



A long-term phase 2 safety and efficacy study of the apical sodium-dependent bile acid transporter inhibitor maralixibat in children with Alagille syndrome: preliminary results from the IMAGINE study

Richard J Thompson
King's College London, London, UK

Co-authors

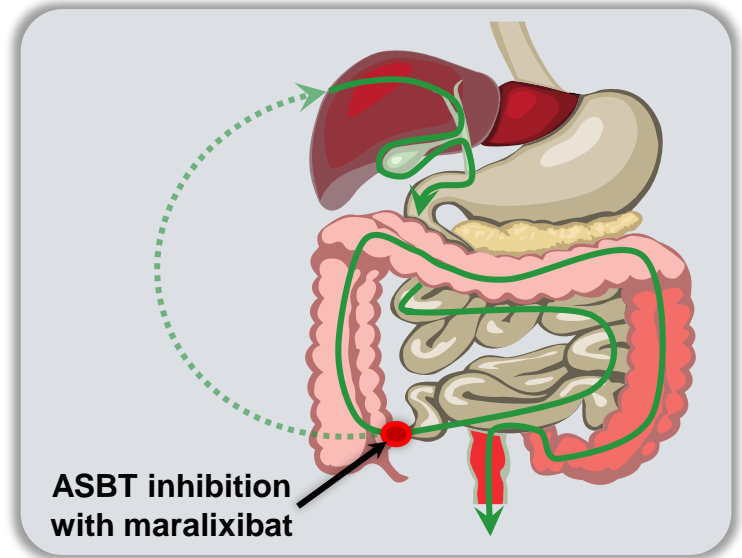
- Alastair Baker,¹ Deirdre A Kelly,² Joan Gu,³ Thomas Jaecklin,⁴ Patricia McClean,⁵ Binita M Kamath,⁶ Benjamin L Shneider⁷
 1. Paediatric Liver Centre, King's College Hospital, London, UK
 2. Liver Unit, Birmingham Children's Hospital, Birmingham, UK
 3. Shire, Lexington, MA, USA
 4. Shire, Zug, Switzerland
 5. Children's Liver Unit, Leeds General Infirmary, Leeds, UK
 6. Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
 7. Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine, Houston, TX, USA

Disclosures

- Note to authors: AASLD will add a disclosures slide based on the information you provided for the abstract submission

Maralixibat: a potential treatment for children with Alagille syndrome

- Alagille syndrome (ALGS) is a genetic disorder affecting multiple organs including the liver^{1,2}
 - ALGS manifests in infancy or childhood
 - Bile duct abnormalities lead to cholestasis and often end-stage liver disease and early death
- Maralixibat is a potent, selective, minimally absorbed inhibitor of the ileal apical sodium-dependent bile acid transporter (ASBT)³
- Pharmacological inhibition of enterohepatic bile acid circulation:
 - can reduce serum bile acid (sBA) levels⁴
 - may relieve symptoms of cholestasis

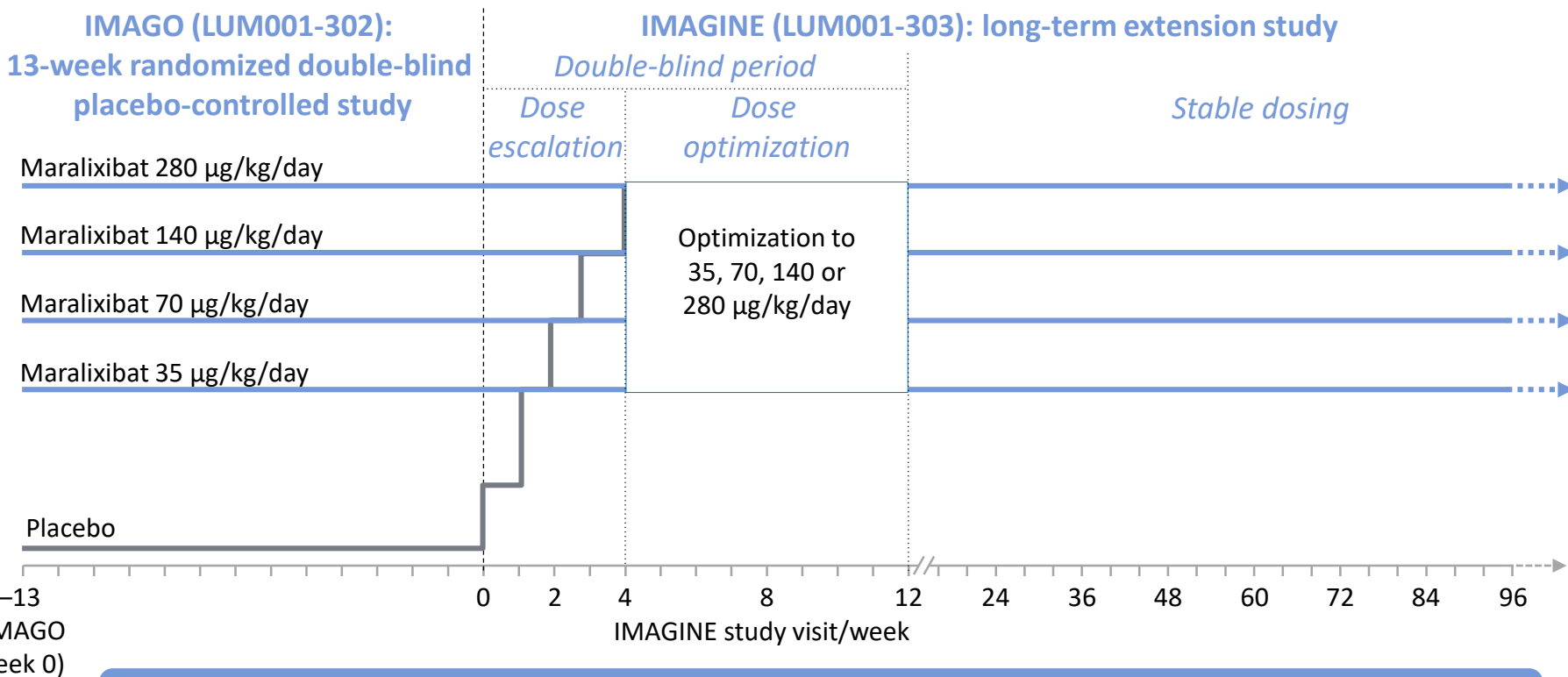


Maralixibat = SHP625 = LUM001

1. Saleh M *et al. Appl Clin Genet* 2016;9:75–82 | 2. Hartley JL *et al. Clin Liver Dis* 2013;17:279–300 |

3. Gedulin B *et al. Hepatology* 2014;60:275A | 4. Mayo MJ *et al. J Hepatol* 2014;64:S197

Study design: IMAGO and the IMAGINE extension



We present results from an *ad hoc* snapshot analysis of data up to week 96

Inclusion/exclusion criteria

Key inclusion criteria

- Completed IMAGO to week 13
- IMAGO inclusion criteria
 - Diagnosis of ALGS
 - Male or female aged 1–18 years
 - sBA > 3 × ULN
 - Intractable pruritus
 - Itch Reported Outcome (ItchRO) average daily score ≥ 2
 - Native liver
 - Consistent caregiver for study

Key exclusion criteria

- Maralixibat-related AE in IMAGO that led to discontinuation
- Non-adherent in IMAGO
- IMAGO exclusion criteria
 - Chronic diarrhea
 - Surgically disrupted enterohepatic circulation
 - Decompensated cirrhosis
 - ALT or AST > 15 × ULN
 - Other liver disease
 - HIV infection
 - Cancers

Reported outcomes and analyses

Outcomes

- Primary efficacy: change in sBA levels from baseline
 - Baseline was IMAGO week 0 (IMAGINE week –13)
- Pruritus assessments
 - ItchRO average daily score (parent-rated e-diary)^a
 - Clinician Scratch Scale (CSS) score (investigator-rated)
- Treatment-related AEs

Analyses

- Initial *ad hoc* analysis of data up to week 96
 - Study database not yet locked
- No inferential statistical hypothesis testing was planned or performed
- Treatment response was defined as:
 - ≥ 70% decrease in sBA levels from IMAGO baseline and
 - > 1.0-point improvement in ItchRO average daily score from IMAGO baseline
 - at ≥ 2 of the last 3 study visits

^aCompleted twice daily during weeks 0–12, 24–28, 44–48, 84–86 and 96–98

Disposition, demographics and disease characteristics

Enrolled participant characteristics (N = 19)

Characteristic	Value
Age, years, median (range)	5.0 (1, 17)
Sex	
Male, n (%)	10 (52.6)
Race, n (%)	
White	16 (84.2)
Country, n (%)	
UK	19 (100)

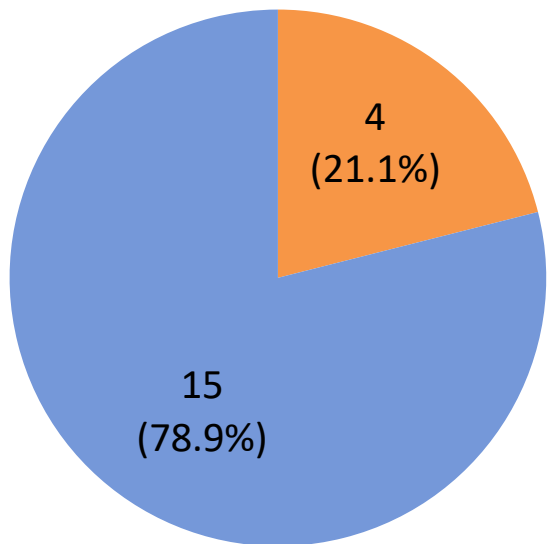
Disposition to week 96

	N
Completed IMAGO	19
Maralixibat	14
Placebo	5
Entered IMAGINE and received maralixibat	19
Did not consent to further extension	12
Completed to week 72	9
Terminated early ^a	3
Consented to further extension	7
Remained in study at week \geq 96	6
Terminated early ^b	1

^aWithdrawal by caregiver (n = 3)

^bAE (n = 1)

Analysis of treatment response



■ Responder
 ■ Non-responder

ID	IMAGINE study week							
	2	4	8	12	24	48	84	96
A	✓	✓	✓	✓	✓		✓	✓
B		✓					✓	✓
C	✓	✓	✓		✓	✓	✓	✓
D	✓		✓	✓	✓		DNC	

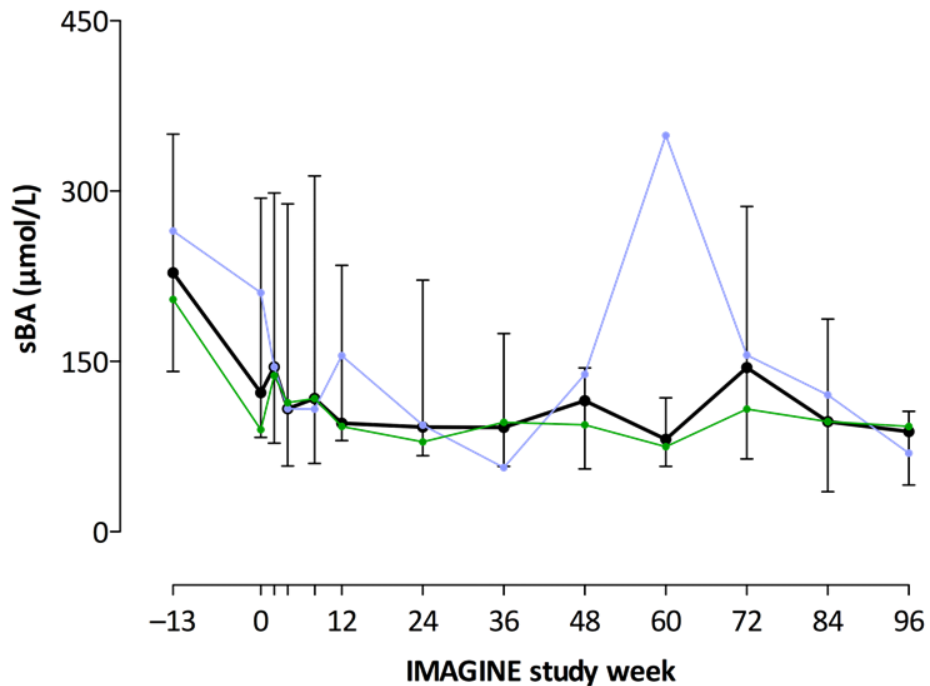
✓ $\geq 70\%$ decrease in sBA *and*
 > 1.0 -point improvement in ItchRO(Obs)^a
 (Required at ≥ 2 of last 3 visits for response)

^aFrom IMAGO baseline (IMAGINE week -13)

DNC, did not consent to optional further extension

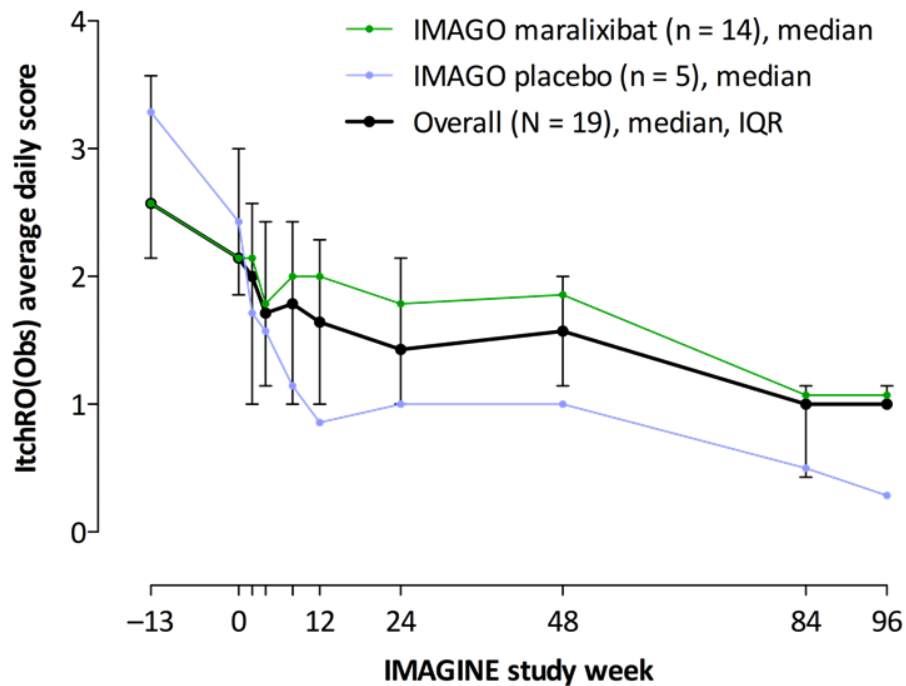
IMAGINE sBA and ItchRO(Obs) results overall and in previous IMAGO treatment subgroups

sBA



●	n = 14	13	13	13	13	12	11	9	4	4
●	n = 5	5	5	5	5	5	3	3	2	2
●	n = 19	18	18	18	18	17	14	12	6	6

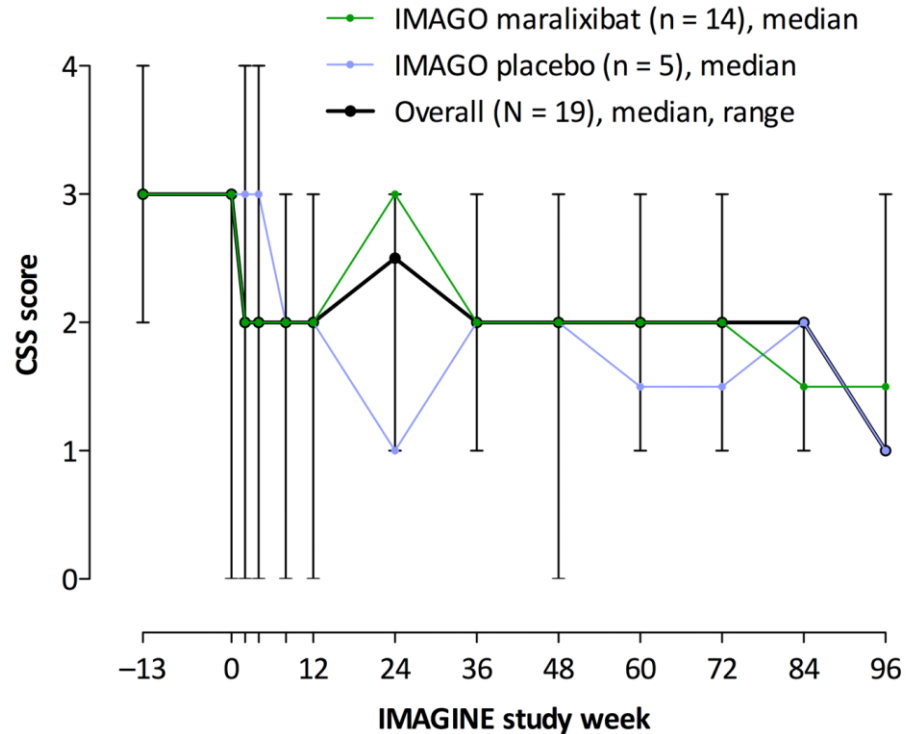
ItchRO(Obs)



● IMAGO maralixibat (n = 14), median
 ● IMAGO placebo (n = 5), median
 ● Overall (N = 19), median, IQR

●	14	14	13	12	12				4	4
●	5	5	5	5	5				2	1
●	19	19	18	17	17				6	5

IMAGINE CSS results overall and in previous IMAGO treatment subgroups



●	n = 14	14	13	13	12	11	11	12	4	4
●	n = 5	5	5	5	5	5	4	4	2	2
●	n = 19	19	18	18	17	16	15	16	6	6

Potentially maralixibat-related treatment-emergent AEs (TEAEs)

TEAE	Participants, n (%)
Any	13 (68.4)
Leading to discontinuation	1 (5.3)
Maximum severity	
Mild	9 (47.4)
Moderate	3 (15.8)
Severe	1 (5.3)
Life-threatening or fatal	0 (0.0)
Serious	1 (5.3)

One participant had a serious maralixibat-related TEAE of ALT increased from week 48 onwards that led to discontinuation at week 58

TEAE	Participants, n (%)
Gastrointestinal	11 (57.9)
Abdominal pain	9 (47.4) ^a
Diarrhoea	6 (31.6)
Abnormal faeces	1 (5.3) ^a
Flatulence	1 (5.3)
Nausea	1 (5.3)
Vomiting	1 (5.3)
Investigations	4 (21.1)
INR increased	2 (10.5)
ALT increased	1 (5.3)
Bilirubin urine	1 (5.3)
Blood bilirubin increased	1 (5.3)
Vitamin D deficiency	2 (10.5)

^aSevere TEAEs in one participant (all others mild/moderate)

INR, international normalized ratio

Summary

- sBA levels and pruritus scores improved with maralixibat treatment in the study population
 - These effects were maintained for up to 96 weeks in this snapshot
- 4/19 participants were classified as responders to maralixibat
- Improvement in parent-rated ItchRO scores appeared greatest in participants who switched from double-blind placebo
- Maralixibat-related AEs were generally gastrointestinal in nature and mild or moderate in severity
 - One participant withdrew because of persistently elevated ALT

Conclusions

- These results suggest that maralixibat provided long-term pruritus relief and reduced sBA levels in a subset of children with ALGS
 - Factors determining response in certain patients remain unclear
- Mild or moderate gastrointestinal AEs were consistent with the mode of action of maralixibat
- Further studies involving more patients and a longer placebo-controlled period are needed to confirm the long-term benefits and risks of maralixibat as a treatment for cholestatic liver disease

Acknowledgements

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