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Selonsertib for non-alcoholic steatohepatitis (NASH)

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LAY SUMMARY

Non-alcoholic fatty liver disease (NAFLD) is a condition in which excess fat is stored in the liver. This build-up of fat is not caused by heavy alcohol use. Two types of NAFLD are simple fatty liver and non-alcoholic steatohepatitis (NASH). Simple fatty liver and NASH are two separate conditions, and people typically develop one or the other. NASH is characterized by inflammation of the liver (hepatitis) and liver cell damage. Inflammation and liver cell damage can cause scarring (fibrosis) of the liver leading to cirrhosis. NASH may lead to other complications such as decompensated cirrhosis of the liver, in which the liver no longer functions, and liver cancer.

Selonsertib is an investigational oral small molecule inhibitor of ASK1, a protein that mediates inflammation, apoptosis (cell death) and fibrosis in settings of oxidative stress. Oxidative stress can be increased in many pathological conditions including liver diseases such as NASH. NASH currently has no effective treatment apart from lifestyle interventions. If licensed, selonsertib will offer a new treatment option for NASH as no effective pharmacological therapies currently exist.

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TARGET GROUP

Non-alcoholic steatohepatitis (advanced fibrosis, stages F3-F4)

TECHNOLOGY

DESCRIPTION

Selonsertib (GS-4997) is a first-in-class, selective, small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1) under development for the treatment of non-alcoholic steatohepatitis (NASH) in adults with advanced liver fibrosis.[1] Inhibition of ASK1, a serine/threonine kinase, has led to improvement in inflammation and fibrosis in animal models of NASH. Selonsertib inhibits ASK1 by competitive binding to the catalytic domain of ASK1. Selonsertib prevents the production of inflammatory cytokines, down-regulates the expression of genes involved in fibrosis, suppresses excessive apoptosis (cell death) and inhibits cellular proliferation.[2]

In phase III clinical trials (STELLAR 3, NCT03053050; STELLAR 4, NCT03053063) selonsertib is randomized to be administered orally at either 6mg or 18mg once daily for up to 240 weeks (versus placebo comparator).[3,4] There are currently no licensed pharmacological therapies for the treatment of NASH in the EU or globally.[5]

Selonsertib is also in phase II development for alcoholic hepatitis.[6]

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

INNOVATION and/or ADVANTAGES

NASH currently has no effective treatment apart from lifestyle interventions, and patients with advanced fibrosis would benefit from new options to halt and/or reverse the progression of their disease.[7] If licensed, selonsertib will offer a new option for the treatment of NASH in adults with advanced liver fibrosis who currently have no effective pharmacological therapies available.

DEVELOPER

Gilead Sciences Ltd

PATIENT GROUP

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) develops in four main stages: simple fatty liver (steatosis), non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.[14] NASH is a more aggressive form of NAFLD where there is inflammation in and around the fatty liver cells, which may cause swelling of the liver and discomfort of the surrounding area. Over a long period of time, ongoing inflammation leads to a built-up of scar tissue. This process is known as fibrosis, the advanced stages of which are known as cirrhosis.[8] Advanced liver fibrosis is defined by NICE as a grade of F3 or above using the Kleiner (NASH-CRN) or the steatosis, activity and fibrosis (SAF) score.[9]

Clinical knowledge of NAFLD is still developing. People most at risk are those who:

- are overweight or obese
- have a poor diet and do little or no exercise
- smoke
- have insulin resistance
- have type 2 diabetes
- have hypertension (high blood pressure)
- have hyperlipidaemia (too much cholesterol and triglyceride in their blood)
- have polycystic ovaries
- have hepatitis B
- have hepatitis C
- are taking certain drugs prescribed for other conditions

It is likely there are other factors which contribute to the disease as not everyone with NAFLD exhibits these risk factors.[8] NAFLD is largely asymptomatic in early stages; occasionally, people with NASH or fibrosis may experience dull or aching pain over the right side of the ribs, fatigue, unexplained weight loss, and weakness.[14]

NASH is also now considered to be one of the main causes of cirrhosis. Cirrhosis is usually the result of long-term, continuous damage to the liver. This occurs when irregular bumps, known as nodules, replace smooth liver tissues. In combination with continued scarring from fibrosis, the liver may run out of healthy cells to support normal function which can lead to complete liver failure (also known as decompensation).[8]

CLINICAL NEED and BURDEN OF DISEASE

NAFLD is one of the most important causes of liver disease worldwide in adults and children. Global prevalence of NAFLD is estimated at 24%; the highest rates are reported from South America and the Middle East, followed by Asia, the USA and Europe.

Data regarding the prevalence of advanced forms of NAFLD and NASH in the general European population are limited.[10] Recent prevalence of NAFLD in the UK is estimated between 20-30%, with approximations of the population presenting with NASH varying from 2-5%.[8,14]

Currently, NASH is primarily identified by performing an invasive liver biopsy which is impractical in view of its risks to health and cost.[9] NAFLD progresses from hepatic steatosis, through inflammatory NASH, to fibrosis or cirrhosis. The rate of progression of NAFLD is variable; obesity and diabetes are associated with an increased risk of progressive disease. The average age of people with NASH is 40-50 years, and 50-60 years for NASH-cirrhosis.[9]

The population eligible to receive selonsertib could not be estimated from available published sources.

PATIENT PATHWAY

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 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 Live Liver Transplantation Services (All Ages). A02/S(HSS)/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[11]

EASL-EASD-EASO: Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. 2016[12]

CURRENT TREATMENT OPTIONS

There are no universally accepted pharmacological therapies for NASH and therapeutic advances have been slow.[13] 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.[14] In cases that have progressed from NASH through fibrosis and cirrhosis, a liver transplant may be the only suitable treatment option.[14]

Recent studies have suggested that pioglitazone, a medication for type 2 diabetes, improves NASH in people who do not have diabetes. A study by the National Institute of Diabetes and Digestive and Kidney Diseases' NASH Clinical Research Network found that treatment with vitamin E or pioglitazone improved NASH in about half of the people treated. Vitamin E may be recommended for people who have NASH but who do not have diabetes or cirrhosis. Further research is needed on the safety and efficacy of pioglitazone for NASH.[15,16] GLP-1RA and SGLT2 inhibitors, which are currently approved for use in diabetes, have also shown early efficacy in NASH.[5]

EFFICACY and SAFETY

Trial	STELLAR 4, NCT03053063; selonsertib vs placebo; phase III

Sponsor	Gilead Sciences
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomized, placebo-controlled, double-blind
Participants	n=883; aged 18-70 years; liver biopsy consistent with NASH and cirrhosis (F4 fibrosis) according to the NASH Clinical Research Network (CRN) classification; laboratory parameters including alanine aminotransferase (ALT) ≤ 8 x upper limit of normal (ULN), creatinine clearance (CLcr) ≥ 30 milliliter/minute (mL/min), as calculated by the Cockcroft-Gault equation, HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 µmol if HbA1c is unable to be resulted)
Schedule	Randomized to selonsortib 6mg plus placebo or 18mg plus placebo or placebo comparator tablets administered orally once daily for up to 240 weeks
Follow-up	Active treatment and follow-up for up to 240 weeks
Primary Outcomes	• Proportion of participants who achieve a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) classification without worsening of NASH [Time Frame: Week 48] • Event-Free Survival (EFS) at Week 240 as assessed by time to the first clinical event [Time Frame: Week 240]
Secondary Outcomes	• Proportion of participants who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240 [Time Frame: Week 240] • Proportion of participants who have a ≥ 1-stage improvement in fibrosis at Week 48 [Time Frame: Week 48] • Proportion of participants who have a ≥ 1-stage improvement in fibrosis at Week 240 [Time Frame: Week 240] • Proportion of participants who have NASH resolution at Week 48 [Time Frame: Week 48] • Proportion of participants who have NASH Resolution at Week 240 [Time Frame: Week 240]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date January 2019, estimated study completion date November 2022

Trial	STELLAR 3, NCT03053050; selonsertib vs placebo; phase III

Sponsor	Gilead Sciences
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomized, placebo-controlled, double-blind
Participants	n=808; aged 18-70 years; liver biopsy consistent with NASH and bridging (F3 fibrosis) according to the NASH CRN classification; laboratory parameters including ALT ≤ 8 x ULN, CLcr ≥ 30 mL/min as calculated by the Cockcroft-Gault equation, HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 µmol if HbA1c is unable to be resulted), HbA1c ≤ 9.5% (or serum fructosamine ≤ 381 µmol if HbA1c is unable to be resulted)
Schedule	Randomized to selonsortib 6mg plus placebo or 18mg plus placebo or placebo comparator tablets administered orally once daily for up to 240 weeks
Follow-up	Active treatment and follow-up for up to 240 weeks
Primary Outcomes	• Proportion of participants who achieve a ≥ 1-stage improvement in fibrosis according to the NASH Clinical Research Network (CRN) Classification Without Worsening of NASH [Time Frame: Week 48] • EFS at Week 240 as assessed by time to the first clinical event [Time Frame: Week 240]
Secondary Outcomes	• Proportion of participants who have progression to cirrhosis by Week 48 [Time Frame: Week 48] • Proportion of participants who have a ≥ 1-stage improvement in fibrosis without worsening of NASH at Week 240 [Time Frame: Week 240] • Proportion of participants who have a ≥ 1-stage improvement in fibrosis at Week 48 [Time Frame: Week 48] • Proportion of participants who have a ≥ 1-stage improvement in fibrosis at Week 240 [Time Frame: Week 240] • Proportion of participants who have NASH resolution without worsening of fibrosis at Week 48 [Time Frame: Week 48] • Proportion of participants who have NASH resolution without worsening of fibrosis at Week 240 [Time Frame: Week 240]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date March 2019, estimated study completion date February 2023

ESTIMATED COST and IMPACT

COST

The cost of selonsertib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- ☒ Reduced mortality/increased length of survival
- ☒ Reduced symptoms or disability
- ☐ 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: Possible impact on existing services, either on the basis of task-shifting or task sharing between primary and secondary care
- ☐ Need for new services
- ☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☒ Other: Uncertain unit cost
- ☐ None identified

OTHER ISSUES

- ☒ None identified

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