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HEALTH TECHNOLOGY BRIEFING
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Obeticholic acid for non-alcoholic steatohepatitis and fibrosis

NIHRIO ID	6477	**NICE ID**	9511
Developer/Company	Intercept Pharmaceuticals Inc.	**UKPS ID**	642881

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

SUMMARY

Obeticholic acid as a tablet is in clinical development for the treatment of advanced liver fibrosis due to non-alcoholic steatohepatitis (NASH). Non-alcoholic fatty liver disease (NAFLD) is the general term for conditions in which an excessive amount of fat is stored in the liver, but where this excess is not caused by heavy alcohol use. A build-up of fat alone is called simple fatty liver (steatosis). NASH occurs when the presence of fat leads to liver cell damage and inflammation (hepatitis). Over time, liver cell damage and inflammation due to NASH can cause scarring (fibrosis) of the liver which may increase until advanced. Once there is advanced fibrosis due to NASH, there is a higher risk of progression to cirrhosis and its complications such as liver failure, liver cancer, and death. Although simple fatty liver, NASH, and advanced fibrosis due to NASH are distinct types of NAFLD in terms of the risk to health they pose, they are considered stages of the same disease through which people will progress if lifestyle interventions are not effective.

Obeticholic acid is a modified form of a bile acid. It works by attaching to receptors in the liver and gut called farnesoid X receptors (FXRs) which control the production of bile. By attaching to these receptors, obeticholic acid reduces the production of bile in the liver, preventing it from building up and damaging the liver tissue. FXRs are also involved in the control of inflammation and fibrosis as well as the handling of fats and glucose in the liver which are important processes in the development of NASH. If licensed, obeticholic acid may offer the first pharmacological treatment option for patients with NASH who currently have few effective therapies available.

PROPOSED INDICATION

Non-cirrhotic non-alcoholic steatohepatitis (NASH) with liver fibrosis.[1]

TECHNOLOGY

DESCRIPTION

Obeticholic acid (Ocaliva; INT-747) is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR is thought to be a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol, as well as, by increasing transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.[2]

In the phase III trial (NCT02548351; REGENERATE), obeticholic acid is administered by 10mg tablet once daily or 25mg tablet once daily for up to 7 years.[1] In the phase III trial (NCT03439254; REVERSE), obeticoholic acid is administered by 10mg tablet once daily for up to 12 months or 10mg once daily for the first 3 months and up to 25mg once daily for the remaining 9 months of the study.[3]

INNOVATION AND/OR ADVANTAGES

The main treatments for patients with non-alcoholic fatty liver disease (NAFLD), irrespective of the stage of progression, are currently based on lifestyle changes, including ponderal decrease and dietary management. A subgroup of patients with more advanced NASH, who are unable to modify their lifestyle successfully, may benefit from pharmaceutical treatment. FXR is a nuclear regulator controlling several key processes involved in hepatic metabolism. NAFLD has been proven to be associated with abnormal FXR activity. Obeticholic acid is a first-in-class selective FXR agonist with anticholestatic and hepato-protective properties. Currently, obeticholic acid is indicated for the treatment of primary biliary cholangitis. However, promising effects of obeticholic acid on NASH and its metabolic features have been reported in several studies.[4] In the phase II trial (NCT01265498; FLINT) obeticholic acid improved the histological features of NASH.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Obeticholic acid is currently indicated in the EU/UK for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. Very common (≥ 1/10) adverse reactions include abdominal pain and discomfort, pruritis and fatigue.[2]

Obeticholic acid is currently in phase II clinical development for primary sclerosing cholangitis and biliary atresia.[6]

Obetichoclic acid is a Breakthrough Therapy by the US FDA for NASH with liver fibrosis in January 2015.[7]

PATIENT GROUP

DISEASE BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is an excess of fat in the liver (steatosis) that is not a result of excessive alcohol consumption or other secondary causes. These secondary causes include side effects of certain medications, hepatitis C virus infection and particular endocrine conditions.[8]

NAFLD can progress through four main stages: simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), NASH with advanced fibrosis, and cirrhosis.[9] NASH is a subset of NAFLD in which there is inflammation in and around the fatty liver cells, which may cause swelling of the liver and discomfort of the surrounding area. NASH is considered a more aggressive form of NAFLD as ongoing inflammation leads to ballooning and a build-up of scar tissue over time. This process is known as fibrosis, the most advanced stage of which is known as cirrhosis. Risk factors for NAFLD include obesity, poor diet, little exercise, smoking, type 2 diabetes and hypertension.[10]

In the absence of significant fibrosis due to NASH, no increased risk of liver related mortality has been shown and reduction in metabolic injury through effective lifestyle intervention and currently available treatment options may be sufficient to promote regression to simple steatosis or the non-NAFLD state. Conversely, once there is significant fibrosis due to NASH, the risk of liver-related mortality increases exponentially with each stage reached, with advanced fibrosis posing the greatest risk.[11] Once the cirrhosis stage is reached, the disease state may no longer be fully reversible and can be associated with multiple complications.[12]

The rate of progression of NAFLD is variable; being overweight and having diabetes are associated with an increased risk of progressive disease. The average age of people with NASH is 40–50 years and for NASH-cirrhosis 50–60 years. However, the emerging epidemic of childhood obesity means that increasing numbers of younger people have NAFLD, with some prevalence studies showing that up to 38% of obese children have evidence of NAFLD. With NAFLD progressing through its spectrum even in childhood, the age that people develop significant liver disease is likely to fall and early diagnosis and management are therefore important at all ages.[8]

CLINICAL NEED AND BURDEN OF DISEASE

There is high variability in the reported prevalence of NAFLD and NASH due to differences in the population studied, definition of the disease, regional aspects, and histological classification systems used to diagnose NASH. Many patients may not have been identified due to a lack of unique characteristics and the requirement of a liver biopsy to confirm diagnosis. NASH is more frequent among patients with type 2 diabetes mellitus and obesity and the symptoms related to these conditions could be masking the underlying liver condition and related symptoms.[13]

Epidemiological data indicates the prevalence of NASH among UK adults could be between 2-3%. Using non-invasive tests, the prevalence of NASH could be as high as 12%. Taking into consideration the asymptomatic nature of NASH, the necessary referral to a liver specialist for diagnosis, and the uncertainty surrounding how best to diagnose NASH patients in the UK (biopsy vs. non-invasive testing), the number of people with undiagnosed NASH could be significantly higher than initially anticipated.[14-17]

The number of total prevalent NAFLD cases in the UK has been estimated to increase from 14.1 million in 2016 to 16.92 million by 2030, including 3 million approximate cases of NASH with fibrosis (stages F1-F4, ranging from minimal to advanced scarring).[14] In 2017-18, hospital episode statistics for England recorded 2,958 finished consultant episodes (FCE) as fatty (change of) liver, not elsewhere classified (ICD 10: K76.0) resulting in 2,402 admissions and 3,572 FCE bed days.[18]

Mortality data from 2015 to 2017 estimate 774 people died in England due to NAFLD, a rate of 0.51 per 100,000 population aged under 75 years. Rates were 5 times higher in the North West region (1.3 per 100,000 aged under 75) than the South West (0.26 per 100,000 aged under 75).[19] More deprived areas experience higher rates of premature deaths from liver disease than less deprived areas.[20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Adopting a healthy lifestyle is the primary means of managing NAFLD including weight loss, diet, exercise (irrespective of weight loss), and cessation of smoking. While NAFLD is not caused by the intake of alcohol, the NHS recommends little to no consumption.[9] Diagnosis of NASH requires a liver biopsy and is defined as presence of hepatic steatosis, ballooning and lobular inflammation with or without fibrosis.[21] In cases that have progressed from NASH through fibrosis and cirrhosis, a liver transplant may be the only suitable treatment option.[9]

The diagnosis of NASH provides important prognostic information and indicates an increased risk of fibrosis progression, cirrhosis and possibly hepatic comorbidities. It may also prompt a closer follow-up and possibly a greater need for more intensive therapy.[22] Liver biopsy is currently the most reliable approach for identifying the presence of steatohepatitis and fibrosis in patients with NAFLD, but it is generally acknowledged that biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality.[23]

Where NAFLD pathways have been established and agreed between primary and secondary care, these focus on early risk stratification of patients likely to have more advanced disease using simple, non-invasive tests made available to GPs. This has enabled secondary care capacity to be prioritised for patients who are most at risk of NASH with advanced fibrosis and so may warrant a biopsy whilst allowing suitable follow up of patients determined to be at lower risk.[24]

European guidelines recommend that patients with NASH and/or fibrosis should be monitored annually, and those with NASH cirrhosis at 6-month intervals.[22]

CURRENT TREATMENT OPTIONS

Although NASH is the most common cause of liver disease in the Western world and among the top three indications for liver transplantation, there are no universally accepted pharmacological therapies and therapeutic advances have been slow. Pioglitazone and vitamin E, whilst unlicensed in NASH, are recommended by guidelines in selected patients. [8,21]

PLACE OF TECHNOLOGY

If licensed, obeticholic acid may offer the first pharmacological treatment option for NASH patients with fibrosis who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**REGENERATE, NCT02548351, EudraCT2015-002560-16; obeticholic acid vs placebo; phase III**
Sponsor	Intercept Pharmaceuticals
Status	Ongoing

Source of Information	Trial registry,[1,25] manufacturer[26,27,a]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, double-blind
Participants	n=2,370 (planned); aged 18-85 yrs; NASH with liver fibrosis stage 2 or 3, or stage 1a or 1b with other risk factors including (BMI ≥30 kg/m^2), type 2 diabetes diagnosed per 2013 American Diabetes Association criteria and ALT >1.5× upper limit of normal (ULN)
Schedule	Randomised to 10 mg obeticholic acid tablet once daily or 25 mg obeticholic acid tablet once daily or placebo tablet once daily
Follow-up	Pts seen every 3 mths for first 18 mths, then every 6 mths for between 5 and 7 yrs
Primary Outcomes	Between baseline and 18 mths: • proportion of obeticholic acid treated pts relative to placebo achieving at least one stage of liver fibrosis improvement with no worsening of NASH, or • proportion of obeticholic acid treated pts relative to placebo achieving NASH resolution with no worsening of liver fibrosis End of study (estimated to be 7 yrs): • Death (all cause), model of end stage liver disease (MELD) score ⩾15, liver transplant, hepatocellular carcinoma (HCC), ascites requiring medical intervention, histological progression to cirrhosis, hospitalization (as defined by a stay of ≥24 hours) for onset of: variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis.
Secondary Outcomes	• Evaluate the effect of obeticholic acid compared to placebo on liver histology in NASH [Time frame: 18 mths and end of study, estimated to be 7 yrs] - Improvement in each histological feature of NASH by at least 1 point - No worsening in fibrosis - Improvement of fibrosis by at least 2 stages - Improvement in NASH by at least 2 points with no worsening of fibrosis - Improvement of fibrosis and NASH as a composite endpoint - Resolution of fibrosis - Histological progression to cirrhosis • Evaluate the effect of obeticholic acid compared to placebo on liver histology in NASH [Time frame: end of study, estimated to be 7 yrs] - Improvement in fibrosis by at least 1 stage with no worsening of NASH - NASH resolution with no worsening of fibrosis • Evaluate the effect of obeticholic acid compared to placebo on liver biochemistry and markers of liver function [Time frame: 18 mths and end of study, estimated to be 7 yrs]
Key Results[b]	From 18 mos interim analysis: • Obeticholic acid 25 mg met the primary fibrosis endpoint at the Month 18 interim analysis • The antifibrotic effect was dose dependent and consistent across endpoints and key subgroups

[a] Information provided by Intercept Pharmaceuticals Ltd.

	• Although the primary NASH resolution endpoint was not met, obeticholic acid ameliorated steatohepatitis based on pathologist overall assessment and improvement in key disease activity parameters • Obeticholic acid rapidly and sustainably improved alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)
Adverse effects (AEs)[b]	From 18 mos interim analysis: • AEs were mostly mild to moderate in severity and were consistent with the known profile of obeticholic acid • The frequency of SAEs was similar across treatment groups and no SAE occurred in >1% of patients in any treatment arm • The incidence of pruritus was highest in the first 3 months and decreased thereafter, and in patients on obeticholic acid 25 mg reporting pruritus, 93% of events were mild to moderate • Hepatic TEAEs were balanced across groups, and hepatic serious adverse events were rare (<1% in all groups) • The incidence of cardiovascular SAEs was low and balanced across groups
Expected reporting date	Estimate study completion date reported as Oct 2022

Trial	**REVERSE, NCT03439254, EudraCT2017-000474-11; obeticholic acid vs placebo; phase III**
Sponsor	Intercept Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[3,28]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, placebo-controlled, double-blind
Participants	n=540 (planned); aged 18 yrs and older; NASH with liver fibrosis stage 4
Schedule	Randomised to 10 mg obeticholic acid tablet once daily for up to 12 mths; or 10 mg obeticholic acid tablet once daily for first 3 mths and then may titrate up to 25 mg obeticholic acid tablets once daily for remaining 9 mths; or placebo tablet once daily for up to 12 mths
Follow-up	Active treatment up to 12 mths, follow-up period not reported
Primary Outcomes	% of subjects with improvement in fibrosis by at least 1 stage with no worsening of NASH, using NASH Clinical Research Network (CRN) scoring system [Time frame: 12 mths]
Secondary Outcomes	• %of subjects with improvement in fibrosis by at least 2 stages, using Ishak scoring criteria [Time frame: 12 mths] • % of subjects with NASH resolution, using the NASH CRN scoring [Time frame: 12 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimate study completion date reported as July 2021

Trial	**FLINT, NCT01265498; obeticholic acid vs placebo; phase II**
Sponsor	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Status	Published
Source of Information	Trial registry[29], publication[5,30]
Location	USA
Design	Randomised, placebo-controlled
Participants	n=283; aged 18 yrs and older; definite or probable NASH
Schedule	Randomised to 25mg obeticholic acid tablet once daily or placebo tablet once daily
Follow-up	Active treatment for 72 wks. Trial stopped early due to good results of interim analysis of initial 219 pts, and final 64 pts followed up for another 24 wks on no treatment.
Primary Outcomes	Hepatic histological improvement in NAFLD activity score (NAS), with improvement defined as no worsening in fibrosis and a decrease in NAS of at least 2 points [Time frame: baseline to 72 wks]

Secondary Outcomes	Secondary outcomes included:
	• Resolution of NASH diagnosis on Wk 72 biopsy
	• Total NAS score: change in score [Time frame: baseline to 72 wks]
	• Improvement and change in score [Time frame: baseline to 72 wks] for:
	  ○ Fibrosis
	  ○ Hepatocellular ballooning
	  ○ Steatosis
	  ○ Lobular inflammation
	  ○ Portal inflammation
	• Changes in a large number of outcomes incl liver tests, lipids, metabolic factors incl weight and body mass index, SF-36 Quality of Life physical and mental components

Key Results	Analysis of 200 pts with baseline and end-of-treatment liver biopsies (weight loss defined as relative decline from baseline to 2% or more at treatment end). Weight loss occurred in 44% (45/102) of obeticholic acid (OCA) treated and 32% (31/98) of placebo-treated pts (P = 0.08). The NAS improved more in those with than without weight loss in both the OCA- (−2.4 vs −1.2, P<0.001) and placebo-treated pts (−1.2 vs −0.5, P = 0.03). ALT levels also improved in those with vs without weight loss in OCA- (−43 vs −34 U/L, P = 0.12) and placebo-treated pts (−29 vs −10 U/L, P = 0.02). However, among those who lost weight, OCA was associated with opposite effects from placebo on changes in alkaline phosphatase (+21 vs −12 U/L, P<0.001), total (+13 vs −14 mg/dL, P = 0.02) and LDL cholesterol (+18 vs −12 mg/dL, P = 0.01), and HbA1c (+0.1 vs −0.4%, P = 0.01). Of total 283 pts: 50 (45%) of 110 pts in the OCA grp who were meant to have biopsies at baseline and 72 weeks had improved liver histology compared with 23 (21%) of 109 such pts in the placebo group (relative risk 1·9, 95% CI 1·3 to 2·8; p=0·0002).
Adverse effects (AEs)	Clinical adverse events were generally mild to moderate in severity and were similar in the two grps for all symptoms except pruritus. Pruritus was reported in 33 (23%) of 141 OCA-treated pts and nine (6%) of 142 placebo-treated pts (p<0·0001). Pruritus was also more severe in the OCA grp, led to the use of antipruritic medications or short periods of withholding treatment in some pts, and treatment discontinuation in one pt.
Expected reporting date	Results first posted on Clinicaltrials.gov in August 2015

ESTIMATED COST

The cost of obeticholic acid is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Non-alcoholic fatty liver disease (NAFLD): assessment and management (NG49). July 2016.
- NICE quality standard. Liver disease (QS152). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Severe and Complex Obesity (All Ages). A05/S/a.

OTHER GUIDANCE

- American Association for the Study of Liver Diseases. The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases. 2018.[23]
- EASL-EASD-EASO. Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. 2016.[22]

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