Pediatric cholestasis: Itching for an alternative to liver transplantation

Mirum-sponsored symposium WCPGHAN 2021

Thursday June 3, 2021

Welcome and introduction

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Speaker disclosures

- **Unrestricted educational grant and consultant:**
  - Mirum, Albireo
- **Consultant:**
  - Audentes

Pediatric cholestasis: Itching for an alternative to liver transplantation

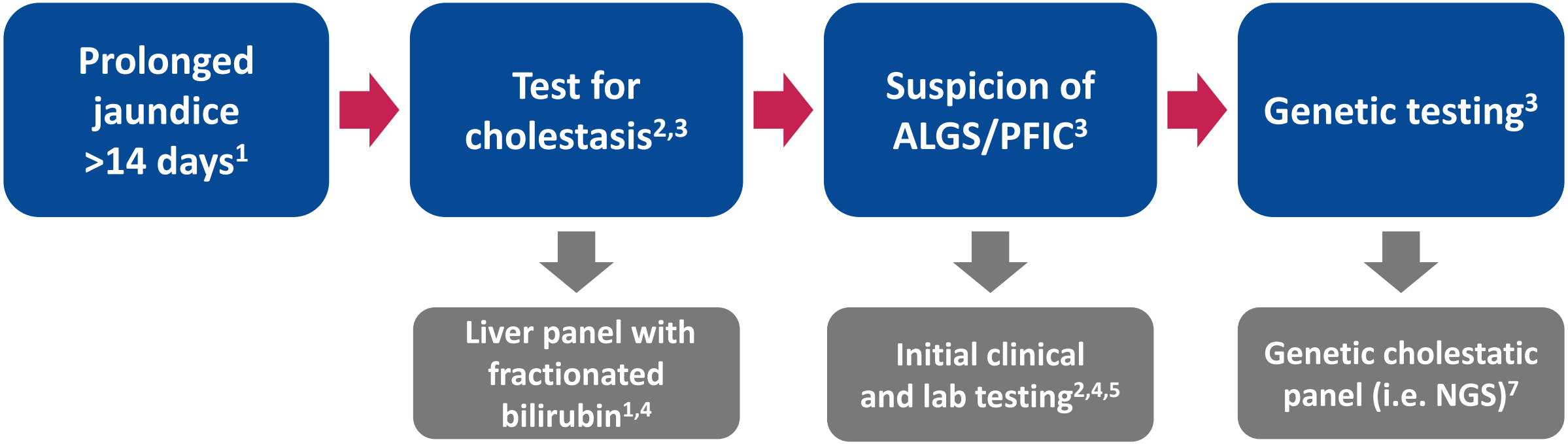
Time (CET)	Topic	Speaker
17:30–17:40	Welcome and introduction	Binita M. Kamath
17:40–18:00	Can novel treatments offer new hope for children with ALGS?	Emmanuel Gonzales
18:00–18:20	Scratching below the surface of PFIC management	Richard Thompson
18:20–18:30	Q&A and Chair’s close	Binita M. Kamath

Please submit any questions in the ‘chat’ function and we will answer as many of these as possible during the Q&A session

Meeting evaluation

We would appreciate it if you could complete the meeting evaluation at the end of the session

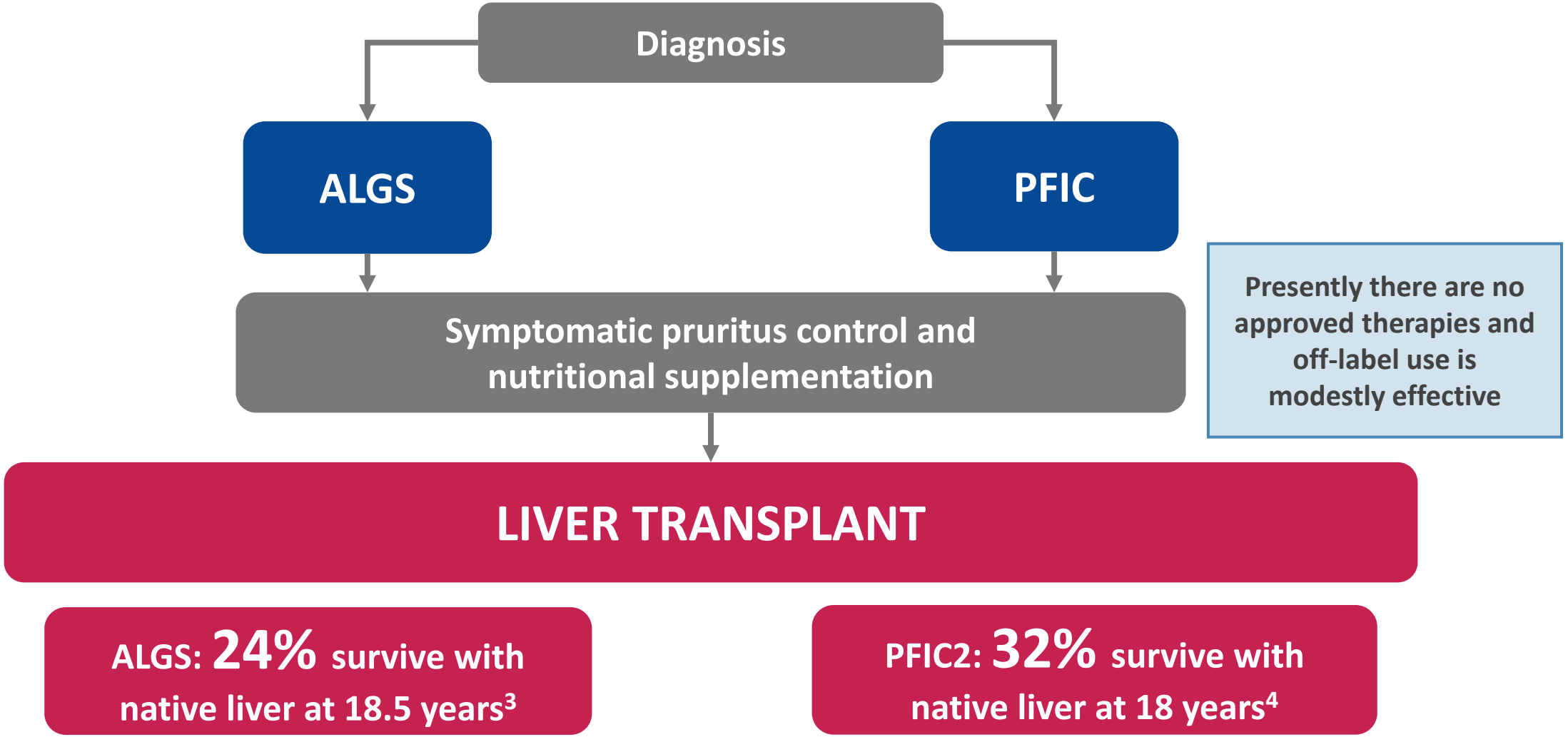
With increasing use of genotyping, liver biopsies are becoming less essential[1–8]



NGS, next generation sequencing.

1. Fawaz R, *et al. JPGN* 2017; **64**:154–168); 2. Amer S & Hajira A. *Gastroenterology Res* 2014; **7**:39–43; 3. Baker A, et al. *Clin Res Hepatol Gastroenterol* 2019; **43**:20–36;
4. Gunaydin M & Cil ATB. *Hepat Med* 2018; **10**:95–104; 5. Goldberg A & Mack CL. *Clin Liver Dis (Hoboken)* 2020; **15**:105–109; 6. Karpen S. *Clin Liver Dis* 2020; **15**:115–119;
7. Ayoub MD, & Kamath BM. *Diagnostics (Basel)* 2020; **10**:907; 8. Kamath BM, et al. *J Pediatr Gastroenterol Nutr* 2018; **67**:148–156.

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



1. Kamath BM, et al. *Hepatol Comms* 2020; **4**:387–398; 2. van Wessel D, et al. *J Hepatol* 2020; **73**:84–93.

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[1]

Impaired school performance[2]

Sleep disturbance and fatigue[2]

Pain[1]

Decreased physical functioning or general health[1]

Mental health/ depression[1]

Negative impact on a child's social activities[1]

Behaviour issues[1]

QoL, quality of life.

1. Elisofon SA, et al. *J Pediatr Gastroenterol Nutr* 2010; **51**:759–765; 2. Kamath BM, et al. *Patient* 2018; **11**:69–82.

Beyond the patient – caregiver impact is also significant[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

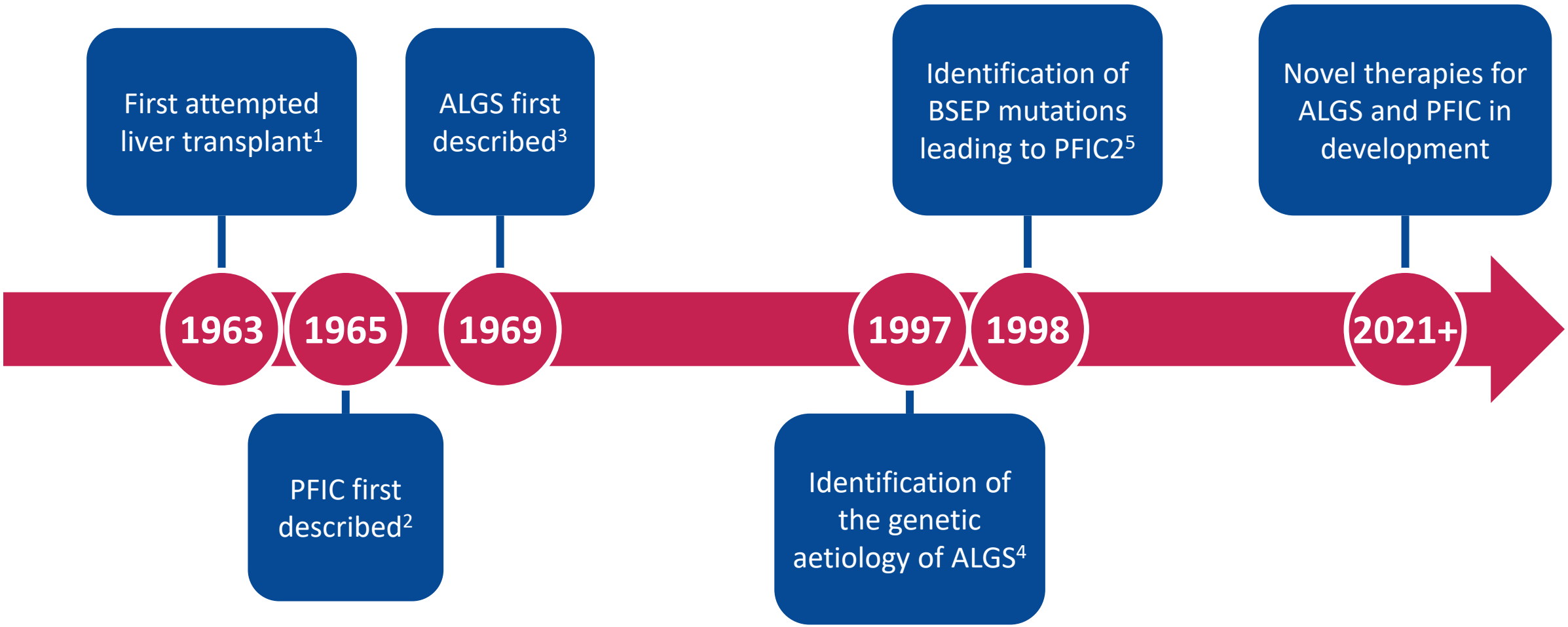
59% receive help from at least one other caregiver

Failure to understand family / caregiver spill over may underestimate the societal impact of rare diseases, as well as the value of new healthcare interventions

HCP, healthcare professional.

1. National Alliance for Caregiving, in partnership with Global Genes, 2018.

Where have we been, and where are we now?

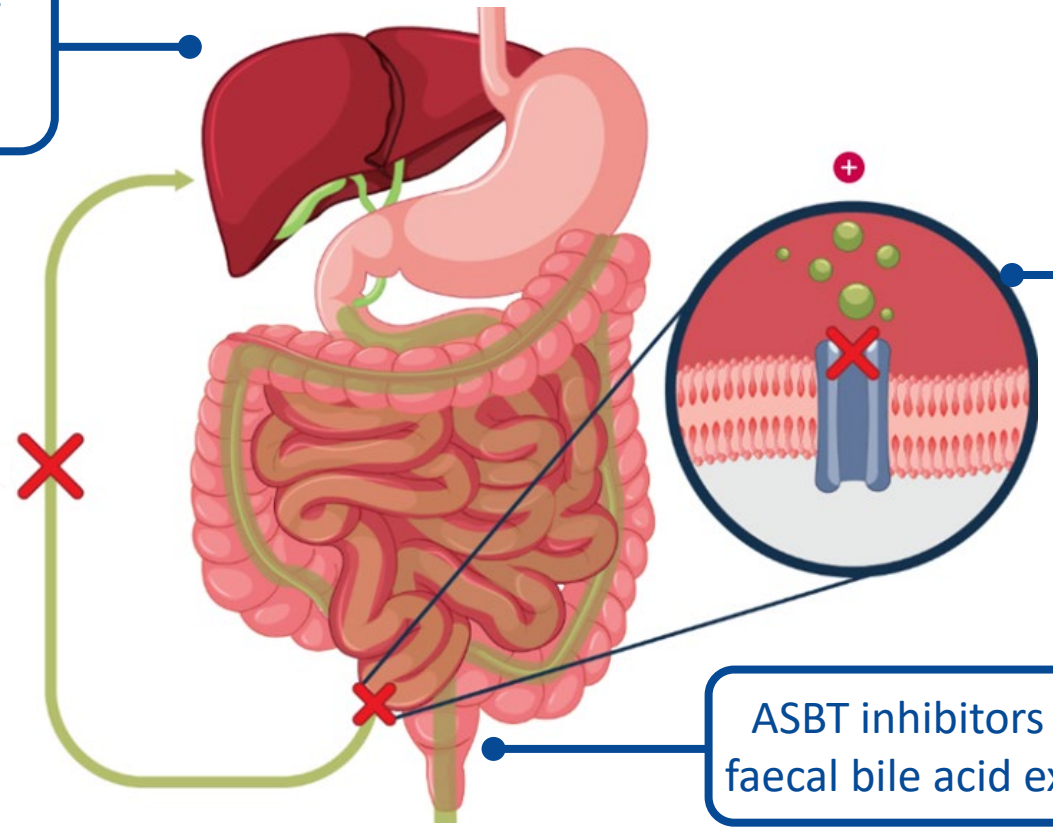


1. Júnior RFM, et al. *Einstein (Sao Paulo)* 2015; **13**:149–152; 2. Clayton RJ, et al. *Am J Dis Child* 1969; **117**:112–124;
3. Krantz ID et al. *J Med Genet* 1997; **34**:152–7; 4. Li L, et al. *Nat Genet* 1997; **16**:243–251; 5. Strautnieks SS, et al. *Nat Genet* 1998; **20**:233–238.

Rationale for ASBT inhibition

ASBT inhibitors reduce the amount of bile acid recycled to the liver[1–4]

Interrupting the enterohepatic circulation reduces manifestations of cholestasis[3,5,6]



Use of an ASBT inhibitor has been shown to decrease serum bile acids[5]

ASBT inhibitors increase faecal bile acid excretion[5,6]

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.

1. Dawson PA. *Handb Exp Pharmacol.* 2011; **201**:169–203; 2. Miethke AG, *et al. Hepatology* 2016; **63**:512–523;
3. Kamath BM, *et al. Liver International* 2020; **00**:1–11; 4. Tiessen RG, *et al. BMC Gastroenterology* 2018; **18**:1–17;
5. Hegade VS, *et al. BMC Gastroenterology* 2016; 16:1–12; 6. Hegade VS, *et al. Ther Adv Gastroenterol* 2016; **9**:376–391.

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[1–3]

- First reported as “arteriohepatic dysplasia”
- Clinical diagnosis (≥3 major criteria out of 5)

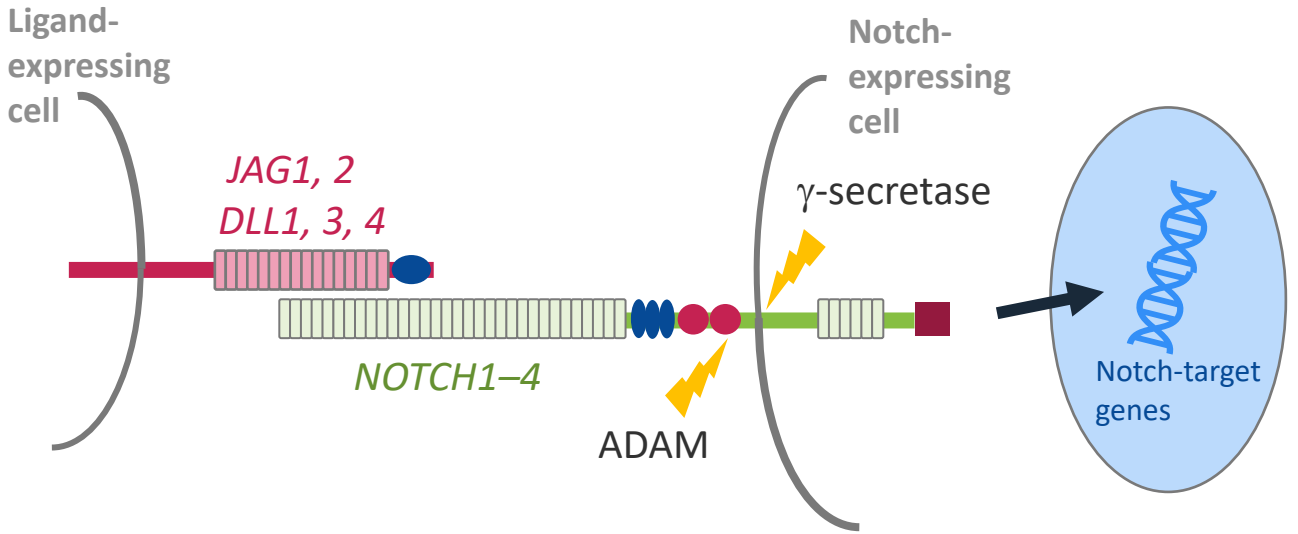
Mutations in *JAG1* (89–94%)

Mutations in *NOTCH2* (2%)

Genotype testing is preferred to confirm the diagnosis

- Incomplete penetrance, variable expressivity

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



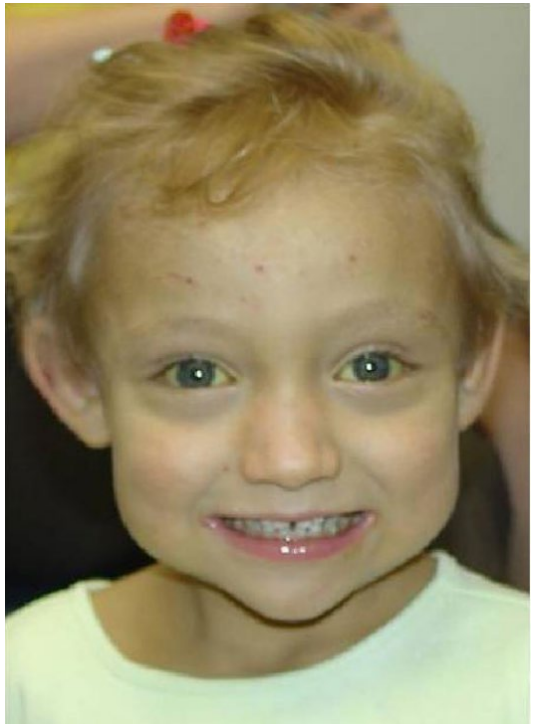
1. Masek J & Andersson ER. *Development* 2017; **144**:1743–1763; 2. Kamath BM, et al. *J Pediatr Gastroenterol Nutr* 2018; **67**:148–156; 3. Kamath BM, et al. *Hepatol Comms* 2020; **4**:387–398.

ALGS is classed as a rare disease[1]

1. Leonard LD, et al. *Eur J Hum Genet* 2014; **22**.

ALGS can result in a broad range of clinical manifestations

- Characteristic facial features[2]
- Hearing loss[3,4]
- Impaired growth[5]
- Skeletal abnormalities, fractures[1,3]
- Renal abnormalities[5]



- Ophthalmic abnormalities[1,7]
- Chronic cholestasis, pruritus, xanthomas[1,5]
- Portal hypertension in early adulthood[3]
- Cardiovascular disease[1]
- Vascular accidents / intracranial bleeding[6,7]

1. Saleh M, et al. *Appl Clin Genet* 2016; **9**:75–82; 2. Ayoub MD & Kamath BM. *Diagnostics (Basel)* 2020; **10**:907; 3. Kamath BM, et al. *Hepatol Comms* 2020; **4**:387–398; 4. Teng CS, et al. *Sci Rep* 2017; **7**:2497;
5. Kamath BM, et al. *J Pediatr Gastroenterol Nutr* 2018; **67**:148–156; 6. Leonard LD, et al. *Eur J Hum Genet* 2014; **22;** 7. Turnpenny P & Ellard S. *Eur J Hum Genet* 2012; **20**:251–257.
Image from Saleh M, et al. *Appl Clin Genet* 2016; **9**:75–82 (Dove Medical Press Ltd).

Management of ALGS aims to alleviate the symptoms of disease[1–3]

There are currently no approved treatments for ALGS

Control of pruritus

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

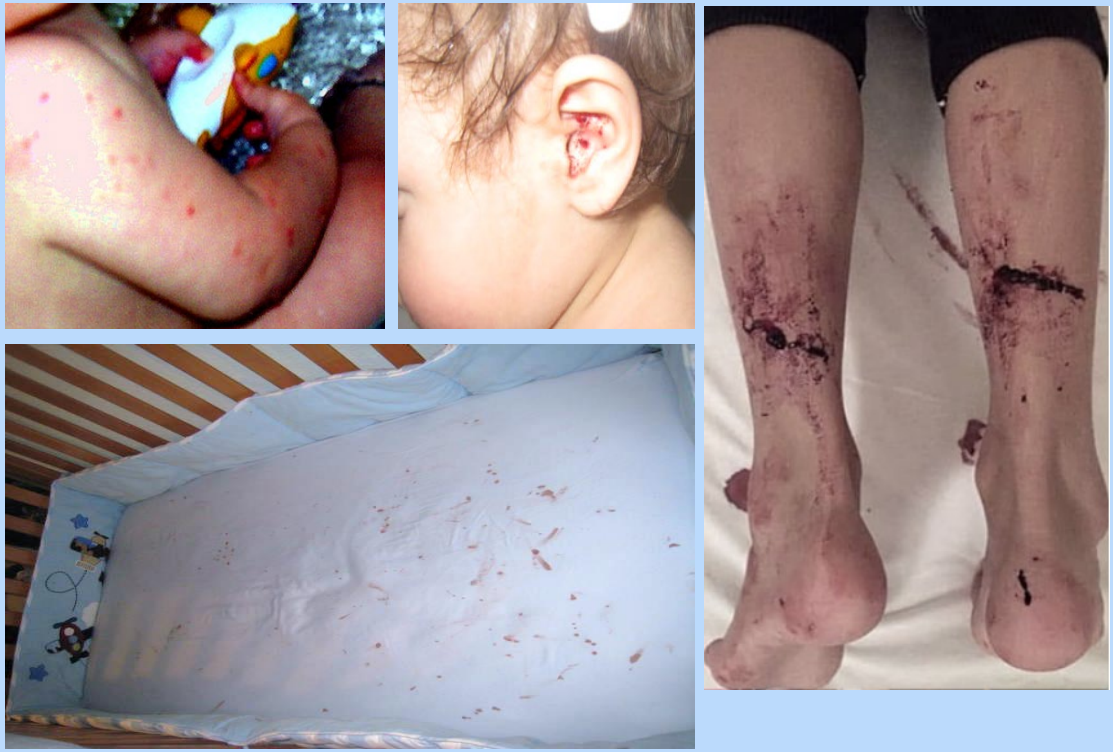
Dietary supplements

Fat-soluble vitamins
Nutritional supplements

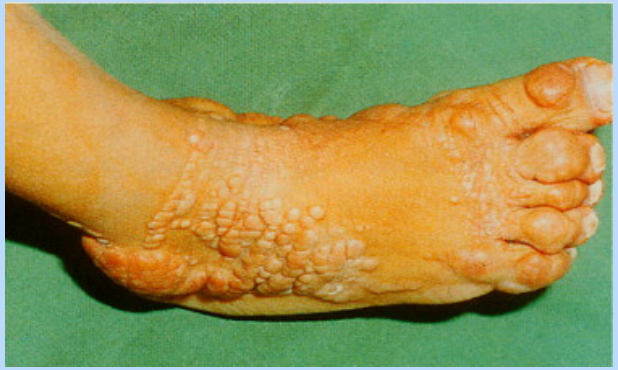
1. Kamath BM, et al. *J Pediatr Gastroenterol Nutr* 2010;**50**:580–586; 2. Thébaut A, et al. *J Pediatr Gastroenterol Nutr.* 2017; **64**:431–435; 3. Mayo MJ, et al. *Hepatology* 2007;**45**:666–674.

Cholestatic clinical manifestations of ALGS may be severe and debilitating[1]

PRURITUS



XANTHOMAS

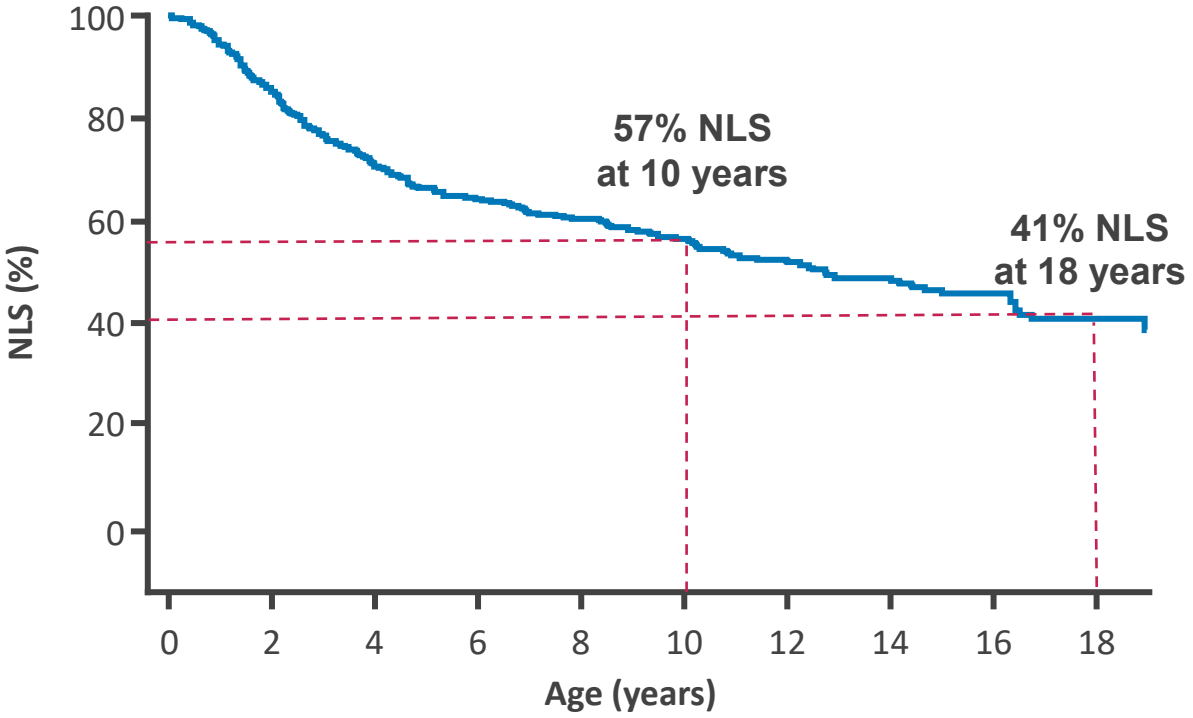


Images sourced from Mirum Pharmaceuticals.

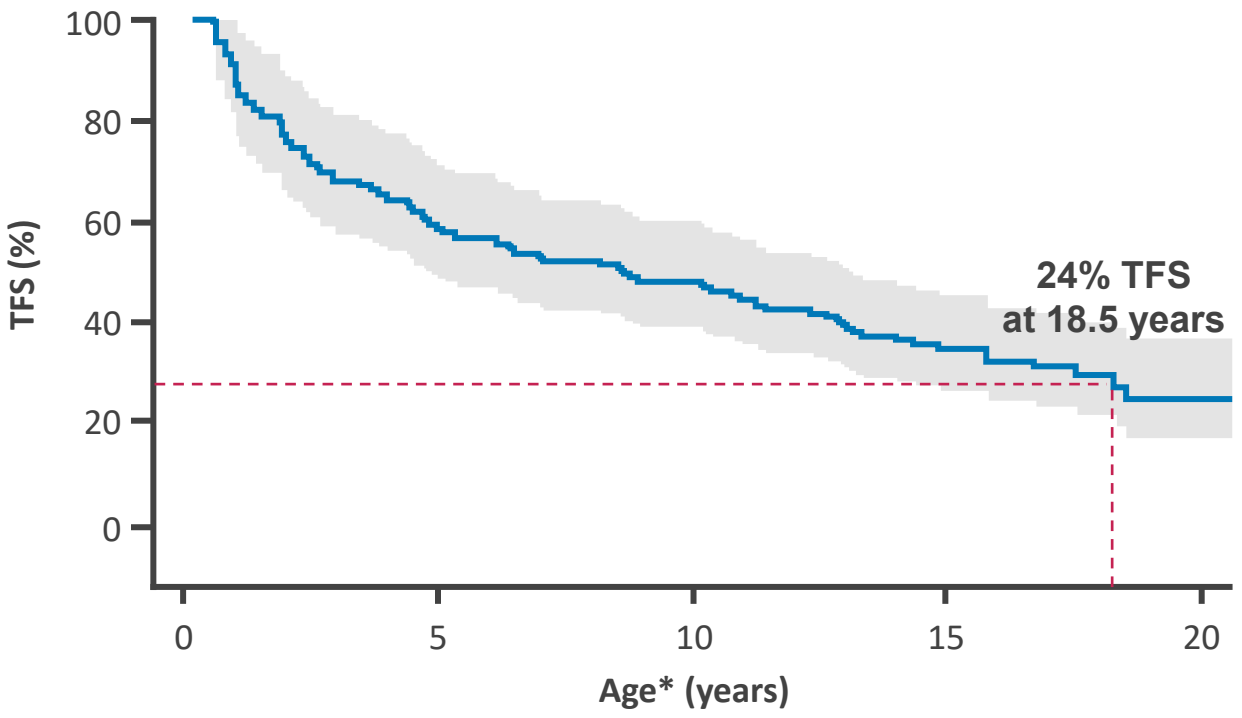
1. Saleh M, et al. *Appl Clin Genet* 2016; **9**:75–82.

Substantial risk for liver transplant in patients with ALGS

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



ChiLDReN (North America network)[2]
TFS in patients with ALGS



No. at risk	46	67	64	35	11

* Left truncated at baseline age.
NLS, native liver survival; TFS, transplant-free survivial.
1. Vandriel SM, *et al*. EASL 2020 (oral presentation); 2. Kamath BM, et al. *Hepatol Comms* 2020; **4**:387–398.

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

LT, liver transplant.

Novel approaches to improve outcomes in ALGS

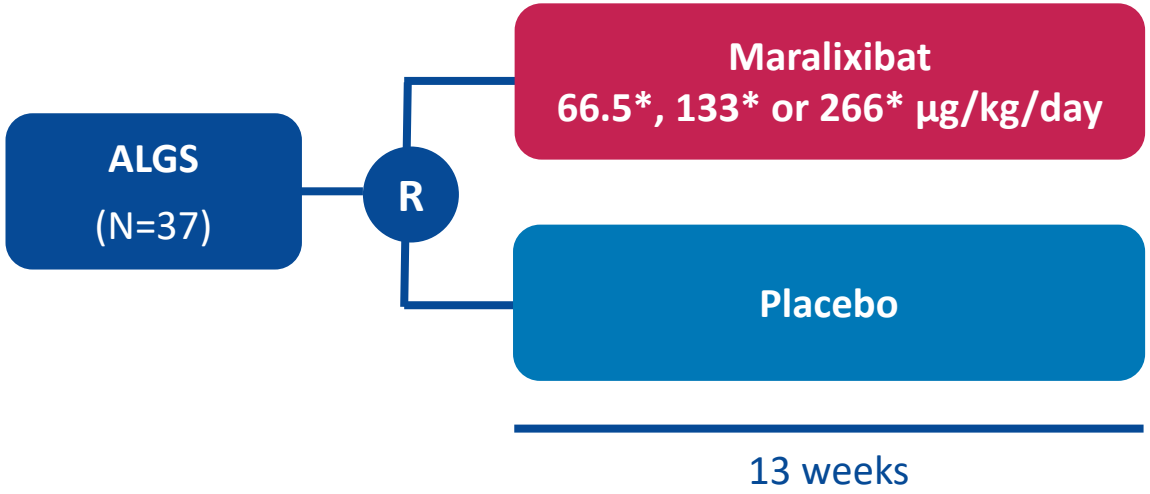
Investigational therapy

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

* 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 ALGS[1]

Investigational therapy



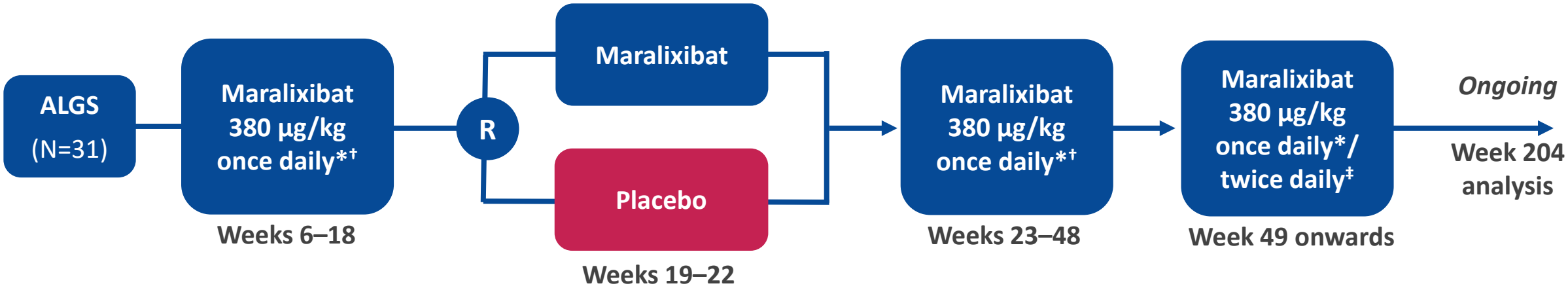
- Primary outcome: change from baseline to Week 13 in ItchRO relative to placebo

- 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

* 0.95 dosing for maralixibat vs 1.0 for maralixibat chloride.
AE, adverse event; ItchRO, Itch-reported outcome; R, randomised; SAE serious adverse event.
1. Schneider B, et al. *Hepatology Comms* 2018; **2**:1184–1198.

ICONIC (LUM001-304): Phase 2 study of maralixibat in ALGS[1]

Investigational therapy



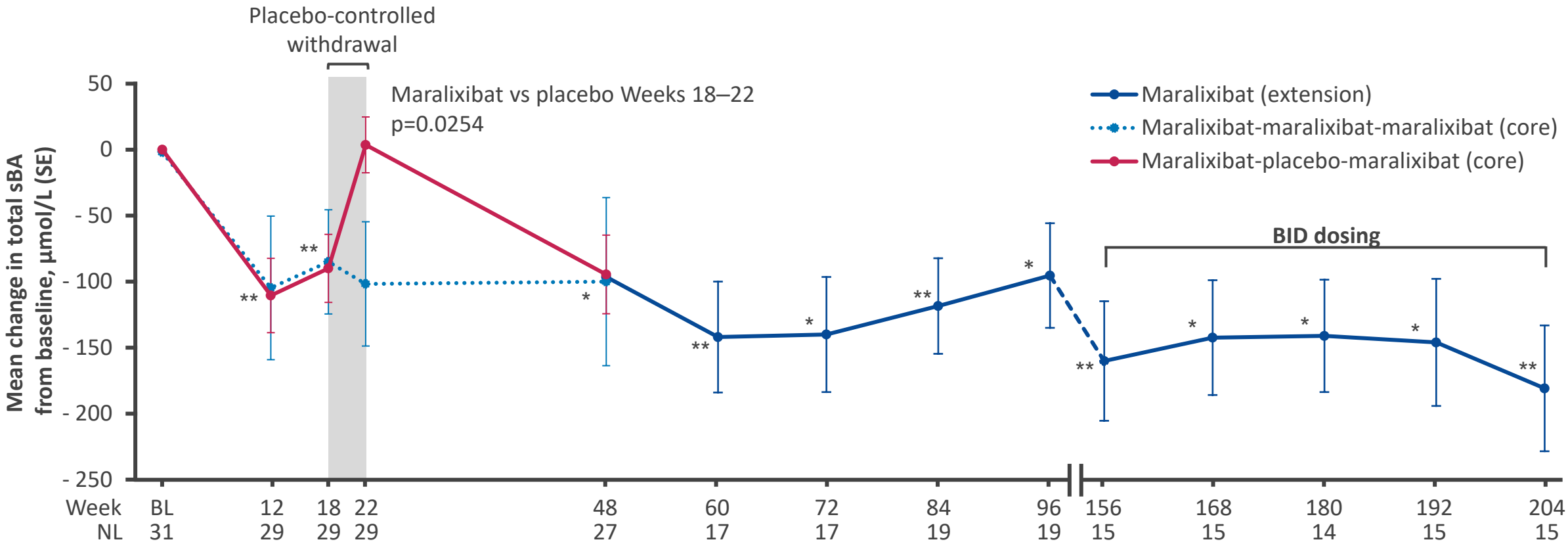
Primary endpoint	Secondary endpoints (weeks 18–22)	Additional endpoints (up to week 96)
• Mean change in sBA levels from Weeks 18–22 (and mean change in those who previously responded to maralixibat) • TEAEs (up to Week 98)	• Change in liver enzymes • Mean change in pruritus (ItchRO)	• Change in sBA; 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.
1. Clinicaltrials.gov: NCT02160782.

Significant reduction in sBA levels was maintained long term

Investigational therapy

Change in total sBA from BL to Week 204 across all participants

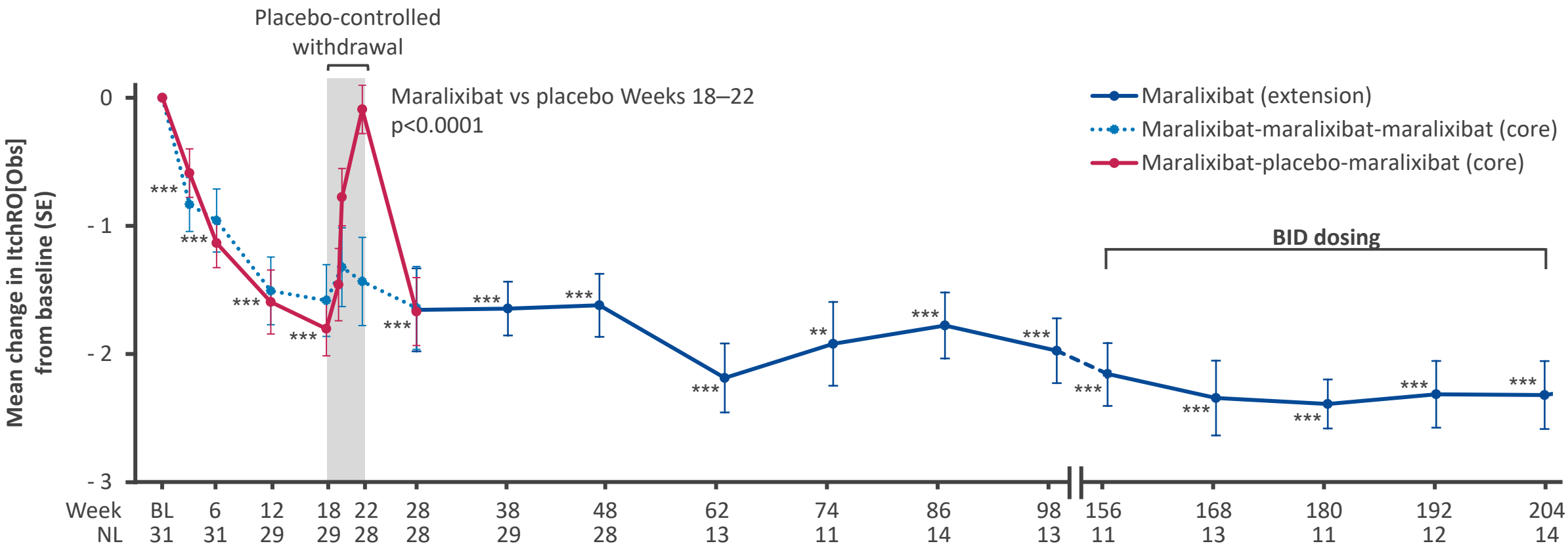


* p<0.05; ** p<0.005 (compared with baseline, overall population).
BL, baseline; BID, twice daily dosing; sBA, serum bile acid; SE, standard error.
1. Gonzales E. NASPGHAN 2020 (oral presentation).

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

Investigational therapy

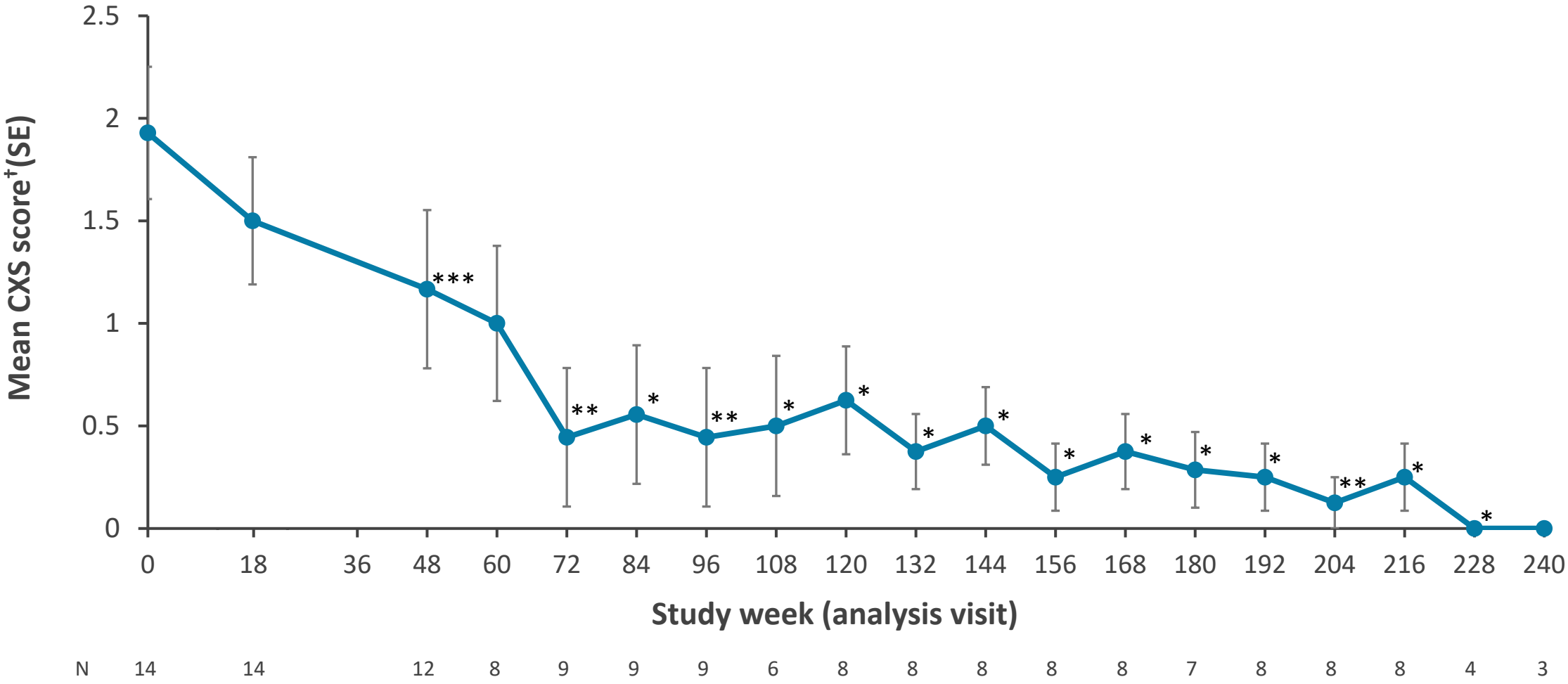
Changes in pruritus from BL to Week 204 (ItchRO[Obs])[1]



** p<0.005; *** p<0.0001 (compared with baseline, overall population).
BL, baseline; BID, twice daily dosing; ItchRO[Obs], Itch Reported outcome [Observer]; SE, standard error.
1. Gonzales E. NASPGHAN 2020 (oral presentation).

Sustained improvements in xanthomas (in those with xanthomas at baseline)[1]

Investigational therapy



* p<0.05; ** p<0.01; *** p<0.001. † Clinician xanthoma score 0–4 scale.
CXS, clinician xanthoma score; SE, standard error.
1. Data on file.

Correlation shown between pruritus and multiple parameters following maralixibat treatment[1]

Investigational therapy

sBA reduction, %	50	60	70	80	90
Change in ItchRO[Obs] score, points	–1.86	–2.12	–2.31	–2.79	–2.71

Parameters correlated with ItchRO[Obs] score at Week 48	*r*	p-value
Clinician Scratch Scale	0.65	0.0002
sBA	0.47	0.0123
PedsQL™ Impact	–0.38	0.0574
Parameters correlated with ItchRO[Obs] score as a change from Baseline to Week 48		
PedsQL™ Fatigue	–0.59	0.0053

sBA 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; sBA, serum bile acid.

1. Gonzales E, et al. Abstract 0341, AASLD 2020.

ICONIC: Safety and tolerability with maralixibat[1]

Investigational therapy

		Randomised withdrawal			
Number of participants, n (%)	**Core study (Weeks 0–18) (N=31)**	**Maralixibat (n=13)**	**Placebo (n=16)**	**Core study (Weeks 23–48) (N=29)**	**Extension phase (Week 49+) (N=29)**
Any TEAE	30 (96.8)	7 (53.8)	12 (75.0)	25 (86.2)	23 (79.3)
Grade 3 or 4 TEAE	6 (19.4)	0	1 (6.3)	2 (6.9)	6 (20.7)
Serious TEAE (all unrelated to maralixibat)	4 (12.9)	1 (7.7)	1 (6.3)	5 (17.2)	5 (17.2)
TEAE leading to death	0	0	0	0	0
TEAE leading to study drug discontinuation	2 (6.5)*	0	0	1 (3.4)*	3 (10.3)†,‡
TEAE potentially related to study drug	12 (38.7)	1 (7.7)	3 (18.8)	1 (3.4)	7 (24.1)

- 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.
1. Gonzales E. NASPGHAN 2020 (oral presentation).

ICONIC: Gastrointestinal tolerability with maralixibat (>5 years of follow-up)[1]

Investigational therapy

Patients experiencing an AE, n (%)	Integrated patient population (N=86)	
	Diarrhoea*	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 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.
1. Kamath BM. WCPGHAN 2021. Poster presentation (H-ePwP-030).

ICONIC: Gastrointestinal tolerability with maralixibat versus placebo

Investigational therapy

Patients experiencing an AE, n (%)	Maralixibat (N=39)		Placebo (N=18)	
	Diarrhoea*	Abdominal pain*	Diarrhoea*	Abdominal pain*
Any severity	17 (43.6)	15 (38.5)	9 (50.0)	5 (27.8)
Mild	16 (41.0)	12 (30.8)	6 (33.3)	3 (16.7)
Moderate	1 (2.6)	3 (7.7)	3 (16.7)	1 (5.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Life-threatening/fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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

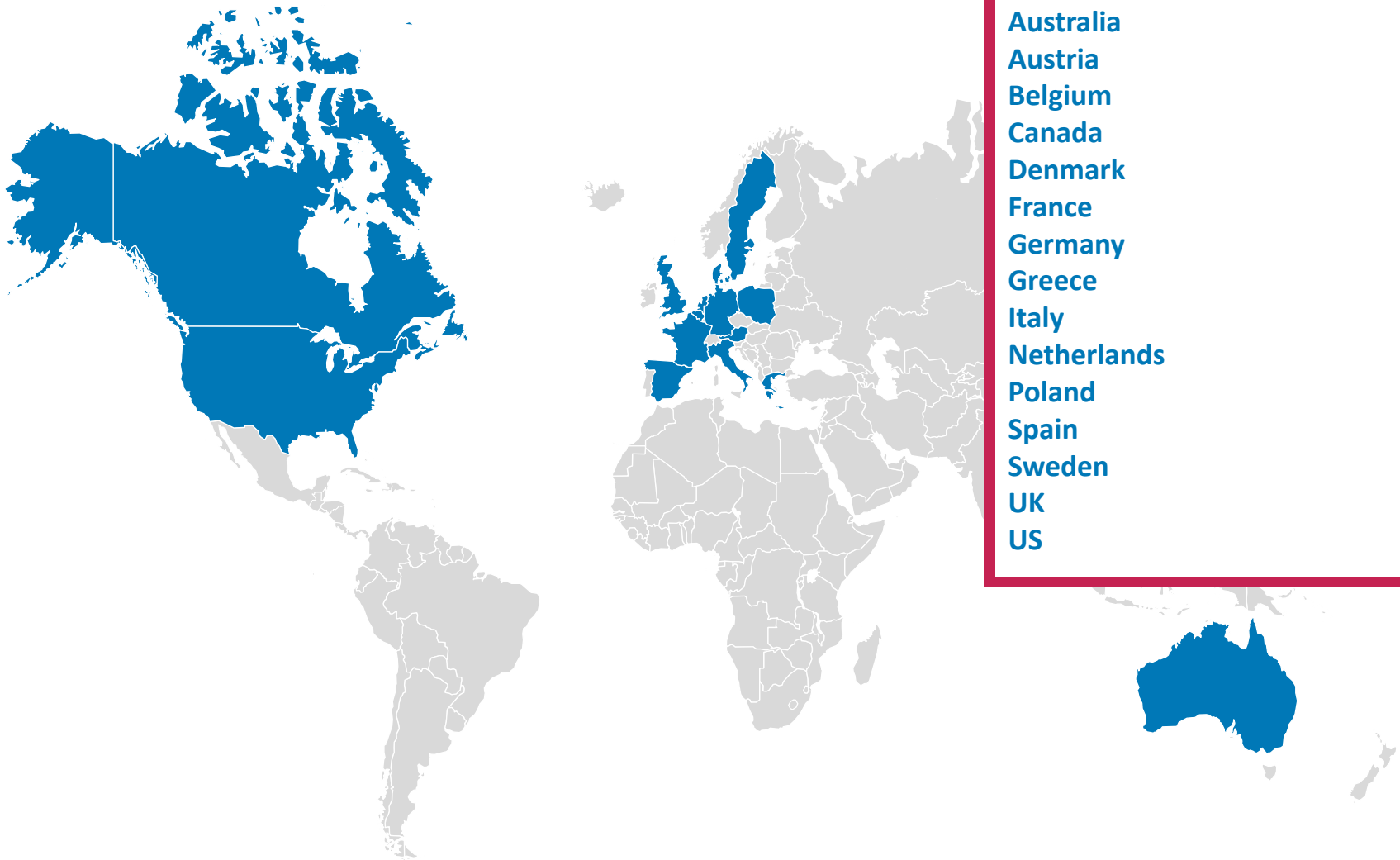
* Includes multiple adverse event terms.
AE, adverse event; GI, gastrointestinal.
1. Kamath BM. WCPGHAN 2021. Poster presentation (H-ePwP-030).

ALGS maralixibat expanded access program[1,2]

Maralixibat 400 µg/kg/day

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



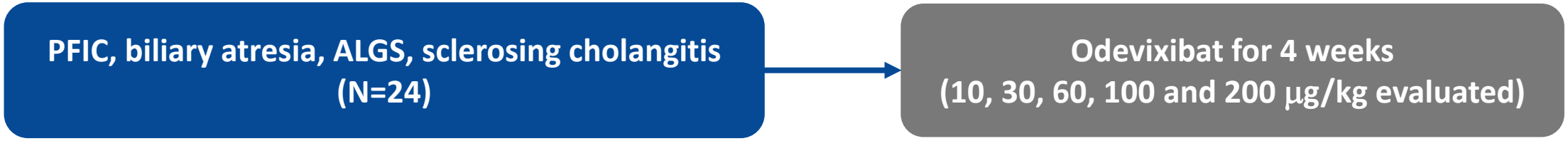
Australia
Austria
Belgium
Canada
Denmark
France
Germany
Greece
Italy
Netherlands
Poland
Spain
Sweden
UK
US

AE, adverse event; CSS, clinician scratch scale.
1. Clinicaltrials.gov: NCT04530994; 2. https://algseap.com/ Accessed May 2021.

Phase 2 study: Odevixibat across children diagnosed with pruritus due to chronic cholestasis[1]

Investigational therapy

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



Primary endpoints	Secondary endpoints
• Safety and tolerability • Explore changes in serum total bile acids after a 4-week treatment period	• Efficacy on liver biochemistry variables and on pruritus parameters • Pharmacokinetic properties • Evaluate changes in VAS itching score after a 4-week treatment period

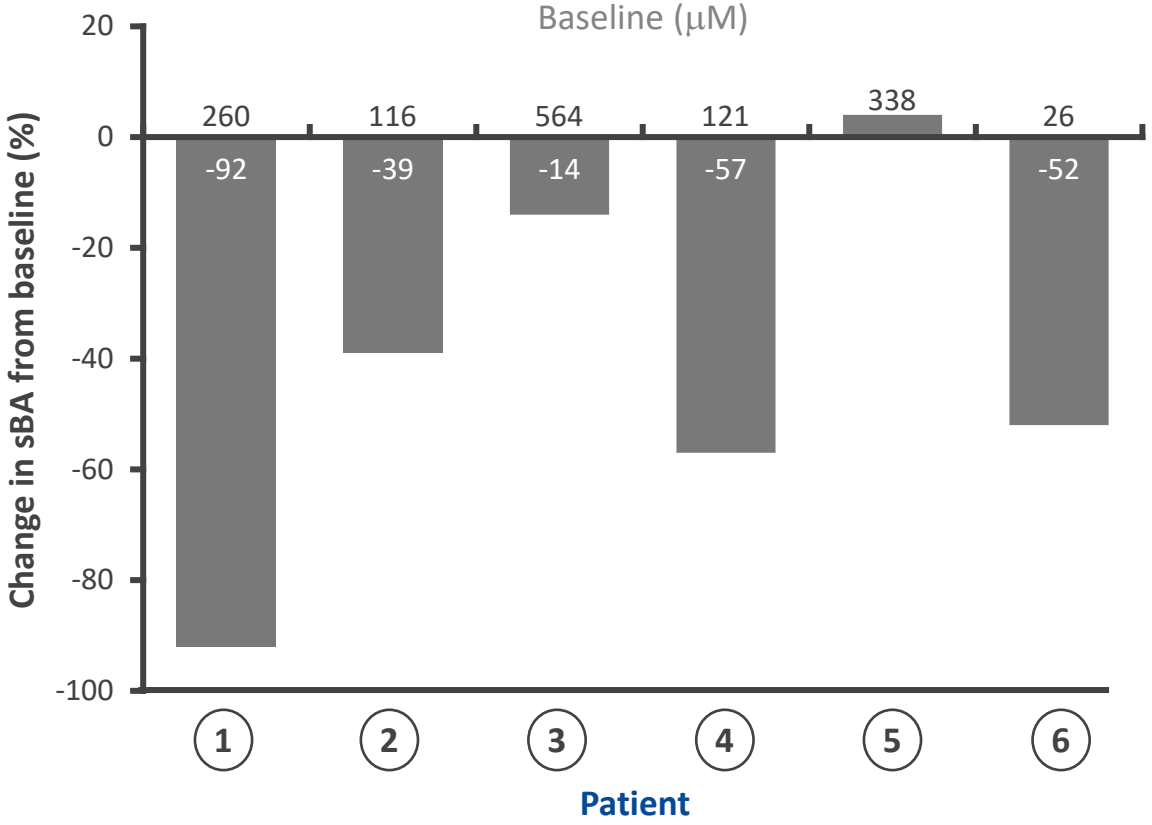
VAS, visual analogue scale.
1. Clinicaltrials.gov: NCT02630875.

Phase 2 study: Mean sBA levels and pruritus scores with odevixibat[1,2]

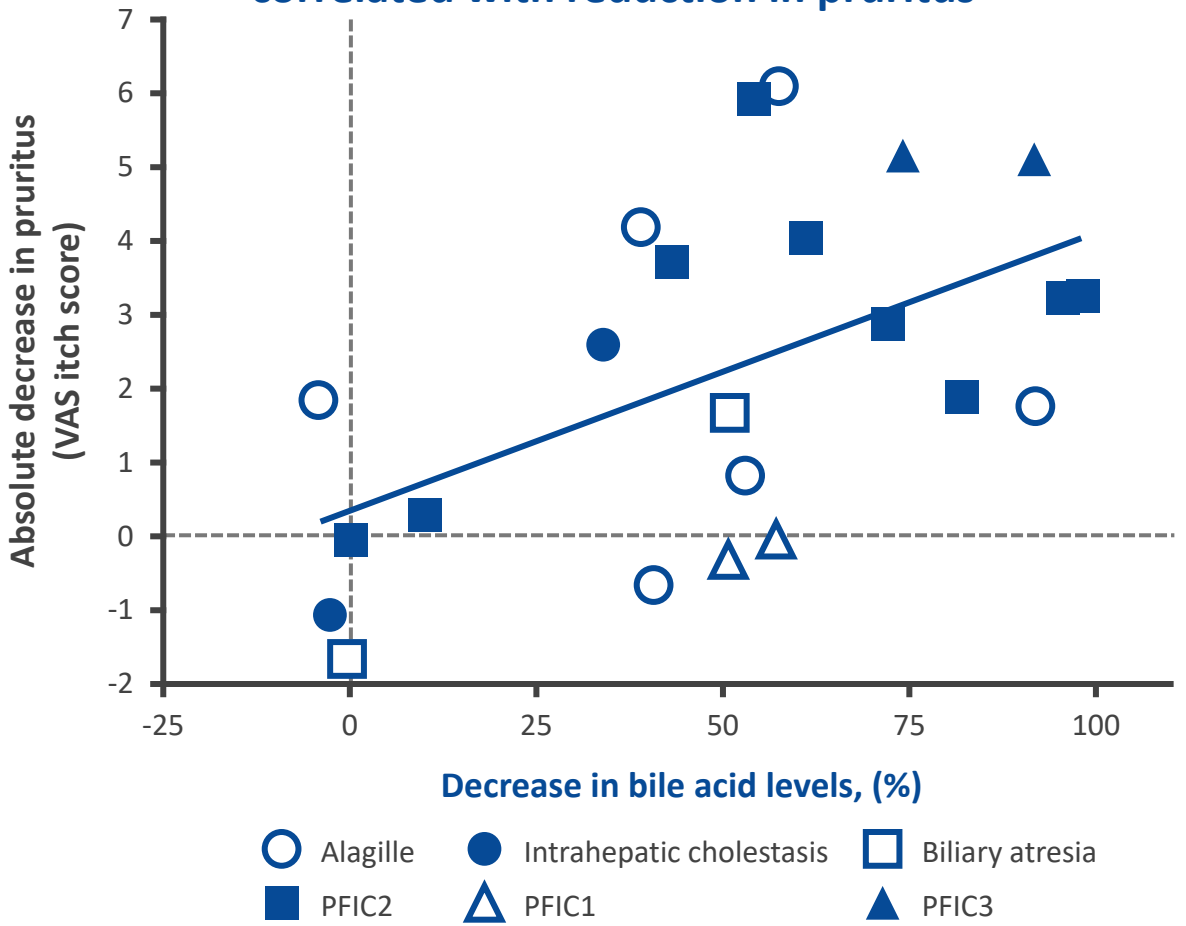
Investigational therapy

ALGS cohort, n=6

sBA reduction from baseline



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.
1. Albireo corporate presentation August 2020; 2. Sturm E, et al. *Hepatology* 2017; **66**:646-47 (Suppl. 1).

Phase 2 study: Safety and tolerability with odevixibat[1]

Investigational therapy

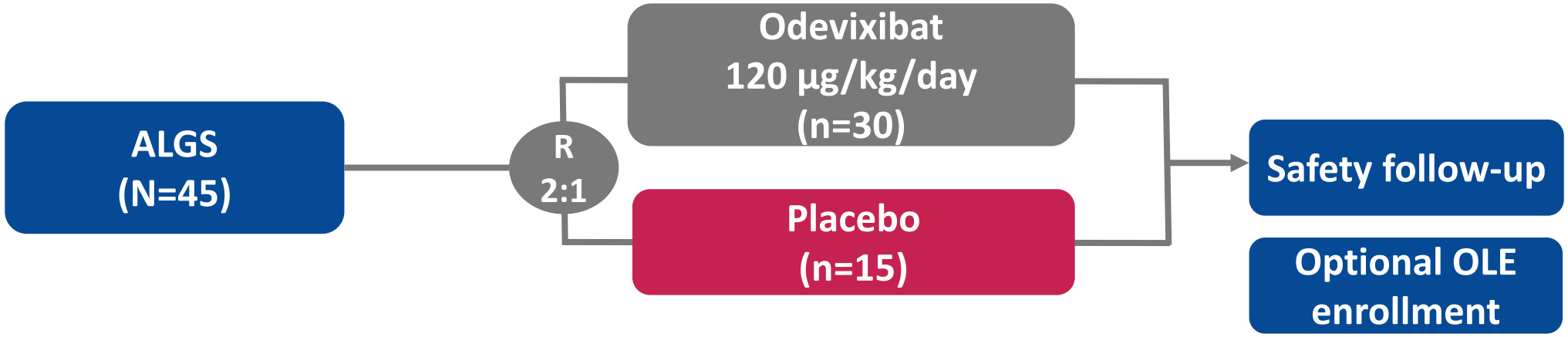
Safety includes entire cohort, n=24

- 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.
1. Albireo corporate presentation August 2020.

Phase 3 study: Odevixibat in ALGS (ASSERT)[1,2]

Investigational therapy



Primary endpoint	Secondary endpoints
• Change from baseline in scratching to Month 6 (Weeks 21–24) as measured by the Albireo ObsRO caregiver instrument	• 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.
1. Albireo corporate presentation May 2021; 2. Clinicaltrials.gov: NCT04674761.

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

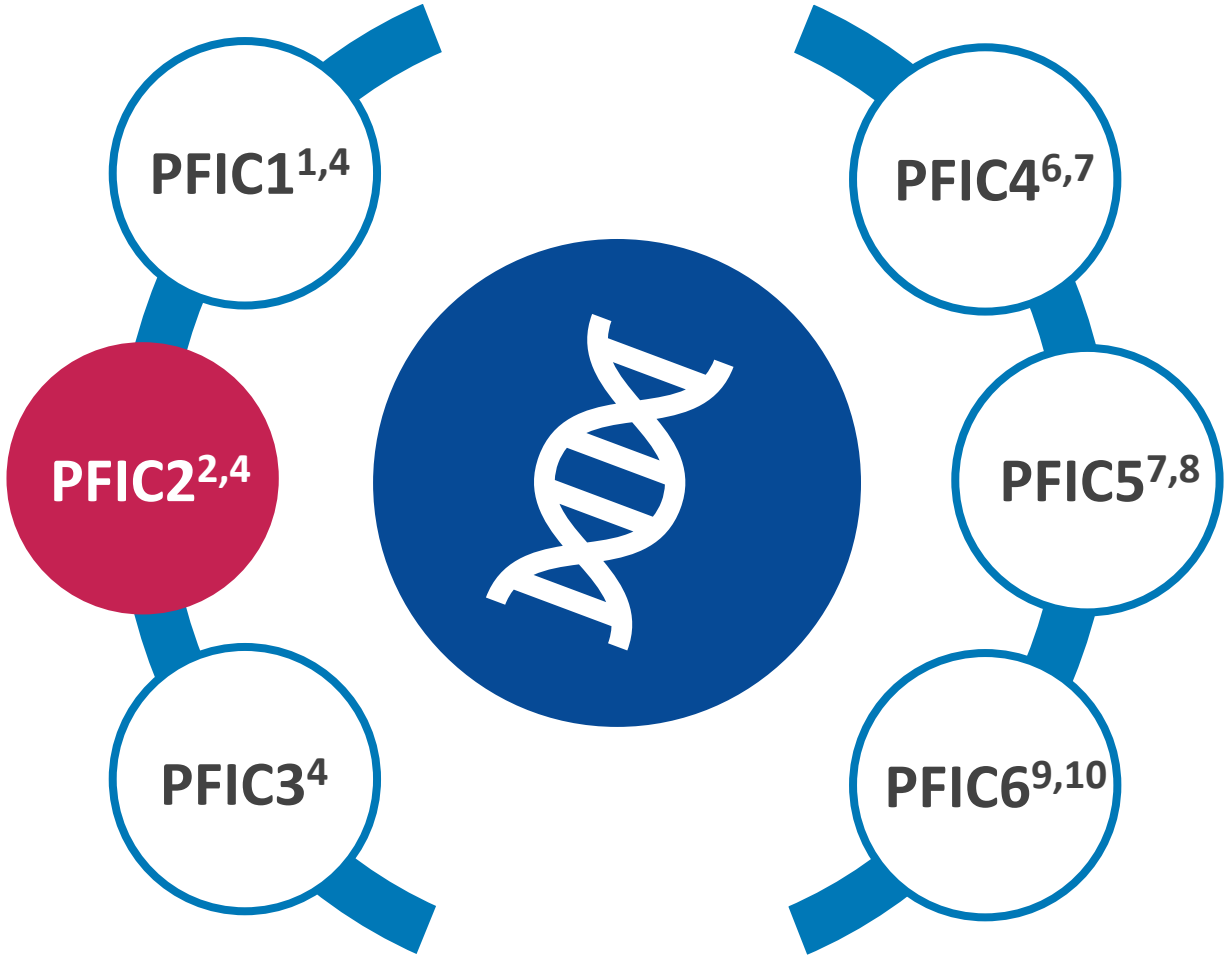
King's College London, London, UK

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

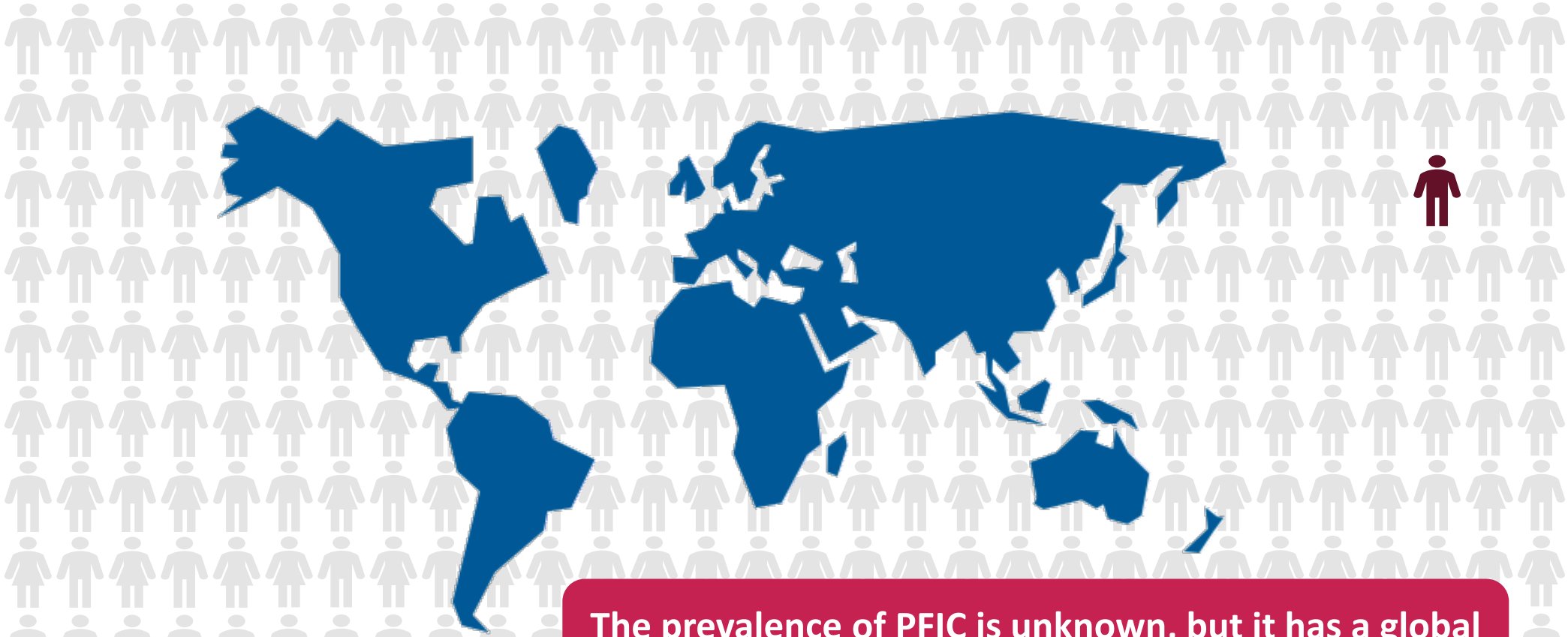
PFIC is an autosomal recessive disorder classified into six subtypes

PFIC is a heterogeneous group of diseases that disrupt bile formation[1–3]



1. Jacquemin E. *Clin Res Hepatol Gastroenterol* 2012; **36** Suppl 1:S26–35; 2. Srivastava A. *J Clin Exp Hepatol* 2014; **4**:25–36; 3. Amer S & Hajira A. *Gastroenterology Res* 2014; **7**:39–43;
4. Baker A, et al. *Clin Res Hepatol Gastroenterol* 2019; **43**:20–36; 5. van Wessel DBE, et al. *J Hepatol* 2020; **73**:84–93; 6. Sambrotta S, et al. *Nat Genet* 2014; **46**:326–328; 7. PFIC.org. Genetics of PFIC: Current status and implications. 2018. https://www.pfic.org/genetics. Accessed January 2021; 8. Gomez-Ospina N, et al. *Nat Commun* 2016; **7**:10713; 9. Qiu YL, et al. *Hepatology* 2017; **65**:1655–1669; 10. Overeem AW, et al. *Hepatology* 2020; **72**:213–229.

PFIC is classed as a rare disease[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)

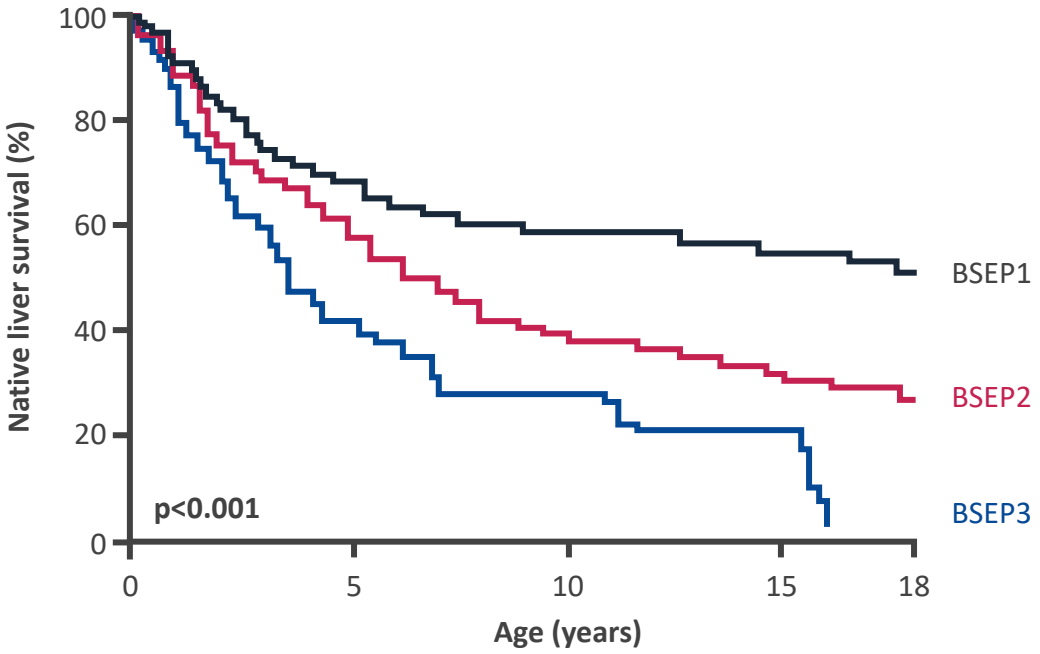
1. Jacquemin E. *Clin Res Hepatol Gastroenterol* 2012; **36** Suppl 1:S26–35; 2. https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=79304&lng=EN Accessed May 2021.

BSEP (PFIC2) is the most common and most aggressive of the PFIC subtypes[1]

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

Mutation	BSEP protein	Predicted severity	Median NLS (years)
At least one copy of p.D482G or p.E297G	Non-truncated (BSEP1)	Mild	20.4
At least one missense mutation other than p.D482G or p.E297G	Non-truncated (BSEP2)	Moderate	7.0
Non-functional protein; nonsense or frameshift (indel) or splice site	Truncated (BSEP3)	Severe	3.5

NLS according to genotype



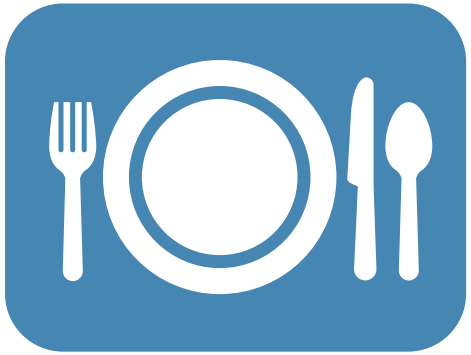
"Reprinted from Journal of Hepatology, 73, van Wessel, 'Genotype correlates with the natural history of severe bile salt export pump deficiency', 84–93, Copyright (2020), with permission from Elsevier.
NLS, native liver survival.
1. van Wessel, et al. *J Hepatol* 2020; **73:**84–93.

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.

1. Amer S & Hajira A. *Gastroenterol Res* 2014; **7:**39–43; 2. Baker A, et al. *Clin Res Hepatol Gastroenterol* 2019; **43**:20–36; 3. Jacquemin E. *Clin Res Hepatol Gastro* 2012; **36**:S26–S35; 4. Davit-Spraul A, et al. *Orphanet J Rare Dis*, 2009; **4**:1–12; 5. Henkel et al. *World J Hepatol* 2019; **11**:450-463; 6. Gunaydin M & Cil ATB. *Hepat Med* 2018; **10**:95–104.

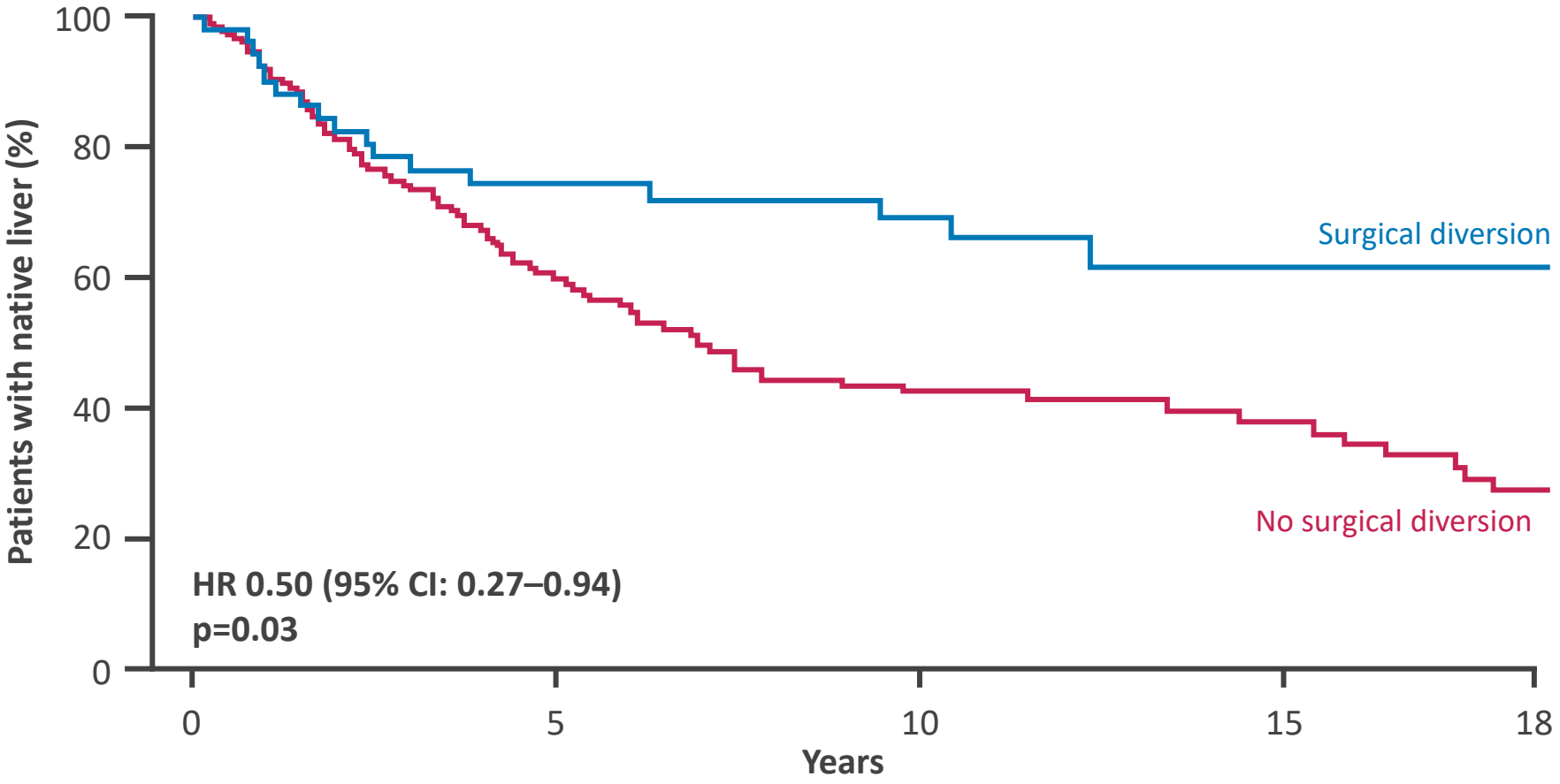
BSEP deficiency (PFIC2) results in a broad range of other clinical manifestations

- Jaundice[1]
- Fat malabsorption[1–3]
- Fat-soluble vitamin deficiency[1,2]
- Failure to thrive during first several months of life[1]
- Excoriation and mutilation of skin[2,3]
- Scleral icterus[2]
- Hepatomegaly[2]
- Portal hypertension within the first year[2]

Approx. 50% of patients require a liver transplant by age 10[4]

1. Amer S & Hajira A. *Gastroenterology Res* 2014; **7**:39–43; 2. Henkel SAF, et al. *World J Hepatol* 2019; **11**:450–463; 3. Gunaydin M & Cil ATB. *Hepat Med* 2018; **10**:95–104; 4. van Wessel DBE, et al. *J Hepatology* 2018;**68:** S626–S627.

Surgical biliary diversion improves outcomes in BSEP1 and 2 (nt-PFIC2)[1]

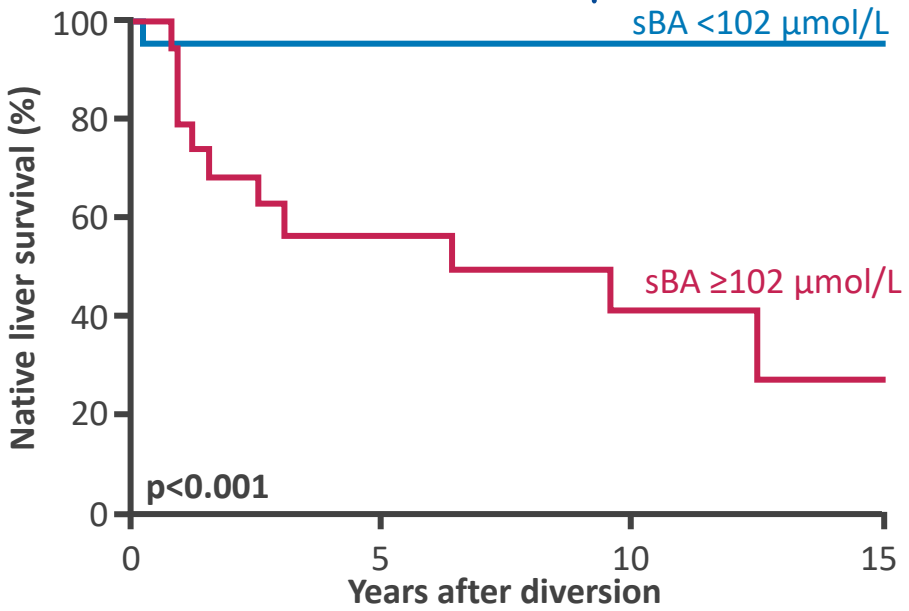


"Reprinted from Journal of Hepatology, 73, van Wessel, 'Genotype correlates with the natural history of severe bile salt export pump deficiency', 84–93, Copyright (2020), with permission from Elsevier.
CI, confidence interval; HR, hazard ratio; nt, non-truncated.

1. van Wessel DBE, et al. *J Hepatol* 2020; **73**:84–93.

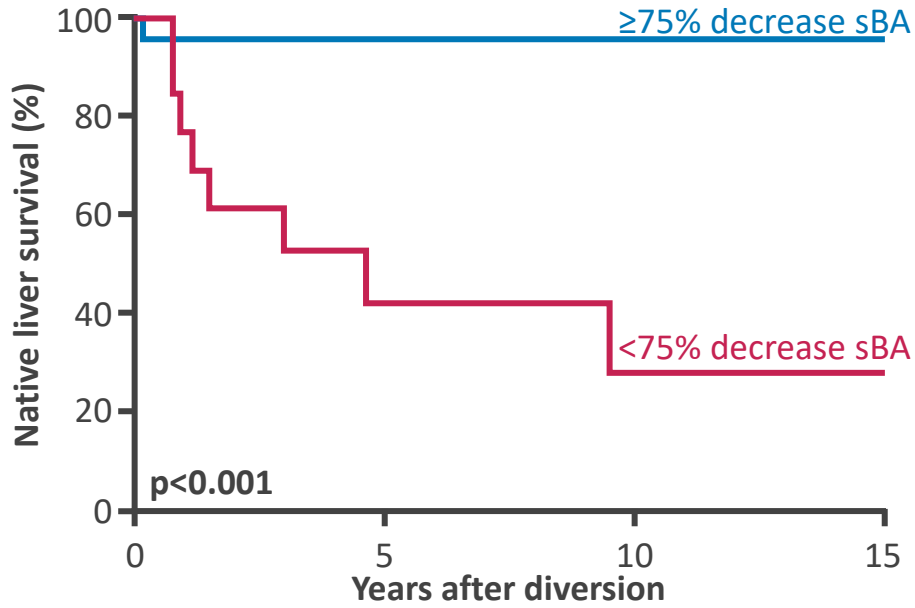
sBA control after surgical biliary diversion is associated with transplant-free survival[1]

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



No. at risk				
sBA <102 µmol/L	27	23	16	9
sBA ≥102 µmol/L	20	8	5	1

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



No. at risk				
<75% decrease sBA	14	4	2	1
≥75% decrease sBA	24	21	14	8

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

"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.

1. van Wessel DBE, et al. *J Hepatol* 2020; **73**:84–93.

Novel approaches to improve outcomes PFIC

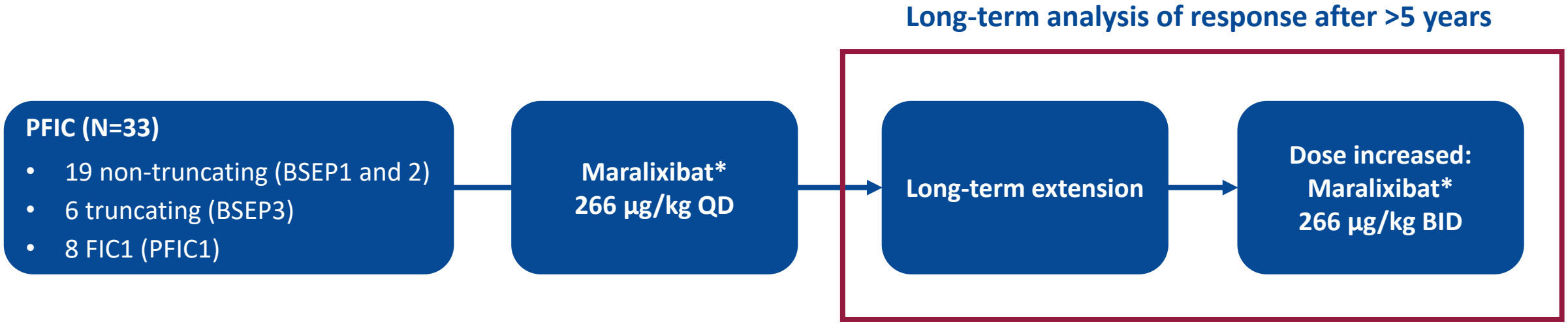
Investigational therapy

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

All clinical trials of novel compounds from ClinicalTrials.gov are listed.
EA, expanded access.
1. https://pfictrial.com.

INDIGO: Phase 2 study of maralixibat to investigate long-term effects of pharmacological interruption of enterohepatic circulation[1,2]

Investigational therapy



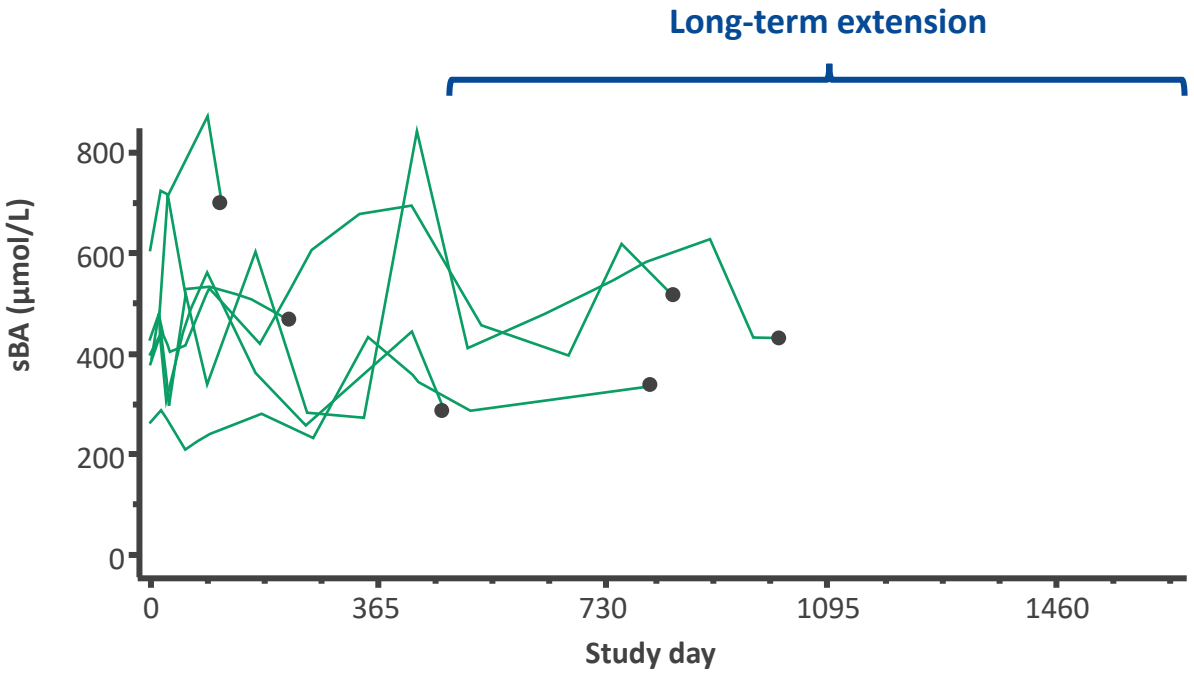
Primary endpoint	Secondary endpoints
• sBA control • ItchRO[Obs] severity of pruritus in PFIC2 (BSEP1–3)	• Growth • QoL • Safety and tolerability

* 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.
1. Clinicaltrials.gov: NCT02057718; 2. Thompson R, et al. EASL 2020; LBO08 (oral presentation).

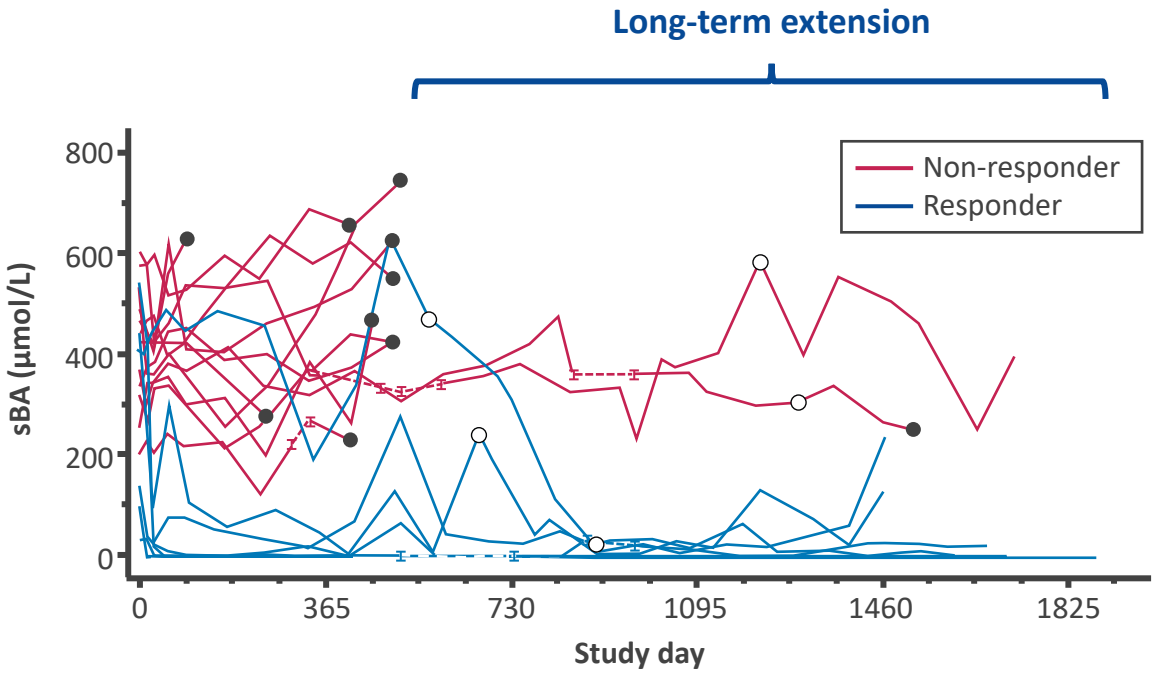
INDIGO: Mean sBA levels with long-term maralixibat treatment[1]

Investigational therapy

Truncating BSEP mutations (BSEP3)



Non-truncating BSEP mutations (BSEP1 & 2)

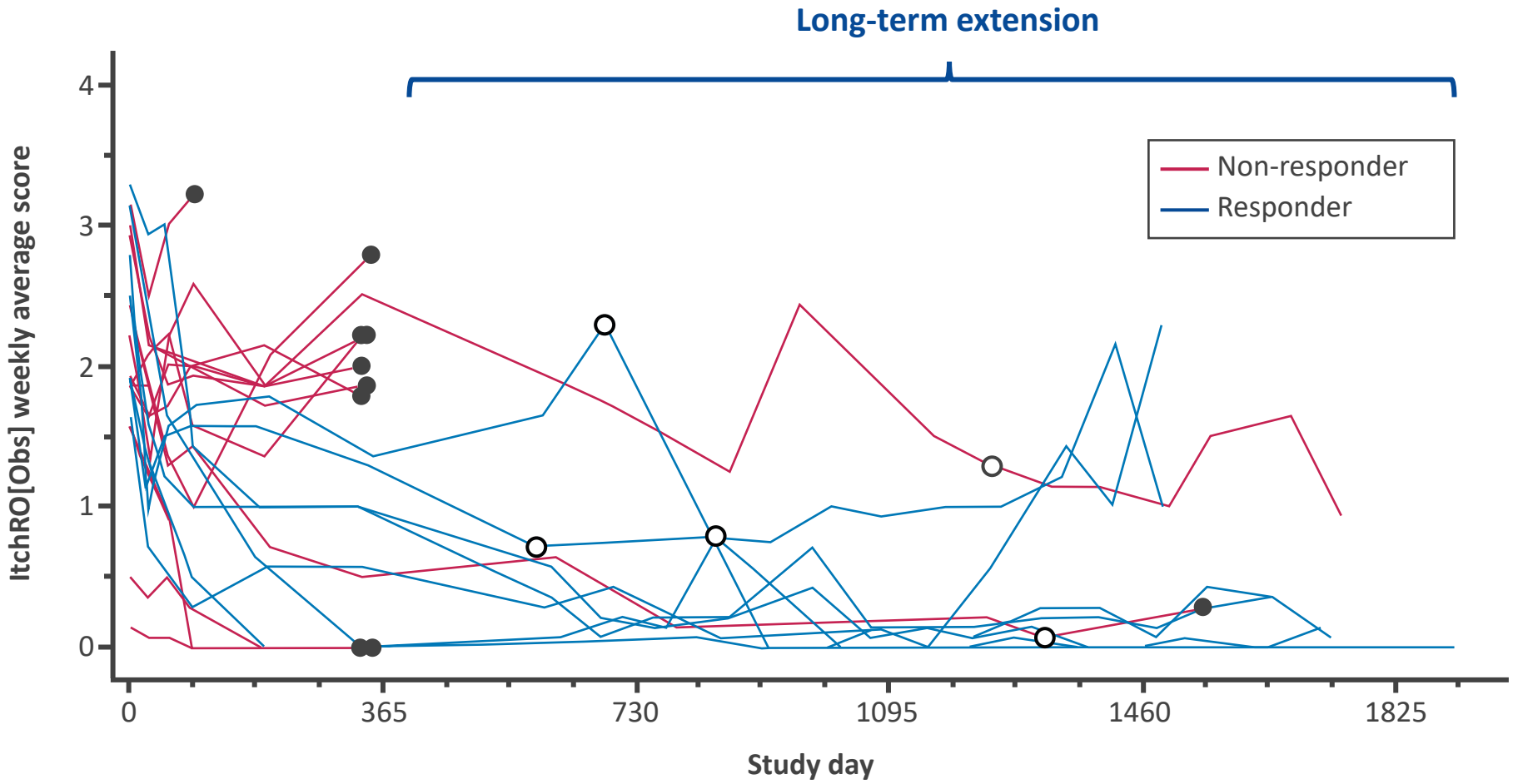


The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing.
sBA, serum bile acid.

1. Thompson R, et al. AASLD 2019 (oral presentation).

INDIGO: Maralixibat results in profound and durable improvements in cholestatic pruritus in patients with BSEP deficiency (PFIC2)[1]

Investigational therapy



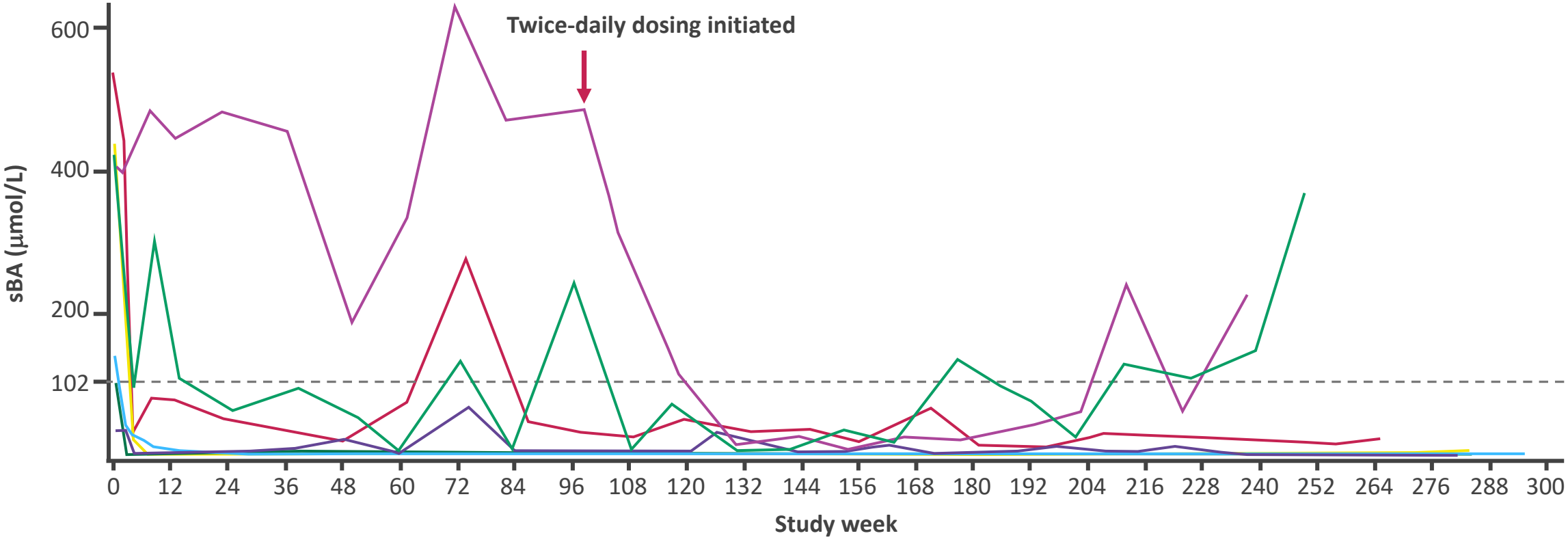
- ItchRO[Obs] response is sustained over years
- 79% (15/19) nt-PFIC2 patients achieved at least a 1-point reduction or a nadir ItchRO score of <1 at any timepoint

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.

1. Thompson R, et al. NASPGHAN 2020 (oral presentation).

INDIGO: sBA control with long-term maralixibat treatment (responders)[1]

Investigational therapy



- 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

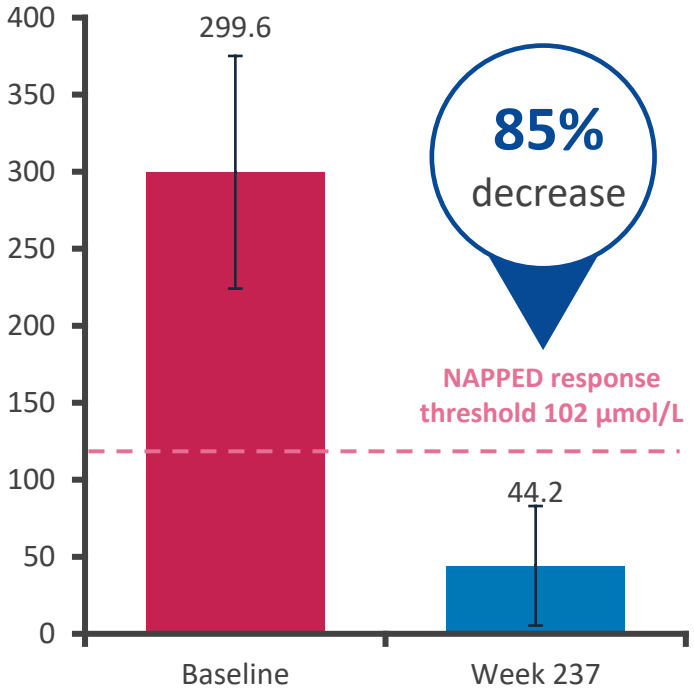
sBA, serum bile acid.

1. Adapted from: Thompson R, et al. EASL 2020; LBO08 (oral presentation).

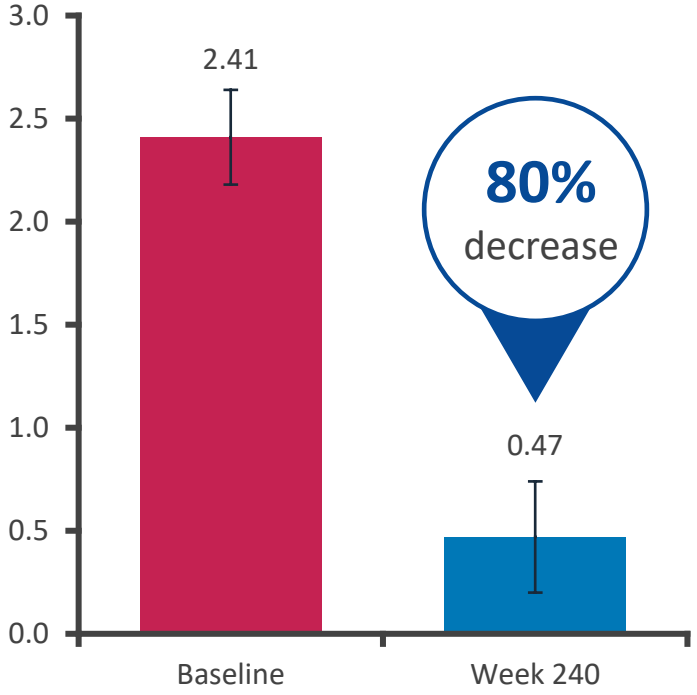
INDIGO: sBA response on maralixibat is associated with pruritus reductions and improved growth (responders), n=7[1]

Investigational therapy

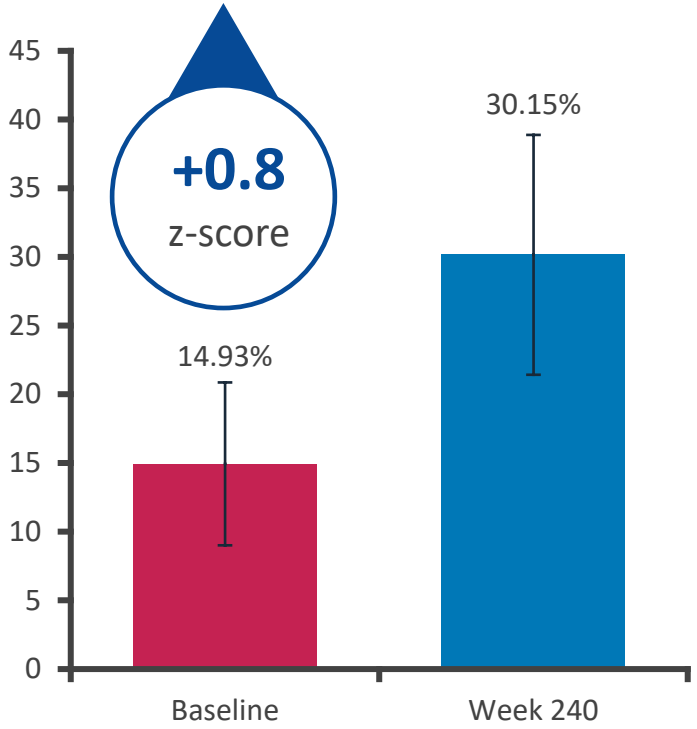
Mean sBA (µmol/L)



Mean ItchRO[Obs]



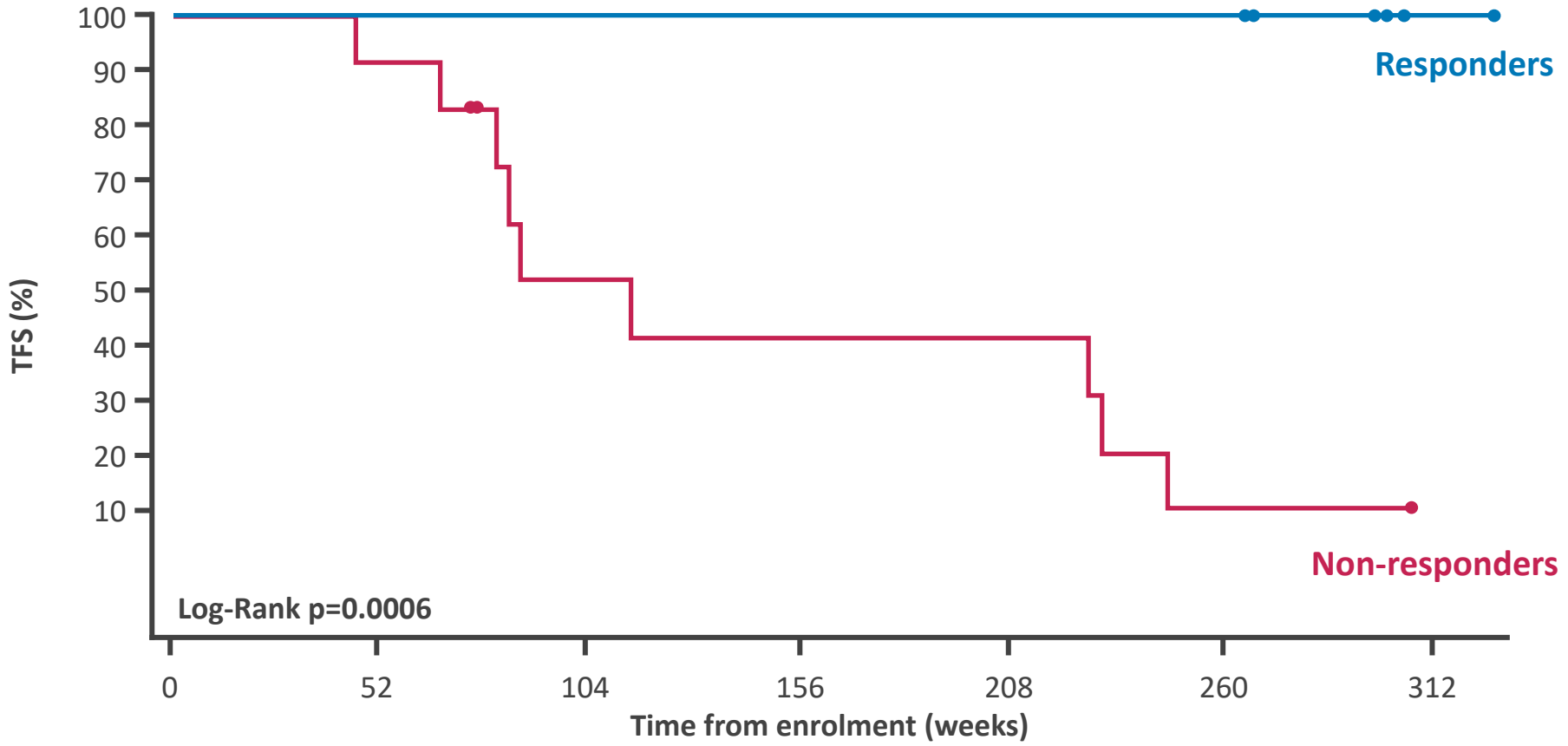
Mean height percentile



Error bars represent standard error of the mean.
ItchRO[Obs], Itch Reported outcome [Observer]; sBA, serum bile acid.
1. Adapted from: Thompson R, et al. NASPGHAN 2020 (poster presentation).

INDIGO: Transplant-free survival in patients with sBA control following maralixibat treatment[1]

Investigational therapy



No. at risk							
Responders	7	7	7	7	7	7	1
Non-responders	12	11	5	4	4	1	0

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

1. Thompson R, et al. EASL 2020; LBO08 (oral presentation).

INDIGO: Safety and tolerability with maralixibat[1]

Investigational therapy

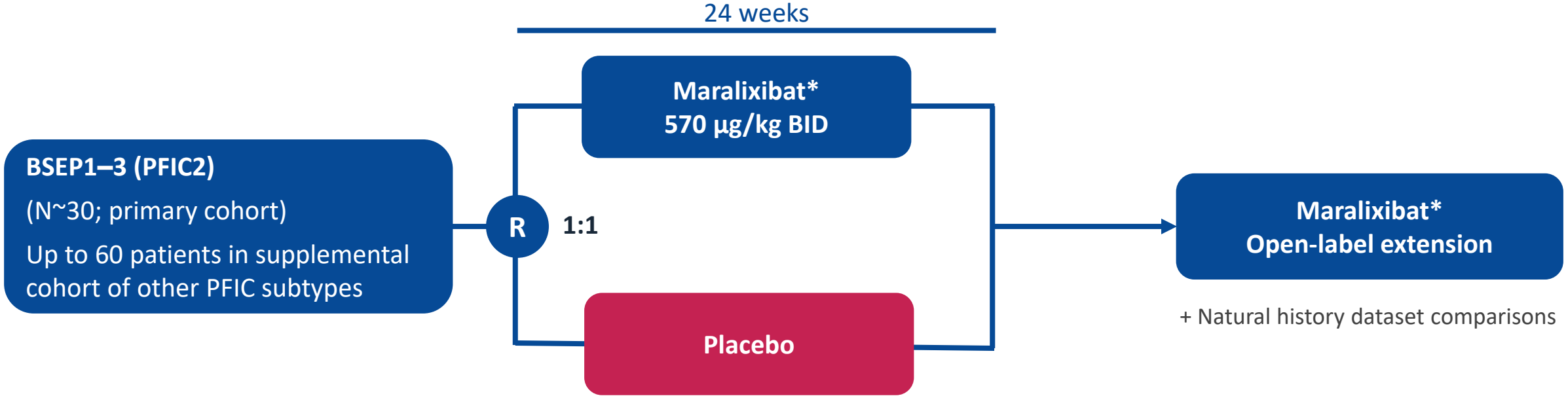
TEAEs	N (%)
Any TEAE	19 (100.0)
Potentially maralixibat-related	15 (78.9)
Leading to discontinuation*	3 (15.8)
Leading to death	0
Any serious TEAE	7 (36.8)
Potentially maralixibat-related*	2 (10.5)

Most frequently reported TEAEs	N (%)
Nasopharyngitis	12 (63.2)
Vomiting	12 (63.2)
Cough	11 (57.9)
Diarrhoea	11 (57.9)
Pyrexia	11 (57.9)
Abdominal pain	9 (47.4)
Oropharyngeal pain	8 (42.1)
Pruritus	8 (42.1)

* Pancreatitis, blood bilirubin increased.
TEAE, treatment-emergent adverse event.
1. Thompson R, et al. EASL 2020; LBO08 (oral presentation).

MARCH-PFIC: Phase 3 maralixibat study in PFIC2 and other PFIC subtypes[1,2]

Investigational therapy

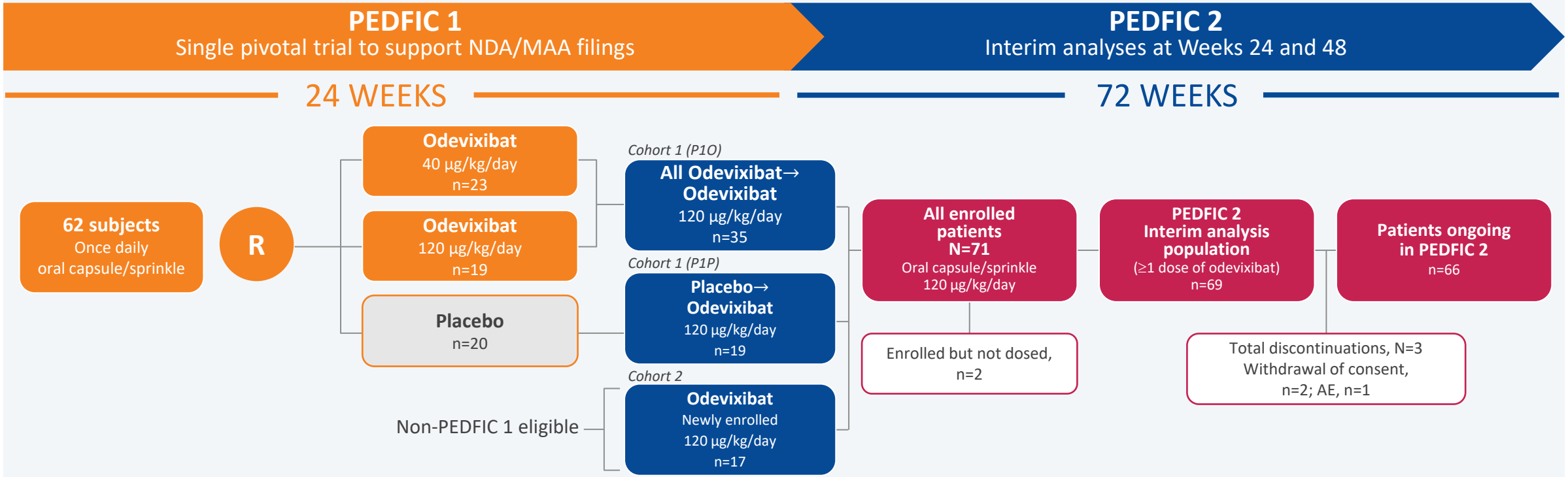


Primary endpoint	Secondary endpoints	Additional endpoints
• ItchRO[Obs] mean change in severity of pruritus	• Pruritus frequency • Change in serum bile acids • Safety	• Supplemental cohort analyses • QoL, growth, other measures

* 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.
1. Clinical trials.gov: NCT03905330; 2. https://pfictrial.com. Accessed May 2021.

PEDFIC 1/2: Phase 3 study of odevixibat in PFIC1 or PFIC2[1–3]

Investigational therapy



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

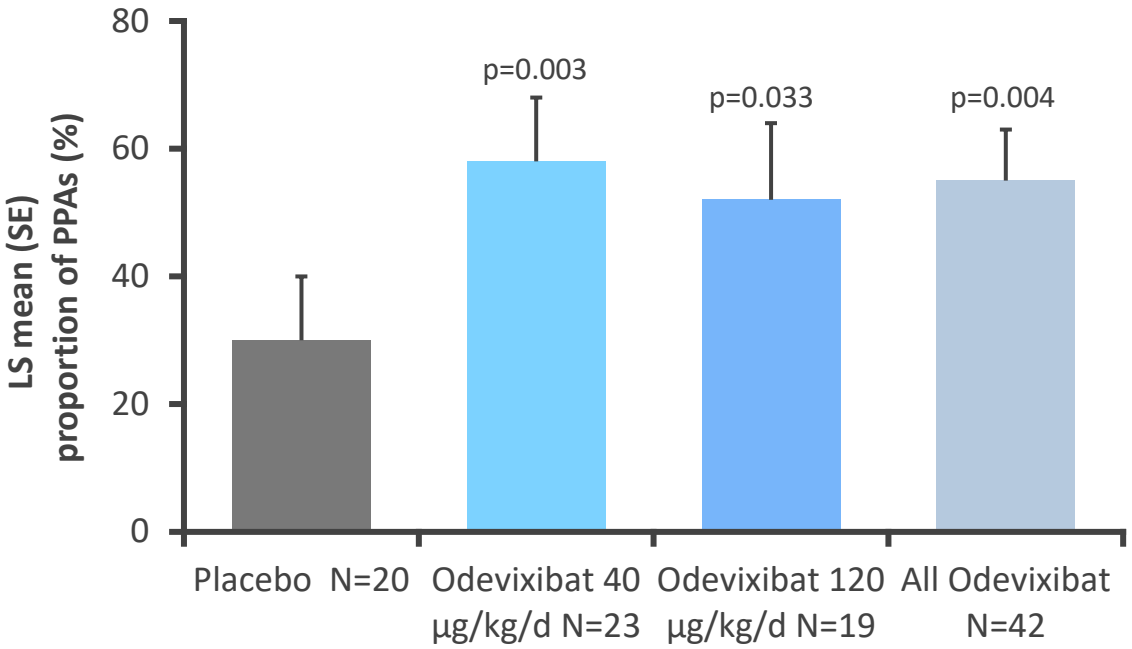
AE, adverse event; AST, aspartate aminotransferase; Fib-4, fibrosis-4 scale; ObsRO, observer-reported outcome; r, randomised; sBA, serum bile acid.

1. Albireo Corporate presentation May 2021; 2. Clinicaltrials.gov: NCT03566238; 3.Clinicaltrials.gov: NCT03659916.

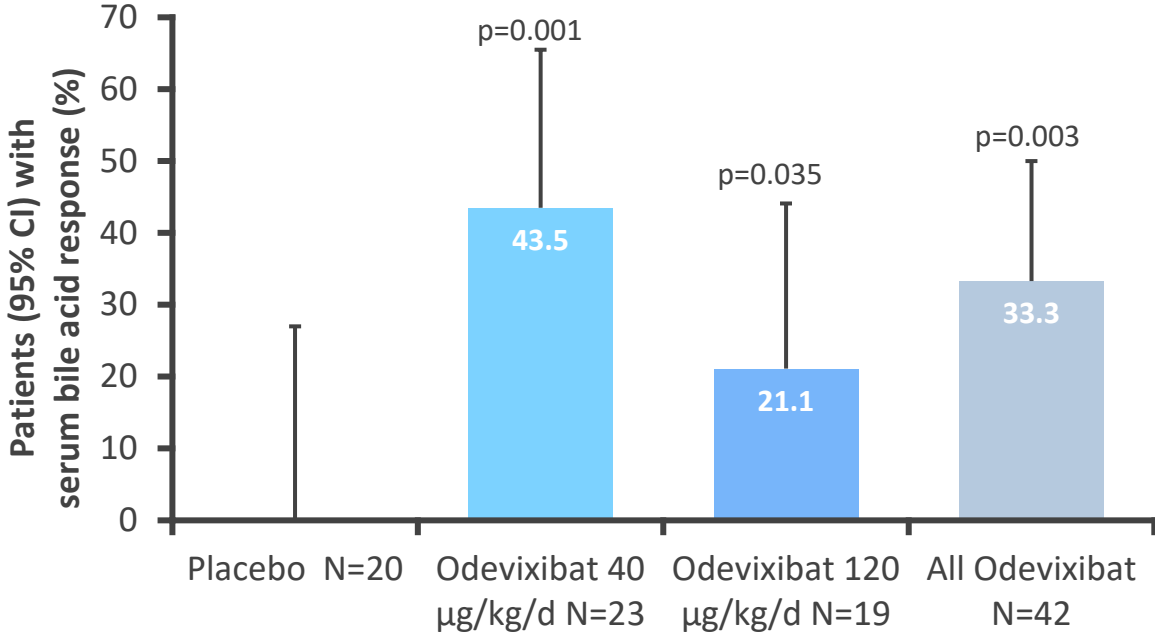
PEDFIC 1: Pruritus control with odevixibat treatment[1]

Investigational therapy

Proportion of positive pruritus assessments (PPA)*



Percentage achieving sBA response at 24 weeks†



* 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.

1. Albireo corporate presentation May 2021.

Pruritus improvement demonstrated in PFIC 1, 2 & 3[1]

Investigational therapy

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

	PFIC1 N=20	PFIC2 N=52	PFIC3 N=5
Patients with improved pruritus score	95%	80%	100%
Mean reduction (points)*	1.3	1.3	2.1

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

PEDFIC 1: Safety and tolerability with odevixibat[1]

Investigational therapy

Summary of TEAEs, n (%)	Placebo (N=20)	Odevixibat 40 µg/kg/day (n=23)	Odevixibat 120 µg/kg/day (n=19)	Odevixibat all doses (N=42)
Any TEAE	17 (85.0)	19 (82.6)	16 (84.2)	35 (83.3)
Mild	6 (30.0)	11 (47.8)	8 (42.1)	19 (45.2)
Moderate	9 (45.0)	7 (30.4)	6 (31.6)	13 (31.0)
Severe	2 (10.0)	1 (4.3)	2 (10.5)	3 (7.1)
Drug-related TEAE	3 (15.0)	7 (30.4)	7 (36.8)	14 (33.3)
Serious TEAEs	5 (25.0)	0	3 (15.8)	3 (7.1)
TEAEs leading to discontinuation	0	0	1 (5.3)	1 (2.4)
Liver-related TEAEs	4 (20.0)	5 (21.7)	6 (31.6)	11 (26.2)
Drug related TEAEs occurring in 2 or more patients in a group, by preferred term				
ALT increased	1 (5.0)	2 (8.7)	2 (10.5)	4 (9.5)
AST increased	1 (5.0)	2 (8.7)	1 (5.3)	3 (7.1)
Blood bilirubin increased	1 (5.0)	2 (8.7)	2 (10.5)	4 (9.5)
Diarrhoea/frequent bowel movements	1 (5.0)	2 (8.7)	2 (10.5)	4 (9.5)

- 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.
1. Albireo corporate presentation May 2021.

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


Q
&
A

Meeting evaluation

We would appreciate it if you could complete the meeting evaluation

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Thank You