Building new treatment paradigms in the management of pediatric cholestasis

Thursday, December 16, 2021
20:00–21:30 EST
Welcome and introduction: The impact of cholestasis

Tamir Miloh, M.D.
Medical Director of Pediatric Transplant Hepatology at the Miami Transplant Institute, USA
**Speaker disclosures**

<table>
<thead>
<tr>
<th>Name</th>
<th>Disclosures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamir Miloh</td>
<td>• T. Miloh is a consultant for, and has received speaker and/or research funding from, Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Alexion Pharmaceuticals, Inc., and Travere Therapeutics, Inc.</td>
</tr>
<tr>
<td>Noelle Ebel</td>
<td>• N. H. Ebel is a consultant for Mirum Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Ryan Himes</td>
<td>• R. Himes is a consultant for, and has received speaker and/or research funding from, Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Alexion Pharmaceuticals, Inc., and Travere Therapeutics, Inc.</td>
</tr>
</tbody>
</table>
# Building new treatment paradigms in the management of pediatric cholestasis

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>20:00–20:15</td>
<td>Chair’s welcome and introduction</td>
<td>Tamir Miloh</td>
</tr>
<tr>
<td>20:15–20:40</td>
<td>Constructing a new approach in the management of ALGS</td>
<td>Noelle Ebel</td>
</tr>
<tr>
<td>20:40–21:00</td>
<td>Establishing new foundations for children with PFIC</td>
<td>Ryan Himes</td>
</tr>
<tr>
<td>21:00–21:10</td>
<td>Structuring new outcomes for biliary atresia</td>
<td>Tamir Miloh</td>
</tr>
<tr>
<td>21:10–21:25</td>
<td>Panel discussion</td>
<td>All</td>
</tr>
<tr>
<td>21:25–21:30</td>
<td>Chair’s close</td>
<td>Tamir Miloh</td>
</tr>
</tbody>
</table>
In cholestatic liver diseases, clinical symptoms and serum laboratory abnormalities occur due to disruption of bile flow.
The pathology of cholestasis and its mechanisms


The disruption of bile flow and accumulation of bile acids can result in cholestasis (characterized by pruritus and jaundice).

<table>
<thead>
<tr>
<th>Cognitive defects(^1)</th>
<th>Impaired school performance(^2)</th>
<th>Sleep disturbance and fatigue(^2)</th>
<th>Pain(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased physical functioning or general health(^1)</td>
<td>Mental health/ depression(^1)</td>
<td>Negative impact on a child’s social activities(^1)</td>
<td>Behavior issues(^1)</td>
</tr>
</tbody>
</table>

Challenges with diagnosis

ALGS, PFIC, and biliary atresia present with many of the same symptoms

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>ALGS(^1)</th>
<th>PFIC(^2)</th>
<th>Biliary atresia(^3,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pale stools, dark urine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vitamin A, D, E, K deficiency</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Primary bone abnormalities</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distinct facial features</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cardiac abnormalities</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Primary symptoms include cholestasis, pruritus, and failure to thrive.

Liver transplantation is frequently required in majority of patients

<table>
<thead>
<tr>
<th>ALGS$^{1,2}$</th>
<th>PFIC$^3$</th>
<th>Biliary atresia$^{4,5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>24%–41%$^*$ TFS by adulthood</td>
<td>32% TFS at 18 years of age</td>
<td>23% TFS by adulthood</td>
</tr>
</tbody>
</table>

**Transplant-free survival in ALGS$^1$**

Transplant-free survival in patients with nt-PFIC2 undergoing surgical biliary diversion

Transplant-free survival in infants with BA who underwent Kasai procedure

Transplant-free survival is poor across ALGS, PFIC, and biliary atresia

$^*$ N = 911. † Left truncated at baseline age. nt, non-truncating; TFS, transplant-free survival.


Complications of liver transplantation

- Cost and availability of procedure and medications
- Hypertension and long-term renal impairment
- De novo autoimmunity
- Lymphoproliferative disease and cancer
- Infection
- Rejection (acute and chronic)
- Bowel perforation
- Vascular and biliary problems
- Re-transplantation and/or additional procedures
- Primary graft non-function
- Death*

Prolonged immunosuppressive medication increases the risk of infections and malignancy, among other complications.

* Between 2009–2013, overall 5-year patient survival in those having pediatric liver transplants was 88.4%.
Traditional process for evaluating neonatal cholestasis

1. If persisting, follow up to test for cholestasis\(^1,3\)
2. Rule out BA or suspicion of ALGS/PFIC
3. Genetic testing\(^4\)

- Prolonged jaundice >14 days\(^1\)
- Assess for acholic stools, fractionated bilirubin, and physical exam\(^1\)
- Liver panel with GGT, fractionated bilirubin, and ultrasound\(^1,2\)
- Biomarkers (MMP-7, sBAs), imaging, IOC and liver biopsy\(^2,5–7\)
- Genetic cholestatic panel (i.e. NGS), single gene or whole exome sequencing\(^7\)

It is recommended that infants with direct bilirubin levels >1.0 mg/dL or >17 μmol/L be referred to a specialist\(^1\)

BA, biliary atresia; GGT, gamma-glutamyltransferase; IOC, intraoperative cholangiogram; MMP-7, matrix metalloproteinase 7; NGS, next-generation sequencing; sBA, serum bile acid.

Serum liver tests usually demonstrate raised values of GGT, disproportionate to other serum markers of liver injury; GGT helps to differentiate between high- and low-to-normal-GGT cholestasis.

High GGT is associated with extrahepatic obstruction of the intercellular junctions and is therefore associated with ALGS and PFIC3.

Low or normal GGT levels are typically found in PFIC1 and 2, as well as other processes.

* Mean value, males range at ≥18 years is 8–61 U/L, females range at ≥18 years is 5–36 U/L. GGT, gamma-glutamyltransferase.

Genetic testing has improved the diagnosis of pediatric cholestatic liver disease

Diagnose cholestatic liver disease in a timely manner; BA is more time-sensitive

Can provide a more accurate diagnosis and can identify a proband for family screening

Rapid single and multigene testing are cost-effective

Comprehensive multigene testing is causing a re-evaluation of the role and utility of liver biopsy

• Multigene panel testing has evolved from Cincinnati 57-, to Emory 66-, to PreventionGenetics 77-gene panels
• Training is crucial as the clinical utility of genetic testing relies on interpretation and classification of variants by specialists
• Turnaround time on genetic testing may be slow

BA, biliary atresia.
Management of cholestatic liver diseases

Correct diagnosis is critical, as inappropriate surgical intervention may worsen outcomes in ALGS.

ALGS patients who underwent a Kasai (n=74) had significantly lower rates of transplant-free survival (p<0.001)⁴

CI, confidence interval; HR, hazard ratio; TFS, transplant-free survival.
Management of cholestatic liver diseases

**Diagnosis**

- ALGS
- PFIC
- Biliary atresia

**Symptomatic control and nutrition optimization**
e.g. pruritus management or FSV supplementation

**Management of chronic liver disease**

- Few approved therapies; other medications such as anti-histamines, rifampin, naltrexone and bile acid sequestrants have modest effects
- IBAT inhibitors work by pharmacologic interruption of enterohepatic circulation of bile acids

FSV, fat-soluble vitamin; IBAT, ileal bile acid transporter.
Enterohepatic circulation of bile acids inhibits further bile acid synthesis and maintains homeostasis

Bile acids are synthesized in the liver and stored in the gall bladder; de novo synthesis only accounts for 5% of bile acids, with 95% reabsorbed and recirculated via IBATs.1,2

Reabsorption (>95%):
• Active uptake by IBAT in the ileum
• Passive absorption in the colon

Excretion via feces (~5%)

Accumulating sBAs can activate liver inflammatory pathways, which can result in cellular liver damage, fibrosis, and cirrhosis.1,3,4

Proinflammatory cytokines such as TNF-α, IL-1, and interferon gamma are secreted, which triggers recruitment of immune cells, causing liver damage.5

If left untreated, the liver will progress to end-stage liver disease, with most patients requiring liver transplantation.6

IBAT, ileal bile acid transporter; IL-1, interleukin 1; sBA, serum bile acid; TNF-α, tumor necrosis factor α.

Enterohepatic circulation of bile acids inhibits further bile acid synthesis and maintains homeostasis

Bile acids are synthesized in the liver and stored in the gall bladder; de novo synthesis only accounts for 5% of bile acids, with 95% reabsorbed and recirculated via IBATs.1,2

Reabsorption (>95%):
- Active uptake by IBAT in the ileum
- Passive absorption in the colon2

Excretion via feces (~5%)

Therapeutic approaches (surgical or pharmacologic) can be taken to block recirculation of bile acids to the liver, thereby reducing the bile acid pool

IBAT, ileal bile acid transporter.
In PFIC2, sBA control after surgical biliary diversion is associated with transplant-free survival

Patients who reached NAPPED threshold based on sBA levels

![Graph showing transplant-free survival](image)

- **sBA <102 µmol/L**
  - No. at risk: 27, 23, 16, 9
  - % transplant-free survival: 100, 80, 60, 40
  - Years after diversion: 0, 5, 10, 15

- **sBA ≥102 µmol/L**
  - No. at risk: 20, 8, 5, 1
  - % transplant-free survival: 100, 80, 60, 40
  - Years after diversion: 0, 5, 10, 15

*Patients who reached NAPPED threshold based on relative sBA reduction*

![Graph showing transplant-free survival](image)

- **≥75% decrease sBA**
  - No. at risk: 14, 4, 2, 1
  - % transplant-free survival: 100, 80, 60, 40
  - Years after diversion: 0, 5, 10, 15

- **<75% decrease sBA**
  - No. at risk: 24, 21, 14, 8
  - % transplant-free survival: 100, 80, 60, 40
  - Years after diversion: 0, 5, 10, 15

*Serum bile acids are a surrogate marker for long-term outcome*

sBA serum bile acid; TFS, transplant-free survival.
IBAT inhibitors: Pharmacologic inhibition of bile acid recirculation

IBAT(i), ileal bile acid transporter (inhibitor); sBA, serum bile acid.


Structure of IBAT figure adapted from: Slijepcevic D & van de Graaf SFJ. Dig Dis 2017;35:251–258. Figure reprinted from The Lancet, 398, Gonzales E, et al., ‘Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study’, 1581–1592, Copyright (2021), with permission from Elsevier.

IBAT inhibitor is administered

Redirects bile acid flow by inhibiting reuptake by IBAT

Interrupts recirculation of bile acids to the liver

Increases fecal bile acid excretion

Structure of IBAT

Clinical effects of IBATi in cholestasis:
- Improvements in pruritus (itch)
- Reductions in sBA
- Improved transplant-free survival
Management of cholestatic liver diseases today: How will we use IBAT inhibitors in clinical practice?

FSV, fat-soluble vitamin; IBAT, ileal bile acid transporter.


ALGS
PFIC
Biliary atresia

Diagnosis

KASAI PROCEDURE

Symptomatic control e.g. pruritus management or FSV supplementation

LIVER TRANSPLANT

Maralixibat approved for treatment of pruritus in ALGS, from September 2021

Odevixibat approved for treatment of pruritus in PFIC from July 2021

FSV, fat-soluble vitamin; IBAT, ileal bile acid transporter.
Constructing a new approach in the management of ALGS

Noelle Ebel, M.D.
Clinical Assistant Professor
Pediatric Transplant Hepatology
Director of the Alagille Syndrome Program, Stanford University, USA
ALGS is a rare autosomal dominant disorder

Mutations in \textit{JAG1} (89–94%)  
Mutations in \textit{NOTCH2} (2–4%)

Notch signaling regulates the development of intrahepatic bile ducts, craniofacial structures, the heart, kidney, spine, and vasculature

Genetic testing is often required to confirm a diagnosis of ALGS

ALGS is classified as a rare disease

ALGS has an incidence of 1 in 30,000–50,000

ALGS genotype displays a variable phenotype

Liver histology showing bile duct paucity

3 out of 5 major clinical features

- **HEPATIC**
  - cholestasis, jaundice

- **CARDIAC**
  - Pulmonary artery stenosis, tetralogy of Fallot

- **FACIAL**
  - high prominent forehead, pointed chin, deep-set eyes

3 out of 7 major clinical features

- **HEPATIC**
  - cholestasis, jaundice

- **CARDIAC**
  - Pulmonary artery stenosis, tetralogy of Fallot

- **FACIAL**
  - high prominent forehead, pointed chin, deep-set eyes

- **SKELETAL**
  - butterfly vertebrae, pathologic fractures

- **RENAL**
  - renal dysplasia, renal tubular acidosis

- **OCULAR**
  - posterior embryotoxon, optic disk drusen

- **VASCULAR**
  - intracranial bleeding, CNS/pulmonary vascular malformations

CNS, central nervous system.
Ayoub MD & Kamath BM. Diagnostics (Basel) 2020; 10:907.
Cholestatic clinical manifestations of ALGS may be severe and debilitating

Case study: A classical presentation of ALGS

Description (current age): 18-month-old male

Initial presentation:
- Neonatal jaundice (>3 weeks at initial presentation)
- Pruritus from ~6 months of age
- Failure to thrive, cholestasis
- Referred to a hepatologist

Medical history: No relevant medical conditions

Physical examination (at 7 months):
- Cardiac murmur
- Referred to a cardiologist
Case study: A classical presentation of ALGS

Laboratory parameters (at 7 months):

- ALT: 225 U/L
- GGT: 100 U/L
- Total bilirubin: 2.7 mg/dL
- Direct bilirubin: 1.9 mg/dL
- sBAs: 187 µmol/L
- Vitamin D: <5 ng/mL

Diagnosis

- ALGS was diagnosed at 8 months old
- A genetic test confirmed the diagnosis

ALT, alanine transaminase; GGT, gamma-glutamyltransferase; sBA, serum bile acid.
Case study: A classical presentation of ALGS

Treatment

- Repeat visits to control intractable pruritus
- Pruritus remains refractory to treatment; patient is put on the liver transplant waiting list
Substantial risk for liver transplant in patients with ALGS

**GALA¹ (Global)**
Transplant-free survival in patients with ALGS presenting with neonatal cholestasis (N = 911)

<table>
<thead>
<tr>
<th>Age* (years)</th>
<th>Transplant-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>41% TFS at 10 years</td>
</tr>
<tr>
<td>18</td>
<td>57% TFS at 10 years</td>
</tr>
</tbody>
</table>

**ChiLDReN (North America network)²**
Transplant-free survival in patients with ALGS

<table>
<thead>
<tr>
<th>Age* (years)</th>
<th>Transplant-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>41% TFS at 18 years</td>
</tr>
<tr>
<td>18</td>
<td>24% TFS at 18.5 years</td>
</tr>
</tbody>
</table>

* Left truncated at baseline age.
TFS, transplant-free survival.
Balancing the scales: Consideration for liver transplant in ALGS?

Benefits of transplant\(^1\)–\(^4\)

- Resolution of pruritus
- Growth improvement
- Improvements in bone mineral density

Risks of transplant\(^5\),\(^6\)

- Post-transplant renal and cardiovascular complications
- Other post-transplant complications: biliary and vascular complications, rejection, infection, life-long immunosuppression
- Graft failure, mortality

Clinical trials in ALGS

ICONIC
Primary endpoint

- Mean change in fasting sBA levels from Weeks 18–22 (and mean change in those who previously responded to maralixibat)

Secondary endpoints

- Change in fasting sBA levels from baseline to Week 18
- Change in pruritus (ItchRO[Obs] and [Pt]) from baseline to Week 18 and from Weeks 18–22
- Change in ALP and ALT from baseline to Week 18 and from Weeks 18–22
- Change in total and direct bilirubin from baseline to Week 18 and from Weeks 18–22

* Equivalent to maralixibat chloride 400 μg/kg; † Includes a 6-week dose-escalation period for participants who received placebo during the randomized withdrawal phase; dosing for maralixibat vs maralixibat chloride.
‡ Twice daily dosing (started after Week 100) was equivalent to maralixibat chloride 800 μg/kg.
ALP, alkaline phosphatase; ALT, alanine transaminase; ItchRO(Obs), Itch-Reported Outcome (Observer); QoL, quality of life; R, randomized; sBA, serum bile acid.
**Significant and sustained improvements in pruritus with maralixibat:**

84% had a clinically meaningful decrease (≥1-point) during the 48-week period

**Mean change in ItchRO(Obs) from baseline (SE)**

- **Week 12:** ITCHRO(Obs) improved significantly from baseline to Week 12 (–1.6; 95% CI: –1.9, –1.2)
- **Week 18:** ITCHRO(Obs) improved significantly from baseline to Week 18 (–1.7; 95% CI: –2.1, –1.4)

*R 95% CI excludes zero (compared with BL, overall population).* †The MRX–PBO–MRX treatment group (n = 16) received PBO during the RWD, whereas the MRX–MRX–MRX treatment group (n = 13) continued to receive MRX.

Dashed lines represent data not shown between Week 98 to Week 156. Numbers represent the numbers of participants reporting each CSS score. Asterisks represents paired t-tests comparing the change from BL (testing if the change was equal to 0 or not). Twelve participants went to BID dosing on the basis of raised sBA in the OLE.

BID, twice daily; BL, baseline; CI, confidence interval; CSS, Clinician Scratch Scale; MRX, maralixibat; OLE, open-label extension; PBO, placebo; RWD, randomized withdrawal period; sBA, serum bile acid; SE, standard error.

Correlation shown between pruritus and multiple parameters following maralixibat treatment

<table>
<thead>
<tr>
<th>Serum bile acid reduction, %</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in ItchRO score, points</td>
<td>−1.86</td>
<td>−2.12</td>
<td>−2.31</td>
<td>−2.79</td>
<td>−2.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters correlated with ItchRO(Obs) score at Week 48</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinician Scratch Scale</td>
<td>0.65</td>
<td>0.0002</td>
</tr>
<tr>
<td>Serum bile acids</td>
<td>0.47</td>
<td>0.0123</td>
</tr>
<tr>
<td>PedsQL™ Impact</td>
<td>−0.38</td>
<td>0.0574</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters correlated with ItchRO(Obs) score as a change from baseline to Week 48</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PedsQL™ Fatigue</td>
<td>−0.59</td>
<td>0.0053</td>
</tr>
</tbody>
</table>

Serum bile acid reductions correlated with reductions in pruritus intensity

ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL™, Pediatric Quality of Life Inventory™; PedsQL™ Fatigue, PedsQL™ Multidimensional Fatigue Scale; PedsQL™ Impact, PedsQL™ Family Impact Total Scale; r, Spearman’s rank correlation.

Significant reduction in serum bile acid level was maintained long term with maralixibat

Changes in sBA from BL to Week 204 across all participants (A) and during the RWD in the primary endpoint responder analysis (B; n = 15). (A) Dashed line represents data not shown between weeks 96 and 156. (B) Of the 15 participants assessed as part of the primary endpoint analysis (participants who had reductions in sBA of ≥50% from BL to Weeks 12 or 18), the PBO group (n=10) received PBO during the RWD whereas the MRX treatment group (n=5) continued to receive MRX. Twelve participants went to BID dosing on the basis of raised sBA in the OLE.

* 95% confidence interval excludes zero (compared with BL, overall population; MRX–MRX–MRX treatment group versus MRX–PBO–MRX treatment group). †The MRX–PBO–MRX treatment group (n = 16) received PBO during the RWD, whereas the MRX–MRX–MRX treatment group (n = 13) continued to receive MRX. BID, twice daily; BL, baseline; CI, confidence interval; MRX, maralixibat; OLE, open-label extension; PBO, placebo; RWD, randomized withdrawal period; sBA, serum bile acid; SE, standard error. Gonzales E, et al. Lancet 2021; 398:1581–1592. Reprinted from The Lancet, 398, Gonzales E, et al., ‘Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study’, 1581–1592, Copyright (2021), with permission from Elsevier.

sBA levels reduced significantly from baseline to Week 12 (–108; 95% CI: –166, –50), and from baseline to Week 18 (–88; 95% CI: –133, –42)
Maralixibat treatment was generally well tolerated

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Open-label period (BL to Week 18) MRX (N = 31)</th>
<th>Randomized RWD (Weeks 19–22) MRX (n = 13) PBO (n = 16)</th>
<th>Stable-dosing period (Weeks 23–48) MRX (N = 29)</th>
<th>Long-term extension (Weeks 48–204) MRX (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with ≥1 TEAE</td>
<td>30 (97)</td>
<td>7 (54)</td>
<td>12 (75)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>TEAEs potentially related to study drug*</td>
<td>12 (39)</td>
<td>1 (8)</td>
<td>3 (19)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>TEAEs leading to study drug discontinuation†</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>22 (71)</td>
<td>2 (15)</td>
<td>3 (19)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (39)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 (42)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (36)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>SAEs</td>
<td>4 (13)</td>
<td>1 (8)</td>
<td>1 (6)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>SAEs potentially related to study drug*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Any TEAE or SAE that was determined by an investigator as related or possibly related to the study drug is considered as potentially related to the study drug. † There were two discontinuations due to TEAEs during the open-label period of the study; one participant discontinued for a serious adverse event deemed unrelated to MRX by the investigator (post-traumatic epidural and subdural hematomas), one participant discontinued for a TEAE deemed possibly related to maralixibat by the investigator (increased serum bilirubin levels). There were two discontinuations due to TEAEs during the long-term extension; one participant discontinued due to a TEAE deemed unrelated to maralixibat by the investigator (acute renal failure), and one participant discontinued due to ALT elevations considered possibly related to study medication by the investigator. A third discontinuation occurred after the period reported here (Week 213) due to an ALT elevation considered related to study drug.

ALT, alanine transaminase; BL, baseline; MRX, maralixibat; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Gastrointestinal tolerability with maralixibat (>5 years of follow-up)

Patients experiencing an adverse event, n (%) | Integrated patient population (N = 86)  
---|---  
| | Diarrhea* | Abdominal pain* |
| Any severity | 49 (57.0) | 46 (53.5) |
| Mild | 42 (48.8) | 34 (39.5) |
| Moderate | 7 (8.1) | 8 (9.3) |
| Severe | 0 (0.0) | 4 (4.7) |
| Life-threatening/fatal | 0 (0.0) | 0 (0.0) |

The majority of GI adverse events occurred within the first 4 weeks of treatment and lasted <1 week. The majority of diarrhea and abdominal pain adverse events were mild to moderate in severity and transient in nature, and there were no GI-related discontinuations of maralixibat

* Includes multiple adverse event terms.
AE, adverse event; GI, gastrointestinal.
## ICONIC: Gastrointestinal tolerability with maralixibat versus placebo

Data from the 13-week placebo group demonstrate that GI events are common in untreated patients, and the rates of diarrhea were similar between maralixibat and placebo, with a slight difference in abdominal pain.

<table>
<thead>
<tr>
<th>Patients experiencing an adverse event, n (%)</th>
<th>Maralixibat (N = 39)</th>
<th>Placebo (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrhea*</td>
<td>Abdominal pain*</td>
</tr>
<tr>
<td>Any severity</td>
<td>17 (43.6)</td>
<td>15 (38.5)</td>
</tr>
<tr>
<td>Mild</td>
<td>16 (41.0)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (2.6)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Life-threatening/fatal</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

* Includes multiple adverse event terms.
AE, adverse event; GI, gastrointestinal.
Predictors of 6-year event-free survival (EFS) in patients with ALGS treated with maralixibat
Event-free survival with maralixibat treatment according to total bilirubin and sBA

Week 48 total bilirubin and sBA levels are predictive of EFS

Data values under each panel indicate the number of patients at each time point. Analysis examined predictors of long-term EFS, including TFS, in patients with ALGS enrolled in 3 clinical trials of maralixibat,1–3 with up to 6 years of follow-up; included patients who were on maralixibat 48 weeks from the first dose and had lab results at 48 weeks were included in the analysis.

Event-free survival with maralixibat treatment according to pruritus and age at initiation

Kaplan–Meier plots of EFS

Change from baseline to Week 48 ItchRO(Obs) (>1 pt reduction)

Age at initiation of maralixibat (months)

6-year EFS: 88% vs 57%
Log-rank p-value = 0.0046

6-year EFS: 83% vs 57%
Log-rank p-value = 0.0059

Data values under each panel indicate the number of patients at each time point. EFS, event-free survival. ItchRO(Obs), Itch-Reported Outcome (Observer); pt, point.

Sokol RJ, et al. Poster presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.
Event-free survival analysis in Alagille syndrome of the GALA clinical research database
Pre-specified selection criteria to ensure GALA external control cohort was aligned with maralixibat entry criteria

• **Aim:** to compare time to first clinical event in maralixibat (MRX)-treated ALGS patients with that seen in external controls

---

**Key inclusion criteria**

- Age at inclusion: ≥1 year and <18 years
- Cholestasis, defined by one or more of the following:
  - Total sBA >3 x ULN
  - Conjugated or direct bilirubin >1 mg/dL
  - Total bilirubin >2 mg/dL
  - GGT >3 x ULN

**Key exclusion criteria**

- ALT >15 x ULN
- Clinical event, defined as BD surgery, liver decompensation (ascites requiring therapy or variceal bleeding), liver transplantation, or death prior to inclusion
- Participation in any intervention clinical study
- Excluded regions in which the MRX ALGS studies were not conducted

---

GALA selected primary analysis N=469

Maralixibat ALGS Studies 301, 302 and 304 and extensions. ALT, alanine transaminase; BD, biliary diversion; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; sBA, serum bile acid; ULN, upper limit of normal. Hansen BE & Kamath BM. Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.
Demographic characteristics are well balanced between the maralixibat and GALA groups

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>MRX cohort N = 84</th>
<th>GALA control N = 469</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (58.3)</td>
<td>274 (58.4)</td>
<td>0.988</td>
</tr>
<tr>
<td>Female</td>
<td>35 (41.7)</td>
<td>195 (41.6)</td>
<td></td>
</tr>
<tr>
<td>Age at BL, years Median (Q1, Q3)</td>
<td>5.6 (2.7, 9.9)</td>
<td>4.3 (2.2, 9.6)</td>
<td>0.078</td>
</tr>
<tr>
<td>Year of birth Mean (Q1, Q3)</td>
<td>2009 (2005, 2012)</td>
<td>2009 (2004, 2013)</td>
<td>0.249</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>41 (48.8)</td>
<td>229 (48.8)</td>
<td>0.945</td>
</tr>
<tr>
<td>North America</td>
<td>34 (40.5)</td>
<td>195 (41.6)</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>9 (10.7)</td>
<td>45 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Mutation*, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAG1</td>
<td>81 (97.6)</td>
<td>330 (95.1)</td>
<td></td>
</tr>
<tr>
<td>NOTCH2</td>
<td>2 (2.4)</td>
<td>17 (4.9)</td>
<td>0.55</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1 (0.2)</td>
<td>37 (9.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Due to more than 20% of the cells having expected counts less than 5, chi-square results may be invalid, and Fisher’s exact test was used instead.
BL, baseline; MRX, maralixibat; Q1, first quartile; Q3, third quartile. Hansen BE & Kamath BM. Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.
### Disease characteristics are well balanced between the maralixibat and GALA groups

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>MRX cohort N = 84</th>
<th>GALA control N = 469</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total bilirubin, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1,Q3)</td>
<td>3.15 (1.00, 8.15)</td>
<td>1.99 (0.60, 11.52)</td>
<td>0.392</td>
</tr>
<tr>
<td>&lt;2 mg/dL</td>
<td>37 (44.0)</td>
<td>235 (50.1)</td>
<td>0.306</td>
</tr>
<tr>
<td>≥2 mg/dL</td>
<td>47 (56.0)</td>
<td>234 (49.9)</td>
<td></td>
</tr>
<tr>
<td><em><em>GGT</em>, log_{10} × ULN</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3, log_{10} × ULN)</td>
<td>1.25 (0.93, 1.44)</td>
<td>1.24 (0.93, 1.52)</td>
<td>0.582</td>
</tr>
<tr>
<td>&lt;3 × ULN</td>
<td>3 (3.6)</td>
<td>6 (1.3)</td>
<td>0.143</td>
</tr>
<tr>
<td>≥3 × ULN</td>
<td>81 (96.4)</td>
<td>463 (98.7)</td>
<td></td>
</tr>
<tr>
<td><strong>ALT, U/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>145 (94, 207)</td>
<td>130 (75, 203)</td>
<td>0.119</td>
</tr>
<tr>
<td><strong>sBA†, µmol/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>200 (81, 371)</td>
<td>125 (39, 260)‡</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Due to more than 20% of the cells having expected counts less than 5, chi-square results may be invalid; † sBA data are limited in the GALA clinical research database since these are not sampled regularly on a clinical basis and Fisher’s exact test was used instead. ‡ Baseline sBA was available for 73 participants in the GALA control group.

**Key baseline characteristics are well-balanced between the MRX cohort and GALA control group**
Maralixibat shows significant improvement in EFS

**EFS: Biliary diversion surgery, decompensation event, liver transplantation, or death**

* Cox regression models: Primary: Cox regression - effect of MRX vs GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).

ALT, alanine transaminase; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan.

Hansen BE & Kamath BM. Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

---

**Primary analysis* – adjusted: HR 0.305 (95% CI: 0.189–0.491), p<0.0001**

**Unadjusted*: HR 0.380 (95% CI: 0.238–0.604), p<0.0001**
### Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary comparison</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP specified</td>
<td>0.305</td>
<td>(0.189, 0.491)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.380</td>
<td>(0.238, 0.604)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted 1</td>
<td>0.301</td>
<td>(0.188, 0.484)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted 2</td>
<td>0.301</td>
<td>(0.188, 0.484)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted 3</td>
<td>0.328</td>
<td>(0.201, 0.535)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Adjusted 4</td>
<td>0.199</td>
<td>(0.099, 0.398)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weighted Std IPTW</td>
<td>0.379</td>
<td>(0.237, 0.605)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Weighted ATT</td>
<td>0.297</td>
<td>(0.165, 0.535)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Sensitivity analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First eligible visit</td>
<td>0.618</td>
<td>(0.369, 1.036)</td>
<td>0.0680</td>
</tr>
<tr>
<td>Date of birth</td>
<td>0.504</td>
<td>(0.320, 0.795)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Last eligible visit</td>
<td>0.241</td>
<td>(0.148, 0.392)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Random visit 1</td>
<td>0.457</td>
<td>(0.284, 0.734)</td>
<td>0.0012</td>
</tr>
<tr>
<td>Random visit 2</td>
<td>0.486</td>
<td>(0.304, 0.777)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Random visit, Method 2</td>
<td>0.439</td>
<td>(0.274, 0.703)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Liver transplant-free survival</td>
<td>0.332</td>
<td>(0.197, 0.559)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Subgroup analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By region North America</td>
<td>0.249</td>
<td>(0.114, 0.542)</td>
<td>0.0005</td>
</tr>
<tr>
<td>By region Europe</td>
<td>0.360</td>
<td>(0.187, 0.693)</td>
<td>0.0022</td>
</tr>
<tr>
<td>By region Australia</td>
<td>0.140</td>
<td>(0.024, 0.832)</td>
<td>0.0306</td>
</tr>
<tr>
<td>By site overlap</td>
<td>0.350</td>
<td>(0.219, 0.587)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>With sBA available</td>
<td>0.245</td>
<td>(0.124, 0.483)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Pruning analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruning 3 month</td>
<td>0.376</td>
<td>(0.230, 0.616)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pruning 6 month</td>
<td>0.432</td>
<td>(0.256, 0.729)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Pruning 12 month</td>
<td>0.503</td>
<td>(0.273, 0.930)</td>
<td>0.0284</td>
</tr>
</tbody>
</table>

### Notes
- ATT, average treatment effect in the treated; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IPTW, inverse probability of treatment weights; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan; sBA, serum bile acid. Hansen BE & Kamath BM. Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.
Clinical trials in ALGS

Odevixibat
Phase 2 study: Odevixibat across children diagnosed with pruritus due to chronic cholestasis

Open-label, dose-finding study (all comers):

PFIC, biliary atresia, ALGS, sclerosing cholangitis (N = 24)

Odevixibat for 4 weeks (10, 30, 60, 100, and 200 µg/kg evaluated)

<table>
<thead>
<tr>
<th>Primary endpoints*</th>
<th>Secondary endpoints*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Change in serum bile acid levels</td>
<td>• Changes in VAS-itch score</td>
</tr>
<tr>
<td></td>
<td>• Changes in Whitington itch</td>
</tr>
<tr>
<td></td>
<td>• Changes in PO-SCORAD itch</td>
</tr>
<tr>
<td></td>
<td>• Changes in sleep disturbance scores</td>
</tr>
<tr>
<td></td>
<td>• Changes in autotaxin, 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19)</td>
</tr>
</tbody>
</table>

Patients received 10–200 µg/kg odevixibat.
PO-SCORAD, Partial Patient-Oriented Scoring Atopic Dermatitis; sBA, serum bile acid; VAS, visual analog scale.
Phase 2 study: Safety and tolerability with odevixibat

Safety includes entire cohort, N = 24

• All patients completed treatment; no evidence of diarrhea during 4-week treatment period, and one mild, transient, possibly treatment-related case of diarrhea after the single 10 μg/kg dose on Day 1

• No adverse events related to treatment during 4-week treatment period
  – Most common adverse: fever, acute otitis media (12.5%)

• No serious adverse events designated as treatment-related (2 deemed unrelated*)

• Decision made not to escalate dose above 200 μg/kg
  – Some elevation of transaminases at 200 μg/kg dose

* Gastroenteritis and influenza.
Phase 3 study: Odevixibat in ALGS (ASSERT)

ALGS (N~45)

R 2:1

Odevixibat 120 μg/kg/day (n = 30)

Placebo (n = 15)

Safety follow-up

Optional open-label extension enrollment

Primary endpoint
• Change from baseline in scratching score to Month 6 as measured by the Albireo ObsRO scratching score

Secondary endpoints
• Serum bile acid levels
• Safety and tolerability

ObsRO, observer-reported outcome; OLE, open-label extension; sBA, serum bile acid.
ALGS is a rare syndrome that may have multisystem involvement and significant disease burden.

Liver involvement is due to intrahepatic bile duct paucity that may result in chronic cholestasis.

Cholestasis presenting with pruritus, xanthomas, and many other clinical manifestations is the leading cause of liver transplantation for children with ALGS.

Refractory pruritus lowers the quality of life for patients and their caregivers. Liver disease in ALGS can progress to cirrhosis and liver transplant.

Maralixibat is now approved for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older.

Clinical trials with IBAT inhibitors are ongoing.
Establishing new foundations for children with PFIC

Ryan Himes, M.D.
Pediatric Hepatologist, Ochsner Hospital for Children, USA
PFIC is an autosomal recessive disorder classified into six subtypes

PFIC is a heterogeneous group of diseases that disrupt bile formation\textsuperscript{1–3}

PFIC is classed as a rare disease

PFIC has a global incidence of 1 in 50,000–100,000 (PFIC2 accounts for approx. half of cases)

BSEP (PFIC2) is the most common and most aggressive of the PFIC subtypes

The clinical severity of BSEP deficiency is linked to the type of ABCB11 mutation and predicts TFS

<table>
<thead>
<tr>
<th>Mutation</th>
<th>BSEP protein</th>
<th>Predicted severity</th>
<th>Median TFS (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one copy of p.D482G or p.E297G</td>
<td>Non-truncated (BSEP1)</td>
<td>Mild</td>
<td>20.4</td>
</tr>
<tr>
<td>At least one missense mutation other than p.D482G or p.E297G</td>
<td>Non-truncated (BSEP2)</td>
<td>Moderate</td>
<td>7.0</td>
</tr>
<tr>
<td>Non-functional protein; nonsense or frameshift (indel) or splice site</td>
<td>Truncated (BSEP3)</td>
<td>Severe</td>
<td>3.5</td>
</tr>
</tbody>
</table>

BSEP, bile salt export pump; TFS, transplant-free survival.

BSEP deficiency (PFIC2) results in a broad range of clinical manifestations

- Jaundice
- Fat malabsorption
- Fat-soluble vitamin deficiency
- Failure to thrive during first several months of life
- Hepatomegaly
- Portal hypertension within the first year
- Pruritus leading to excoriation and mutilation of skin
- Scleral icterus

Approx. 50% of patients require a liver transplant by age 10

BSEP, bile salt export pump.
## Case study: A classical presentation of PFIC

<table>
<thead>
<tr>
<th>Description (current age):</th>
<th>4-year-old female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial presentation (at 5 months):</strong></td>
<td></td>
</tr>
<tr>
<td>• Scratching to the point of bleeding and ecchymoses on her abdomen, back, and legs</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history:</strong></td>
<td>No relevant medical conditions</td>
</tr>
<tr>
<td><strong>Physical examination:</strong></td>
<td>Physical examination showed neither icterus nor hepatosplenomegaly</td>
</tr>
<tr>
<td><strong>Laboratory parameters:</strong></td>
<td></td>
</tr>
<tr>
<td>• AST 223 U/L; ALT 334 U/L</td>
<td></td>
</tr>
<tr>
<td>• Total bilirubin 3.4 mg/dL; direct bilirubin 2.8 mg/dL</td>
<td></td>
</tr>
<tr>
<td>• GGT 33 U/L</td>
<td></td>
</tr>
<tr>
<td>• Partial thromboplastin time, 90.8 seconds; prothrombin time, &gt; 120.0 seconds</td>
<td></td>
</tr>
<tr>
<td>• INR &gt;13.7</td>
<td></td>
</tr>
<tr>
<td>• sBA test not conducted</td>
<td></td>
</tr>
<tr>
<td>• Albumin 2.3 g/dL</td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyltransferase; INR, international normalized ratio; sBA, serum bile acid.

Case study: A classical presentation of PFIC

**Initial treatment:**
- Intravenous vitamin K; admitted for further evaluation

**Follow-up evaluations:**
- Persistent cholestasis; direct bilirubin 7.5 mg/dL
- Low 25-OH vitamin D (<5 ng/mL) and alpha-tocopherol (0.8 mg/L)
- Infectious workup negative for CMV, EBV, HIV, HCV, HBV, HSV
- Total sBA elevated at 205.3 µmol/L

**Liver biopsy:**
- Mild chronic portal inflammation, periportal fibrosis, ballooning hepatocytes, significant cholestasis, and early bile duct loss with ductular proliferation

**Diagnosis:**
- Genetic test confirmed biallelic pathogenic sequence variants in *ABCB11* and a diagnosis of PFIC2

---

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; sBA, serum bile acid.

Persisting symptoms at follow-up visit:

• Pruritus continued despite the use of ursodiol, rifampin, cholestyramine, and hydroxyzine
• Problems sleeping and significant skin damage
Beyond the patient – caregiver impact is also significant

A survey carried out in caregivers of patients with rare diseases found caregivers faced the following:

- **67%** emotional stress
- **86%** financial hardship because of their caregiver role
- **89%** need to educate HCPs
- **41%** fair/poor emotional or mental health
- **53%** feel alone
- **59%** receive help from at least one other caregiver

Failure to understand family / caregiver spill-over may lead to underestimates of the societal impact of rare diseases, as well as the value of new healthcare interventions.
## Case study: A classical presentation of PFIC

**Persisting symptoms at subsequent follow-up visits:**
- Intractable pruritus, despite the subsequent use of rifampin, cholestyramine, and hydroxyzine

**Surgical approaches:**
- Ileal exclusion performed at 12 months with no relief of pruritus and continued high total bile acid level of 147.4 µmol/L following bile acid test

Patient continued to deteriorate and a partial internal biliary diversion was recommended

---

Surgical interventions in PFIC

Schematic representation of an ileal exclusion

Schematic representation of a partial internal biliary diversion

Surgical biliary diversion improves outcomes in BSEP1 and 2 (nt-PFIC2)


BSEP, bile salt export pump; CI, confidence interval; HR, hazard ratio; nt, non-truncated.


**Case study: A classical presentation of PFIC**

**Surgery:**
- Partial internal biliary diversion was carried out at 15 months of age

**Outcome of surgery:**
- Pruritus improved initially and sBA levels normalized for 8 months
- Pruritus ultimately returned, with sBA increasing to 239.2 µmol/L
- Patient continued to have low vitamin E and D levels, despite high-dose supplementation

Patient now listed for a living related donor liver transplant
Clinical trials in PFIC

INDIGO
**INDIGO: Phase 2 study of maralixibat to investigate long-term effects of pharmacological interruption of enterohepatic circulation**

**PFIC (N = 33)**
- 19 non-truncating (BSEP1 and 2)
- 6 truncating (BSEP3)
- 8 FIC1 (PFIC1)

**Primary endpoint**
- Change from baseline to Week 13 in fasting sBA level

**Secondary endpoints**
- Change from baseline to Week 13 in pruritus, measured by ItchRO(Obs) and ItchRO(Pt)
- Change from baseline to Week 13 in ALT, total and direct bilirubin

**Maralixibat**
- 266 µg/kg QD

**Long-term extension**

**Dose increased: maralixibat**
- 266 µg/kg BID

**Long-term analysis of response after >5 years**

---

* Dosing for maralixibat vs maralixibat chloride (266 µg maralixibat is equivalent to 280 µg maralixibat chloride). BID, twice daily dosing; BSEP, bile salt export pump; FIC, familial intrahepatic cholestasis; ItchRO(Obs), Itch-Reported Outcome (Observer); ItchRO(Pt), Itch-Reported Outcome (Patient); QD, daily dosing; sBA, serum bile acid.

**INDIGO: Mean sBA levels with long-term maralixibat treatment**

The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing.

**BSEP, bile salt export pump; sBA, serum bile acid.**


---

**Truncating BSEP mutations (BSEP3)**

**Non-truncating BSEP mutations (BSEP1 & 2)**

---

The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing. BSEP, bile salt export pump; sBA, serum bile acid.

INDIGO: Maralixibat results in profound and durable improvements in cholestatic pruritus in patients with nt BSEP deficiency (PFIC2)

Long-term extension

• ItchRO(Obs) response is sustained over years
• 79% (15/19) nt-PFIC2 patients achieved at least a 1-point reduction or a nadir ItchRO(Obs) score of <1 at any timepoint

The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing. ItchRO(Obs) score: 0–4 observer-rated pruritus scale. ItchRO(Obs), Itch-Reported Outcome (Observer); nt, non-truncated.

INDIGO: sBA control with long-term maralixibat treatment (responders)

- No clinical events have been observed.
- Six out of seven patients met one or both NAPPED criteria* by Week 4
  - Seventh sBA responder observed after twice-daily dosing at Week 97
- Two patients have come off the transplant waiting list.

* Either serum bile acid concentration below 102 µmol/L or a decrease of at least 75%.

sBA, serum bile acid.

INDIGO: sBA response on maralixibat is associated with pruritus reductions and improved growth (responders), n = 7

Error bars represent standard error of the mean.
ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid.
INDIGO: Transplant-free survival in patients with sBA control following maralixibat treatment


No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>7 7 7 7 7 7 1</td>
<td></td>
</tr>
<tr>
<td>Non-responders</td>
<td>12 11 5 4 4 1 0</td>
<td></td>
</tr>
</tbody>
</table>

sBA, serum bile acid; TFS, transplant-free survival.

Log-Rank p=0.0006

Responders

Non-responders
**INDIGO: Safety and tolerability with maralixibat**

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>19 (100.0)</td>
</tr>
<tr>
<td>Potentially maralixibat-related</td>
<td>15 (78.9)</td>
</tr>
<tr>
<td>Leading to discontinuation*</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Leading to death</td>
<td>0</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Potentially maralixibat-related*</td>
<td>2 (10.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most frequently reported TEAEs</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (63.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (42.1)</td>
</tr>
</tbody>
</table>

*Pancreatitis, blood bilirubin increased. TEAE, treatment-emergent adverse event.*

Clinical trials in PFIC

MARCH-PFIC
MARCH-PFIC: Phase 3 maralixibat study in PFIC2 and other PFIC subtypes

PFIC2 (N~30; primary cohort)
Other PFIC subtypes (N~60; supplemental cohort)

Primary endpoint
- ItchRO(Obs) mean change in severity of pruritus

Secondary endpoints
- Pruritus frequency
- Change in serum bile acids
- Safety

Additional endpoints
- Supplemental cohort analyses
- QoL, growth, other measures

* Dosing for maralixibat vs maralixibat chloride (570 µg maralixibat is equivalent to 600 µg maralixibat chloride).

BID, twice daily dosing; ItchRO(Obs), Itch-Reported Outcome (Observer); QoL, quality of life.

Clinical trials in PFIC

PEDFIC1 and PEDFIC2
PEDFIC 1/2: Phase 3 study of odevixibat in PFIC1 or PFIC2

PEDFIC 1
Single pivotal trial to support NDA/MAA filings

24 WEEKS

- Odevixibat
  - 40 µg/kg/day
  - n = 23
- Odevixibat
  - 120 µg/kg/day
  - n = 19
- Placebo
  - n = 20

62 subjects
Once daily oral capsule/sprinkle

R

Cohort 1 (P1O)

All odevixibat → Odevixibat
- 120 µg/kg/day
- n = 35

Cohort 1 (P1P)

Placebo → Odevixibat
- 120 µg/kg/day
- n = 19

Cohort 2

Odevixibat
- Newly enrolled
- 120 µg/kg/day
- n = 17

Non-PEDFIC 1 eligible

PEDFIC 2
Interim analyses at Weeks 24 and 48

72 WEEKS

- All enrolled patients
  - N = 71
  - Oral capsule/sprinkle
  - 120 µg/kg/day

Enrolled but not dosed, n = 2

PEDFIC 2
Interim analysis population
(≥1 dose of odevixibat)
- N = 69

Patients ongoing in PEDFIC 2
- N = 66

Total discontinuations, N = 3
- Withdrawal of consent, n = 2; AE, n = 1

Primary endpoints
- Pruritus (Albireo ObsRO instrument)
- sBA responder rate (reach ≤70 µmol/L or a reduction of 70%)

Secondary endpoints
- All-cause mortality
- Number undergoing biliary diversion surgery or liver transplantation
- Change in growth
- Change in Fib-4 score
- AST:platelet index
- End-stage liver disease
- Change in use of anti-pruritic medication

AE, adverse event; AST, aspartate transaminase; Fib-4, fibrosis-4 scale; MAA, marketing authorisation application; NDA, New Drug Application; ObsRO, observer-reported outcome; R, randomized; sBA, serum bile acid.

PEDFIC 1: Pruritus control with odevixibat treatment

**Proportion of positive pruritus assessments (PPAs)**

- Placebo N = 20
- Odevixibat 40 μg/kg/d n = 23
- Odevixibat 120 μg/kg/d n = 19
- All odevixibat N = 42

* PPAs defined as a scratching score of ≤1 or a ≥1-point drop from baseline on an observer-reported instrument; † Serum bile acid response: serum bile acids ≤70 μmol/L at Week 24 or a reduction from baseline to Week 24 of ≥70%.

**Percentage achieving sBA response at 24 weeks**

- Placebo N = 20
- Odevixibat 40 μg/kg/d N = 23
- Odevixibat 120 μg/kg/d N = 19
- All odevixibat N = 42

CI, confidence interval; LS, least squares; sBA, serum bile acid; SE, standard error.

Albireo corporate presentation May 2021.
Pruritus improvement demonstrated in PFIC1, 2, & 3

Percentage of patients with improvement in pruritus with odevixibat treatment (>1-point decrease deemed clinically relevant)

<table>
<thead>
<tr>
<th></th>
<th>PFIC1 N = 20</th>
<th>PFIC2 N = 52</th>
<th>PFIC3 N = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with improved pruritus score</td>
<td>95%</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Mean reduction (points)*</td>
<td>1.3</td>
<td>1.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Duration of odevixibat treatment 4–112 weeks.
* Reduction from baseline pruritus score (0 to 4-point scale).
Albireo corporate presentation May 2021.
# PEDFIC 1: Safety and tolerability with odevixibat

## Summary of TEAEs, n (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N = 20)</th>
<th>Odevixibat 40 μg/kg/day (n = 23)</th>
<th>Odevixibat 120 μg/kg/day (n = 19)</th>
<th>Odevixibat all doses (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>17 (85.0)</td>
<td>19 (82.6)</td>
<td>16 (84.2)</td>
<td>35 (83.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (30.0)</td>
<td>11 (47.8)</td>
<td>8 (42.1)</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (45.0)</td>
<td>7 (30.4)</td>
<td>6 (31.6)</td>
<td>13 (31.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (10.0)</td>
<td>1 (4.3)</td>
<td>2 (10.5)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Drug-related TEAE</td>
<td>3 (15.0)</td>
<td>7 (30.4)</td>
<td>7 (36.8)</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>5 (25.0)</td>
<td>0</td>
<td>3 (15.8)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation</td>
<td>0</td>
<td>0</td>
<td>1 (5.3)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Liver-related TEAEs</td>
<td>4 (20.0)</td>
<td>5 (21.7)</td>
<td>6 (31.6)</td>
<td>11 (26.2)</td>
</tr>
</tbody>
</table>

### Drug related TEAEs occurring in 2 or more patients in a group, by preferred term

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Placebo (N = 20)</th>
<th>Odevixibat 40 μg/kg/day (n = 23)</th>
<th>Odevixibat 120 μg/kg/day (n = 19)</th>
<th>Odevixibat all doses (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT increased</td>
<td>1 (5.0)</td>
<td>2 (8.7)</td>
<td>2 (10.5)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>AST increased</td>
<td>1 (5.0)</td>
<td>2 (8.7)</td>
<td>1 (5.3)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>1 (5.0)</td>
<td>2 (8.7)</td>
<td>2 (10.5)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>Diarrhea/frequent bowel movements</td>
<td>1 (5.0)</td>
<td>2 (8.7)</td>
<td>2 (10.5)</td>
<td>4 (9.5)</td>
</tr>
</tbody>
</table>

- No deaths or drug-related serious AEs were reported; 1 patient in the odevixibat 120 μg/kg/day arm discontinued due to diarrhea

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; sBA, serum bile acid; TEAE, treatment-emergent adverse event. Albireo corporate presentation May 2021.
PFIC summary

PFIC is a heterogeneous group of autosomal-recessive diseases that disrupt bile formation

PFIC2 (BSEP): most common and aggressive of the PFIC subtypes; genotype affects severity

PFIC presents as cholestasis, often with significant pruritus

PFIC can progress to cirrhosis, end-stage liver disease and liver failure

NAPPED data: sBA is a marker for long-term outcome, providing a rationale for IBAT inhibition

Odevixibat is approved for the treatment of pruritus in patients 3 months of age and older with PFIC
Planning new outcomes for biliary atresia

Tamir Miloh, M.D.
Medical Director of Pediatric Transplant Hepatology at the Miami Transplant Institute, USA
Biliary atresia is a progressive cholangiopathy of infancy and displays as a rapidly developing fibrotic process.

- The etiology of biliary atresia is unknown. Evidence supports the existence of numerous factors.
- There are different types of biliary atresia including:
  - Anatomy of the ducts involved (proximal distal)
  - Cystic BA
  - BA-associated splenic malformation (BASM)
  - Syndromic BA
  - BA association with other congenital disorders

Factors implicated in the etiology and pathogenesis of BA:

- Genes: ADD3, FOXA2, GPC1, EFEMP1, STIP1, PKDIL1
- Injury: Viruses, Toxins, Inflammation, Vascular insults
- Birth: Kasai
- Developmental susceptibility
- Progression: Progressive cholangiopathy, Progressive fibrosis

To be performed before onset of progressive fibrosis and cirrhosis

References:
Biliary atresia is classified as a rare disease

United States:
Incidence ~1 in 12,000 live births

Europe:
Incidence ~1 in 18,000 live births

Japan:
Incidence ~1 in 5,000 live births

There is considerable geographic variation in the incidence of biliary atresia, but the underlying reasons are unknown; however, females are more commonly affected.

Biliary atresia may appear similar to other neonatal cholestatic diseases at presentation

Overlapping features

- **Alpha-1 antitrypsin deficiency**
  - Can show features (e.g. biochemical, HIDA and histology) that closely mimic BA despite being a non-obstructive process

- **ALGS**
  - Ductular proliferation is present early in a small number of infants with ALGS, and ductopenia can occur later on

- **Neonatal sclerosing cholangitis**
  - Histopathology closely resembles BA

Exclude other diagnoses

- Phenotype/genotype for alpha-1
- Clinical and/or genetic investigation for ALGS, family history, involvement of extrahepatic organs
- Cholangiogram for patency of bile ducts and immune workup

A diagnosis of BA is confirmed with intraoperative cholangiogram and supportive histology of resected material

---

BA, biliary atresia; HIDA, hepatobiliary iminodiacetic acid.
Performing the Kasai procedure early is associated with higher transplant-free survival and improved jaundice clearance.

England and Wales data: Infants with isolated biliary atresia (N = 318) were divided by age at surgery; French data: A total of 685 children were included in the analysis.

Performing Kasai procedures early correlates with higher transplant-free survival


<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>N</th>
<th>Time of Kasai procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>30 days</td>
</tr>
<tr>
<td>United States</td>
<td>5-year overall survival</td>
<td>816</td>
<td>63%</td>
</tr>
<tr>
<td>1976–1989</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>4-year transplant-free</td>
<td>312</td>
<td>49%</td>
</tr>
<tr>
<td>1985–2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>5-year transplant-free</td>
<td>695</td>
<td>58%</td>
</tr>
<tr>
<td>1986–2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>2-year transplant-free</td>
<td>100</td>
<td>70%</td>
</tr>
<tr>
<td>1997–2000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age cutoffs among studies varied, but all showed better outcomes when the Kasai procedure was performed earlier.
Lower total bilirubin after Kasai procedure is a positive predictive marker for TFS

Kaplan-Meier plots of TFS based on total bilirubin and albumin levels 3 months post-Kasai

Kaplan-Meier analysis of outcome based on total bilirubin level 3 months post-Kasai

Total serum bilirubin level measured at 3 months post-Kasai is a marker of response that predicts TFS

TB, total bilirubin; TFS, transplant-free survival.

Implementation of bilirubin screening in neonates has resulted in Kasai’s being performed at an earlier age

- In a study of 61 patients with biliary atresia, it was found that at 24 to 48 hours of life, direct bilirubin levels are higher in those with biliary atresia compared to controls
- Direct bilirubin levels continue to increase up to 96 hours of life

Age at time of Kasai (US hospitals)

Before bilirubin screening implemented

- Kasai at 36 days

After bilirubin screening implemented

- Kasai at 56 days

The implementation of bilirubin (direct or conjugated) screening resulted in children undergoing the Kasai procedure at significantly younger ages

Serum bile acid levels 6 months post-Kasai predict transplant and death


In patients achieving bile flow with the Kasai procedure, sBA measured 6 months post-Kasai can predict long-term outcomes

Transplant/death (p=0.0006)

Transplant-free survival

≤40 μmol/L
>40 μmol/L

Time from Kasai to transplant/death (months)

Regular laboratory threshold is 10 μmol/L

≤40 μmol/L
43
34
23
18
14
7
2

>40 μmol/L
96
69
50
42
28
14
7

2.3% (1/43)
32.3% (31/96)
How to improve outcomes for patients with biliary atresia
START study: High-dose steroids given post-Kasai did not decrease TFS or improve biliary drainage (bilirubin <1.5 mg/dL after 6 months)

Good bile drainage defined as serum total bilirubin level of less than 1.5 mg/dL in a participant alive with native liver. BA, biliary atresia; SAE, serious adverse events; TFS, transplant-free survival.


Steroid treatment was also associated with earlier onset of SAEs in children with BA

Good bile drainage defined as serum total bilirubin level of less than 1.5 mg/dL in a participant alive with native liver. BA, biliary atresia; SAE, serious adverse events; TFS, transplant-free survival.

The implementation of IBAT inhibitors on biliary atresia outcomes

- When analyzed over 5 studies, average 20-year TFS in biliary atresia was estimated at 29%\(^1\text{-}^5\)
- Unique indications for liver transplant in biliary atresia include:\(^1\text{-}^6\)
  - Failed Kasai procedure
  - Late diagnosis, cirrhosis, and no Kasai
  - Recurrent bacterial cholangitis, resistant bacteria, fungal infection, and bile lakes leading to life-threatening sepsis

- There is an unmet need for therapies that could reduce the need for liver transplant in biliary atresia
- IBAT inhibitors could reduce sBAs, improve nutrition, and reduce the rate of fibrosis, progression, pruritus and other extrahepatic complications associated with end-stage liver disease\(^1\text{-}^4\text{,}^7\)

EMBARK: Phase 2 study of maralixibat in children with biliary atresia

Biliary atresia (N=72) 1:1 Maralixibat up to 570 μg/kg twice daily

Optional OLE enrollment up to a total of 104 weeks

Placebo

Core study (26 weeks)

Primary endpoint

• Change in total bilirubin levels from baseline to Week 26

Secondary endpoints

• Change in total sBAs from baseline to Week 26
• Proportion of subjects with total bilirubin levels <2 mg/dL at Week 26
• Time to liver transplantation or death
• Change in ALT, GGT, and platelets from baseline to Week 26
• Mean change in serum albumin from baseline to Week 26

ALT, alanine transaminase; GGT, gamma-glutamyltransferase; OLE, open label extension; sBA, serum bile acid.
BOLD: Phase 3 study of odevixibat in children with biliary atresia

**Primary endpoint**
- Proportion of patients with liver transplant after 104 weeks of treatment

**Secondary endpoints**
- Time to onset of any sentinel events
- Time to PELD score >15 from baseline to Week 104
- Total bilirubin and sBA levels from baseline to Weeks 13, 26, 52, and 104

PELD, pediatric end-stage liver disease; sBA, serum bile acid.
Biliary atresia is progressive obliterative cholangiopathy of infancy.

Early diagnosis is crucial to differentiate biliary atresia from ALGS and other diseases, and is associated with improved transplant-free survival for children with biliary atresia.

Biliary atresia remains the leading indication for liver transplantation in children across age groups.

Kasai portoenterostomy procedure is the standard of care to re-establish bile flow.

Lower serum bile acids are a powerful prognostic marker after a successful Kasai procedure.

Trials of IBAT inhibitors are underway in children with biliary atresia (following Kasai procedure) to improve transplant-free survival.
Where have we been, and where are we now?

- First attempted liver transplant: 1963
- PFIC first described: 1965
- ALGS first described: 1969
- Identification of the genetic etiology of ALGS: 1997
- Identification of BSEP mutations leading to PFIC: 1998
- Novel therapies targeting interruption of enterohepatic recirculation of bile acids: 2020
- Maralixibat approved for pruritus in ALGS: 2021
- Odevixibat approved for pruritus in PFIC: 2021

BSEP, bile salt export pump.

IMPORTANT: Meeting evaluation

Please complete the meeting evaluation

Please scan the QR code to download the presentation slides