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HEALTH TECHNOLOGY BRIEFING
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Maralixibat for Progressive Familial Intrahepatic Cholestasis Type 2

NIHRIO ID	10743	**NICE ID**	7878
Developer/Company	Mirum Pharmaceuticals	**UKPS ID**	Not Available

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

SUMMARY

Maralixibat is in clinical development for the treatment of Progressive Familial Intrahepatic Cholestasis Type 2 (PFIC2). PFIC2 is an inherited condition that causes progressive liver disease, which normally leads to liver failure. This disease predominantly affects children. In PFIC2, bile acids, part of the fluid produced by the liver, which helps digestion, build up in liver cells, becoming toxic to the liver. If left untreated, this leads to end stage liver disease, increased risk of developing hepatocellular carcinoma (a form of liver cancer) and death. There are currently few effective treatments for PFIC patients and the condition can lead to the need for a liver transplant.

Maralixibat is an orally administered drug that is expected to reduce the level of bile acids. It is expected to interfere with the process by which most bile acids in the intestines are recovered and delivered back to the liver through the blood, thereby reducing the liver damage and itching seen in patients with PFIC2. If licensed, maralixibat will provide the first disease-modifying treatment option for patients with PFIC2, a disease of unmet clinical need.

PROPOSED INDICATION

Treatment of Progressive Familial Intrahepatic Cholestasis type 2 (PFIC2) in patients one year of age and older.[1-4]

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 and other symptoms of cholestatic liver diseases.[5]

Maralixibat is currently in clinical development for the treatment of Progressive Familial Intrahepatic Cholestasis. Maralixibat has been studied in the ongoing INDIGO phase 2 study (NCT02057718). INDIGO is an open label phase 2 trial of maralixibat at doses of 280 mcg/kg once daily or 280 mcg/kg twice daily depending on level of response for 124 weeks of treatment.[2,6]

A phase III clinical trial (MARCH-PFIC, NCT03905330) in children with PFIC2 is also underway with a six month primary endpoint and subsequent roll-over to open label therapy long-term. The regime for this trial is maralixibat oral solution (up to 600 microgram per kilogram [mcg/kg]) orally twice daily for 26 weeks.[1]

INNOVATION AND/OR ADVANTAGES

There are no approved drug therapies for PFIC2. Patients are sometimes treated with antibiotics or antihistamines but these are not effective in all cases. There is also no conclusive evidence that demonstrates they stop the progression of liver disease which can lead to patients needing surgery and liver transplants.[7]

Maralixibat is a potential new treatment option for PFIC2 that may help reduce elevated bile acid levels (cholestasis) thereby delaying liver events (surgery, transplant, liver cancer or death) and alleviate the intense itch associated with PFIC2.[8]

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 Drug Designation for the treatment of progressive familial intrahepatic cholestasis.[9]

Maralixibat received FDA Breakthrough Therapy Designation for progressive familial intrahepatic cholestasis type 2 (PFIC2) in June 2016.[10]

Maralixibat is in phase II clinical development for Cholestatic Liver Disease and Alagille Syndrome.[11]

PATIENT GROUP

DISEASE BACKGROUND

Progressive familial intrahepatic cholestasis type 2 (PFIC2) is one of a heterogeneous group of autosomal recessive disorders that disrupt bile formation and present with cholestasis of hepatocellular origin.[12] Specific gene defects have been identified for three subtypes of PFIC, affecting bile acid secretion or phospholipid secretion.[7] PFIC2 is caused by impaired bile salt secretion due to defects in ABCB11, a gene encoding the bile salt export pump protein (BSEP) hence it is sometimes referred to as BSEP deficiency.[13] With the liver cells' ability to secrete bile impaired, build up causes liver disease in affected individuals. PFIC2 usually appears in the first few months of life and the disease predominantly affects children.[12,14]

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.[7] The 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.[15]

PFIC2 eventually progresses to cause life-threatening complications including the formation of fibrous tissue (fibrosis) and liver regeneration with scarring (cirrhosis) in the liver, resulting in liver failure. Without surgical intervention, these complications may develop by the end of the first decade of life. Children with PFIC2 may have a greater risk of developing a form of liver cancer known as hepatocellular carcinoma, potentially before the age of one.[7]

CLINICAL NEED AND BURDEN OF DISEASE

PFIC affects males and females in equal numbers. The exact incidence is unknown, but these disorders are extremely rare. In their milder forms these disorders often go unrecognized or misdiagnosed, meaning they may be under-diagnosed, making it difficult to determine their true frequency in the general population.[7] While the exact prevalence remains unknown, the estimated prevalence at birth varies between 1 in 50,000 and 1 in 100,000.[13] PFIC2 is the most common subtype and is diagnosed in 50-60 % of all PFIC patients.[16]

It is thought that PFIC represents the cause of cholestasis in 10–15% of children, and 10–15% of liver transplantation indications in children.[12] Only 33% of PFIC2 patients survive with their native liver by adulthood.[17]

PFIC is included in the ICD-10 code group K76.8 "Other specified diseases of the liver". Hospital Episode Statistics from England recorded 2,147 finished consultant episodes, 1,542 admissions and 437 day cases with the code K76.8 in 2018-19.[18]

The average age at onset is 3 months, although some patients do not develop symptoms until later childhood or adolescence. PFIC can progress rapidly and cause cirrhosis during infancy, or may progress slowly with minimal scarring well into adolescence. Few patients survive into the third decade of life without treatment.[19] In England in 2018, 23 deaths were recorded with ICD-10 code K76.8 as the underlying cause of death.[20]

The population likely to be eligible to receive maralixibat could not be estimated from available published sources.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

No specific therapy exists for individuals with PFIC. Treatment is directed toward the specific symptoms that are apparent in each individual. Supplemental treatment with vitamins and nutrients is essential for individuals with malabsorption. Such treatment may include restoring vitamins A, D, E, and K. Calcium, phosphate, and zinc supplementation may also be required.[7]

In some PFIC2 patients, surgical biliary diversion can also relieve pruritus and slow disease progression. However, most PFIC patients are ultimately candidates for liver transplantation. Monitoring of hepatocellular carcinoma should be offered from the first year of life.[13]

CURRENT TREATMENT OPTIONS

There are no satisfactory treatments authorised in the EU for PFIC2.[9]

Ursodeoxycholic acid is often the initial treatment option for affected individuals and may be effective in some cases to prevent liver damage.[13] Additional drug therapies that have been used to treat individuals with PFIC include phenobarbital, rifampin, cholestyramine, and antihistamines. These therapies can alleviate or improve some of the clinical symptoms such as intense itching. However, they are not effective in all cases and there is no conclusive evidence that demonstrates that they stop the progression of liver disease.[7]

PLACE OF TECHNOLOGY

If licensed, maralixibat will provide the first disease-modifying treatment option for patients with progressive familial intrahepatic cholestasis type 2, who have few effective, and no approved, treatments available.

CLINICAL TRIAL INFORMATION

Trial	**MARCH-PFIC,** NCT03905330, EudraCT 2019-001211-22; MRX-502: 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 - ongoing** **Location:** EU (including the UK), Canada, United States and other countries.	NCT04185363; MRX-503: 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** **Location: United States**
Trial design	Randomised, parallel assignment, double-blind, placebo-controlled	Open label extension, single group assignment
Population	N=30, aged ≥12 months and < 18 years of age at the time of consent	N= 30, aged 1 to 18 Years, Completion of study MRX-502
Intervention(s)	Maralixibat oral solution (up to 600 microgram per kilogram [mcg/kg]) orally twice daily for 26 weeks	Maralixibat oral solution (up to 600 microgram per kilogram [mcg/kg]) twice daily for up to 104 weeks

Comparator(s)	Matched placebo	None
Outcome(s)	Primary outcome(s): Treatment response as measured by the mean change in pruritus severity as assessed by the Observer rated Itch Reported Outcome (ItchRO [Obs]) [Time frame: Between baseline and week 15 through 26] See trial record for full list of other outcomes	Primary outcome(s): Incidence of Treatment Emergent Adverse Events (TEAEs) during the study [Time frame: From baseline through study completion, up to 104 weeks] See trial record for full list of other outcomes
Results (efficacy)	-	-
Results (safety)	-	-

Trial	**INDIGO,** NCT02057718**, EudraCT** 2013-003833-14**;** Open Label Study of the Efficacy and Long Term Safety of LUM001, 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 - ongoing** **Location:** EU countries (including UK) and the United States
Trial design	Open label, single group assignment
Population	N=33, aged 12 months to 18 years, diagnosis of PFIC. This includes: • 19 nt-PFIC2 (matching expected indication) • 6 truncating-PFIC2 • 8 PFIC1
Intervention(s)	Maralixibat escalated up to 280mcg per kg once daily or 280mcg/kg BID.[21]
Comparator(s)	None
Outcome(s)	Primary outcome(s): To evaluate the Safety and Tolerability of LUM001 in Pediatric Participants with Progressive Familial Intrahepatic Cholestasis (PFIC) [Time frame: from start of study treatment until Weeks 13 and 48] See trial record for full list of other outcomes.
Results (efficacy)	The mean (SD) serum Bile Acid (sBA) reduction at week 13 was 29 µmol/L and sBA reduction at week 48 was 59 µmol/L. Six patients experienced sBA normalization (≤8.5 µmol/L) or reduction from baseline by ≥70% and ItchRO of 0 or improvement ≥1.0 point (responders). After 48 and 72 weeks of treatment height z-score mean change from baseline was 0.55 (0.33) and 0.61 (0.23) in responders, compared to −0.29 (0.52) and −0.59 (0.73) in non- or partial responders ($p < 0.05$). Weight z-score mean change from baseline was 0.42 (0.29) and 0.32 (0.25) in responders and −0.29 (0.30) and −0.37 (0.51) in non-or partial responders ($p < 0.05$). Statistically significant differences were seen at 24 weeks of treatment and onwards.[21]

Results (safety)	Treatment emergent adverse events (TEAEs) were reported in all patients, 22 related to maralixibat, 15 had serious TEAEs, one led to discontinuation. The most frequent TEAEs were pyrexia, diarrhoea, cough and abdominal pain.[21]

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.
- 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.[22]

ADDITIONAL INFORMATION

Mirum Pharmaceuticals did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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