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Volixibat for non-alcoholic steatohepatitis (NASH)

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LAY SUMMARY

Non-alcoholic steatohepatitis (NASH) is a condition of liver inflammation and damage caused by a build-up of fat in the liver. It is part of a group of conditions called non-alcoholic fatty liver disease (NAFLD) and is associated with obesity and type 2 diabetes. As the liver inflammation progresses, it can lead to liver fibrosis (scarring), cirrhosis (severe scarring) and eventually liver failure or a requirement for liver transplantation. Approximately one fifth to one third of people with NAFLD will develop NASH.

Currently, there are no approved therapies for the treatment of NASH, but doctors recommend dietary changes and exercise to prevent or slow disease progression. Volixibat is a new experimental once-daily oral tablet that may improve NASH by targeting and blocking a protein (apical sodium-dependent bile acid transporter) found in the liver. This is thought to improve liver function by reducing the amount of cholesterol (fatty substance) in this organ. If licensed, volixibat has the potential to establish itself as a single-agent and the first treatment specifically for NASH.

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TARGET GROUP

Non-alcoholic steatohepatitis (NASH) in adults with liver fibrosis – first line

TECHNOLOGY

DESCRIPTION

Volixibat (SHP626; formerly LUM002) is under development for the treatment of NASH. Volixibat is a highly potent, minimally absorbed, competitive inhibitor of the apical sodium-dependent bile acid transporter (ASBT), a transmembrane protein localized on the luminal surface of ileal enterocytes. Inhibition of bile acid (BA) reabsorption via ASBTs in the terminal ileum increases faecal BA excretion and reduces recirculation of BA back to the liver via the hepatic portal vein. This interruption of the enterohepatic circulation is proposed to stimulate de novo synthesis of BA from cholesterol in the liver, which maintains a constant pool of BA. Corroborating research indicates that increases in serum levels of 7α-hydroxy-4-cholesten-3-one (C4, a biomarker of BA synthesis) are observed following inhibition of the ASBT.[1]

In an ongoing phase II clinical trial, volixibat is administered orally in a dose-finding capacity, at 5mg, 10mg or 20mg, once daily.[2] The treatment period is 48 weeks long with a follow-up visit scheduled 4 weeks after treatment ends.[3]

Volixibat does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

There is a large unmet need for the treatment of NASH as there are no approved therapies currently on the market. There is also an urgent need for a pharmacological option that can specifically target NASH, either by reducing the excessive fat build-up in the liver or by controlling the inflammation and fibrosis in NASH patients. As the disease has a complex pathophysiology and is chronic by nature, it is essential that treatment options have a low side effect profile, without causing further harm to patients who are likely to be suffering from multiple comorbidities. NASH patients generally lack physical fitness and are unable to endure additional physical stresses that may be caused by potential NASH therapies or drugs treating other chronic conditions.[4]

Results from a phase I clinical trial demonstrated minimal systemic absorption for volixibat suggesting that it may not have clinically significant effects on the metabolism of other drugs. A low potential for drug–drug interactions would be beneficial for a potential NASH treatment as the patient population often receives numerous pharmacotherapies for associated comorbidities. Additionally the adverse events for volixibat were considered mild and predominantly gastrointestinal in nature.[1]

If licensed, volixibat has the potential to be the first licensed treatment option for NASH. Additional findings from phase II clinical trials, however, are required to understand its safety and efficacy in NASH patients.

DEVELOPER

Shire Pharmaceutical Ltd

AVAILABILITY, LAUNCH or MARKETING

Volixibat was awarded Fast Track designation by the FDA for the investigational treatment of adults who have NASH with liver fibrosis in July 2016.[5]

The company's regulatory and marketing plans were not available at the time of writing this briefing.

PATIENT GROUP

BACKGROUND

NASH is a severe form of non-alcoholic fatty liver disease (NAFLD). Approximately one fifth to one third of patients with NAFLD will develop NASH.[6] It is characterised by the accumulation of excessive fat in the liver (steatosis) combined with inflammation and features of hepatocyte injury (ballooning).[7] Several risk factors have been found to be associated with NASH including: metabolic syndrome (diabetes, hypertension, obesity, high triglyceride levels or low levels of high density lipoprotein cholesterol), age and a family history of diabetes.[7] The majority of those who develop NASH are between the ages of 40 and 60 years old, and the disease occurs more commonly in women than in men.[8] As NASH is a more aggressive form of NAFLD, over an extended period of time it can lead to the proliferation of scar-tissue (fibrosis) as well as other serious complications like liver cirrhosis.[7] Only patients with histologically proven NASH tend to develop progressive liver disease; however, when in conjunction with diabetes, insulin resistance and other pre-existing conditions, this progression becomes more likely. Although the development of NASH has been observed in patients with diabetes, it is commonly seen in those who lack any visible symptoms or abnormalities in their liver enzymes.[9] Additionally, prospective cohort studies have found that when in the presence of fibrosis, there is a higher rate of morbidity and mortality in NASH compared to NAFLD.[10]

Fibrosis is a common pathological feature of chronic liver disease; it results from unregulated wound-healing and is characterised by the progressive replacement of functional hepatic tissue with highly cross-linked collagen I/III-rich extracellular matrix.[11] Initially a fibrous expansion occurs in portal areas, which is followed by a few bridges or septa forming. The final stage before cirrhosis becomes severe fibrosis, is characterised by the presence of numerous bridges or septa with occasional nodules.[12] It is important to note that advanced fibrosis is often observed in diabetic patients without symptoms, signs, or liver enzyme abnormalities.[9]

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of NASH is difficult to estimate and is not precisely known as many patients are asymptomatic. However, estimates suggest that 2 to 5% of the UK population have NASH.[13] In the USA, NASH is now considered the second most common condition for liver transplantation after chronic hepatitis C, and is still growing.[14] Prospective, long-term, histological follow-up studies involving patients with NASH have reported that liver fibrosis develops in up to 43% of individuals.[15,16]

In 2015-2016, there were 4,973 admissions due to inflammatory liver disease, unspecified (ICD-K75) in England, resulting in 42,661 bed days and 8,597 finished consultant episodes.[17] In England and Wales, 1,775 deaths from fibrosis and cirrhosis of liver were registered during 2014 (ICD-10 K74).[18]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Obesity: identification, assessment and management (CG189). November 2014
- NICE guidelines. Non-alcoholic fatty liver disease (NAFLD): assessment and management (NG49). July 2016
- NICE guidelines. Cirrhosis in over 16s: assessment and management (NG50). July 2016
- NICE quality standard. Obesity in adults: prevention and lifestyle weight management programmes (QS111). January 2016

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard contract for Hepatobiliary and Pancreas (Adult). A02/S/a
- NHS England. 2013/14 NHS Standard Contract for Severe and Complex Obesity (All Ages). A05/S/a
- NHS England. Clinical Commissioning Policy: Complex and Specialised Obesity Surgery. NHSCB/A05/P/a. April 2013

OTHER GUIDANCE

Yorkshire and Humber Liver Network. Primary Care Guidance Program: Non-Alcohol related Fatty Liver Disease (NAFLD) Guidance on Management in Primary Care. 2016.

American College of Gastroenterology: Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. 2012.

CURRENT TREATMENT OPTIONS

Currently there are no approved therapies recommended for the treatment of NASH in the UK, but making healthy lifestyle choices and maintaining a healthy weight (by eating a well-balanced diet and engaging in regular physical exercise) are recommended as the best ways to prevent the condition.[19] Additional treatment may be recommended for associated comorbidities such as high blood pressure, diabetes and high cholesterol.[8]

Guidelines recommend that for patients with biopsy-proven NASH and where lifestyle intervention has failed, either liver-directed pharmacotherapy with pioglitazone or vitamin E can be considered, although neither pioglitazone nor vitamin E have a UK marketing authorisation for this indication.[20]

Worsening liver fibrosis may lead to the development of cirrhosis, which is irreversible, and may lead, in turn, to a progressive loss of liver function. A liver transplant may be required in severe cases.[21]

EFFICACY and SAFETY

Trial	NCT02787304; volixibat (experimental dose 1) vs volixibat (experimental dose 2) vs volixibat (experimental dose 3) vs placebo
Sponsor	Shire Pharmaceutical Ltd
Status	Ongoing
Source of Information	Trial registry,[2] Global Data[3]
Location	EU (incl UK), USA and Canada.
Design	Randomised, placebo-controlled, dose-finding study
Participants	n=266 (estimated); aged 18-80 years; adults with non-alcoholic steatohepatitis
Schedule	Randomised to receive volixibat capsule at a dose of 5 mg orally once daily in a double-blinded fashion; or receive 10 mg volixibat capsule orally once daily in a double-blinded fashion; or receive 20 mg volixibat capsule orally once daily in a double-blinded fashion; or receive placebo capsule orally once daily in a double-blinded fashion
Follow-up	48 week treatment period and a 4 week follow-up visit after treatment ends
Primary Outcomes	Number of subjects achieving binary response on liver histology between volixibat and placebo at week 48 [time frame: baseline to week 48]
Secondary Outcomes	Change from baseline to week 48 on liver histology Change from baseline to week 48 on hepatic steatosis Change from baseline to week 48 on liver histology Resolution of NASH at Week 48 Change from baseline to week 48 on serum liver-related biochemistry Change from baseline to week 48 on metabolic indicators Change from baseline to week 48 on serum lipids
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as July 2020

ESTIMATED COST and IMPACT

COST

The cost of volixibat is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival	☒ Reduced symptoms or disability
☒ Other: *improved quality of life for carers and improved patient convenience*	☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services	☒ Decreased use of existing services
☐ Re-organisation of existing services	☐ Need for new services
☐ Other	☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs	☐ Reduced drug treatment costs
☐ Other increase in costs	☐ Other reduction in costs
☐ Other	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified	☒ None identified

INFORMATION FROM

Information was received by Shire Pharmaceutical Ltd

Shire Pharmaceutical Ltd 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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