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Health Technology Briefing
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Linerixibat for treating pruritus associated with primary biliary cholangitis

Company/Developer	GSK

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 11898	NICE ID: 10136	UKPS ID: 650660

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Linerixibat is in clinical development for the treatment of primary biliary cholangitis (PBC). PBC is a chronic autoimmune disease where bile (digestive fluid) flow from the liver is disrupted (i.e., cholestasis), resulting in excess bile acids in circulation. Cholestatic pruritus is an itch which is internal and cannot be relieved by scratching. The cause of pruritus in PBC is unclear but it is thought that these circulating bile acids have a role. Pruritus is debilitating and can cause fatigue, sleep disturbance, suicidal ideation and in some cases, a need for a liver transplant in the absence of liver failure. The cause of PBC is unknown but immune, autoimmune, environmental, and genetic factors can play a role. There is a significant unmet need in the management of pruritus in PBC with no new pharmacological therapies approved since the 1960s.

Linerixibat is a drug administered orally as a tablet that blocks the resorption of bile acids in the small intestine, reducing pruritic bile acids in circulation. Linerixibat has shown significant improvement in itching when administered in clinical trials. This has the potential to improve quality of life in affected patients. If licensed, linerixibat will offer an alternative treatment option for adults with pruritus associated with PBC.

Proposed Indication

Pruritus in patients with primary biliary cholangitis (PBC).[1]

Technology

Description

Linerixibat (GSK2330672) is a minimally absorbed oral small molecule ileal bile acid transporter (IBAT) inhibitor.[2] It blocks the resorption of bile acids in the small intestine, which reduces pruritic bile acids in circulation.[3]

Linerixibat is in phase 3 clinical development for the treatment of moderate to severe pruritus associated with PBC (NCT04950127, NCT04167358) .[1,4-6] It will be administered as an oral tablet.[1]

Key Innovation

Cholestatic pruritus in PBC is a condition in which there is a significant unmet need with no new pharmacological therapies approved since the 1960s. Patients with cholestatic pruritus can have persistent, intense, and deep itch, which is rarely relieved by scratching.[3] Conventional therapies lack long-term efficacy and have side effects.[7] Colestyramine is the drug of choice for treating cholestatic itch in the UK, however, it does not exert strong anti-pruritic effects in most patients. It also has possible adverse effects that are mainly in the gastrointestinal tract including bloating, abdominal discomfort, and malabsorption of fat and fat-soluble vitamins. It is also often not well tolerated by patients due to its unpleasant taste.[8,9] It can also interfere with absorption of other medications.[7]

Targeting bile acid reuptake with linerixibat may provide relief for patients with PBC and cholestatic pruritus, along with improvements in health-related quality of life (HRQOL) relating to itch.[2] Phase 2 trial (NCT02966834) data suggest that linerixibat may provide relief to patients suffering the debilitating impact of cholestatic pruritus associated with primary biliary cholangitis.[3] Twice-daily dosing with linerixibat was associated with greater itch improvement.[2] If licensed, linerixibat will offer an additional treatment option for cholestatic pruritus associated with PBC.

Regulatory & Development Status

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

Linerixibat has the following regulatory designations/awards:

- An orphan drug in the EU in November 2021 for primary biliary cholangitis.[10]

Patient Group

Disease Area and Clinical Need

PBC (formerly known as primary biliary cirrhosis) is a life-long, autoimmune, cholestatic liver disease that is a rare but important cause of chronic liver disease.[11] Cholestasis is defined as a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts.[12] In PBC, bile flow from the liver is disrupted. The resulting excess bile acids in circulation are thought to cause cholestatic pruritus, an internal itch that cannot be relieved by scratching. Cholestatic pruritus can be debilitating, leading to fatigue, sleep disturbance, suicidal ideation and even liver transplant in the absence of liver failure.[3] Although there is no primary rash associated with cholestatic pruritus,

patients who have cholestatic itch often present with secondary lesions from scratching in an attempt to alleviate pruritus.[13] The exact cause of PBC is unknown. Possible immunological, autoimmune, genetic, and/or environmental factors are under investigation as potential causes.[14]

Current estimates for the UK suggest that PBC has a prevalence of 35 people per 100,000, with the implication that there are about 20,000 patients in the UK.[15] Pruritus is reported among 80% to 100% of patients with cholestatic liver disease.[13] That means we can estimate that between 16,000-20,000 patients with PBC have cholestatic pruritus.[13,15] Primary biliary cholangitis is most often diagnosed in women over the age of 50 years.[16] In England (2021-22), there were 700 finished consultant episodes (FCEs) and 437 admissions for a primary diagnosis of PBC (ICD-10 code K74.3), which resulted in 234 day cases and 2,133 FCE bed days. There were 1,249 finished consultant episodes (FCEs) and 1,139 admissions for a primary diagnosis of pruritus (ICD-10 code L29), which resulted in 488 day cases and 760 FCE bed days.[17]

Recommended Treatment Options

Currently the following treatments used for cholestatic pruritus are:[8]

- Colestyramine.
- Rifampicin (unlicensed indication)
- Where previous therapy has proved ineffective or was not tolerated, other drugs including sertraline (unlicensed indication) and naltrexone hydrochloride (unlicensed indication), may be used to treat cholestatic pruritus. However, their use is limited due to significant side-effects.

In the UK, Ursodeoxycholic acid (UDCA) is the main treatment for PBC, although it does not improve symptoms such as itchy skin or fatigue. Colestyramine (previously called cholestyramine) is a medicine widely used to treat the itchiness associated with PBC.[18]

The National Institute for Health and Care Excellence (NICE) currently recommend obeticholic acid as a treatment option for treating PBC in combination with ursodeoxycholic acid for patients whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.[19]

Clinical Trial Information

Trial	**GLISTEN;** NCT04950127; A Two-part, Randomized, Placebo Controlled, Double Blind, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Linerixibat for the Treatment of Cholestatic Pruritus in Participants With Primary Biliary Cholangitis (PBC) **Phase III –** Recruiting **Location(s)** – 8 countries in EU, UK USA, Canada and other counties **Primary completion date –** May 2024
Trial Design	Randomised, parallel assignment, double masked
Population	N = 230 (estimated); Participants who have documented PBC; Participants who have moderate to severe itch; aged 18 to 80 years
Intervention(s)	Linerixibat
Comparator(s)	Placebo

Outcome(s)	Primary outcome measures: • Change from Baseline in Monthly Itch Scores over 24 weeks using Numerical Rating Scale (NRS) [Time Frame: Baseline and up to 24 weeks] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**GLIMMER; NCT02966834; EudraCT- 2016-002416-41;** A Randomized, Double-blind, Multi-dose, Placebo-controlled Study to Evaluate the Efficacy, Safety and Tolerability of GSK2330672 Administration for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis (GLIMMER: GSK2330672 trial of IBAT Inhibition With Multidose Measurement for Evaluation of Response) **Phase II –** Completed **Location(s) –** 5 countries in EU, UK, USA, Canada and other countries **Study completion date –** April 2020
Trial Design	Randomised, parallel assignment, double masked
Population	N=147 (actual); aged 18 to 80 years; proven PBC; itch severity at >=4 on a 0 to 10 point scale for the majority of time
Intervention(s)	Linerixibat film-coated tablets
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: • Mean Change From Baseline at Week 16 in the Mean Worst Daily Itch Score [Time Frame: Baseline and Week 16] See trial record for full list of other outcomes.
Results (efficacy)	One hundred forty-seven patients received placebo (n = 36) or linerixibat (once daily: 20 mg, n = 16; 90 mg, n = 23; 180 mg, n = 27; twice daily: 40 mg, n = 23; 90 mg, n = 22). Linerixibat groups exhibited ≥2-point mean reductions in MWDI from baseline at week 16; however, differences from placebo were not significant. Post hoc analysis of change from baseline in monthly itch score over the treatment period (Phase 3 endpoint) showed significant differences between placebo and linerixibat 180 mg once daily (P = .0424), 40 mg twice daily (P = .0105), and 90 mg twice daily (P = .0370). A significant relationship between total daily dose and response was observed post hoc in the per protocol population (P = .0542).[2]
Results (safety)	Due to the mechanism of action of linerixibat, the most common adverse events were diarrhoea and abdominal pain.[3]

Trial	**LLSAT**; NCT04167358; EudraCT-2019-003158-10; Long-term Safety and Tolerability Study of Linerixibat for the Treatment of Cholestatic Pruritus in Participants With Primary Biliary Cholangitis **Phase III –** Recruiting **Location(s) –** 5 countries in EU, UK, USA, Canada and other countries **Primary completion date –** December 2025
Trial Design	Single group assignment, open label
Population	N = 305 (estimated); Participants with a diagnosis of PBC and a history of associated pruritus as evidenced by randomisation into a prior eligible linerixibat clinical trial (BAT117213, GLIMMER or GLISTEN); aged 18 to 80 years.
Intervention(s)	Linerixibat
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Number of participants with non-serious adverse events (AEs) and Serious AEs (SAEs) [Time Frame: Up to 66 months] • Number of participants with Severe AEs [Time Frame: Up to 66 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT01899703; A Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Repeat Doses of GSK2330672 Administration in Patients With Primary Biliary Cirrhosis (PBC) and Symptoms of Pruritus **Phase II –** Completed **Location(s) –** UK **Study completion date –** October 2015
Trial Design	Randomised, crossover assignment, double masked
Population	N = 22 (actual); aged 18 to 75 years; proven or likely PBC; symptoms of pruritis; on a stable dose of UDCA for >8 weeks
Intervention(s)	Linerixibat oral preserved solution
Comparator(s)	Placebo oral preserved solution
Outcome(s)	Primary outcome measures: • Number of participants with any on-treatment AE or SAE from Baseline to Day 56 [Time Frame: Up to Day 56] • Change from Baseline in white blood cell count (WBC), total neutrophil, lymphocyte, monocyte, eosinophil, basophil, and platelet counts at Day

	28, Day 42, and Follow-up (Day 56) [Time Frame: Baseline, Day 28, Day 42 and Follow-up (Day 56)] • Change from Baseline in haemoglobin and mean corpuscle haemoglobin concentration (MCHC) at Day 28, Day 42, and Follow-up (Day 56) [Time Frame: Baseline, Day 28, Day 42 and Follow-up (Day 56)] See trial record for full list of other outcomes.
Results (efficacy)	After linerixibat treatment, the percentage changes from baseline itch scores were -57% (95% CI -73 to -42, p<0·0001) in the NRS, -31% (-42 to -20, p<0·0001) in the PBC-40 itch domain and -35% (-45 to -25, p<0·0001) in the 5-D itch scale. linerixibat produced significantly greater reduction from baseline than the double-blind placebo in the NRS (-23%, 95% CI -45 to -1; p=0·037), PBC-40 itch domain, (-14%, -26 to -1; p=0·034), and 5-D itch scale (-20%, -34 to -7; p=0·0045). After linerixibat treatment, serum total bile acid concentrations declined by 50% (95% CI -37 to -61, p<0·0001) from 30 to 15 µM, with a significant 3·1-times increase (95% CI 2·4 to 4·0, p<0·0001) in serum C4 concentrations from 7·9 to 24·7ng/mL.[20]
Results (safety)	Linerixibat treatment for 14 days was safe with no serious adverse events reported. Diarrhoea was the most frequent adverse event during treatment with linerixibat (seven with linerixibat vs one with placebo) and headache was the most frequent adverse event during treatment with placebo (seven with placebo vs six with linerixibat).[20]

Estimated Cost

The estimated drug cost for linerixibat is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Obeticholic acid for treating primary biliary cholangitis (TA443). April 2017.

NHS England (Policy/Commissioning) Guidance

- No relevant guidance found.

Other Guidance

- American Association for the Study of Liver Diseases. Primary Biliary Cholangitis: 2018 Practice Guidance From the American Association for the Study of Liver Diseases. 2020.[21]
- The British Society of Gastroenterology and UK-PBC. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. 2018.[11]
- European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. 2017.[22]

Additional Information

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