

**NIHR Innovation Observatory
Evidence Briefing: September 2017****Seladelpar for primary biliary cirrhosis – second or
subsequent line**

NIHRIO (HSRIC) ID: 11843

NICE ID: 9219

LAY SUMMARY

Primary biliary cirrhosis (PBC), is a long-term liver disease in which the pipes (ducts) that transports bile in the liver become damaged. PBC causes the build-up of bile in the liver and eventually may lead to scarring. Nine out of ten people with PBC are women. The exact cause of PBC is not known, although family history, when combined with lifestyle may increase the risk of getting PBC. The most common symptoms of PBC are itchy skin and fatigue, however, up to half of people with PBC do not have any symptoms until extensive liver damage occurs.

Seladelpar is a new drug currently being developed and tested to treat PBC. It acts by promoting the natural transportation and storage of bile within the liver. It is currently taken as a capsule in doses of 2 mg, 5mg, 10mg, or 20mg once a day. If licensed in the UK, seladelpar could provide an additional treatment option for people with PBC.

This briefing is based on information available at the time of research 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.

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

TARGET GROUP

Primary biliary cirrhosis – second or subsequent line

TECHNOLOGY

DESCRIPTION

Seladelpar (MBX-8025, RWJ-800025) is under development for the treatment of the autoimmune disease primary biliary cirrhosis (PBC).¹ Seladelpar is a potent, selective agonist for the peroxisome proliferator-activated receptor-delta (PPAR-delta), which is implicated in bile acid homeostasis.² PPARs are nuclear transcription factors that regulates genes involved in lipid storage and transport (particularly in fatty acid oxidation) and insulin signaling and sensitivity. PPAR-delta is produced in virtually all of the cells throughout the body and may have roles in energy metabolism and reducing inflammation.³

In the first phase II PBC study, referred to as the 'high dose' study (50 mg and 200 mg; CB8025-21528), seladelpar showed pronounced decreases in biochemical markers of cholestasis and in 7 α -hydroxy-4-cholestene-3-one (C4), which is the common precursor for CA and CDCA, and has been used as a serum marker for the rate of bile acid synthesis C4. However, seladelpar treatment was associated with a dose-dependent elevation in transaminases. This signal was not observed in prior clinical studies in other subject populations with normal hepatic function. Besides elevation in transaminases, seladelpar was generally well tolerated. There was no evidence that seladelpar induced or worsened pruritus.

Based on the results of this study a second phase II study (CB8025-21629) was initiated to study lower doses (2 mg, 5 mg and 10 mg). In this clinical trial, seladelpar was administered orally at 2 mg, 5mg, 10mg, or 20mg once daily for an 8-week active treatment period (with the potential to titrate up or down to 5mg or 25mg in the extension period for up to 52 weeks).⁴

Seladelpar does not currently have marketing authorisation in the EU for any indication. Seladelpar is currently in a planned phase III trial for PBC.⁵

INNOVATION and/or ADVANTAGES

In a phase II study of seladelpar in patients with PBC, the drug was effective in reducing alkaline phosphatase (AP) to normal levels in some patients. Based on interim results, 18% and 45% reach \leq upper limit of normal for the 5 and 10 mg groups, respectively. AP is an established surrogate marker of disease progression in PBC and is a key component in the composite endpoint for regulatory approval for a treatment in PBC.³ If licensed, seladelpar could offer patients significant advantages over existing treatments and has the potential to be an improved second-line therapy for PBC.²

DEVELOPER

CymaBay Therapeutics, Inc.

PATIENT GROUP

BACKGROUND

PBC, also known as primary biliary cholangitis, is a chronic liver disease characterised by the progressive destruction of the small bile ducts in the liver. It is thought to be an auto-immune disease, where T-cells progressively damage the cells lining the bile ducts and hepatocytes, eventually resulting in blockage that obstructs the flow of bile from the liver into the small intestine.^{6,7} The consequent increase in intracellular levels of bile and other toxins gradually leads to chronic liver inflammation, fibrosis and eventually cirrhosis, which can eventually lead to liver failure if left untreated.⁸

Although it is not known what causes the immune system to malfunction and attack the bile ducts, a combination of genetic and environmental factors (infection, chemicals and smoking) are thought to play a role. PBC is thought to occur mostly in women with less than 10% cases found in men. Symptoms usually include fatigue, itchy skin, mild jaundice, dry eyes and dry mouth, and are frequently accompanied by symptoms of other autoimmune disorders.⁶

Many people with PBC may live with very few problems for many years, even decades however, PBC can have a major impact on people's day-to-day lives. For example, it may reduce the body's ability to digest food properly, especially fats and they may not cope very well with toxins such as alcohol and some medicines.⁹

CLINICAL NEED and BURDEN OF DISEASE

The estimated prevalence of PBC in the UK is approximately 35 per 100,000 population, equating to approximately 20,000 people in England.¹⁰ About 90% cases occur in women, aged between 40 and 60, although it can be diagnosed at any age from 20 onwards.⁶ In 2015-16, there were 781 hospital admissions in England due to PBC (ICD10 K74.3), accounting for 1,192 finished consultant episodes and 4,003 bed days.¹¹

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

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Obeticholic acid for treating primary biliary cholangitis (TA443). April 2017.
- NICE guideline. Cirrhosis in over 16s: assessment and management (NG50). July 2016.
- NICE interventional procedure guidance. Living-donor liver transplantation (IPG535). November 2015.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard contract for hepatobiliary and pancreas (adult). A02/S/a.

OTHER GUIDANCE

- The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines. The diagnosis and management of patients with primary biliary cholangitis. *Journal of Hepatology* 2017 Vol 67, pg 145-172.
- The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines. Primary Biliary Cirrhosis. *Hepatology* 2009 Vol 50, pg 291-308

CURRENT TREATMENT OPTIONS

There is no cure for PBC but there are a number of treatments that focus on slowing the progress of the disease and relieving symptoms. Making healthy lifestyle choices such as maintaining a healthy weight, not regularly drinking more than 14 units of alcohol a week and stopping smoking can reduce the symptoms of PBC. The National Health Service (NHS) also recommends that people with PBC avoid non-steroid anti-inflammatory drugs such as aspirin because the damage to the liver can affect its ability to process them.¹²

The mainstay of risk reducing therapy is ursodeoxycholic acid (UDCA) which is recommended for first line treatment of PBC. It can help reduce the risk and rate of liver damage in most people. In the UK 80% of patients respond to UDCA and have normal or near-normal life expectancy.¹³ NICE guidelines also recommend the use of obeticholic acid (Ocaliva) for the treatment of PBC in adults in combination with UDCA for people whose disease has responded inadequately to UDCA or as monotherapy for people who cannot tolerate ursodeoxycholic acid.¹⁴

EFFICACY and SAFETY

Trial	NCT02955602, CB8025-21629; adults aged 18 to 75 years; MBX-8025, 5mg vs 10mg vs 25mg; phase II with an extension
Sponsor	CymaBay Therapeutics, Inc.
Status	Ongoing, recruiting
Source of Information	Trial registry ⁴
Location	Germany, UK, USA and Canada
Design	Randomised, Uncontrolled, parallel assignment, open-label
Participants	N=128 (planned); aged 18-75 years; primary biliary cholangitis; inadequate response to prior therapy including ursodeoxycholic acid.
Schedule	Randomised to MBX-8025 hard capsule at a dose of 5 mg or 10 mg, orally, once daily for 8 weeks The dose might be up- or down-titrated after safety and efficacy data review of the first 8 weeks of treatment Extension: 1 mg, 2 mg, 5 mg, 10 mg, 15 mg or 20 mg. Subjects will initially enter the extension on their assigned dose. During the extension, a subject's dose might be re-adjusted for safety or efficacy reasons

Follow-up	Not reported
Primary Outcomes	To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, 10 mg, and 20 mg over 8 weeks of treatment
Secondary Outcomes	To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, 10 mg, and 20 mg over 12 and 26 weeks of treatment; To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, 10 mg, and 20 mg over 52 weeks of treatment; To evaluate the pharmacokinetics (PK) of MBX-8025 Exploratory; To evaluate the effect of MBX-8025 on bile acids, additional markers of inflammation and renal function MBX-8025 doses of 1 mg and 15 mg may be evaluated if dose adjustment occurs
Key Results	Interim results show that the mean transaminase levels decreased over the course of treatment and a significant reduction in alkaline phosphatase from baseline was observed.
Adverse effects (AEs)	-
Expected reporting date	

ESTIMATED COST and IMPACT

COST

The cost of seladelpar is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability: <i>a potential improvement in quality of life</i> |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input checked="" type="checkbox"/> Other: <i>uncertain unit cost compared to existing treatments</i> | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

REFERENCES

- ¹ CymaBay Therapeutics. *CymaBay Pipeline: Seladelpar*. Available from: http://www.cymabay.com/pipeline_seladelpar.html [Accessed 24 August 2017]
- ² Jones D, Boudes PF, Swain MG, Bowlus CL, Galambos MR, Bacon BR, Doerffel Y, Gitlin N, Gordon SC, Odin JA, Sheridan D. Seladelpar (MBX-8025), a selective PPAR- δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. *The Lancet Gastroenterology & Hepatology*. 2017 Aug 14.
- ³ GlobalData. *Seladelpar lysine: Drug Detailed Information*. Available from: <https://pharma.globaldata.com/ProductsView.aspx?id=PD&ProductId=2413&ProductType=0,1> [Accessed 25 August 2017, log-in required]
- ⁴ ClinicalTrials.gov *MBX-8025 in Subjects With Primary Biliary Cholangitis (PBC) (8 Week, Dose Ranging, Open Label, Randomized Phase 2 With an Extension)*. Available from: <https://clinicaltrials.gov/ct2/show/NCT02955602> [Accessed 25 August 2017]
- ⁵ GlobalData. *Drug Detailed Information – Seladelpar Lysine*. Available from: <https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=2413> [Accessed 25 August 2017, log-in required]
- ⁶ NHS Choices. *Primary biliary cirrhosis – Causes*. Available from: <http://www.nhs.uk/Conditions/Primary-biliary-cirrhosis/Pages/Causes.aspx> [Accessed 25 August 2017]
- ⁷ Patient Info. *Primary Biliary Cholangitis*. Available from: <https://patient.info/health/primary-biliary-cholangitis-leaflet> [Accessed 25 August 2017]
- ⁸ Selmi C, Bowlus CL, Gershwin ME, Coppel RL. Primary biliary cirrhosis. *The Lancet*. 2011 May 13;377(9777):1600-9.
- ⁹ British Liver Trust. *Primary Biliary Cholangitis/Cirrhosis*. Available from: <https://www.britishlivertrust.org.uk/liver-information/liver-conditions/primary-biliary-cirrhosis/> [Accessed 25 August 2017]
- ¹⁰ UK-PBC. *Epidemiology of PBC*. Available from: <http://www.uk-pbc.com/about/aboutpbc/epidemiology-of-pbc/> [Accessed 25 August 2017]
- ¹¹ NHS Digital. *Hospital Episode Statistics for England: Admitted Patient Care statistics*. Office of National Statistics. 2015-16.
- ¹² NHS Choices. *Primary biliary cirrhosis – Treatment*. Available at: <http://www.nhs.uk/Conditions/Primary-biliary-cirrhosis/Pages/Treatment.aspx> [Accessed 25 August 2017]

¹³ UK-PBC. *Treating PBC*. Available from: <http://www.uk-pbc.com/about/aboutpbc/treating-pbc/> [Accessed 25 August 2017]

¹⁴ NICE technology appraisal. *Obeticholic acid for treating primary biliary cholangitis (TA443)*. Available from: <https://www.nice.org.uk/guidance/ta443/chapter/1-Recommendations> [Accessed 25 August 2017]