NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2023

Resmetirom for non-alcoholic steatohepatitis

Company/Developer	Madrigal Pharmaceuticals Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 13175	NICE ID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Resmetirom is currently in clinical development for the treatment of non-alcoholic steatohepatitis (NASH). NASH is caused by an accumulation of fat in the liver that results in inflammation and damage to the liver. It belongs to a class of diseases known as non-alcoholic fatty liver disease (NAFLD); it is an advanced form of the disease. The persistent inflammation may lead to the formation of scar tissue around the liver and associated blood vessels. If neglected, it can get worse to the point where the liver shrinks and develops lumps and scars; this irreversible damage can result in liver failure (when the liver stops functioning normally) and liver cancer. The early stage of NAFLD may have no symptoms, but as the liver damage gets worse the following symptoms may present, fatigue, weight loss, general weakness, and an ache in the upper right part of the belly. Risk factors of NASH include obesity, type 2 diabetes, high cholesterol, high triglyceride, and metabolic syndrome. There are currently no approved medicinal products for the treatment of NASH, but healthy lifestyle choices and dietary changes are recommended.

Resmetirom is a liver-directed, once-daily dosing, orally active, medicine that reduces the build-up of fat in the liver. If licensed, resmetirom may be the first medicinal product approved for the treatment of NASH with liver fibrosis.

Proposed Indication

For the treatment of adults with non-alcoholic steatohepatitis (NASH) and fibrosis, to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation.[1-5]

Technology

Description

Resmetirom (MGL-3196) is a liver-directed, orally active, selective thyroid hormone receptor-β (THR-β) agonist. It is designed to improve NASH by increasing hepatic fat metabolism and reducing lipotoxicity.[6] The activation of THR increases cholesterol metabolism via expression of the enzyme CYP7A1 and reduces de novo lipogenesis (DNL) through the suppression of hepatic sterol regulatory element binding protein-1 (SREBP-1) expression. These effects suggest potential therapeutic benefits in patients with dyslipidaemia and increased DNL such as those with NASH.[7] This significantly decreases intra-hepatic lipids mainly through increased mitochondrial β oxidation and improving hepatocyte mitochondrial function in NASH patients. Resmetirom is hypothesised to reduce very low-density lipoproteins cholesterol production and secretion from the liver leading to lower concentrations of plasma LDL cholesterol and triglycerides.[6]

Resmetirom is currently in phase III clinical development for adult patients that have NASH with fibrosis. In phase III clinical trials (MAESTRO-NASH-OUTCOMES, NCT05500222; MAESTRO-NAFLD, NCT04197479; MAESTRO-NAFLD-OLE, NCT04951219; MAESTRO-NASH, NCT03900429), resmetirom is administered orally, once daily at a dosing of either 80mg or 100 mg.[1,3-5]

Key Innovation

Currently, there are no licensed therapies for the treatment of NASH, despite its prevalence and clinical significance, while the incidence of NASH is increasing globally.[8,9] The primary current management of NASH remains lifestyle and diet changes.[10] Resmetirom has the potential to become the first therapy approved for NASH patients with liver fibrosis. [11,12]

If licensed, resmetirom will treat NASH with fibrosis, while improving multiple atherogenic lipid profiles, which would reduce morbidity and mortality from liver disease.[11,13]

Regulatory & Development Status

Resmetirom does not currently have marketing authorisation in the EU/UK for any indication.

Resmetirom is currently only in phase II/III clinical trials for NASH and NAFLD.[1-5]

Resmetirom has the US FDA Breakthrough Therapy designation for NASH in April 2023.[14]

Patient Group

Disease Area and Clinical Need

NASH is becoming the most important aetiology for advanced liver disease, it is an advanced form of non-alcoholic fatty liver disease (NAFLD) and is closely associated with metabolic diseases and obesity.[8,13] Apoptosis and liver damage may occur in liver cells because of an excess of free fatty acids and the synthesis of intermediaries such ceramides and phospholipids. NASH is associated with persistent liver cell injury leading to fibrosis and in a subset may progress to cirrhosis, end-stage-liver-disease, and

hepatocellular cancer.[15,16] Liver fibrosis occurs when excessive amounts of scar tissue build up in the liver due to repetitive or long-lasting injury or inflammation.[17] NASH with moderate fibrosis (fibrosis stage 2) is characterised by some scarring as a result of inflammation. The damage can be mostly repaired, and the liver is likely still functioning normally, while NASH with advanced fibrosis (fibrosis stage 3) is characterised by major scarring and it is crucial to stop additional injury and scarring at this point to prevent NAFLD from getting worse.[18] Established risk factors for NASH include, obesity, type 2 diabetes, dyslipidaemia, hypertension, insulin resistance, genetic variation linked to patatin-like phospholipase domain-containing protein 3 (PNPLA3), aspartate aminotransferase (AST) and alanine transaminase (ALT) levels and metabolic syndrome.[19] People with NASH or fibrosis do not usually experience any symptoms of NAFLD in the early stages but may occasionally experience symptoms in the more advanced stages. These include symptoms such as a dull or aching pain in the top right of the tummy (over the lower right side of the ribs), extreme tiredness, unexplained weight loss and weakness.[20]

Modelling research conducted across China, France, Germany, Italy, Japan, Spain, United Kingdom, and the United States, estimates that 3-5% of adults have NASH and between 2016 and 2030, it is predicted that the prevalence of NASH will rise by 15%-56% across these countries. NAFLD cases are projected to grow in the UK from 14.08 million in 2016 (21.9%) to 16.92 (24.7%) million by 2030, while the prevalence of NASH is projected to rise from 4.1% in 2016 to approximately 5.5% by 2030.[21]

In England, in 2021-2022, there were 3,760 finished consultant episodes (FCE) for fatty liver (ICD-10 code: K76.0), resulting in 3,078 hospital admissions and 4,273 FCE bed days and 1,791-day cases. In the same year, there were 660 FCE for hepatic fibrosis (ICD-10 code: K74.0), resulting in 601 hospital admissions and 549 FCE bed days and 480-day cases.[22]

Recommended Treatment Options

There are currently no licensed or National Institute for Health and Care Excellence (NICE) recommended treatment options for NAFLD/NASH. Making healthy lifestyle choices can help and treatment may be recommended for associated conditions or complications such as high blood pressure, diabetes and cholesterol.[23]

Clinical Trial Information

Trial	**MAESTRO-NASH-OUTCOMES; NCT05500222** A phase 3 study to evaluate the effect of resmetirom on clinical outcomes in patients with well-compensated NASH cirrhosis. **Phase III** - Recruiting **Location(s)** - United States **Primary completion date**- August 2025
Trial Design	Randomised, triple masking, parallel assignment.
Population	N= 700 (estimated) adult patients with well-compensated (Child-Pugh A) NASH cirrhosis
Intervention(s)	80 mg of resmetirom once daily given orally in the morning.
Comparator(s)	Matching placebo daily
Outcome(s)	• To determine the incidence of adjudicated composite clinical outcome event [Time Frame: Baseline up to Month 36]

	This includes any event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal haemorrhage, and confirmed increase of MELD score from <12 to.>/= 15 due to liver disease. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information		
Trial	**MAESTRO-NAFLD1; NCT04197479** A 52-week, phase 3 study to evaluate the safety and biomarkers of resmetirom (MGL-3196) in non-alcoholic fatty liver disease (NAFLD) patients. **Phase III** – Active, not recruiting. **Location(s)** – United States **Primary completion date** – December 2022	**MAESTRO-NAFLD-OLE; NCT04951219** A 52-week, phase 3, open-label extension study, with a single-blind lead-in, to evaluate safety and biomarkers of resmetirom (MGL-3196) in patients with non-alcoholic fatty liver disease (NAFLD), MAESTRO-NAFLD-Open-label-extension. **Phase III** - Recruiting **Location(s)** – United States **Primary completion date** - April 2024
Trial Design	Randomised, quadruple masking, parallel assignment	Randomised, triple masking, parallel assignment
Population	N= 1400 (estimated) adult patients with NASH or NAFLD.	N= 1000 (estimated) adult patients that participated in MAESTRO-NAFLD-1
Intervention(s)	80mg or 100mg of resmetirom once daily tablet	Resmetirom 80 mg or 100mg for first 12 weeks followed by resmetirom 100 mg for weeks 12-52. Resmetirom 100 mg for an additional 52 weeks
Comparator(s)	Matching placebo tablets	Matching placebo tablets
Outcome(s)	• The effect of once daily, oral administration of 80 or 100 mg resmetirom versus placebo on the incidence of adverse events. [Time Frame: 52 weeks] • The effect of once daily, oral administration of 80 or 100 mg resmetirom versus placebo on the percent change in low density lipoprotein C (LDL-C)	• The effect of once daily, oral administration of 80 or 100 mg resmetirom versus placebo on the incidence of adverse events. [Time Frame: 52 weeks] • Percent change in the hepatic fat fraction as determined by MRI-PDFF from baseline [Time Frame: 16 weeks]

	from baseline to Week 24 [Time Frame: 24 weeks] See trial record for full list of other outcomes.	See trial record for full list of other outcomes
Results (efficacy)	Resmetirom was safe and well-tolerated at 80 and 100 mg once a day dosing, additionally, resmetirom helped patients with presumed non-alcoholic steatohepatitis (NASH) achieve significant, clinically relevant reductions in liver fat and atherogenic lipids.[24]	-
Results (safety)	The frequency of serious adverse events was similar across treatment arms and discontinuation for adverse events was low.[24]	-

Clinical Trial Information	
Trial	**MAESTRO-NASH; NCT03900429** A phase 3, multinational, double-blind, randomized, placebo-controlled study of MGL-3196 (Resmetirom) in patients with non-alcoholic steatohepatitis (NASH) and fibrosis to resolve NASH and reduce progression to cirrhosis and/or hepatic decompensation. **Phase III-** Recruiting **Locations:** 8 EU countries, UK, United States, Canada, Australia, and others **Primary completion date-** December 2022
Trial Design	Randomised, quadruple masking, parallel assignment
Population	N= 2000 (estimated); adult patients with NASH and fibrosis stage 2 or 3.
Intervention(s)	80mg or 100mg of resmetirom once daily tablet.
Comparator(s)	Matching placebo
Outcome(s)	• To determine the effect of 80 or 100 mg MGL-3196 vs matching placebo on liver biopsy (NASH CRN score) at week 52 compared with baseline. • To determine time to experiencing an adjudicated Composite Clinical Outcome events like all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or variceal haemorrhage], histological progression to cirrhosis, and a confirmed increase of MELD score from <12 to ≥15) (Final Primary Endpoint, at 54 months) See trial record for full list of other outcomes

Results (efficacy)	The trial achieved both liver histological improvement endpoints that FDA proposed as reasonably likely to predict clinical benefit to support accelerated approval for the treatment NASH with liver fibrosis.[25,26]
Results (safety)	Large safety database established.[26]

Clinical Trial Information	
Trial	**NASH;** NCT02912260; A phase 2, multi-centre, double-blind, randomized, placebo-controlled study of MGL-3196 in patients with non-alcoholic steatohepatitis. **Phase II –** Unknown **Location(s):** United States **Primary completion date:** October 2017
Trial Design	Randomised, quadruple masking, parallel assignment
Population	N=125 (actual); adult participants with biopsy-proven NASH with fibrosis stage 1-3
Intervention(s)	Once-daily oral resmetirom
Comparator(s)	Matching placebo
Outcome(s)	Change from baseline in hepatic fat fraction assessed by MRI-PDFF (Time Frame: 12 weeks) See trial record for full list of other outcomes
Results (efficacy)	There was a sustained highly statistically significant reduction in liver fat(36.3%) at 12 weeks, based on MRI–proton density fat fraction (MRI-PDFF) in MGL-3196 treated as compared with placebo patients(9.6%) and a statistically significant resolution of NASH that correlated with reduction in liver fat on MRI-PDFF which provided evidence for efficacy at an approvable endpoint for Phase 3 development in NASH.[27]
Results (safety)	MGL-3196 was well tolerated with mostly mild and a few moderate adverse events which were balanced between drug treated and placebo patients. There was an increase in incidence of mild loose stools in MGL-3196-treated, often a single episode, at the start of treatment and incidence of loose stools was not increased later in the study.[27]

Estimated Cost
The cost of resmetirom is not yet known.

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.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- 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]
- British Society of Gastroenterology. NAFLD- diagnosis, assessment and management (2022).[29]

Additional Information

Madrigal Pharmaceuticals Inc. did not enter information 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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