FILFOIE

Filière de Santé Maladies Rares du Foie de l’Adulte et de l’Enfant

Inhibiteurs d’ASBT dans le prurit cholestatique

E Gonzales
Dérivation biliaire partielle externe
- bénéfice chez certains patients PFIC1 et PFIC2
- possible bénéfice dans le Syndrome d’Alagille

Dérivation biliaire partielle interne

Iléal bypass

• **Inhibiteurs d’ASBT**: « dérivation chimique»
Dérivation biliaire partielle externe

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- possible bénéfice dans le Syndrome d’Alagille

Dérivation biliaire partielle interne

Iléal bypass

• **Inhibiteurs d’ASBT**: « dérivation chimique»

Whittington PF et al., Gastroenterology 1988
Balistreri W et al. Hepatology 2005
Stapelbroek et al. J Hepatol 2010
The ileal bile acid transporter (IBAT, SLC10A2), also called apical sodium-dependent bile salt transporter (ASBT), is a key element in the enterohepatic circulation of bile acids.

- Integral brush border membrane glycoprotein mainly expressed in the distal ileum
- Responsible for the reabsorption of about 95% of the intestinal bile acids, predominantly in the glycine- or taurine-conjugated form, that are then recirculated to the liver via portal venous blood.
- Lowering the bile acid pool by IBAT inhibition may emerge as an option for the treatment of cholestatic pruritus.
Inhibiteurs d’ASBT dans le prurit cholestatique
highly potent, soluble, minimally absorbed, selective inhibitor of the human IBAT.

GSK2330672

LUM001 (SHP625, Maralixibat), Lumena/Shire/Mirum

A4250, Albireo
2 Essais de phase 1 (59 volontaires sains)

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A Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Repeat Doses of GSK2330672 Administration in Subjects With Primary Biliary Cirrhosis (PBC) and Symptoms of Pruritus

Adults (18-75) with Primary Biliary Cirrhosis (PBC) and Symptoms of Pruritus, stable dose of UDCA, AP<10N

Study design

GSK2330672 : 45 mg twice per day on days 1–3, 90 mg twice daily on days 4–14

Study Type : Interventional (Clinical Trial)
Actual Enrollment : 22 participants
Allocation : Randomized
Intervention Model : Crossover Assignment
Masking : Double (Participant, Investigator)
Outcomes

1- Safety / tolerability

2- Changes from baseline pruritus
Serum total bile acids, C4, parameters of UDCA

Exploratory : FGF19, ATX
Overall good tolerance

The most common GSK2330672-related adverse event was diarrhoea but no patient discontinued the drug or had their dose decreased secondary to diarrhoea.
GSK2330672 reduced itch intensity significantly more than the double-blind placebo in all three scales.

- **0–10 numerical rating scale**
  - $-57\%$ (95% CI $-73$ to $-42$, $p<0.0001$)

- **PBC-40 itch domain score**
  - $-30\%$ ($-42$ to $-20$, $p<0.0001$)

- **5-D itch scale**
  - $-35\%$ ($-45$ to $-25$, $p<0.0001$)
With GSK2330672 treatment:

- decrease serum total bile acids
- increase in serum C4 concentration
- decrease serum concentrations of conjugated BA
- increase in serum UDCA
- decrease in ATX activity and FGF19 concentration

**serum total bile acids**
Maralixibat : LUM001, SHP625

CLARITY : A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi) in Combination With Ursodeoxycholic Acid (UDCA) in Patients With Primary Biliary Cirrhosis

*Mayo MJ et al J Hepatol 2016 Volume 64, Issue 2, Supplement, Page S197*
66 PBC patients, aged 18–80 y with pruritus

Randomization in two cohorts:
1) lopixibat 10 mg or placebo
2) lopixibat 20 mg or placebo

13-week treatment:
dose-escalation (3–4w)
stable-dosing periods (9–10w)

Endpoints:
-1 change in Adult ItchRO weekly sum score
-2 serum BA, C4 and ALP
Conclusions:

• Reductions in Adult ItchRO weekly sum score did not differ significantly between lopixibat and placebo. A large placebo effect may have confounded assessment of pruritus.

• However, sBA reductions and C4 increases reached nominal significance for lopixibat vs placebo, suggesting pharmacological activity.

• The safety profile of lopixibat was consistent with previous clinical experience.

Most common adverse events (AEs) for lopixibat and placebo were:
diarrhea (61.9% and 25.0%, respectively), nausea (23.8% and 16.7%), abdominal pain upper (23.8% and 8.3%) and abdominal pain (23.8% and 4.2%).
Two patients discontinued lopixibat due to abdominal pain and diarrhea (nonserious AEs). One patient had a drug-related, serious AE (abdominal pain), but completed the study.
A4250, Albireo Pharma, Sweden

A4250 prevented damage to the liver and bile ducts and decreased elevated liver enzymes and bile acid levels in the mdr2−/− animal model of cholestasis


phase 1 study of healthy subjects, A4250 was well tolerated and dose-dependently reduced serum bile acid levels


A4250PBCpruritus : open-label exploratory phase IIa study (NCT02360852)

A4250PBCpruritus study flow scheme and individual outcome of the 10 participating patients with PBC on continuous UDCA 10–15 mg/kg/d (non responder) and bile acid sequestrant.

All nine patients that were exposed to study medication reported improvements of pruritus starting already on the second day of medication.

A4250 substantially improved cholestatic pruritus

Poor digestive tolerance: five out of nine patients that were exposed to study medication discontinued after two to seven days due to abdominal pain and diarrhoea

Dans la PBC les Inhibiteurs d’ASBT A4250 diminuent sBA, ATX, FGF19, augmentent le C4 et semblent réduire le prurit (A4250, GSK2330672)

La tolérance digestive est médiocre en particulier quand ils sont administrés en une prise par jour (études avec A4250 et LUM001).
- Diminution des doses et répartition en deux prises
- Possible rôle des chélateurs d’acides biliaires

En cours

Randomized, Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of GSK2330672 Administration for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis
Inhibiteurs d’ASBT dans le prurit cholestatique chez l’enfant

A4250, Albireo

LUM001 (SHP625, Maralixibat), Lumena/Shire/Mirum
A4250-003: phase 2, single- and multiple-dose, open-label, multicenter study (NCT02630875)

- pediatric patients (age 1–18 years)

**Inclusion criteria**
- diagnosis of pruritus due to chronic cholestatic disease
- elevated serum total bile acids ≥2 times the upper limit of normal (ULN),
- a score of ≥3 on an 11-point visual analogue scale (VAS) for itch averaged over 7 days.

**Exclusion criteria**
- decompensated liver disease, structural abnormality of the gastrointestinal (GI) tract, except biliary diversion procedures; or pruritus caused by any condition other than cholestasis.

- Use of drugs with effects on bile acid concentration in the GI tract or drugs with known effects on GI motility were prohibited

- Other drugs or natural products were allowed during the study provided the dose was stable (selective serotonin reuptake inhibitors, tricyclic antidepressants, fiber supplementation, or yogurt variants) and treatment with UDCA, rifampicin, and antihistamines.
**Efficacy**

- Primary efficacy endpoint: the change from baseline in serum bile acid levels

- Secondary efficacy endpoints:
  - change in weekly mean severity of self-reported symptom scores (daily diary using the following scales: VAS-itch, Whittington itch, Partial Patient-Oriented Scoring Atopic Dermatitis (PO-SCORAD) itch, and PO-SCORAD sleep disturbance.
  - change from baseline to the end of the 4-week treatment period in FGF19, C4 and ATX (exploratory)

**Safety**

- Primary safety endpoint: incidence of treatment-emergent SAEs based on spontaneous or solicited patient reports.

- Secondary safety assessments included the occurrence of treatment-emergent AEs (TEAEs), including AE severity and relationship to study drug.

**Pharmacokinetics**

- Plasma concentration of A4250 was assessed before and 1, 2, 4, and 8 hours after the single dose of A4250 administered at baseline, and before the last dose of the 4-week treatment period.
Inhibiteurs d’ASBT dans le prurit cholestatique : A4250

-14  -7  0  7  14  21  28  35  42  49  56

Day

Baseline Pruritus and Sleep Scores
Baseline Bile Acids

Safety Monitoring Period
PK

End-of-Treatment Pruritus and Sleep Scores
End-of-Treatment Bile Acids

Screening period (day -14 to -10)
A4250 treatment (5 sequentially escalating dose cohorts of 10, 30, 60, 100, or 200 μg/kg)

Single Dose of A4250
4-Week Treatment With Daily A4250
Follow-up
### Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (range), y</td>
<td>6.5 ± 4.6 (1–17)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>PFIC 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>PFIC 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>PFIC 3</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Intrahepatic cholestasis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Receiving UDCA treatment, n (%)</td>
<td>19 (79.2)</td>
</tr>
<tr>
<td>Receiving rifampicin treatment, n (%)</td>
<td>11 (45.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One patient re-entered

<sup>b</sup>Two patients re-entered.

<sup>c</sup>One patient re-entered (intrahepatic cholestasis associated with microvillous atrophy).

PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation; UDCA, ursodeoxycholic acid.

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# Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD (range)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bile acids, µmol/L</td>
<td>235 ± 153 (26–564)</td>
<td>~20 x ULN</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
<td>40 ± 48 (3–202)</td>
<td>~2.5 x ULN</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>41 ± 4 (35–49)</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.0 ± 0.2 (0.9–1.8)</td>
<td></td>
</tr>
<tr>
<td>Mean 7-day VAS</td>
<td>6 ± 2 (4–10)</td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>109 ± 83 (33–390)</td>
<td>~2 x ULN²</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>107 ± 68 (38–335)</td>
<td>~2 x ULN²</td>
</tr>
</tbody>
</table>

*Normal range varies by age and gender.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; SD, standard deviation; ULN, upper limit of normal; VAS, visual analogue scale.

Change from baseline in serum bile acids at the end of the 4-week treatment period in A) all patients and B) the subgroup of patients with PFIC.
Change from baseline in plasma ATX levels at the end of the 4-week treatment period
Mean absolute change from baseline in assessments of pruritus and sleep disturbance at the end of the 4-week treatment period.
Correlation between changes in serum bile acids and assessments of pruritus and sleep disturbance at the end of the 4-week treatment period compared with baseline.

\[ aP=0.008 \text{ (n=23); Pearson r=0.54} \]

\[ bP=0.004 \text{ (n=23); Pearson r=0.58} \]

\[ cP=0.006 \text{ (n=22); Pearson r=0.57} \]

\[ dP=0.005 \text{ (n=22); Pearson r=0.57} \]
Correlation between serum bile acids, serum ATX, VAS score at baseline and during therapy

**Pearson r=0.67; P=0.001**

**Pearson r=0.33; P=0.12**

**Pearson r=0.60; P=0.003**

**Pearson r=0.39; P=0.075**
Maralixibat : LUM001, SHP625

• **Syndrome d’Alagille**

**IMAGO** : Evaluation of LUM001 in the Reduction of Pruritus in Alagille Syndrome
NCT02057692 (negative) (AASLD2017) (UK)

**ITCH** : Randomized multi-center 13-week trial comparing 3 maralixibat doses (70, 140, 280 μg/kg/day) vs. placebo (n=8-11-6-12) in ALGS patients (AASLD2017) (USA)


• **PFIC**

**INDIGO** : phase 2 open-label safety and efficacy study of maralixibat in children with PFIC (AASLD2017)
• Double-blind, randomized, placebo-controlled phase 2b trial
• Children (1-18) with Alagille syndrome (AGS) confirmed by JAGGED/NOTCH2 genotyping and symptoms of pruritus, stable dose of UDCA/rifampicin, ALT<15N
Endpoints:
- 1 change in ItchRO week 13
- 2 change serum BA, ALT, bilirubin, cholesterol, C4

Adverse events: safety tolerability
**Inhibiteurs d’ASBT dans le prurit cholestatique : LUM001**

**Table 1. Analysis of Primary Endpoint: Change from Baseline to Week 13 in ITCHRO (OBS)**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Treatment Group</th>
<th>Baseline Mean (SEM)</th>
<th>LS Means Change (SEM)</th>
<th>95% CI</th>
<th>P value</th>
<th>Treatment Compared to Placebo</th>
<th>Difference in LS Means (SEM)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maralixibat</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70 µg/kg/day</td>
<td>8</td>
<td>3.2 (0.23)</td>
<td>-1.5 (0.30)</td>
<td>(-2.1, -0.9)</td>
<td>&lt;.001</td>
<td>-0.89 (0.40)</td>
<td>(-1.70, -0.08)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>140 µg/kg/day</td>
<td>11</td>
<td>2.7 (0.16)</td>
<td>-1.5 (0.26)</td>
<td>(-2.0, -1.0)</td>
<td>&lt;.001</td>
<td>-0.91 (0.35)</td>
<td>(-1.62, -0.19)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>280 µg/kg/day</td>
<td>6</td>
<td>3.3 (0.24)</td>
<td>-0.6 (0.36)</td>
<td>(-1.3, -0.1)</td>
<td>0.093</td>
<td>-0.04 (0.44)</td>
<td>(-0.94, 0.86)</td>
<td>0.930</td>
</tr>
<tr>
<td></td>
<td>Maralixibat</td>
<td>17</td>
<td>2.9 (0.15)</td>
<td>-1.1 (0.21)</td>
<td>(-1.5, -0.1)</td>
<td>&lt;.001</td>
<td>-0.47 (0.33)</td>
<td>(-1.14, 0.20)</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>Maralixibat</td>
<td>25</td>
<td>3.0 (0.13)</td>
<td>-1.2 (0.18)</td>
<td>(-1.6, -0.8)</td>
<td>&lt;.001</td>
<td>-0.61 (0.31)</td>
<td>(-1.24, 0.01)</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12</td>
<td>2.8 (0.15)</td>
<td>-0.6 (0.25)</td>
<td>(-1.1, -0.1)</td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Primary endpoints was not reached
- Trend decrease sBA, increase C4
- Overall LUM001 is safe and well tolerated

INDIGO: phase 2 open-label safety and efficacy study of maralixibat in children with PFIC
Inclusion/exclusion criteria and outcomes

Key inclusion criteria

• Aged 1–18 years
• Clinically diagnosed PFIC
• Two mutant \textit{ABCB11} or \textit{ATB8B1} alleles

Key exclusion criteria

• Surgically disrupted enterohepatic circulation
• Liver transplant
• Decompensated cirrhosis

Key outcomes

• Levels of cholestasis biomarkers
  – sBA (primary efficacy measure)
  – ALT, AST, bilirubin and C4 in serum
• Pruritus assessments
  – ItchRO(Obs) weekly average score (parent-rated e-diary)
  – CSS score (investigator-rated)
• HRQoL assessment
  – PedsQL total score (parent-rated)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, \(7\alpha\)-hydroxy-4-cholesten-3-one; CSS, clinician scratch scale; HRQoL, health-related quality of life; ItchRO(Obs), Itch-Reported Outcome (Observer); PedsQL, Paediatric Quality of Life Inventory
Responders at week 48: 6/26 patients, all with PFIC2

<table>
<thead>
<tr>
<th>Responders (n = 6)</th>
<th>Response indicators (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, n</td>
<td>sBA levels, n</td>
</tr>
<tr>
<td>PFIC1 (ATP8B1 mutation)</td>
<td>Normalized (≤ 8.5 µmol/L)</td>
</tr>
<tr>
<td>PFIC2 (ABCB11 mutation)</td>
<td>Reduced by ≥ 70% or ≥ 80% from baseline</td>
</tr>
<tr>
<td>Reached week 48, n</td>
<td></td>
</tr>
<tr>
<td>Maralixibat dose, n</td>
<td></td>
</tr>
<tr>
<td>280 µg/kg/day</td>
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</tbody>
</table>

- Responders at week 48: 6/26 patients, all with PFIC2
Summary and conclusions

- ASBT blockade with maralixibat appears to benefit a subset of children with PFIC2
  - Normalization or substantial reduction in sBA levels
  - Complete or substantial relief of pruritus
  - Improvement in HRQoL
  - Normalization of bilirubin and liver enzyme levels, if elevated
- Gastroenteric infections may interfere with maralixibat treatment
- Future genetic studies may identify the responding subset
  - 6/20 children with PFIC2 and 0/6 with PFIC1 were responders at week 48
- Further studies of ASBT inhibitors in children with PFIC are warranted
• Efficacité PFIC > AGS

• Tolérance enfants > adultes

• En cours:

A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children With Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC1)

• A venir :

Drogue LUM001 (PFIC)
Combinaison inhibiteur d’ASBT et pharmacothérapie ciblée dans les PFIC
Extension des indications en particulier au Syndrome d’Alagille
Prise en charge du prurit cholestatique chez l’enfant

**Treatments non spécifiques**

*Mesures générales*
- Lutter contre la xérose: émollients
- Prise en charge d’une dermatose associée
- Ongles courts, hygiène
- Température, textiles...

*AUDC (600mg/m².j)

1ère ligne

+ Rifampicine
5 à 20mg/kg/j en 1 à 2 prises

2ème ligne

*Évaluation par une équipe spécialisée*

<table>
<thead>
<tr>
<th>Sertraline</th>
<th>Naltrexone</th>
<th>Inclusion Protocole thérapeutique? (ASBTi)</th>
</tr>
</thead>
</table>

prurit persistant

3ème ligne

*Techniques invasives (DBE, MARS, TH)*

**Évaluation de l’efficacité**
Quantification du prurit
- EVA (0-10)
- Lésions de grattage
- Réveils nocturnes