Health Technology Briefing
October 2023

Semaglutide for non-cirrhotic non-alcoholic steatohepatitis

Company/Developer	Novo Nordisk Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 13408	NICE TSID: Not available	UKPS ID: 670242

Licensing and Market Availability Plans

Currently in Phase II/III clinical trials.

Summary

Non-alcoholic steatohepatitis (NASH) is a more serious, progressive form of non-alcohol-related fatty liver disease (NAFLD) that involves the accumulation of fat and inflammation in the liver. The word 'steato' in NASH refers to fat while hepatitis refers to inflammation and damage to the liver. This inflammation can lead to scarring of liver tissue, which is called fibrosis. Over time, this scarring can worsen and lead to cirrhosis, which can lead to liver cancer. Some symptoms may include severe tiredness, weight loss, yellowing of the skin or eyes, spiderlike blood vessels on the skin or long-lasting itching. A person may not have symptoms even if they develop cirrhosis due to NASH. There are currently no approved medications to treat NAFLD even though the prevalence of NASH in the UK is projected to rise from 4.1% in 2016 to approximately 5.5% by 2030. Doctors typically recommend weight loss to reduce fat, inflammation, and fibrosis (scarring in the liver).

Semaglutide is from a class of drugs called glucagon-like peptide-1 (GLP-1) receptor agonists typically used in treating diabetes. It works by increasing the amount of insulin in the body and delaying how quickly food moves through the digestive system. As a result, semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. Semaglutide has the potential to become the first therapy approved for NASH patients with liver fibrosis.

Proposed Indication

For the treatment of adult patients with non-cirrhotic non-alcoholic steatohepatitis (NASH).[1]

Technology

Description

Semaglutide (NN9535) belongs to a class of drugs called glucagon-like peptide-1 (GLP-1) receptor agonists typically used in treating diabetes to help lower blood sugar levels and promote weight loss. It has a 94% similarity to human GLP-1, a physiological hormone that the small intestine makes and performs multiple actions in glucose and appetite regulation, and in the cardiovascular system.[2,3] Semaglutide acts as a GLP-1 receptor agonist that works by mimicking the human GLP-1 and selectively binds to and activates the GLP-1 receptor, to reduce blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying, which means that your body releases less glucose (sugar) from the food you eat into your bloodstream.[3] As a result, semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high-fat foods.[3]

Semaglutide 2.4 mg is currently in phase III clinical development for the treatment of adults with non-cirrhotic non-alcoholic steatohepatitis.[1] In the phase III trial (NCT04822181), semaglutide is administered subcutaneously (under the skin) once weekly. There will be a period of dose escalation before reaching the target dose.[1]

Key Innovation

There are currently no approved medications to treat NASH or NAFLD despite increasing incidence rates of NASH.[4,5] Doctors recommend weight loss to reduce fat, inflammation, and fibrosis (scarring in the liver).[4]

Hence, there is a need for additional treatment options that will improve disease outcomes for people with NASH who have liver fibrosis. Semaglutide has the potential to become the first therapy approved for NASH patients with liver fibrosis. It is a GLP-1 receptor agonist that has been found to be effective in the treatment of NASH.[6-8] A phase 2 study found that treatment with semaglutide resulted in a significantly higher percentage of NASH resolution vs placebo.[9] If licensed, Semaglutide will offer an additional treatment option for adult patients with non-cirrhotic NASH.

Regulatory & Development Status

Semaglutide currently possesses marketing authorization in the EU/UK for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.[3]

Semaglutide is in phase III/II clinical development for several indications some of which include the following:[10]

- Type 2 diabetes
- Overweight and obesity
- Chronic kidney disease
- Alzheimers disease
- Heart failure

Patient Group

Disease Area and Clinical Need

NASH is a more serious, progressive form of NAFLD that involves the accumulation of fat and inflammation in the liver.[11,12] The word 'steato' in NASH refers to fat while hepatitis refers to inflammation and damage to the liver.[13] This inflammation can lead to scarring of liver tissue, which is called fibrosis.[11,12] Over time, this scarring can worsen and lead to cirrhosis (permanent scarring and hardening of the liver), which can lead to liver cancer.[11,12,14] Once a diagnosis has been made, the rate of disease progression is represented by the NASH Clinical Research Network (CRN) fibrosis score: 0 (none), 1 (mild or moderate), 2 (replacement of liver tissue with scar tissue and portal veins wall thickening), 3 (advanced liver fibrosis or bridging fibrosis) and 4 (cirrhosis).[15-18] NASH is a silent disease with few or no symptoms. A person may not have symptoms even if they develop cirrhosis due to NASH.[19] Still, when present, some symptoms may include severe tiredness, weight loss, yellowing of the skin or eyes, spiderlike blood vessels on the skin or long-lasting itching.[14] The risk of NAFLD often increases with being overweight, having abnormal levels of fats in your blood, as well as conditions such as type 2 diabetes, heart or circulatory disease, and metabolic syndrome.[13,19]

Majority of NASH patients go undiagnosed, as it is estimated that people undiagnosed with NASH make up 88% of total prevalence in countries namely the United Kingdom, Germany, Italy, France, and Spain.[20] This can lead to delayed treatment and greater economic and wellbeing costs.[20] A study estimated that the prevalence of NASH in the UK (all ages) is projected to rise from 4.1% in 2016 to approximately 5.5% by 2030. It also estimates that NAFLD cases are projected to grow the most in the UK by 20.2% from 14.08 million in 2016 to 16.92 million by 2030.[21] NASH incidence estimates for the UK have not been reported. However, in about one-fifth of patients, NAFLD progresses to NASH.[22] In England, in 2022-2023, there were 3,873 finished consultant episodes (FCE) for a primary diagnosis of fatty liver disease (ICD-10 code: K76.0), resulting in 3,199 hospital admissions and 4,700 FCE bed days and 1,879 day cases. In the same year, there were 693 FCE for a primary diagnosis of hepatic fibrosis (ICD-10 code: K74.0), resulting in 613 hospital admissions and 771 FCE bed days and 491 day cases.[23]

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatments for NASH or NAFLD.

Clinical Trial Information

Trial	**ESSENCE**, NCT04822181, 2019-004594-44; The Effect of Semaglutide in Subjects With Non-cirrhotic Non-alcoholic Steatohepatitis. **Phase III** – recruiting. **Location(s):** 18 EU countries, UK, USA, Canada, and other countries **Primary completion date**: April 2028
Trial Design	Randomized, parallel assignment, double masking.
Population	N = 1200 (planned); subjects with histological evidence of NASH and fibrosis stage 2 or stage 3; aged 18 years and older.
Intervention(s)	Semaglutide subcutaneously (once weekly)
Comparator(s)	Placebo subcutaneously (once weekly)
Outcome(s)	Primary outcome measures:

	• Part 1: Resolution of steatohepatitis and no worsening of liver fibrosis (Yes/No) [Time frame: From randomisation (week 0) to week 72] • Part 1: Improvement in liver fibrosis and no worsening of steatohepatitis (Yes/No) [Time frame: From randomisation (week 0) to week 72] • Part 2: Time to first liver-related clinical event (composite endpoint) [Time frame: From randomisation (week 0) to week 240] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03987451, 2018-004484-31; Investigation of Efficacy and Safety of Semaglutide s.c. Once weekly Versus Placebo in Subjects With Non-alcoholic Steatohepatitis and Compensated Liver Cirrhosis. **Phase II** – completed. **Location(s):** 3 EU countries, UK and USA. **Actual study completion date**: June 10, 2021
Trial Design	Randomized, parallel assignment, quadruple masking
Population	N = 71 (actual); subjects with histologic evidence of NASH and fibrosis stage 4; aged 18 to 75 years old (both inclusive).
Intervention(s)	Semaglutide subcutaneously once weekly (2.4 mg)
Comparator(s)	Matched placebo
Outcome(s)	At least 1 stage of liver fibrosis improvement with no worsening of NASH after 48 weeks (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation, hepatocyte ballooning or steatosis according to NASH CRN criteria) [Time frame: From baseline (week 0) to visit 12 (week 48)]. See trial record for full list of other outcomes.
Results (efficacy)	After 48 weeks there was no statistically significant difference between the treatment and placebo groups in proportion of patients with an improvement in liver fibrosis of one stage or more without worsening of NASH (5 of 47 patients in the semaglutide groups vs 7 of 24 in the placebo group; odds ratio (OR) = 0.28, 95% CI: 0.06 to 1.24). There was also no significant difference between the groups in the proportion of patients who achieved NASH resolution (p = 0.29).[24]
Results (safety)	Similar proportions of patients in each group reported adverse events (42 of 47 patients in the semaglutide group vs 19 of 24 in the placebo group) and serious events (6 of 47 vs 2 of 24, respectively). The most common adverse events were nausea (21 of 47 vs 4 of 24), diarrhoea (9 of 47 vs 2 of 24) and vomiting (8 of 47 vs 0 of 24). Hepatic and renal function remained table. There were no decompensating events or deaths.[24]

Trial	NCT02970942; This Trial is Conducted Globally. The Aim of This Trial is to Investigate Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects with Non-alcoholic Steatohepatitis. **Phase II** - Completed **Location(s)**: 9 EU countries, UK, USA, Canada, and other countries **Actual study completion date**: March 19, 2020
Trial Design	Randomized, parallel assignment, double-blind
Population	N = 320 (actual); male or female participants with local histological diagnosis and confirmation of NASH; aged 18-75 years (both inclusive) (for Japan: male or female aged 20-75 years (both inclusive)
Intervention(s)	Semaglutide subcutaneously at doses 0.1 mg, 0.2 mg, or 0.4 mg (once daily).
Comparator(s)	Matched placebo
Outcome(s)	Percentage of Participants with Non- Alcoholic Steatohepatitis (NASH) Resolution Without Worsening of Fibrosis After 72 Weeks (Yes/No) [Time frame: After 72 weeks]. See trial record for full list of other outcomes.
Results (efficacy)	The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis was 40% in the 0.1mg group, 36% in the 0.2mg group, 59% in the 0.4mg group, and 17% in the placebo group ($p<0.001$ for semaglutide 0.4mg vs placebo). An improvement in fibrosis stage occurred in 43% of the patients in the 0.4mg and in 33% of patients in the placebo group ($p = 0.48$). The mean percent weight loss was 13% in the 0.4mg group and 1% in the placebo group.[9]
Results (safety)	The incidence of nausea, constipation, and vomiting was higher in the 0.4-mg group than in the placebo group (nausea, 42% vs. 11%; constipation, 22% vs. 12%; and vomiting, 15% vs. 2%). Malignant neoplasms were reported in 3 patients who received semaglutide (1%) and in no patients who received placebo. Overall, neoplasms (benign, malignant, or unspecified) were reported in 15% of the patients in the semaglutide groups and in 8% in the placebo group; no pattern of occurrence in specific organs was observed.[9]

Estimated Cost

The NHS indicative cost of 1 mg/0.74 ml solution of Ozempic, a brand of semaglutide in a 3 ml pre-filled injection pen is £73.25.[25]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Obeticholic acid for treating liver fibrosis in people with steatohepatitis. (GID-TA10606). Expected date of issue to be confirmed.

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

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and Pancreas (adult) A02/S/a

Other Guidance

- McPherson, Stuart, et al. Quality standards for the management of non-alcoholic fatty liver disease (NAFLD): consensus recommendations from the British Association for the Study of the Liver and British Society of Gastroenterology NAFLD Special Interest Group. 2022.[26]
- Francque Sven M., et al. Non-alcoholic fatty liver disease: A patient guideline. 2021.[27]
- European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. 2016.[28]
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Additional Information

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