Pediatric cholestasis: Itching for an alternative to liver transplantation

Mirum-sponsored symposium WCPGHAN 2021
Thursday June 3, 2021
Welcome and introduction

Binita M. Kamath

The Hospital for Sick Children, Toronto, Ontario, Canada
Speaker disclosures

• **Unrestricted educational grant and consultant:**
  – Mirum, Albireo
• **Consultant:**
  – Audentes
## Pediatric cholestasis: Itching for an alternative to liver transplantation

<table>
<thead>
<tr>
<th>Time (CET)</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>17:30–17:40</td>
<td>Welcome and introduction</td>
<td>Binita M. Kamath</td>
</tr>
<tr>
<td>17:40–18:00</td>
<td>Can novel treatments offer new hope for children with ALGS?</td>
<td>Emmanuel Gonzales</td>
</tr>
<tr>
<td>18:00–18:20</td>
<td>Scratching below the surface of PFIC management</td>
<td>Richard Thompson</td>
</tr>
<tr>
<td>18:20–18:30</td>
<td>Q&amp;A and Chair’s close</td>
<td>Binita M. Kamath</td>
</tr>
</tbody>
</table>

Please submit any questions in the ‘chat’ function and we will answer as many of these as possible during the Q&A session.
We would appreciate it if you could complete the meeting evaluation at the end of the session

Thank You
With increasing use of genotyping, liver biopsies are becoming less essential\textsuperscript{1–8}

NGS, next generation sequencing.

There are currently no approved pharmacological treatment options for ALGS or PFIC.


Presently there are no approved therapies and off-label use is modestly effective.

**Symptomatic pruritus control and nutritional supplementation**

**LIVER TRANSPLANT**

**ALGS**
- 24% survive with native liver at 18.5 years

**PFIC**
- 32% survive with native liver at 18 years

Cholestatic liver diseases significantly impact patient quality of life

Children with a history of chronic cholestatic liver disease may experience increased risk of long-term cognitive deficits and decreased QoL.


- Cognitive defects
- Impaired school performance
- Sleep disturbance and fatigue
- Pain
- Decreased physical functioning or general health
- Mental health/depression
- Negative impact on a child’s social activities
- Behaviour issues

QoL, quality of life.
Beyond the patient – caregiver impact is also significant\textsuperscript{1}

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

\textsuperscript{1}National Alliance for Caregiving, in partnership with Global Genes, 2018.
Where have we been, and where are we now?

- **First attempted liver transplant**
  - 1963

- **ALGS first described**
  - 1965

- **PFIC first described**
  - 1969

- **Identification of the genetic aetiology of ALGS**
  - 1997

- **Identification of BSEP mutations leading to PFIC**
  - 1998

- **Novel therapies for ALGS and PFIC in development**
  - 2021+

Rationale for ASBT inhibition

By reducing bile acids, ASBTi have been shown to improve pruritus and other QoL measures

ASBT, apical sodium-dependent bile acid transporter; ASBTi, apical sodium-dependent bile acid transporter inhibition; QoL, quality of life.

Can novel treatments offer new hope for children with ALGS?

Emmanuel Gonzales

Hépatologie Pédiatrique, Hôpital Bicêtre, AP-HP. Université Paris-Saclay, Le Kremlin-Bicêtre, France
Speaker disclosures

- **Consultant:**
  - Albireo, CTRS, Mirum
ALGS is a rare, developmental, autosomal dominant disorder\textsuperscript{1–3}

- First reported as “arteriohepatic dysplasia”
- Clinical diagnosis (≥3 major criteria out of 5)
- Incomplete penetrance, variable expressivity

Mutations in \textit{JAG1} (89–94%)

Mutations in \textit{NOTCH2} (2%)

Genotype testing is preferred to confirm the diagnosis

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

ALGS is classed as a rare disease

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

ALGS can result in a broad range of clinical manifestations

- Characteristic facial features
- Hearing loss
- Impaired growth
- Skeletal abnormalities, fractures
- Renal abnormalities

- Ophthalmic abnormalities
- Chronic cholestasis, pruritus, xanthomas
- Portal hypertension in early adulthood
- Cardiovascular disease
- Vascular accidents / intracranial bleeding


Management of ALGS aims to alleviate the symptoms of disease\textsuperscript{1–3}

There are currently no approved treatments for ALGS

<table>
<thead>
<tr>
<th>Control of pruritus</th>
<th>Medications</th>
<th>Main side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ursodeoxycholic acid (UDCA)</td>
<td>Diarrhea, abdominal pain, worsening liver complications (high-dose)</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>Red urine coloration, idiosyncratic hypersensitivity reactions, hepatitis</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Bile salt binding agents (e.g. cholestyramine; colesevelam)</td>
<td>Constipation, abdominal pain, hyperchloremic metabolic acidosis, exacerbation of fat-soluble vitamin malabsorption</td>
</tr>
<tr>
<td></td>
<td>Lipid-lowering agents (e.g. atorvastatin)</td>
<td>Headaches, increased transaminases</td>
</tr>
<tr>
<td></td>
<td>Naltrexone</td>
<td>Symptoms of opioid withdrawal</td>
</tr>
<tr>
<td></td>
<td>Sertraline (serotonin reuptake inhibitor)</td>
<td>Agitation, skin reactions, vomiting, transient arterial hypertension</td>
</tr>
</tbody>
</table>

Dietary supplements

<table>
<thead>
<tr>
<th>Fat-soluble vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional supplements</td>
</tr>
</tbody>
</table>

Cholestatic clinical manifestations of ALGS may be severe and debilitating\textsuperscript{1}

Images sourced from Mirum Pharmaceuticals.
Substantial risk for liver transplant in patients with ALGS

GALA\(^1\) (Global)
NLS in patients with ALGS presenting with neonatal cholestasis (N=911)

57% NLS at 10 years
41% NLS at 18 years

ChiLDReN (North America network)\(^2\)
TFS in patients with ALGS

24% TFS at 18.5 years

* Left truncated at baseline age.
NLS, native liver survival; TFS, transplant-free survival.
Balancing the scales: When to refer patients to liver transplant?

- Normalise bile flow and cure cholestasis
- Growth improvement
- Decrease the risk of fracture

- Contraindication: cardiac, vascular
- Usually not a formal indication
- Usual non-specific complication of LT
- Vascular issues
- Worsening of renal disease
Novel approaches to improve outcomes in ALGS

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Design</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maralixibat</td>
<td>NCT04530994</td>
<td>EA</td>
<td>-</td>
<td>A Maralixibat Expanded Access Program for Patients With Cholestatic Pruritus Associated With ALGS</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT02160782 (ICONIC)</td>
<td>2</td>
<td>31</td>
<td>Safety and Efficacy Study of LUM001 With a Drug Withdrawal Period in Participants With ALGS</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT01903460 (IMAGO)</td>
<td>2</td>
<td>20</td>
<td>Safety and Efficacy Study of LUM001 in the Treatment of Cholestatic Liver Disease in Patients With ALGS</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT02047318 (IMAGINE)</td>
<td>2</td>
<td>19</td>
<td>An Extension Study to Evaluate the Long-Term Safety and Durability of Effect of LUM001 in the Treatment of Cholestatic Liver Disease in Subjects With ALGS</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT02057692 (ITCH)</td>
<td>2</td>
<td>37</td>
<td>Evaluation of LUM001 in the Reduction of Pruritus in ALGS</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT02117713 (IMAGINE-II)</td>
<td>2</td>
<td>34</td>
<td>An Extension Study to Evaluate the Long-Term Safety and Durability of Effect of LUM001 in the Treatment of Cholestatic Liver Disease in Pediatric Subjects With ALGS</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT04729751 (RISE)</td>
<td>2</td>
<td>12</td>
<td>A Study to Evaluate the Safety and Tolerability of Maralixibat in Infant Participants With Cholestatic Liver Diseases Including PFIC and ALGS</td>
<td>Not yet recruiting</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT04168385 (MERGE)</td>
<td>2</td>
<td>54</td>
<td>A Long-Term Safety Study of Maralixibat in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study</td>
<td>Ongoing by invitation</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT02630875</td>
<td>2</td>
<td>24</td>
<td>An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children With Cholestatic Pruritus</td>
<td>Completed</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT04674761 (ASSERT)</td>
<td>3</td>
<td>45*</td>
<td>A Phase 3 Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of Odevixibat (A4250) in Patients With ALGS</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

* N=45 from latest Albireo corporate presentation May 2021; additional information from ClinicalTrials.gov.
EA, expanded access.
All clinical trials of novel compounds from ClinicalTrials.gov are listed.
The ITCH trial suggested maralixibat may reduce pruritus in ALGS¹

- Primary outcome: change from baseline to Week 13 in ItchRO relative to placebo

- Statistically significant decreases were observed with doses of 70 and 140 µg/kg/day (p=0.014), but not 280 µg/kg/day (p=0.44) or all doses combined (p=0.055)

- A 1-point reduction in pruritus was more common in maralixibat- vs placebo-treated participants (caregiver ItchRO: 65% vs 25%, p=0.06; clinician score: 76% vs 25%, p=0.01)

- AEs and SAEs were similar between maralixibat and placebo

---

ICONIC (LUM001-304): Phase 2 study of maralixibat in ALGS¹

Primary endpoint
- Mean change in sBA levels from Weeks 18–22 (and mean change in those who previously responded to maralixibat)
- TEAEs (up to Week 98)

Secondary endpoints (weeks 18–22)
- Change in liver enzymes
- Mean change in pruritus (ItchRO)

Additional endpoints (up to week 96)
- Change in sBA; change in BA synthesis
- Change in liver enzymes
- Change in pruritus (ItchRO and CSS)
- Biochemical markers of cholestasis
- Change in xanthomas
- QoL; patient/caregiver impressions

* Equivalent to maralixibat chloride 400 μg/kg; † Includes a 6-week dose-escalation period for participants who received placebo during the randomised withdrawal phase; dosing for maralixibat vs maralixibat chloride; ‡ Twice daily dosing (started after Week 100) was equivalent to maralixibat chloride 800 μg/kg.

BA, bile acids; CSS, clinician scratch scale; ItchRO, Itch Reported outcome; QoL, quality of life; R, randomised; sBA, serum bile acid; TEAEs, treatment-emergent adverse events.

Significant reduction in sBA levels was maintained long term

**p<0.05; **p<0.005 (compared with baseline, overall population).


* p<0.05; ** p<0.005 (compared with baseline, overall population).

BL, baseline; BID, twice daily dosing; sBA, serum bile acid; SE, standard error.

Significant and sustained improvements in pruritus
84% patients had a clinically meaningful decrease (≥1-point) during the 48-week period

Changes in pruritus from BL to Week 204 (ItchRO[Obs])¹

Placebo-controlled withdrawal

Maralixibat vs placebo Weeks 18–22
p<0.0001

** p<0.005; *** p<0.0001 (compared with baseline, overall population).

Mean change in ItchRO[Obs] from baseline (SE)

Week BL 12 18 22 48 62 74 86 98 156 168 180 192 204

Maralixibat (extension)
Maralixibat-maralixibat-maralixibat (core)
Maralixibat-placebo-maralixibat (core)

BL, baseline; BID, twice daily dosing; ItchRO[Obs], Itch Reported outcome [Observer]; SE, standard error.

Sustained improvements in xanthomas (in those with xanthomas at baseline)\(^1\)

* \(p<0.05\); ** \(p<0.01\); *** \(p<0.001\).

† Clinician xanthoma score 0–4 scale.

CXS, clinician xanthoma score; SE, standard error.

Correlation shown between pruritus and multiple parameters following maralixibat treatment

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; sBA, serum bile acid.

Parameters correlated with ItchRO[Obs] score at Week 48

<table>
<thead>
<tr>
<th>Parameter</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>sBA</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>

Parameters correlated with ItchRO[Obs] score as a change from Baseline to Week 48

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PedsQL™ Fatigue</td>
<td>–0.59</td>
<td>0.0053</td>
</tr>
</tbody>
</table>

sBA reductions correlated with reductions in pruritus intensity
### ICONIC: Safety and tolerability with maralixibat

**Randomised withdrawal**

<table>
<thead>
<tr>
<th>Number of participants, n (%)</th>
<th>Core study (Weeks 0–18) (N=31)</th>
<th>Maralixibat (n=13)</th>
<th>Placebo (n=16)</th>
<th>Core study (Weeks 23–48) (N=29)</th>
<th>Extension phase (Week 49+) (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>30 (96.8)</td>
<td>7 (53.8)</td>
<td>12 (75.0)</td>
<td>25 (86.2)</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>Grade 3 or 4 TEAE</td>
<td>6 (19.4)</td>
<td>0</td>
<td>1 (6.3)</td>
<td>2 (6.9)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Serious TEAE (all unrelated to maralixibat)</td>
<td>4 (12.9)</td>
<td>1 (7.7)</td>
<td>1 (6.3)</td>
<td>5 (17.2)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>TEAE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>2 (6.5)*</td>
<td>0</td>
<td>0</td>
<td>1 (3.4)*</td>
<td>3 (10.3)†‡</td>
</tr>
</tbody>
</table>

- TEAE potentially related to study drug
  - 12 (38.7) in Core study (Weeks 0–18), 1 (7.7) in Maralixibat, 3 (18.8) in Placebo, 1 (3.4) in Core study (Weeks 23–48), 7 (24.1) in Extension phase (Week 49+).

- Fourteen participants remain on maralixibat, with median treatment duration of 1469.5 days (210 weeks; 4 years).

**Maralixibat is well tolerated with few subjects who discontinued due to AEs. Most events were GI-related, mild to moderate in severity and self-limiting**

---

* Infection; intracranial bleeding; increased bilirubin levels; all unrelated to maralixibat; † Elevated ALT and/or AST levels (n=2); hypertension/renal failure unrelated to maralixibat (n=1); ‡ Third discontinuation occurred after the data cutoff, bringing n to 14.

ALT, alanine aminotransferase; AST, aspartate transaminase; GI, gastrointestinal; TEAE, treatment-emergent adverse event.

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

* Includes multiple adverse event terms.

AE, adverse event; GI, gastrointestinal.


<table>
<thead>
<tr>
<th>Patients experiencing an AE, n (%)</th>
<th>Integrated patient population (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrhoea*</td>
</tr>
<tr>
<td>Any severity</td>
<td>49 (57.0)</td>
</tr>
<tr>
<td>Mild</td>
<td>42 (48.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7 (8.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Life-threatening/fatal</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

The majority of GI AEs occurred within the first 4 weeks of treatment and lasted <1 week in duration. The majority of diarrhoea and abdominal pain AEs 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

<table>
<thead>
<tr>
<th>Patients experiencing an AE, n (%)</th>
<th>Maralixibat (N=39)</th>
<th>Placebo (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrhoea*</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>

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

* Includes multiple adverse event terms.
AE, adverse event; GI, gastrointestinal.
ALGS maralixibat expanded access program\textsuperscript{1,2}

Programme criteria

- ALGS diagnosis
- >1 year of age with moderate to severe pruritus
- No access to ongoing ALGS clinical trials
- Safety and tolerability evaluated on an ongoing basis

Maralixibat 400 µg/kg/day

Australia
Austria
Belgium
Canada
Denmark
France
Germany
Greece
Italy
Netherlands
Poland
Spain
Sweden
UK
US

AE, adverse event; CSS, clinician scratch scale.
Phase 2 study: Odevixibat across children diagnosed with pruritus due to chronic cholestasis¹

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

<table>
<thead>
<tr>
<th>PFIC, biliary atresia, ALGS, sclerosing cholangitis (N=24)</th>
<th>Odevixibat for 4 weeks (10, 30, 60, 100 and 200 µg/kg evaluated)</th>
</tr>
</thead>
</table>

**Primary endpoints**

- Safety and tolerability
- Explore changes in serum total bile acids after a 4-week treatment period

**Secondary endpoints**

- Efficacy on liver biochemistry variables and on pruritus parameters
- Pharmacokinetic properties
- Evaluate changes in VAS itching score after a 4-week treatment period

---

VAS, visual analogue scale.

Phase 2 study: Mean sBA levels and pruritus scores with odevixibat\textsuperscript{1,2}

**ALGS cohort, n=6**

**sBA reduction from baseline**

<table>
<thead>
<tr>
<th>Patient</th>
<th>sBA reduction from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-92</td>
</tr>
<tr>
<td>2</td>
<td>-39</td>
</tr>
<tr>
<td>3</td>
<td>-14</td>
</tr>
<tr>
<td>4</td>
<td>-57</td>
</tr>
<tr>
<td>5</td>
<td>338</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
</tr>
</tbody>
</table>

Baseline (µM): 260, 116, 564, 121, 338, 26

- Change in sBA from baseline
- Absolute decrease in pruritus (VAS itch score)

**Reduction in serum bile acid levels correlated with reduction in pruritus**

Patients received 10–200 µg/kg odevixibat.

* Pruritus measured by VAS itch.

sBA, serum bile acid; VAS, visual analogue scale.

Phase 2 study: Safety and tolerability with odevixibat

Safety includes entire cohort, n=24

• All patients completed treatment; no evidence of diarrhoea during 4-week treatment period
• No AEs related to treatment during 4-week treatment period
  – Most common AEs: pyrexia, ear infections (12.5%)
• No SAEs designated as treatment related (two deemed unrelated)
• Decision made not to dose escalate above 200 μg/kg
  – Some transaminase elevations at 200 μg/kg

AE, adverse event; SAE, serious adverse event.
Phase 3 study: Odevixibat in ALGS (ASSERT)\textsuperscript{1,2}

| ALGS (N=45) | R 2:1 | Odevixibat 120 μg/kg/day (n=30) | Placebo (n=15) | Safety follow-up | Optional OLE enrollment |

- **Primary endpoint**
  - Change from baseline in scratching to Month 6 (Weeks 21–24) as measured by the Albireo ObsRO caregiver instrument

- **Secondary endpoints**
  - Serum bile acid levels
  - Safety and tolerability

**Key eligibility criteria**

- Patient (of any age) with genetically confirmed diagnosis of ALGS
- History of significant pruritus
- Elevated sBA level

ObsRO, observer-reported outcome; OLE, open-label extension; sBA, serum bile acid.
There remains a high unmet need in ALGS

ALGS is a rare, developmental, multisystem and often debilitating disease

Liver involvement is due to intrahepatic bile duct paucity resulting in chronic cholestasis

Cholestasis manifested by pruritus and xanthomas is the leading cause of liver transplantation

There are currently no approved treatments; management aims to alleviate pruritus

ASBT inhibition has demonstrated promising clinical results
Scratching below the surface of PFIC management

Richard Thompson
King's College London, London, UK
Speaker disclosures

• **Consultancy:**
  – Mirum, Albireo, Generation Bio, Qing Bile Therapeutics, Horizon Pharma, Alnylam, Sana Biotechnology, EVOX Therapeutics, Rectify Therapeutics

• **Shares/options:**
  – Qing Bile Therapeutics, Generation Bio, Rectify Therapeutics
PFIC is a heterogeneous group of diseases that disrupt bile formation\(^1\)\(^–\)\(^3\)

PFIC is classed as a rare disease\textsuperscript{1,2}


The prevalence of PFIC is unknown, but it 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 \textit{ABCB11} mutation and predicts NLS.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>BSEP protein</th>
<th>Predicted severity</th>
<th>Median NLS (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>


NLS, native liver survival.

Management approaches for BSEP (PFIC2)¹–⁶

There are currently no approved treatments for BSEP (PFIC2)

Control pruritus
- UDCA
- Cholestyramine
- Rifampicin
- Other medicines

Supplemental dietary treatments
- Medium chain triglyceride
- Fat soluble vitamins
- Nutritional supplements

Treat the disease
- Biliary diversion
- Liver transplantation

UDCA, ursodeoxycholic acid.
BSEP deficiency (PFIC2) results in a broad range of other clinical manifestations


- Jaundice
- Fat malabsorption
- Fat-soluble vitamin deficiency
- Failure to thrive during first several months of life
- Excoriation and mutilation of skin
- Scleral icterus
- Hepatomegaly
- Portal hypertension within the first year
- Approx. 50% of patients require a liver transplant by age
Surgical biliary diversion improves outcomes in BSEP1 and 2 (nt-PFIC2)\textsuperscript{1}

\begin{itemize}
\item CI, confidence interval; HR, hazard ratio; nt, non-truncated.
\item \textsuperscript{1} van Wessel DBE, et al. \textit{J Hepatol} 2020; 73:84–93.
\end{itemize}

\*Reprinted from Journal of Hepatology, 73, van Wessel, ‘Genotype correlates with the natural history of severe bile salt export pump deficiency’, 84–93, Copyright (2020), with permission from Elsevier.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{surgical_diversion_graph.png}
\caption{Kaplan-Meier survival curves for patients with native liver, with and without surgical diversion. HR 0.50 (95% CI: 0.27–0.94), \(p=0.03\).}
\end{figure}
sBA control after surgical biliary diversion is associated with transplant-free survival\(^1\)

---

**NLS after SBD in patients with sBA < or ≥102 µmol/L**

- sBA <102 µmol/L
- sBA ≥102 µmol/L

**NLS after SBD in patients with a relative decrease in sBA of < or ≥75%**

- <75% decrease sBA
- ≥75% decrease sBA

---

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

---

\(^1\) Reprinted from Journal of Hepatology, 73, van Wessel, ‘Genotype correlates with the natural history of severe bile salt export pump deficiency’, 84–93, Copyright (2020), with permission from Elsevier.

NLS, native liver survival; sBA serum bile acid; SBD, surgical biliary diversion.

Novel approaches to improve outcomes PFIC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Design</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maralixibat</td>
<td>NCT02057718 (INDIGO)</td>
<td>2</td>
<td>33</td>
<td>Open Label Study to Evaluate Efficacy and Long-Term Safety of LUM001 in the Treatment of Cholestatic Liver Disease in Patients With PFIC</td>
<td>Completed</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT03905330 (MARCH-PFIC)</td>
<td>3</td>
<td>90(^1)</td>
<td>A Study to Evaluate the Efficacy and Safety of Maralixibat in Subjects With PFIC (n~30 nt-PFIC2; n ≤60 other PFIC subtypes)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT04185363 (MARCH-ON)</td>
<td>3</td>
<td>30</td>
<td>An Extension Study of Maralixibat in Patients With PFIC</td>
<td>Ongoing by invitation</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT04168385 (MERGE)</td>
<td>2</td>
<td>54</td>
<td>A Long-Term Safety Study of Maralixibat in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study</td>
<td>Ongoing by invitation</td>
</tr>
<tr>
<td>Maralixibat</td>
<td>NCT04729751 (RISE)</td>
<td>2</td>
<td>12</td>
<td>A Study to Evaluate the Safety and Tolerability of Maralixibat in Infant Participants With Cholestatic Liver Diseases Including PFIC and ALGS</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT04483531 (PEDFIC 1)</td>
<td>EA</td>
<td>-</td>
<td>Odevixibat (A4250) for the Treatment of Progressive Familial Intrahepatic Cholestasis (Expanded Access Program)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT02630875</td>
<td>2</td>
<td>24</td>
<td>An Exploratory Phase II Study to Demonstrate the Safety and Efficacy of A4250 in Children With Cholestatic Pruritus</td>
<td>Completed</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT03566238 (PEDFIC 2)</td>
<td>3</td>
<td>62</td>
<td>A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children With PFIC1/2</td>
<td>Completed</td>
</tr>
<tr>
<td>Odevixibat</td>
<td>NCT03659916 (PEDFIC 2)</td>
<td>3</td>
<td>120</td>
<td>An Open-label Extension Study to Evaluate Long-term Efficacy and Safety of A4250 in Children With PFIC1/2</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

All clinical trials of novel compounds from ClinicalTrials.gov are listed.
EA, expanded access.
INDIGO: Phase 2 study of maralixibat to investigate long-term effects of pharmacological interruption of enterohepatic circulation\textsuperscript{1,2}

**Primary endpoint**
- sBA control
- ItchRO[Obs] severity of pruritus in PFIC2 (BSEP1–3)

**Secondary endpoints**
- Growth
- QoL
- Safety and tolerability

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

**Maralixibat* 266 µg/kg QD**

**Long-term extension**

**Dose increased: Maralixibat* 266 µg/kg BID**

---

* Dosing for maralixibat vs maralixibat chloride (266 µg maralixibat is equivalent to 280 µg maralixibat chloride).
BID, twice daily dosing; ItchRO[Obs], Itch Reported outcome [Observer]; QD, daily dosing; QoL, quality of life; 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.
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.
INDIGO: Maralixibat results in profound and durable improvements in cholestatic pruritus in patients with BSEP deficiency (PFIC2)\(^1\)

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.


- ItchRO(Obs) response is sustained over years
- 79% (15/19) nt-PFIC2 patients achieved at least a 1-point reduction or a nadir ItchRO score of <1 at any timepoint
INDIGO: sBA control with long-term maralixibat treatment (responders)\(^1\)

- 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

sBA, serum bile acid.

INDIGO: sBA response on maralixibat is associated with pruritus reductions and improved growth (responders), n=71


---

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>0</th>
<th>52</th>
<th>104</th>
<th>156</th>
<th>208</th>
<th>260</th>
<th>312</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td><strong>Non-responders</strong></td>
<td>12</td>
<td>11</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

TFS (%)

Log-Rank p=0.0006
### INDIGO: Safety and tolerability with maralixibat

*Pancreatitis, blood bilirubin increased.

TEAE, treatment-emergent adverse event.


<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>Diarrhoea</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.

MARCH-PFIC: Phase 3 maralixibat study in PFIC2 and other PFIC subtypes¹,²

**BSEP1–3 (PFIC2)**
(N~30; primary cohort)
Up to 60 patients in supplemental cohort of other PFIC subtypes

**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.

# 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

### 72 WEEKS

- **Odevixibat**
  - 120 µg/kg/day
  - n=35
- **Placebo**
  - n=19

Non-PEDFIC 1 eligible

## PEDFIC 2
**Interim analyses at Weeks 24 and 48**

### 24 WEEKS

- **Odevixibat**
  - 120 µg/kg/day
  - n=19
- **Enrolled but not dosed, n=2**
- **Total discontinuations, N=3**
  - Withdrawal of consent, n=2; AE, n=1

### 72 WEEKS

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

## 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 aminotransferase; Fib-4, fibrosis-4 scale; ObsRO, observer-reported outcome; r, randomised; sBA, serum bile acid.
**PEDFIC 1: Pruritus control with odevixibat treatment**

*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%.

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

Pruritus improvement demonstrated in PFIC 1, 2 & 3\textsuperscript{1}

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).
### PEDFIC 1: Safety and tolerability with odevixibat

<table>
<thead>
<tr>
<th>Summary of TEAEs, n (%)</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></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>Diarrhoea/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 diarrhoea

---

* Odevixibat 40 mg/kg/day and 120 mg/kg/day; † Reduction of ≥70% sBA or reaching ≤70 mmol/L sBA level.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; sBA, serum bile acid; TEAE, treatment-emergent adverse event.

There remains a high unmet need in PFIC

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

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

PFIC typically presents as intrahepatic cholestasis

There are currently no approved treatments for PFIC

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

ASBT inhibition has demonstrated promising clinical results
We would appreciate it if you could complete the meeting evaluation

Scan the QR code to download the presentation slides