Building new treatment paradigms in the management of pediatric cholestasis

Thursday, December 16, 2021
20:00–21:30 EST

Welcome and introduction: The impact of cholestasis

Tamir Miloh, M.D.

Medical Director of Pediatric Transplant Hepatology at the Miami Transplant Institute, USA

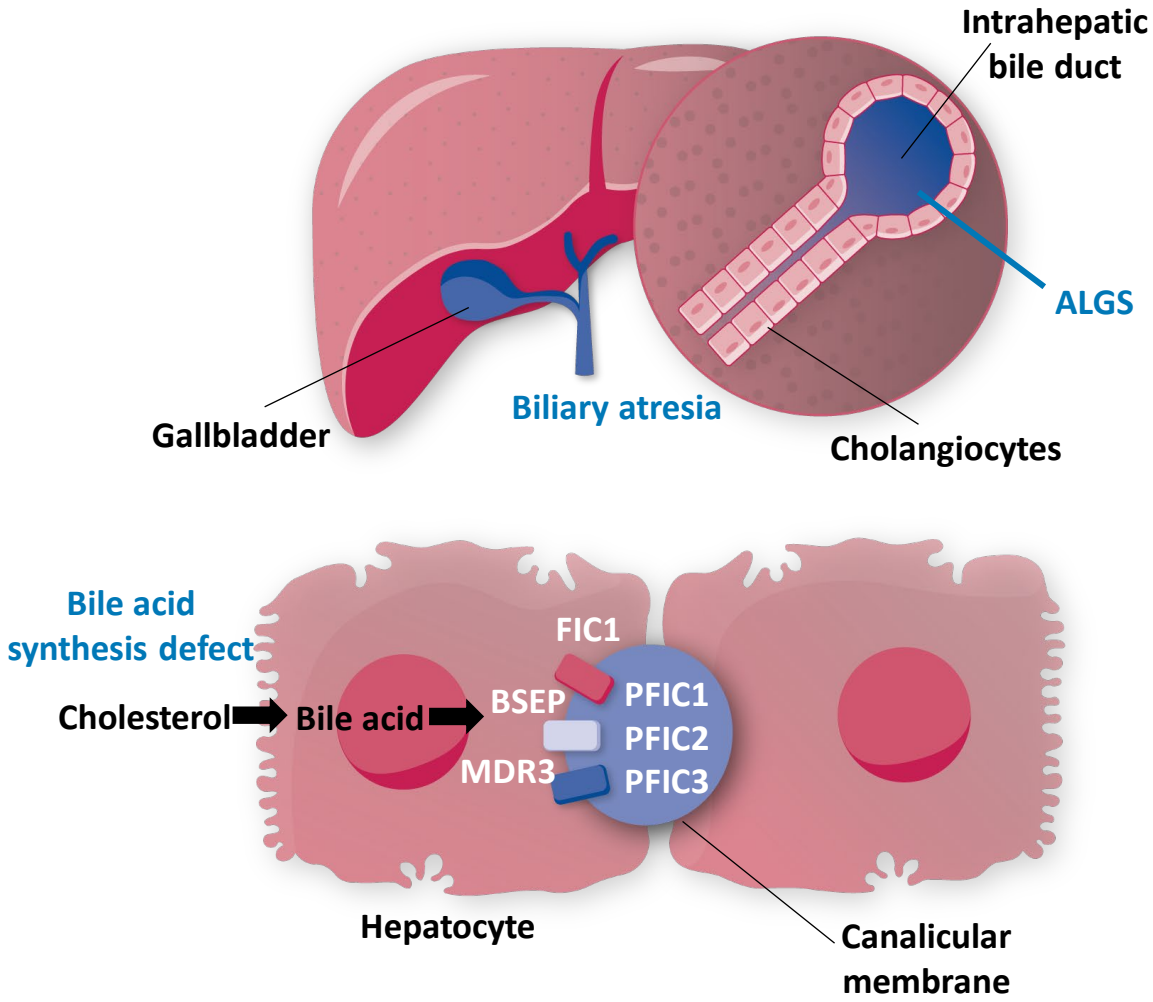
Speaker disclosures

Tamir Miloh	• T. Miloh is a consultant for, and has received speaker and/or research funding from, Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Alexion Pharmaceuticals, Inc., and Travere Therapeutics, Inc.
Noelle Ebel	• N. H. Ebel is a consultant for Mirum Pharmaceuticals, Inc.
Ryan Himes	• R. Himes is a consultant for, and has received speaker and/or research funding from, Mirum Pharmaceuticals, Inc., Albireo Pharma, Inc., Alexion Pharmaceuticals, Inc., and Travere Therapeutics, Inc.

Building new treatment paradigms in the management of pediatric cholestasis

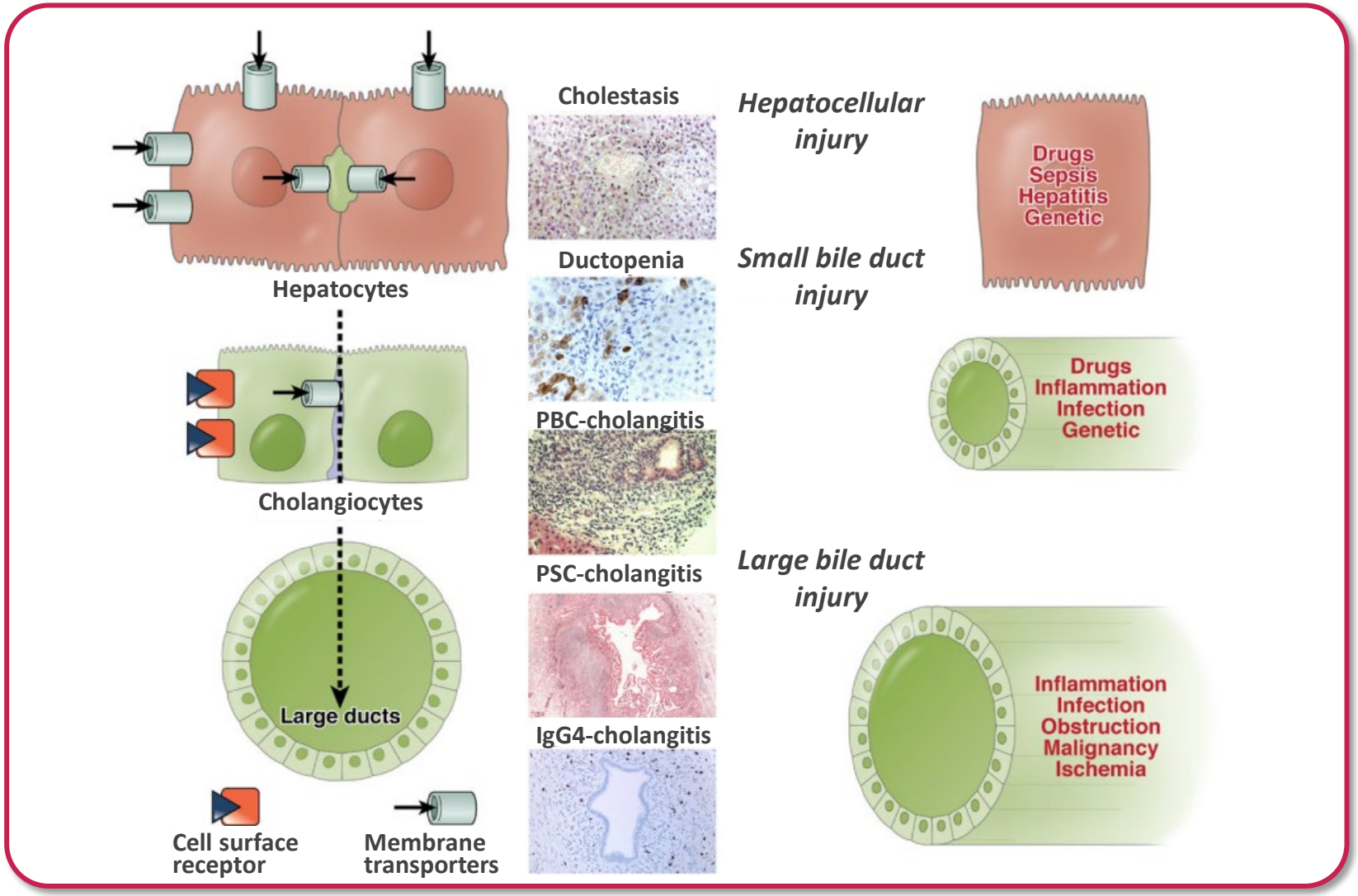
Time	Topic	Speaker
20:00–20:15	Chair’s welcome and introduction	Tamir Miloh
20:15–20:40	Constructing a new approach in the management of ALGS	Noelle Ebel
20:40–21:00	Establishing new foundations for children with PFIC	Ryan Himes
21:00–21:10	Structuring new outcomes for biliary atresia	Tamir Miloh
21:10–21:25	Panel discussion	All
21:25–21:30	Chair’s close	Tamir Miloh

In cholestatic liver diseases, clinical symptoms and serum laboratory abnormalities occur due to disruption of bile flow



A-1-AT, alpha-1 antitrypsin; BSEP, bile salt export pump; FIC1, familial intrahepatic cholestasis 1; MDR3, multidrug resistance 3. Feldman AG & Sokol RJ. *Nat Rev Gastroenterol Hepatol* 2019; **16**:346–360.

The pathology of cholestasis and its mechanisms



Reprinted from *Gastroenterology*, 139, Hirschfield GM, *et al*., 'Pathogenesis of cholestatic liver disease and therapeutic approaches', 1481–1496, Copyright (2010), with permission from Elsevier.

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

Children may experience increased risk of long-term cognitive deficits and decreased quality of life

Cognitive defects[1]

Impaired school performance[2]

Sleep disturbance and fatigue[2]

Pain[2]

Decreased physical functioning or general health[1]

Mental health/ depression[1]

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

Behavior issues[1]

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

Challenges with diagnosis

Primary symptoms include cholestasis, pruritus, and failure to thrive

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

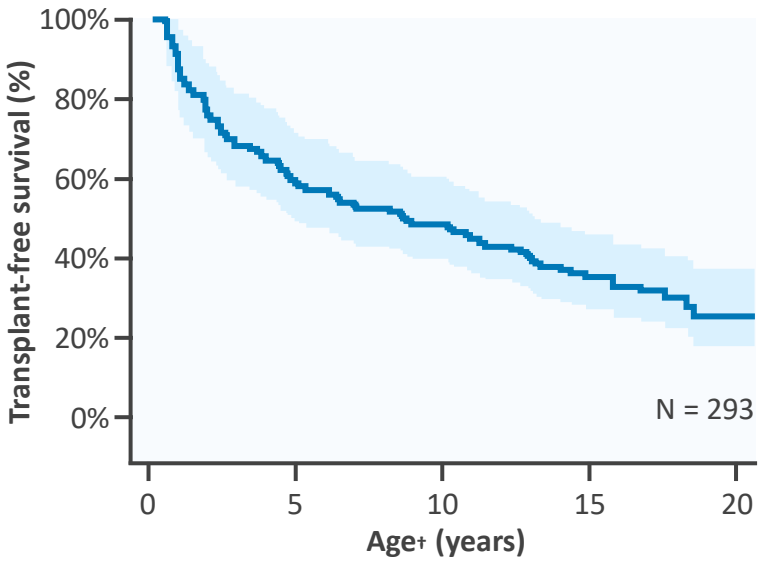
Symptoms and signs	ALGS[1]	PFIC[2]	Biliary atresia[3,4]
Pruritus	✓	✓	
Jaundice	✓	✓	✓
Failure to thrive	✓	✓	✓
Pale stools, dark urine	✓	✓	✓
Hepatomegaly	✓	✓	✓
Vitamin A, D, E, K deficiency	✓	✓	✓
Primary bone abnormalities	✓		
Distinct facial features	✓		
Primary cardiac abnormalities	✓		✓

1. NORD. Alagille syndrome. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/ Accessed November 19, 2021; 2. Children's liver disease foundation. PFIC. Available at: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis. Accessed November 19, 2021; 3. NORD. Biliary atresia. Available at: https://rarediseases.org/rare-diseases/extrahepatic-biliary-atresia/. Accessed November 19, 2021; 4. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175.

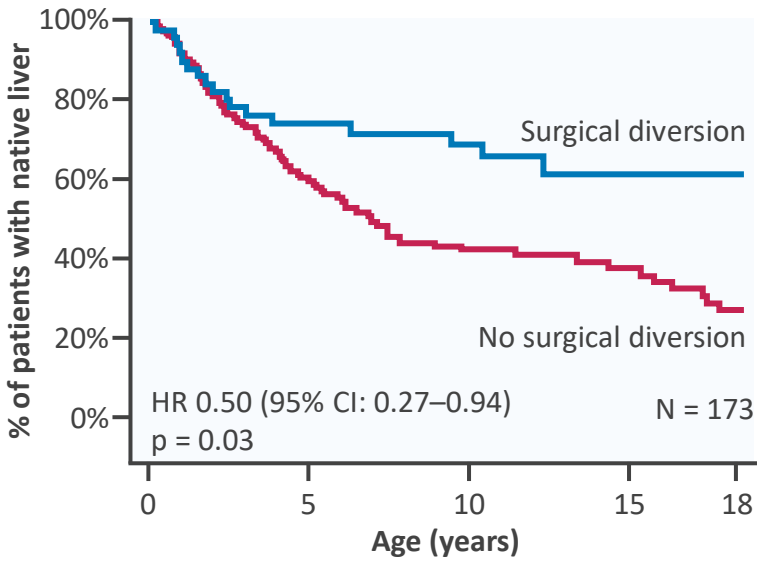
Liver transplantation is frequently required in majority of patients

ALGS[1,2]	PFIC2[3]	Biliary atresia[4,5]
24%–41%* TFS by adulthood	32% TFS at 18 years of age	23% TFS by adulthood

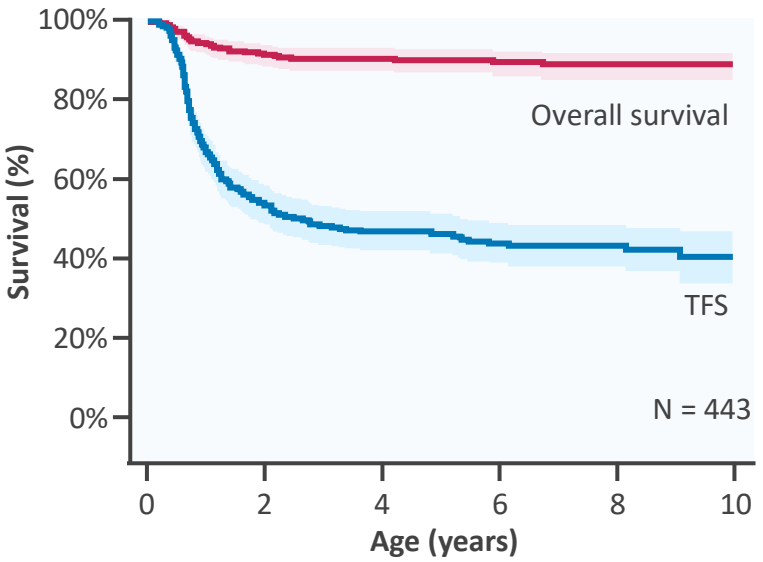
Transplant-free survival in ALGS[1]



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



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



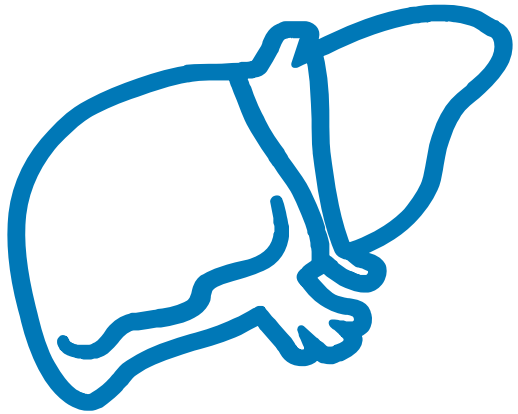
Transplant-free liver survival is poor across ALGS, PFIC, and biliary atresia

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

1. Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398; 2. Vandriel SM, *et al.* EASL 2020 (oral presentation); 3. Van Wessel DBE, *et al. J Hepatol* 2020; **73**:84–93, reprinted from *Journal of Hepatology*, 73, van Wessel DBE, *et al.*, 'Genotype correlates with the natural history of severe bile salt export pump deficiency', 84–93, Copyright (2020), with permission from Elsevier.; 4. Lakshminarayanan B & Davenport M. *J Autoimmun* 2016; **73**:1–9, reprinted from *Journal of Autoimmunity*, 73, Lakshminarayanan B & Davenport M, 'Biliary atresia: A comprehensive review', 1–9, Copyright (2016), with permission from Elsevier.; 5. Lykavieris P, *et al. Hepatology* 2005; **41:** 366–371.

Liver transplants are associated with a number of challenges

Complications of liver transplantation



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

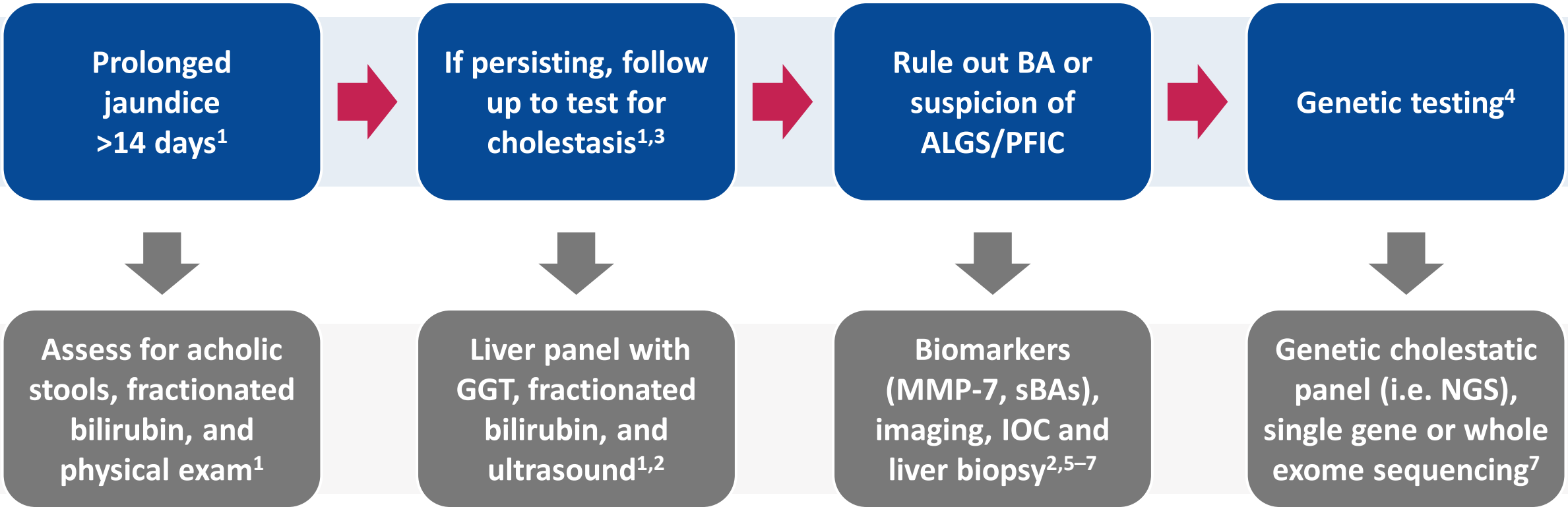
Prolonged immunosuppressive medication increases the risk of infections and malignancy, among other complications

* Between 2009–2013, overall 5-year patient survival in those having pediatric liver transplants was 88.4%.

Muiesan P, *et al. J Hepatol* 2007; **46**:340–348; Kelly DA, *et al. Liver Transpl* 2013; **19**:798–825; Miloh T, *et al. Liver Transpl* 2017; **23**:244–256; Bucuvalas JC, *et al. Liver Transpl* 2004; **10**:1011–1017; Kwong A, *et al. Am J Transplant* 2020; **20** Suppl s1:193–299.

Traditional process for evaluating neonatal cholestasis

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



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

1. Fawaz R, *et al. J Pediatr Gastroenterol Nutr* 2017; **64**:154–168; 2. Gunaydin M & Cil ATB. *Hepat Med* 2018; **10**:95–104; 3. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175; 4. Baker A, *et al. Clin Res Hepatol Gastroenterol* 2019; **43**:20–36; 5. Amer S & Hajira A. *Gastroenterology Res* 2014; **7**:39–43; 6. Goldberg A & Mack CL. *Clin Liver Dis (Hoboken)* 2020; **15**:105–109; 7. Ayoub MD & Kamath BM. *Diagnostics (Basel)* 2020; **10**:907.

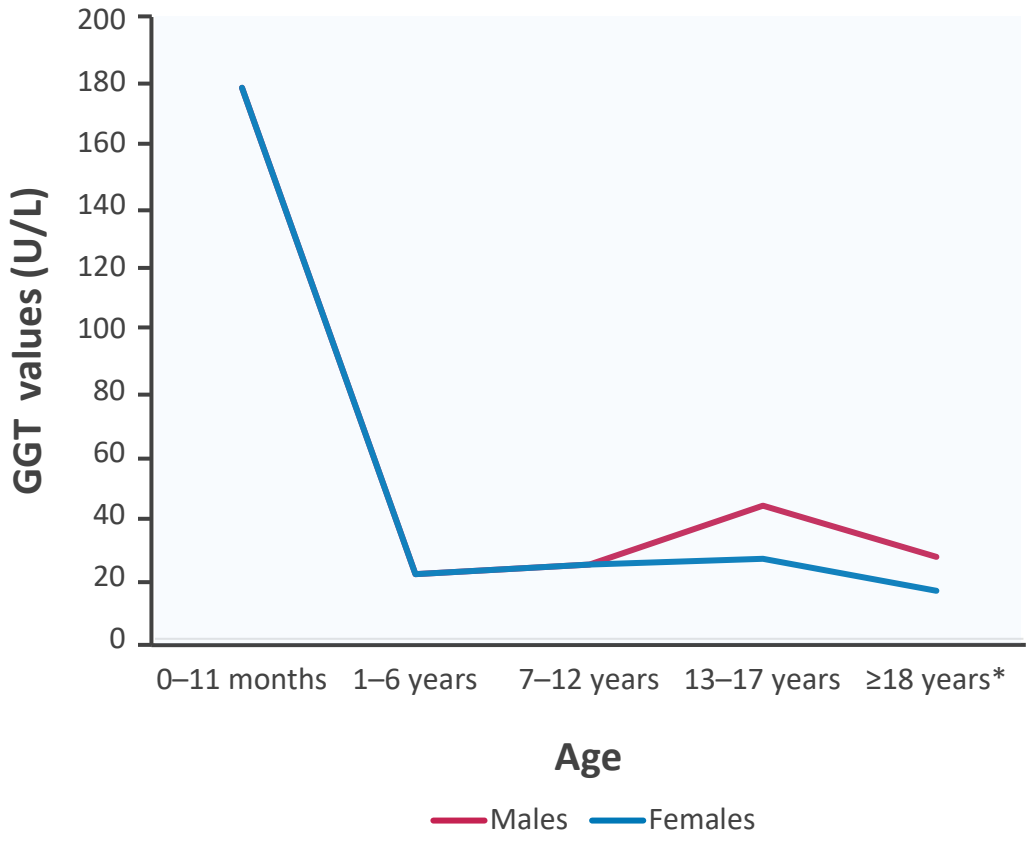
The role of GGT in diagnosis

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

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

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

Normal GGT levels in children from birth



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

Onofrio FQ & Hirschfield GM. *Clin Liver Dis (Hoboken)* 2020; **15**:110–114; Mandato C, *et al. Ital J Pediatr* 2019; **45**:83; Mayo Clinic Laboratories, Serum Gamma-Glutamyltransferase 2021. Available at: https://pediatric.testcatalog.org/show/GGT. Accessed November 19, 2021.

Genetic testing has improved the diagnosis of pediatric cholestatic liver disease

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

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

Rapid single and multigene testing are cost-effective

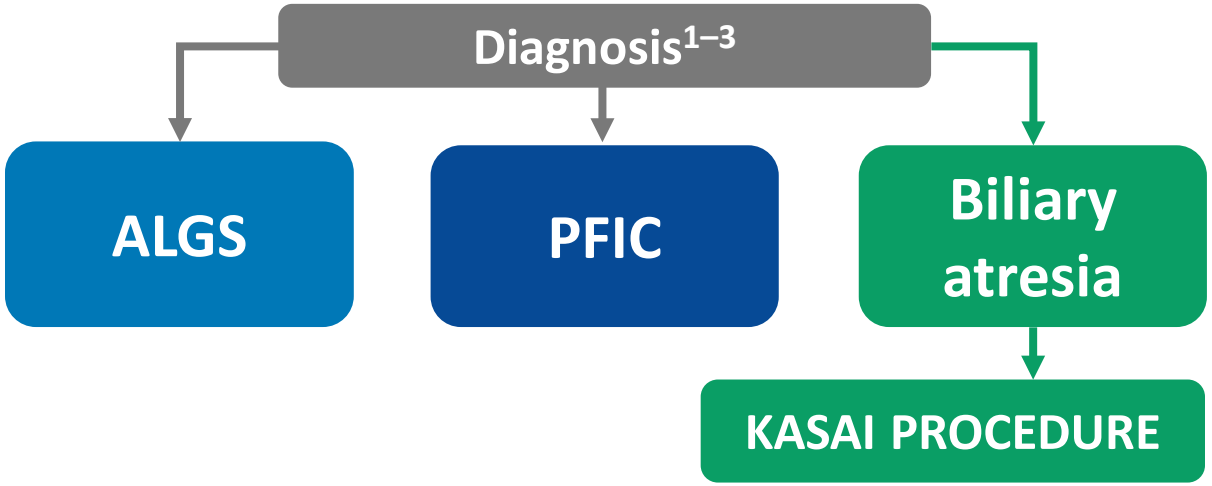
Comprehensive multigene testing is causing a re-evaluation of the role and utility of liver biopsy

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

BA, biliary atresia.

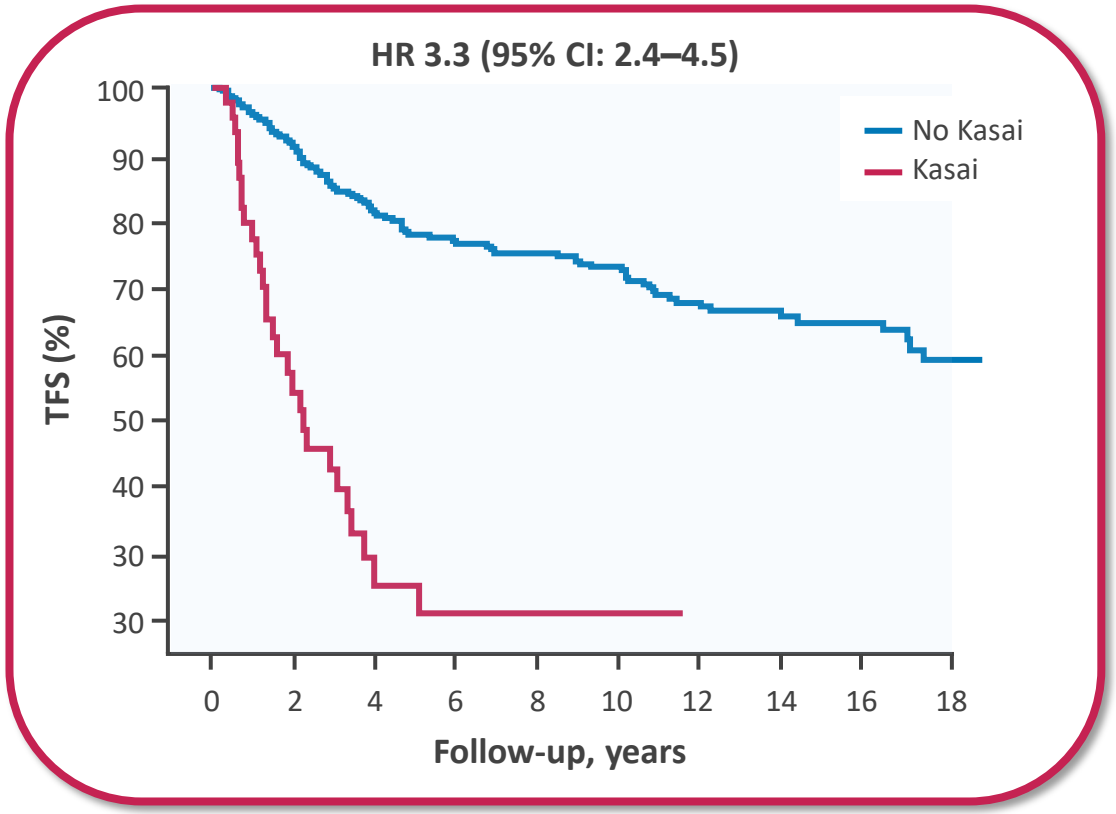
Karpen SJ, *et al. J Pediatr Gastroenterol Nutri* 2021; **72**:654–660; https://travere.com/diagnostic-testing-programs/. Accessed November 19, 2021.

Management of cholestatic liver diseases



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

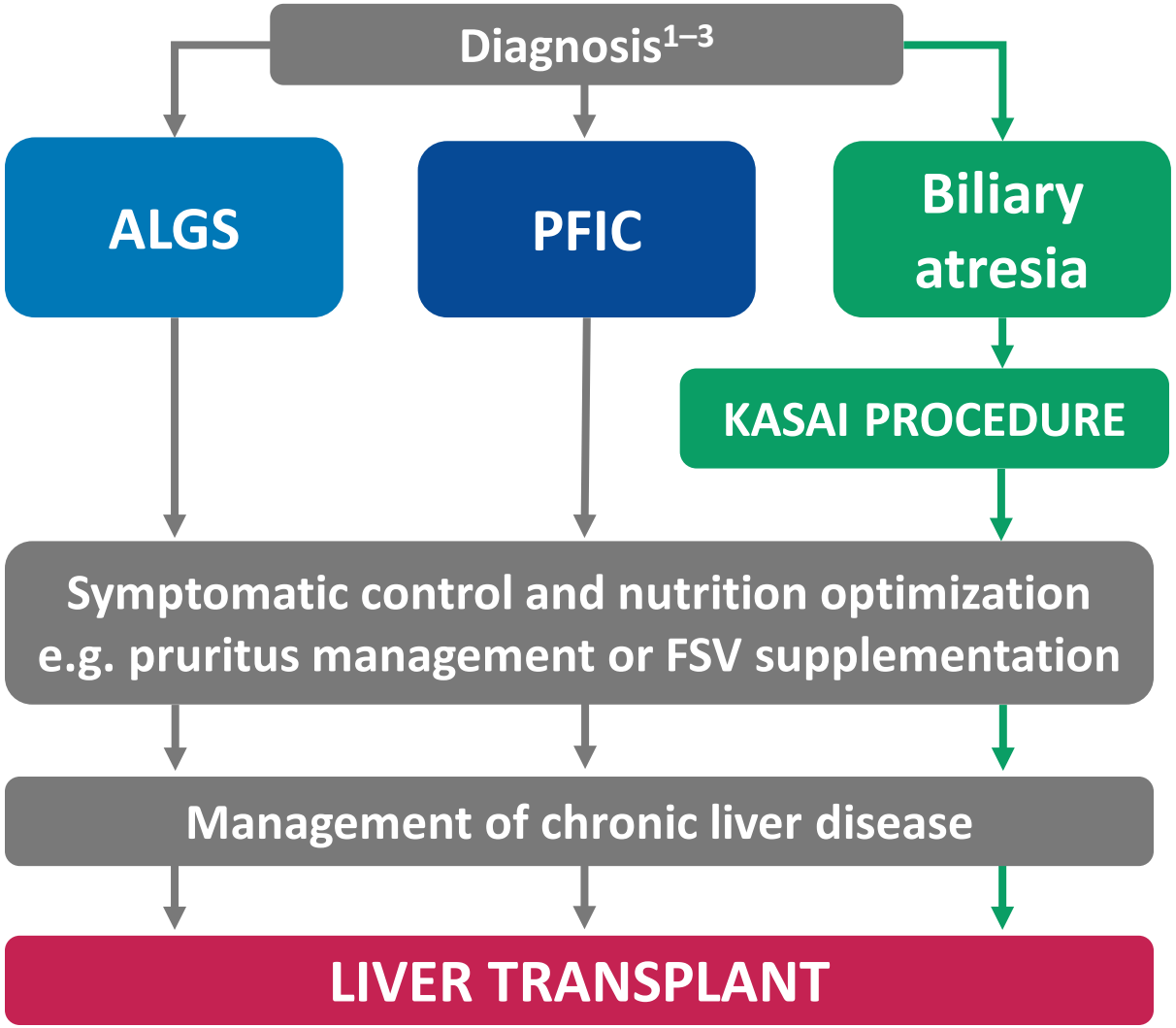
ALGS patients who underwent a Kasai (n=74) had significantly lower rates of transplant-free survival (p<0.001)[4]



CI, confidence interval; HR, hazard ratio; TFS, transplant-free survival.

1. Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398; 2. van Wessel D, *et al. J Hepatol* 2020; **73**:84–93; 3. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175;
4. Vandriel SM, *et al.* International Liver Congress (EASL) 2020 (oral presentation).

Management of cholestatic liver diseases



Few approved therapies; other medications such as anti-histamines, rifampin, naltrexone and bile acid sequestrants have modest effects

IBAT inhibitors work by pharmacologic interruption of enterohepatic circulation of bile acids

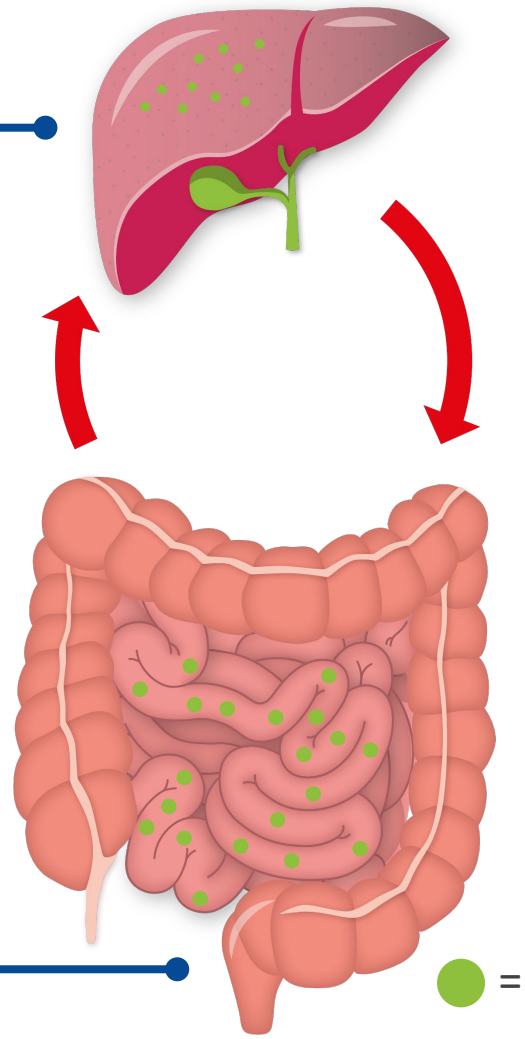
FSV, fat-soluble vitamin; IBAT, ileal bile acid transporter. 1. Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398; 2. van Wessel D, *et al. J Hepatol* 2020; **73**:84–93;
3. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175; 4. Kamath BM, *et al. J Pediatr Gastroenterol Nutr* 2010; **50:**580–586; 5. Amer S & Hajira A. *Gastroenterol Res* 2014; **7:**39–43;
6. Baker A, *et al. Clin Res Hepatol Gastroenterol* 2019; **43:**20–36; 7. Gunaydin M & Cil ATB. *Hepat Med* 2018; **10:**95–104.

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

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

Reabsorption (>95%):
- Active uptake by IBAT in the ileum
- Passive absorption in the colon[2]

Excretion via feces (~5%)



= Bile acid

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

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

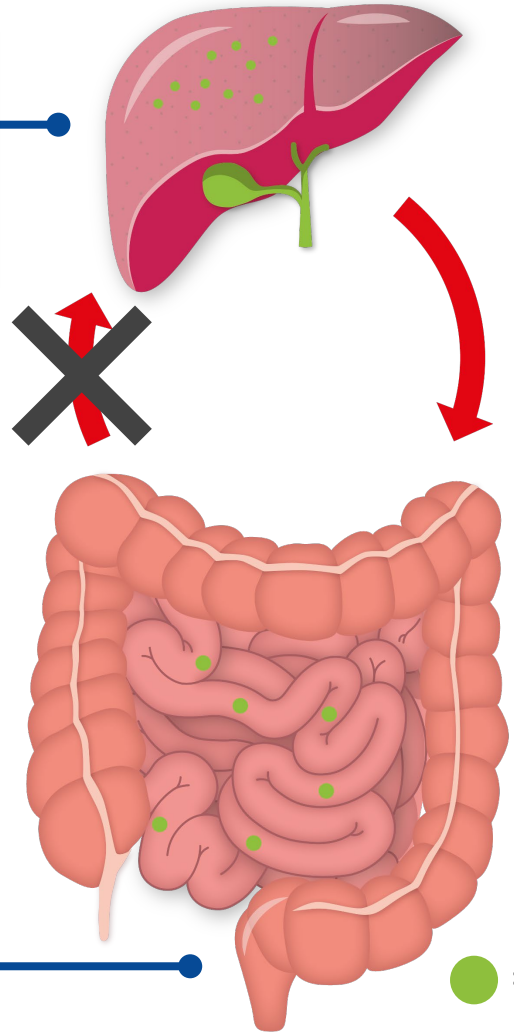
If left untreated, the liver will progress to end-stage liver disease, with most patients requiring liver transplantation[6]

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

1. Kamath BM, *et al. Liver International* 2020; **40**:1812–1822; 2. Di Ciaula A, *et al. Ann Hepatol* 2017; **16**:s4–s14; 3. Baker A, *et al. Clin Res Hepatol Gastroenterol* 2019; **43**:20–36; 4. Cai S-Y & Boyer JL. *Ann Transl Med* 2021; **9**:737; 5. Hirschfield GM, *et al. Gastroenterology* 2010; **139**:1481–1496; 6. Srivastava A. *J Clin Exp Hepatol* 2014; **4**:25–36.

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

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



Reabsorption (>95%):
- Active uptake by IBAT in the ileum
- Passive absorption in the colon[2]

Excretion via feces (~5%)

= Bile acid

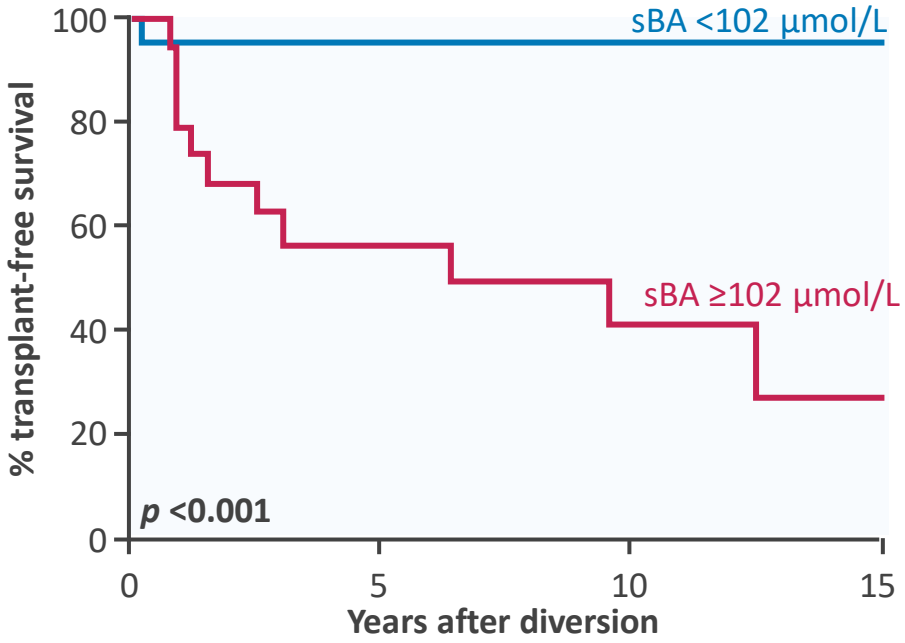
Therapeutic approaches (surgical or pharmacologic) can be taken to block recirculation of bile acids to the liver, thereby reducing the bile acid pool

IBAT, ileal bile acid transporter.

1. Kamath BM, *et al. Liver International* 2020; **40**:1812–1822; 2. Di Ciaula A, *et al. Ann Hepatol* 2017; **16**:s4–s14.

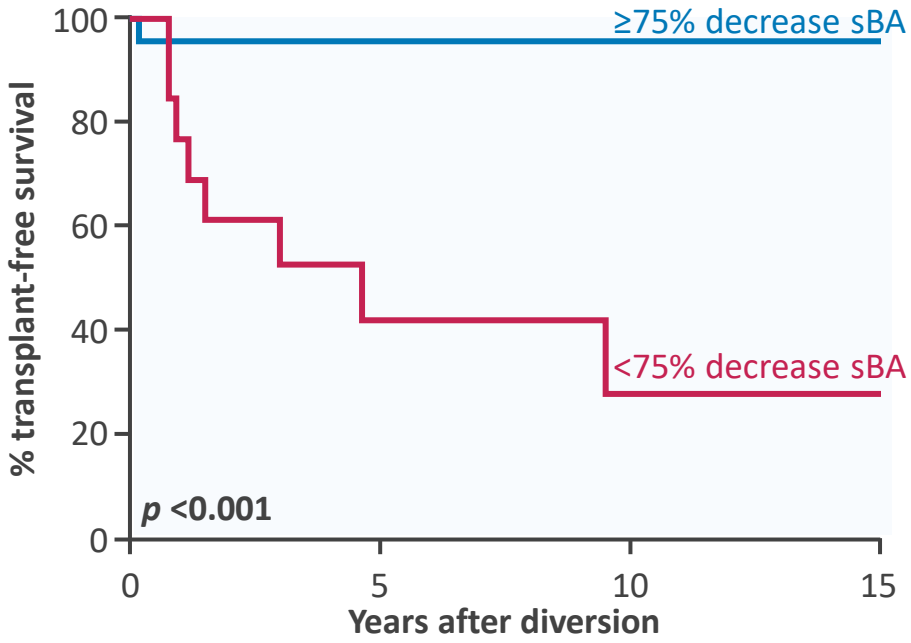
In PFIC2, sBA control after surgical biliary diversion is associated with transplant-free survival

Patients who reached NAPPED threshold based on sBA levels



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

Patients who reached NAPPED threshold based on relative sBA reduction

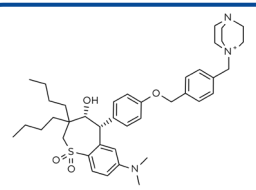


No. at risk				
<75% decrease sBA	14	4	2	1
≥75% decrease sBA	24	21	14	8

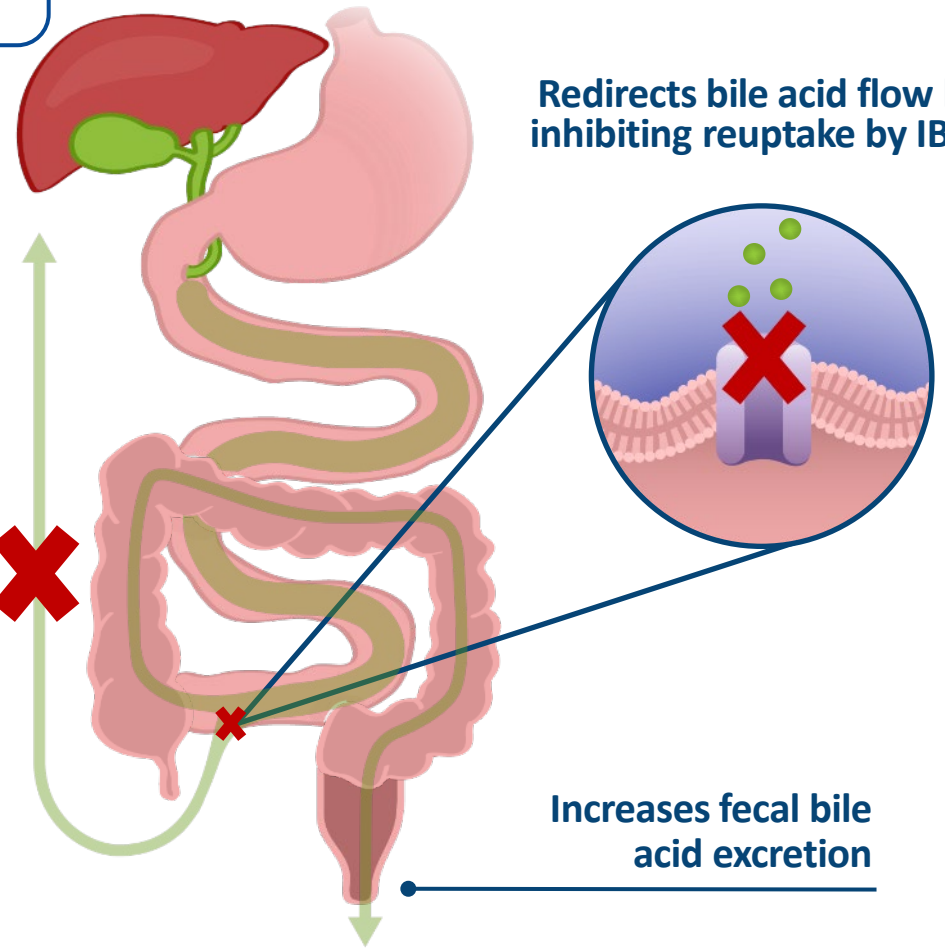
Serum bile acids are a surrogate marker for long-term outcome

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

IBAT inhibitors: Pharmacologic inhibition of bile acid recirculation



IBAT inhibitor is administered

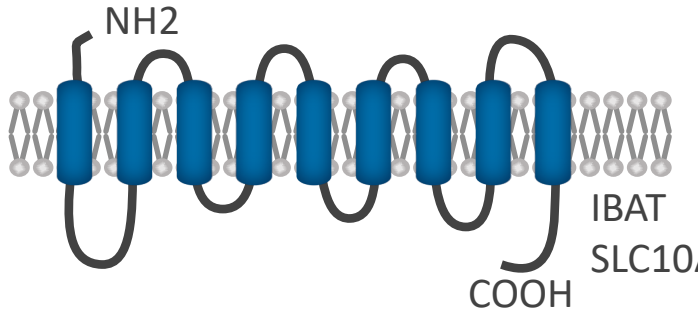


Redirects bile acid flow by inhibiting reuptake by IBAT

Interrupts recirculation of bile acids to the liver

Increases fecal bile acid excretion

Structure of IBAT



Clinical effects of IBATi in cholestasis:

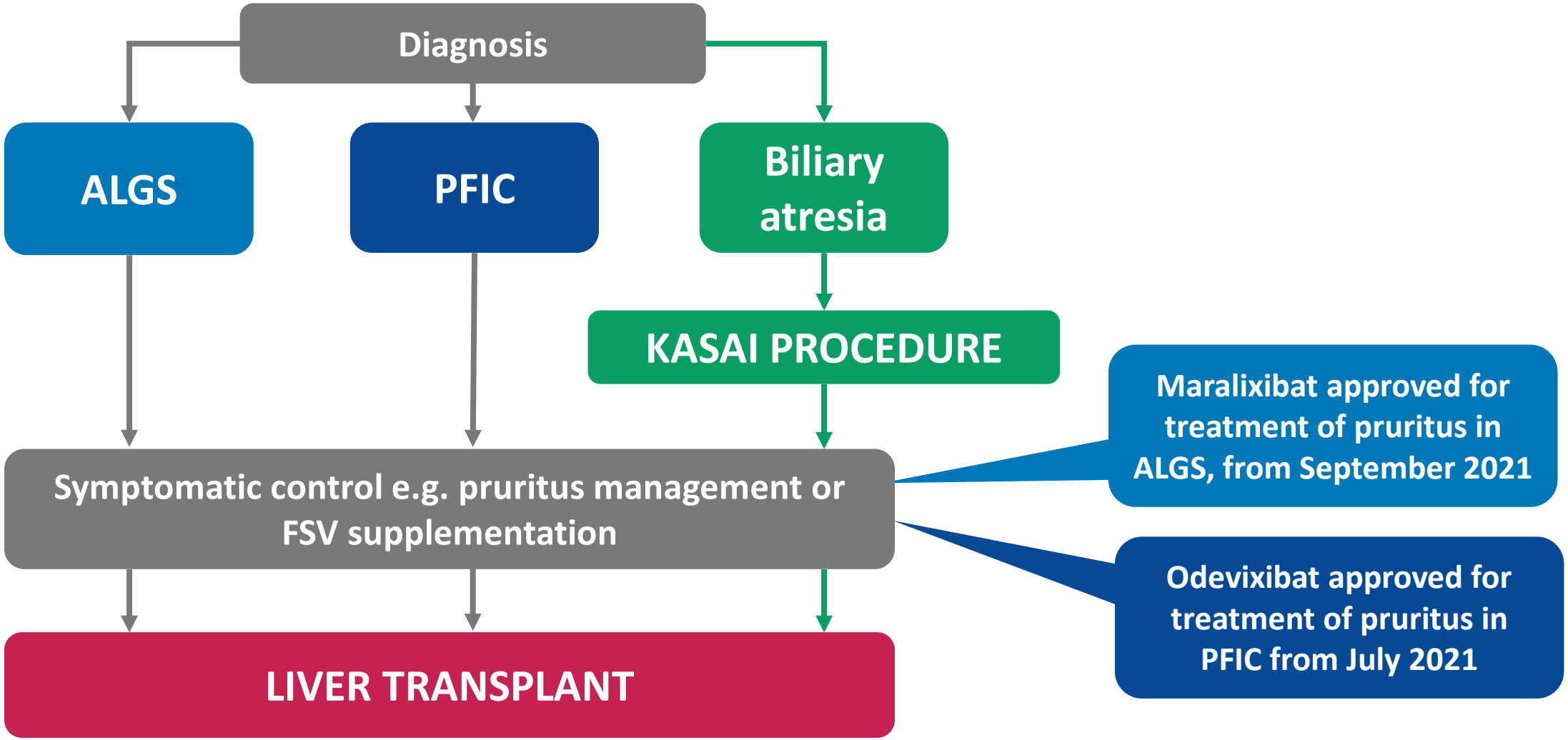
- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved transplant-free survival

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

Gonzales E, *et al. Lancet* 2021; **398**:1581–1592; Tiessen RG *et al. BMC Gastroenterology* 2018; **18**:3.

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

Management of cholestatic liver diseases today: How will we use IBAT inhibitors in clinical practice?



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

Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398; van Wessel D, *et al. J Hepatol* 2020; **73**:84–93; Feldman AG & Mack CL *J Pediatr Gastroenterol Nutr* 2015; **61**: 167–175; Albireo Pharma, Inc. Bylvay™ (odevixibat). Prescribing Information. 2021. Accessed online at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215498s000lbl.pdf on November 15, 2021; Mirum Pharmaceuticals Inc. LIVMARLI™ (maralixibat) Prescribing Information. 2021. Accessed online at https://files.mirumpharma.com/livmarli/livmarli-prescribinginformation.pdf on November 19, 2021.

Constructing a new approach in the management of ALGS

Noelle Ebel, M.D.

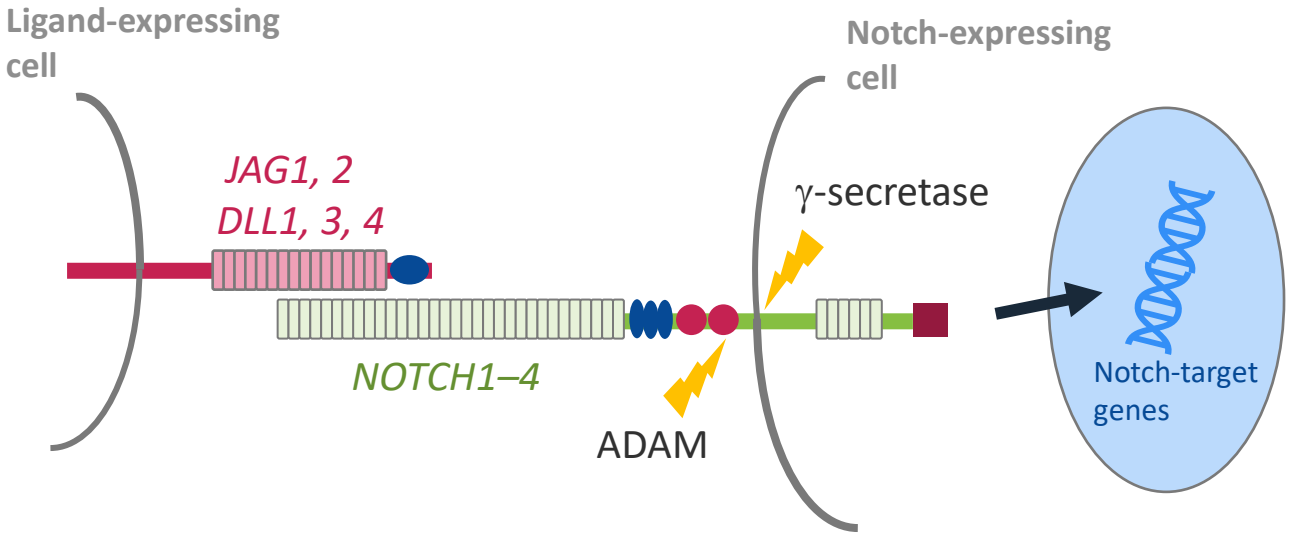
Clinical Assistant Professor
Pediatric Transplant Hepatology
Director of the Alagille Syndrome Program, Stanford University, USA

ALGS is a rare autosomal dominant disorder

Mutations in *JAG1* (89–94%)

Mutations in *NOTCH2* (2–4%)

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



Genetic testing is often required to confirm a diagnosis of ALGS

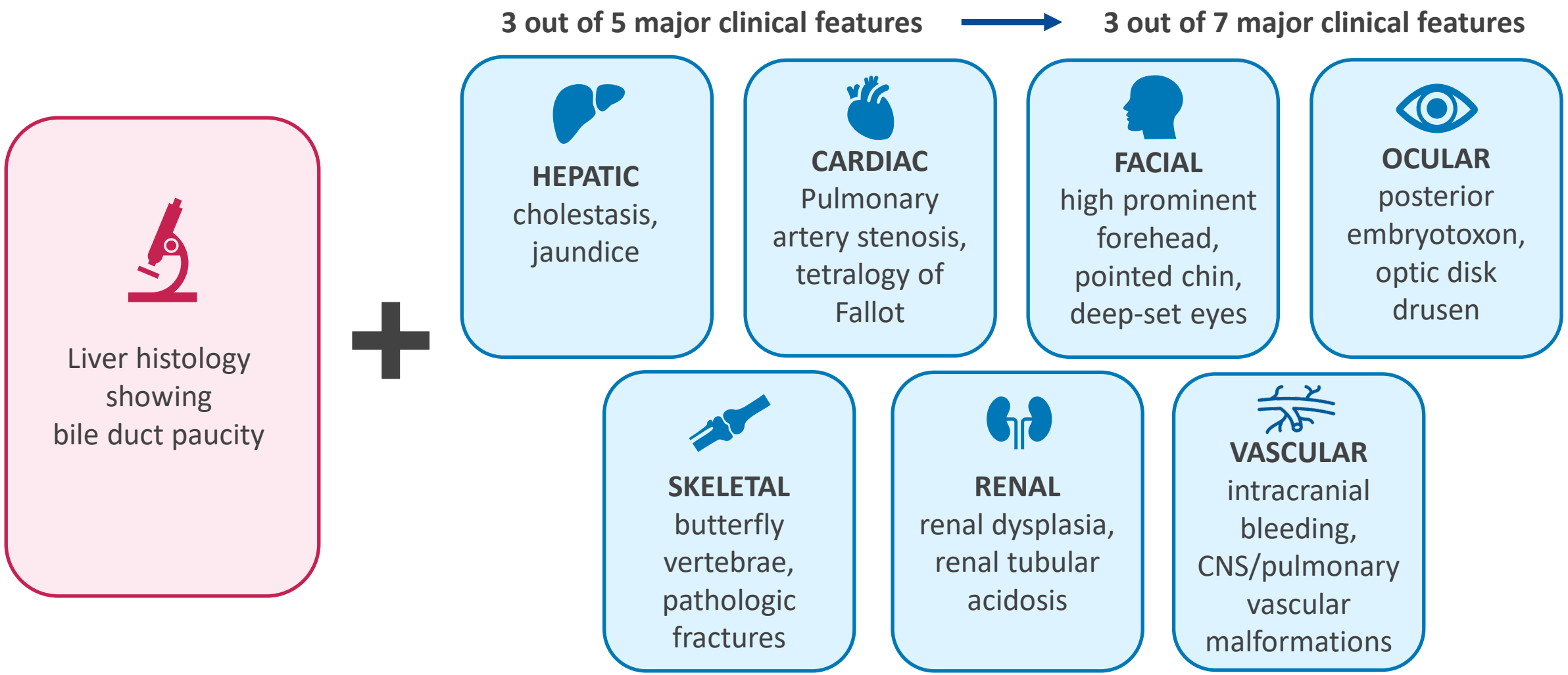
Masek J & Andersson ER. *Development* 2017; **144**:1743–1763; Kamath BM, *et al. J Pediatr Gastroenterol Nutr* 2018; **67**:148–156; Kamath BM, *et al. Hepatol Comms* 2020; **4**:387–398.

ALGS is classified as a rare disease

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

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

ALGS genotype displays a variable phenotype

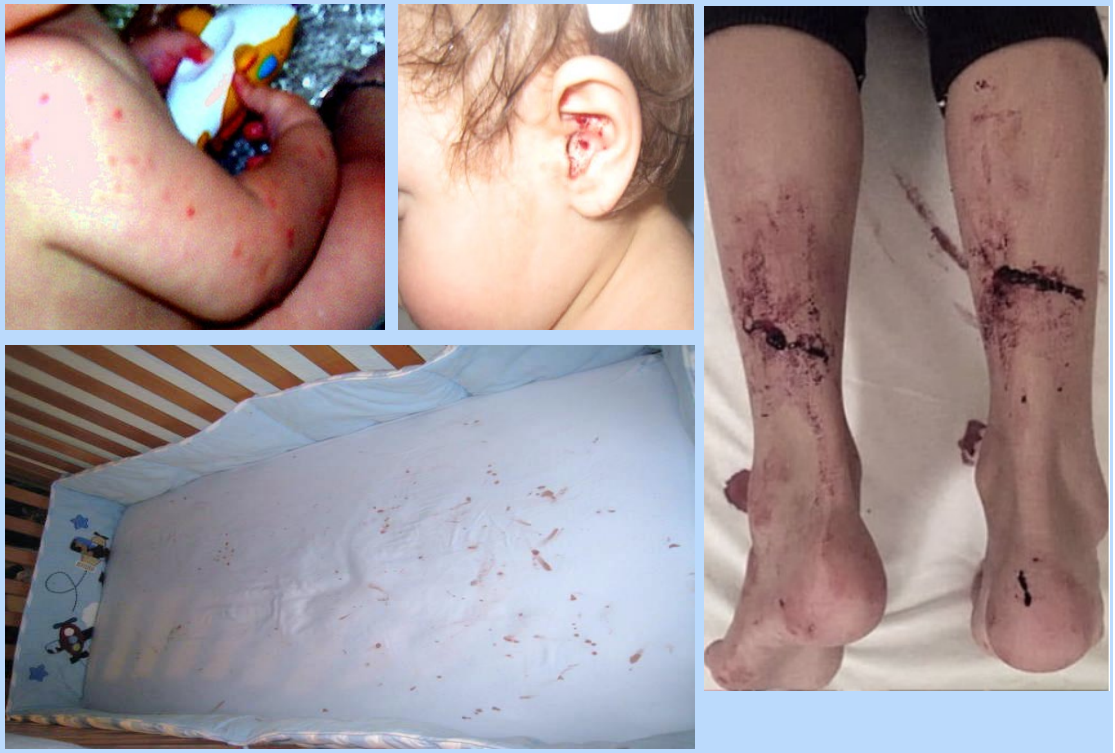


CNS, central nervous system.

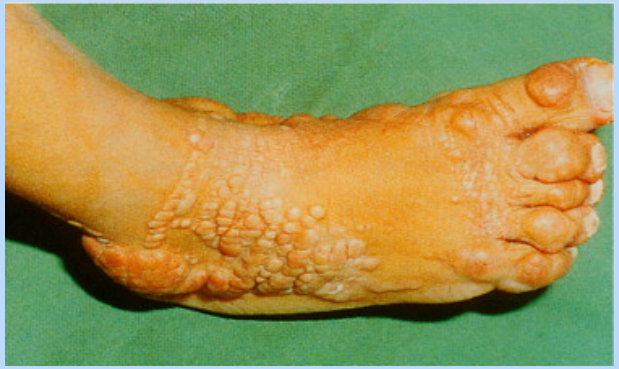
Ayoub MD & Kamath BM. *Diagnostics (Basel)* 2020; **10**:907.

Cholestatic clinical manifestations of ALGS may be severe and debilitating

PRURITUS



XANTHOMAS



Images sourced from Mirum Pharmaceuticals.
Saleh M, *et al. Appl Clin Genet* 2016; **9**:75–82.

Case study: A classical presentation of ALGS

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

Initial presentation:

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

Medical history: No relevant medical conditions

Physical examination (at 7 months):

- Cardiac murmur
- Referred to a cardiologist

Case study: A classical presentation of ALGS

Laboratory parameters (at 7 months):

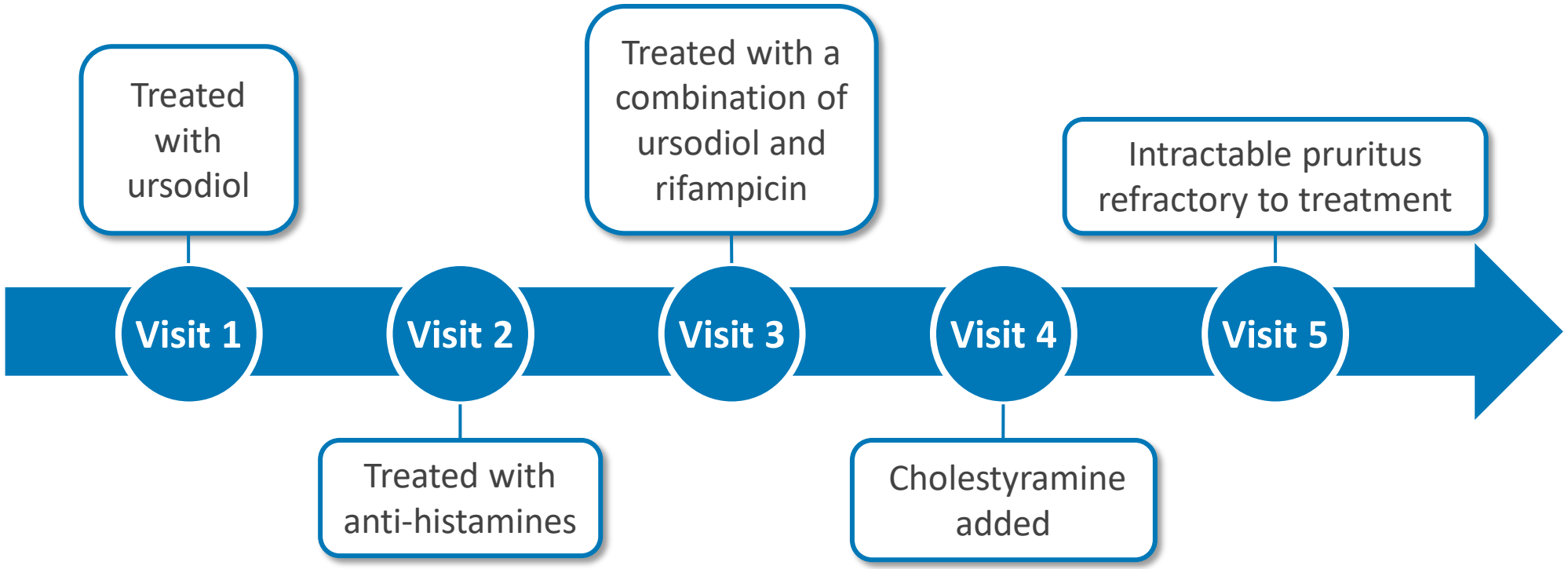
- ALT: 225 U/L
- GGT: 100 U/L
- Total bilirubin: 2.7 mg/dL
- Direct bilirubin: 1.9 mg/dL
- sBAs: 187 µmol/L
- Vitamin D: <5 ng/mL

Diagnosis

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

ALT, alanine transaminase; GGT, gamma-glutamyltransferase; sBA, serum bile acid.

Case study: A classical presentation of ALGS

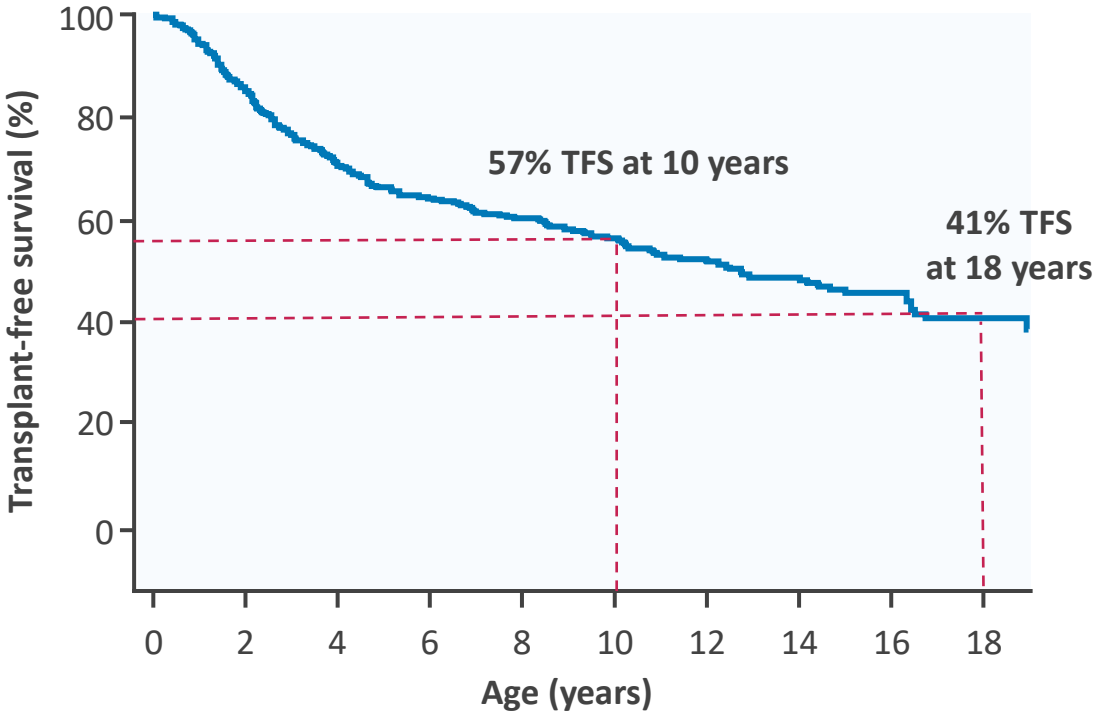


Treatment

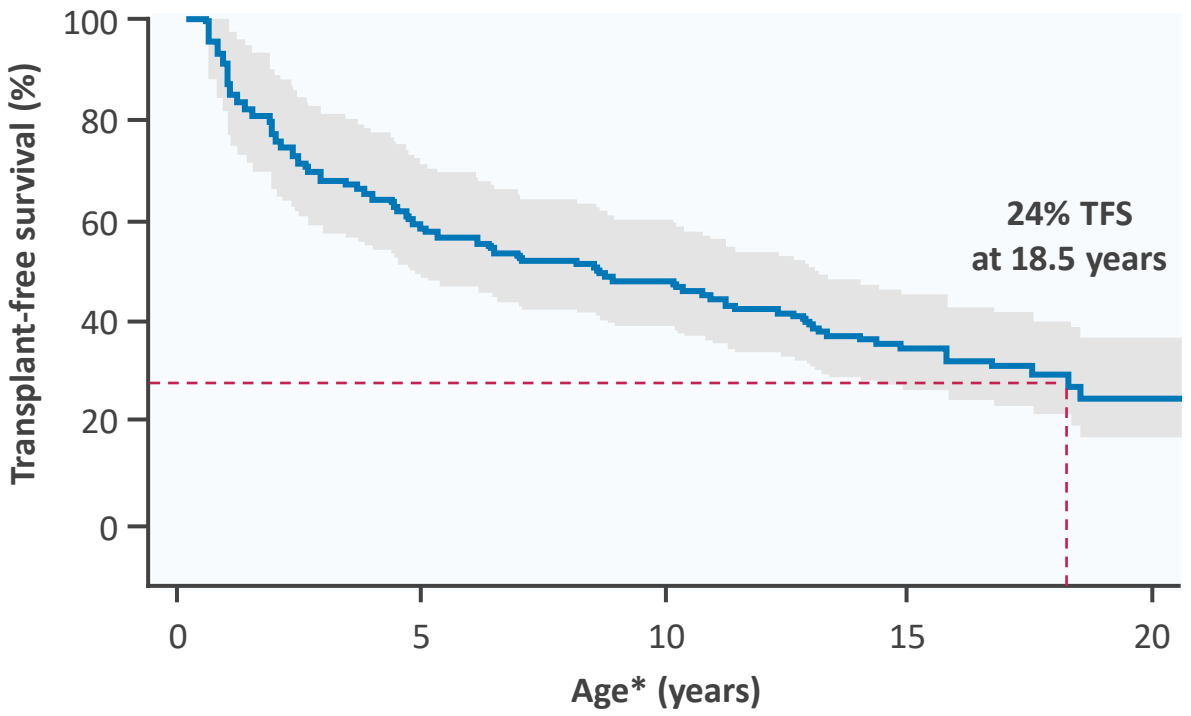
- Repeat visits to control intractable pruritus
- Pruritus remains refractory to treatment; patient is put on the liver transplant waiting list

Substantial risk for liver transplant in patients with ALGS

GALA[1] (Global)
Transplant-free survival in patients with ALGS presenting with neonatal cholestasis (N = 911)



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



No. at risk	46	67	64	35	11

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

Balancing the scales: Consideration for liver transplant in ALGS?

Benefits of transplant[1–4]

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

Risks of transplant[5,6]

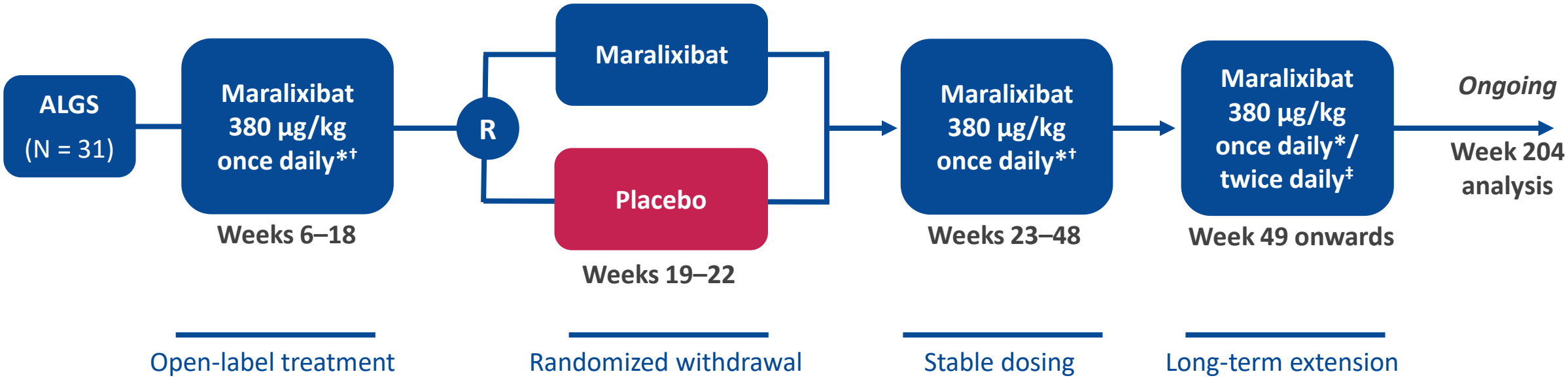
- Post-transplant renal and cardiovascular complications
- Other post-transplant complications: biliary and vascular complications, rejection, infection, life-long immunosuppression
- Graft failure, mortality

1. Lee C-N, *et al. Pediatr Neonatol* 2014; **55:** 135–138; 2. Lykavieris P, *et al. Gut* 2001; **49:** 431–435; 3. Loomes KM, *et al. Hepatology* 2019; **69:** 245–257; 4. Guthery SL, *et al. Liver Transpl* 2003; **9:** 365–370; 5. Muiesan P, *et al. J Hepatol* 2007; **46**:340–348; 6. Bonou M, *et al. Diagnostics (Basel)* 2021; **11:** 75.

Clinical trials in ALGS

ICONIC

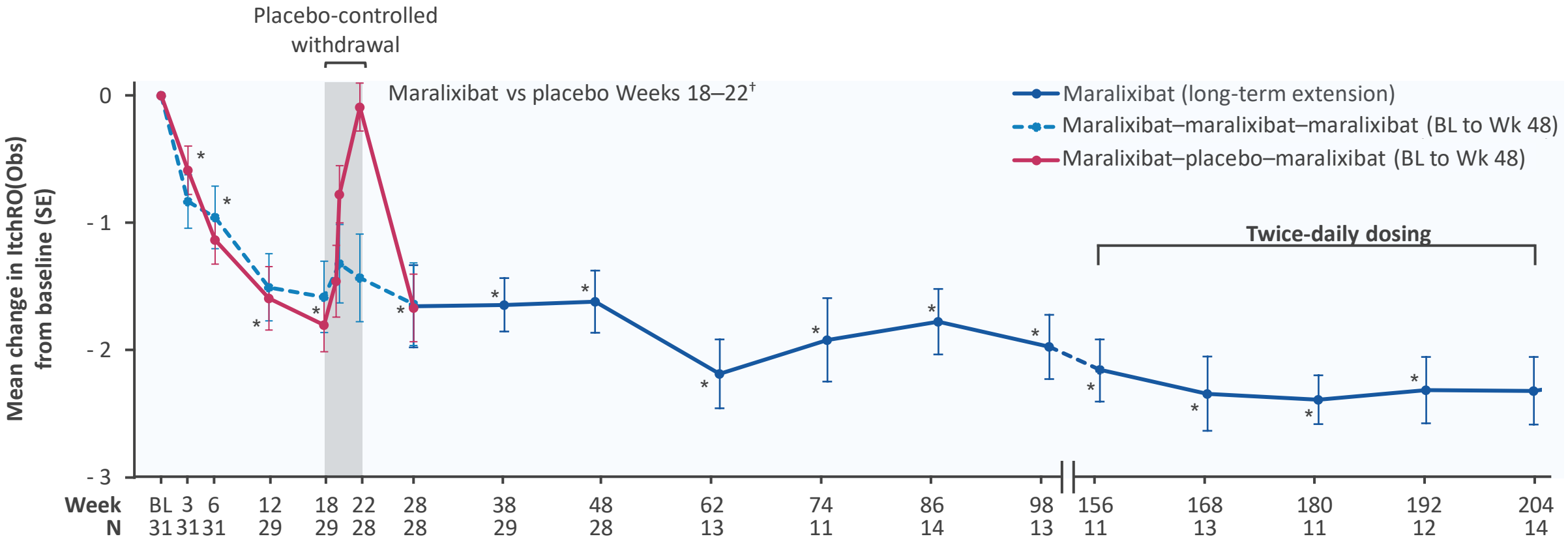
ICONIC (LUM001-304): Phase 2 study of maralixibat in ALGS



Primary endpoint	Secondary endpoints
• Mean change in fasting sBA levels from Weeks 18–22 (and mean change in those who previously responded to maralixibat)	• Change in fasting sBA levels from baseline to Week 18 • Change in pruritus (ItchRO[Obs] and [Pt]) from baseline to Week 18 and from Weeks 18–22 • Change in ALP and ALT from baseline to Week 18 and from Weeks 18–22 • Change in total and direct bilirubin from baseline to Week 18 and from Weeks 18–22

* Equivalent to maralixibat chloride 400 µg/kg; † Includes a 6-week dose-escalation period for participants who received placebo during the randomized withdrawal phase; dosing for maralixibat vs maralixibat chloride.
‡ Twice daily dosing (started after Week 100) was equivalent to maralixibat chloride 800 µg/kg.
ALP, alkaline phosphatase; ALT, alanine transaminase; ItchRO(Obs), Itch-Reported Outcome (Observer); QoL, quality of life; R, randomized; sBA, serum bile acid.
ClinicalTrials.gov. ID: NCT02160782. Accessed online at https://clinicaltrials.gov/ct2/show/NCT02160782 on November 17, 2021; Gonzales E, *et al. Lancet* 2021; **398:** 1581–1592.

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



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

Changes in pruritus from baseline to Week 204 (ItchRO[Obs]), and during the RWD (prespecified pruritus endpoint; N = 29). Proportions of CSS scores at baseline, Week 18, Week 48 and Week 204 (N = 28 at Week 48).
* 95% CI excludes zero (compared with BL, overall population).†The MRX–PBO–MRX treatment group (n = 16) received PBO during the RWD, whereas the MRX–MRX–MRX treatment group (n = 13) continued to receive MRX.
Dashed lines represent data not shown between Week 98 to Week 156. Numbers represent the numbers of participants reporting each CSS score. Asterisks represents paired t-tests comparing the change from BL (testing if the change was equal to 0 or not). Twelve participants went to BID dosing on the basis of raised sBA in the OLE.
BID, twice daily; BL, baseline; CI, confidence interval; CSS, Clinician Scratch Scale; MRX, maralixibat; OLE, open-label extension; PBO, placebo; RWD, randomized withdrawal period; sBA, serum bile acid; SE, standard error.
Gonzales E, *et al. Lancet* 2021; **398:**1581–1592. Reprinted from The Lancet, 398, Gonzales E, *et al.*, 'Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study', 1581–1592, Copyright (2021), with permission from Elsevier.

Correlation shown between pruritus and multiple parameters following maralixibat treatment

Serum bile acid reduction, %	50	60	70	80	90
Change in ItchRO score, points	–1.86	–2.12	–2.31	–2.79	–2.71

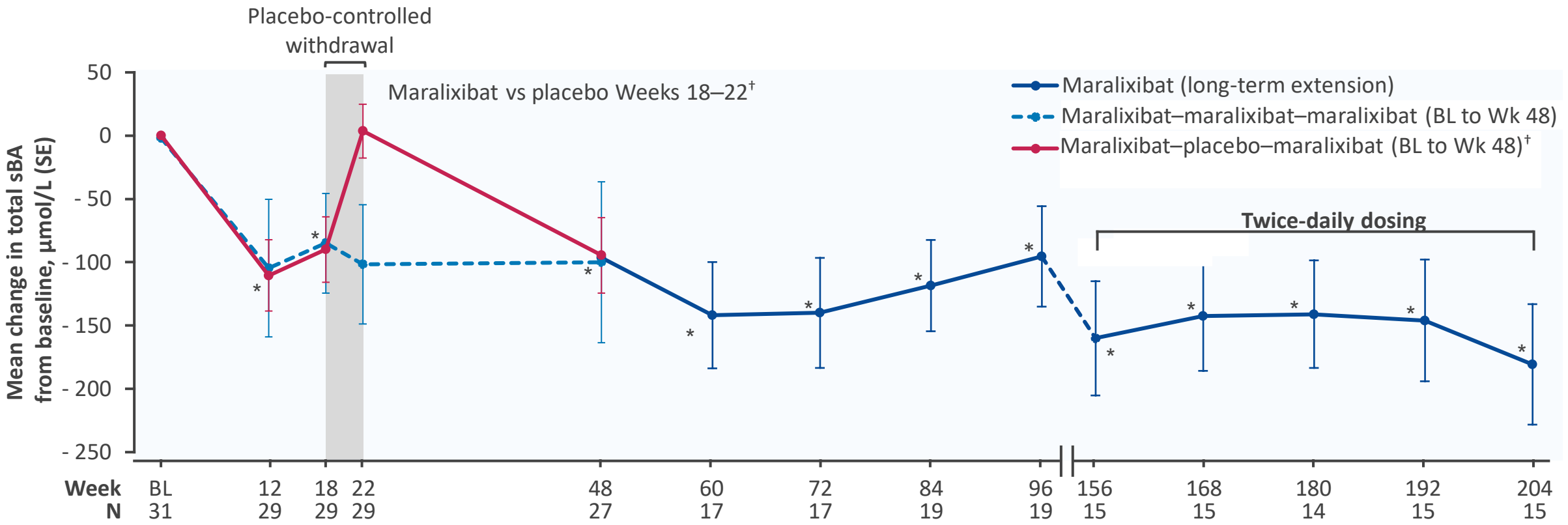
Parameters correlated with ItchRO(Obs) score at Week 48	*r*	p-value
Clinician Scratch Scale	0.65	0.0002
Serum bile acids	0.47	0.0123
PedsQL™ Impact	–0.38	0.0574
Parameters correlated with ItchRO(Obs) score as a change from baseline to Week 48		
PedsQL™ Fatigue	–0.59	0.0053

Serum bile acid reductions correlated with reductions in pruritus intensity

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

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

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



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

Changes in sBA from BL to Week 204 across all participants (A) and during the RWD in the primary endpoint responder analysis (B; n = 15). (A) Dashed line represents data not shown between weeks 96 and 156.
(B) Of the 15 participants assessed as part of the primary endpoint analysis (participants who had reductions in sBA of ≥50% from BL to Weeks 12 or 18), the PBO group (n=10) received PBO during the RWD whereas the MRX treatment group (n=5) continued to receive MRX. Twelve participants went to BID dosing on the basis of raised sBA in the OLE.
* 95% confidence interval excludes zero (compared with BL, overall population; MRX–MRX–MRX treatment group versus MRX–PBO–MRX treatment group). †The MRX–PBO–MRX treatment group (n = 16) received PBO during the RWD, whereas the MRX–MRX–MRX treatment group (n = 13) continued to receive MRX. BID, twice daily; BL, baseline; CI, confidence interval; MRX, maralixibat; OLE, open-label extension; PBO, placebo; RWD, randomized withdrawal period; sBA, serum bile acid; SE, standard error. Gonzales E, *et al. Lancet* 2021; **398**:1581–1592. Reprinted from The Lancet, 398, Gonzales E, *et al.*, 'Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study', 1581–1592, Copyright (2021), with permission from Elsevier.

Maralixibat treatment was generally well tolerated

n (%)	Open-label period (BL to Week 18) MRX (N = 31)	Randomized RWD (Weeks 19–22) MRX (n = 13)	Randomized RWD (Weeks 19–22) PBO (n = 16)	Stable-dosing period (Weeks 23–48) MRX (N = 29)	Long-term extension (Weeks 48–204) MRX (N = 23)
Participants with ≥1 TEAE	30 (97)	7 (54)	12 (75)	25 (86)	23 (100)
TEAEs potentially related to study drug*	12 (39)	1 (8)	3 (19)	1 (3)	8 (35)
TEAEs leading to study drug discontinuation†	2 (7)	0 (0)	0 (0)	1 (3)	2 (9)
Gastrointestinal disorders	22 (71)	2 (15)	3 (19)	14 (48)	16 (70)
Abdominal pain	12 (39)	1 (8)	1 (6)	6 (21)	12 (52)
Diarrhea	13 (42)	1 (8)	1 (6)	5 (17)	7 (30)
Vomiting	11 (36)	1 (8)	1 (6)	3 (10)	8 (35)
SAEs	4 (13)	1 (8)	1 (6)	5 (17)	6 (26)
SAEs potentially related to study drug*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Diarrhea and abdominal pain were the most frequent AEs and occurred with a similar incidence between the MRX and PBO groups during the randomized withdrawal period

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

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

Gonzales E, *et al. Lancet* 2021; **398**:1581–1592 (Supplemental).

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

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

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

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

ICONIC: Gastrointestinal tolerability with maralixibat versus placebo

Patients experiencing an adverse event, n (%)	Maralixibat (N = 39)		Placebo (N = 18)	
	Diarrhea*	Abdominal pain*	Diarrhea*	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 diarrhea were similar between maralixibat and placebo, with a slight difference in abdominal pain

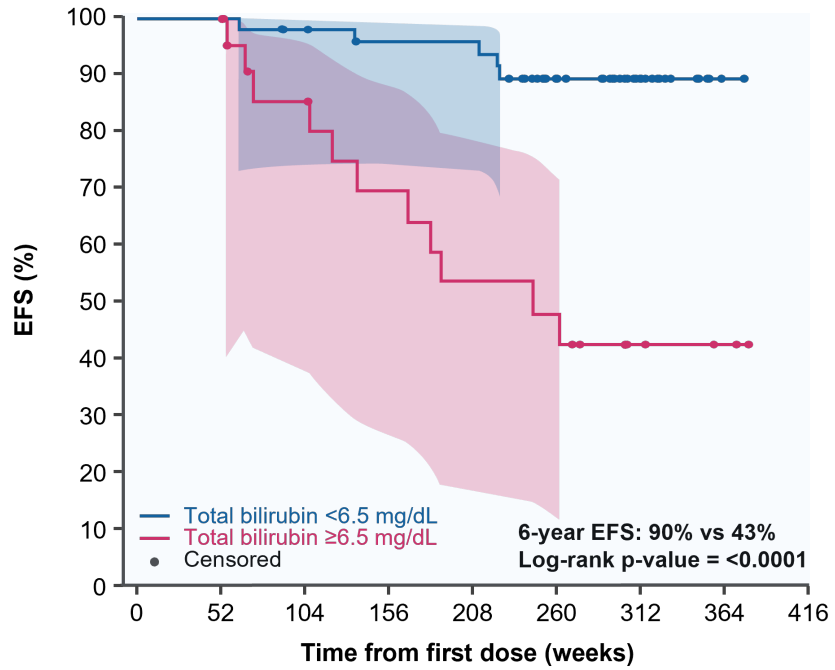
* Includes multiple adverse event terms.
AE, adverse event; GI, gastrointestinal.
Kamath BM. WCPGHAN 2021. Poster presentation (H-ePwP-030).

Predictors of 6-year event-free survival (EFS) in patients with ALGS treated with maralixibat

Event-free survival with maralixibat treatment according to total bilirubin and sBA

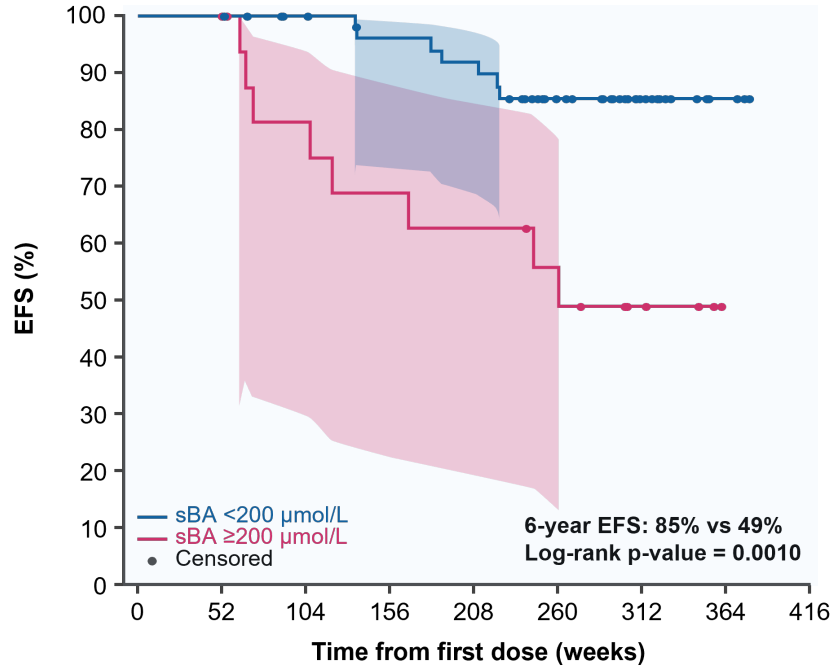
Kaplan–Meier plots of EFS

Week 48 total bilirubin (mg/dL)



Total bilirubin <6.5 mg/dL	52	52	48	45	45	32	14	1	0
Total bilirubin ≥6.5 mg/dL	24	24	17	13	10	9	4	2	0

Week 48 sBA (µmol/L)



sBA <200 µmol/L	56	56	51	46	44	32	14	3	0
sBA ≥200 µmol/L	18	18	13	11	10	8	4	0	0

Week 48 total bilirubin and sBA levels are predictive of EFS

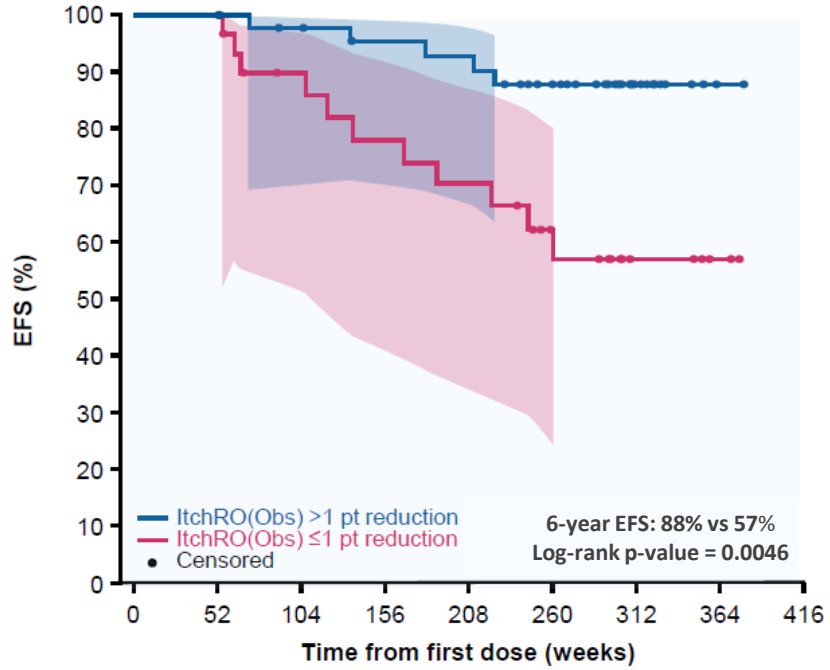
Data values under each panel indicate the number of patients at each time point. Analysis examined predictors of long-term EFS, including TFS, in patients with ALGS enrolled in 3 clinical trials of maralixibat,[1–3] with up to 6 years of follow-up; included patients who were on maralixibat 48 weeks from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

EFS, event-free survival; sBA, serum bile acid; 1. ClinicalTrials.gov ID: NCT02047318. 2. ClinicalTrials.gov ID: NCT02160782. 3. ClinicalTrials.gov ID: NCT02117713. All accessed online at: https://clinicaltrials.gov/ on October 21, 2021; 4. Sokol RJ, *et al.* Poster presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

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

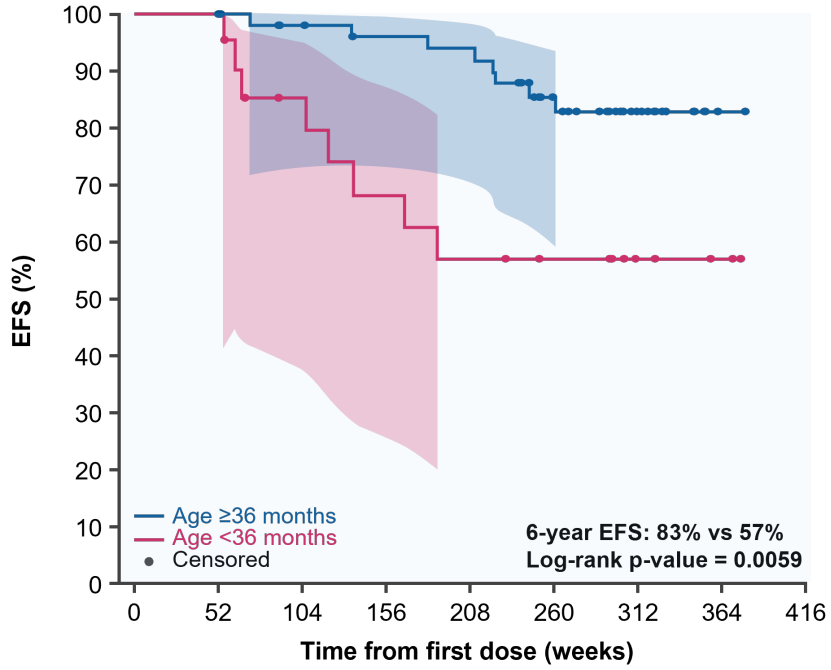
Kaplan–Meier plots of EFS

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



ItchRO(Obs) >1 pt reduction	46	46	42	38	37	29	13	1	0
ItchRO(Obs) ≤1 pt reduction	30	30	23	20	18	12	5	2	0

Age at initiation of maralixibat (months)



Age ≥36 months	55	55	50	46	45	33	14	1	0
Age <36 months	21	21	15	12	10	8	4	2	0

Change from baseline to Week 48 ItchRO(Obs) and age at initiation of maralixibat are predictive of EFS

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

Sokol RJ, *et al.* Poster presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

Event-free survival analysis in Alagille syndrome of the GALA clinical research database

Pre-specified selection criteria to ensure GALA external control cohort was aligned with maralixibat entry criteria

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

Key inclusion criteria

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

Key exclusion criteria

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

GALA selected primary analysis N=469

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

AASLD Nov. 12-15, 2021
The Liver Meeting®

Demographic characteristics are well balanced between the maralixibat and GALA groups

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

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

AASLD Nov. 12-15, 2021
The Liver Meeting®

Disease characteristics are well balanced between the maralixibat and GALA groups

GALA
The Global ALagille Alliance Study

Baseline characteristic		MRX cohort N = 84	GALA control N = 469	*p*-value
Total bilirubin, mg/dL	Median (Q1,Q3)	3.15 (1.00, 8.15)	1.99 (0.60, 11.52)	0.392
	<2 mg/dL	37 (44.0)	235 (50.1)	0.306
	≥2 mg/dL	47 (56.0)	234 (49.9)	
GGT*	Median (Q1, Q3), log_{10} × ULN	1.25 (0.93, 1.44)	1.24 (0.93, 1.52)	0.582
	<3 × ULN	3 (3.6)	6 (1.3)	0.143
	≥3 × ULN	81 (96.4)	463 (98.7)	
ALT, U/L	Median (Q1, Q3)	145 (94, 207)	130 (75, 203)	0.119
sBA†, µmol/L	Median (Q1, Q3)	200 (81, 371) (*0% not measured*)	125 (39, 260)‡ (*85% not measured*)	0.003

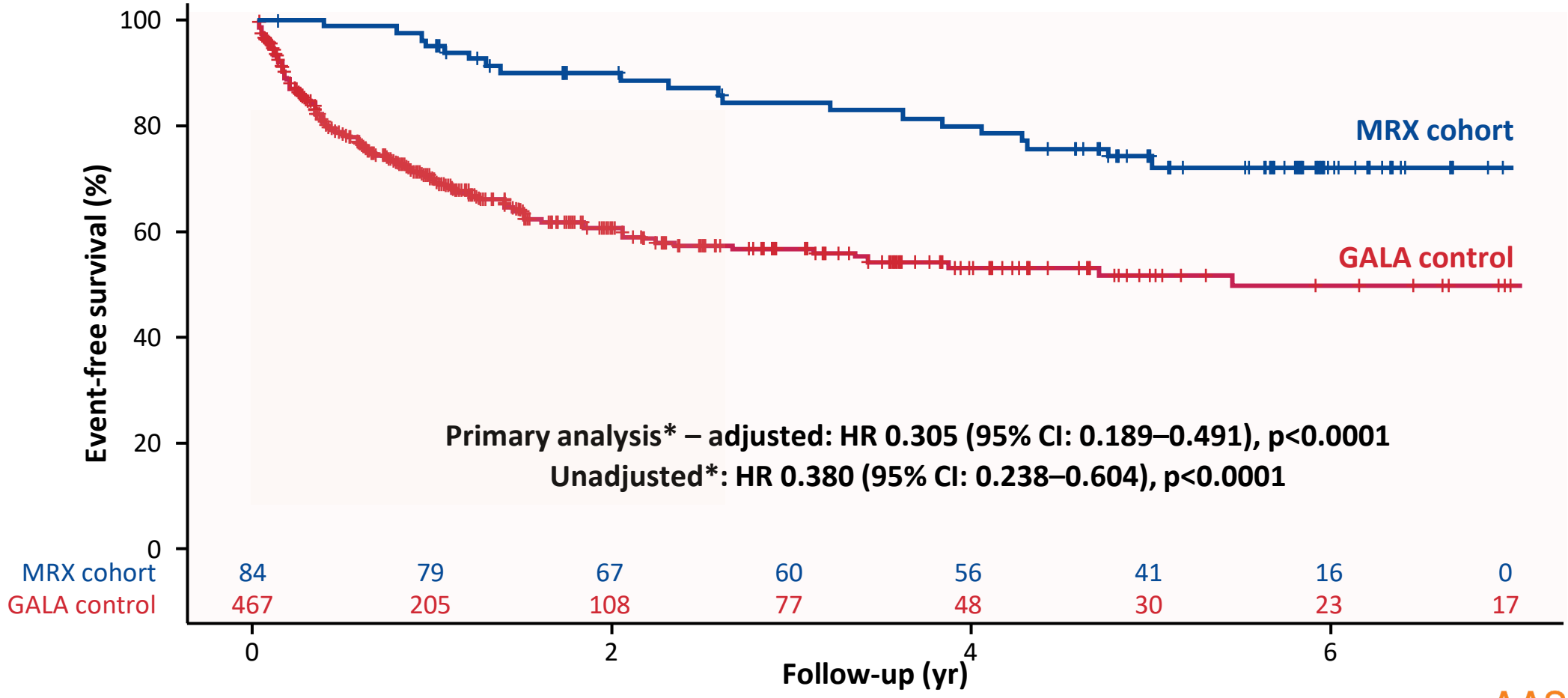
Key baseline characteristics are well-balanced between the MRX cohort and GALA control group

* Due to more than 20% of the cells having expected counts less than 5, chi-square results may be invalid; † sBA data are limited in the GALA clinical research database since these are not sampled regularly on a clinical basis and Fisher's exact test was used instead. ‡ Baseline sBA was available for 73 participants in the GALA control group.
ALT, alanine transaminase; GGT, gamma-glutamyltransferase; MRX, maralixibat; sBA, serum bile acid; ULN, upper limit of normal. Hansen BE & Kamath BM. Application of real-world evidence analytics: A 6-year event-free survival analysis in Alagille syndrome of the GALA clinical research database and maralixibat treated patients. Oral presentation at the American Association for the Study of Liver Diseases (AASLD) The Liver Meeting™ Digital Experience (TLMdX; Virtual); USA; November 12–15, 2021.

AASLD Nov. 12-15, 2021
The Liver Meeting®

Maralixibat shows significant improvement in EFS

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



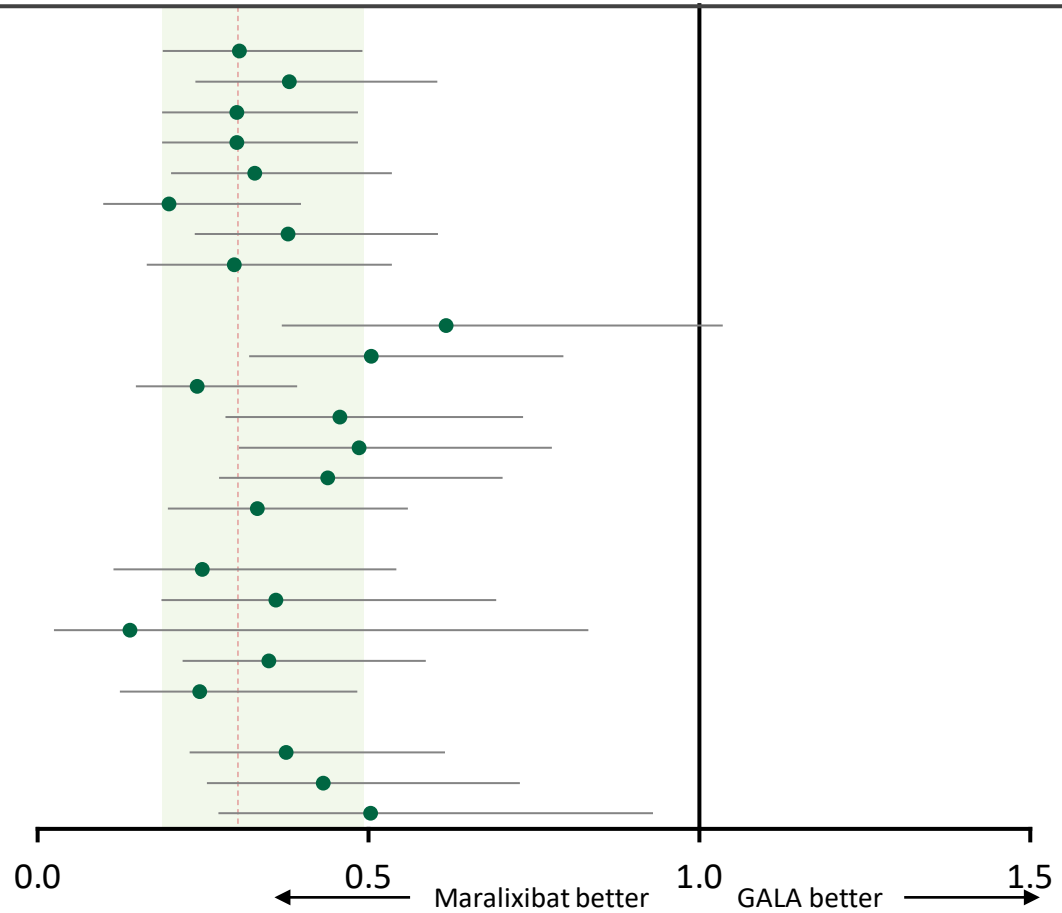
* Cox regression models: Primary: Cox regression - effect of MRX vs GALA log likelihood test adjusted for age, sex, bilirubin, and ALT (according to the SAP).
ALT, alanine transaminase; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ML, maximum likelihood; MRX, maralixibat; SAP, statistical analysis plan.

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

AASLD The Liver Meeting® Nov. 12-15, 2021

Consistent results observed across several sensitivity analyses

Estimated HR (95% CI) of EFS in MRX Cohort vs. GALA Control



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

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

AASLD Nov. 12-15, 2021
The Liver Meeting®

Clinical trials in ALGS

Odevixibat

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

Investigational therapy

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

PFIC, biliary atresia, ALGS, sclerosing cholangitis (N = 24) → **Odevixibat for 4 weeks (10, 30, 60, 100, and 200 μg/kg evaluated)**

Primary endpoints*	Secondary endpoints*
• Change in serum bile acid levels	• Changes in VAS-itch score • Changes in Whitington itch • Changes in PO-SCORAD itch • Changes in sleep disturbance scores • Changes in autotaxin, 7α-hydroxy-4-cholestene-3-one (C4) and fibroblast growth factor 19 (FGF19)

* All efficacy endpoints were measured from baseline to the end of the 4-week treatment period. PO-SCORAD, Partial Patient-Oriented Scoring Atopic Dermatitis; VAS, visual analogu scale.

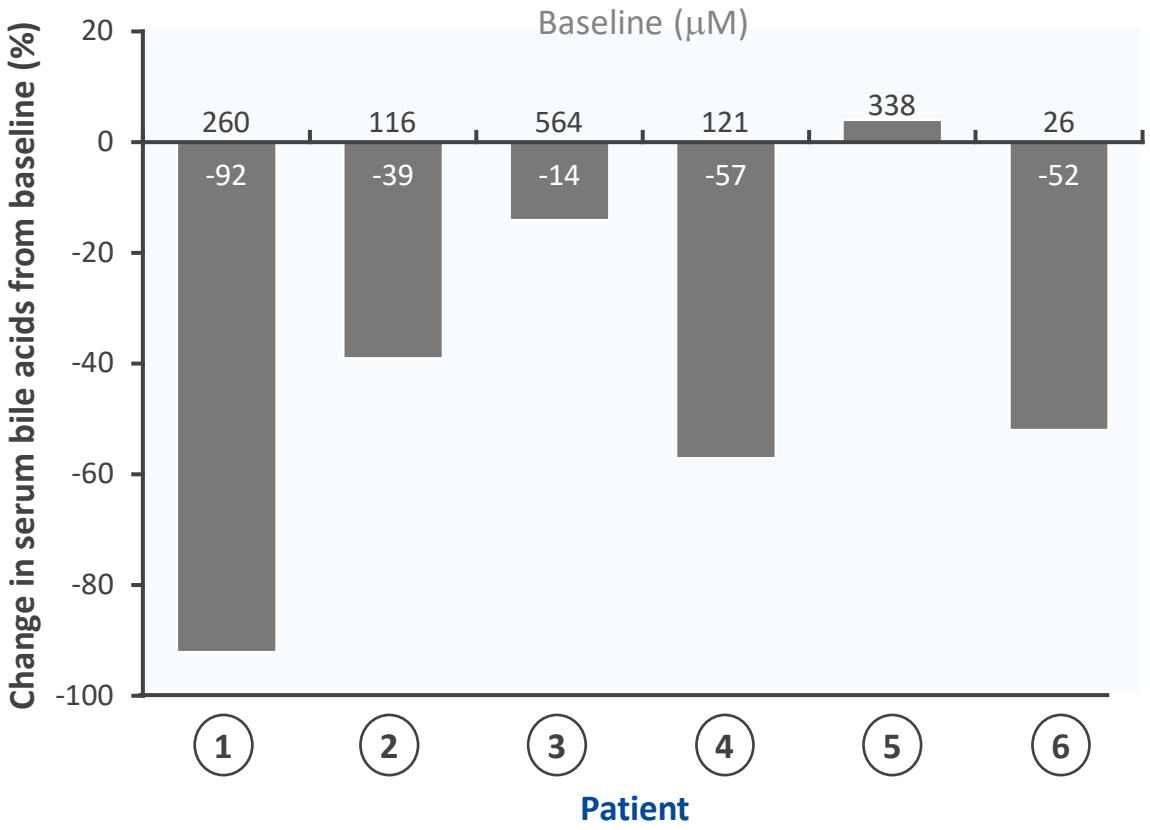
Baumann U, *et al. Clin Res Hepatol Gastroenterol* 2021; **45**: 101751; ClinicalTrials.gov. ID: NCT02630875. Accessed online at https://clinicaltrials.gov/ct2/show/NCT02630875 on November 19, 2021.

Phase 2 study: Mean serum bile acid levels and pruritus scores with odevixibat

Investigational therapy

ALGS cohort, N = 6

Serum bile acid reduction from baseline



Change from baseline

Parameter	Baseline, mean ± SD	End of treatment, mean ± SD	Change from baseline, mean ± SD
VAS-itch	6.2 ± 1.9	3.9 ± 3.2	–2.2 ± 2.3
PO-SCORAD itch	6.0 ± 2.2	3.8 ± 3.0	–2.0 ± 2.3
Whitington itch	2.6 ± 0.8	1.7 ± 1.2	–0.8 ± 1.0
PO-SCORAD sleep	5.3 ± 2.8	3.4 ± 3.1	–1.8 ± 2.3

For most patients, sleep and pruritus scores improved

Patients received 10–200 μg/kg odevixibat.
PO-SCORAD, Partial Patient-Oriented Scoring Atopic Dermatitis; sBA, serum bile acid; VAS, visual analog scale.
Albireo corporate presentation August 2020; Baumann U, *et al. Clin Res Hepatol Gastroenterol* 2021; **45**: 101751.

Phase 2 study: Safety and tolerability with odevixibat

Investigational therapy

Safety includes entire cohort, N = 24

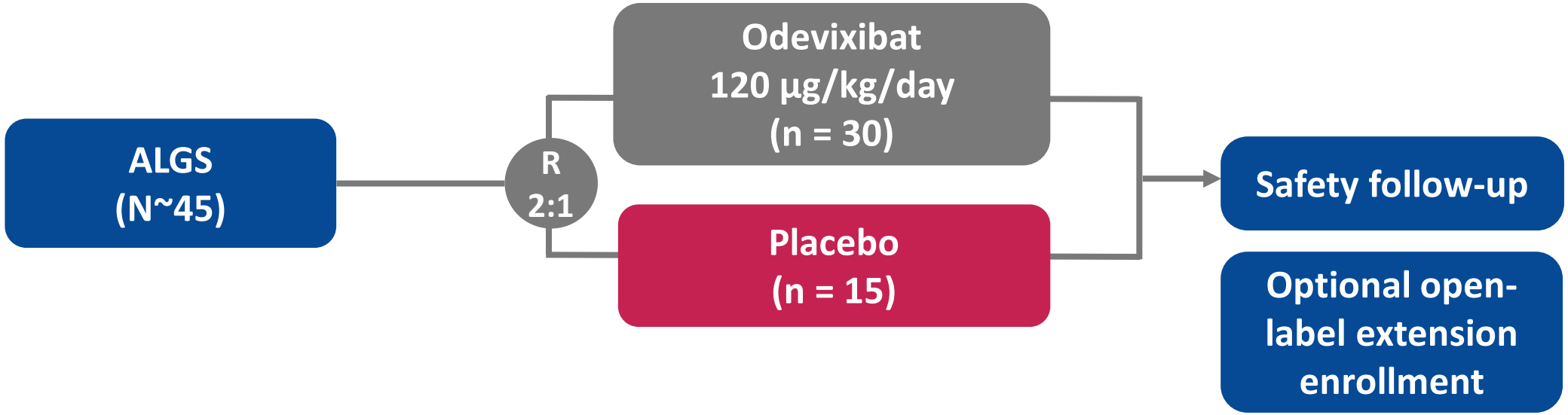
- All patients completed treatment; no evidence of diarrhea during 4-week treatment period, and one mild, transient, possibly treatment-related case of diarrhea after the single 10 µg/kg dose on Day 1
- No adverse events related to treatment during 4-week treatment period
  - Most common adverse: fever, acute otitis media (12.5%)
- No serious adverse events designated as treatment-related (2 deemed unrelated*)
- Decision made not to escalate dose above 200 µg/kg
  - Some elevation of transaminases at 200 µg/kg dose

* Gastroenteritis and influenza.

Baumann U, *et al. Clin Res Hepatol Gastroenterol* 2021; **45**: 101751.

Phase 3 study: Odevixibat in ALGS (ASSERT)

Investigational therapy



Primary endpoint	Secondary endpoints
• Change from baseline in scratching score to Month 6 as measured by the Albireo ObsRO scratching score	• Serum bile acid levels • Safety and tolerability

ObsRO, observer-reported outcome; OLE, open-label extension; sBA, serum bile acid.
Albireo corporate presentation May 2021; ClinicalTrials.gov. ID: NCT04674761. Accessed online at https://clinicaltrials.gov/ct2/show/NCT04674761 on November 19, 2021.

ALGS summary

- ALGS is a rare syndrome that may have multisystem involvement and significant disease burden
- Liver involvement is due to intrahepatic bile duct paucity that may result in chronic cholestasis
- Cholestasis presenting with pruritus, xanthomas, and many other clinical manifestations is the leading cause of liver transplantation for children with ALGS
- Refractory pruritus lowers the quality of life for patients and their caregivers. Liver disease in ALGS can progress to cirrhosis and liver transplant
- Maralixibat is now approved for the treatment of cholestatic pruritus in patients with ALGS 1 year of age and older
- Clinical trials with IBAT inhibitors are ongoing

IBAT, ileal bile acid transporter.

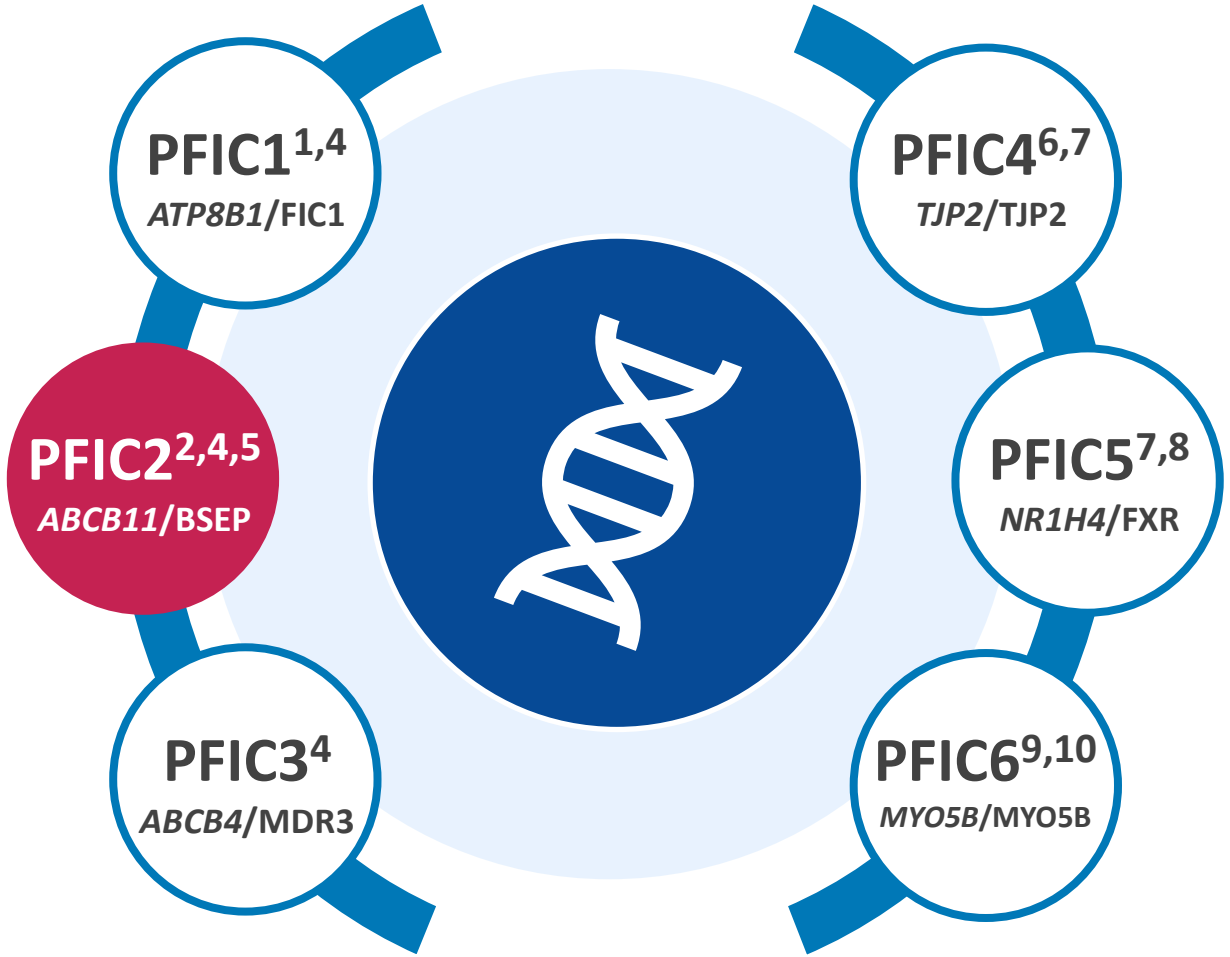
Establishing new foundations for children with PFIC

Ryan Himes, M.D.

Pediatric Hepatologist,
Ochsner Hospital for Children, USA

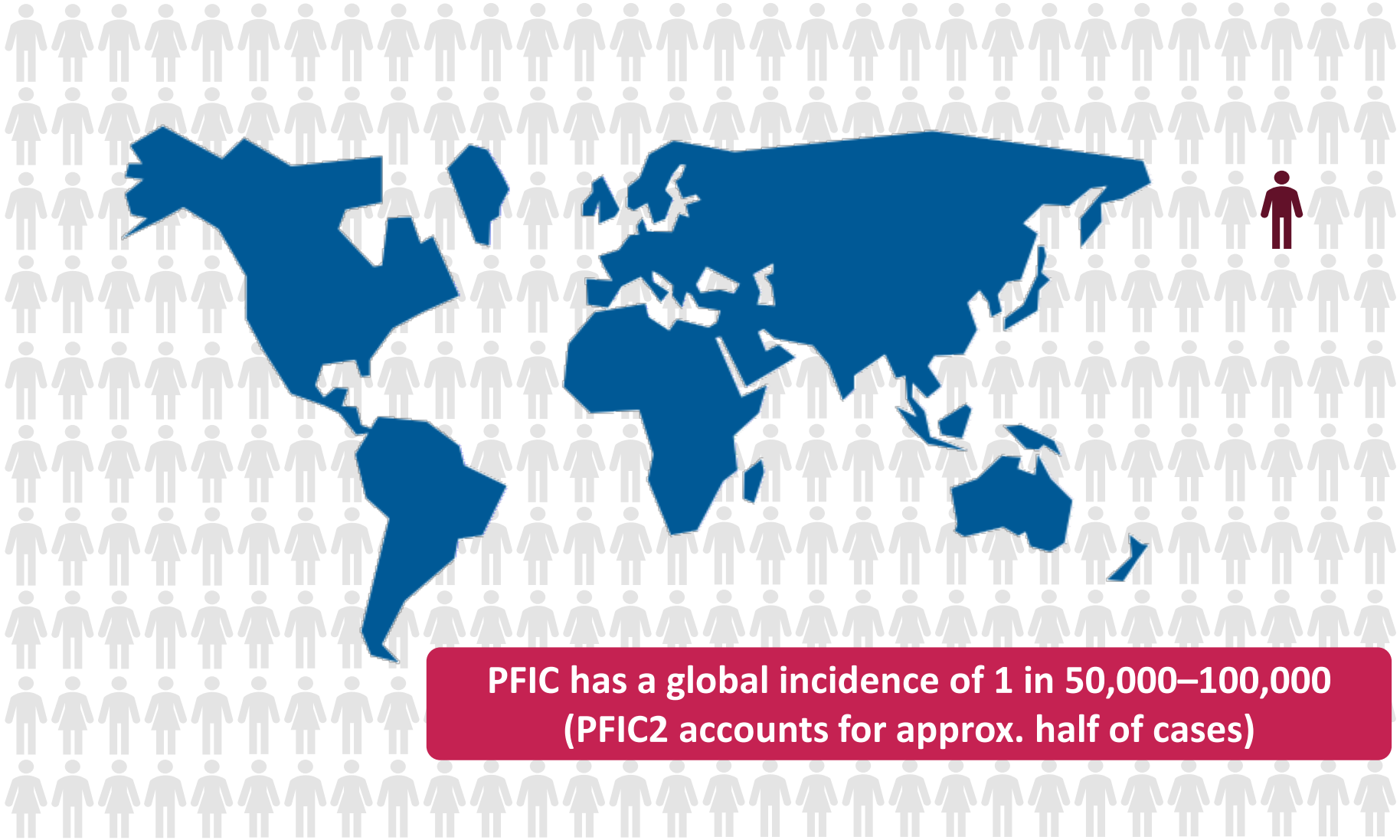
PFIC is an autosomal recessive disorder classified into six subtypes

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



1. Jacquemin E. *Clin Res Hepatol Gastroenterol* 2012; **36** Suppl 1:S26–S35; 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 September 15, 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



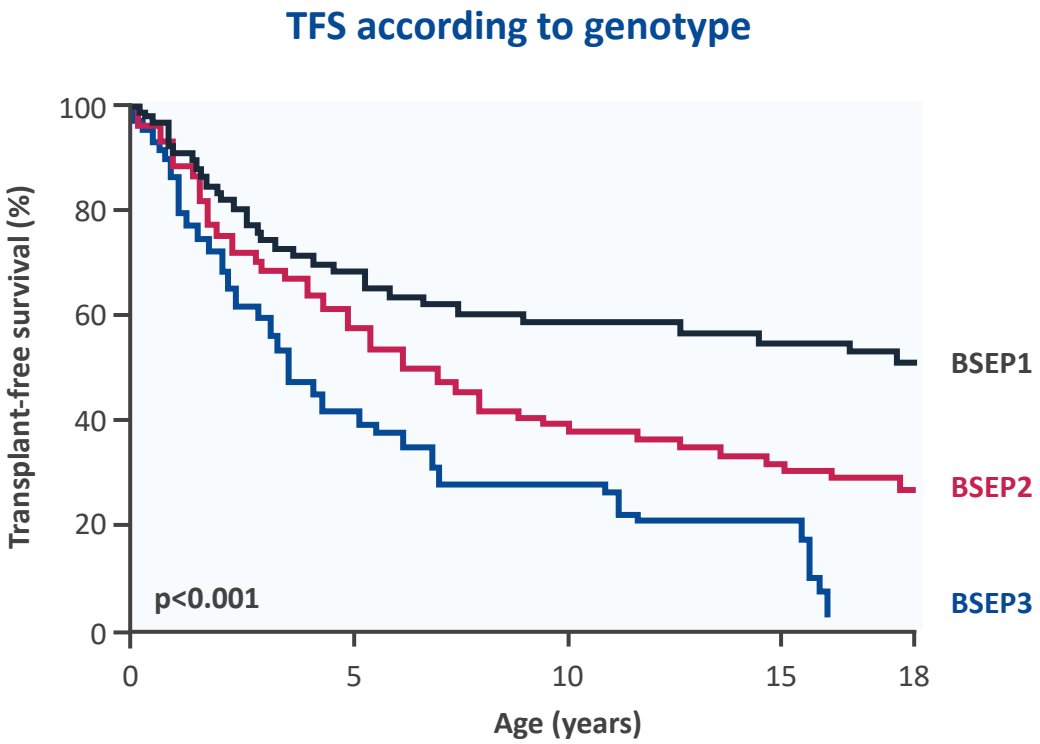
PFIC has a global incidence of 1 in 50,000–100,000 (PFIC2 accounts for approx. half of cases)

Jacquemin E. *Clin Res Hepatol Gastroenterol* 2012; **36** Suppl 1:S26–S35; Orphanet, 2011. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=79304&lng=EN; Accessed September 15, 2021.

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

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

Mutation	BSEP protein	Predicted severity	Median TFS (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



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

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

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

- Jaundice[2]
- Fat malabsorption[3,4]
- Fat-soluble vitamin deficiency[2,3]
- Failure to thrive during first several months of life[2]
- Pruritus leading to excoriation and mutilation of skin[3,4]
- Scleral icterus[3]
- Hepatomegaly[3]
- Portal hypertension within the first year[3]

Approx. 50% of patients require a liver transplant by age 10[1]

BSEP, bile salt export pump.

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

Case study: A classical presentation of PFIC

Description (current age): 4-year-old female

Initial presentation (at 5 months):

- Scratching to the point of bleeding and ecchymoses on her abdomen, back, and legs

Medical history: No relevant medical conditions

Physical examination: Physical examination showed neither icterus nor hepatosplenomegaly

Laboratory parameters:

- AST 223 U/L; ALT 334 U/L
- Total bilirubin 3.4 mg/dL; direct bilirubin 2.8 mg/dL
- GGT 33 U/L
- Partial thromboplastin time, 90.8 seconds; prothrombin time, > 120.0 seconds
- INR >13.7
- sBA test not conducted
- Albumin 2.3 g/dL

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

Tibesar E, *et al. Case Rep Pediatr* 2014; **2014**:185923.

Case study: A classical presentation of PFIC

Initial treatment:

- Intravenous vitamin K; admitted for further evaluation

Follow-up evaluations:

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

Liver biopsy:

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

Diagnosis:

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

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

Tibesar E, *et al. Case Rep Pediatr* 2014; **2014**:185923.

Impact of symptoms on quality of life

Persisting symptoms at follow-up visit:

- Pruritus continued despite the use of ursodiol, rifampin, cholestyramine, and hydroxyzine
- Problems sleeping and significant skin damage

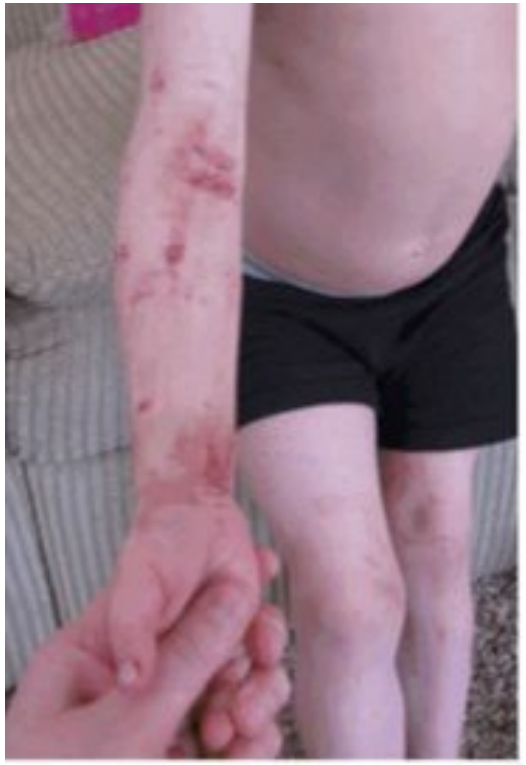


Image source: Mirum Pharmaceuticals. Tibesar E, *et al. Case Rep Pediatr* 2014; **2014**:185923;
PFIC: A guide. Children's Liver Disease Foundation. Available at: https://childliverdisease.org/wp-content/uploads/2019/07/Click-here-to-download-CLDFs-PFIC-leaflet.pdf. Accessed November 18, 2021.

Beyond the patient – caregiver impact is also significant

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

67% emotional stress

86% financial hardship because of their caregiver role

89% need to educate HCPs

41% fair/poor emotional or mental health

53% feel alone

59% receive help from at least one other caregiver

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

HCP, healthcare professional.
National Alliance for Caregiving, in partnership with Global Genes, 2018.

Case study: A classical presentation of PFIC

Persisting symptoms at subsequent follow-up visits:

- Intractable pruritus, despite the subsequent use of rifampin, cholestyramine, and hydroxyzine

Surgical approaches:

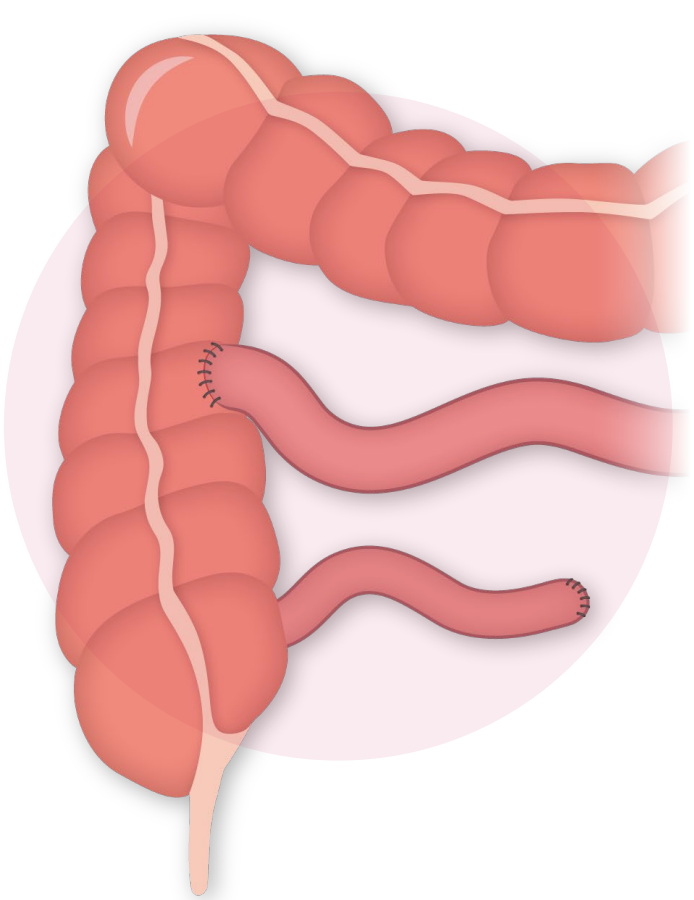
- Ileal exclusion performed at 12 months with no relief of pruritus and continued high total bile acid level of 147.4 μmol/L following bile acid test

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

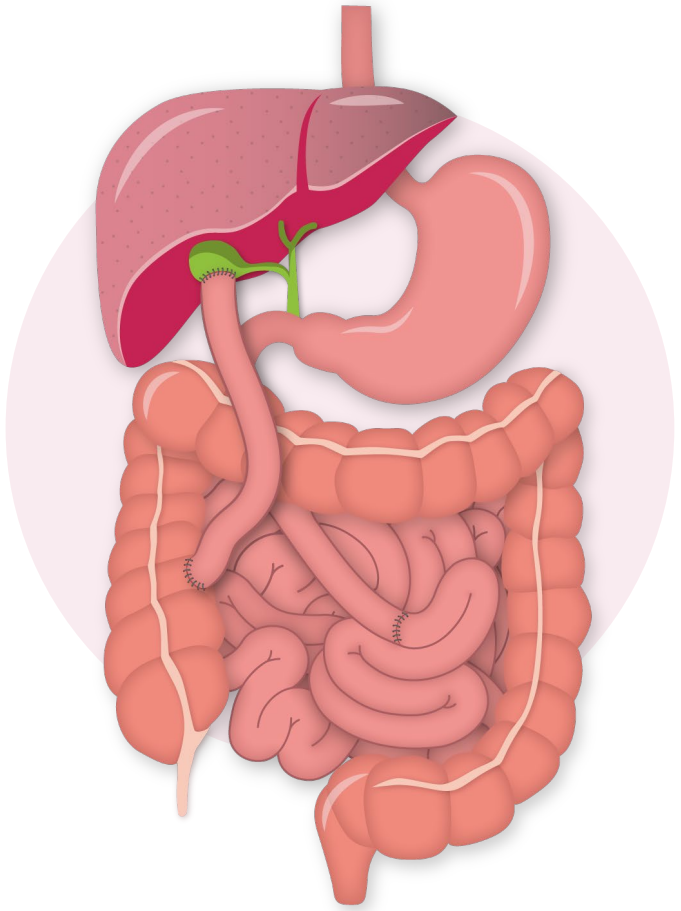
Tibesar E, *et al. Case Rep Pediatr* 2014; **2014**:185923.

Surgical interventions in PFIC

Schematic representation of an ileal exclusion

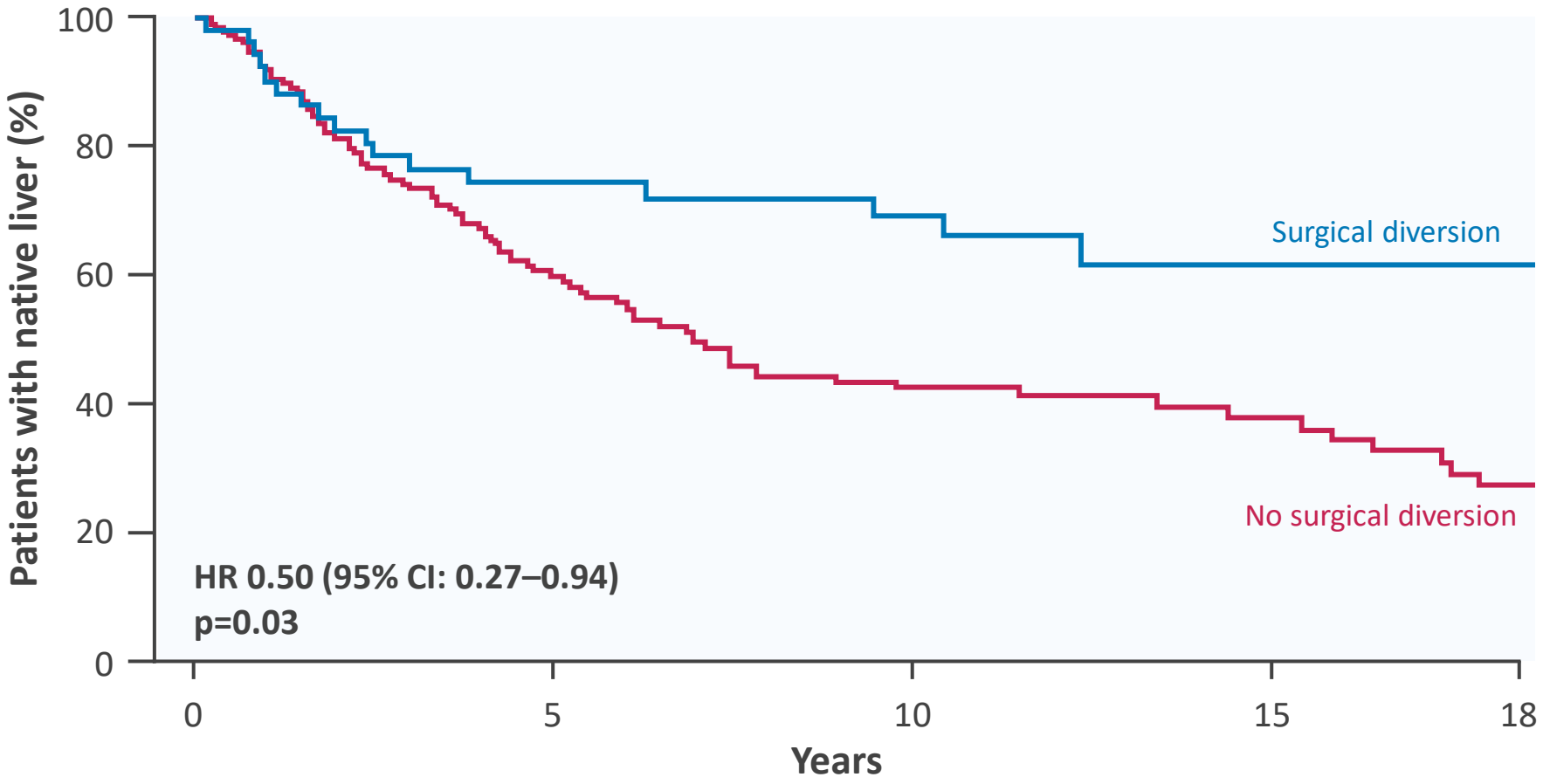


Schematic representation of a partial internal biliary diversion



Adapted from: Lemoine C & Superina R. *Semin Pediatr Surg* 2020; **29:** 150946. Reprinted from *Seminars in Pediatric Surgery*, 29, Lemoine C & Superina R., 'Surgical diversion of enterohepatic circulation in pediatric cholestasis', 150946, Copyright (2020), with permission from Elsevier.

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



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

Case study: A classical presentation of PFIC

Surgery:

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

Outcome of surgery:

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

Patient now listed for a living related donor liver transplant

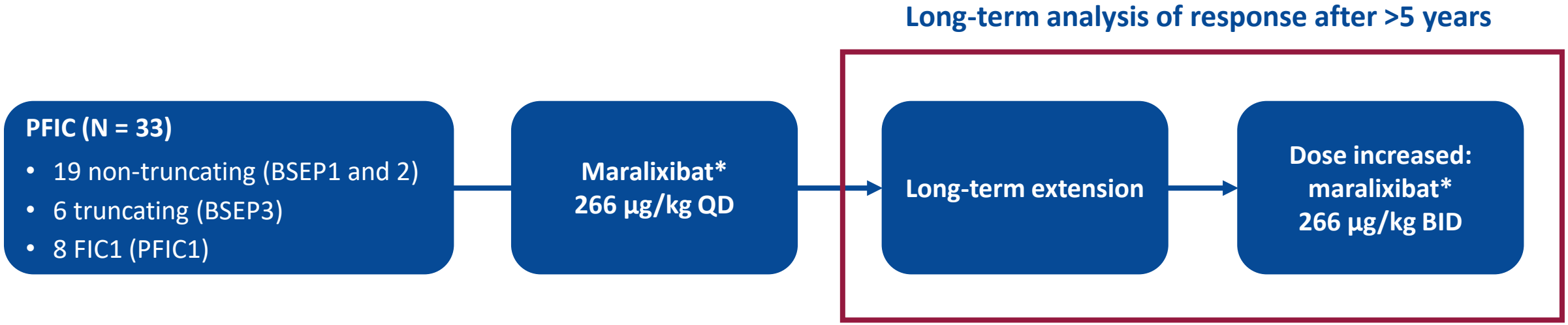
sBA, serum bile acid.
Tibesar E, *et al. Case Rep Pediatr* 2014; **2014**:185923.

Clinical trials in PFIC

INDIGO

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

Investigational therapy



Primary endpoint	Secondary endpoints
• Change from baseline to Week 13 in fasting sBA level	• Change from baseline to Week 13 in pruritus, measured by ItchRO(Obs) and ItchRO(Pt) • Change from baseline to Week 13 in ALT, total and direct bilirubin

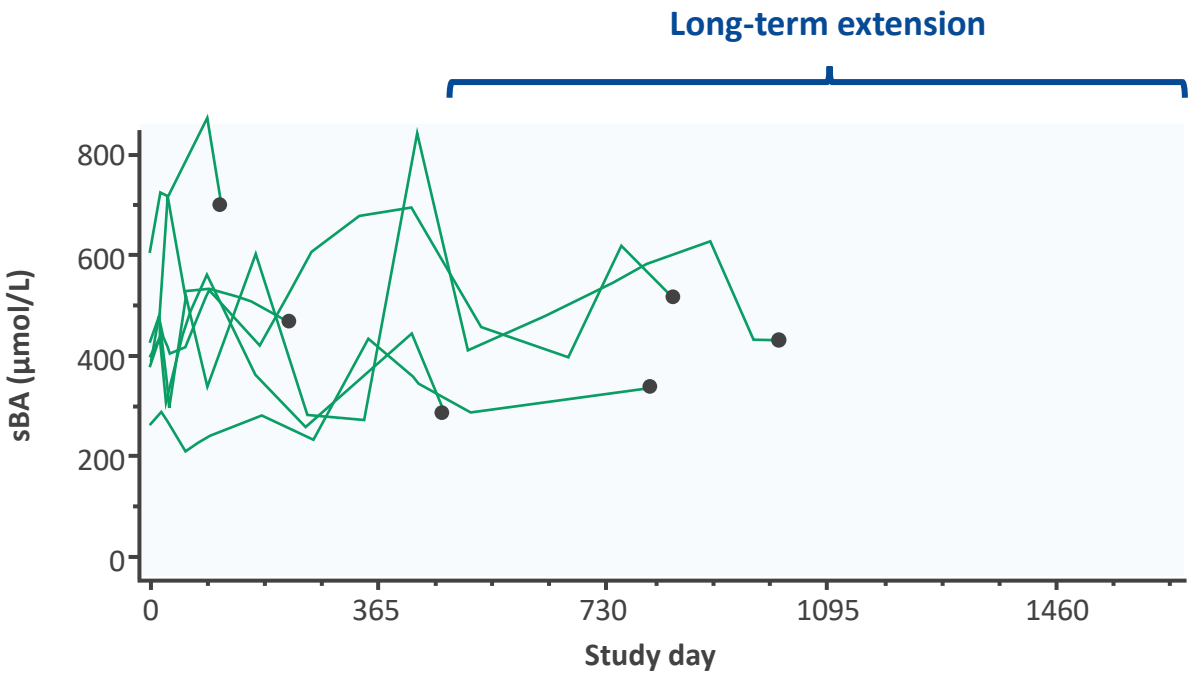
* Dosing for maralixibat vs maralixibat chloride (266 µg maralixibat is equivalent to 280 µg maralixibat chloride). BID, twice daily dosing; BSEP, bile salt export pump; FIC, familial intrahepatic cholestasis; ItchRO(Obs), Itch-Reported Outcome (Observer); ItchRO(Pt), Itch-Reported Outcome (Patient);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

ClinicalTrials.gov. ID: NCT02057718. Accessed online at https://clinicaltrials.gov/ct2/show/NCT02057718 on November 19, 2021; Thompson R, *et al.* Oral presentation, presented at EASL 2020, Virtual Meeting; Thompson R, *et al.* Poster presentation, presented at NASPGHAN 2020, Virtual Meeting.

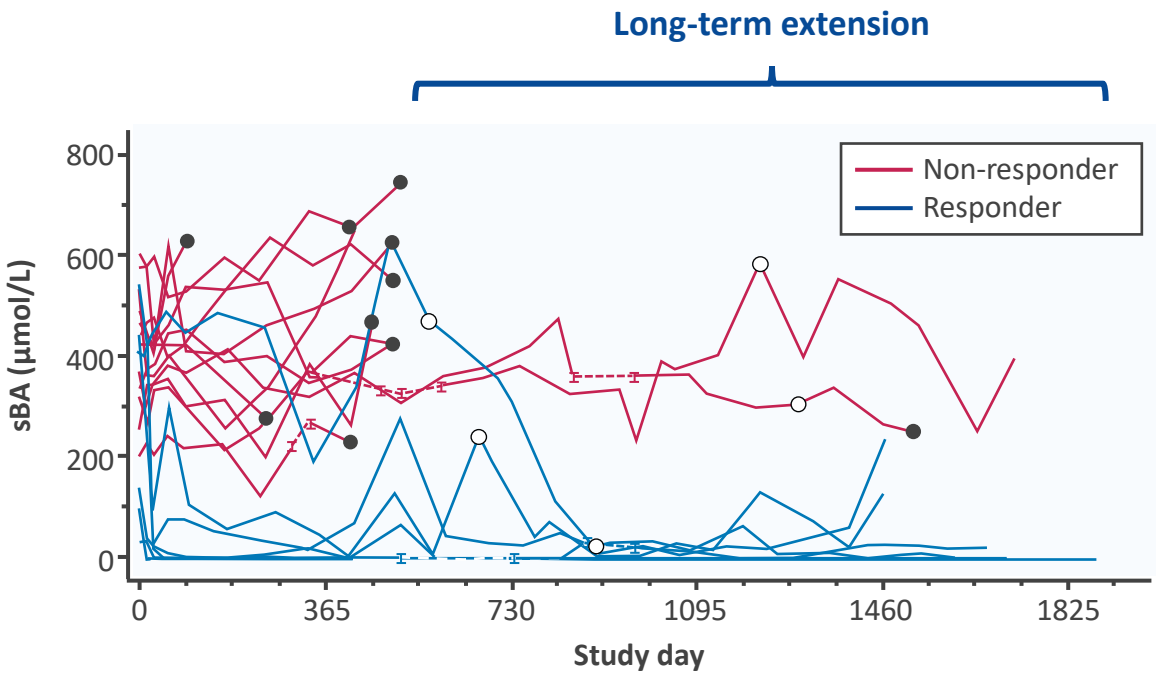
INDIGO: Mean sBA levels with long-term maralixibat treatment

Investigational therapy

Truncating BSEP mutations (BSEP3)



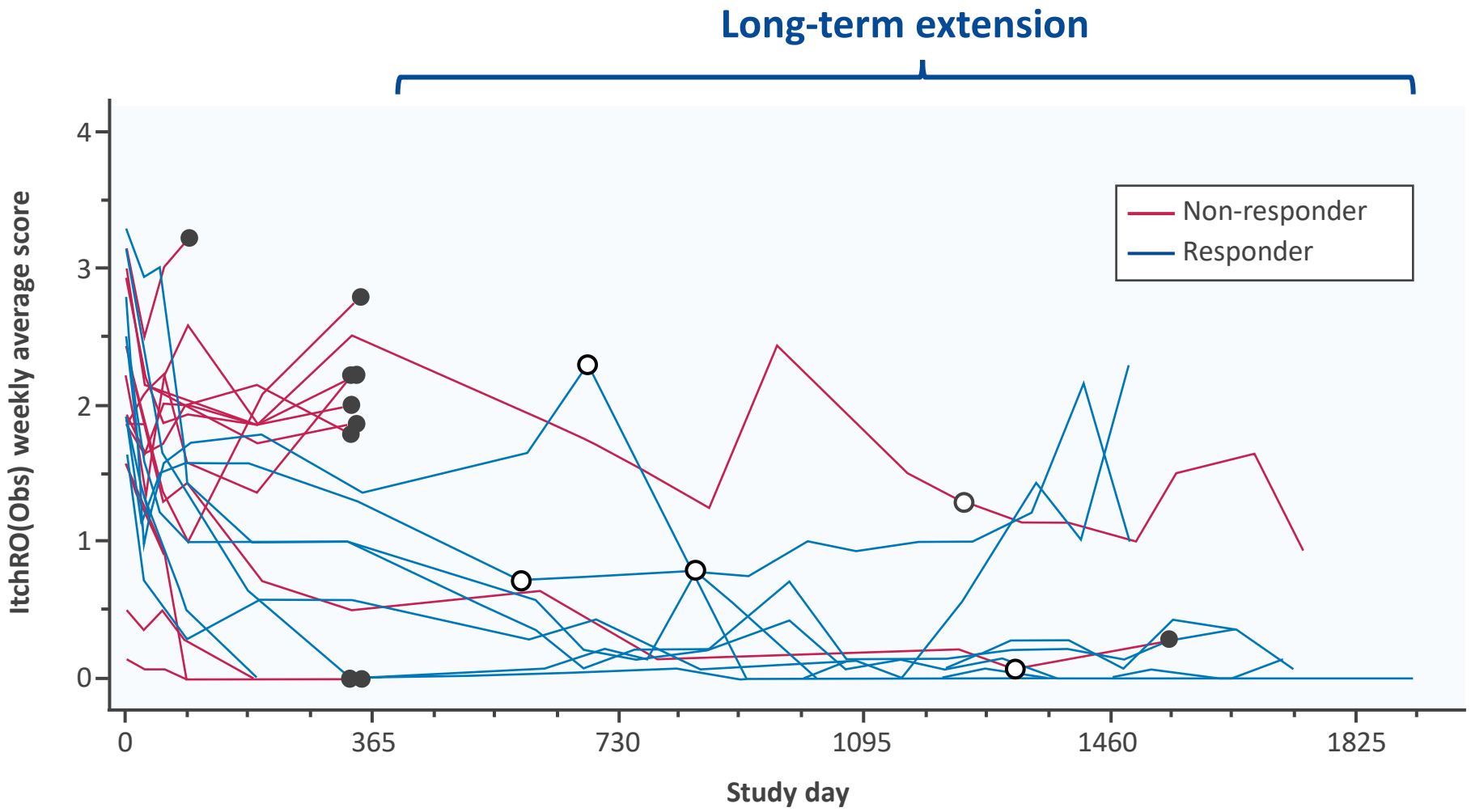
Non-truncating BSEP mutations (BSEP1 & 2)



The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing.
BSEP, bile salt export pump; sBA, serum bile acid.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

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

Investigational therapy

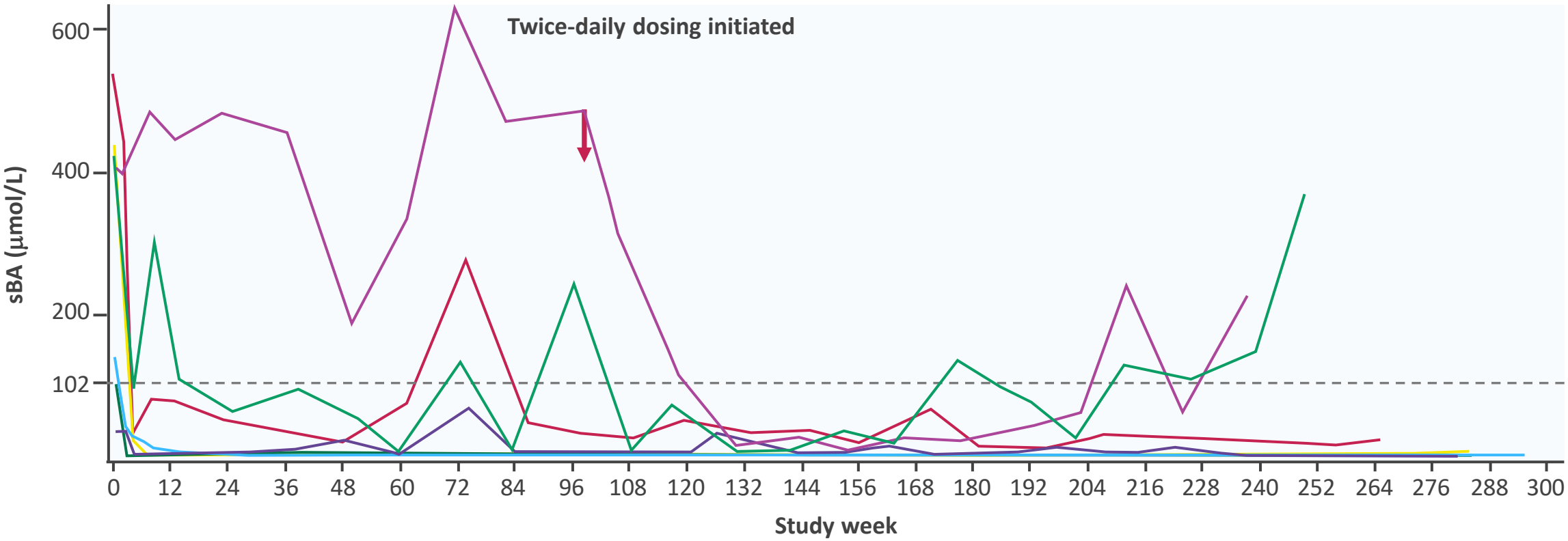


- ItchRO(Obs) response is sustained over years
- 79% (15/19) nt-PFIC2 patients achieved at least a 1-point reduction or a nadir ItchRO(Obs) score of <1 at any timepoint

The black filled circle refers to treatment discontinuation. The white filled circle refers to the start of BID dosing. ItchRO(Obs) score: 0–4 observer-rated pruritus scale.
ItchRO(Obs), Itch-Reported Outcome (Observer); nt, non-truncated.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

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

Investigational therapy

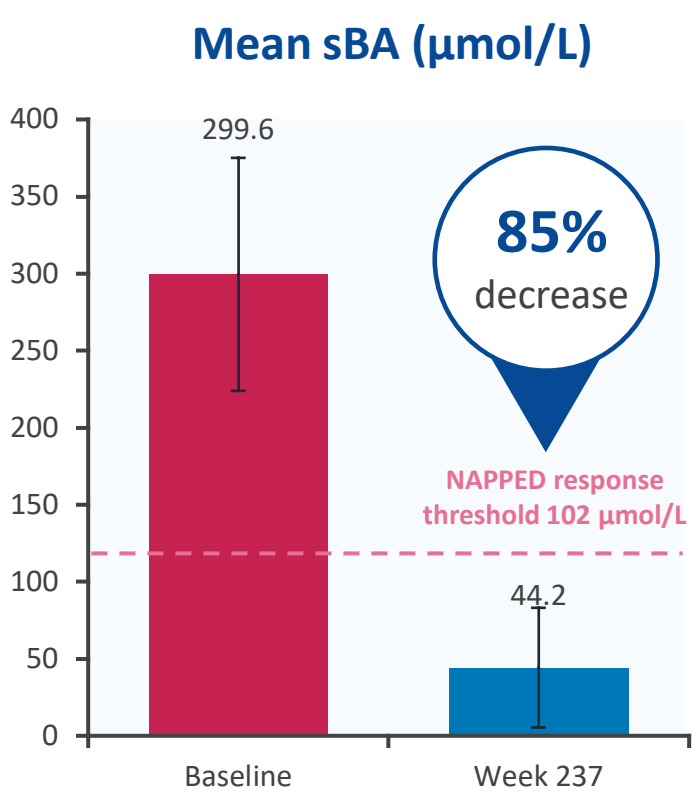


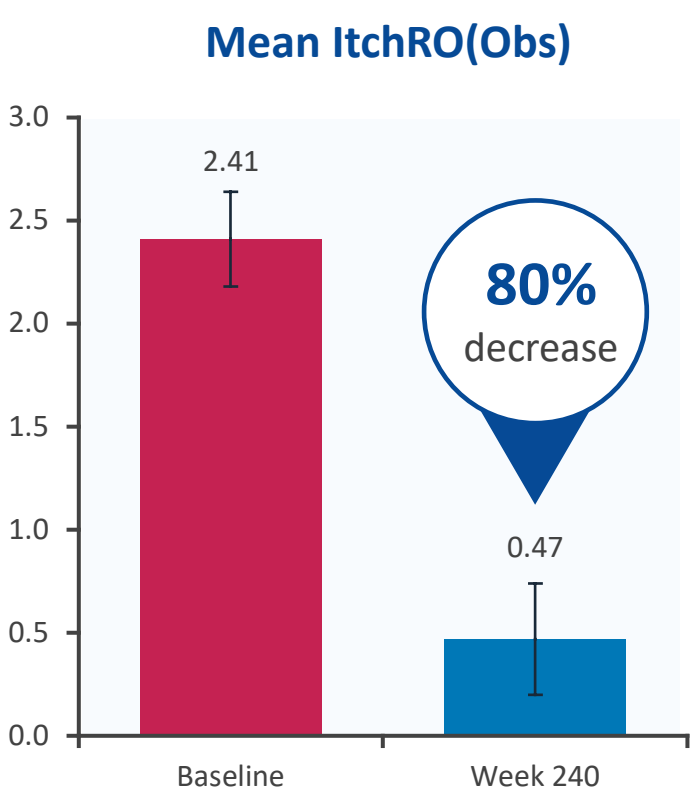
- No clinical events have been observed
- Six out of seven patients met one or both NAPPED criteria* by Week 4
  - Seventh sBA responder observed after twice-daily dosing at Week 97
- Two patients have come off the transplant waiting list

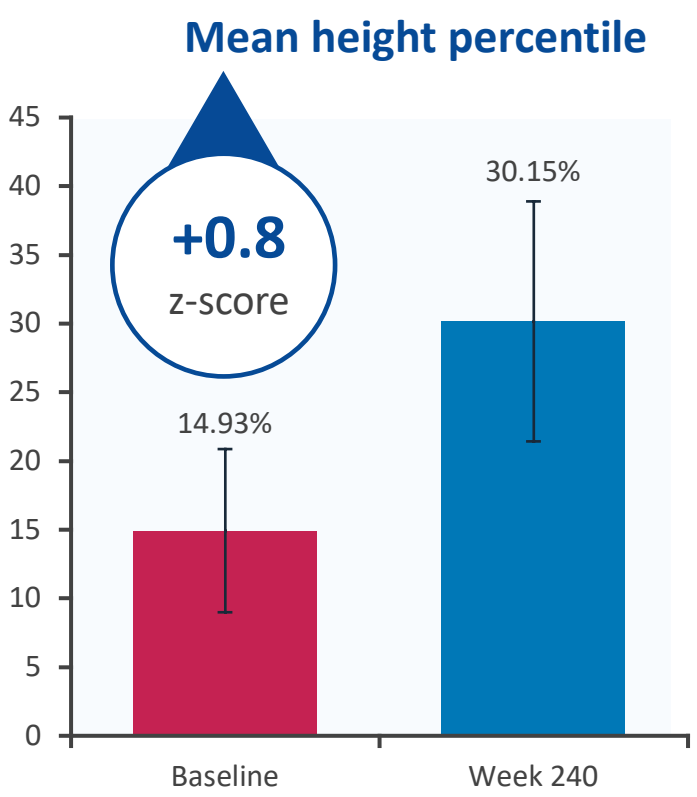
* Either serum bile acid concentration below 102 µmol/L or a decrease of at least 75%.
sBA, serum bile acid.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

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

Investigational therapy



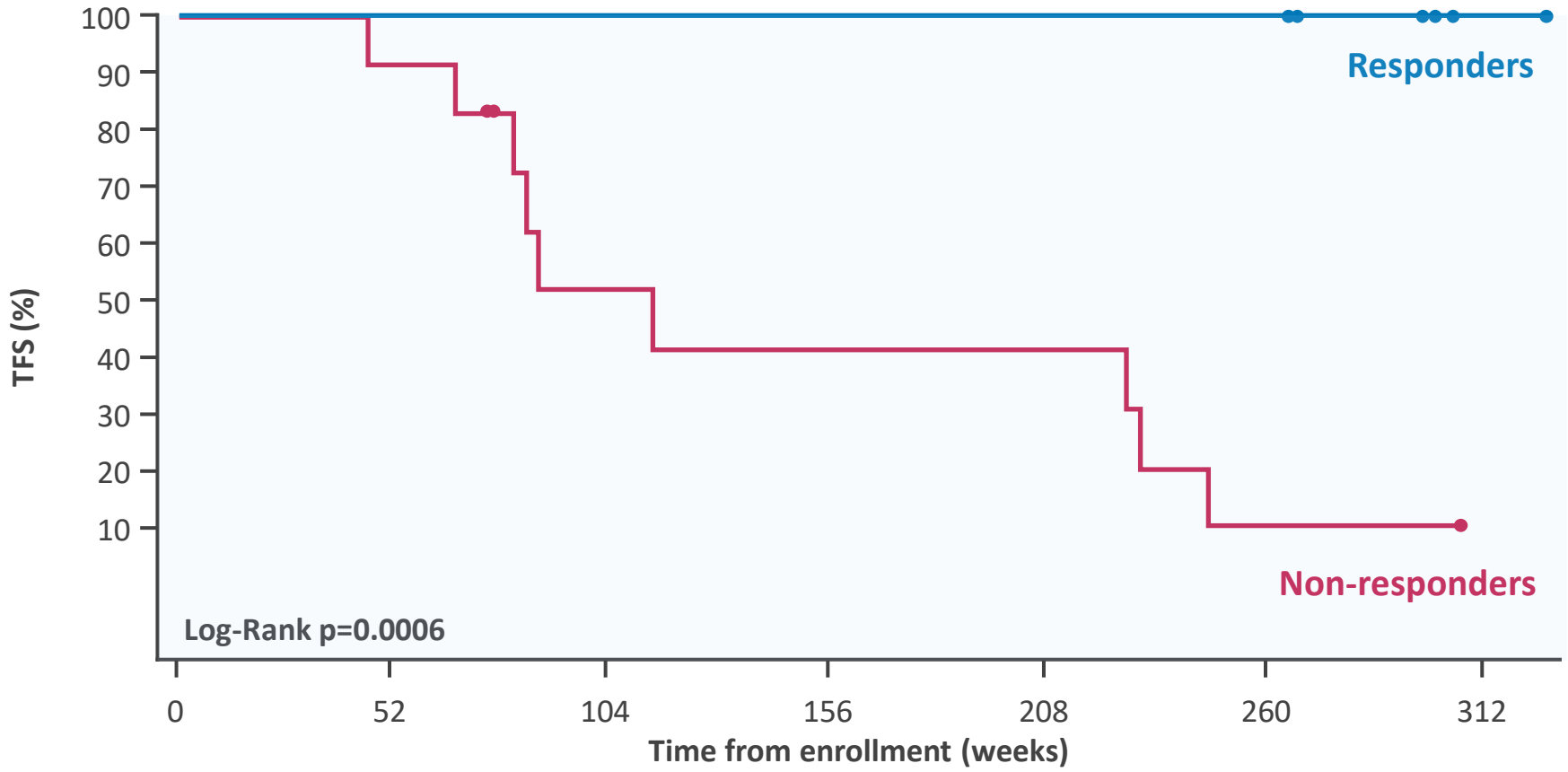




Error bars represent standard error of the mean.
ItchRO(Obs), Itch-Reported Outcome (Observer); sBA, serum bile acid.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

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

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.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

INDIGO: Safety and tolerability with maralixibat

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)
Diarrhea	11 (57.9)
Pyrexia	11 (57.9)
Abdominal pain	9 (47.4)
Oropharyngeal pain	8 (42.1)
Pruritus	8 (42.1)

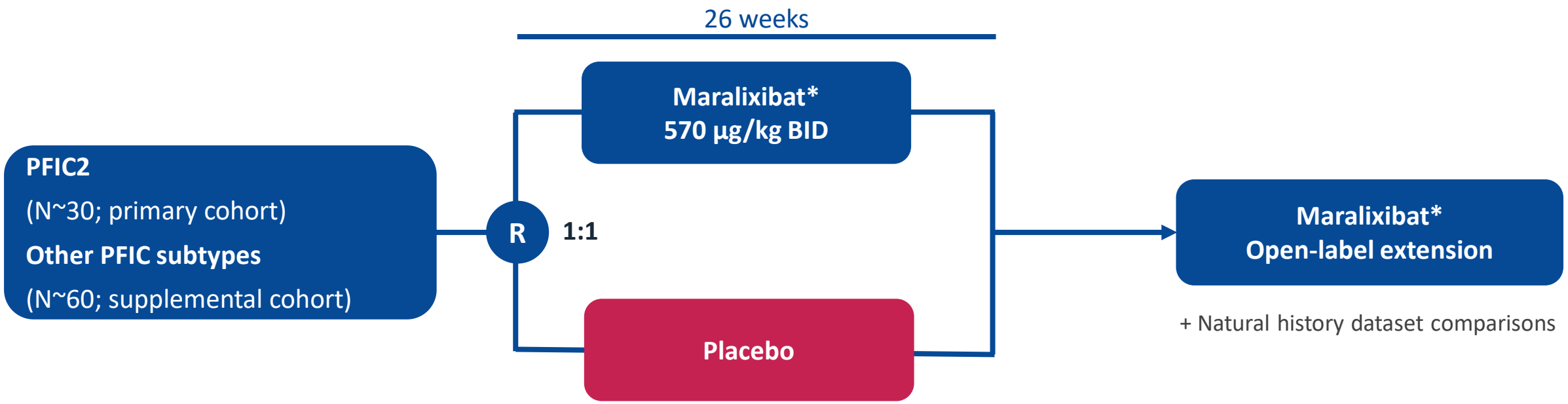
* Pancreatitis, blood bilirubin increased.
TEAE, treatment-emergent adverse event.
Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

Clinical trials in PFIC

MARCH-PFIC

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

Investigational therapy



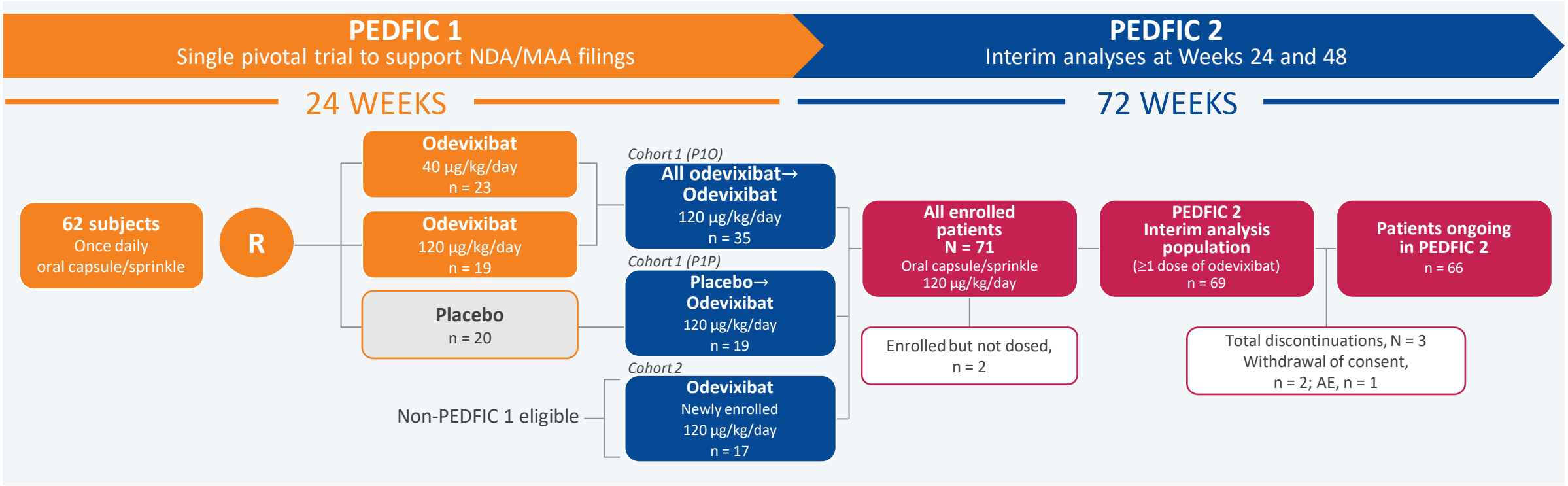
Primary endpoint	Secondary endpoints	Additional endpoints
• ItchRO(Obs) mean change in severity of pruritus	• Pruritus frequency • Change in serum bile acids • Safety	• Supplemental cohort analyses • QoL, growth, other measures

* 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.
ClinicalTrials.gov. ID: NCT03905330. Accessed online at https://clinicaltrials.gov/ct2/show/NCT03905330 on November 19, 2021; Mirum, 2021. Available at: https://pfictrial.com; Accessed September 15, 2021; Thompson R, *et al.* Oral presentation, presented at WCPGHAN 2021, Virtual Meeting.

Clinical trials in PFIC

PEDFIC1 and PEDFIC2

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



Primary endpoints

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

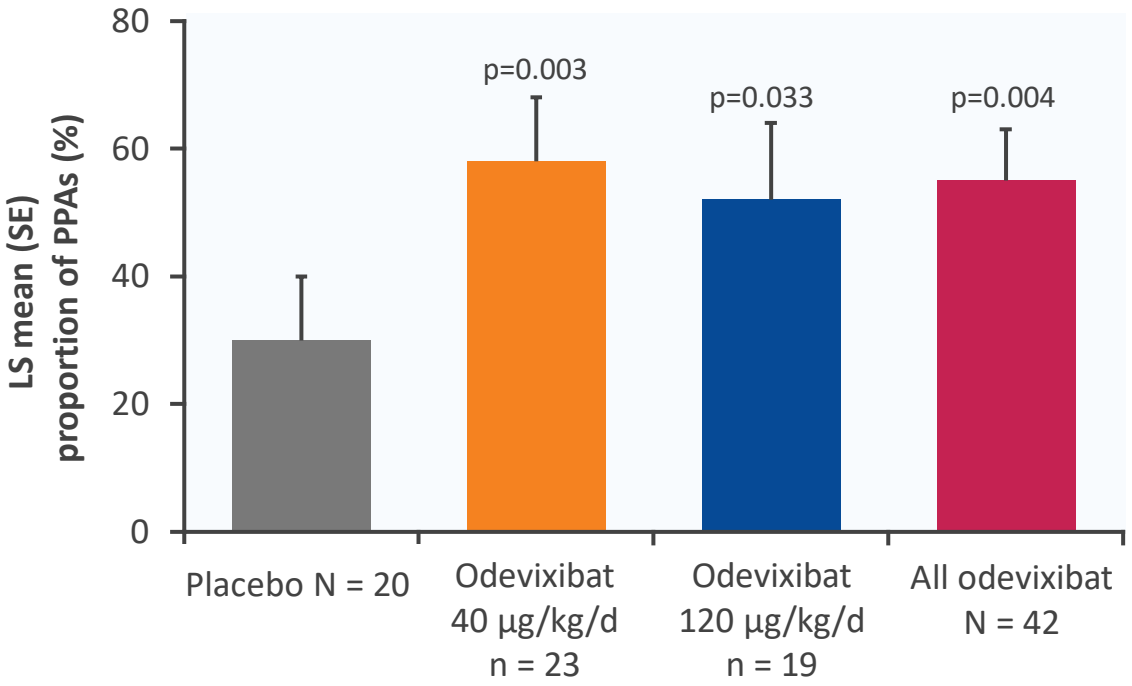
Secondary endpoints

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

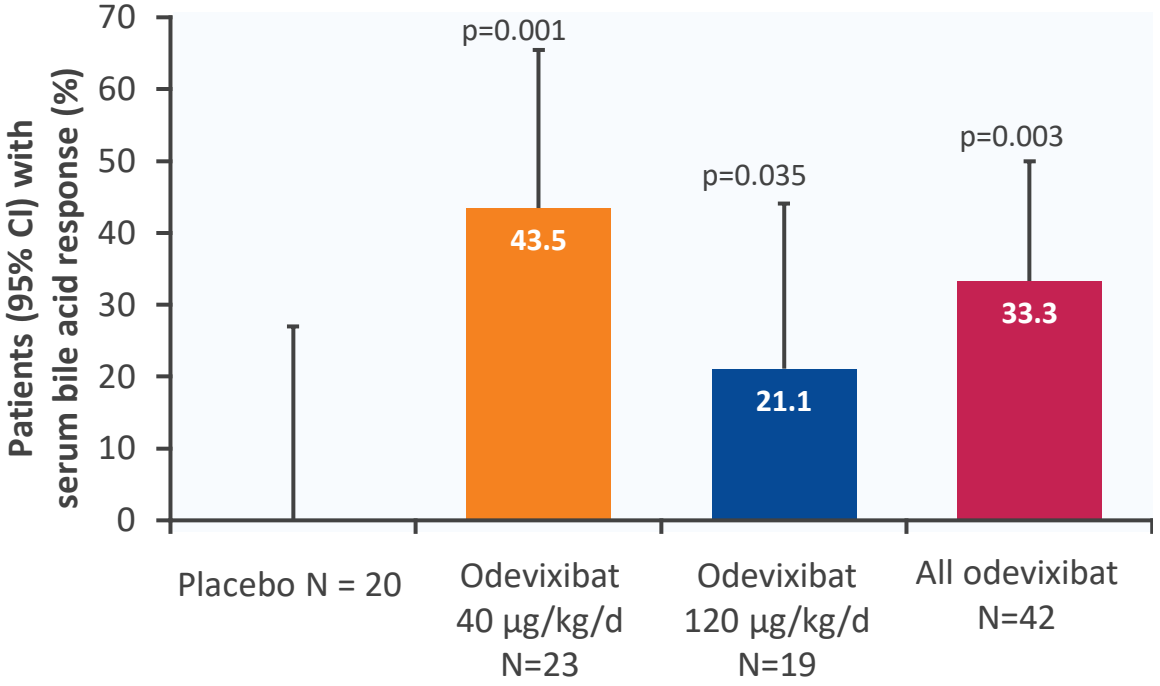
AE, adverse event; AST, aspartate transaminase; Fib-4, fibrosis-4 scale; MAA, marketing authorisation application; NDA, New Drug Application; ObsRO, observer-reported outcome; R, randomized; sBA, serum bile acid.
Albireo Corporate presentation May 2021; ClinicalTrials.gov. ID: NCT03566238. Accessed online at https://clinicaltrials.gov/ct2/show/NCT03566238 on September 15, 2021;
ClinicalTrials.gov. ID: NCT03659916. Accessed online at https://clinicaltrials.gov/ct2/show/NCT03659916 on November 10, 2021.

PEDFIC 1: Pruritus control with odevixibat treatment

Proportion of positive pruritus assessments (PPAs)*



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.
Albireo corporate presentation May 2021.

Pruritus improvement demonstrated in PFIC1, 2, & 3

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

	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).
Albireo corporate presentation May 2021.

PEDFIC 1: Safety and tolerability with odevixibat

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)
Diarrhea/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 diarrhea

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

PFIC summary

- PFIC is a heterogeneous group of autosomal-recessive diseases that disrupt bile formation
- PFIC2 (BSEP): most common and aggressive of the PFIC subtypes; genotype affects severity
- PFIC presents as cholestasis, often with significant pruritus
- PFIC can progress to cirrhosis, end-stage liver disease and liver failure
- NAPPED data: sBA is a marker for long-term outcome, providing a rationale for IBAT inhibition
- Odevixibat is approved for the treatment of pruritus in patients 3 months of age and older with PFIC

IBAT, ileal bile acid transporter.

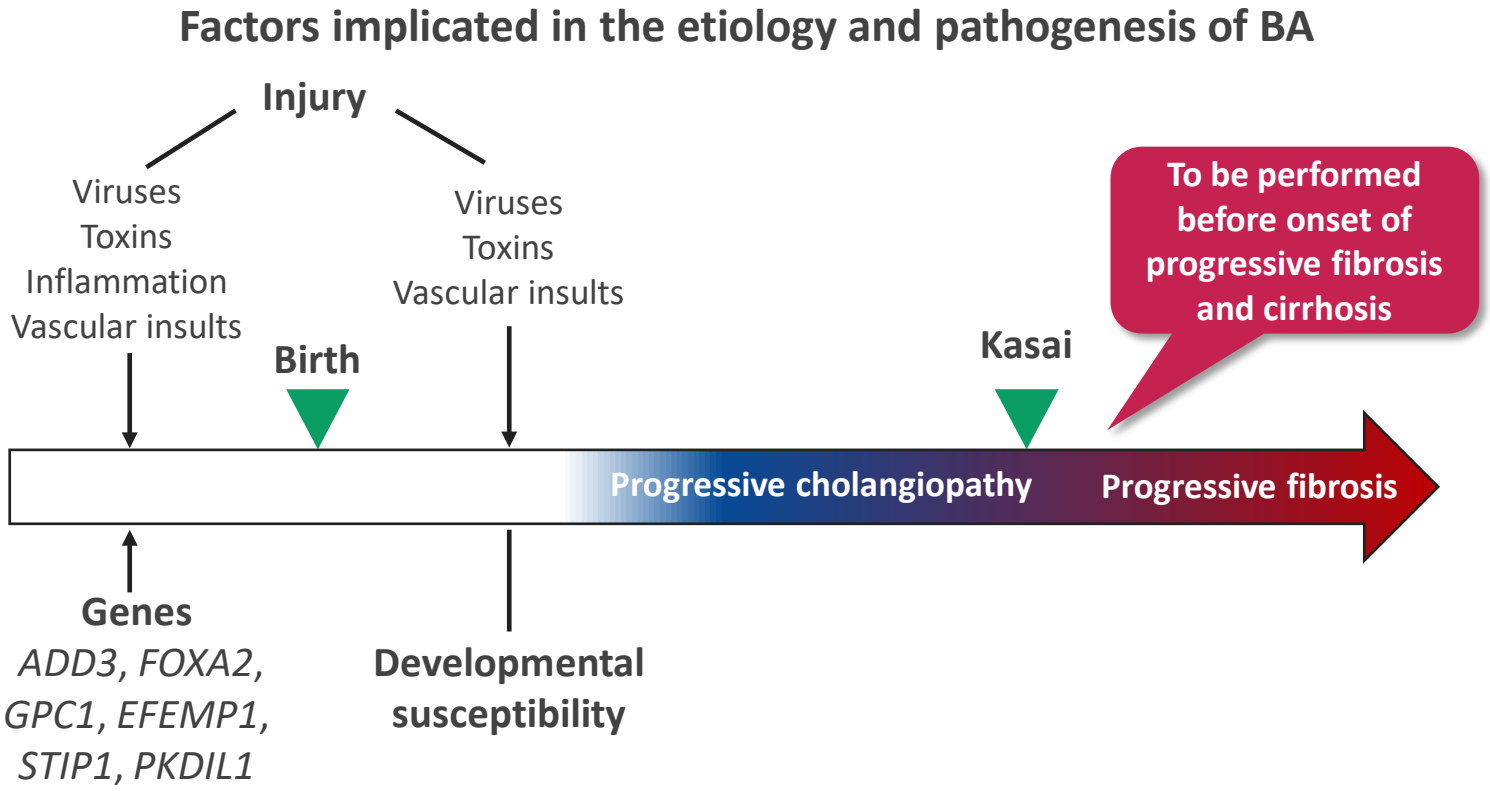
Planning new outcomes for biliary atresia

Tamir Miloh, M.D.

Medical Director of Pediatric Transplant Hepatology at the Miami Transplant Institute, USA

Biliary atresia is a progressive cholangiopathy of infancy and displays as a rapidly developing fibrotic process

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



BA, biliary atresia; BASM, biliary atresia splenic malformation.

Mathur P, *et al. J Neonatal Surg* 2014; **3:**9; Mysore KR, *et al. J Pediatr Gastroenterol Nutr* 2019; **69**:396–403; Verkade HJ, *et al. J Hepatol* 2016; **65**:631–642; Bezerra JA, *et al. Hepatology* 2018; **68:**1163–1173; Schwarz KB, *et al. Hepatology* 2013; **58:**1724–1731; Zhan J, *et al. Asian J Surg* 2017; **40:**429–433; Bezerra JA, *et al. JAMA* 2014; **311:** 1750–1759.

Biliary atresia is classified as a rare disease

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

Europe:
Incidence ~1 in 18,000 live births[1]

Japan:
Incidence ~1 in 5,000 live births[2]

There is considerable geographic variation in the incidence of biliary atresia, but the underlying reasons are unknown; however, females are more commonly affected[3]

1. Feldman AG & Mack CL. *J Pediatr Gastroenterol Nutr* 2015; **61**:167–175; 2. Friedmacher F, *et al. J Hepatobiliary Pancreat Sci* 2019; **26**:201–210; 3. Mezina A & Karpen S. *Dig Dis* 2015; **33**:408–414.

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

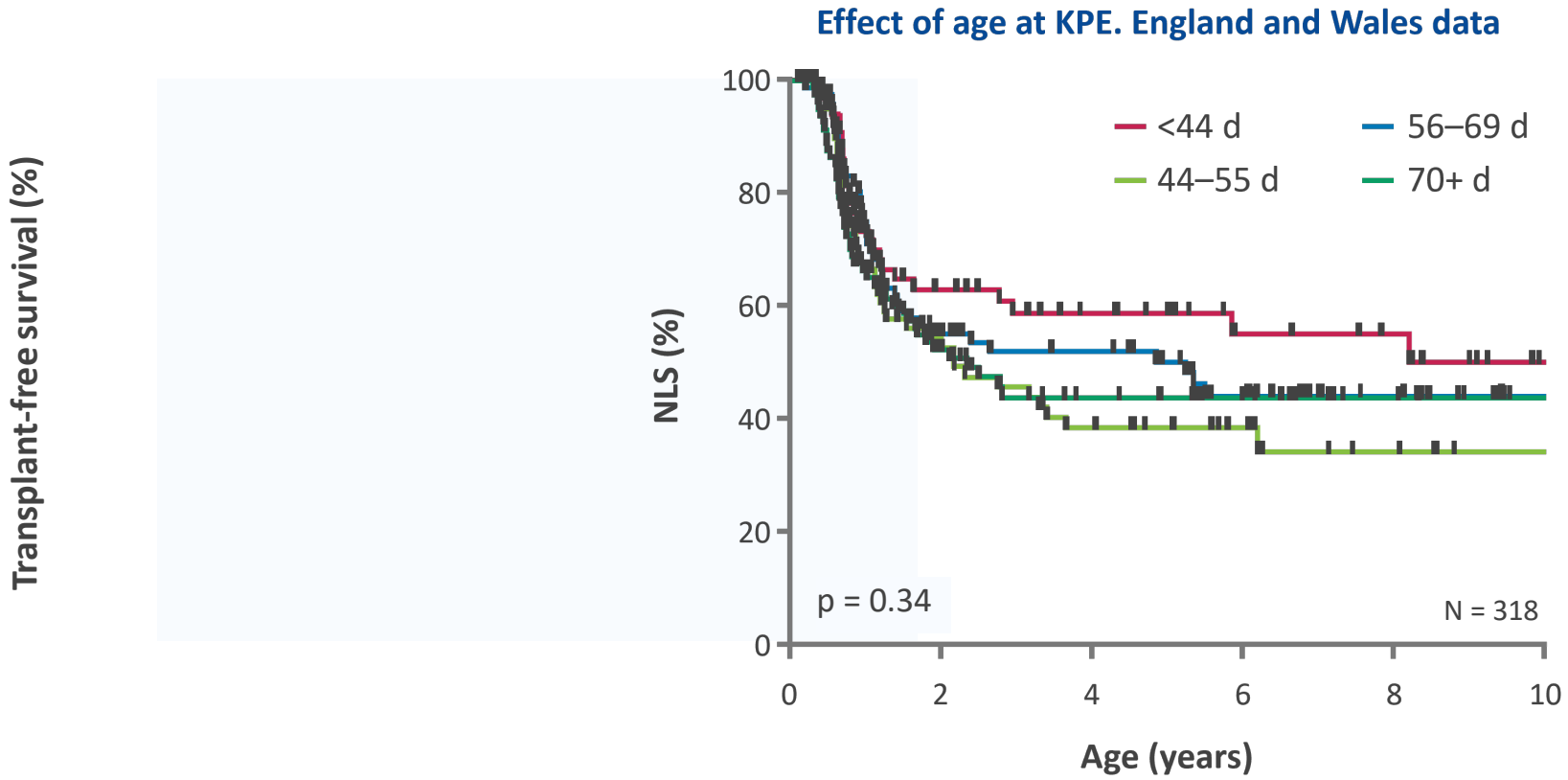
	Alpha-1 antitrypsin deficiency[1]	ALGS[2,3]	Neonatal sclerosing cholangitis[4,5]
Overlapping features	Can show features (e.g. biochemical, HIDA and histology) that closely mimic BA despite being a non-obstructive process	Ductular proliferation is present early in a small number of infants with ALGS, and ductopenia can occur later on	Histopathology closely resembles BA
Exclude other diagnoses	Phenotype/genotype for alpha-1	Clinical and/or genetic investigation for ALGS, family history, involvement of extrahepatic organs	Cholangiogram for patency of bile ducts and immune workup

A diagnosis of BA is confirmed with intraoperative cholangiogram and supportive histology of resected material[5]

BA, biliary atresia; HIDA, hepatobiliary iminodiacetic acid.

1. Moreira RK, *et al. Arch Pathol Lab Med* 2012; **136**:746–760; 2. Turnpenny PD & Ellard S. *Eur J Hum Genet* 2012; **20**:251–257; 3. Mysore KR, *et al. Pediatr Gastroenterol Nutr* 2019; **69**:396–403;
4. Shetty NS & Shah I. *J Family Med Prim Care* 2016; **5**:863–864; 5. Fawaz R, *et al. J Pediatr Gastroenterol Nutr* 2017; **64**:154–168.

Performing Kasai procedures early associated with higher transplant-free survival



Performing the Kasai procedure early is associated with higher transplant-free survival and improved jaundice clearance

d, days; KPE, Kasai portoenterostomy.
England and Wales data: Infants with isolated biliary atresia (N = 318) were divided by age at surgery; French data: A total of 685 children were included in the analysis.
Davenport M, *et al. J Pediatr Surg* 2011; **46**:1689–1694, reprinted from *Journal of Pediatric Surgery*, 46, Davenport M, *et al.*, 'Biliary atresia in England and Wales: results of centralization and new benchmark', 1689–1694, Copyright (2011), with permission from Elsevier.

Performing Kasai procedures early correlates with higher transplant-free survival

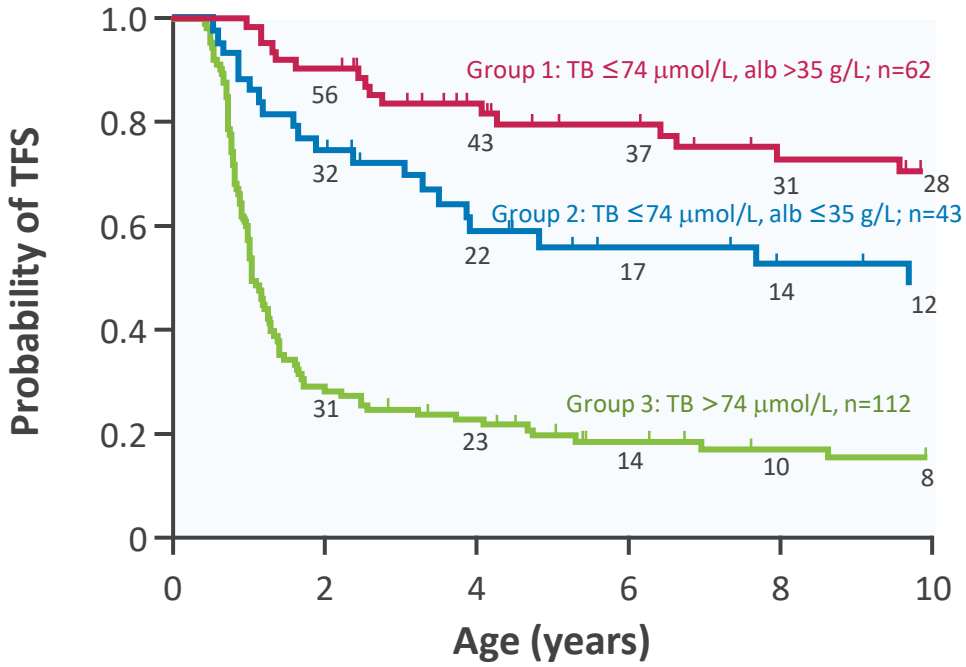
Study	Outcome	*N*	Time of Kasai procedures: 30 days	60 days	90 days	120 days
United States 1976–1989	5-year overall survival	816	**63%**	44%	40%	29%	29%
Canada 1985–2002	4-year transplant-free	312	**49%**	36%		28%
France 1986–2002	5-year transplant-free	695	**58%**	41%	42%	36%	26%	27%
United States 1997–2000	2-year transplant-free	100	**70%**	54%	50%	50%

Age cutoffs among studies varied, but all showed better outcomes when the Kasai procedure was performed earlier

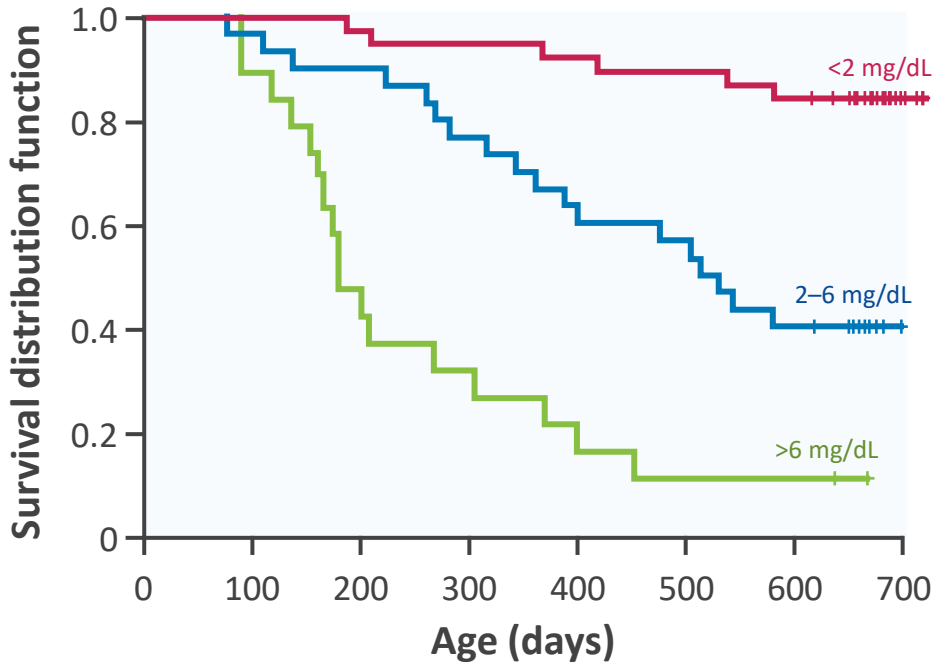
Mysore KR, *et al.* 'Biliary Atresia as a Disease Starting In Utero: Implications for Treatment, Diagnosis, and Pathogenesis', *Journal of Pediatric Gastroenterology and Nutrition* 2019; **69**(4):396–403, https://journals.lww.com/jpgn/Fulltext/2019/10000/Biliary_Atresia_as_a_Disease_Starting_In_Utero_.3.aspx.

Lower total bilirubin after Kasai procedure is a positive predictive marker for TFS

Kaplan-Meier plots of TFS based on total bilirubin and albumin levels 3 months post-Kasai[1]



Kaplan-Meier analysis of outcome based on total bilirubin level 3 months post-Kasai[2]



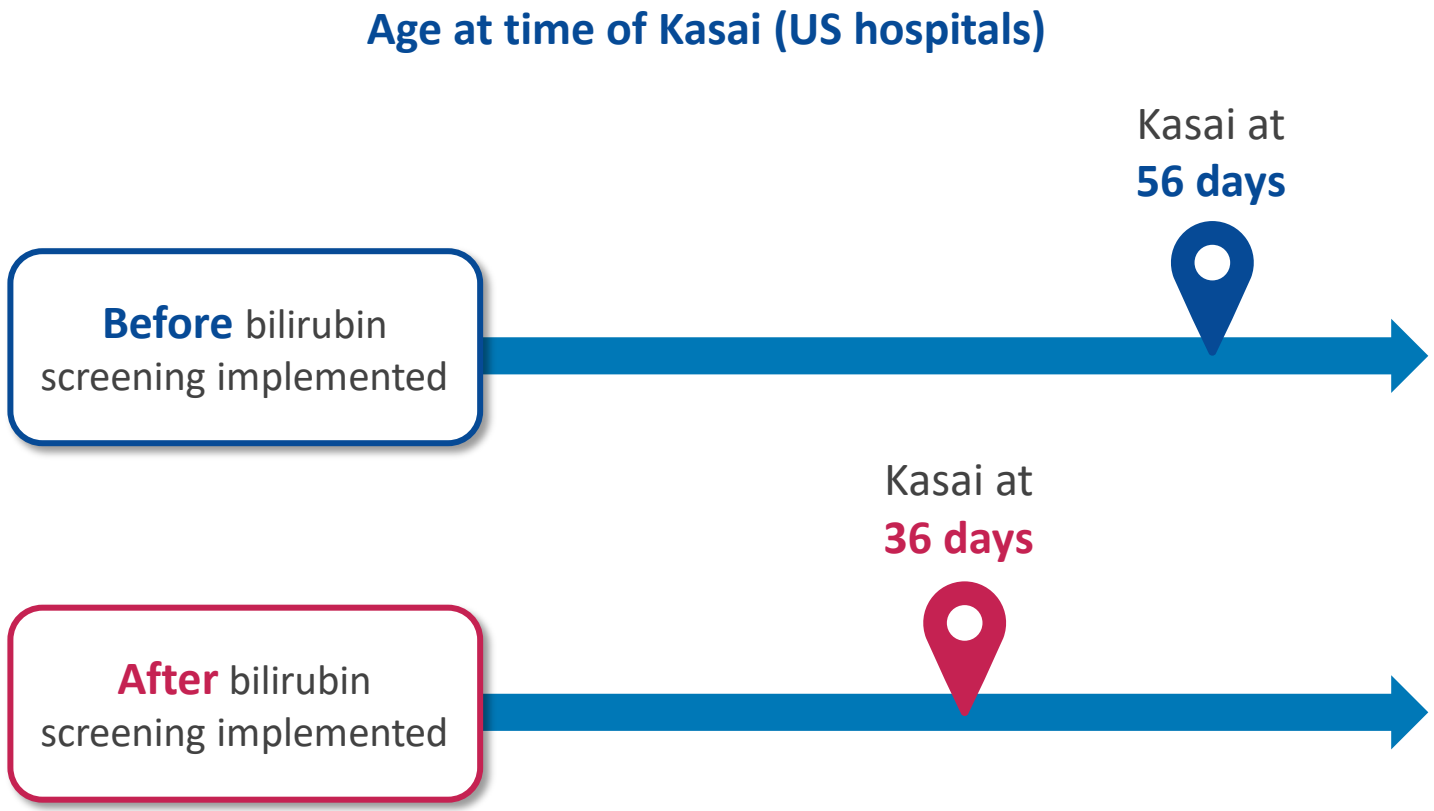
Total serum bilirubin level measured at 3 months post-Kasai is a marker of response that predicts TFS[2]

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

1. Nightingale S, *et al.* 'Early Posthepatoportoenterostomy Predictors of Native Liver Survival in Biliary Atresia', *Journal of Pediatric Gastroenterology and Nutrition* 2017; **64**(2):203–209, https://journals.lww.com/jpgn/Fulltext/2017/02000/Early_Posthepatoportoenterostomy_Predictors_of.10.aspx; 2. Shneider BL, *et al. Pediatr* 2006; **148:**467–474, reprinted from *The Journal of Pediatrics*, 148, Schneider BL, *et al.*, 'A multicenter study of the outcome of biliary atresia in the United States, 1997 to 2000', 467–474, Copyright (2006), with permission from Elsevier.

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

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



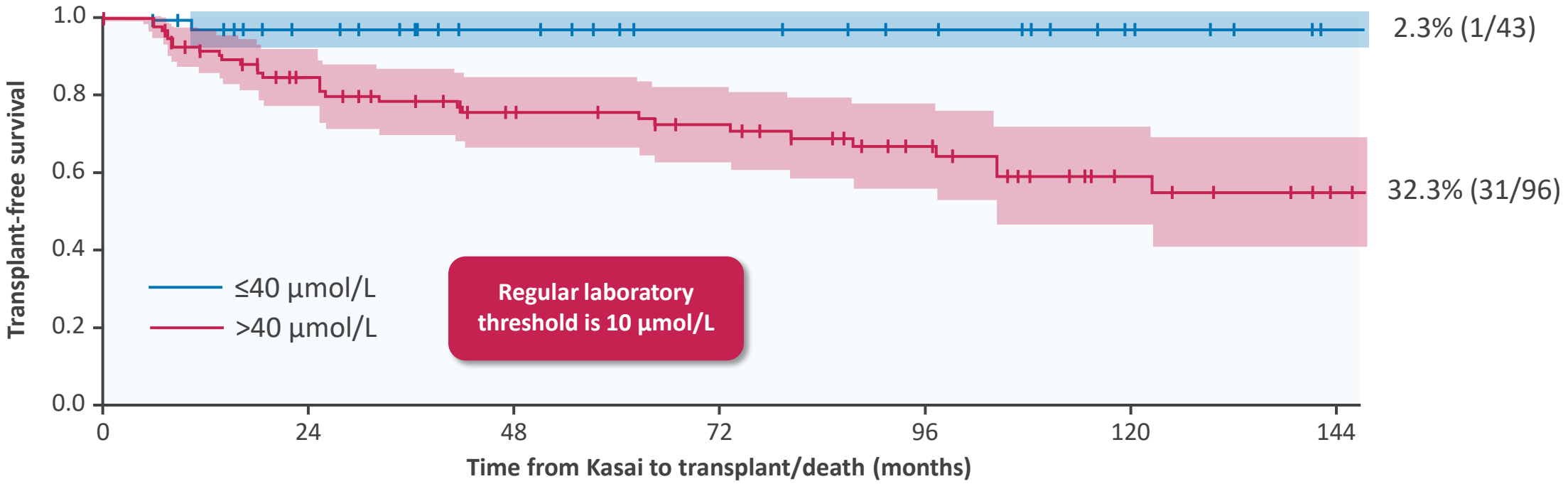
The implementation of bilirubin (direct or conjugated) screening resulted in children undergoing the Kasai procedure at significantly younger ages

BA, biliary atresia; HoL, hours of life.

Harpavat S, *et al. JAMA* 2020; **323**:1141–1150; Harpavat S, *et al. Pediatrics* 2011; **128**:1428–1433.

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

Transplant/death (p=0.0006)



≤40 µmol/L	43	34	23	18	14	7	2
>40 µmol/L	96	69	50	42	28	14	7

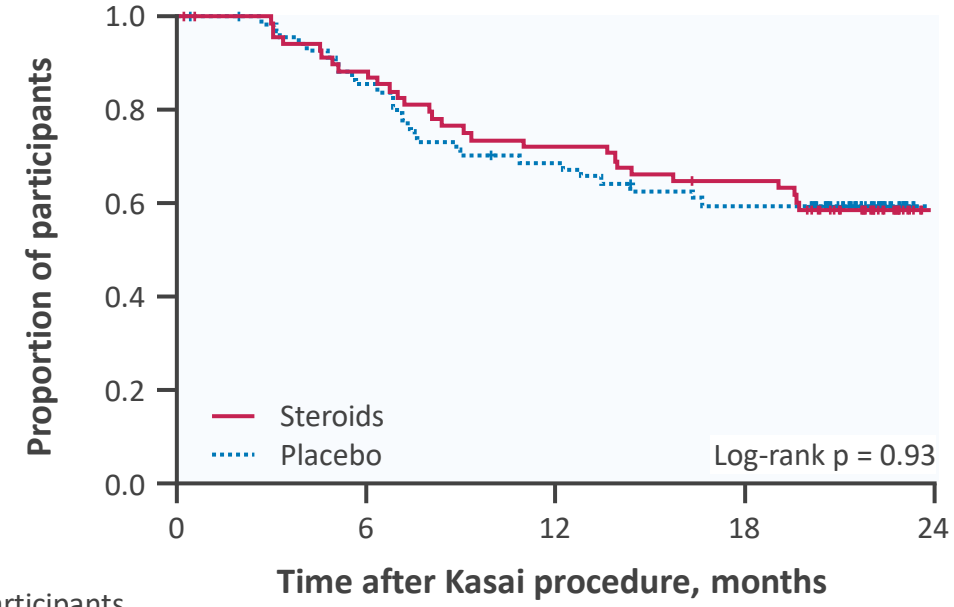
In patients achieving bile flow with the Kasai procedure, sBA measured 6 months post-Kasai can predict long-term outcomes

Harpavat S, *et al.* AASLD 2020 (oral).

How to improve outcomes for patients with biliary atresia

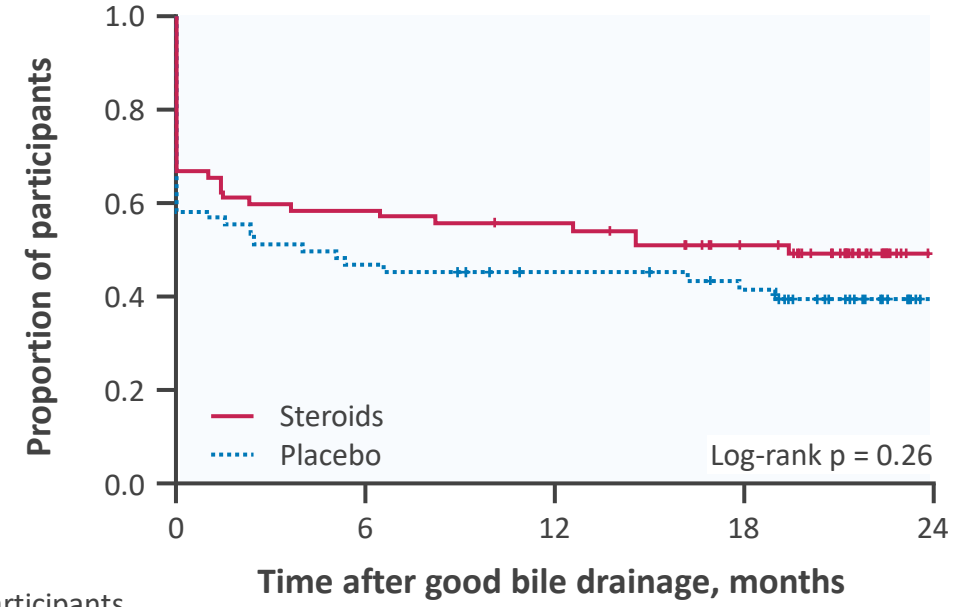
START study: High-dose steroids given post-Kasai did not decrease TFS or improve biliary drainage (bilirubin <1.5 mg/dL after 6 months)

Kaplan-Meier analysis of survival with native liver based on steroid use or placebo post-Kasai procedure



No. of participants					
Steroids	70	60	49	43	0
Placebo	70	57	45	38	2

Kaplan-Meier analysis of duration of good bile drainage based on steroid use or placebo post-Kasai procedure



No. of participants					
Steroids	70	41	37	29	0
Placebo	70	32	26	22	0

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

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

The implementation of IBAT inhibitors on biliary atresia outcomes

- When analyzed over 5 studies, average 20-year TFS in biliary atresia was estimated at 29%[1–5]

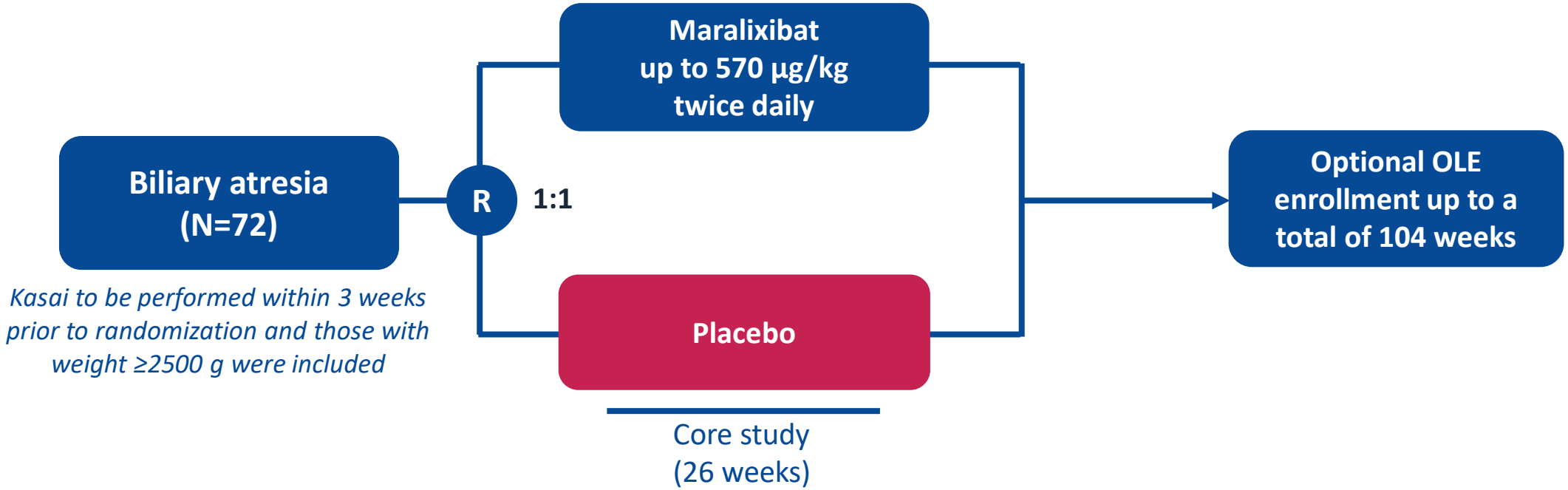
- Unique indications for liver transplant in biliary atresia include:[1–6]
  - Failed Kasai procedure
  - Late diagnosis, cirrhosis, and no Kasai
  - Recurrent bacterial cholangitis, resistant bacteria, fungal infection, and bile lakes leading to life-threatening sepsis

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

1. Lykavieris P, *et al. Hepatol* 2005; **41**:366–371; 2. Shinkai M, *et al. J Pediatr Gastroenterol Nutr* 2009; **48**:442–450; 3. de Vries W, *et al. Clin Gastroenterol Hepatol* 2011; **9**:1086–1091; 4. Chardot C, *et al. J Hepatol* 2013; **58**:1209–1217; 5. Wong CWY, *et al. J Pediatr Gastroenterol Nutr* 2018; **66**:570–574; 6. Sundaram SS, *et al. Liver Transpl* 2017; **23**:96–109; 7. Gonzales E, *et al. Lancet* 2021; **398**:1581–1592.

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

Investigational therapy



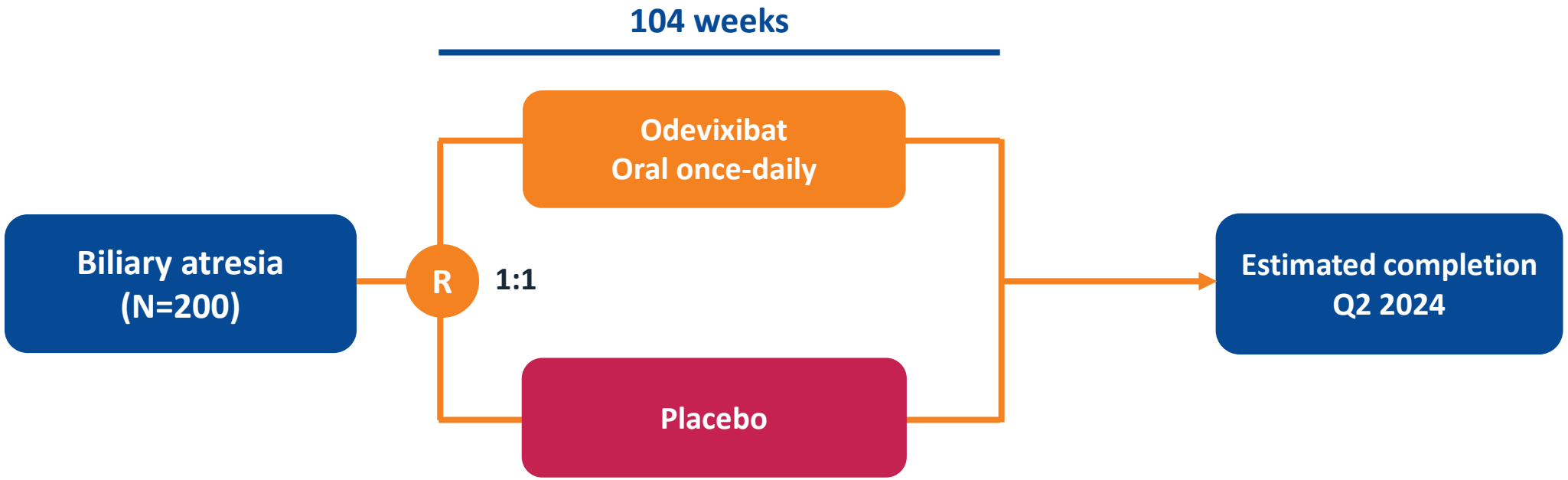
Kasai to be performed within 3 weeks prior to randomization and those with weight ≥2500 g were included

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

ALT, alanine transaminase; GGT, gamma-glutamyltransferase; OLE, open label extension; sBA, serum bile acid.
ClinicalTrials.gov. ID: NCT04524390. Accessed online at https://clinicaltrials.gov/ct2/show/NCT04524390 November 19, 2021.

BOLD: Phase 3 study of odevixibat in children with biliary atresia

Investigational therapy



Primary endpoint	Secondary endpoints
• Proportion of patients with liver transplant after 104 weeks of treatment	• Time to onset of any sentinel events • Time to PELD score >15 from baseline to Week 104 • Total bilirubin and sBA levels from baseline to Weeks 13, 26, 52, and 104

PELD, pediatric end-stage liver disease; sBA, serum bile acid.
ClinicalTrials.gov. ID: NCT04336722. Accessed online at https://clinicaltrials.gov/ct2/show/NCT04336722 November 19, 2021.

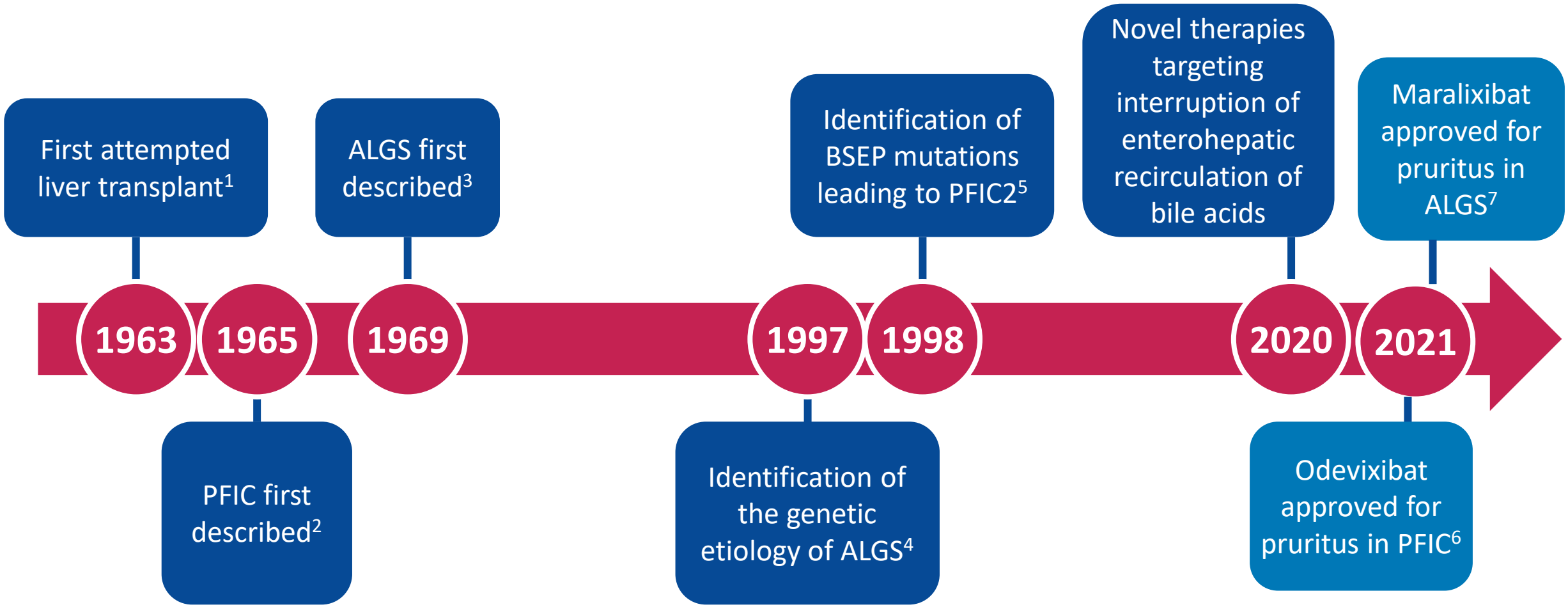
Biliary atresia summary

- Biliary atresia is progressive obliterative cholangiopathy of infancy
- Early diagnosis is crucial to differentiate biliary atresia from ALGS and other diseases, and is associated with improved transplant-free survival for children with biliary atresia
- Biliary atresia remains the leading indication for liver transplantation in children across age groups
- Kasai portoenterostomy procedure is the standard of care to re-establish bile flow
- Lower serum bile acids are a powerful prognostic marker after a successful Kasai procedure
- Trials of IBAT inhibitors are underway in children with biliary atresia (following Kasai procedure) to improve transplant-free survival

IBAT, ileal bile acid transporter.

Q & A

Where have we been, and where are we now?



BSEP, bile salt export pump.

1. Meirelles Júnior RF, *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**:152–157; 4. Li L, *et al. Nat Genet* 1997; **16**:243–251; 5. Strautnieks SS, *et al. Nat Genet* 1998; **20**:233–238; 6. Albireo Pharma, Inc. Bylvay™ (odevixibat). Prescribing Information. 2021. Accessed online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215498s000lbl.pdf on November 15, 2021; 7. Mirum Pharmaceuticals Inc. LIVMARLI™ (maralixibat) Prescribing Information. 2021. Accessed online at: https://files.mirumpharma.com/livmarli/livmarli-prescribinginformation.pdf on October 20, 2021.

IMPORTANT: Meeting evaluation

Please complete the meeting evaluation

Please scan the QR code to download the presentation slides

Thank You