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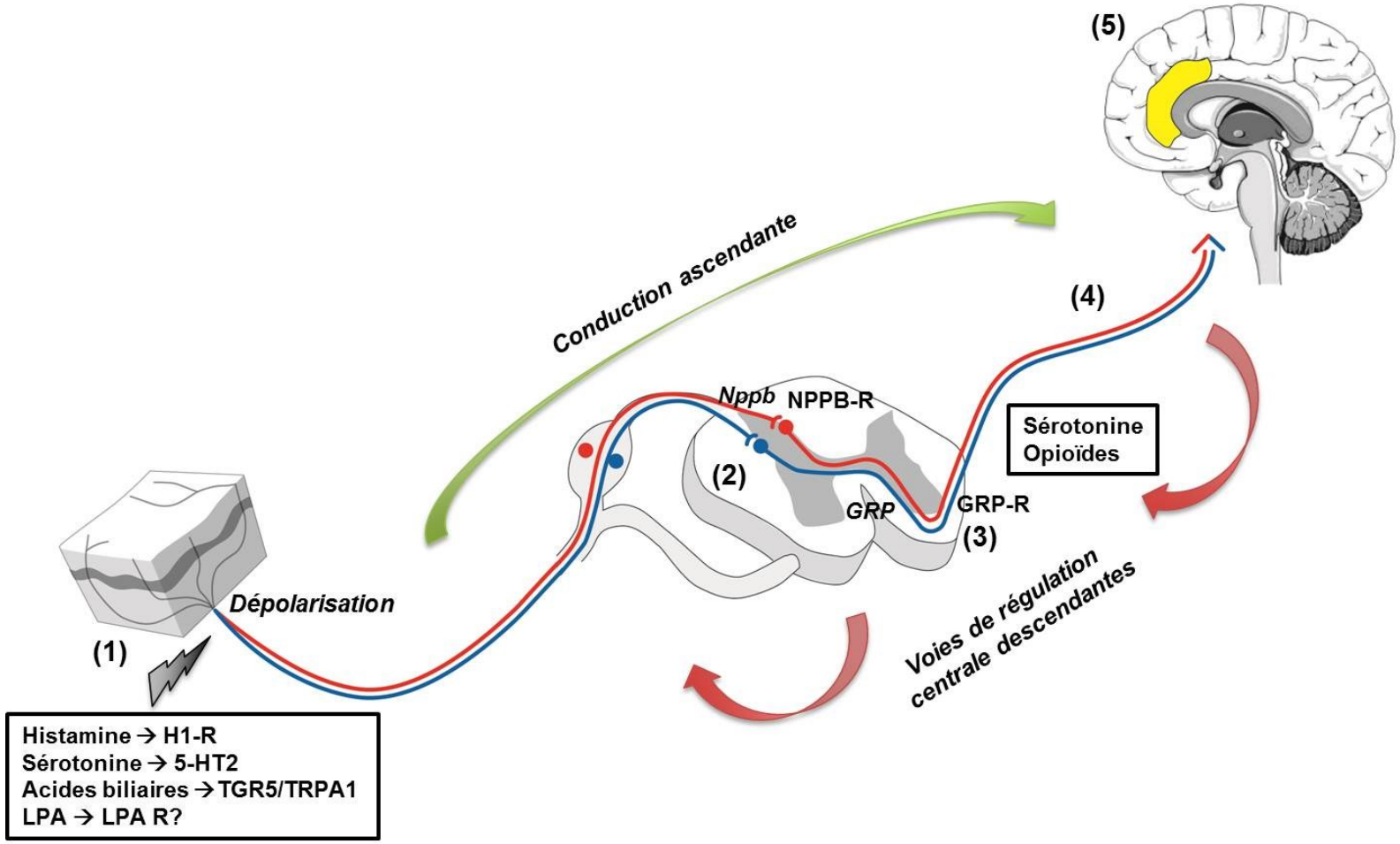
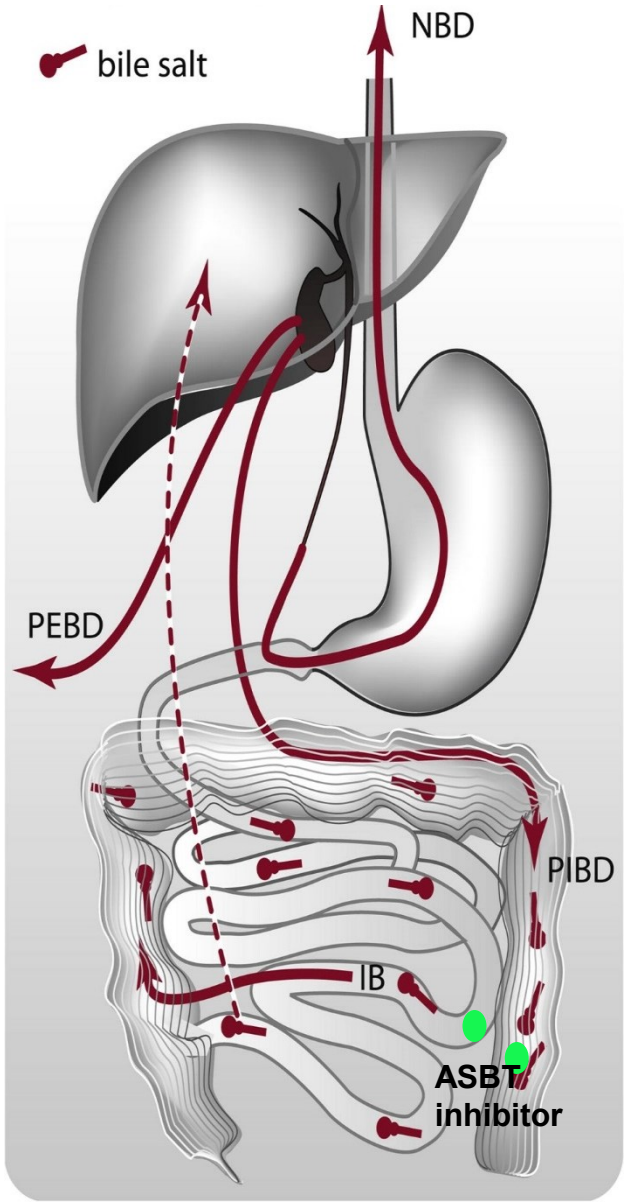
Inhibiteurs d'ASBT dans le prurit cholestatique

E Gonzales

Physiopathologie du prurit



Physiopathologie du prurit



Dérivation biliaire partielle externe

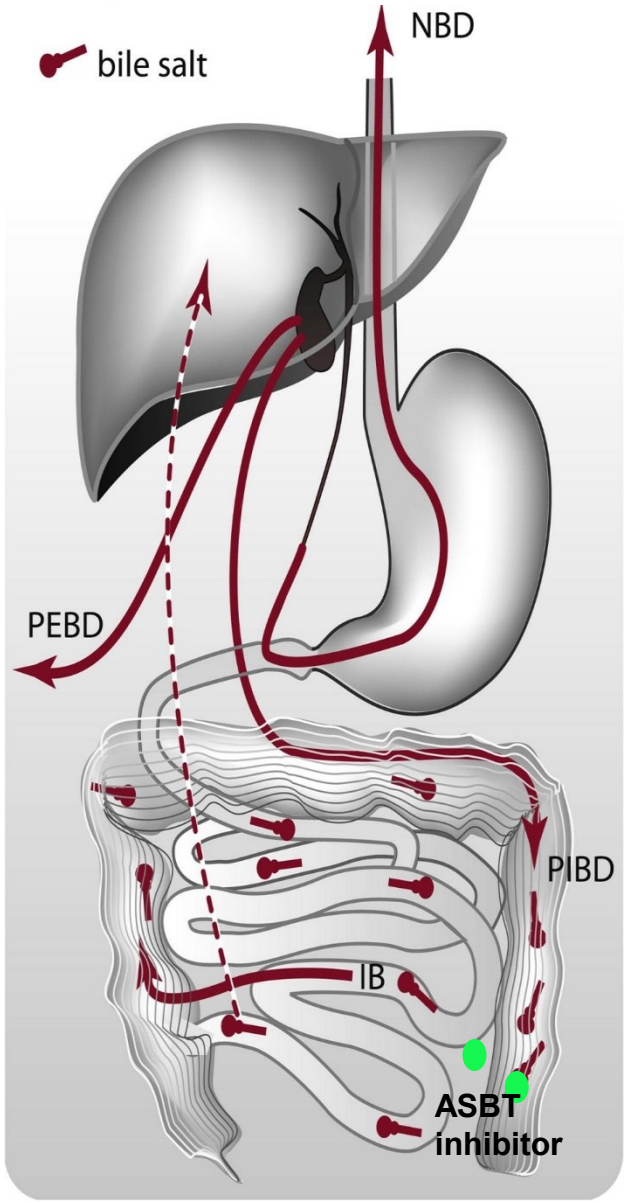
- bénéfice chez certains patients PFIC1 et PFIC2
- possible bénéfice dans le Syndrome d'Alagille

Dérivation biliaire partielle interne

Iléal bypass

- **Inhibiteurs d'ASBT**: « dérivation chimique»

Dérivation biliaire et cholestases génétiques : PFIC1-2, AGS



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»

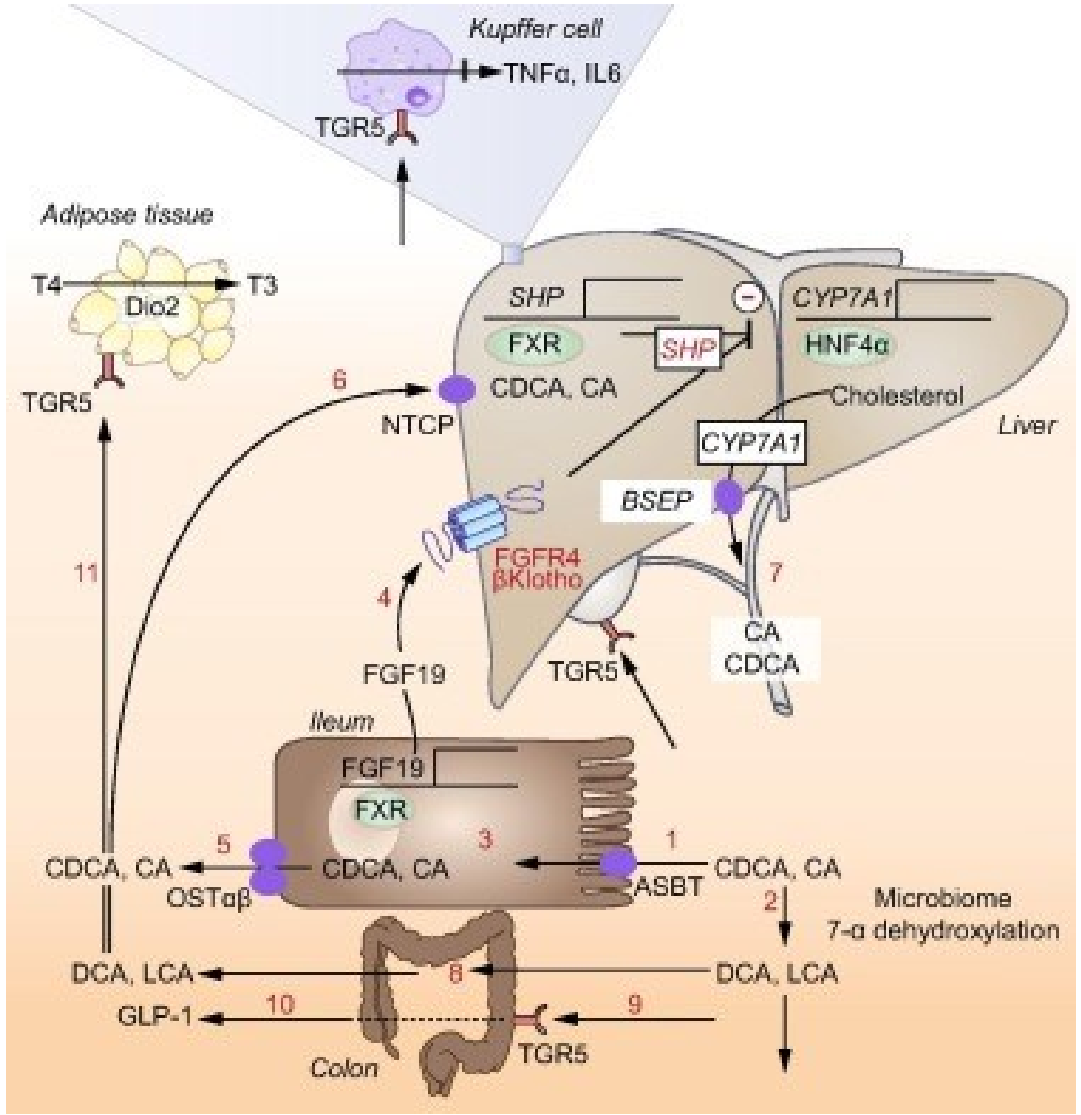
Whitington PF et al., Gastroenterology 1988
Balistreri W et al. Hepatology 2005
Stapelbroek et al. J Hepatol 2010

Inhibiteurs d'ASBT dans le prurit cholestatique

- 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



Beuers U et al., Journal of Hepatology 2015

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

Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672

2 Essais de phase 1 (59 volontaires sains)

2 Essais de phase 1 (59 volontaires sains)

Wu Y, Aquino CJ, Cowan DJ, et al. Discovery of a highly potent, nonabsorbable apical sodium-dependent bile acid transporter inhibitor (GSK2330672) for treatment of type 2 diabetes. J Med Chem 2013; 56: 5094–114.

Nunez DJ, Yao X, Lin J, et al. Glucose and lipid effects of the ileal apical sodium-dependent bile acid transporter inhibitor GSK2330672: double-blind randomized trials with type 2 diabetes subjects taking metformin. Diabetes Obes Metab 2016; 18: 654–62.

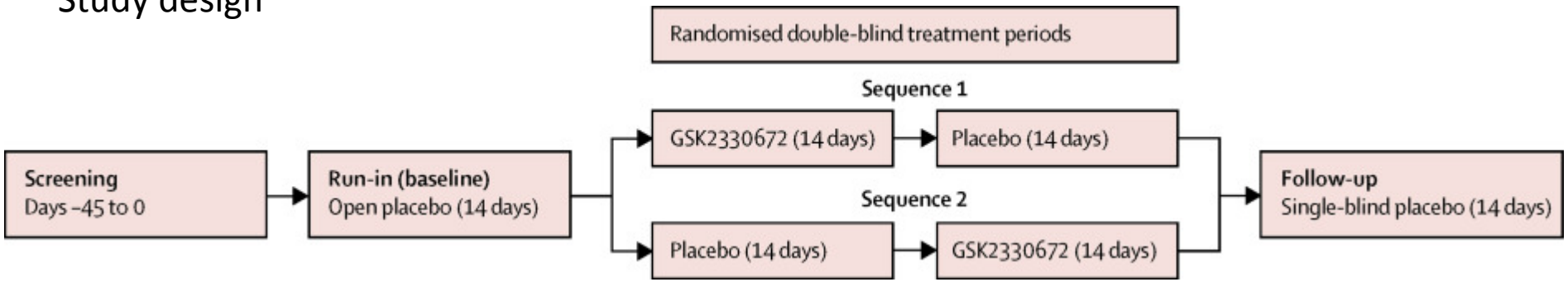
A Study to Evaluate the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of Repeat Doses of GSK2330672 Administration in Subjects With Primary Biliary Cirrhosis (PBC) and Symptoms of Pruritus

Hegade VS, Kendrick SF, Dobbins RL, Miller SR, Thompson D, Richards D, Storey J, Dukes GE, Corrigan M, Oude Elferink RP, Beuers U, Hirschfield GM, Jones DE. Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study. Lancet. 2017;389:1114-1123.

Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672

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)

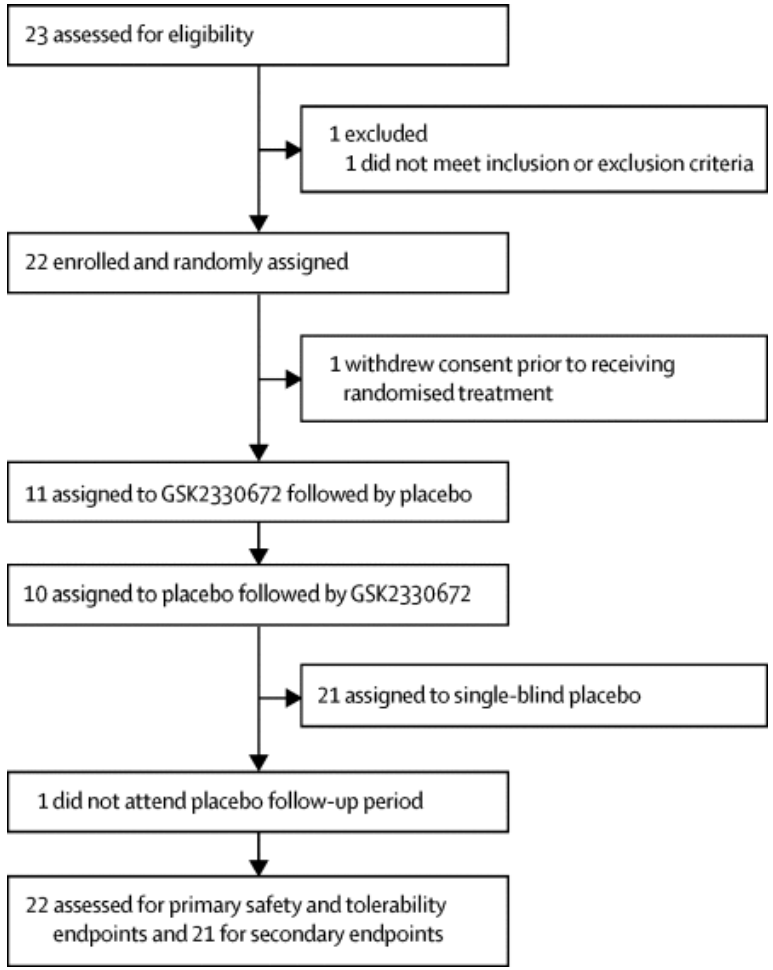
Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672

Outcomes

1- Safety / tolerability

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

Exploratory : FGF19, ATX



Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672

	Placebo run-in (n=22), n (%)	GSK2330672 (n=21), n (%)	Placebo (n=21), n (%)
Participants with any adverse event	15 (68)	17 (81)	17 (81)
Gastrointestinal system			
Diarrhoea	1 (5)	7 (33)	1 (5)
Upper abdominal pain	0	3 (14)	1 (5)
Abdominal distension	0	3 (14)	1 (5)
Abdominal pain	0	3 (14)	0
Vomiting	0	1 (5)	2 (10)
Nausea	0	2 (10)	0
Nervous system			
Headache	7 (32)	6 (29)	7 (33)
Dizziness	1 (5)	1 (5)	2 (10)
Paraesthesia	0	0	2 (10)
Infections			
Nasopharyngitis	0	1 (5)	2 (10)
General			
Fatigue	0	0	2 (10)

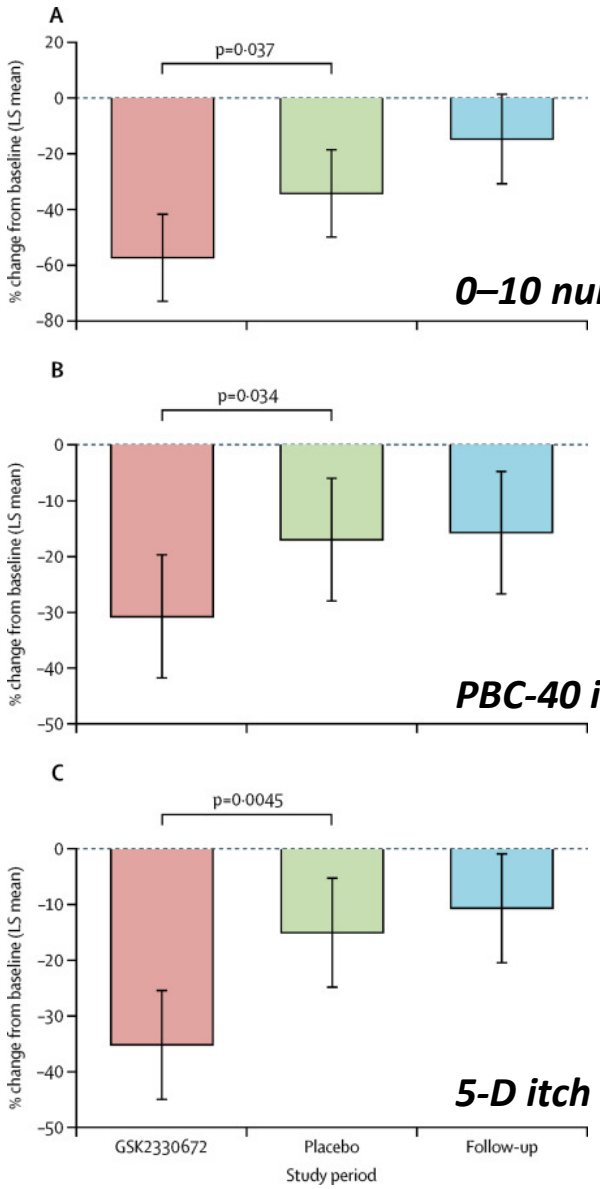
Adverse events were monitored from day 1 to 56 of the study including follow-up period. Data are in n (%). The listed adverse events (any severity) have an incidence greater than one patient (5%) in any treatment period.

***Table 2*: Summary of adverse events**

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.

Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672



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)

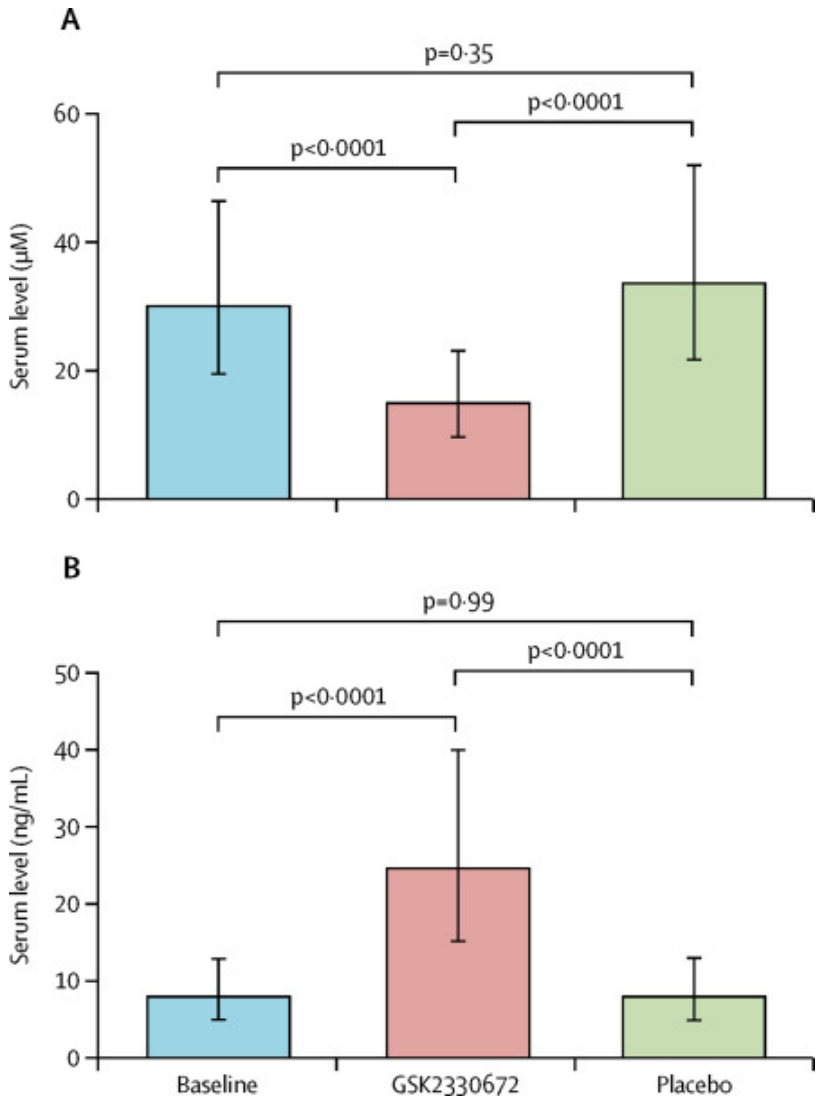
PBC-40 itch domain score

–30% (–42 to –20, p<0·0001)

5-D itch scale

–35% (–45 to –25, p<0·0001)

Inhibiteurs d'ASBT dans le prurit cholestatique : GSK2330672



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

C4

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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 2016Volume 64, Issue 2, Supplement, Page S197

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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

Table 1. Summary of outcomes at week 13/ET (modified intent-to-treat population)

Outcome	Lopixibat (overall) (n = 42)	Placebo (n = 24)
ItchRO weekly sum score		
Baseline	50.10 (45.88, 54.33)	51.83 (46.71, 56.96)
Week 13/ET	23.98 (18.39, 29.57)	27.50 (19.19, 35.81)
LSM change from baseline	−26.49 (−31.78, −21.19)	−23.36 (−30.32, −16.39)
	$p < 0.0001$	$p < 0.0001$
LSM difference versus placebo	−3.13 (−11.89, 5.63)	
	$p = 0.4773$[a]	
Fasting sBA levels (µmol/L)		
Baseline	42.785 (20.975, 64.595)	55.767 (26.878, 84.655)
Week 13/ET	30.984 (20.147, 41.821)	56.699 (23.931, 89.467)
LSM change from baseline	−14.226 (−28.213, −0.240)	10.053 (−8.687, 28.793)
	$p = 0.0463$	$p = 0.2874$
LSM difference versus placebo	−24.279 (−47.667, −0.891)	
	$p = 0.0421$	
Serum C4 levels (ng/mL)		
Baseline	15.95 (11.50, 20.4)	19.30 (7.21, 31.38)
Week 13/ET	29.54 (20.28, 38.80)	17.10 (4.49, 29.71)
LSM change from baseline	13.49 (5.98, 21.00)	−2.21 (−12.53, 8.10)
	$p = 0.0007$	$p = 0.6692$
LSM difference versus placebo	15.70 (2.92, 28.49)	
	$p = 0.0170$	
ALP levels (U/L)		
Baseline	272.9 (213.6, 332.2)	264.9 (200.6, 329.2)
Week 13/ET	277.1 (217.5, 336.7)	271.1 (196.3, 345.9)
LSM change from baseline	4.9 (−19.5, 29.2)	7.3 (−24.7, 39.3)
	$p = 0.6913$	$p = 0.6496$
LSM difference versus placebo	−2.4 (−42.6, 37.8)	
	$p = 0.9036$	

Mayo MJ et al J Hepatol 2016 Volume 64, Issue 2, Supplement, Page S197

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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.

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.

Mayo MJ et al J Hepatol 2016 Volume 64, Issue 2, Supplement, Page S197

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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

Baghdasaryan A, Fuchs CD, Osterreicher CH, et al. Inhibition of intestinal bile acid absorption improves cholestatic liver and bile duct injury in a mouse model of sclerosing cholangitis. J Hepatol 2016;64:674-81.

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

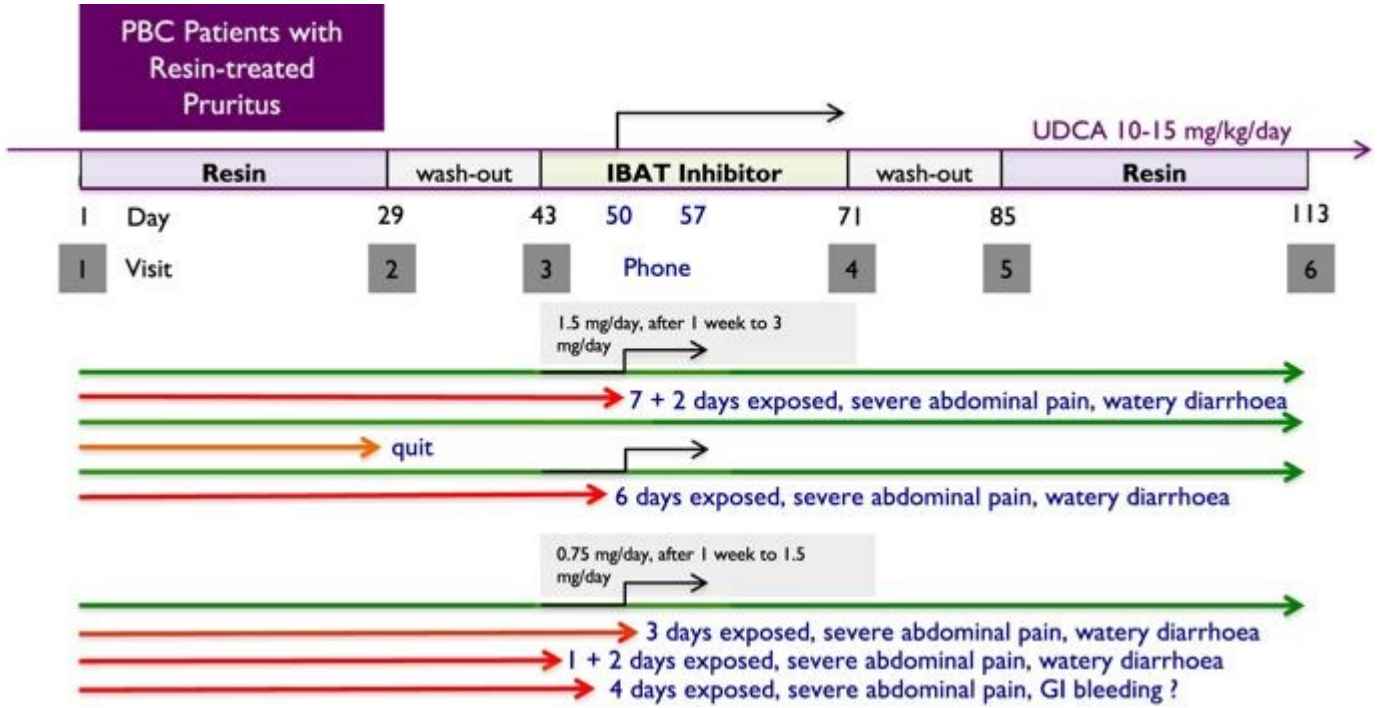
Graffner H, Gillberg PG, Rikner L, Marschall HU. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. Aliment Pharmacol Ther 2016;43:303-10.

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

Al-Dury S, Wahlström A, Wahlin S, Langedijk J, Elferink RO, Ståhlman M, Marschall HU. Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis. Sci Rep. 2018;8:6658.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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

Al-Dury S, Wahlström A, Wahlin S, Langedijk J, Elferink RO, Ståhlman M, Marschall HU. Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis. Sci Rep. 2018;8:6658.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

Pat Nr	Visit 1 On usual Resin	Visit 2 End of Resin 1	Visit 3 Wash-out Resin	Visit 4 End of A4250	Visit 5 Wash-out A4250	Visit 6 End of Resin 2
day	1	29	43	71	85	113
Itching disturbed my sleep						
Patient 1	1	2	1	1	1	1
Patient 2	2	2	2	1	3	3
Patient 3	3	3	3	1	4	4
Patient 4	4	5	3	3	4	5
I scratched so much I made my skin row						
Patient 1	1	4	5	1	1	3
Patient 2	3	3	3	2	4	4
Patient 3	1	1	1	1	1	3
Patient 4	5	5	3	2	5	5
I felt embarrassed because of the itching						
Patient 1	1	1	1	1	1	3
Patient 2	2	2	2	1	3	3
Patient 3	1	1	1	1	1	3
Patient 4	5	5	3	3	5	5

In the last four weeks:

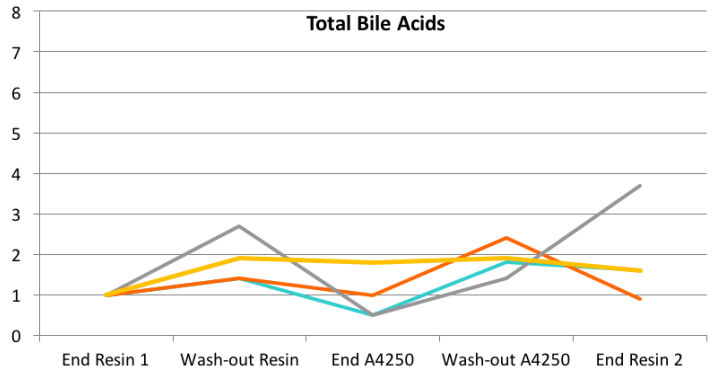
1	Never
2	Rarely
3	Sometimes
4	Most of the time
5	Always

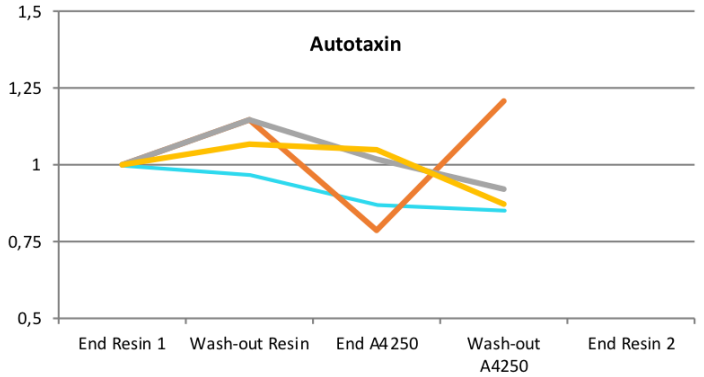
PBC-40 itch domain score

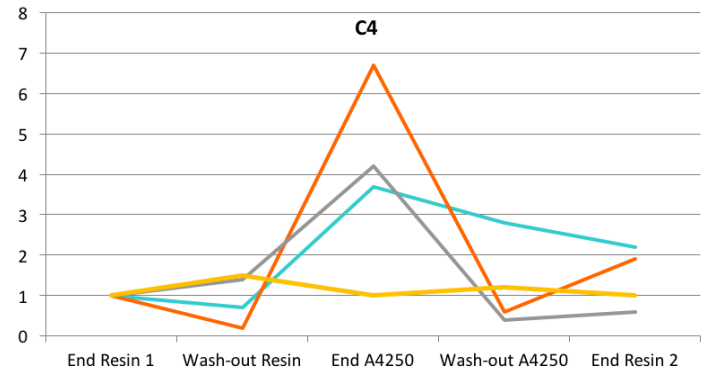
5-D itch scale
Quality of sleep

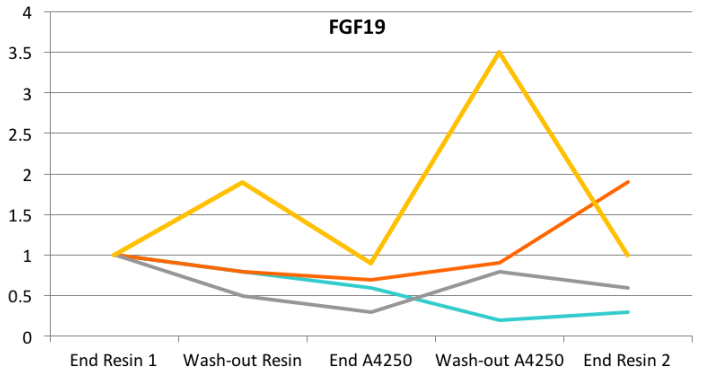
Al-Dury S, Wahlström A, Wahlin S, Langedijk J, Elferink RO, Ståhlman M, Marschall HU. Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis. Sci Rep. 2018;8:6658.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250









- 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

Al-Dury S, Wahlström A, Wahlin S, Langedijk J, Elferink RO, Ståhlman M, Marschall HU. Pilot study with IBAT inhibitor A4250 for the treatment of cholestatic pruritus in primary biliary cholangitis. Sci Rep. 2018;8:6658.

Inhibiteurs d'ASBT dans le prurit cholestatique de la PBC

- 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

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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, Whitington 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

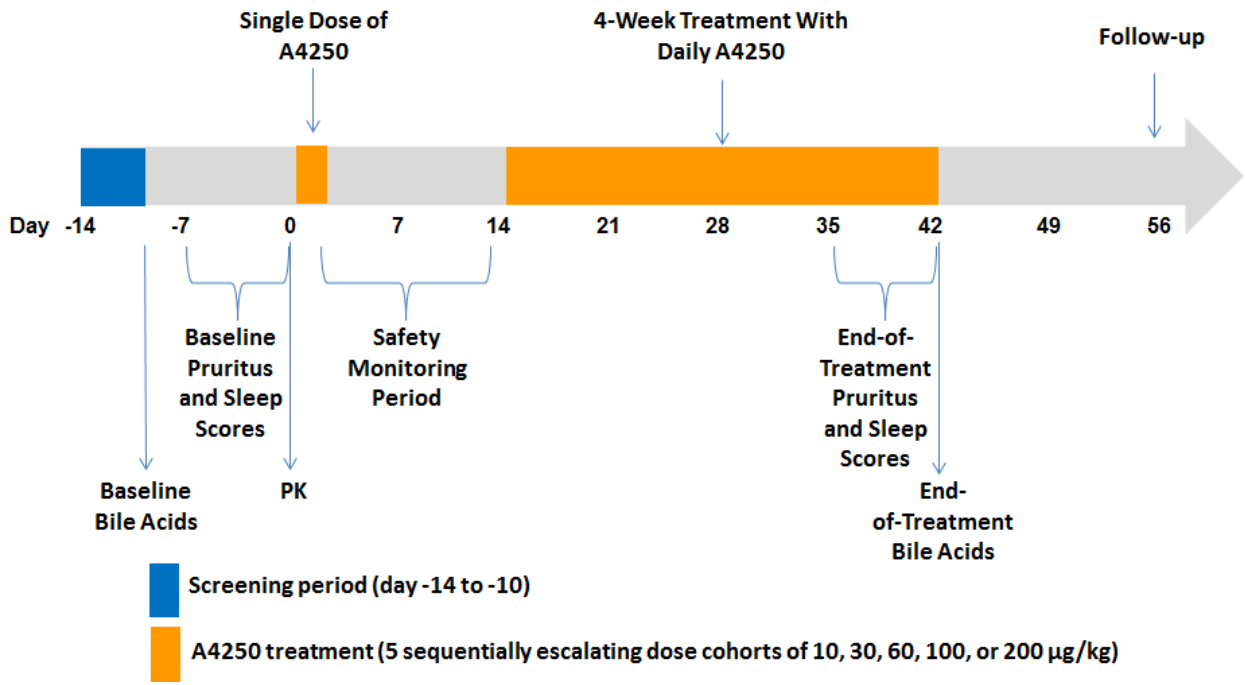
- Primary safety endpoint : incidence of treatment-emergent SAEs based on spontaneous or solicited patient reports.

- 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



Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

Patient Demographics

Parameter	N=24
Age, mean ± SD (range), y	6.5 ± 4.6 (1–17)
Sex, n (%)	
Male	15 (62.5)
Female	9 (37.5)
Diagnosis, n (%)	
PFIC 1[a]	2 (8.3)
PFIC 2[b]	9 (37.5)
PFIC 3	2 (8.3)
Alagille syndrome	6 (25.0)
Biliary atresia	3 (12.5)
Intrahepatic cholestasis[c]	2 (8.3)
Receiving UDCA treatment, n (%)	19 (79.2)
Receiving rifampicin treatment, n (%)	11 (45.8)

[a]One patient re-entered
[b]Two patients re-entered.
[c]One patient re-entered (intrahepatic cholestasis associated with microvillous atrophy).
PFIC, progressive familial intrahepatic cholestasis; SD, standard deviation; UDCA, ursodeoxycholic acid.

Sturm, E. et al. The ileal bile acid transport inhibitor A4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: final results from a multiple-dose, open-label, multinational study. Hepatology 66, 646A (2017).

Presented at the 68th Annual Meeting of the American Association for the Study of Liver Diseases, October 20–24, 2017, Washington, DC, USA.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

Baseline Disease Characteristics

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

[a]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.

Sturm, E. et al. The ileal bile acid transport inhibitor A4250 reduced pruritus and serum bile acid levels in children with cholestatic liver disease and pruritus: final results from a multiple-dose, open-label, multinational study. Hepatology 66, 646A (2017).

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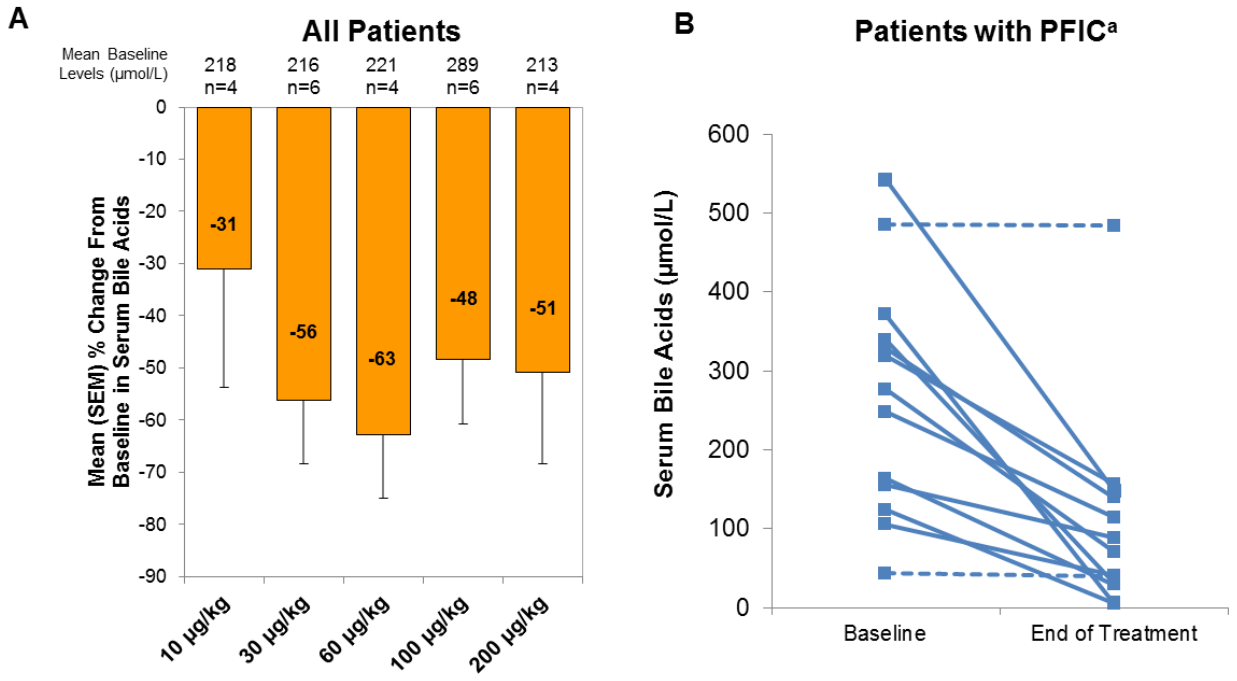
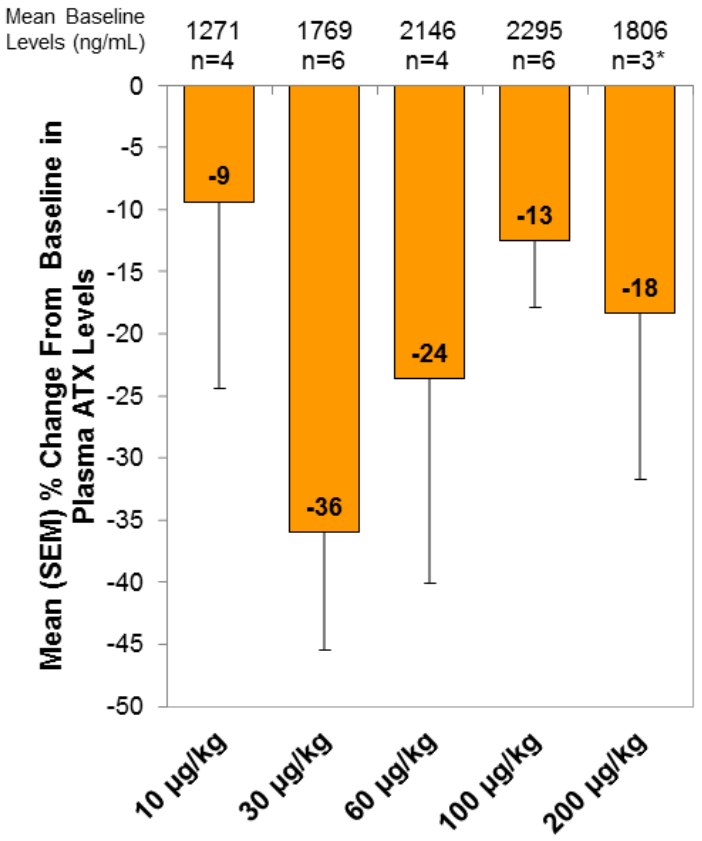
Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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



Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

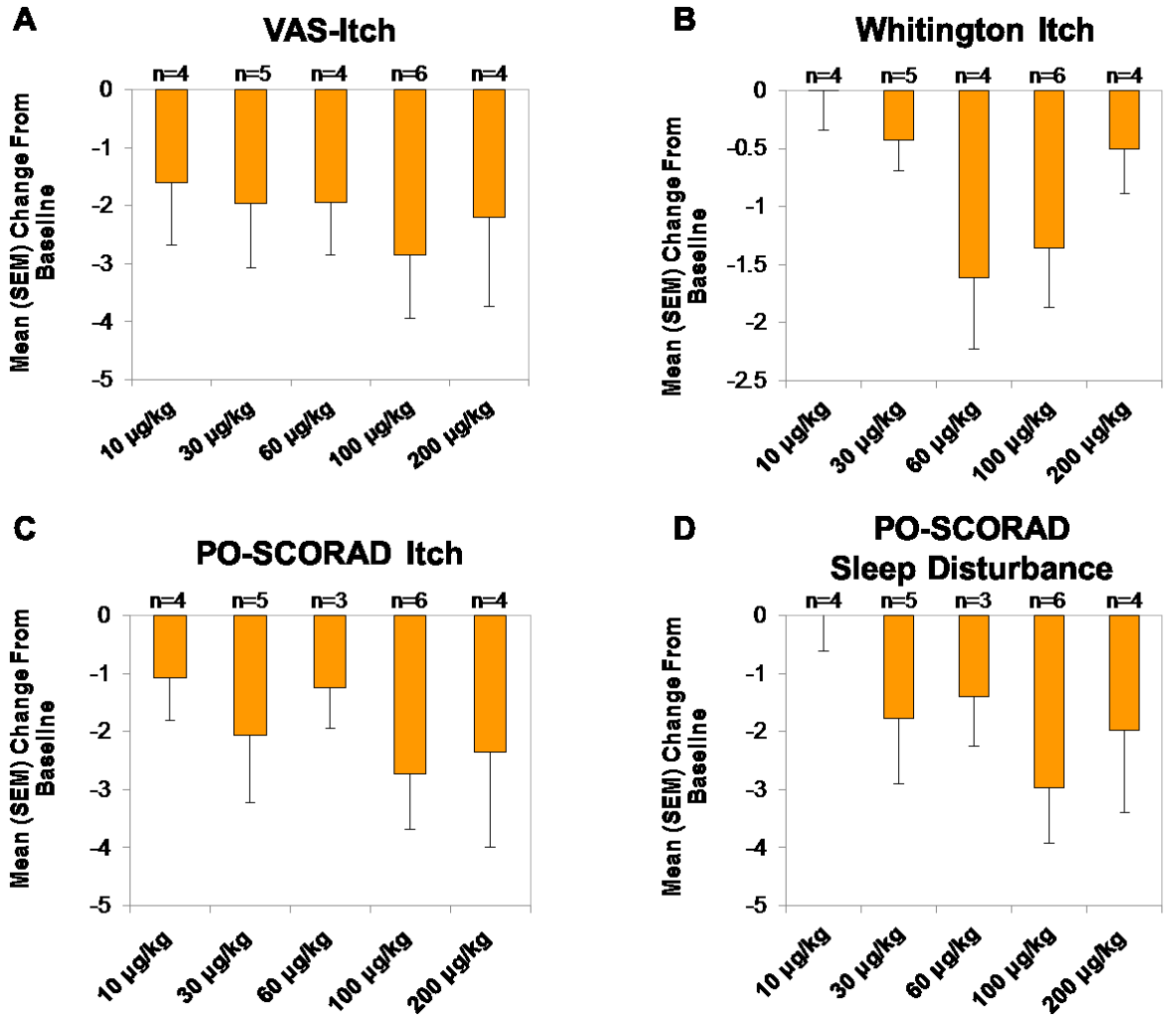
Change from baseline in plasma ATX levels at the end of the 4-week treatment period



Presented at the 53rd Annual International Liver Congress, 11–15 April, 2018, Paris, France

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

Mean absolute change from baseline in assessments of pruritus and sleep disturbance at the end of the 4-week treatment period



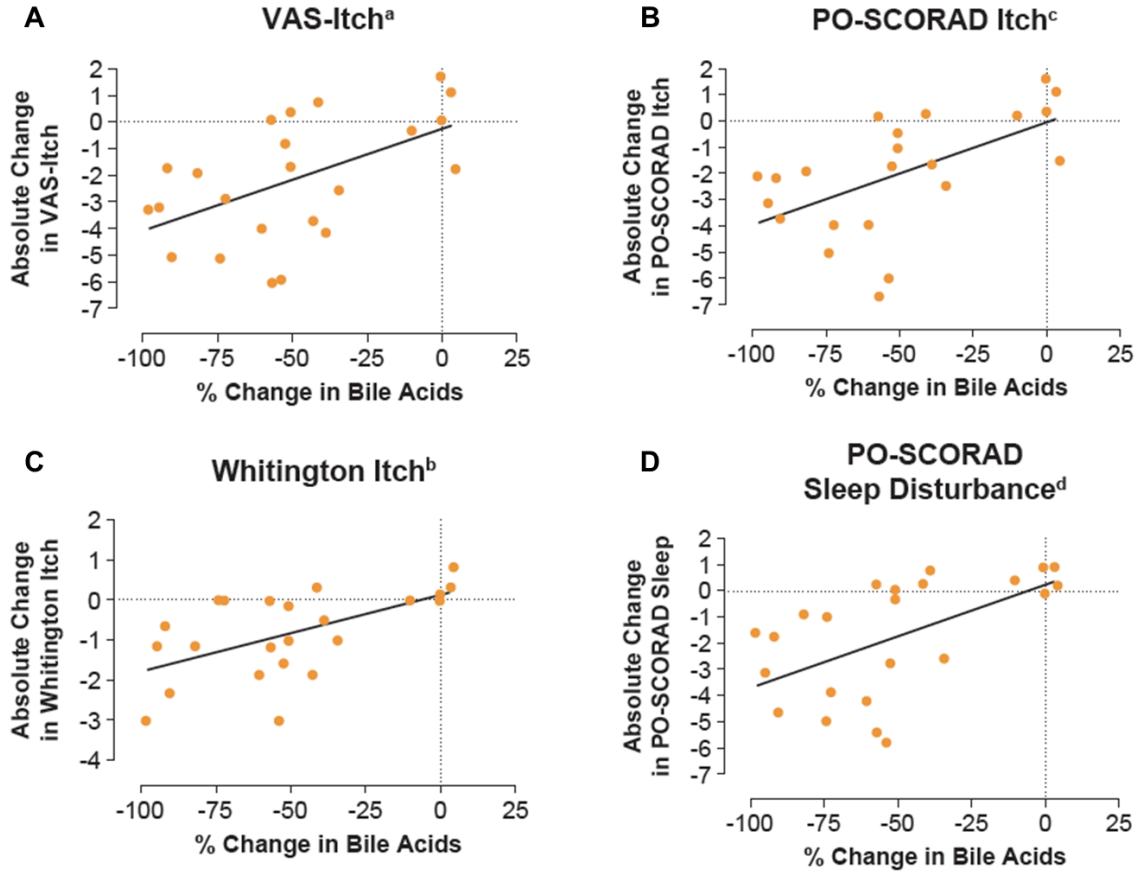
Presented at the 68th Annual Meeting of the American Association for the Study of Liver Diseases, October 20–24, 2017, Washington, DC, USA.

Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

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

[a]*P*=0.008 (n=23); Pearson r=0.54

[b]*P*=0.004 (n=23); Pearson r=0.58



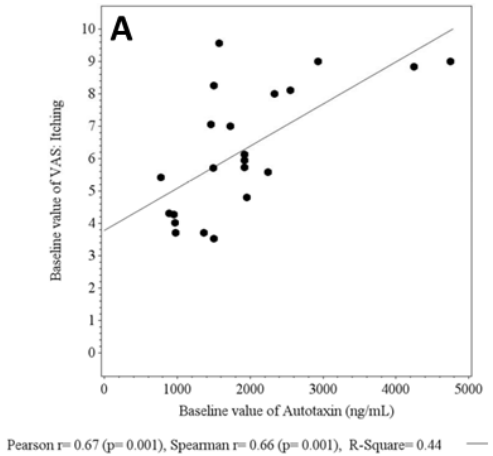
[c]*P*=0.006 (n=22); Pearson r=0.57

[d]*P*=0.005 (n=22); Pearson r=0.57

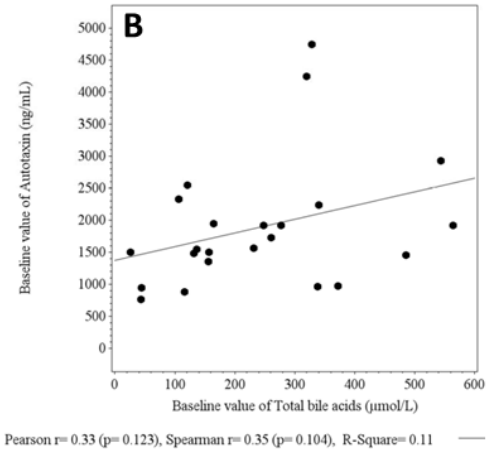
Inhibiteurs d'ASBT dans le prurit cholestatique : A4250

Correlation between serum bile acids, serum ATX, VAS score at baseline and during therapy

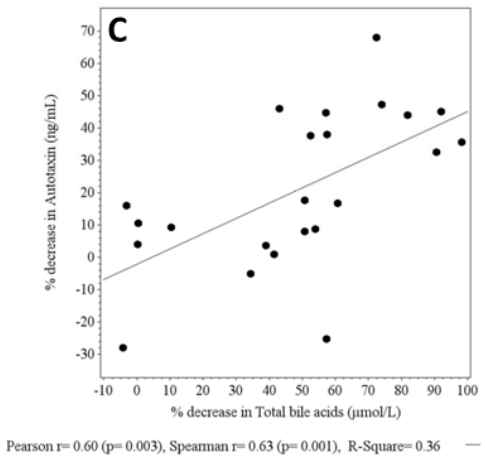
Pearson r=0.67; *P*=0.001



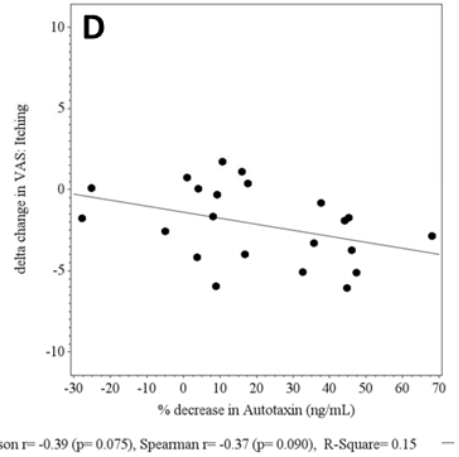
Pearson r=0.33; *P*=0.12



Pearson r=0.60; *P*=0.003



Pearson r=0.39; *P*=0.075



Presented at the 53rd Annual International Liver Congress, 11–15 April, 2018, Paris, France

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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)

Placebo-Controlled Randomized Trial of an Intestinal Bile Salt Transport Inhibitor for Pruritus in Alagille Syndrome. Shneider BL, Spino C, Kamath BM, Magee JC, Bass LM, Setchell KD, Miethke A, Molleston JP, Mack CL, Squires RH, Murray KF, Loomes KM, Rosenthal P, Karpen SJ, Leung DH, Guthery SL, Thomas D, Sherker AH, Sokol RJ; Childhood Liver Disease Research Network. Hepatol Commun. 2018 Sep 24;2(10):1184-1198.

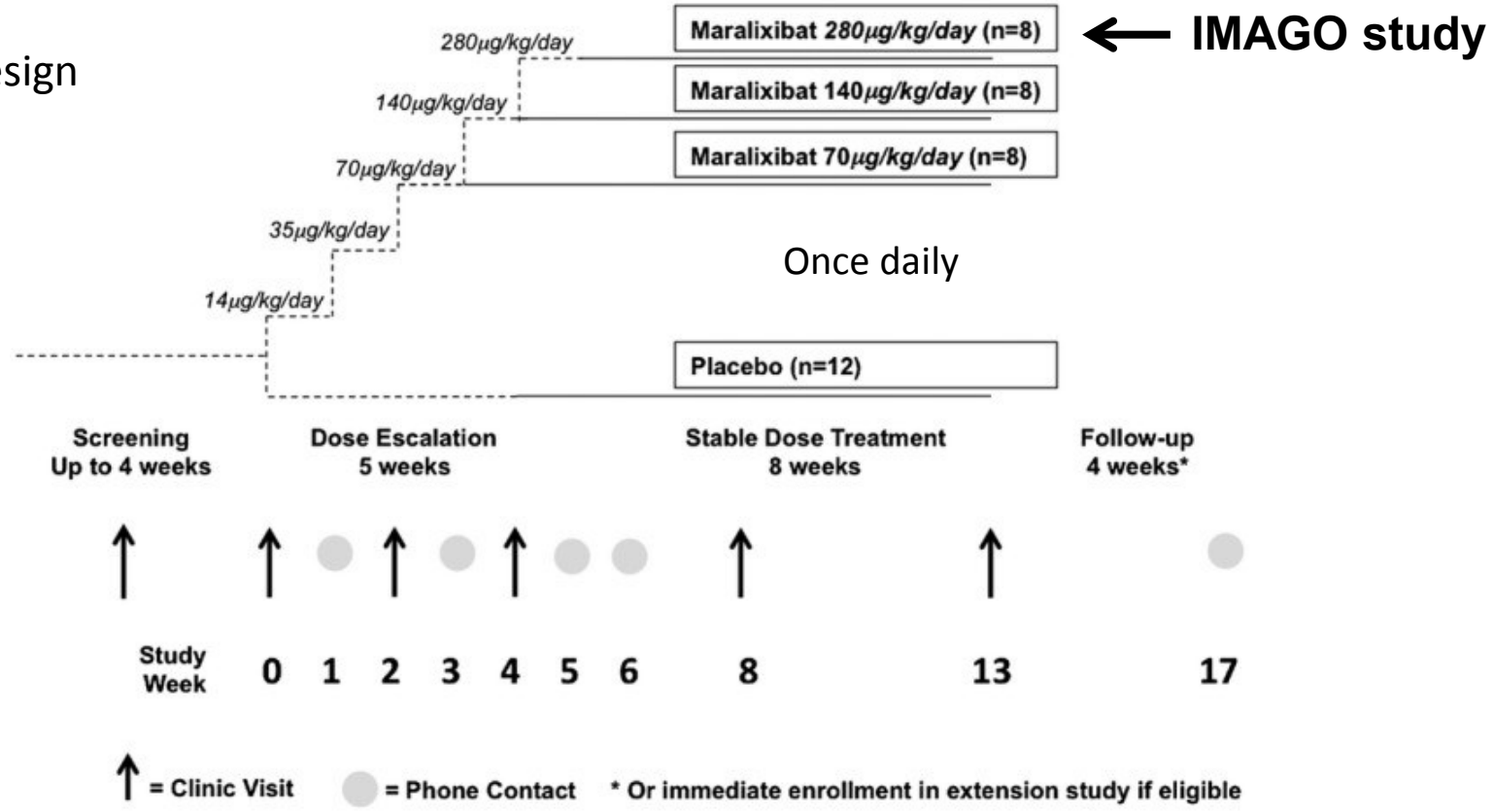
- **PFIC**

INDIGO: phase 2 open-label safety and efficacy study of maralixibat in children with PFIC (AASLD2017)

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

- 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

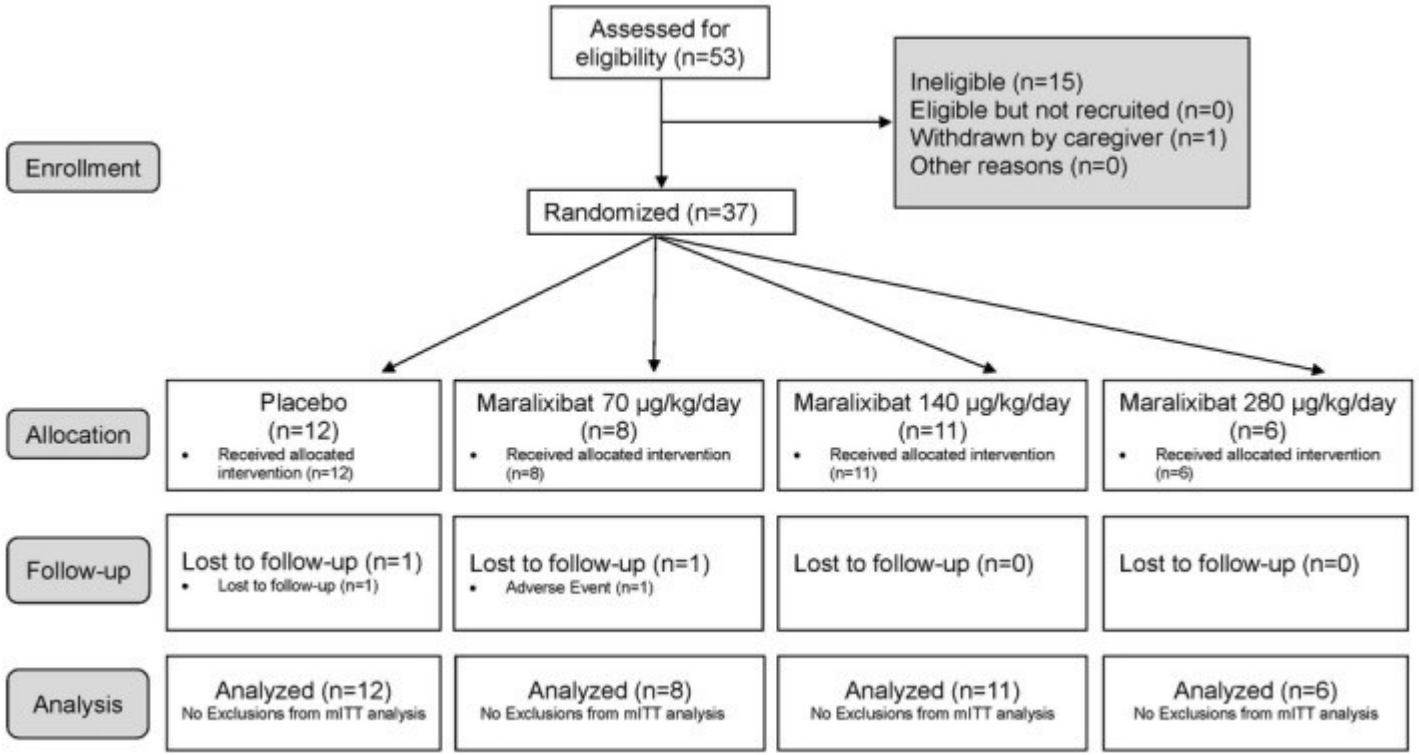
Study design



Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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)

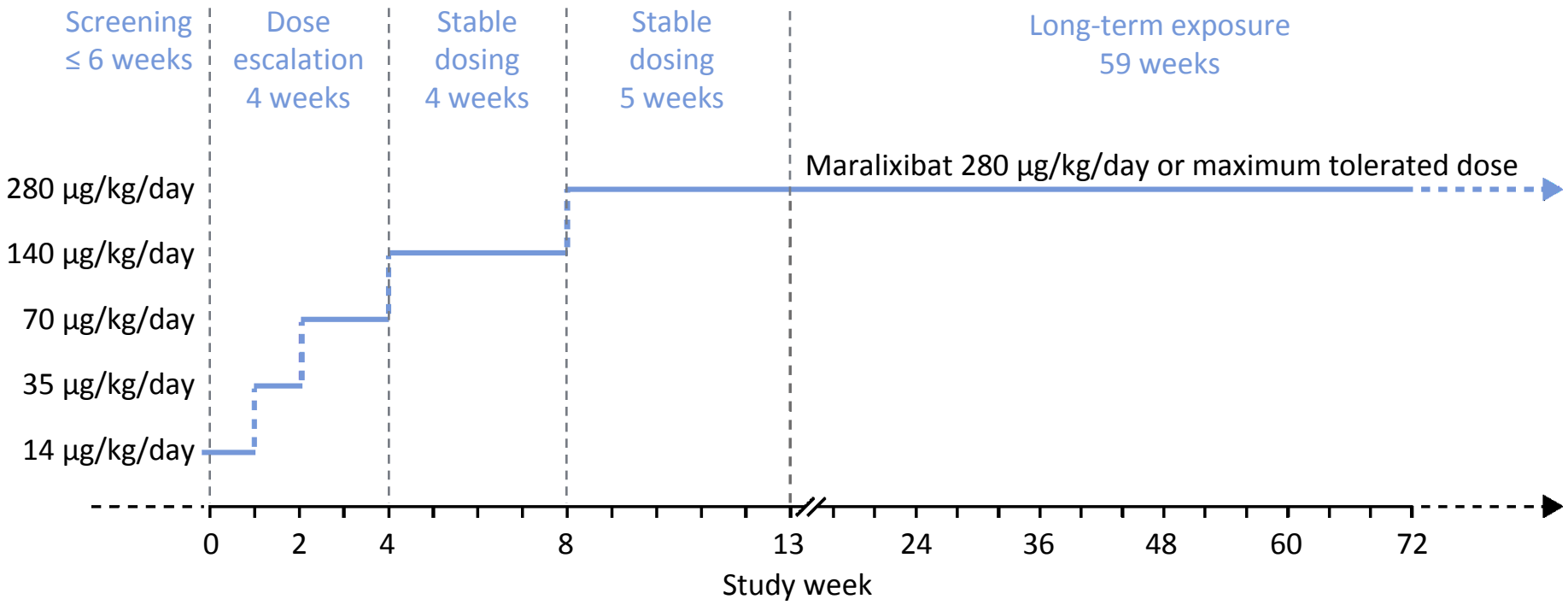
			Change From Baseline			Treatment Compared to Placebo		
Outcome Measure Treatment Group Maralixibat	n	Baseline Mean (SEM)	LS Means Change (SEM)	95% CI	*P* value	Difference in LS Means (SEM)	95% CI	*P* value
ItchRO(Obs) average daily score								
70 µg/kg/day	8	3.2 (0.23)	−1.5 (0.30)	(−2.1, −0.9)	<.001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

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

Placebo-Controlled Randomized Trial of an Intestinal Bile Salt Transport Inhibitor for Pruritus in Alagille Syndrome. Shneider BL, Spino C, Kamath BM, Magee JC, Bass LM, Setchell KD, Miethke A, Molleston JP, Mack CL, Squires RH, Murray KF, Loomes KM, Rosenthal P, Karpen SJ, Leung DH, Guthery SL, Thomas D, Sherker AH, Sokol RJ; Childhood Liver Disease Research Network. Hepatol Commun. 2018 Sep 24;2(10):1184-1198.

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

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 *ABCB11* or *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, 7α-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

Inhibiteurs d'ASBT dans le prurit cholestatique : LUM001

Responders at week 48: 6/26 patients, all with PFIC2

Responders (n = 6)

Diagnosis, n	
PFIC1 (*ATP8B1* mutation)	0
PFIC2 (*ABCB11* mutation)	6
Reached week 48, n	6
Maralixibat dose, n	
280 µg/kg/day	6

Response indicators (n = 6)

sBA levels, n	
Normalized (≤ 8.5 µmol/L)	4
Reduced by ≥ 70% or ≥ 80% from baseline	2
ItchRO score, n	
Zero (no pruritus)	2
Improved by ≥ 1.0 points from baseline	4

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

Inhibiteurs d'ASBT dans le prurit cholestatique de l'enfant

- **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