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Newcastle University

Health Technology Briefing
May 2023

Elafibranor for previously treated primary biliary cholangitis

Company/Developer	Ipsen Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 20436	NICE TSID: Not available	UKPS ID: 667841

Licensing and Market Availability Plans

Currently in Phase II/III trials.

Summary

Elafibranor is currently in clinical development for the treatment of adults with primary biliary cholangitis (PBC) who are either unable to tolerate treatment with ursodeoxycholic acid (UDCA) or show inadequate response to UDCA. Primary biliary cholangitis is a disease in which there is long-term damage to the small bile ducts in the liver. These ducts transport fluid called bile from the liver to the intestines, where it helps to digest fats. Because of the damage to the ducts, bile acids, essential components of bile, build up in the liver causing damage to liver tissue and leading to liver cirrhosis (scarring of the liver). Primary biliary cholangitis is a long-term debilitating and life-threatening disease because it can lead to liver cirrhosis and liver failure, and may increase the risk of liver cancer.[1] There are very few treatments for this disease and an estimated 40% of treated patients in the UK do not respond favourably to existing treatment. The symptoms of PBC can significantly impair quality of life.

Elafibranor is a type of agonist (chemical) and is expected to work by attaching to and activating receptors (targets) called 'PPAR receptors', which control the levels of bile acid. By activating PPARs, this medicine is expected to reduce the levels of bile acid build up, thereby reducing damage of liver tissue that occurs in primary biliary cholangitis. If licensed, elafibranor will offer an additional treatment option for patients with PBC who currently have no well-tolerated therapies available.

Proposed Indication

For the treatment of adults with primary biliary cholangitis (PBC) and inadequate response or Intolerance to UDCA.[2]

Technology

Description

Elafibranor (GFT-505) is a dual agonist of the peroxisome proliferator activated receptor (PPAR) alpha and delta receptors. PPAR activation is associated mechanistically with bile acid detoxification, regulation of bile acid synthesis, metabolism, and transport, which control levels of bile acid.[3,1] PPAR-alpha is predominantly expressed in the liver, and PPAR-delta and -gamma are more ubiquitously expressed in metabolic active tissues.[3] By activating the PPAR receptors, elafibranor is expected to reduce the levels of bile acid build up, thereby reducing damage of liver tissue that occurs in PBC.[1]

Elafibranor is currently in clinical development for the treatment of adults aged 18 – 75 with PBC.[2] In the phase III clinical trial (ELATIVE; NCT04526665), elafibranor is administered orally as 80 mg tablet per day.[2]

Key Innovation

Currently, the only drugs licensed for PBC in the UK are UDCA and obeticholic acid (OCA).[4,5] UDCA is recommended as the first line treatment.[6] OCA in combination with UDCA is also recommended when response to UDCA has been inadequate, or as monotherapy in patients intolerant of UDCA.[7] Forty percent of patients respond incompletely to UDCA and remain high-risk.[8] This necessitates the need for second line treatment options that can target other stages within the complex pathogenesis of PBC. PPAR are members of a nuclear receptor family that help modulate hepatic lipid metabolism.[9] They include PPAR-alpha, -gamma, and -delta, which are targeted by therapies aiming at inhibiting bile acid synthesis, reducing oxidative stress and inflammatory responses, and ultimately improving PBC.[9] Elafibranor is a promising second-line treatment that targets and activates the PARP-alpha and –delta receptors to control levels of bile acid.[3]

Elafibranor has shown highly significant results in the phase II clinical trial (NCT03124108) in patients with PBC, while maintaining a favourable tolerability profile and lack of demonstrated safety concerns.[10] Results showed a 41–48% reduction in alkaline phosphatase (ALP) of patients who received elafibranor compared with a 3% increase in group of placebo.[10] If licensed, elafibranor will offer an additional treatment option for patients with PBC who currently do not tolerate available therapies.

Regulatory & Development Status

Elafibranor does not currently have marketing authorisation in the EU/UK for any indication.

Elafibranor is currently in phase II and III clinical development for the treatment of:[11]

- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Elafibranor has the following regulatory designations and awards:

- An orphan drug designation in the EU for the treatment of PBC in July 2019.[1]
- Breakthrough Therapy designation by the US FDA in April 2019.[12]

Elafibranor also received a product-specific waiver in 2020 from the European Medicines Agency (EMA) for all subsets of the pediatric population and for the condition of PBC on the grounds that PBC occurs only in adult populations.[13]

Patient Group

Disease Area and Clinical Need

PBC is a rare, progressive autoimmune cholestatic liver disease characterised by long-term damage to the small bile ducts in the liver, which transport bile from the liver to the intestines to digest fats. This damage results in bile and bile acid build up in the liver causing damage to liver tissue. If left untreated or patient is unresponsive to treatment, it can lead to liver cirrhosis (scarring of the liver), and subsequently to liver failure.[1,14] Early symptoms may include fatigue (the most common symptom), itchy skin (pruritus), and abdominal pain. As the disease progresses, people with PBC may develop weakness, nausea, diarrhoea, swelling in the legs and feet (oedema), bone and joint pain, jaundice, dark urine, and xanthomas (fat build-up under the surface of the skin).[15,16] The symptoms of PBC can significantly impair quality of life.[16] Although the exact cause of the disease is not known, PBC is thought to be caused by a combination of autoimmune factors, genetic susceptibility and environmental triggers.[16] PBC mostly affects women and usually appears during middle age or older.[14] The disease is mostly represented in late adulthood, with 65 years as the mean age at diagnosis.[17]

Approximately 25% of patients with PBC are women younger than 40 years of age, and about 10% of patients are men.[14] In accordance with the largest English epidemiological study, PBC is a rare disease, with a prevalence of about 35/100,000 and an annual incidence of 2–3 per 100,000.[18,19] This implies there are about 20,000 PBC patients in the UK.[20] In England, 2021 – 22, there were 700 finished consultant episodes (FCEs) (167 for males and 533 for females) and 437 admissions for primary biliary cirrhosis (ICD10 K74.3), which resulted in 2,133 FCE bed days and 234 day cases.[21]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends UDCA for the management of PBC, including those with asymptomatic disease.[22] OCA in combination with UDCA is also recommended when response to UDCA has been inadequate, or as a monotherapy in patients intolerant of UDCA.[7]

Clinical Trial Information

Trial	**ELATIVE;** NCT04526665, EudraCT 2019-004941-34; A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients With Primary Biliary Cholangitis With Inadequate Response or Intolerance to Ursodeoxycholic Acid. **Phase III –** Active, not recruiting **Location(s):** Five EU countries, UK, USA, Canada, and other countries **Primary completion date:** September 2023
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo controlled
Population	N=150 (planned); subjects with a definite or probable PBC diagnosis taking UDCA for at least 12 months (stable dose ≥ 3 months) prior to screening visit or unable to tolerate UDCA treatment (no UDCA for ≥ 3 months) prior to screening (per country standard-of-care dosing); aged 18 – 75 years.
Intervention(s)	Oral elafibranor 80mg
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Effect of elafibranor (80 mg/day) on cholestasis [Time frame: from baseline to 52 weeks of treatment]

	See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT03124108, EudraCT 2016-003817-80; A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Elafibranor at Doses of 80 mg and 120mg After 12 Weeks of Treatment in Patients With Primary Biliary Cholangitis and Inadequate Response to Ursodeoxycholic Acid. **Phase II** – Completed **Location(s):** Three EU countries, UK, and USA **Actual study completion date:** October 2018
Trial Design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=45 (actual); subjects with a definite or probable PBC diagnosis taking UDCA for at least 12 months prior to screening visit; aged 18 – 75 years.
Intervention(s)	• Oral elafibranor 80 mg • Oral elafibranor 120 mg
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: Relative change from baseline in serum alkaline phosphatase (ALP) levels at week 12 (endpoint) [Time frame: baseline, week 12 (endpoint)] See trial record for a full list of other outcomes.
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of elafibranor is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Linerixibat for treating pruritus in people with primary biliary cholangitis TS ID 10136 (GID-TA11307). Expected date of issue to be confirmed.
- NICE technology appraisal. Obeticholic acid for treating primary biliary cholangitis (TA443). April 2017
- NICE clinical guideline. Cirrhosis in over 16s: assessment and management (NG50). July 2016.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- British Society of Gastroenterology (BSG). BSG and UKPBC primary biliary cholangitis treatment and management guidelines. 2018.[23]
- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. 2017 [24]

Additional Information

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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.