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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2021

Maralixibat for cholestatic liver disease in patients with Alagille syndrome

NIHRIO ID	9218	**NICE ID**	7895
Developer/Company	Mirum Pharmaceuticals	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Maralixibat is in clinical development for the treatment of Alagille syndrome. Alagille syndrome is an inherited developmental disorder, caused by a mutation in the JAG1 gene or in the Notch2 gene. The mutation causes problems with early embryonic development leading to abnormalities in various parts of the body. Most patients with this disorder have liver abnormalities resulting from having too few bile ducts. Due to the reduced number of ducts, bile acids build up in the liver and damage the liver tissue as well as causing severe itching which can significantly limit quality of life and sleep. Alagille syndrome is a long-term debilitating and life-threatening disease that has no approved treatments and many patients require liver transplants before adulthood.

Maralixibat is an orally administered drug that blocks certain channels called ileal bile acid transporters through which the bile acids leave the intestine to reach the blood vessels that carry them back to the liver. By blocking these channels, maralixibat is expected to help reduce the amount of toxic bile acids in the liver, thereby reducing the itching and other quality of live measures in patients with Alagille syndrome. If licensed, maralixibat will provide a treatment option for patients with Alagille syndrome, a disease of unmet clinical need.

PROPOSED INDICATION

Treatment of cholestatic disease in patients with Alagille Syndrome aged 1 year and older.[1-5]

TECHNOLOGY

DESCRIPTION

Maralixibat (LUM001, SHP-625) is a novel, oral, minimally absorbed selective inhibitor of the apical sodium-dependent bile acid transporter (ASBT). ASBT is present in the small intestine and mediates the uptake of bile acids in the intestines, recycling them back to the liver. ASBT inhibition results in more bile acids being excreted in the faeces, leading to lower levels of bile acids systemically, thereby reducing bile acid mediated liver damage. This leads to improvements in liver function, pruritus, xanthomas (lipid accumulation in the skin), quality of life (QOL), growth and other symptoms of cholestatic liver diseases.[6]

Maralixibat is currently in clinical development for the treatment of Alagille Syndrome. In phase II trials (ICONIC, NCT02160782) patients received maralixibat administered orally a dosage of up to 400 µg/kg twice daily.[2-5,7]

INNOVATION AND/OR ADVANTAGES

For patients with Alagille syndrome there are no approved treatment options for treating cholestatic liver disease and the associated pruritus. Antihistamines, rifampin, ursodeoxycholic acid, cholestyramine, naltrexone, and sertraline may be used but clinical experience suggests that these drugs have variable efficacy in reducing pruritus or improving liver health.[8,9]

Infants and children with Alagille syndrome who do not respond to pharmacologic therapy may be treated with liver transplantation and only 24-41% of patients remain transplant free by adulthood.[10,11] The mechanism of action of maralixibat aims to lower the levels of serum bile acids through ASBT inhibition, hopefully achieving the pruritus reduction without liver transplantation.[8]

In the Phase 2 ICONIC study in children with Alagille syndrome, maralixibat treatment led to improvement in pruritus, xanthomas and bile acids over 48 weeks which were maintained with long-term treatment over 191 weeks. Long-term treatment with maralixibat in the ICONIC trial also resulted in clinically and statistically significant improvements in height z-scores from baseline to week 191.[12] All of these findings were statistically significant.[13] In the ITCH and IMAGINE trials children with Alagille syndrome who received 48 weeks of maralixibat had clinically meaningful reduction in pruritus and improvement in quality of life. These changes persisted for at least 96 weeks in those who were able to continue to receive maralixibat.[14]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Maralixibat does not currently have Marketing Authorisation in the EU/UK for any indication.

In January 2014, maralixibat was granted orphan designation for the treatment of Alagille syndrome.[15]

In October 2019, the FDA granted maralixibat Breakthrough Therapy Designation for the treatment of pruritus associated with Alagille syndrome in patients 1 year of age and older.[16] Maralixibat is in phase II clinical development for biliary atresia, and phase III development for Progressive Familial Intrahepatic Cholestasis (PFIC).[17]

PATIENT GROUP

DISEASE BACKGROUND

Alagille syndrome is a rare genetic disorder caused by a mutation in the JAG1 or in the Notch2 gene, which are involved in embryonic development in utereo.[15,18] These mutations are inherited as autosomal dominant traits, however in about half of cases the mutation occurs as a new change ("de novo") in the individual and was not inherited from a parent.[19] In patients with Alagille syndrome, multiple organ systems may be affected by the mutation, including the liver, heart, kidneys and central nervous system. It is reported that 79% of Alagille patients present with neonatal cholestatis.[11] In the liver, the mutation causes the bile ducts to be abnormally narrow, malformed and reduced in number, leading to bile accumulation in the hepatocytes. The accumulation of bile acids prevents the liver from working properly to eliminate waste from the bloodstream (cholestasis) and leads to progressive liver disease. Studies have suggested only 24 to 41% of patients have transplant free survival by adulthood.[10,11]

Signs and symptoms arising from liver damage in Alagille syndrome may include jaundice, pruritus and xanthomas, which are disfiguring cholesterol deposits under the skin. The pruritus experienced by patients with Alagille syndrome is among the most severe in any chronic liver disease and is present in most affected children by the third year of life.[16] The intense pruritus can often be debilitating, causing cutaneous mutilation and disruption of sleep, psychosocial issues and school activities.[8] Individuals with Alagille syndrome can develop abnormalities of certain blood vessels (vascular anomalies) including those in the brain, liver, lungs, heart, and kidneys. Intracranial bleeding and other vascular anomalies are potentially life-threatening complications and account for a significant percentage of mortality and morbidity in Alagille syndrome.[19]

CLINICAL NEED AND BURDEN OF DISEASE

Alagille syndrome affects males and females in equal numbers.[19] Based on European data the prevalence of Alagille syndrome is estimated to be 0.8 per 100,000 births.[20] Some cases of Alagille syndrome may go undiagnosed and is often misdiagnosed making it difficult to determine the true frequency of Alagille syndrome in the general population.[19]

Alagille syndrome is included in the ICD-10 code group Q44.7 “Other congenital malformations of liver”. Hospital Episode Statistics recorded 78 finished consultant episodes, 66 admissions and 26 day cases with the code Q44.7 in England in 2019-20.[21] In England and Wales in 2019, 1 death was recorded with ICD-10 code Q44.7.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of Alagille syndrome is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists and is usually carried out at a limited number of treatment centers. Pediatricians, gastroenterologists, cardiologists, ophthalmologists, and other healthcare professionals may need to systematically and comprehensively plan an affect child’s treatment.[19] Treatment is non-specific and includes high-carbohydrates and high-medium chain triglyceride diets and vitamin supplementation. The associated pruritus may be reduced by cholestyramine or rifampin.[18]

Infants and children with Alagille syndrome who do not respond to pharmacologic therapy are often treated with liver transplantation and in one analysis, only 24% of patients remained transplant free by age 18.[10] Cardiac or vascular procedures may be required for significant symptomatic lesions.[18]

CURRENT TREATMENT OPTIONS

There are no authorised pharmacologic treatments in the EU for Alagille syndrome.[15]

PLACE OF TECHNOLOGY

If licensed, maralixibat will provide a medicinal treatment option for patients with Alagille syndrome aged 1 year and older, who have few effective treatment options.

CLINICAL TRIAL INFORMATION

Trial	**ITCH, LUM001-301, NCT02057692;** The Evaluation of the Intestinal Bile Acid Transport (IBAT) Inhibitor LUM001 in the Reduction of Pruritus in Alagille Syndrome, a Cholestatic Liver Disease **Phase II** - Completed **Location:** Canada and United states. **Primary completion date:** November 2016	**IMAGINE-II, LUM001-305,** NCT02117713; A Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects With Alagille Syndrome **Phase II –** Completed, extension **Location:** Canada and United States **Primary completion date:** June 2020
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled.	Multicentre, single group assessment, extension study
Population	N= 37, aged 12 months to 18 years, diagnosis of Alagille Syndrome with evidence of cholestasis and moderate to severe pruritus.	N=34, aged 1 year to 18 years, completed participation in the LUM001-301 protocol.
Intervention(s)	The dose escalation phase started with 14 microgram per kilogram per day (mcg/kg/day) per week on Week 1 up to 280 mcg/kg/day for a maximum up to 5 weeks, until they reached the planned stable dose of 70, 140 and 280 mcg/kg/day and continued up to Week 13.[8]	Maralixibat (LUM001) as oral solution once daily based on participant's weight.
Comparator(s)	Placebo.	None.
Outcome(s)	Primary outcome(s): • Change from Baseline to Endpoint (Week 13/Early Termination) in Pruritus [Time frame: baseline, week 13/early termination].	Primary outcome(s): • Number of participants with adverse events as a measure of safety and tolerability [Time frame: baseline to Week 216]

	See trial record for full list of other outcomes.	See trial record for full list of other outcomes.
Results (efficacy)	• In the first analysis of the primary efficacy endpoint, the mean adjusted difference between maralixibat and placebo was −0.47 (95% CI, −1.14, 0.20; P = 0.16). Relative to placebo, significant decreases were observed with the individual doses of 70 and 140 µg/kg/day (mean adjusted difference, −0.89; P = 0.032; and mean adjusted difference, −0.91; P = 0.014, respectively). No change was observed in the group receiving 280 µg/kg/day (mean adjusted difference, −0.04; P = 0.44). The change in maralixibat relative to placebo was not statistically significant (mean adjusted difference, 0.61; P = 0.055).[8] See trial record for full results.	• Mean ItchRO and clinician scratch score (CSS) decreased while PedsQL increased from ITCH baseline to week 48 of IMAGINE II with stability of response through week 96 and beyond for an average of 92 additional weeks in selected participants.[14] • At week 48 cholesterol, serum bile acids and platelets decreased, ALT and GGT increased, while total bilirubin and albumin were unchanged. Height (+0.4) and weight (+0.3) z-scores increased with 96 weeks of Maralixibat (MRX). [14]
Results (safety)	• Treatment emergent Adverse Events (AEs) were common and comparable in participants receiving maralixibat and placebo. Given the proposed mechanism of action of maralixibat, gastrointestinal AEs, including diarrhoea and abdominal pain, were of special interest and found to occur at similar rates in maralixibat-treated and placebo-treated participants (overall gastrointestinal, 52% versus 58%; diarrhoea, 32% versus 50%; abdominal pain, 16% versus 17%, respectively).[8] See trial for full results.	• 7/34 (21%) participants had at least one SAE during IMAGINE II.[14] • 14 participants were withdrawn before the completion of IMAGINE II (3 caregiver withdrawal, 3 elevated ALT, 2 liver transplant, 1 each hematochezia, pancreatitis, nonadherence, progressive cholestasis, elevated total bilirubin, autoimmune hepatitis).[14]

Trial	**ICONIC, LUM001-304, NCT02160782, EudraCT** 2013-005373-43**;** Long-Term, Open-Label Study With a Double-Blind, Placebo-Controlled, Randomized Drug Withdrawal Period of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in Patients With Alagille Syndrome **Phase II** - Completed **Location:** EU (inc UK) countries and Australia. **Primary completion date**: May 2020
Trial design	Open-label study with a double-blind, placebo-controlled, randomised drug withdrawal period.

Population	N = 31, aged 12 months to 18 years, Alagille syndrome, evidence of cholestasis (one or more of the following): total serum bile acid > 3x ULN for age; conjugated bilirubin > 1 mg/dL; fat soluble vitamin deficiency otherwise unexplainable; GGT > 3x ULN for age; intractable pruritus explainable only by liver disease.
Intervention(s)	Maralixibat (LUM001) administered orally once a day up to 400 microgram per kilogram per day up to 52 weeks.
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome(s): • Mean change from week 18 to week 22 of Fasting Serum Bile Acid Levels [Time frame: week 18, week 22] • Number of participants with Treatment-emergent Adverse Events (TEAEs) [Time frame: from start of study drug administration up to 98 weeks] See trial record for full list of other outcomes.
Results (efficacy)	• Treatment with maralixibat significantly reduced serum bile acids (sBA) levels compared to placebo during the withdrawal period. Maralixibat treatment also led to clinically relevant and statistically significant improvements in itch severity, and xanthoma severity over the course of the study.[13] • Consistent with results reported after 48 weeks of treatment with maralixibat, reductions in serum bile acids and pruritus (itching), were statistically significant and further improved in the participants who remained on maralixibat through 191 weeks of treatment compared to baseline ($p<0.005$ and $p<0.0001$, respectively).[23]
Results (safety)	• Maralixibat was generally well tolerated. The most frequent Treatment Emergent Adverse Events (TEAEs) were diarrhoea and abdominal pain.[23]

Trial	**MERGE, MRX-800;** NCT04168385**;** A Long-Term Safety Study of Maralixibat, an Apical Sodium Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study **Phase II** - Enrolling by invitation **Location(s):** EU (inc UK) countries, Australia, Canada and Unites States. **Primary completion date:** December 2022
Trial design	Single group assignment, open label
Population	N = 54 enrolled, subjects diagnosed with cholestatic liver disease (including, but not limited to ALGS or PFIC) who have previously participated in a maralixibat clinical study, having completed the End of Treatment (EOT) visit the aforementioned studies.
Intervention(s)	Maralixibat oral solution (up to 900 mcg/kg) orally twice daily
Comparator(s)	None
Outcome(s)	Primary outcome(s); • Frequency of reported adverse events [Time Frame: From baseline through study completion, up to 2 years] See trial record for full list of other outcomes.
Results (efficacy)	-

Results (safety)	-

Trial	**IMAGO, LUM001-302, NCT01903460, EudraCT 2012-005346-38;** A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Paediatric Patients With Alagille Syndrome **Phase II - completed** **Location:** United Kingdom **Primary completion date:** February 2015	**IMAGINE, LUM001-303, NCT02047318, EudraCT 2013-003832-54;** A Multicentre Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects With Alagille Syndrome **Phase II – Completed, extension** **Location:** United Kingdom **Primary completion date:** June 2020
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled	Open label, multicentre, single group assignment.
Population	N= 20, aged 12 months to 18 years, diagnosis of Alagille Syndrome with evidence of cholestasis and moderate to severe pruritus, no history of surgical interruption of enterohepatic circulation.	N=19, aged 12 months to 18 years, completed participation in protocol LUM001-302 with intractable pruritis, sBA >3 ULN, ItchRO ≥2 with treatment out to week 96.
Intervention(s)	Maralixibat (LUM001) administered orally either 140 µg/kg/day or 280 µg/kg/day.[24]	Maralixibat (LUM001) with the objective of achieving optimal control of pruritus at a dose level that is tolerated by the participant and up to a maximum daily dose of 560 micrograms per kilogram (mcg/kg).
Comparator(s)	Placebo.	None.
Outcome(s)	Primary outcome(s): • Change from Baseline to Week 13 (End of Treatment) in Fasting Serum Bile Acid Level [Time frame: Baseline to 13 weeks or end of treatment] See trial record for full list of other outcomes.	Primary outcome(s): • Number of Participants with Clinically Significant Changes in Vital Signs Reported as Adverse Events [Time frame: up to 72 weeks] • Number of Participants with Clinically Significant Changes in Laboratory Parameters Reported as Adverse Events [Time frame: up to 72 weeks] See trial record for full list of other outcomes.
Results (efficacy)	The primary and secondary endpoints of the study were not met.	-

	See trial for full results.	
Results (safety)	• There were no treatment emergent serious adverse events in this study. The most common adverse events were diarrhoea and abdominal pain, which are consistent with clinical experience.[24] See trial for full results.	-

ESTIMATED COST

The cost of maralixibat is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract: Specialist Liver Disease Service (Children). E03/S(HSS)/d.
- NHS England. 2013/14 NHS Standard Contract: Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the Management of Cholestatic Liver Diseases.2009.[25]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. A Multicenter Extension Study to Evaluate the Long-Term Safety and Durability of the Therapeutic Effect of LUM001, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Subjects With Alagille Syndrome. *Trial: NCT02057692*. 2019;Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02117713.

2 Clinicaltrials.gov. Safety and Efficacy Study of LUM001 With a Drug Withdrawal Period in Participants With Alagille Syndrome (ALGS) (ICONIC). *NCT02160782,*. 2019;Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02160782.

3 Clinicaltrials.gov. MRX-800: A Long-Term Safety Study of Maralixibat in the Treatment of Cholestatic Liver Disease in Subjects Who Previously Participated in a Maralixibat Study

(MERGE). *Trial ID: NCT04168385,*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT04168385.
4 clinicaltrials.gov. A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of LUM001, an Apical Sodium-dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Paediatric Patients With Alagille Syndrome. *Trial ID: NCT01903460*. 2013;Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT01903460.
5 Clinicaltrials.gov. Open Label Study to Evaluate Efficacy and Long Term Safety of LUM001 in the Treatment of Cholestatic Liver Disease in Patients With Progressive Familial Intrahepatic Cholestasis (INDIGO). *Trial ID: NCT02057718,*. 2014. Available from: https://clinicaltrials.gov/ct2/show/NCT02057718.
6 Mirum pharma. *Programs.* Available from: https://mirumpharma.com/programs/ [Accessed 4 January 2021].
7 Emmanuel Gonzales PV, Ed Tucker, Thomas Jaecklin, Will Garner, Emmanuel Jacquemin, Binita M Kamath,. Pruritus intensity is associated with cholestasis biomarkers and quality of life measures after maralixibat treatment in children with Alagille syndrome *American Association for the Study of Liver Diseases,*. 2020;Poster Presentation. Available from: https://mirumpharma.com/wp-content/uploads/2020/11/96af196c7474-MRX_1.pdf.
8 Shneider BL, Spino C, Kamath BM, Magee JC, Bass LM, Setchell KD, et al. Placebo-Controlled Randomized Trial of an Intestinal Bile Salt Transport Inhibitor for Pruritus in Alagille Syndrome. *Hepatology communications*. 2018;2(10):1184-98. Available from: https://doi.org/10.1002/hep4.1244.
9 Kamath BM, Stein P, Houwen RHJ, Verkade HJ. Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver international : official journal of the International Association for the Study of the Liver*. 2020;40(8):1812-22. Available from: https://doi.org/10.1111/liv.14553.
10 Kamath BM, Ye W, Goodrich NP, Loomes KM, Romero R, Heubi JE, et al. Outcomes of Childhood Cholestasis in Alagille Syndrome: Results of a Multicenter Observational Study. *Hepatology communications*. 2020;4(3):387-98. Available from: https://doi.org/10.1002/hep4.1468.
11 Vandriel S, Liting L, She H, Wang J-S, Czubkowski P, Jankowska I, et al. Clinical Features and Natural History of 1154 Alagille Syndrome Patients: Results from the International Multicenter GALA Study Group. *The Digital International Liver Congress 2020 - Journal of Hepatology,*. 2020. Available from: https://www.researchgate.net/publication/343877964_Clinical_Features_and_Natural_History_of_1154_Alagille_Syndrome_Patients_Results_from_the_International_Multicenter_GALA_Study_Group.
12 Emmanuel Gonzales. *Durability of Treatment Effect with Long-Term Maralixibat in Children with Alagille Syndrome: 4-Year Safety and Efficacy.* 2019. Available from: https://mirumpharma.com/wp-content/uploads/2019/11/AASLD-ICONIC-long-term_FINAL-Presented_V2.pdf [Accessed 19 February 2021].
13 Mirum pharma. *Mirum Pharmaceuticals Presents New Data Demonstrating Durable Improvements in Clinical Outcome Measures in Patients with PFIC2 and Alagille Syndrome Treated with Maralixibat.* 2019. Available from: https://www.prnewswire.com/news-releases/mirum-pharmaceuticals-presents-new-data-demonstrating-durable-improvements-in-clinical-outcome-measures-in-patients-with-pfic2-and-alagille-syndrome-treated-with-maralixibat-300831721.html [Accessed 4 January 2021].
14 Dr. Benjamin L. Shneider DCS, Dr. Binita M Kamath, Dr. John C. Magee, MD, Dr. Estella M Alonso, MD, FAASLD, Dr. Alexander Miethke, et al,. LO5: PRELIMINARY ANALYSIS OF ITCH AND IMAGINE II – OUTCOME OF LONG-TERM ADMINISTRATION OF MARALIXIBAT IN CHILDREN WITH ALAGILLE SYNDROME *American Association For The Study Of Liver Disease,*. 2020;Abstract. Available from: https://assets.website-files.com/5f3d77cd56d46907a50fb8d9/5f9d9c2057efc43f55b78db7_2020%20TLMdX%20Late-breaking%20Abstracts-%20Oct%2030.pdf.
15 European medicines Agency. *EU/3/13/1214.* 2019. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3131214 [Accessed 22 February 2021].
16 Business Wire. *Mirum Pharmaceuticals Announces Breakthrough Therapy Designation for Maralixibat for the Treatment of Pruritus Associated with Alagille Syndrome.* 2019. Available from: https://www.businesswire.com/news/home/20191028005198/en/Mirum-

Pharmaceuticals-Announces-Breakthrough-Therapy-Designation-Maralixibat [Accessed 14 Feb 2020].
17 Clinicaltrials.gov. *LUM001 OR Maralixibat | Phase 2, 3*. 2020. Available from: https://clinicaltrials.gov/ct2/results?term=LUM001+OR+Maralixibat&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 4 January 2021].
18 Orphanet. *Alagille syndrome.* 2009. Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=253&Disease_Disease_Search_diseaseGroup=Alagille-Syndrome&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Alagille-syndrome&title=Alagille%20syndrome&search=Disease_Search_Simple [Accessed 4 January 2021].
19 National Organization of Rare Disorders. *Alagille Syndrome.* 2016. Available from: https://rarediseases.org/rare-diseases/alagille-syndrome/ [Accessed 4 January 2021].
20 Orphanet. *Prevalence and incidence of rare diseases: bibliographic data*. 2020. Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf.
21 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20
22 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality: 2019*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/the21stcenturymortalityfilesdeathsdataset
23 Mirum pharma. *Mirum Pharmaceuticals Presents Data Demonstrating Long-term Durability of Treatment Effect of Maralixibat in Children With Cholestatic Liver Diseases.* 2019. Available from: https://ir.mirumpharma.com/news-releases/news-release-details/mirum-pharmaceuticals-presents-data-demonstrating-long-term [Accessed
24 CISION. *Shire Reports Topline Results from First of Three Placebo-Controlled Phase 2 Studies of SHP625 (LUM001) in Children with Alagille Syndrome.* 2015. Available from: https://www.prnewswire.com/news-releases/shire-reports-topline-results-from-first-of-three-placebo-controlled-phase-2-studies-of-shp625-lum001-in-children-with-alagille-syndrome-499149311.html [Accessed 4 January 2021].
25 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009 Aug;51(2):237-67. Available from: https://doi.org/10.1016/j.jhep.2009.04.009.

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