GASTROENTEROLOGY AND HEPATOLOGY

Cite as: Archiv EuroMedica. 2026. 16; 5. DOI 10.35630/2026/16/Iss.5.09

Received 19 September 2026;
Accepted 27 October 2026;
Published 27 October 2026

IBAT INHIBITION IN CHRONIC CHOLESTATIC LIVER DISEASES: FROM PRURITUS CONTROL TO POTENTIAL DISEASE MODIFICATION

Dagmara Laufer[1], Filip Chodań[1], Adam Miler[1], Estera Sośniecka[1], Olga Klimczak[1], Krystian Domeracki[1] ✉

[1] Medical University of Silesia, Katowice, Poland

✉ krystiandomeracki5@icloud.com

ABSTRACT

Background

Chronic cholestatic liver diseases disrupt bile acid homeostasis and may cause severe pruritus that impairs quality of life. Conventional treatments often provide incomplete relief. Ileal bile acid transporter (IBAT) inhibition reduces enterohepatic bile acid recirculation, offering a targeted approach to cholestatic pruritus.

Aim

To synthesize the current evidence on IBAT inhibition in chronic cholestatic liver diseases, focusing on its mechanisms of action, efficacy in controlling pruritus, effects on liver-related outcomes, safety, and potential for disease modification.

Materials and Methods

PubMed, Google Scholar, and ClinicalTrials.gov were searched for publications from January 2016 to August 2026; the final search was on 25 August 2026. Clinical, observational, preclinical, and guideline-based evidence on IBAT inhibition in chronic cholestatic liver diseases was narratively synthesized, focusing on efficacy, safety, liver-related outcomes, and potential disease modification.

Results

IBAT inhibitors reduced pruritus and serum bile acids in several cholestatic disorders, with effects varying across studies. Odevixibat and maralixibat improved pruritus in PFIC and Alagille syndrome, while linerixibat showed efficacy in PBC. Evidence for volixibat remains preliminary. Observational associations with improved native liver and event-free survival do not establish disease modification. Diarrhea was the most common adverse event; fat-soluble vitamin deficiency and liver test abnormalities are additional safety concerns.

Conclusions

IBAT inhibition represents an established therapeutic approach for cholestatic pruritus in selected cholestatic disorders. However, its effects on long-term liver disease progression, the need for liver transplantation, and mortality remain unestablished. Further adequately powered, long-term studies using clinically meaningful endpoints are needed to determine whether sustained IBAT inhibition can modify the natural history of chronic cholestatic liver disease.

Keywords: IBAT inhibition; odevixibat; maralixibat; linerixibat; volixibat; cholestatic pruritus

INTRODUCTION

Chronic cholestatic liver diseases comprise a heterogeneous group of disorders characterized by impaired bile formation, secretion, or flow, resulting in the accumulation of bile acids and other biliary constituents within the liver and systemic circulation [1]. Among the most clinically relevant entities are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), which predominantly affect adults, as well as inher-

ited cholestatic disorders such as progressive familial intrahepatic cholestasis (PFIC) and Alagille syndrome (ALGS), which commonly present during childhood [2–5].

Despite substantial differences in their etiology, genetic background, and anatomical site of biliary dysfunction, these diseases share disturbances in bile acid homeostasis and enterohepatic bile acid circulation as important components of their pathophysiology [1,6]. Persistent retention of potentially toxic bile acids may promote hepatocellular and cholangiocyte injury, inflammatory responses, and activation of fibrogenic pathways, thereby contributing to progressive liver fibrosis and, in advanced cases, cirrhosis, hepatic decompensation, and liver failure [1,6,7]. In patients with advanced or treatment-refractory disease, liver transplantation may ultimately become necessary, particularly in the setting of decompensated liver disease or severe disease-related complications [8–10].

Pruritus is one of the most characteristic and burdensome extrahepatic manifestations of cholestatic liver disease. Although nonspecific and therefore not diagnostic of any particular cholestatic disorder, cholestatic pruritus may occur across a broad spectrum of diseases, including PBC, PSC, PFIC, and ALGS, as well as transient or nonchronic cholestatic conditions such as biliary obstruction and intrahepatic cholestasis of pregnancy.

Its prevalence varies substantially according to the underlying disease, disease stage, and method of assessment. In a recent systematic review and meta-analysis including more than 13,000 patients with PBC, pruritus was reported in approximately 33% of patients, whereas a prospective multicenter study found pruritus in 52.7% of patients with PSC [11,12]. In inherited cholestatic disorders, pruritus is particularly prominent, with severe pruritus reported in approximately 76–80% of patients with PFIC and pruritus affecting approximately 59–88% of patients with ALGS [4,13].

Beyond its subjective discomfort, persistent cholestatic pruritus may cause excoriations and other skin lesions and substantially interfere with sleep, daily functioning, and psychological well-being. Severe pruritus has been associated with sleep disturbance, fatigue, impaired concentration, irritability, and reduced school or work performance, particularly in patients with inherited cholestatic disorders [14]. In adults with PBC and PSC, clinically significant pruritus is likewise associated with impaired health-related quality of life, sleep disturbances, and psychological distress [15,16].

The pathogenesis of cholestatic pruritus is complex and remains incompletely understood. Although bile acids accumulate during cholestasis, their circulating concentra-

tions do not consistently correlate with the presence or severity of pruritus, indicating that bile acid retention alone is insufficient to explain the development of itch [17,18]. Several pruritogenic pathways have been implicated, including bile acid-mediated activation of sensory neurons, autotaxin (ATX)–lysophosphatidic acid (LPA) signaling, and opioid, serotonergic, and histaminergic pathways [18,19]. Among these mechanisms, ATX-mediated generation of LPA has emerged as an important pathway, with serum ATX activity correlating with itch intensity in patients with cholestatic disorders [19]. More recently, the Mas-related G protein-coupled receptor X4 (MRGPRX4), expressed on human sensory neurons, has been identified as a bile acid-responsive receptor that may directly contribute to cholestatic itch [20]. Overall, cholestatic pruritus appears to result from interactions between circulating pruritogenic mediators and peripheral sensory pathways rather than from bile acid accumulation alone.

Management of cholestatic pruritus remains challenging, and treatment recommendations have historically been based on a stepwise approach [21]. Bile acid sequestrants, particularly cholestyramine, are generally recommended as first-line pharmacological therapy, followed by rifampicin, opioid antagonists such as naltrexone, and selective serotonin reuptake inhibitors such as sertraline in patients with persistent symptoms. However, the evidence supporting these conventional therapies is heterogeneous, with several recommendations based on relatively small clinical trials and variable treatment responses. Rifampicin, although considered one of the most effective conventional agents, may be limited by hepatotoxicity and other adverse effects, while opioid antagonists and sertraline are frequently associated with tolerability limitations. Consequently, a substantial proportion of patients remain symptomatic despite conventional treatment [22]. In selected patients with severe, treatment-refractory cholestatic pruritus, interventional approaches may be considered, including biliary drainage, surgical interruption of the enterohepatic circulation, extracorporeal therapies such as albumin dialysis or plasmapheresis, and, in highly selected cases, liver transplantation [23]. These therapeutic challenges underscore the need for novel and more molecularly targeted approaches to the management of cholestatic pruritus. Among emerging therapeutic strategies, pharmacological inhibition of the ileal bile acid transporter (IBAT) has attracted increasing scientific and clinical interest. The growing body of literature addressing IBAT inhibition across different chronic cholestatic liver diseases, together with the expanding number of investigated agents and clinical settings, warrants a comprehensive synthesis of the current evidence.

Although the antipruritic efficacy of IBAT inhibitors has been demonstrated in several cholestatic disorders, it remains unclear whether sustained treatment reduces liver

disease progression, the need for transplantation, or mortality.

AIM

The aim of this narrative review was to critically evaluate the current evidence on IBAT inhibition in chronic cholestatic liver diseases, including the mechanisms underlying its therapeutic effects, its efficacy in controlling cholestatic pruritus, effects on liver-related outcomes, safety profile, and potential for disease modification.

Objectives

1. To summarize the molecular basis and mechanisms underlying the therapeutic effects of IBAT inhibition in chronic cholestatic liver diseases.
2. To critically evaluate the available evidence on the efficacy and safety of IBAT inhibitors, with particular emphasis on the control of cholestatic pruritus and their effects on biochemical and liver-related outcomes.
3. To assess the current clinical and regulatory landscape of IBAT inhibitors, distinguish established indications from investigational applications, and examine their potential for disease modification, while identifying key limitations and gaps in the current evidence.

METHODS

This narrative review was conducted following a structured search of the available scientific literature. Relevant publications were identified through searches of PubMed, Google Scholar, and ClinicalTrials.gov. The primary search included studies published between January 2016 and August 2026, with the final search performed on 25 August 2026. Earlier publications were considered when they provided fundamental insights into bile acid physiology, enterohepatic circulation, IBAT biology, the pathophysiology of cholestatic pruritus, or landmark studies that remained relevant to the development of IBAT-targeted therapies.

Search terms were tailored to the requirements of each database. The PubMed search employed combinations of the following terms: ("cholestatic liver disease" OR cholestasis OR "primary biliary cholangitis" OR PBC OR "primary sclerosing cholangitis" OR PSC OR "progressive familial intrahepatic cholestasis" OR PFIC OR "Alagille syn-

drome" OR ALGS) AND ("ileal bile acid transporter" OR IBAT OR "apical sodium-dependent bile acid transporter" OR ASBT OR "bile acid transporter inhibitor" OR odevixibat OR maralixibat OR linerixibat OR volixibat OR elobixibat OR "IBAT inhibitor") AND (pruritus OR itch OR "bile acid" OR fibrosis OR "liver outcomes" OR "disease modification" OR safety OR efficacy). Additional searches were performed using the individual names of IBAT inhibitors and the specific cholestatic diseases in order to identify relevant clinical and mechanistic studies that might not have been retrieved by the primary search strategy.

In Google Scholar, combinations of the keywords chronic cholestatic liver disease, cholestasis, primary biliary cholangitis, primary sclerosing cholangitis, progressive familial intrahepatic cholestasis, Alagille syndrome, IBAT, ileal bile acid transporter, ASBT, odevixibat, maralixibat, linerixibat, volixibat, elobixibat, cholestatic pruritus, bile acids, liver outcomes, fibrosis, disease modification, clinical trial, and treatment outcomes were used. ClinicalTrials.gov was searched using disease-specific and drug-specific terms to identify completed, ongoing, and recently reported clinical trials evaluating IBAT inhibition in cholestatic disorders.

Sources eligible for inclusion comprised English-language randomized controlled trials, prospective and retrospective clinical studies, observational studies, preclinical and experimental research, clinical practice guidelines, review articles, and relevant clinical trial registry records addressing IBAT inhibition or its biological and clinical relevance in chronic cholestatic liver diseases. Preclinical studies were included primarily when they provided relevant information on the molecular mechanisms of IBAT inhibition, bile acid homeostasis, or potential disease-modifying effects and were not used to draw conclusions regarding clinical efficacy or safety. Relevant conference abstracts without a corresponding full-text publication were also eligible for inclusion when they provided pertinent clinical or mechanistic information. Manufacturer-provided communications were considered supplementary sources when relevant information could not be adequately obtained from peer-reviewed publications or other publicly available sources, and their content was interpreted cautiously in light of their non-peer-reviewed nature. Sources were excluded if they were unrelated to IBAT inhibition or chronic cholestatic liver disease, did not provide relevant mechanistic or clinical information, consisted of letters lacking relevant original data, were duplicate reports, or were publications in languages other than English.

The screening process involved an initial assessment of titles and abstracts, followed by full-text evaluation of potentially relevant publications. Data extracted from the included sources comprised the mechanism of IBAT inhibition, characteristics of the in-

vestigated agent, study design and phase, patient population and underlying cholestatic disease, treatment duration and dose, effects on pruritus and patient-reported outcomes, biochemical and liver-related outcomes, safety findings, and regulatory status, where applicable. Particular attention was given to the maturity of the available evidence and to the distinction between established clinical indications and investigational applications. The included evidence was subsequently synthesized narratively according to the underlying disease, therapeutic agent, clinical indication, and outcome domain.

Overall, 59 publications and registry records met the eligibility criteria and were included in the final narrative synthesis. As this work represents a narrative review, the literature selection and synthesis were descriptive and were not conducted according to a formal systematic review protocol.

RESULTS

The ileal bile acid transporter (IBAT), also known as the apical sodium-dependent bile acid transporter (ASBT) and encoded by SLC10A2, is a key component of the enterohepatic circulation of bile acids. It is expressed predominantly on the apical membrane of terminal ileal enterocytes, where it mediates the sodium-dependent uptake of bile acids from the intestinal lumen. Bile acids subsequently undergo intracellular transport and are exported across the basolateral membrane before returning to the liver through the portal circulation, thereby allowing efficient recycling of the bile acid pool. Experimental studies have demonstrated the central role of SLC10A2 in intestinal bile acid reclamation, with loss of transporter function resulting in marked impairment of bile acid absorption and interruption of enterohepatic circulation [24–26].

Pharmacological inhibition of IBAT reduces ileal bile acid reabsorption, thereby increasing fecal bile acid excretion and decreasing enterohepatic bile acid recycling. This leads to a reduction in the circulating bile acid pool and induces compensatory changes in hepatic bile acid synthesis. By altering enterohepatic bile acid homeostasis, IBAT inhibition may consequently reduce the systemic exposure to bile acids implicated in cholestatic pruritus [27].

Several IBAT inhibitors, including odevixibat, maralixibat, linerixibat, and volixibat, have been investigated across different chronic cholestatic liver diseases, with clinical development focusing primarily on the management of cholestatic pruritus.

Odevixibat

The efficacy of odevixibat in progressive familial intrahepatic cholestasis (PFIC) was evaluated in the phase III PEDFIC 1 trial, a 24-week, randomized, double-blind, placebo-controlled study including 62 children with PFIC type 1 or 2. Patients were randomly assigned to receive once-daily odevixibat at doses of 40 µg/kg/day (n=23), 120 µg/kg/day (n=19), or placebo (n=20). Pruritus response was assessed using the observer-reported outcome (ObsRO) scratching score, a caregiver-reported measure of scratching severity rated on a 5-point scale from 0 (no scratching) to 4 (worst possible scratching). A positive pruritus assessment (PPA) was defined as a scratching score of ≤1 or a reduction of at least 1 point from baseline. Two primary endpoints were assessed: the proportion of positive pruritus assessments (PPAs) over 24 weeks and the proportion of patients achieving a serum bile acid response at week 24. The proportion of PPAs was significantly higher in the pooled odevixibat group than in the placebo group (55% vs. 30%; mean difference, 25.0%; 95% CI, 8.5–41.5; p=0.0038). Similarly, a serum bile acid response was achieved by 33% of patients receiving odevixibat compared with none of the patients receiving placebo (adjusted difference, 30.7%; 95% CI, 12.6–48.8; p=0.0030). The most common treatment-emergent adverse events were diarrhoea or frequent bowel movements, occurring in 31% of patients receiving odevixibat and 10% of those receiving placebo. Overall, odevixibat significantly reduced pruritus and serum bile acid concentrations compared with placebo and was generally well tolerated [28].

Long-term efficacy and safety of odevixibat were investigated in PEDFIC 2, an open-label, single-arm phase III extension study with a planned treatment duration of 72 weeks. The study enrolled 69 patients receiving odevixibat at 120 µg/kg/day: patients previously treated with odevixibat in PEDFIC 1 (cohort 1A; n=34), those previously receiving placebo (cohort 1B; n=19), and newly enrolled patients (cohort 2; n=16). The interim analysis assessed outcomes through Week 24 of PEDFIC 2, corresponding to up to 48 weeks of cumulative treatment in cohort 1A and 24 weeks in cohorts 1B and 2. Reductions in serum bile acid concentrations were observed across all cohorts, with mean decreases of 201, 144, and 104 µmol/L in cohorts 1A, 1B, and 2, respectively. Serum bile acid response criteria were met by 55%, 27%, and 36% of patients, respectively. Improvements in pruritus were sustained. The proportions of positive pruritus assessments were 33%, 56%, and 62% in cohorts 1A, 1B, and 2, respectively.

In cohort 1A, the mean pruritus score decreased by 1.6 points from the PEDFIC 1 baseline. Growth parameters also improved in continuously treated patients, with mean

height and weight Z-scores increasing by 0.4 points each. Changes in hepatic biochemical markers varied across cohorts, although reductions in selected parameters, including ALT, AST, and total bilirubin, were observed. Improvements in sleep-related outcomes were also reported, including a reduced need for assistance with falling asleep and soothing [29].

The PEDFIC 2 study has since been completed, although the full 72-week results have not yet been published in a peer-reviewed full-text article [30].

Real-world evidence further supported the efficacy of odevixibat in PFIC. Di Giorgio et al. conducted a multicentre prospective study including 24 children with PFIC (median age, 6.6 years), of whom 16 (67%) had classical PFIC subtypes (PFIC1–3) and 8 (33%) had rarer forms, including PFIC4, PFIC5, PFIC6, and PFIC9. Patients received odevixibat at 40 µg/kg/day, with escalation to 120 µg/kg/day when required, and were followed for 6 months. Serum bile acid concentrations decreased markedly, from a median of 317.1 µmol/L at baseline to 45.6 µmol/L at Month 6 ($p<0.001$). Overall, 75% of patients achieved the predefined serum bile acid response, defined as a ≥70% reduction from baseline or a serum bile acid concentration below 70 µmol/L. Pruritus also improved, with a mean reduction in the Physician Global Impression of Symptoms score of 1.7 points and a pruritus response observed in 73% of patients. Importantly, the reduction in pruritus correlated significantly with the reduction in serum bile acids at both Month 3 (Spearman's $\rho=0.54$; $p=0.007$) and Month 6 ($\rho=0.45$; $p=0.037$), supporting a relationship between biochemical response to IBAT inhibition and symptomatic improvement. A baseline serum bile acid concentration above 333.5 µmol/L was associated with a 17-fold higher risk of treatment non-response ($p<0.001$). Dose escalation was required in 30% of patients, while no serious adverse events were reported [31].

Recent evidence has also highlighted potential biomarkers of response to odevixibat. In a blinded post hoc analysis of 41 patients with BSEP deficiency enrolled in the PEDFIC programme, pretreatment serum bile acid composition was assessed to identify predictors of subsequent biochemical response. Responders had higher pretreatment proportions of unconjugated cholic acid and chenodeoxycholic acid, while the combined concentration of these bile acids showed the strongest discriminatory performance (AUC 0.76, 95% CI 0.61–0.92; $p=0.001$). When at least one of three predefined bile acid cutoffs was met, 36 of 41 patients (87.8%) were correctly classified as subsequent responders or non-responders, with 89.5% sensitivity and 86.4% specificity. These findings suggest that pretreatment bile acid composition may help identify patients with BSEP deficiency who are more likely to respond to IBAT inhibition and

support the concept that residual biliary bile acid secretory capacity may influence treatment efficacy [32].

Additional real-world evidence has emerged from patients with PFIC1 who had previously undergone liver transplantation. In a retrospective multicentre case series of nine patients, odevixibat was administered primarily for post-transplant diarrhoea and/or hepatic steatosis, at doses of 30–120 µg/kg/day for a median of 13 months. Most patients experienced improvement in diarrhoea and its impact on daily activities, while hepatic steatosis improved in three of five patients with available pre- and post-treatment assessments and remained unchanged in two. Although these findings suggest that IBAT inhibition may have clinical effects even after liver transplantation, the small sample size and retrospective design limit their generalisability and preclude conclusions regarding causality [33].

The efficacy of odevixibat in Alagille syndrome (ALGS) was evaluated in the phase III ASSERT trial, a double-blind, randomized, placebo-controlled study. Fifty-two children with genetically confirmed ALGS, significant pruritus, and elevated serum bile acid concentrations were randomized 2:1 to receive odevixibat 120 µg/kg/day (n=35) or placebo (n=17) for 24 weeks. Odevixibat significantly reduced caregiver-reported scratching compared with placebo. Mean scratching scores decreased from 2.8 at baseline to 1.1 at Weeks 21–24 in the odevixibat group, corresponding to an LS mean change of −1.7, compared with −0.8 with placebo; the between-group difference was −0.9 points (95% CI, −1.4 to −0.3; p=0.0024). The antipruritic effect emerged early during treatment and was sustained throughout the 24-week study period. Odevixibat also significantly reduced serum bile acid concentrations. Mean serum bile acids decreased from 237 to 149 µmol/L with odevixibat, compared with an increase from 246 to 271 µmol/L with placebo. The LS mean change was −90 µmol/L with odevixibat versus +22 µmol/L with placebo, yielding a between-group difference of −113 µmol/L (95% CI, −179 to −47; p=0.0012). Thus, the reduction in pruritus was accompanied by a substantial reduction in circulating bile acid burden.

The clinical effects of odevixibat extended beyond pruritus intensity. Improvements were observed across several sleep-related outcomes, including measures of difficulty falling asleep, the need for nocturnal soothing, and sleeping with a caregiver, suggesting that reduction of cholestatic pruritus may translate into broader improvements in nighttime functioning. Patient- and caregiver-reported quality-of-life measures also generally favoured odevixibat, although these findings were less robust than the primary pruritus and key secondary serum bile acid endpoints. In contrast, no convincing treatment-related improvement in growth parameters was demonstrated during the

24-week study, with changes in height, weight, and BMI Z-scores showing little difference between treatment groups.

Similarly, hepatic biochemical parameters were not established as efficacy endpoints. Changes in transaminases and other liver tests were heterogeneous, and transient increases in ALT and/or AST occurred in some odevixibat-treated patients without evidence suggesting drug-induced liver injury. These findings therefore do not currently provide sufficient evidence that odevixibat modifies the underlying hepatic disease in ALGS. Odevixibat was generally well tolerated. Diarrhoea was the most common treatment-emergent adverse event, occurring in 29% of patients receiving odevixibat compared with 6% receiving placebo, while serious adverse events occurred in 14% and 12%, respectively. No patients discontinued treatment because of adverse events and no deaths occurred [34].

The phase III BOLD trial (NCT04336722) evaluated odevixibat in 254 children with biliary atresia following Kasai hepatoportoenterostomy, with native liver survival as the primary endpoint. Preliminary topline results indicated that odevixibat did not significantly improve native liver survival compared with placebo. As full efficacy and safety results have not yet been published, these findings should be considered preliminary [35]. Ongoing studies, including the ASSERT-EXT extension study and prospective real-world registries in ALGS and PFIC, are expected to provide further data on the long-term efficacy and safety of odevixibat [36–38].

Maralixibat

In the phase 2 ICONIC study, Gonzales et al. evaluated maralixibat in 31 children with Alagille syndrome (ALGS), cholestasis, and severe pruritus. Following 18 weeks of open-label treatment with maralixibat at 380 µg/kg once daily, participants were randomized to either continue maralixibat or switch to placebo for 4 weeks. During the randomized withdrawal period, discontinuation of maralixibat resulted in a significant increase in serum bile acid (sBA) concentrations of 94 µmol/L (95% CI, 23–164) and worsening of pruritus by 1.7 points (95% CI, 1.2–2.2), whereas both effects were maintained in patients continuing active treatment.

The primary endpoint was achieved, with a least-squares mean treatment difference in sBA change of −117 µmol/L (95% CI, −232 to −2). From baseline to week 48, maralixibat treatment was associated with reductions in sBA concentrations of 96 µmol/L (95% CI, −162 to −31) and pruritus severity of 1.6 points (95% CI, −2.1 to −1.1). Among patients who continued treatment through week 204 (n=15), these improvements were main-

tained, supporting the durability of the biochemical and symptomatic effects of long-term IBAT inhibition. Maralixibat was generally well tolerated, with gastrointestinal adverse events being the most frequently reported and predominantly mild-to-moderate in severity [39].

Further analyses of maralixibat-treated patients demonstrated that the clinical benefits extended beyond pruritus control. In the ICONIC cohort, patients achieving a clinically meaningful reduction in pruritus also showed improvements in fatigue and family impact, indicating a beneficial effect on health-related quality of life. Moreover, long-term follow-up of adolescents receiving maralixibat showed persistent reductions in pruritus and serum bile acid concentrations into young adulthood, supporting the durability of treatment effects over time [40–42].

Moreover, in a long-term analysis of 76 patients treated with maralixibat for a median of 4.7 years, 16 clinical events occurred, including liver transplantation (n=10), hepatic decompensation (n=3), death (n=2), and surgical biliary diversion (n=1). Overall 6-year event-free and transplant-free survival were 76% and 79%, respectively. Importantly, patients who achieved a >1-point reduction in pruritus at week 48 had higher 6-year event-free survival than those without such improvement (88% vs. 57%; p=0.005); similarly, event-free survival was higher among patients with week-48 serum bile acid concentrations <200 µmol/L (85% vs. 49%; p=0.001) and total bilirubin <6.5 mg/dL (90% vs. 43%; p<0.0001). These parameters were also predictive of 6-year transplant-free survival, suggesting that early biochemical and symptomatic responses to maralixibat may be associated with more favorable long-term clinical outcomes [43].

As presented in Table 1 in the phase 2 INDIGO study, 33 children with PFIC received maralixibat, including 8 patients with FIC1 deficiency and 25 with BSEP deficiency; among the latter, 19 had at least one non-truncating BSEP (nt-BSEP) mutation and 6 had biallelic truncating BSEP (t-BSEP) mutations. Although no significant reduction in serum bile acids (sBA) was observed in the overall population at week 13 (−16.9 µmol/L; 95% CI, −74.8 to 41.1; p=0.884), treatment response differed substantially according to genetic subtype. Seven patients with nt-BSEP deficiency met the predefined sBA response criterion (>75% reduction from baseline or sBA <102 µmol/L), whereas no patient with FIC1 or t-BSEP deficiency achieved this endpoint. Six of the seven nt-BSEP responders achieved the response during once-daily treatment, with one additional response following dose escalation to twice-daily administration. Among responders, sBA reductions were accompanied by clinically meaningful improvements in pruritus, as well as improvements in growth parameters and quality of life, and these effects

were sustained during long-term follow-up. After more than 5 years of treatment, all seven sBA responders remained alive with their native liver and without surgical biliary diversion [44].

The efficacy of maralixibat was subsequently evaluated in the phase 3 MARCH-PFIC trial, a multicentre, randomized, double-blind, placebo-controlled study including 93 children with PFIC. In the primary BSEP cohort, maralixibat significantly reduced morning Itch Reported Outcome Observer assessment (ItchRO(Obs)) scores compared with placebo over 26 weeks (least-squares mean change, −1.7 vs −0.6; between-group difference, −1.1; 95% CI, −1.8 to −0.3; p=0.0063). ItchRO(Obs) is a caregiver-reported instrument specifically developed to assess pruritus severity in children with cholestatic liver disease. Parents or caregivers complete an electronic diary twice daily, in the morning and evening, using a 5-point scale ranging from 0 (no itching) to 4 (very severe itching), with higher scores indicating more severe pruritus. Maralixibat also produced a marked reduction in total serum bile acids (−176 vs +11 µmol/L), corresponding to a between-group difference of −187 µmol/L (95% CI, −293 to −80; p=0.0013).

Improvements in serum bile acids were accompanied by favorable changes in biochemical markers of liver disease, although these effects were less consistent than the reductions in bile acids. Importantly, the prognostic significance of serum bile acid concentrations should be distinguished from the efficacy outcomes assessed in the 26-week MARCH-PFIC trial. Previous observational and retrospective studies in patients with BSEP deficiency following surgical biliary diversion associated a reduction in serum bile acids of at least 75% or to below 102 µmol/L with longer native liver survival. These prognostic thresholds informed the predefined biochemical response criterion used in MARCH-PFIC; 50% of patients receiving maralixibat versus 7% receiving placebo met this criterion, although the 26-week trial did not establish whether achieving this response improved native liver survival. The most common adverse event was diarrhea, reported in 57% of maralixibat-treated patients versus 20% of placebo-treated patients; events were predominantly mild or moderate and transient [45].

Long-term data from the open-label MARCH-ON extension further demonstrated sustained improvements in markers of cholestasis and liver health. Among 33 patients who received maralixibat continuously from the MARCH study, the benefits observed during the initial 26 weeks were maintained through week 52, with significant reductions in pruritus (−2.13; p<0.0001), serum bile acids (−200 µmol/L; p=0.0004), and bilirubin (−2.64 mg/dL; p=0.0084), together with improvements in height and weight z-scores (+0.54 and +0.44, respectively). Similarly, patients who switched from placebo to maralixibat (n=24) experienced significant reductions in pruritus (−1.05; p=0.0017)

and serum bile acids (−141 µmol/L; p=0.0003) after 26 weeks of treatment. These sustained improvements in pruritus, bile acid accumulation, bilirubin, and growth suggest a broader beneficial effect of prolonged IBAT inhibition on liver health beyond symptomatic control. However, as MARCH-ON is an open-label extension and these results were reported as a conference abstract, they should be considered supportive rather than definitive evidence of disease modification [46].

In the 2026 EASL analysis, 41 maralixibat-treated patients with genetically confirmed non-truncating BSEP or FIC1 deficiency were compared with 256 untreated patients from the NAPPED natural-history cohort after adjustment for baseline characteristics using inverse probability of treatment weighting. At 3 years, event-free survival, defined as freedom from surgical biliary diversion, liver transplantation, or death, was significantly higher in maralixibat-treated patients than in untreated patients (74% vs 42%; HR, 0.29; 95% CI, 0.16–0.54; p<0.0001). Surgical biliary diversion-free survival was also markedly higher with maralixibat (98% vs 67%; HR, 0.05; 95% CI, 0.01–0.39; p=0.0036). The association with improved outcomes remained significant in a sensitivity analysis excluding patients who experienced an event during the first 6 months (EFS HR, 0.46; 95% CI, 0.23–0.91; p=0.0252) [47].

The first proof-of-concept study of IBAT inhibition in PSC evaluated maralixibat in 27 adults treated for 14 weeks. Maralixibat significantly reduced serum bile acids by 16.7% (−14.84 µmol/L; 95% CI, −27.25 to −2.43; p=0.0043), with a greater reduction of 40.0% (−22.3 µmol/L; 95% CI, −40.38 to −4.3; p=0.004) among patients with elevated baseline serum bile acids. Pruritus also improved, although the magnitude of benefit varied according to baseline severity. The mean Adult Itch Reported Outcome (ItchRO) weekly sum score decreased by 8.4% in the overall population (p=0.0495) and by 12.6% among patients reporting pruritus at baseline (p=0.0275), while patients with severe baseline pruritus (adult ItchRO daily average score ≥3) experienced a 70% reduction (p=0.0078). Adult ItchRO is a patient-reported outcome measure used to assess pruritus severity in adults, typically on a 0–10 numerical rating scale, with higher scores indicating more severe itching. In contrast, no significant improvements were observed in liver enzymes, and increases in conjugated bilirubin of uncertain clinical significance were reported. Thus, this study provided proof-of-concept that IBAT inhibition can reduce circulating bile acids and cholestatic pruritus in PSC, particularly in patients with more severe symptoms, but did not provide evidence of an effect on biochemical disease progression [48].

Linerixibat

Early clinical studies established the proof of concept for linerixibat in PBC. In a phase 2a crossover trial, GSK2330672 significantly reduced pruritus and serum bile acids compared with placebo, with a 50% reduction in serum bile acids ($p < 0.0001$) [49]. Subsequently, the phase 2b GLIMMER trial evaluated different linerixibat doses in 147 patients; although the primary endpoint was not significantly different from placebo, post hoc analyses showed significant reductions in itch severity with several dosing regimens, supporting further phase 3 development [15,50].

The pivotal phase 3 GLISTEN trial evaluated linerixibat 40 mg twice daily in 238 patients with primary biliary cholangitis and moderate-to-severe pruritus. Over 24 weeks, linerixibat significantly reduced pruritus compared with placebo, with a least-squares mean change in WI-NRS of −2.86 versus −2.15 and a between-group difference of −0.72 (95% CI, −1.15 to −0.28; $p=0.0013$). The Worst Itch Numeric Rating Scale (WI-NRS) is a patient-reported 11-point numerical rating scale ranging from 0 (no itch) to 10 (worst imaginable itch), used to assess the severity of the patient's worst itching, with higher scores indicating more severe pruritus. The effect was evident as early as week 2 (−1.78 vs −1.07; between-group difference, −0.71; 95% CI, −1.07 to −0.34; $p < 0.001$). At week 24, 56% versus 43% of patients achieved a ≥3-point reduction in pruritus and 41% versus 29% achieved a ≥4-point reduction. Linerixibat also significantly improved pruritus-related sleep interference (−2.77 vs −2.24; between-group difference, −0.53; 95% CI, −0.98 to −0.07; $p=0.024$).

Despite these symptomatic benefits, no favorable effect on conventional biochemical markers of cholestatic disease was demonstrated: the mean change in alkaline phosphatase was +10.61 versus −8.03 IU/L and in bilirubin +1.77 versus −0.31 µmol/L, respectively, for linerixibat and placebo. In contrast, pharmacodynamic analyses demonstrated significant effects on the bile acid pathway, including increased C4 and reductions in FGF19, total serum bile acids, autotaxin, and IL-31, with reductions in total serum bile acids and IL-31 correlating with improvements in pruritus. Gastrointestinal adverse events were frequent, particularly diarrhea (61% vs 18%) and abdominal pain (18% vs 3%); liver test abnormalities occurred in 14% versus 6% of patients, including ALT elevations in 9% versus 3%, although these were generally asymptomatic and not associated with clinically significant hyperbilirubinemia [51].

Volixibat

In the phase IIb VANTAGE trial, volixibat was evaluated in 31 patients with primary biliary cholangitis (PBC) and moderate-to-severe cholestatic pruritus, randomized to receive volixibat 20 mg twice daily (n=10), 80 mg twice daily (n=10), or placebo (n=11) for 28 weeks as shown in Table 1. At Week 28, volixibat produced a mean reduction of 3.78 points from baseline in the Adult ItchRO score, with a placebo-adjusted reduction of 2.51 points (p=0.0004). Both doses showed similar antipruritic effects. Additionally, 70% of volixibat-treated patients achieved a reduction in serum bile acids of at least 50%. Improvements in fatigue and sleep-related outcomes were also reported, alongside reductions in interleukin-31 (IL-31) concentrations. Volixibat was generally well tolerated, with diarrhoea being the most common adverse event. However, no clinically meaningful improvements in conventional liver biochemical markers were observed, and these interim findings did not establish a disease-modifying effect [52].

Preliminary results from the phase 2b VISTAS trial evaluated volixibat 20 mg twice daily in 158 adults with PSC, including 111 patients with moderate-to-severe pruritus in the primary analysis cohort. Over 28 weeks, volixibat significantly reduced pruritus compared with placebo, with a mean change in Adult ItchRO of −2.72 versus −1.08 and a placebo-adjusted difference of −1.64 points ($p < 0.0001$). A ≥2-point reduction in pruritus was achieved by 55.6% of patients receiving volixibat compared with 26.3% receiving placebo (p=0.0019). Importantly, volixibat also reduced serum bile acids (−33.7 vs +2.1 µmol/L; placebo-adjusted difference −35.8 µmol/L; p=0.0324), supporting the expected pharmacodynamic effect of IBAT inhibition. Improvements in sleep interference were also observed (placebo-adjusted difference −5.69; p=0.0011), whereas the effect on fatigue did not reach statistical significance. The study did not provide evidence of disease modification, as hard outcomes such as transplantation, hepatic decompensation, or mortality were not assessed over the 28-week treatment period. Gastrointestinal adverse events were common, and treatment discontinuation occurred more frequently with volixibat than placebo (9.1% vs 2.5%) [53]. Table 1 summarizes the efficacy and safety of IBAT inhibitors in cholestatic liver diseases.

Table 1. Comparative Summary of Clinical Trials Evaluating Ileal Bile Acid Transporter (IBAT) Inhibitors in Cholestatic Pruritus and Cholestatic Liver Diseases

DRUG	DISEASE	STUDY	POPULATION	DURATION	CONTROL	PRURITUS	LIVER FUNCTION / BILE ACIDS	SAFETY	REFERENCES
Odevixibat	PFIC	PEDFIC 1, phase III	62	24 weeks	Placebo	Positive pruritus assessments: 55% vs 30%	sBA response: 33% vs 0%	Diarrhoea and frequent bowel movements: 31% vs 10%	[28]
Odevixibat	PFIC	PEDFIC 2, phase III extension	69	24 weeks (planned for 72)	Open-label	Mean pruritus score −1.6 in continuously treated patients	sBA: −201 µmol/L in continuously treated patients	GI AEs (adverse events) predominated	[29,30]
Odevixibat	PFIC	Real-world prospective study	24	6 months	None	Pruritus response: 73%	sBA: 317.1 → 45.6 µmol/L	No serious AEs	[31]
Odevixibat	ALGS	ASSERT, phase III	52	24 weeks	Placebo	Scratching score: −1.7 vs −0.8	sBA: −90 vs +22 µmol/L	Diarrhoea: 29% vs 6%	[34]
Odevixibat	Biliary atresia	BOLD, phase III	254	—	Placebo	Not assessed as a primary endpoint	No significant improvement in native liver survival	Preliminary safety data	[35]
Maralixibat	ALGS	ICONIC, phase II	31	22 weeks + extension	Placebo withdrawal	Pruritus worsened by 1.7 points after withdrawal	sBA increased by 94 µmol/L after withdrawal	Mainly mild–moderate GI AEs	[39]
Maralixibat	PFIC	INDIGO, phase II	33	13 weeks + long-term follow-up	None	Improvement among sBA responders	7 nt-BSEP patients achieved sBA response	Generally well tolerated	[44]
Maralixibat	PFIC	MARCH-PFIC, phase III	93	26 weeks	Placebo	ItchRO(Obs): −1.7 vs −0.6	sBA: −176 vs +11 µmol/L	Diarrhoea: 57% vs 20%	[45]
Maralixibat	PFIC	MARCH-ON, extension	57	52 weeks	Open-label	−2.13 in continuously treated patients	sBA: −200 µmol/L; bilirubin: −2.64 mg/dL	Generally tolerated	[46]
Maralixibat	PFIC	EASL 2026 analysis, observational data	41 vs 256	3 years	NAPPED natural-history cohort	—	Event-free survival: 74% vs 42%	Not reported	[47]
Maralixibat	PSC	Phase II proof-of-concept	27	14 weeks	None	Adult ItchRO: −8.4% overall; −70% in severe pruritus	sBA: −16.7%	Generally tolerated	[48]

Linerixibat	PBC	GLISTEN, phase III	238	24 weeks	Placebo	WI-NRS: −2.86 vs −2.15	No meaningful improvement in conventional liver markers	Diarrhoea: 61% vs 18%	[51]
Volixibat	PBC	VANTAGE, phase IIb, interim	31	28 weeks	Placebo	Adult ItchRO: −3.78; placebo-adjusted −2.51	≥50% sBA reduction: 70%; no meaningful liver biochemical improvement	GI AEs common	[52]
Volixibat	PSC	VISTAS, phase IIb, preliminary	158	28 weeks	Placebo	Adult ItchRO: −2.72 vs −1.08	sBA: −33.7 vs +2.1 µmol/L	Discontinuation: 9.1% vs 2.5%	[53]

Abbreviations: PFIC, progressive familial intrahepatic cholestasis; ALGS, Alagille syndrome; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; sBA, serum bile acids; GI AEs, gastrointestinal adverse events; nt-BSEP, non-truncating bile salt export pump variants; ItchRO, Itch Reported Outcome; ItchRO(Obs), observer-reported ItchRO; WI-NRS, Worst Itch Numeric Rating Scale; EASL, European Association for the Study of the Liver.

Note: Outcome definitions, scales, and assessment periods differ across studies; results should not be directly compared.

DISCUSSION

The findings of this review support IBAT inhibition as an effective therapeutic approach to cholestatic pruritus, while providing considerably less conclusive evidence for modification of the underlying liver disease. The antipruritic effect was demonstrated across PFIC, ALGS, PBC, and PSC, and was generally accompanied by reductions in serum bile acids, supporting the biological rationale for interrupting enterohepatic bile acid circulation [27–29,34,45,48,51–53].

The evidence is strongest in PFIC and ALGS, where odevixibat and maralixibat have been evaluated in randomized controlled trials and have received marketing authorization. However, their approved indications differ by jurisdiction. In the European Union, odevixibat is authorized for PFIC in patients aged 6 months and older, whereas maralixibat is authorized for cholestatic pruritus in patients with ALGS aged 2 months and older and for PFIC in patients aged 3 months and older. In the United States, the FDA has approved odevixibat for pruritus in patients with PFIC aged 3 months and older and for

cholestatic pruritus in patients with ALGS aged 12 months and older; maralixibat is approved for cholestatic pruritus in patients with ALGS aged 3 months and older and for pruritus in patients with PFIC aged 1 year and older. Furthermore, in March 2026, the FDA approved linerixibat for the treatment of cholestatic pruritus associated with PBC in adults [54–59].

These approvals primarily address cholestatic pruritus and should not be interpreted as establishing disease-modifying efficacy. The strength of the evidence should, however, be considered in the context of the rarity and heterogeneity of the underlying diseases. The pivotal randomized trials enrolled relatively small populations, which limits the precision of safety estimates and the ability to detect differences in uncommon clinical outcomes [28,34,45]. Furthermore, treatment response is not uniform across genetic subtypes. The differential response observed according to BSEP and FIC1 status, together with the association between pretreatment bile acid composition and subsequent response to odevixibat, suggests that residual hepatic bile acid secretory capacity may influence treatment efficacy [32,44].

These observations support a more individualized interpretation of IBAT inhibition, particularly in PFIC, rather than assuming a comparable response across all molecular subtypes.

In PBC and PSC, the available evidence is primarily supportive of symptomatic benefit. Although linerixibat and volixibat reduced pruritus in the studies included in this review, improvements in conventional biochemical markers of liver disease were not consistently demonstrated [48,51–53]. This discrepancy is important because reduction in serum bile acids or improvement in pruritus cannot, by themselves, establish an effect on hepatic disease progression. The available pharmacodynamic findings confirm target engagement, but whether modification of enterohepatic bile acid circulation can alter the long-term course of acquired cholestatic liver diseases remains unresolved [51–53].

The most important uncertainty concerns the proposed disease-modifying effect of IBAT inhibition. Long-term observations with odevixibat and maralixibat provide signals that sustained biochemical and symptomatic responses may be associated with more favorable clinical outcomes [29,43–47]. However, the evidentiary basis remains insufficient to establish causality. Much of the available long-term evidence derives from open-label extensions, observational studies, retrospective analyses, or comparisons with natural-history cohorts rather than randomized trials [29,33,43,46,47]. Such designs are particularly vulnerable to selection bias and confounding by baseline disease

severity and treatment responsiveness. The association between treatment response and subsequent native liver or event-free survival may therefore reflect, at least in part, the characteristics of patients who respond to therapy rather than a direct effect of IBAT inhibition on disease progression [43,47]. Conversely, the phase 3 BOLD trial did not meet its primary endpoint of improving native liver survival compared with placebo [35]. This finding indicates that a disease-modifying benefit on native liver survival was not demonstrated in this trial, rather than establishing the absence of any treatment effect.

Another limitation is the heterogeneity of outcome assessment across studies. Different pruritus scales, biochemical response criteria, treatment durations, patient populations, and genetic backgrounds make direct comparison between individual agents and disease groups difficult [28,31,34,39,44,45,48,51,53]. Several clinically relevant observations also originate from open-label extensions or conference reports rather than fully published randomized studies, further limiting the certainty of the evidence [29,46,47]. Consequently, the current literature supports the symptomatic efficacy of IBAT inhibition more convincingly than its effect on long-term hepatic outcomes.

The safety profile appears relatively consistent across the available studies, with gastrointestinal adverse events, particularly diarrhea, representing the main tolerability concern [28,34,39,45,51,53]. Patients with chronic cholestatic diseases may already have deficiencies of vitamins A, D, E, and K due to impaired intestinal fat absorption. Because IBAT inhibition may further affect fat-soluble vitamin status, baseline assessment and periodic monitoring are important, with supplementation when deficiencies are identified. Liver test abnormalities, including elevations in aminotransferases and bilirubin, have also been reported, although their frequency and clinical significance vary between agents and patient populations. Accordingly, liver tests should be assessed before treatment initiation and monitored during therapy, with management of abnormalities guided by the prescribing information for the individual drug [54,55]. These considerations highlight the importance of long-term safety surveillance, particularly in patients with advanced cholestasis or pre-existing nutritional deficiencies.

Overall, the evidence addresses the objectives of this review with differing levels of certainty. The molecular rationale for IBAT inhibition and its antipruritic efficacy are well supported, whereas evidence for an effect on the natural history of cholestatic liver disease remains preliminary. The principal unmet need is therefore not further demonstration that IBAT inhibition can reduce pruritus, but determination of whether sustained modulation of bile acid circulation can prevent hepatic disease progression.

Future studies should prioritize long-term follow-up and clinically meaningful endpoints, including native liver survival, transplantation, hepatic decompensation, and mortality, while accounting for disease etiology and genetic subtype. Until such evidence becomes available, IBAT inhibitors should be regarded primarily as targeted antipruritic therapies, with disease-modifying potential remaining an important but unproven therapeutic hypothesis.

Limitations

This narrative review was limited to English-language sources and did not employ a systematic review methodology; therefore, relevant studies may have been missed, and selection bias cannot be excluded. Some findings were available only as conference abstracts or manufacturer communications, limiting the assessment of their methods and results. Several publications represent follow-up or secondary analyses of the same study populations and should not be interpreted as independent evidence. Differences in diseases, genetic subtypes, outcome definitions, and follow-up durations further limit comparisons. Evidence concerning long-term liver outcomes remains largely observational and does not establish a causal effect of IBAT inhibition on disease progression.

CONCLUSION

IBAT inhibition has demonstrated clinically meaningful antipruritic efficacy across PFIC, ALGS, PBC, and PSC, accompanied by reductions in circulating bile acids in several treatment settings. Odevixibat and maralixibat have established therapeutic applications in selected inherited cholestatic disorders, while linerixibat and volixibat have expanded the investigation of IBAT inhibition to PBC and PSC.

Although improvements in selected biochemical and patient-reported outcomes have been observed, the effects of IBAT inhibitors on long-term liver disease progression, the need for liver transplantation, and mortality remain unestablished. Long-term observations, particularly in PFIC, support further investigation of IBAT inhibition as a potential strategy to modify the course of chronic cholestatic disease. Overall, IBAT inhibition represents an evolving therapeutic approach with an established role in cholestatic pruritus, whereas its potential disease-modifying effects remain to be defined.

DISCLOSURE

Author Contributions

Conceptualization: Estera Sośniecka, Filip Chodań.
Methodology: Krystian Domeracki, Adam Miler, Olga Klimczak.
Formal analysis: Dagmara Laufer, Krystian Domeracki.
Investigation and data collection: Krystian Domeracki, Filip Chodań, Adam Miler, Dagmara Laufer, Estera Sośniecka.
Writing, original draft preparation: Krystian Domeracki, Estera Sośniecka, Filip Chodań, Adam Miler, Olga Klimczak.
Writing, review and editing: Krystian Domeracki, Dagmara Laufer, Filip Chodań, Adam Miler.
Supervision: Dagmara Laufer.

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding

This work received no external funding.

Conflict of Interest

The authors declare no conflicts of interest.

Use of Artificial Intelligence

Artificial intelligence tools, including ChatGPT and other OpenAI systems, were used for language editing and structural refinement. All changes made with the assistance of these tools were reviewed and verified by the authors, who take full responsibility for the final content of the manuscript.

REFERENCES

1. Zeng J, Fan J, Zhou H. Bile acid-mediated signaling in cholestatic liver diseases. Cell Biosci. 2023 Apr 29;13(1):77. https://doi.org/10.1186/s13578-023-01035-1

2. Houri I, Hirschfield GM. Primary Biliary Cholangitis: Pathophysiology. Clin Liver Dis. 2024 Feb;28(1):79–92. https://doi.org/10.1016/j.cld.2023.06.006
3. Assis DN, Bowlus CL. Recent Advances in the Management of Primary Sclerosing Cholangitis. Clin Gastroenterol Hepatol. 2023 Jul;21(8):2065–75. https://doi.org/10.1016/j.cgh.2023.04.004
4. Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019 Feb;43(1):20–36. https://doi.org/10.1016/j.clinre.2018.07.010
5. Ayoub MD, Kamath BM. Alagille Syndrome: Current Understanding of Pathogenesis, and Challenges in Diagnosis and Management. Clin Liver Dis. 2022 Aug;26(3):355–70. https://doi.org/10.1016/j.cld.2022.03.002
6. Fuchs CD, Simbrunner B, Baumgartner M, Campbell C, Reiberger T, Trauner M. Bile acid metabolism and signalling in liver disease. J Hepatol. 2025 Jan;82(1):134–53. https://doi.org/10.1016/j.jhep.2024.09.032
7. Aseem SO, Hylemon PB, Zhou H. Bile Acids and Biliary Fibrosis. Cells. 2023 Mar 2;12(5):792. https://doi.org/10.3390/cells12050792
8. Kavallar AM, Mayerhofer C, Aldrian D, Okamoto T, Müller T, Vogel GF. Management and outcomes after liver transplantation for progressive familial intrahepatic cholestasis: A systematic review and meta-analysis. Hepatol Commun. 2023 Oct 1;7(10):e0286. https://doi.org/10.1097/HC9.0000000000000286
9. Trivella J, John BV, Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023 Jun 1;7(6):e0179. https://doi.org/10.1097/HC9.0000000000000179
10. Carbone M, Della Penna A, Mazzarelli C, De Martin E, Villard C, Bergquist A, et al. Liver Transplantation for Primary Sclerosing Cholangitis (PSC) With or Without Inflammatory Bowel Disease (IBD)-A European Society of Organ Transplantation (ESOT) Consensus Statement. Transpl Int. 2023;36:11729. https://doi.org/10.3389/ti.2023.11729
11. Chung AHL, Tan JJR, Yap RXJ, Loo JH, Tay WX, Singh CL, et al. Symptom burden and treatment patterns in primary biliary cholangitis: A systematic review and meta-analysis. Hepatol Commun. 2026 Jun 1;10(6):e0940. https://doi.org/10.1097/HC9.0000000000000940
12. Hussain N, Motta RV, Gungabissoon U, Casillas L, Mukherjee S, Ribeiro A, et al. Pruritus is common in primary sclerosing cholangitis, persists over time, and its intensity is associated with disease severity: a multicentre, prospective observational study. Hepatology. 2026 Aug 1;84(2):353–66. https://doi.org/10.1097/HEP.0000000000001634

13. 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. 2018 Aug;67(2):148–56. https://doi.org/10.1097/MPG.0000000000001958

14. Jones-Hughes T, Campbell J, Crathorne L. Epidemiology and burden of progressive familial intrahepatic cholestasis: a systematic review. Orphanet J Rare Dis. 2021 Jun 3;16(1):255. https://doi.org/10.1186/s13023-021-01884-4

15. Smith HT, Das S, Fettiplace J, von Maltzahn R, Troke PJF, McLaughlin MM, et al. Pervasive role of pruritus in impaired quality of life in patients with primary biliary cholangitis: Data from the GLIMMER study. Hepatol Commun. 2025 Mar 1;9(3):e0635. https://doi.org/10.1097/HC9.0000000000000635

16. Kruk B, Raszeja-Wyszomirska J, Krawczyk M, Milkiewicz P. Fatigue and itch severity in patients with PBC and PSC: Prospective analysis of two large cohorts. Eur J Clin Invest. 2025;55(7):e70041. https://doi.org/10.1111/eci.70041

17. Freedman MR, Holzbach RT, Ferguson DR. Pruritus in cholestasis: No direct causative role for bile acid retention. Am J Med. 1981 May 1;70(5):1011–6. https://doi.org/10.1016/0002-9343(81)90857-3

18. Kremer AE, Bolier R, van Dijk R, Oude Elferink RPJ, Beuers U. Advances in pathogenesis and management of pruritus in cholestasis. Dig Dis. 2014;32(5):637–45. https://doi.org/10.1159/000360518

19. Kremer AE, Martens JJWW, Kulik W, Ruëff F, Kuiper EMM, van Buuren HR, et al. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. Gastroenterology. 2010 Sep;139(3):1008–18, 1018.e1. https://doi.org/10.1053/j.gastro.2010.05.009

20. Meixiong J, Vasavda C, Snyder SH, Dong X. MRGPRX4 is a G protein-coupled receptor activated by bile acids that may contribute to cholestatic pruritus. Proc Natl Acad Sci U S A. 2019 May 21;116(21):10525–30. https://doi.org/10.1073/pnas.1903316116

21. Weisshaar E, Müller S, Szepietowski Jc, Dalgard F, Garcovich S, Kupfer J, et al. European Guideline on Chronic Pruritus. Acta Derm Venereol. 2025 Aug 22;105:44220. https://doi.org/10.2340/actadv.v105.44220

22. Tandon P, Rowe BH, Vandermeer B, Bain VG. The Efficacy and Safety of Bile Acid Binding Agents, Opioid Antagonists, or Rifampin in the Treatment of Cholestasis-Associated Pruritus. Am J Gastroenterol. 2007 Jul;102(7):1528–36. https://doi.org/10.1111/j.1572-0241.2007.01200.x

23. Verkade HJ, Felzen A, Keitel V, Thompson R, Gonzales E, Strnad P, et al. EASL Clinical Practice Guidelines on genetic cholestatic liver diseases. J Hepatol. 2024 Aug 1;81(2):303–25. https://doi.org/10.1016/j.jhep.2024.04.006

24. Craddock AL, Love MW, Daniel RW, Kirby LC, Walters HC, Wong MH, et al. Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter. Am J Physiol. 1998 Jan;274(1):G157–69. https://doi.org/10.1152/ajpgi.1998.274.1.G157

25. Oelkers P, Kirby LC, Heubi JE, Dawson PA. Primary bile acid malabsorption caused by mutations in the ileal sodium-dependent bile acid transporter gene (SLC10A2). J Clin Invest. 1997 Apr 15;99(8):1880–7. https://doi.org/10.1172/JCI119355

26. Dawson PA, Haywood J, Craddock AL, Wilson M, Tietjen M, Kluckman K, et al. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. J Biol Chem. 2003 Sep 5;278(36):33920–7. https://doi.org/10.1074/jbc.M306370200

27. Graffner H, Gillberg PG, Rikner L, Marschall HU. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. Aliment Pharmacol Ther. 2016;43(2):303–10. https://doi.org/10.1111/apt.13457

28. Thompson RJ, Arnell H, Artan R, Baumann U, Calvo PL, Czubkowski P, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2022 Sep 1;7(9):830–42. https://doi.org/10.1016/S2468-1253(22)00093-0

29. Thompson RJ, Artan R, Baumann U, Calvo PL, Czubkowski P, Dalgic B, et al. Interim results from an ongoing, open-label, single-arm trial of odevixibat in progressive familial intrahepatic cholestasis. JHEP Rep. 2023 Aug;5(8):100782. https://doi.org/10.1016/j.jhepr.2023.100782

30. Albireo, an Ipsen Company. An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2) [Clinical trial registration] [Internet]. clinicaltrials.gov; 2026 Aug [cited 2026 Sep 14]. Clinical trial registration no.: NCT03659916. Available from: https://clinicaltrials.gov/study/NCT03659916

31. Di Giorgio A, Sciveres M, Fuoti M, Calvo P, Cananzi M, Lleo A, et al. Real-world experience with odevixibat in children with progressive familial intrahepatic cholestasis. JHEP Rep. 2025 Apr;7(4):101309. https://doi.org/10.1016/j.jhepr.2024.101309

32. Nomden M, Kuipers F, Lexmond WS, Gu T, Valcheva V, Lindström E, et al. Pretreatment serum bile acid composition and predictability of subsequent response to odevixibat in patients with bile salt export pump (BSEP) deficiency. Hepatology. 2026 Apr 1;83(4):708–20. https://doi.org/10.1097/HEP.0000000000001430

33. Vogel GF, Kathemann S, Pietrobattista A, Maggiore G, Aldrian D, Sciveres M, et al. Odevixibat after liver transplant in patients with progressive familial intrahepatic

cholestasis type 1: A case series. J Pediatr Gastroenterol Nutr. 2025 Dec;81(6):1410–21. https://doi.org/10.1002/jpn3.70227

34. Ovchinsky N, Aumar M, Baker A, Baumann U, Bufler P, Cananzi M, et al. Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2024 Jul;9(7):632–45. https://doi.org/10.1016/S2468-1253(24)00074-8

35. Ipsen provides update on Phase III BOLD trial in biliary atresia. Global [Internet]. [cited 2026 Sep 17]. Available from: https://www.ipsen.com/press-release/ipsen-provides-update-on-phase-iii-bold-trial-in-biliary-atresia-3332691/

36. Ipsen. Prospective Registry-Based Study Evaluating the Effectiveness and Safety of Odevixibat in Participants With Alagille Syndrome (ALGS) [Clinical trial registration] [Internet]. clinicaltrials.gov; 2026 Aug [cited 2026 Sep 15]. Clinical trial registration no.: NCT06850038. Available from: https://clinicaltrials.gov/study/NCT06850038

37. Albireo, an Ipsen Company. An Open Label Study to Evaluate the Long-term Safety and Efficacy of Odevixibat (A4250) in Patients With Alagille Syndrome (ASSERT-EXT) [Clinical trial registration] [Internet]. clinicaltrials.gov; 2026 Aug [cited 2026 Sep 15]. Clinical trial registration no.: NCT05035030. Available from: https://clinicaltrials.gov/study/NCT05035030

38. Ipsen. Registry to Document Treatment Effectiveness, Safety, Including Prospective Long-term Outcomes in Participants With Progressive Familial Intrahepatic Cholestasis (PFIC) Who Take Odevixibat (Bylvay). [Clinical trial registration] [Internet]. clinicaltrials.gov; 2026 Aug [cited 2026 Sep 15]. Clinical trial registration no.: NCT07588880. Available from: https://clinicaltrials.gov/study/NCT07588880

39. Gonzales E, Hardikar W, Stormon M, Baker A, Hierro L, Gliwicz D, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. Lancet. 2021 Oct 30;398(10311):1581–92. https://doi.org/10.1016/S0140-6736(21)01256-3

40. Kamath BM, Goldstein A, Howard R, Garner W, Vig P, Marden JR, et al. Maralixibat Treatment Response in Alagille Syndrome is Associated with Improved Health-Related Quality of Life. J Pediatr. 2023 Jan;252:68–75.e5. https://doi.org/10.1016/j.jpeds.2022.09.001

41. Hirschfield G, Vandriel SM, Mogul DB, Baek M, Vig P, Kamath BM. Maralixibat Reduces Serum Bile Acids and Improves Cholestatic Pruritus in Adolescents With Alagille Syndrome. Liver Int. 2025 Feb;45(2):e16201. https://doi.org/10.1111/liv.16201

42. Shneider BL, Spino CA, Kamath BM, Magee JC, Ignacio RV, Huang S, et al. Impact of long-term administration of maralixibat on children with cholestasis secondary to

Alagille syndrome. Hepatol Commun. 2022 Aug;6(8):1922–33. https://doi.org/10.1002/hep4.1992

43. Sokol RJ, Gonzales EM, Kamath BM, Baker A, Vig P, Mogul DB, et al. Predictors of 6-year event-free survival in Alagille syndrome patients treated with maralixibat, an ileal bile acid transporter inhibitor. Hepatology. 2023 Dec 1;78(6):1698–710. https://doi.org/10.1097/HEP.0000000000000502

44. Loomes KM, Squires RH, Kelly D, Rajwal S, Soufi N, Lachaux A, et al. Maralixibat for the treatment of PFIC: Long-term, IBAT inhibition in an open-label, Phase 2 study. Hepatol Commun. 2022 Sep;6(9):2379–90. https://doi.org/10.1002/hep4.1980

45. Miethke AG, Moukarzel A, Porta G, Covarrubias Esquer J, Czubkowski P, Ordonez F, et al. Maralixibat in progressive familial intrahepatic cholestasis (MARCH-PFIC): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2024 Jul;9(7):620–31. https://doi.org/10.1016/S2468-1253(24)00080-3

46. Miethke A, Moukarzel A, Porta G, Covarrubias Esquer J, Czubkowski P, Ordonez F, et al. Long-term maintenance of response and improved liver health with maralixibat in patients with progressive familial intrahepatic cholestasis (PFIC): data from the MARCH-ON study. J Hepatol. 2023;78(Suppl 1):S123. https://doi.org/10.1016/S0168-8278(23)00615-3.

47. Afonso PM, de Groot ADE, Nomden M, Mian P, Shneider B, Gonzalès E, et al. OS-086 Event-free survival of maralixibat-treated patients with progressive familial intrahepatic cholestasis compared with aligned real-world data of untreated patients from NAPPED. J Hepatol. 2026;84(Suppl 1):S55–57. https://doi.org/10.1016/S0168-8278(26)00396-X.

48. Bowlus CL, Eksteen B, Cheung AC, Thorburn D, Moylan CA, Pockros PJ, et al. Safety, tolerability, and efficacy of maralixibat in adults with primary sclerosing cholangitis: Open-label pilot study. Hepatol Commun. 2023 Jun 1;7(6):e0153. https://doi.org/10.1097/HC9.0000000000000153

49. Hegade VS, Kendrick SFW, Dobbins RL, Miller SR, Thompson D, Richards D, et al. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. Lancet. 2017 Mar 18;389(10074):1114–23. https://doi.org/10.1016/S0140-6736(17)30319-7

50. Levy C, Kendrick S, Bowlus CL, Tanaka A, Jones D, Kremer AE, et al. GLIMMER: A Randomized Phase 2b Dose-Ranging Trial of Linerixibat in Primary Biliary Cholangitis Patients With Pruritus. Clin Gastroenterol Hepatol. 2023 Jul;21(7):1902–1912.e13. https://doi.org/10.1016/j.cgh.2022.10.032

51. Hirschfield GM, Bowlus CL, Jones DEJ, Kremer AE, Mayo MJ, Tanaka A, et al. Linerixibat in patients with primary biliary cholangitis and cholestatic pruritus (GLISTEN): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2026 Jan;11(1):22–33. https://doi.org/10.1016/S2468-1253(25)00192-X

52. Heneghan M, Shiffman M, Weinstein D, Ankoma-Sey V, Assy PN, Chiang DJ, et al. OS-059 Volixibat for the treatment of cholestatic pruritus in primary biliary cholangitis: an adaptive, randomized, placebo-controlled phase 2b trial (VANTAGE): 28-week interim results. J Hepatol. 2025;82(Suppl 1):S44–45. https://doi.org/10.1016/S0168-8278(25)00374-5.

53. Levy C, Hirschfield GM, Shiffman M, Awoniyi M, Joshi D, Weinstein D, et al. LBO-006 Efficacy and safety of volixibat, an IBAT inhibitor, in patients with primary sclerosing cholangitis and moderate-to-severe pruritus: results of the VISTAS trial. J Hepatol. 2026;84(Suppl 1):S10–11. https://doi.org/10.1016/S0168-8278(26)00310-7.

54. Bylvay | European Medicines Agency (EMA) [Internet]. 2021 [cited 2026 Oct 18]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/bylvay

55. Livmarli | European Medicines Agency (EMA) [Internet]. 2022 [cited 2026 Oct 18]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/livmarli

56. Yi S, Kim I, Hager R, Strazzeri MM, Garrard L, Matsubayashi T, et al. Food and Drug Administration Approval Summary: Odevixibat (Bylvay) for the Treatment of Pruritus With Progressive Familial Intrahepatic Cholestasis. Gastro Hep Adv. 2025;4(4):100596. https://doi.org/10.1016/j.gastha.2024.100596

57. Deeks ED. Odevixibat: First Approval. Drugs. 2021 Oct 1;81(15):1781–6. https://doi.org/10.1007/s40265-021-01594-y

58. Hoy SM. Linerixibat: First Approval. Drugs. 2026 Sep 1;86(9):1545–51. https://doi.org/10.1007/s40265-026-02349-3

59. Shirley M. Maralixibat: First Approval. Drugs. 2022 Jan 1;82(1):71–6. https://doi.org/10.1007/s40265-021-01649-0

‹ back