Health Technology Briefing
March 2023

Maralixibat chloride for Progressive familial intrahepatic cholestasis

Company/Developer	Mirum Pharma Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 36332	NICE ID: 11853	UKPS ID: 658465

Licensing and Market Availability Plans

Currently in clinical development.

Summary

Maralixibat is in clinical development for treating Progressive Familial Intrahepatic Cholestasis (PFIC). PFIC is the name given to a group of rare genetic disorders affecting the liver and impacting newborns, infants, and children. In PFIC, bile acids, which are produced by the liver to help digestion, build up in liver cells (cholestasis), causing liver disease. As a result of the cholestasis, patients can experience distressing symptoms such as pruritis (itching), jaundice, failure to thrive and a fat-soluble vitamin deficiency secondary to impaired absorption of fats. PFIC progresses at varying rates depending on the type. Patients may require liver transplantation due to intractable pruritus, impaired growth, or progressive liver disease with fibrosis usually developing into cirrhosis within the first decade of life. In severe cases, it can lead to end stage liver disease, increased risk of developing hepatocellular carcinoma (a form of liver cancer) and death.

Maralixibat is an orally delivered medicine that blocks a protein called ileal bile acid transporter (IBAT) to prevent bile acids from leaving the gut and circulating back to the liver. This reduces the amount of bile acid accumulating in the liver, reducing liver damage and pruritus in patients with PFIC. Maralixibat may offer an additional treatment option for patients with PFIC.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Treatment of Progressive Familial Intrahepatic Cholestasis (PFIC).[1]

Technology

Description

Maralixibat chloride (LIVMARLI) is a novel, oral, minimally-absorbed selective inhibitor of the ileal bile acid transported (IBAT). IBAT is present in the small intestine and mediates the uptake of bile acids in the intestines, recycling them back to the liver.[2,3] IBAT 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.

In the pivotal study MRX-502 (MARCH-PFIC; NCT03905330), maralixibat has been evaluated in a phase III randomised double blind placebo controlled trial up to 26 weeks followed by an open label extension MRX-503 (MARCH-ON; NCT04185363) up to 104 weeks in patients aged 1 to 18 years at doses up to 600 microgram (µg)/kilogram (kg) (equivalent to 570 µg /kg maralixibat free base) twice daily.[4,5] Maralixibat has also been studied in PFIC 1 and 2 patients aged 12 months to 18 years in the LUM001-501 (INDIGO; NCT02057718) trial. LUM001-501 is an open label phase 2 trial of maralixibat at doses of up to 280µg/kg once daily or 280 µg/kg twice daily depending on level of response from week 72 onwards.[6,7] An open label phase II trial, MRX-801 (RISE; NCT04729751) is currently underway to investigate treatment efficacy and safety of maralixibat of up to up to 600µg/kg (equivalent to 570 mcg/kg maralixibat free base) twice daily for a minimum of 13 weeks in a younger cohort of infants with progressive familial intrahepatic cholestasis from 0 to 364 days.[8]

Key Innovation

Given the limited efficacy of antipruritic medications and the risks and burden of surgical interventions, there remains a high unmet need for alternative treatments for patients with PFIC.[6] Maralixibat is a potential new treatment option for PFIC that acts to reduce elevated bile acid levels (cholestasis) and alleviate pruritus associated with PFIC, consistent across all PFIC types.[9,10]

Regulatory & Development Status

Maralixibat currently has a marketing authorization in the EU/UK in the treatment of cholestatic pruritus in patients with Alagille syndrome who are at least two months of age.[11, 12]

In January 2014, Maralixibat was granted Orphan Drug Designation in the EU for the treatment of progressive familial intrahepatic cholestasis.[13]

Maralixibat received FDA Breakthrough Therapy Designation for progressive familial intrahepatic cholestasis type 2 (PFIC2) in June 2016.[14]

Maralixibat is in phase II and III clinical development for Alagille Syndrome and Biliary Atresia.[15]

Patient Group

Disease Area and Clinical Need

PFIC is a group of rare, life-threatening autosomal-recessive diseases related to functional deficiencies in the hepatocyte transporters resulting in the accumulation of toxic bile acids. Three main types of PFIC have been identified.[16] The most prevalent PFIC2, often called bile salt export pump (BSEP) disease, is

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

caused by mutations in the ABCB11 gene.[17] PFIC1 is caused by mutations in the ATP8B1 gene, and PFIC3 by mutations in the ABCB4 gene.[18] Rarer types, such as PFIC4, PFIC5 and PFIC6, have been identified. In PFIC1 and PFIC2, symptoms usually occur in the first months of life.[19,20] PFIC3 can also appear later in infancy, childhood or even young adulthood.[21] Approximately one third of PFIC cases are PFIC3.[22] Initial symptoms associated with PFIC may be foul smelling, greasy stools or watery diarrhoea, jaundice, pruritus (itching), failure to thrive, vitamin deficiencies and enlarged liver.[16] All PFIC types share manifestations of cholestasis, including elevated serum bile acids, elevated serum bilirubin levels and severe pruritus impacting patient quality of life. Pruritus has been described as extremely distressing and debilitating and is often the goal of surgical therapy and liver transplant, even prior to liver progression. Complications of PFIC include formation of fibrous tissue (fibrosis) and liver regeneration with scarring (cirrhosis) in the liver, which may result in liver failure.[23] PFIC progresses at varying rates depending on the type but usually develops into cirrhosis within the first decade of life. It is fatal if untreated.[21] Data suggests 32% of people with PFIC remain transplant-free at 18 years of age.[24]

The prevalence of PFIC in England is unknown but worldwide estimates range between 1 per 50,000 to 1 per 100,000 live births.[17,25] The PFIC2 subtype reportedly represents half of all PFIC cases.[17] In England, 2021-22, there were 2,501 finished consultant episodes (FCE) and 1,796 admissions for the broad indication (ICD-10 code K76.8 "other specified diseases of liver"), it is unclear what percentage PFIC makes up of the broad ICD-10 indication, which resulted in 6,896 FCE bed days and 543 day cases.[26]

Recommended Treatment Options

Odevixibat is currently recommended by NICE for treating PFIC in people aged six months and over.[21]

Treatment and management strategies and use of off-label medicines can be used with the intention of alleviating symptoms of the condition. Management may include dietary modifications to optimise nutrient absorption and promote growth, such as, medium chain triglyceride formula and fat-soluble vitamins and calcium supplementation. Off-label medicines, such as, Cholestyramine, Ursodeoxycholic Acid, Rifampicin, Phenobarbiton may be prescribed to either reduce pruritus, jaundice, and improve liver function. Surgical interventions like partial external biliary diversion or partial internal drainage, internal ileal exclusion and in the most severe cases liver transplantation may also be provided.[23,27]

Clinical Trial Information

Trial	**MARCH-PFIC, MRX-502 NCT03905330:** Randomized Double-blind Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Maralixibat in the Treatment of Subjects With Progressive Familial Intrahepatic Cholestasis (PFIC) **Phase III –** Completed **Location(s):** 7 EU countries, UK, USA, Canada and other countries	**MARCH-ON, MRX-503, NCT04185363:** An Open-label Extension Study to Evaluate the Long-term Safety and Efficacy of Maralixibat in the Treatment of Subjects With Progressive Familial Intrahepatic Cholestasis (PFIC) **Phase III extension** – Enrolling by invitation

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

	Actual study completion date: September 2022	**Location:** 7 EU countries, UK, USA, Canada and other countries **Estimated primary completion date:** September 2024
Trial Design	Randomised, parallel assignment, double-blind, placebo-controlled Open label extension.	Open label extension, single group assignment
Population	N=93 (actual), aged 1 to 17 years old. - N=64 All-PFIC cohort - N=29 Exploratory cohort	N= 90 (estimated), aged 1 to 18 Years
Intervention(s)	Maralixibat chloride oral solution up to 600 µg/kg orally twice daily for 26 weeks.	Maralixibat oral solution (up to 600 µg/kg t) twice daily for up to 104 weeks
Comparator(s)	Matched placebo	None
Outcome(s)	Primary outcome(s): Mean change in the morning ItchRO (Obs) severity score between baseline and average of week 15 and 26. See trial record for full list of other outcomes	Primary outcome(s): Incidence of Treatment Emergent Adverse Events from baseline to completion up to 104 weeks. See trial record for full list of other outcomes
Results (efficacy)	The primary endpoint was met (p=0.0098); with statistically significant effects in all PFIC subtypes and improvements in total bilirubin and growth compared to placebo.[28]	-
Results (safety)	The safety profile is reportedly comparable to previously published data. Commonly reported treatment emergent adverse events was diarrhoea.[28]	-

Clinical Trial Information	
Trial	**RISE, MRX-801, NCT04729751;** Open-Label, Phase 2 Study to Evaluate the Safety and Tolerability of Maralixibat in the Treatment of Infants with Cholestatic Liver Diseases Including Progressive Familial Intrahepatic Cholestasis and Alagille Syndrome. **Phase II** – Recruiting **Location(s):** Three EU countries, UK, USA, and other countries **Primary competition date:** March 2023
Trial Design	Open label, single group assignment
Population	N=12 (estimated); N=6 patients with Alagille syndrome and N=6 patients with Progressive Familial Intrahepatic Cholestasis aged between 0 days to 364 days old.
Intervention(s)	600 µg/kg oral solution of maralixibat chloride twice daily

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: - Frequency of treatment-emergent adverse events from baseline to week 13. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	**INDIGO, LUM001-501,** NCT02057718; Open Label Study of the Efficacy and Long Term Safety of LUM001 (Maralixibat), an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi), in the Treatment of Cholestatic Liver Disease in Pediatric Patients With Progressive Familial Intrahepatic Cholestasis **Phase II -** Completed **Location(s):** Two EU countries, UK and the United States **Actual completion date:** May 2020
Trial Design	Open label, single group assignment
Population	N=33 (actual), aged 12 months to 18 years, diagnosis of PFIC.
Intervention(s)	Maralixibat chloride up to 280µg/kg from weeks 0-72 escalated up to 280µg/kg twice daily from week 72 onwards.[6]
Comparator(s)	None
Outcome(s)	Primary outcome(s): - Change in fasting serum bile acid levels from baseline to endpoint at week 13. See trial record for full list of other outcomes.
Results (efficacy)	See trial record for results
Results (safety)	See trial record for results

Estimated Cost

The cost of maralixibat was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

- NICE Highly specialised technology appraisal. Odevixibat for treating progressive familial intrahepatic cholestasis [HST17] February 2022.

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.
- NHS England. 2013/14 NHS Standard Contract for Liver Disease (Children). E03/S(HSS)/a.
- NHS England. Standard Contract Paediatric Medicine: Gastroenterology, Hepatology and Nutrition. E03/S/c

Other Guidance

- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the Management of Cholestatic Liver Diseases.2009.[29]

Additional Information

References

1 Mirum Pharmaceuticals. *Development pipeline*. 2022. Available from: https://mirumpharma.com/our-science/pipeline/ [Accessed 04 March 2023].

2 Mirum Pharmaceuticals. *The rare liver diseases that need our attention*. Available from: https://mirumpharma.com/our-science/disease-focus/ [Accessed 14 February 2023].

3 European Medicines Agency. *Assessment Report Livmarli*. European Medicines Agency,; 2022. Available from: https://www.ema.europa.eu/en/documents/assessment-report/livmarli-epar-public-assessment-report_en.pdf.

4 ClinicalTrial.gov. *A Study to Evaluate the Efficacy and Safety of Maralixibat in Subjects With Progressive Familial Intrahepatic Cholestasis (MARCH-PFIC) (MARCH-PFIC)*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03905330?term=NCT03905330&draw=2&rank=1 [Accessed 04 March 2023].

5 ClinicalTrials.gov. *An Extension Study of Maralixibat in Patients With Progressive Familial Intrahepatic Cholestasis (PFIC). Trial ID: NCT04185363*. 2019. Status: Enrolling by invitation. Available from: https://clinicaltrials.gov/ct2/show/NCT04185363?id=NCT04185363&draw=2&rank=1&load=cart [Accessed 24 March 2023].

6 Loomes KM, Squires RH, Kelly D, Rajwal S, Soufi N, Lachaux A, et al. Maralixibat for the treatment of PFIC: Long-term, IBAT inhibition in an open-label, Phase 2 study. *Hepatology Communications*. 2022;6(9):2379-90. https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep4.1980.

7 ClinicalTrial.gov. *Open Label Study to Evaluate Efficacy and Long Term Safety of LUM001 (Maralixibat) in the Treatment of Cholestatic Liver Disease in Patients With Progressive Familial Intrahepatic Cholestasis (INDIGO)*. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT02057718?term=NCT02057718&draw=2&rank=1 [Accessed 04 March 2023].

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

8 ClinicalTrials.gov. *A Study to Evaluate the Safety and Tolerability of Maralixibat in Infant Participants With Cholestatic Liver Diseases Including Progressive Familial Intrahepatic Cholestasis (PFIC) and Alagille Syndrome (ALGS). (RISE)*. 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04729751 [Accessed 04 March 2023].

9 Healio Hepatology. *Maralixibat bile acid inhibitor enters phase 3 trial for pediatric PFIC*. 2019. Available from: https://www.healio.com/news/hepatology/20190711/maralixibat-bile-acid-inhibitor-enters-phase-3-trial-for-pediatric-pfic.

10 Miethke E MA, Porta G, Covarrubias Esquer J, Czubkowski P, et al. Efficacy and Safety of Maralixibat in Patients with Progressive Familial Intrahepatic Cholestasis (MARCH-PFIC): A Randomized Placebo-Controlled Phase 3 Study. *AASLD The Liver Meeting*. 2022.

11 European Medicines Agency (EMA). *Summary of opinion: Livmarli*. 2022. Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-livmarli_en.pdf [Accessed 15 February 2023].

12 European Medicines Agency (EMA). *Livmarli*. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/livmarli [Accessed 24 March 2023].

13 European Medicines Agency. *EU/3/13/1216: Orphan designation for the treatment of progressive familial intrahepatic cholestasis*. 2014. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-13-1216.

14 Cision PR Newswire. *Shire Receives FDA Breakthrough Therapy Designation for SHP621 and SHP625, Investigational Products for Rare Gastrointestinal Conditions*. 2016. Available from: https://www.prnewswire.com/news-releases/shire-receives-fda-breakthrough-therapy-designation-for-shp621-and-shp625-investigational-products-for-rare-gastrointestinal-conditions-582662891.html.

15 ClinicalTrial.gov. *Maralixibat chloride phase 2,3*. 2023. Available from: https://clinicaltrials.gov/ct2/results?term=Maralixibat+chloride&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply.

16 National Organisation of Rare Disorders (NORD). *Low Gamma-GT Familial Intrahepatic Cholestasis*. 2020. Available from: https://rarediseases.org/rare-diseases/low-gamma-gt-familial-intrahepatic-cholestasis/?filter=ovr-ds-resources.

17 Orphanet. *Progressive familial intrahepatic cholestasis*. 2011. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=172.

18 Sticova E, Jirsa M. ABCB4 disease: Many faces of one gene deficiency. *Annals of Hepatology*. 2020;19(2):126-33. Available from: https://doi.org/10.1016/j.aohep.2019.09.010.

19 Jacquemin E. Progressive familial intrahepatic cholestasis. *Clinics and Research in Hepatology and Gastroenterology*. 2012;36:S26-S35. https://www.sciencedirect.com/science/article/pii/S2210740112700189.

20 Morris AL, Bukauskas K, Sada RE, Shneider BL. Byler Disease: Early Natural History. *Journal of Pediatric Gastroenterology and Nutrition*. 2015;60(4):460-6. https://journals.lww.com/jpgn/Fulltext/2015/04000/Byler_Disease__Early_Natural_History.12.aspx.

21 National Institute for Health and Care Excellence (NICE). *Odevixibat for treating progressive familial intrahepatic cholestasis [HST17].* 2022. Available from: https://www.nice.org.uk/guidance/hst17/chapter/1-Recommendations.

22 Baussan C, Cresteil D, Gonzales E, Raynaud N, Dumont M, Bernard O, et al. Genetic cholestatic liver diseases: the example of progressive familial intrahepatic cholestasis and related disorders. *Acta Gastroenterologica Belgica*. 2004;67(2):179-83.

23 Childrens Liver Disease Foundation. *Progressive Familial Intrahepatic Cholestasis*. 2021. Available from: https://childliverdisease.org/liver-information/childhood-liver-conditions/progressive-familial-intrahepatic-cholestasis/.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

24 van Wessel DBE, Thompson RJ, Gonzales E, Jankowska I, Sokal E, Grammatikopoulos T, et al. Genotype correlates with the natural history of severe bile salt export pump deficiency. *Journal of Hepatology*. 2020;73(1):84-93. Available from: https://doi.org/10.1016/j.jhep.2020.02.007.

25 National Institue for Health and Care Excellence (NICE). *Odevixibat for treating progressive familial intrahepatic cholestasis*. 2022. Available from: https://www.nice.org.uk/guidance/hst17/chapter/2-The-condition.

26 National Health Service 75 Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22.

27 Gunaydin M, Bozkurter Cil AT. Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment. *Hepatic Medicine: Evidence and Research*. 2018;10:95-104. Available from: https://doi.org/10.2147/hmer.S137209.

28 Mirum Pharmaceuticals. *Positive Topline Data Announced from Mirum's LIVMARLI Phase 3 MARCH Study in Progressive Familial Intrahepatic Cholestasis (PFIC)*. Press release 24 October 2022. Available from: https://ir.mirumpharma.com/news-events/News/news-details/2022/Positive-Topline-Data-Announced-from-Mirums-LIVMARLI-Phase-3-MARCH-Study-in-Progressive-Familial-Intrahepatic-Cholestasis-PFIC/default.aspx [Accessed 15 February 2023].

29 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of cholestatic liver diseases. *Journal of Hepatology*. 2009;51(2):237-67. https://www.sciencedirect.com/science/article/pii/S0168827809003092.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.