisystemic effects, developing therapies that focus on interrupting the enterohepatic circulation and reducing the bile acid pool are key [72,73].

Mechanism of IBAT inhibitors for the treatment of cholestatic pruritus in ALGS

Due to its key role in bile acid reuptake, the IBAT inhibitor is a rational target for pharmacologic interruption of bile acid recirculation [74,75]. IBATs are responsible for the reabsorption of about 95% of intestinal bile acids [76]. Inhibition of IBATs results in a reduction in bile acid reabsorption, which is associated with an increase in the levels of bile acids excreted in the feces and a decrease in the levels of bile acids returning to the liver [77,78].

Maralixibat for the treatment of cholestatic pruritus in patients with ALGS

Maralixibat is a novel oral IBAT inhibitor with minimal systemic absorption and is the first medication approved to treat cholestatic pruritus in patients with ALGS ≥3 months of age in the US and ≥2 months of age in the EU [79,80]. It is also approved for the treatment of cholestatic pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) ≥12 months of age in the US and for the treatment of PFIC in patients ≥3 months of age in the EU [79,80].

Gonzales *et al.* reported the findings from the pivotal ICONIC trial [13]. The ICONIC trial was a placebo-controlled, randomized withdrawal, phase 2b study with an open-label extension in children (aged 1–18 years) with ALGS. The ICONIC trial had 3 prespecified periods in the core study: (1) an open-label run-in period from baseline to Week 18; (2) a 4-week double-blind, placebo-controlled randomized withdrawal period (RWD) from Weeks 19 to 22, in which all patients were randomly assigned to remain on maralixibat or receive placebo; and (3) an open-label period from Weeks 23 to 48. After the core study, participants had the option of continuing into the open-label extension. Data out to 204 weeks were discussed in the manuscript.

In ICONIC, the primary efficacy end point was the mean change in serum bile acid (sBA) levels during the RWD in participants who previously achieved an sBA reduction from baseline to Week 12 or 18 that was met through treatment with maralixibat. There were significant differences in sBA between the maralixibat group and the placebo group during the RWD (mean difference, -114 μmol/l; $p < 0.05$), with sBA levels of those in the placebo group returned to levels similar to baseline values. Once all participants had resumed treatment with maralixibat, significant sBA reduction was observed from baseline to Week 48 and maintained up to Week 204 (-181 μmol/l vs baseline; $p < 0.05$). These findings demonstrate the long-term efficacy of maralixibat in decreasing sBA levels.

For cholestatic pruritus, measured by Itch-Reported Outcome (Observer) (ItchRO[Obs]), a significant improvement was seen from baseline to Week 18 (ItchRO[Obs], -1.7 [$p < 0.05$]). During the RWD, the effect was maintained in the maralixibat group, but not in the placebo group, with statistical significance demonstrated between the two groups. In the first 48 weeks, 84% of participants had a ≥1-point decrease (clinically meaningful improvement) in their ItchRO(Obs) score at least once. The results for the Clinician Scratch Scale (CSS) were consistent with those for ItchRO(Obs), demonstrating the efficacy of maralixibat in decreasing cholestatic pruritus.

A significant correlation between decreasing sBA and ItchRO(Obs), as reported in ICONIC, demonstrated the causal relationship between the two key clinical markers [13,81].

Shneider *et al.* presented the impact of maralixibat on sBA levels from a pooled analysis (n = 57) of 4 maralixibat clinical studies (ITCH [NCT02057692], IMAGO [NCT01903460], IMAGINE [NCT02047318, long-term follow-up of IMAGO] and IMAGINE-II [NCT02117713, long-term follow-up of ITCH]) [82]. The results showed a -80 μmol/l change from baseline sBA to Week 48. In addition, Kamath *et al.* reported that mean height Z-scores significantly increased from baseline to Week 204 in patients with an sBA response (<200 μmol/l) at Week 48 ($p = 0.0013$). There was no significant change in height Z-scores among patients with sBA ≥200 μmol/l [83].

Safety findings from Gonzales *et al.* 2021a [13] and Shneider *et al.* [82] demonstrated that long-term maralixibat usage was generally well tolerated, with the most common AEs being diarrhea, vomiting and abdominal pain. These events were mild to moderate in severity and transient in nature, with most occurring within the first 4 weeks of treatment and resolving within 1 week.

The impact of maralixibat on HRQoL

Kamath *et al.* [14] reported that pruritus response (≥1-point reduction in ItchRO[Obs]) to maralixibat at Week 48 was associated with statistically significant and clinically meaningful improvements in patients' HRQoL, specifically with sleep-related assessments. The HRQoL items of "trouble sleeping," "difficulty sleeping through the night," and "feeling tired upon waking" had differences of 45.4, 52.9 and 72.4 from baseline to Week 48 in responders versus nonresponders ($p < 0.01$, $p < 0.01$ and $p < 0.001$, respectively). Changes in FIS were also statistically significant and clinically meaningful.

The impact of maralixibat on native liver survival in patients with ALGS

Vandriel *et al.* reported from the largest global ALGS registry, GALA, that the rate of native liver survival at 5, 10 and 18 years was 66.8%, 54.4% and 40.3%, respectively [10]. The cumulative incidence of liver transplant 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), respectively. 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). As previously mentioned, native liver survival rates in patients with ALGS who underwent a surgical biliary diversion revealed a 1.9-fold greater risk of liver transplant/death (95% CI: 1.3–3.0; $p < 0.001$).

Hansen *et al.* [84] performed a comparison between the natural history data from the GALA registry and the pooled maralixibat trials by applying key maralixibat eligibility criteria to GALA patient data. Six-year event-free survival (EFS) rates in the maralixibat group were significantly better than in the GALA control group, 73% and 50%, respectively ($p < 0.0001$), indicating the benefit of maralixibat on EFS in patients with ALGS.

Rosenthal *et al.* [85] reported on 10 ALGS patients who were <1 year of age enrolled in the open-label phase II RISE (MaRalixibat Infant Safety Evaluation) study. Patients received maralixibat for 13 weeks and reported an overall mean change in sBA of -72 μmol/l at Week 13 and was well tolerated.

Odevixibat for the treatment of cholestatic pruritus in patients with ALGS

Odevixibat is an IBAT inhibitor that was recently approved for the treatment of cholestatic pruritus in patients with ALGS ≥12 months of age in the US and is also approved for the treatment of pruritus in patients with PFIC ≥3 months of age in the US and ≥6 months of age in the EU [86,87]. Ovchinsky *et al.* [88,89,90] evaluated the efficacy and safety of odevixibat in patients with ALGS (n = 52) in the pivotal, phase III, double-blind, randomized, placebo-controlled ASSERT clinical trial. The core trial was 24 weeks in duration with an option to enroll in the open-label extension (ASSERT-EXT). The primary pruritus end point was change in scratching from baseline to month 6 (Weeks 21–24), as measured by the PRUCISION observer-reported outcome (ObsRO) caregiver instrument. Pruritus was significantly improved with odevixibat (120 μg/kg/day) versus placebo at the 6-month time point (change from baseline -1.7 vs -0.8; $p = 0.0024$). Bile acid concentration was also significantly reduced with odevixibat versus placebo at month 6 (change from baseline -90 μmol/l vs 22 μmol/l; $p = 0.0012$). The overall incidence of TEAEs was similar across the odevixibat-treated and placebo groups (74% vs 71%).

In the ASSERT-EXT open-label extension (Ovchinsky *et al.*) [91], patients in both the odevixibat and placebo arms received odevixibat for an additional 12 weeks. Patients in the placebo-odevixibat arm showed improvements in pruritus after beginning odevixibat, while improvements were sustained in the odevixibat-odevixibat group. The same trends were observed when evaluating reductions in bile acids.

The impact of odevixibat on HRQoL

In the ASSERT trial, sleep parameters were assessed in both the patients with ALGS and their caregivers. Significant reductions in days sleeping alongside a caregiver ($p \leq 0.001$), days with help falling asleep ($p \leq 0.01$), days with soothing ($p \leq 0.001$) and daytime tiredness ($p \leq 0.05$) were observed with odevixibat compared with placebo [88].

Additional studies on all off-label or unapproved interventions to treat cholestatic pruritus, including usage of approved medications at lower doses, in patients with ALGS can be found in Appendix E.

Discussion

A comprehensive systematic literature review was conducted to identify the epidemiological, clinical, psychosocial and economic burden in ALGS. This review built upon a previous review conducted in 2018 by Kamath *et al.* [94], which focused on liver-related outcomes and identified the epidemiological, natural history, economic and psychosocial burden of ALGS. No studies reporting prevalence or incidence rates met the inclusion criteria for the

literature review. The multisystemic nature of ALGS, the heavy medical and psychosocial burden on both patients and caregivers and the considerable economic costs involved in treatment of ALGS are additional facets of the condition that must be taken into account to understand the full impact of this rare disease.

As derived from this review, ALGS is a rare, life-threatening and devastating disease affecting children. The epidemiological, HRQoL, economic burden and clinical aspects of the disease have been explored and demonstrate recurring themes in terms of how morbidities are measured, with both sBA levels and PedsQL being preferred consistently. The development and approval of disease-modifying treatment options such as IBAT inhibitors in this space give hope for those impacted by the debilitating disease of ALGS.

Advances in molecular diagnosis have helped broaden our understanding of the phenotype associated with *JAG1* and *NOTCH2* variants. However, the lack of genotype–phenotype correlations limits the use of genetic data in clinical practice, as the identification of a disease-causing variant does not provide information about the severity or the individual clinical course of disease. Historically, epidemiological estimates of ALGS (1:30,000 to 1:50,000) are based on the associated genetic variants; however, prevalence based on clinical criteria may produce a lower estimate. New pathogenic variants continue to be described [105] and the estimated prevalence could potentially increase again.

The natural history, morbidity and mortality associated with ALGS were typically defined through single centers, with the majority of the data being outdated. It is acknowledged that where race/ethnicity was reported, the majority of the trials were conducted in White populations. However, there was an effort toward inclusion of underrepresented populations and those limited data are consistent with what was observed in the White population. Vandriel *et al.* [10] presented the most comprehensive natural history data to date using the GALA database, which encompassed centers of various sizes across 29 countries and provided real-world natural history information on liver disease associated with ALGS. The all-cause mortality rate was 8.5% in this cohort. The most common cause of death was complications related to liver or liver transplantation, followed by cardiovascular-related complications, with the majority of deaths occurring before the age of 5 years, indicating the importance of early detection and management.

Pediatric liver transplantation is associated with significant healthcare resource utilization (HRU), including lifelong inpatient and outpatient medical visits and cost burden [16]. Substantial costs of liver transplant evolve from inpatient hospital stays over the first 6 months post-transplantation. Although not included in the aforementioned study, organ availability, medical follow-up and treatment costs required for lifelong immunosuppressive medications are substantial, further increasing HRU. Immunosuppressants have cardiac and renal side effects, which could negatively impact the progression of the underlying disease. Because of the multisystemic nature of ALGS and the high prevalence of cardiac anomalies, some patients may not be eligible for liver transplant due to their cardiac function. Moreover, the GALA study demonstrated that 18% of patients died due to their underlying cardiac complications. Similarly, renal abnormalities have been found in 39% of patients with ALGS, which can lead to complications managing posttransplant immunosuppressive therapy [8,10,16]. Evidence from the recent analysis comparing long-term transplant-free survival in the GALA natural history cohort and the maralixibat cohort suggest that utilization of a pharmacologic interventional therapy may be able to delay and/or reduce the need for liver transplantation and associated complications, potentially leading to a paradigm shift in the treatment of ALGS.

Additional studies focused on pediatric cholestatic liver diseases and the economic and HRU burden of ALGS demonstrated that outpatient visits accounted for the majority of total number of visits [16,70]. These outpatient visits incur a high burden to both the healthcare system and caregivers due to planning and coordination. This demonstrates the high medical resource use of cholestatic liver disease, with a significant number of hospital stays and visits to healthcare professionals. Future studies may inform the impact of a disease-modifying medication for the treatment of ALGS, such as maralixibat, on total cost of care.

The anxiety, fatigue and emotional distress associated with unrelenting itching and scratching severely impact the HRQoL of patients and their caregivers/family. Because of this, children with ALGS may experience increased risk of long-term cognitive deficits and decreased QoL if the pruritus and other symptoms are not controlled [47,48]. Rare diseases, like ALGS, pose specific challenges not only to the patients who are affected but also to their caregivers and families. Parents of children with ALGS face pervasive challenges in meeting medical and social care needs, including emotional, psychosocial, financial and educational [106,107,108]. Failure to understand family/caregiver spillover may lead to underestimates of the societal impact of ALGS as well as the value of new therapeutic interventions.

In recent years, the treatment landscape of ALGS has evolved. Currently, off-label use of treatments such as UDCA, rifampicin and cholestyramine [46,109,110] are still used to provide symptomatic relief despite variable

efficacy and safety concerns, along with the inevitable disease progression toward liver transplantation. The recent approval in both the US and EU of IBAT inhibitors for the treatment of cholestatic pruritus in patients with ALGS has significantly changed the treatment landscape for these patients [79,80]. In clinical studies, maralixibat has demonstrated reduction in sBA and has provided significant and durable improvements in clinically meaningful outcomes in patients with ALGS, including cholestatic pruritus, growth, QoL, sleep and xanthomas [13]. Maralixibat may be considered a disease-modifying treatment since data have shown it can prolong the time to, or reduce the need for, liver transplantation in most patients. This is important because older patients overall have better outcomes post-transplant, including lower rates of rejection and retransplantation. Conversely, younger patients (aged <1 year) have higher rates of rejection, retransplantation and death [84,111]. Odevixibat, another IBAT inhibitor, has been recently approved for the treatment of cholestatic pruritus in patients with ALGS aged ≥1 year in the US and the peer-reviewed publication published in 2024 [89] was captured in the final search date of this review (31 July 2024). Patients saw a decrease in sBA and ItchRO scores when treated with odevixibat in comparison to placebo.

The key limitations of this literature review include a gap in cost-effectiveness analysis for ALGS treatments, with no papers identified. There were also limited findings in the literature for HRQoL burden, cost and resource use studies in ALGS, likely due to the lack of a disease-specific International Classification of Diseases (ICD) code available during the publication of those manuscripts. Since then, the ICD-10 code has been added for ALGS (Q44.71). Due to the pace of research and emerging literature in the field, there may be relevant papers published in the literature after the systematic literature review cutoff date.

This literature review comprehensively explored existing publications to quantify the main epidemiological, burden, cost and resource use and HRQoL outcomes of ALGS and also focused on the newly approved IBAT inhibitors, maralixibat and odevixibat, for the treatment of cholestatic pruritus in patients with ALGS along with off-label medications used for treatment. The recent development of IBAT inhibitors presents a novel tool to reduce sBA, control pruritus and potentially delay and/or reduce the need for liver transplantation in these patients. Specifically, the impact of maralixibat in reducing sBA affects additional manifestations of cholestasis, including reductions in xanthomas and improvements in growth, which contribute to the decision-making process to list a patient for liver transplantation [84]. Based on their disease-modifying potential and ability to transform the lives of patients with ALGS through amelioration of cholestatic-related symptoms along with improvement in HRQoL, IBAT inhibitors are the new standard of care for long-term treatment of patients with ALGS.

Summary points

- Alagille syndrome (ALGS) is a rare, life-threatening, multisystem disease that typically presents in the first 3 months of life with a broad range of clinical manifestations, including cardiac, renal, liver, neurological and vascular disorders. Extensive disease burden, characterized by the wide variety of clinical manifestations, leads to collateral mortality issues in patients with ALGS.
- The multisystemic nature of ALGS, the significant medical and psychosocial burden on both patients and caregivers, and the considerable economic costs involved in treatment of ALGS must be taken into account to understand the full impact of this rare disease. The anxiety, fatigue and emotional distress associated with unrelenting itching and scratching severely impact the health-related quality of life (HRQoL) of patients and their caregivers/family.
- Patients with ALGS have high medical resource use with a significant number of hospital stays and visits to healthcare professionals, underscoring the need for disease-modifying medications to help reduce healthcare costs.
- Prior to the development and approval of ileal bile acid transporter (IBAT) inhibitors, for the treatment of cholestatic pruritus in ALGS, the management of pruritus has been largely supportive; however, pruritus is often refractory to treatment with choleretic agents and is a leading indication for liver transplantation.
- The recent development of IBAT inhibitors presents a novel tool to reduce serum bile acid, control pruritus and potentially delay and/or reduce the need for liver transplantation in these patients.
- Based on their disease-modifying potential and ability to transform the lives of patients with ALGS through amelioration of cholestatic-related symptoms along with improvement in HRQoL, IBAT inhibitors are the future standard of care for long-term treatment of patients with ALGS.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2024-0188

Author contributions

All authors were involved in the analysis, writing, review and decision to submit the manuscript.

Financial disclosure

This study and analysis was funded by Mirum Pharmaceuticals, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

P Bufler has nothing to disclose. R Howard, L Quadrado, G Lacey, J Terner-Rosenthal, A Goldstein and P Vig are employees of and shareholders in Mirum Pharmaceuticals, Inc. D Kelly has received grants from Albireo, AbbVie, Gilead Sciences and Mirum Pharmaceuticals, Inc., is a consultant for Alnylam, Intercept, Mirum Pharmaceuticals, Inc., Takeda, Freeline, GSK, Orphalan, Albireo and Astra Zeneca and has received honoraria from Mirum Pharmaceuticals, Inc. The authors have no other competing interests or relevant affiliations with any organization/entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing dislcosure

Editorial support for the development of this manuscript was provided by Precision AQ and funded by Mirum Pharmaceuticals, Inc.

References

1. Kamath BM, Baker A, Houwen R, Todorova L, Kerkar N. Systematic review: the epidemiology, natural history, and burden of Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 67(2), 148–156 (2018).
2. Saleh M, Kamath BM, Chitayat D. Alagille syndrome: clinical perspectives. *Appl Clin Genet.* 9, 75–82 (2016).
3. Turnpenny PD, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. *Eur. J. Hum. Genet.* 20(3), 251–257 (2012).
4. Li L, Krantz ID, Deng Y *et al.* Alagille syndrome is caused by mutations in human JAGGED1, which encodes a ligand for NOTCH1. *Nat. Genet.* 16(3), 243–251 (1997).
5. McDaniell R, Warthen DM, Sanchez-Lara PA *et al.* NOTCH2 mutations cause Alagille syndrome, a heterogeneous disorder of the notch signaling pathway. *Am. J. Hum. Genet.* 79(1), 169–173 (2006).
6. Oda T, Elkahloun AG, Pike BL *et al.* Mutations in the human JAGGED1 gene are responsible for Alagille syndrome. *Nat. Genet.* 16(3), 235–242 (1997).
7. Gilbert MA, Spinner NB. Alagille syndrome: genetics and functional models. *Curr Pathobiol Rep.* 5(3), 233–241 (2017).
8. Kamath BM, Yin W, Miller H *et al.* Outcomes of liver transplantation for patients with Alagille syndrome: the studies of pediatric liver transplantation experience. *Liver Transpl.* 18(8), 940–948 (2012).
9. Pollock G, Minuk GY. Diagnostic considerations for cholestatic liver disease. *J. Gastroenterol. Hepatol.* 32(7), 1303–1309 (2017).
10. Vandriel SM, Li LT, She H *et al.* Natural history of liver disease in a large international cohort of children with Alagille syndrome: results from the GALA study. *Hepatology* 77(2), 512–529 (2023).
11. Lykavieris P, Hadchouel M, Chardot C, Bernard O. Outcome of liver disease in children with Alagille syndrome: a study of 163 patients. *Gut* 49(3), 431–435 (2001).
12. Emerick KM, Rand EB, Goldmuntz E *et al.* Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 29(3), 822–829 (1999).
13. Gonzales E, Hardikar W, Stormon M *et al.* Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet* 398(10311), 1581–1592 (2021).
14. Kamath BM, Goldstein A, Howard R *et al.* Maralixibat treatment response in Alagille syndrome is associated with improved health-related quality of life. *J. Pediatr.* 252, 68–75 (2023).
15. Menon J, Shanmugam N, Vij M, Rammohan A, Rela M. Multidisciplinary management of Alagille syndrome. *J. Multidiscip. Healthc.* 15, 353–364 (2022).
16. Miloh T, Goldstein A, Howard R *et al.* Costs of pediatric liver transplantation among commercially insured and Medicaid-insured patients with cholestasis in the US. *Liver Transpl.* 29(7), 735–744 (2023).

17. Centre for Reviews and Dissemination. *CRD's guidance for undertaking reviews in health care [Internet]*. CRD, University of York (2009) (Accessed: 13 August 2023). https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf
18. Gilbert MA, Bauer RC, Rajagopalan R *et al.* Alagille syndrome mutation update: comprehensive overview of JAG1 and NOTCH2 mutation frequencies and insight into missense variant classification. *Hum. Mutat.* 40(12), 2197–2220 (2019).
19. Kamath B, Shneider B, Spino C *et al.* Unraveling the relationship between itching, scratch scales and biomarkers in children with Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 65(Suppl. 2), S57–S58 (2017).
20. Lin YH, Lin CC, Wang CC *et al.* Long-term renal dysfunction after pediatric living donor liver transplantation. *Liver Transplant.* 18, S215 (2012).
21. Vandriel S, Li L, She H *et al.* Phenotypic divergence of JAGGED1 and NOTCH2-associated Alagille syndrome: results from the international multicenter GALA study group. *Hepatology* 72, 882A–884A (2020).
22. Ahn KJ, Yoon JK, Kim GB *et al.* Alagille syndrome and a JAG1 mutation: 41 cases of experience at a single center. *Korean J. Pediatr.* 58(10), 392–397 (2015).
23. El-Koofy NM, El-Mahdy R, Fahmy ME *et al.* Alagille syndrome: clinical and ocular pathognomonic features. *Eur. J. Ophthalmol.* 21(2), 199–206 (2011).
24. Cho SJ, Perito ER, Shafizadeh N, Kim GE. Dialogs in the assessment of neonatal cholestatic liver disease. *Hum. Pathol.* 112, 102–115 (2021).
25. Gill KG. Congenital musculoskeletal anomalies - key radiographic findings. *Pediatr. Radiol.* 52(4), 777–785 (2022).
26. Li J, Wu H, Chen S *et al.* Clinical and genetic characteristics of Alagille syndrome in adults. *J Clin Transl Hepatol.* 11(1), 156–162 (2023).
27. Kohaut J, Pommier R, Guerin F *et al.* Abdominal arterial anomalies in children with Alagille syndrome: surgical aspects and outcomes of liver transplantation. *J. Pediatr. Gastroenterol. Nutr.* 64(6), 888–891 (2017).
28. Lykavieris P, Crosnier C, Trichet C, Meunier-Rotival M, Hadchouel M. Bleeding tendency in children with Alagille syndrome. *Pediatrics* 111(1), 167–170 (2003).
29. Quiros-Tejeira RE, Ament ME, Heyman MB *et al.* Variable morbidity in Alagille syndrome: a review of 43 cases. *J. Pediatr. Gastroenterol. Nutr.* 29(4), 431–437 (1999).
30. Kamath BM, Ye W, Goodrich NP *et al.* Outcomes of childhood cholestasis in Alagille syndrome: results of a multicenter observational study. *Hepatol. Commun.* 4(3), 387–398 (2020).
31. Loomes KM, Spino C, Goodrich NP *et al.* Bone density in children with chronic liver disease correlates with growth and cholestasis. *Hepatology* 69(1), 245–257 (2019).
32. Ayoub MD, Kamath BM. Alagille syndrome: diagnostic challenges and advances in management. *Diagnostics (Basel)* 10(11), (2020).
33. Olsen IE, Ittenbach RF, Rovner AJ *et al.* Deficits in size-adjusted bone mass in children with Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 40(1), 76–82 (2005).
34. Garcia MA, Ramonet M, Ciocca M *et al.* Alagille syndrome: cutaneous manifestations in 38 children. *Pediatr. Dermatol.* 22(1), 11–14 (2005).
35. Gopal A, Starr M, Obeid A *et al.* Predictors of vision loss after surgery for macula-sparing rhegmatogenous retinal detachment. *Curr. Eye Res.* 47(8), 1209–1217 (2022).
36. Paez-Escamilla M, Scanga HL, Liasis A, Nischal KK. Macular atrophy in JAG1-related Alagille syndrome: a case series. *Ophthalmic Genet.* 43(2), 230–234 (2022).
37. Leung DH, Sorensen LG, Ye W *et al.* Neurodevelopmental outcomes in children with inherited liver disease and native liver. *J. Pediatr. Gastroenterol. Nutr.* 74(1), 96–103 (2022).
38. Englert C, Grabhorn E, Burdelski M, Ganschow R. Liver transplantation in children with Alagille syndrome: indications and outcome. *Pediatr. Transplant.* 10(2), 154–158 (2006).
39. Ferrara G, Giani T, Lieberman SM *et al.* Alagille syndrome and chronic arthritis: an international case series. *J. Pediatr.* 218, 228–230.e1 (2020).
40. Mainwaring RD, Felmly LM, Collins RT, Hanley FL. Impact of liver dysfunction on outcomes in children with Alagille syndrome undergoing congenital heart surgery. *Eur. J. Cardiothorac. Surg.* 63(1), (2022).
41. Kasahara M, Kiuchi T, Inomata Y *et al.* Living-related liver transplantation for Alagille syndrome. *Transplantation* 75(12), 2147–2150 (2003).
42. Vandriel S, Liting L, She H *et al.* Clinical features and natural history of 1154 Alagille syndrome patients: results from the international multicenter GALA study group. *J. Hepatol.* 73, S554–S555 (2020).
43. Vandriel S, Wang JS, Li L *et al.* Clinical features and outcomes in an international cohort of 731 Alagille syndrome patients from 19 countries. *Hepatology* 70, 55A–56A (2019).
44. Kamath BM, Stein P, Houwen RHJ, Verkade HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver Int.* 40(8), 1812–1822 (2020).

45. Mayo MJ, Pockros PJ, Jones D *et al.* A randomized, controlled, phase 2 study of maralixibat in the treatment of itching associated with primary biliary cholangitis. *Hepatol Commun.* 3(3), 365–381 (2019).
46. Kronsten V, Fitzpatrick E, Baker A. Management of cholestatic pruritus in paediatric patients with Alagille syndrome: the King's College Hospital experience. *J. Pediatr. Gastroenterol. Nutr.* 57(2), 149–154 (2013).
47. Elisofon SA, Emerick KM, Sinacore JM, Alonso EM. Health status of patients with Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 51(6), 759–765 (2010).
48. Kamath BM, Abetz-Webb L, Kennedy C *et al.* Development of a novel tool to assess the impact of itching in pediatric cholestasis. *Patient* 11(1), 69–82 (2018).
49. Emerick KM, Elias MS, Melin-Aldana H *et al.* Bile composition in Alagille syndrome and PFIC patients having partial external biliary diversion. *BMC Gastroenterol.* 8, 47 (2008).
50. Verkade HJ, Bezerra JA, Davenport M *et al.* Biliary atresia and other cholestatic childhood diseases: advances and future challenges. *J. Hepatol.* 65(3), 631–642 (2016).
51. Emerick KM, Whitington PF. Partial external biliary diversion for intractable pruritus and xanthomas in Alagille syndrome. *Hepatology* 35(6), 1501–1506 (2002).
52. Shneider BL, Spino C, Kamath BM *et al.* Placebo-controlled randomized trial of an intestinal bile salt transport inhibitor for pruritus in Alagille syndrome. *Hepatol Commun.* 2(10), 1184–1198 (2018).
53. Wang KS, Tiao G, Bass LM *et al.* Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. *Hepatology* 65(5), 1645–1654 (2017).
54. Valamparampil JJ, Reddy MS, Shanmugam N *et al.* Living donor liver transplantation in Alagille syndrome-single center experience from south Asia. *Pediatr. Transplant.* 23(8), e13579 (2019).
55. Black K, Ziogas IA, Thurm C *et al.* Pediatric liver transplant survival in Alagille syndrome is comparable to biliary atresia - a linked database analysis. *J. Pediatr. Gastroenterol. Nutr.* 75(3), 257–263 (2022).
56. Habash N, Ibrahim SH. The Global Alagille Alliance study: redefining the natural history of Alagille syndrome. *Hepatology* 77(2), 347–349 (2023).
57. Gliwicz-Miedzinska D, Czubkowski P, Jankowska I, Kalicinski P, Pawlowska J. Liver transplantation in Alagille syndrome patients. *Pediatr. Transplant.* 17, 73–73 (2013).
58. OPTN/SRTR 2022 annual data report [Internet]. HRSA. (Accessed: 29 April 2024). https://srtr.transplant.hrsa.gov/annual_reports/2022_ADR_Preview.aspx
59. Chmielik LP, Mielnik-Niedzielska G, Kasprzyk A, Stankiewicz T, Niedzielski A. Physical and psychosocial concept domains related to health-related quality of life (HRQL) in 50 girls and 52 boys between 5 and 18 years old in Poland using the Parent-Reported 50-Item Child Health Questionnaire (CHQ-PF50). *Med. Sci. Monit.* 28, e936801 (2022).
60. Dolezalova P, Ruperto N, Nemcova D *et al.* The Czech version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin. Exp. Rheumatol.* 19(23 Suppl. 4), S45–S49 (2001).
61. Ruperto N, Ravelli A, Pistorio A *et al.* Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. *Clin. Exp. Rheumatol.* 19(23 Suppl. 4), S1–S9 (2001).
62. Kamath BM, Chen Z, Romero R *et al.* Quality of life and its determinants in a multicenter cohort of children with Alagille syndrome. *J. Pediatr.* 167(2), 390–396.e393 (2015).
63. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul. Pediatr.* 3(6), 329–341 (2003).
64. Quadrado L, Mogul D, Gurevich A *et al.* Patient and caregiver burden associated with caring for a child with Alagille syndrome: mixed-methods development of health state vignettes. *Presented at the The Professional Society for Health Economics and Outcomes Research (ISPOR) Europe*. Vienna, Austria; and Virtual (November 6–9, 2022).
65. Quadrado L, Mogul D, Gurevich A *et al.* Caregiver burden associated with caring for a child with Alagille syndrome: a multi-national, quantitative analysis. *Pediatr Gastroenterol Hepatol Nutr.* 75(1), S403–S404 (2022).
66. Annunziato RA, Stuber ML, Supelana CJ *et al.* The impact of caregiver post-traumatic stress and depressive symptoms on pediatric transplant outcomes. *Pediatr. Transplant.* 24(1), e13642 (2020).
67. ClinicalTrials.gov. NCT02160782. (Accessed: 9 December 2024). https://clinicaltrials.gov/study/NCT02160782
68. Gonzales EMS E, Stormon M, Sokal E *et al.* Phase 2 open-label study with a placebo-controlled drug withdrawal period of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with Alagille syndrome: 48-week interim efficacy analysis. *J. Hepatol.* 70, e119–e120 (2019).
69. Gonzales E, Hardikar W, Stormon M *et al.* Maralixibat treatment significantly reduces pruritus and serum bile acids in patients with Alagille syndrome: results from a randomized phase II study with 4 years of follow-up. https://ssrn.com/abstract=3756810 (Accessed: 13 August 2023) (2021).

70. Ebel NH, Goldstein A, Howard R *et al.* Health care resource utilization by patients with Alagille syndrome. *J. Pediatr.* 253, 144–151 (2023).
71. Bhalerao A, Mannu GS. Management of pruritus in chronic liver disease. *Dermatol. Res. Pract.* 2015, 295891 (2015).
72. Rodrigo M, Dong X, Chien D, Karnsakul W. Cholestatic pruritus in children: conventional therapies and beyond. *Biology (Basel)* 12(5), (2023).
73. Kamath BM, Loomes KM, Piccoli DA. Medical management of Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 50(6), 580–586 (2010).
74. Dawson PA, Lan T, Rao A. Bile acid transporters. *J. Lipid Res.* 50(12), 2340–2357 (2009).
75. Xiao L, Pan G. An important intestinal transporter that regulates the enterohepatic circulation of bile acids and cholesterol homeostasis: the apical sodium-dependent bile acid transporter (SLC10A2/ASBT). *Clin. Res. Hepatol. Gastroenterol.* 41(5), 509–515 (2017).
76. Al-Dury S, Marschall HU. Ileal bile acid transporter inhibition for the treatment of chronic constipation, cholestatic pruritus, and NASH. *Front. Pharmacol.* 9, 931 (2018).
77. Miethke AG, Zhang W, Simmons J *et al.* Pharmacological inhibition of apical sodium-dependent bile acid transporter changes bile composition and blocks progression of sclerosing cholangitis in multidrug resistance 2 knockout mice. *Hepatology* 63(2), 512–523 (2016).
78. Tiessen RG, Kennedy CA, Keller BT *et al.* Safety, tolerability and pharmacodynamics of apical sodium-dependent bile acid transporter inhibition with volixibat in healthy adults and patients with type 2 diabetes mellitus: a randomised placebo-controlled trial. *BMC Gastroenterol.* 18(1), 3 (2018).
79. European Medicines Agency (EMA). Livmarli oral solution. Summary of product characteristics. (2024) (Accessed: 25 July 25 2024). https://www.ema.europa.eu/en/documents/product-information/livmarli-epar-product-information_en.pdf
80. Food and Drug Administration (FDA). Livmarli (maralixibat) oral solution. Prescribing information. (2024) (Accessed: 15 August 2024). https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214662s000lbl.pdf
81. Gonzales EM, Vig P, Tucker E *et al.* Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome. *Hepatology* 72(Suppl. 1), 223A (2020).
82. Shneider BL, Spino CA, Kamath BM *et al.* Impact of long-term administration of maralixibat on children with cholestasis secondary to Alagille syndrome. *Hepatol. Commun.* 6(8), 1922–1933 (2022).
83. Kamath BM, Mogul DB, Baek M, Nunes T, Vig P. Maralixabat improves growth in patients with alagile syndrome: a 4-year analysis. *Presented at the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Annual Meeting*. Copenhagen, Denmark (June 22–25, 2022).
84. Hansen BE, Vandriel SM, Vig P *et al.* Event-free survival of maralixibat-treated patients with Alagille syndrome compared to a real-world cohort from GALA. *Hepatology* 79(6), 1279–1292 (2023).
85. Rosenthal P, Thompson R, Jankowska I *et al.* Safety and tolerability of maralixibat in infants from 2 months of age with Alagille syndrome or progressive familial intrahepatic cholestasis: results from the RISE study. *J. Pediatr. Gastroenterol. Nutr.* 77(1 Suppl. 1), S262–S263 (2023).
86. Food and Drug Administration (FDA). Bylvay (odevixibat). Prescribing information. (2021) (Accessed: 29 April 2024) https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215498s000lbl.pdf
87. European Medicines Agency (EMA). Bylvay (odevixibat). Summary of product characteristics. (2024) (Accessed: 29 April 2024). https://www.ema.europa.eu/en/documents/product-information/bylvay-epar-product-information_en.pdf
88. Ovchinsky N, Aumar M, Alastair Baker A *et al.* Efficacy and safety of odevixibat in patients with Alagille syndrome: top-line results from ASSERT, a phase III, double-blind, randomized, placebo-controlled study. *Presented at the American Association for the Study of Liver Disease (AASLD) The Liver Meeting*. Washington, DC, USA (November 4–8, 2022).
89. Ovchinsky N, Aumar M, Baker A *et al.* Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase III, double-blind, randomised, placebo-controlled trial. *The Lancet Gastroenterology & Hepatology* 9(7), 632–645 (2024).
90. Ovchinsky N, Savage J, Kjems L, Horn P. The ASSERT study: a phase III double-blind, randomized, placebo-controlled study of the safety and efficacy of odevixibat in patients with Alagille syndrome. *J. Pediatr. Gastroenterol. Nutr.* 73(1 Suppl. 1), S191–S192 (2021).
91. Ovchinsky N, Aumar M, Baker A *et al.* Efficacy and safety of odevixibat in patients with Alagille syndrome: interim results from the open-label, phase III ASSERT-EXT study. *J. Pediatr. Gastroenterol. Nutr.* 76(Suppl. 1), 701–703 (2023).
92. Foster B, Gauthier M, Vig P *et al.* PIH76 Itch reported outcome tool for caregivers of pediatric patients with cholestatic liver disease: an analysis of validation and scoring from the ICONIC maralixibat study. *Value Health* 23, S166 (2020).
93. Gonzales EM, Sturm E, Stormon M *et al.* Durability of treatment effect with long-term maralixibat in children with Alagille syndrome: 4-year safety and efficacy results from the ICONIC study. *Hepatology* 70, 1479A (2019).
94. Kamath B, Goldstein A, Howard R *et al.* Response to treatment with maralixibat in Alagille syndrome is associated with improved health-related quality of life. *J. Pediatr. Gastroenterol. Nutr.* 73(Suppl. 1), S207–S208 (2021).

95. ClinicalTrials.gov. NCT01903460. (Accessed: 9 December 9 2024). https://clinicaltrials.gov/study/NCT01903460?cond=NCT01903460&rank=1

96. ClinicalTrials.gov. NCT04168385. (Accessed: 9 December 9 2024). https://clinicaltrials.gov/study/NCT04168385?cond=NCT04168385%20&rank=1

97. The GLobal ALagille Alliance Study (GALA). Participating Centres. (Accessed: 13 August 2023). https://www.galastudy.com/participating-centres

98. Murray K, Kamath B, Gonzales E *et al.* Clinical benefits of maralixibat for patients with Alagille syndrome are durable through 7 years of treatment: data from the MERGE study. *Presented at the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Annual Meeting (NASPGHAN)*. Hollywood, Florida, USA (November 6–9, 2024).

99. ClinicalTrials.gov. NCT04729751. (Accessed: 9 December 9 2024). https://clinicaltrials.gov/study/NCT04729751?cond=NCT04729751&rank=1

100. Gonzales E, Jankowska I, Horslen S *et al.* Safety and tolerability of maralixibat in infants from 2 months of age with Alagille syndrome or progressive familial intrahepatic cholestasis: results from the RISE study. *J. Pediatr. Gastroenterol. Nutr.* 76(Suppl. 1), 777 (2023).

101. Ovchinsky N, Aumar M, Baker AJ *et al.* Outcomes with odevixibat treatment in patients with Alagille syndrome: analysis of pruritus responders from the phase III ASSERT study. *Hepatology* 78, S2106–S2107 (2023).

102. Ovchinsky N, Aumar MB, Baker A *et al.* Changes in hepatic parameters in patients with Alagille syndrome treated with odevixibat: pooled data from the phase III ASSERT and ASSERT-EXT studies. *J. Pediatr. Gastroenterol. Nutr.* 77(1 Suppl. 1), S256–S257 (2023).

103. Gonzales E, Jankowska I, Horslen SP *et al.* Safety and tolerability characterization of maralixibat in infants with ALGS from 2 months of age: interim results from the RISE study. *Hepatology* 77(5), E135 (2023).

104. Ovchinsky N, Aumar M, Baker A *et al.* Efficacy and safety of odevixibat in patients with Alagille syndrome: top-line results from ASSERT, a phase III, double-blind, randomized, placebo-controlled study. *J. Pediatr. Gastroenterol. Nutr.* 76(Suppl. 1), 698–700 (2023).

105. Gilbert MA, Keefer-Jacques E, Jadhav T *et al.* Functional characterization of 2,832 JAG1 variants supports reclassification for Alagille syndrome and improves guidance for clinical variant interpretation. *Am. J. Hum. Genet.* 111(8), 1656–1672 (2024).

106. Cardinali P, Migliorini L, Rania N. The caregiving experiences of fathers and mothers of children with rare diseases in Italy: challenges and social support perceptions. *Front Psychol.* 10, 1780 (2019).

107. Dogba MJ, Bedos C, Durigova M *et al.* The impact of severe osteogenesis imperfecta on the lives of young patients and their parents - a qualitative analysis. *BMC Pediatr.* 13, 153 (2013).

108. Miyazaki ET, Dos Santos R Jr, Miyazaki MC *et al.* Patients on the waiting list for liver transplantation: caregiver burden and stress. *Liver Transpl.* 16(10), 1164–1168 (2010).

109. Kronsten VT, Fitzpatrick E, Baker A. Management of pruritus in paediatric patients with Alagille syndrome: a review of 15 years' experience. *J. Pediatr. Gastroenterol. Nutr.* 52, E83 (2011).

110. Thebaut A, Habes D, Gottrand F *et al.* Sertraline as an additional treatment for cholestatic pruritus in children. *J. Pediatr. Gastroenterol. Nutr.* 64(3), 431–435 (2017).

111. Kwong AJ, Devuni D, Wang C *et al.* Outcomes of liver transplantation among older recipients with nonalcoholic steatohepatitis in a large multicenter US cohort: the re-evaluating age limits in transplantation consortium. *Liver Transpl.* 26(11), 1492–1503 (2020).