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Cenicriviroc for non-alcoholic steatohepatitis (NASH)

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LAY SUMMARY

Non-alcoholic steatohepatitis (NASH) is 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), hypertension (high blood pressure) in the blood vessels of the digestive system, liver cancer, and eventually liver failure or a requirement for liver transplantation.

Currently, no therapies are approved for the treatment of NASH, however doctors recommend dietary changes and exercise to prevent or slow disease progression. Cenicriviroc is a new experimental once-daily oral tablet that may improve liver fibrosis in patients with NASH by targeting and blocking the immune and inflammatory pathways responsible for fibrosis. If licensed, cenicriviroc has the potential to establish itself as both a single-agent and as a cornerstone treatment for NASH.

TARGET GROUP

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

TECHNOLOGY

DESCRIPTION

Cenicriviroc (CVC; TAK-652; TBR-652) is a dual inhibitor of chemokine receptor 5 (CCR5) and chemokine receptor 2 (CCR2) pathways under development for the treatment of NASH in adults with liver fibrosis.[1] Immune and inflammatory responses to liver cell damage are mediated through a well-described signalling network of liver and immune cells. When fat accumulates in the liver it causes tissue injury which is sensed by Kupffer cells and which subsequently activate and respond to liver cell damage. Activated Kupffer cells initiate an inflammatory response to the liver injury and with other pro-inflammatory macrophages activate hepatic stellate cells that differentiate into cells responsible for liver fibrosis. The CCR2 and CCR5 signalling pathways play a central role throughout this process.[1]

In a phase II clinical trial, cenicriviroc was administered orally at 150mg once daily in the morning with food for 2 years.[2]

Cenicriviroc does not currently have marketing authorisation in the EU for any indication.

Cenicriviroc is currently in a phase III trial for the treatment of liver fibrosis in adult subjects with NASH[3] and phase II trials for:

- Primary sclerosing cholangitis[4]
- Prediabetes or type 2 diabetes mellitus (T2DM) and Non Alcoholic Fatty Liver Disease (NAFLD).[5]

INNOVATION and/or ADVANTAGES

If licensed, this novel drug will offer an additional treatment option for patients with NASH, a condition for which there is currently no approved therapy.[6]

DEVELOPER

Tobira Therapeutics, Inc.

AVAILABILITY, LAUNCH or MARKETING

The company anticipate a market launch in the EU in 2019.[1]

PATIENT GROUP

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a relatively recent disease. Largely lifestyle related, it is not linked to excess alcohol consumption but is commonly associated with obesity and obesity-related disorders (e.g. type 2 diabetes mellitus [T2DM] and metabolic syndrome).[7] NAFLD represents a spectrum of liver conditions, ranging from fatty liver through to cirrhosis and liver cancer.[8] NASH is a more aggressive form of NAFLD where there is inflammation in and around the fatty liver cells developing over a long period of time. This ongoing inflammation leads to a build-up of scar tissue in the liver (fibrosis) and can lead to cirrhosis.[9]

NASH is often termed a silent killer as there are minimal symptoms. It is seen more often in women than in men and more frequently in people with diabetes, obesity, and insulin resistance with ages ranging between 40 and 60 years.[10] In later stages of the disease, patients report symptoms of fatigue, weight loss, weakness and a dull or aching pain over the lower right side of the ribs. Having high levels of fat in the liver is also associated with an increased risk of comorbidities such as diabetes, heart attacks and strokes. If cirrhosis develops in patients, more severe symptoms develop such as yellowing of the skin and the whites of the eyes, itchy skin, and swelling in the legs, ankles, feet or stomach.[11]

CLINICAL NEED and BURDEN OF DISEASE

The prevalence of NASH is difficult to estimate and is not precisely known as many patients are thought to remain asymptomatic. However, estimates suggest that about 2 to 5% of the UK population have NASH.[12] 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.[13]

The population likely to be eligible to receive cenicriviroc could not easily be estimated from available routine published sources.

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.[14]
- 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.[7]

CURRENT TREATMENT OPTIONS

Currently no therapies are approved and recommended for the treatment of NASH in the UK, but making healthy lifestyle choices, maintaining a healthy weight by eating a well-balanced diet and taking regular exercise is the best way to prevent NASH.[9]

Treatment may be recommended for associated conditions such as high blood pressure, diabetes and high cholesterol.[11] Guidelines recommend that patients with biopsy-proven NASH, where lifestyle intervention has failed, either liver-directed pharmacotherapy with pioglitazone or vitamin E can be considered. Neither pioglitazone nor vitamin E have a UK marketing authorisation for this indication.[15]

EFFICACY and SAFETY

Trial	Non-alcoholic steatohepatitis in adults with liver fibrosis (AURORA), NCT03028740; Cenicriviroc; cenicriviroc vs placebo; phase III
Sponsor	Tobira Therapeutics, Inc
Status	Ongoing, recruiting participants
Source of Information	Trial registry[3]
Location	USA and Puerto Rico
Design	Randomised, placebo-controlled
Participants	N= 2,000 (planned); aged 18 to 75 years; adult subjects with NASH

Schedule	Participants randomised to one of 2 treatment arms at baseline: one cenicriviroc tablet at a dose of 150mg once daily and placebo tablet once daily until trial is complete
Follow-up	Active treatment period for up to 12 to 36 months, follow-up period 24 months.
Primary Outcomes	Liver histology (baseline and week 12), improvement in fibrosis of at least 1 stage on the NASH CRN system and no worsening of steatohepatitis, liver related clinical outcomes and all-cause mortality (end of study est. 5 years)
Secondary Outcomes	Liver histology (60 months), improvement in fibrosis by at least 1 stage and no worsening of steatohepatitis (end of study est. 5 years)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

Trial	Cenicriviroc for the treatment of NASH in adult subjects with liver fibrosis (CENTAUR), NCT02217475; Cenicriviroc; cenicriviroc vs placebo; phase IIb extension	Rollover study for efficacy of NASH in participants with liver fibrosis, NCT03059446; Cenicriviroc; cenicriviroc (single group assignment); phase IIa extension
Sponsor	Tobira Therapeutics, Inc	Tobira Therapeutics, Inc.
Status	Ongoing	Ongoing
Source of Information	Trial registry[2]	Trial registry[16]
Location	EU (incl. UK), USA, Australia and Hong Kong	EU (incl. UK), USA, Australia and Hong Kong
Design	Randomised, parallel assignment, double blind	Non-randomised, non-controlled, single intervention group
Participants	N=289; aged 18 to 75 years; NASH in adults with liver fibrosis; first line therapy	N=200 (planned); aged 18 to 75 years; non-alcoholic steatohepatitis; successful completion of both treatment period 1 and treatment period 2, of the CENTAUR study (652-2-203), including a year 2 liver biopsy
Schedule	Randomised to 150mg tablet once daily in the morning with food for 2 years or placebo once daily in the morning with food for year 1 then cenicriviroc 150	Cenicriviroc (CVC) 150 mg tablet once daily in the morning with food until CVC is commercially available or the study is terminated

	mg tablet once daily in the morning with food for year 2	
Follow-up	Not reported	Not reported
Primary Outcomes	Histological improvement in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) score with no concurrent worsening of fibrosis stage (NASH CRN system) [time frame: year 1]	Number of participants with treatment-emergent adverse events (AE).
Secondary Outcomes	Complete resolution of steatohepatitis with no concurrent worsening of fibrosis stage [time frame: year 1]	Not reported.
Key Results	Not reported	Not reported
Adverse effects (AEs)	-	-
Expected reporting date	-	-

ESTIMATED COST and IMPACT

COST

The cost of cenicriviroc is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other*: potential improvement in quality of life for carers improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment)*

☐ 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: *unknown cost of new therapy*	☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*	☒ None identified

REFERENCES

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