Health Technology Briefing
August 2024

Obicetrapib or obicetrapib-ezetimibe for primary hypercholesterolaemia or mixed dyslipidaemia

Company/Developer	Menarini Pharma UK Srl

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35280	NICE ID: Not available	UKPS ID: 673025

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Obicetrapib or obicetrapib-ezetimibe is in clinical development for treating primary hypercholesterolaemia (PH) or mixed dyslipidaemia in adults on maximally tolerated lipid-lowering therapy, that is patients that fail to reach treatment goals inspite of being on highest tolerated dose of lipid-lowering therapy. High levels of cholesterol in the blood (hypercholesterolaemia) may be caused by genetic defects (as seen in familial (inherited) hypercholesterolaemia) or when genes and other factors such as lifestyle habits interact, as seen in non-familial hypercholesterolaemia. With hypercholesterolaemia, the liver is less able to remove excess 'bad' cholesterol, known as low-density lipoprotein cholesterol (LDL-C). This means the LDL-C level in the blood can get too high, increasing the risk of cardiovascular (heart and blood vessel) disease.

Obicetrapib works by potently reducing LDL-C, while ezetimibe inhibits the intestinal absorption of cholesterol. If licensed, obicetrapib as a monotherapy or in a fixed dose combination with ezetimibe may offer an additional treatment option for treating PH, or mixed dyslipidaemia as an adjunct to diet in patients on maximally tolerated lipid-lowering therapy.

Proposed Indication

Treatment of hypercholesterolaemia in adults on maximally tolerated lipid lowering therapies.[1-5]

Technology

Description

Obicetrapib (TA8995) [6] is a novel, selective cholesteryl ester transfer protein (CETP) inhibitor that potently decreases low-density lipoprotein-cholesterol (LDL-C) and increases high-density lipoprotein-cholesterol (HDL-C) and a number of apoA1-containing lipoproteins. The reduction in LDL-C that occurs with CETP inhibition is based on an upregulation of LDL receptors and a consequent increased fractional catabolic rate of Apo B-containing lipoproteins.[7]

Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related plant sterols. The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.[8]

Obicetrapib and obicetrapib-ezetimibe are currently in clinical development for treating hypercholesterolaemia in adults on maximally tolerated lipid-lowering therapy. In phase III clinical trial (TANDEM; NCT06005597), participants with heterozygous familial hypercholesterolaemia (HeFH) and/or atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors are administered obicetrapib 10 mg and ezetimibe 10 mg fixed-dose combination, obicetrapib 10 mg monotherapy or ezetimibe 10 mg monotherapy orally once daily for an 84 day treatment period.[1]

Key Innovation

Lipid-lowering therapies are known to reduce LDL-C, thereby reducing cardiovascular risks. For instance, statins are the standard of care and have a proven efficacy in lowering LDL-C.[9] Ezetimibe can be a second lipid-lowering drug in addition to treatment with statins when LDL-C treatment goals are not met or as a single drug in case of statin intolerance.[10] Other lipid-lowering therapies include bempedoic acid and proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeted therapy.[11,12]

However, there is considerable variability in individuals to lipid lowering therapies and many individuals at risk of cardiovascular disease fail to achieve LDL-C goals. There is an unmet medical need for patients who have ASCVD or who are at risk of ASCVD and unable to achieve sufficient and sustained LDL-C reduction with existing lipid-lowering therapies.[13] Studies reported that between 61.8% to 95.4% high risk patients do not reach the European Atherosclerosis Society and European Society of Cardiology (EAS/ESC) guidelines for LDL-C targets of less than 2.5mmol/L, while 68.1% to 96% of very high risk patients do not achieve the EAS/ESC guideline LDL-C target of less than 1.8mmol/L.[14,15]

If licensed, obicetrapib or obicetrapib-ezetimibe may offer an additional treatment option as an add-on to current lipid-lowering therapies in high-risk and very high-risk patients who have not achieved their LDL-C reduction treatment goals.

Regulatory & Development Status

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

Obicetrapib-Ezetimibe does not currently have marketing authorisation in the EU/UK for any indication.

Obicetrapib is in phase II clinical development for the treatment of Alzheimer's desease.[16]

Obicetrapib-Ezetimibe is in phase III clinical development for the treatment of coronary artery disease. [17]

Patient Group

Disease Area and Clinical Need

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated LDL-C.[18] Primary hypercholesterolaemia is a genetically heterogeneous metabolic disorder and encompasses heterozygous familial hypercholesterolaemia (HeFH), homozygous FH, and non-familial polygenic hypercholesterolaemia, which is the most common.[19] HeFH is an inherited disorder of a defective gene for the condition from one parent only, characterised by a high serum cholesterol concentration.[20] Mixed dyslipidaemia is defined as elevations in LDL-C and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.[18] Management of elevated LDL-C is central to preventing atherosclerotic cardiovascular disease (ASCVD) and key to reducing the risk of ASCVD events.[21]
LDL-C and other apolipoprotein B (apoB)-containing lipoproteins, including very low-density lipoproteins (VLDL) and their remnants, intermediate density lipoproteins (IDL), and lipoprotein, are major and causal risk factors for ASCVD.[22] LDL-C is not merely a biomarker of increased risk but a causal factor in the pathophysiology of ASCVD. ASCVD and its clinical manifestations are the leading cause of morbidity and mortality throughout the world.[9] HeFH may have visible signs of high cholesterol such as tendon xanthomata (swellings made from cholesterol on the knuckles, hands, knees, or Achilles tendon), xanthelasmas (yellow bumps of cholesterol near the inner corner of the eyes), corneal arcus (pale white ring around the iris).[23]

The prevalence of HeFH in the UK population is estimated to be between 1 in 250 and 1 in 500, which means that between approximately 130,000 and 260,000 people are affected.[20] It was estimated in 2015 that primary non-familial hypercholesterolaemia affects about 4% of the adult population, approximately 1.5 million people in England.[18] In England in 2022-2023, there were 22,175 finished consultant episodes (FCE) for atherosclerosis (ICD-10 code I70), resulting in 16,636 hospital admissions, 144,543 FCE bed days, and 4,141 day cases.[24]

Recommended Treatment Options
The National Institute for Health and Care Excellence (NICE) recommends the following treatments for managing people with primary heterozygous familial hypercholesterolaemia whose LDL-C levels are not adequately controlled despite maximally tolerated lipid-lowering therapy: [18 20 25] • alirocumab • evolocumab NICE recommends the following treatments for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia:[20,25-28] • statins • ezetimibe • ezetimibe, co-administered with initial statin therapy • ezetimibe and either alirocumab or evolocumab when LDL-C levels are not adequately controlled despite maximally tolerated lipid-lowering therapy • inclisiran when LDL-C levels are not adequately controlled despite maximally tolerated lipid-lowering therapy, or when statins are contraindicated or not tolerated • bempedoic acid with ezetimibe when ezetimibe alone does not control LDL-C well enough, or when statins are contraindicated or not tolerated

Clinical Trial Information	
Trial	**PREVAIL;** NCT05202509; Placebo controlled, double blind, randomised cardiovascular outcome study to evaluate the effect of 10 mg obicetrapib in participants with Atherosclerotic Cardiovascular Disease (ASCVD) not adequately controlled despite maximally tolerated lipid modifying therapies **Phase III –** Active, not recruiting **Location:** Thirteen EU countries, UK, USA, Canada and other countries **Primary completion date –** November 2026
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=9541(actual) adults aged 18 years and older with established ASCVD on maximally tolerated lipid-modifying therapy with fasting LDL-C ≥ 55mg/dL, fasting triglyceride < 400mg/dL and estimated glomerular filtration rate ≥ 30 mL/min
Intervention(s)	10 mg obicetrapib oral tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome; To evaluate the effect of obicetrapib on the risk of Major Adverse Cardiovascular Event (MACE), 30 months after randomisation of the last participant

Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**TANDEM; NCT06005597;** A placebo-controlled, double-blind, randomised, phase 3 study to evaluate the effect of obicetrapib 10 mg and ezetimibe 10 mg fixed dose combination daily on top of maximally tolerated lipid-modifying therapy in participants with Heterozygous Familial Hypercholesterolaemia (HeFH) and/or ASCVD or multiple ASCVD risk factors **Phase III –** Active, not recruiting **Location:** USA **Primary completion date -** September 2024
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N=407 (estimated), adults aged 18 years and older with HeFH and/or ASCVD or multiple ASCVD risk factors, on maximally tolerated lipid-modifying therapy with LDL-C ≥ 70 mg/dL
Intervention(s)	• 10mg obicetrapib and 10mg ezetimibe tablet in fixed-dose combination • 10mg obicetrapib tablet monotherapy • 10mg ezetimibe capsule monotherapy
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s); • effect of combination therapy compared to placebo on LDL-C at day 84 • effect of combination therapy compared to ezetimibe 10 mg monotherapy on LDL-C at day 84 • effect of combination therapy compared to obicetrapib 10 mg monotherapy on LDL-C at day 84 See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**BROOKLYN; NCT05425745;** A placebo-controlled, double-blind, randomised, phase 3 study to evaluate the effect of 10 mg obicetrapib in participants with a history of HeFH who are not adequately controlled by their lipid modifying therapies **Phase III -** Completed **Location(s):** Four EU countries, UK, USA, Canada and other countries **Study completion date -** May 2024

Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N= 354 (actual), adults aged 18 years and older with history of HeFH, on treatment with maximally tolerated lipid modifying therapy for at least 8 weeks prior to screening, with fasting serum LDL-C ≥70 mg/dL (≥1.80 mmol/L)
Intervention(s)	10 mg obicetrapib oral tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome; Percent change in LDL-C from baseline to Day 84 in obicetrapib group compared to placebo group See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**BROADWAY; NCT05142722;** A placebo-controlled, double-blind, randomised phase 3 study to evaluate the effect of 10mg obicetrapib in participants with HeFH and/or ASCVD who are not adequately controlled by their lipid modifying therapies **Phase III -** Active, not recruiting **Location(s):** Four EU countries, USA and other countries **Study completion date -** December 2023
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N= 2532 (actual) adults aged 18 years and older with HeFH and/or a history of established ASCVD on maximally tolerated lipid-modifying therapy for at least 8 weeks, with fasting serum LDL-C of ≥ 55 to < 100 mg/dL (≥1.4 to <2.6 mmol/L) at screening
Intervention(s)	10mg obicetrapib oral tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome; Percent change in LDL-C from baseline to Day 84 in obicetrapib group compared to placebo group See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ROSE2;** NCT05266586; A placebo-controlled, double-blind, randomised, phase 2 study to evaluate the effect of obicetrapib 10 mg daily in combination with ezetimibe 10 mg daily as an adjunct to high-intensity statin therapy: The ROSE 2 study **Phase II –** Completed **Location(s):** USA **Actual study completion date -** September 2022
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N= 119 (actual); adults aged 18-75 years, LDL-C > 70 mg/dL and Triglyceride (TG)< 400 mg/dL on treatment with a high-intensity statin therapy
Intervention(s)	• 10mg obicetrapib oral tablet • 10mg obicetrapib oral tablet and 10 mg ezetimibe oral capsule
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes(s); • Mean percent change in Low-Density Lipoprotein Cholesterol (LDL-C) for combination treatment group compared with the placebo group [Friedewald] • Median percent change in Low-Density Lipoprotein Cholesterol (LDL-C) for combination treatment group compared with the placebo group [Friedewald] See trial record for full list of other outcomes
Results (efficacy)	Friedewald-calculated LDL-C, the primary endpoint, was reduced from baseline by a median of 63.4% with obicetrapib and ezetimibe in combination, compared with a reduction of 43.5% with obicetrapib monotherapy and a 6.35% reduction with placebo (p<0.0001 vs. placebo for both). Results for LDL-C measured by the Friedewald calculation were comparable to those measured by PUC (−62.8%, −43.6%, and −3.95% for the obicetrapib plus ezetimibe combination, obicetrapib monotherapy, and placebo groups, respectively)[29]
Results (safety)	Treatment-emergent adverse events were reported by 35 (29.4%) of the 119 participants in the safety population: 16 participants (40.0%) in the placebo group, 8 participants (20.5%) in the obicetrapib 10 mg group, and 11 participants (27.5%) in the combination obicetrapib plus ezetimibe group. Most events were classified as mild or moderate in severity. Five participants discontinued the study due to adverse events: 2 (5.0%) in the placebo group, 2 (5.1%) in the obicetrapib 10 mg group, and 1 (2.5%) in the combination obicetrapib plus ezetimibe group[29]

Clinical Trial Information	
Trial	**ROSE;** NCT04753606; A placebo-controlled, double-blind, randomized, phase 2 dose-finding study to evaluate the effect of obicetrapib as an adjunct to high-intensity statin therapy **Phase II** - Completed **Location(s):** USA **Actual study completion date** - May 2021
Trial Design	Randomised, double-blind, parallel assignment, placebo-controlled
Population	N= 120 (actual); adults aged 18-75 years with LDL-C > 70 mg/dL and Triglyceride (TG)< 400 mg/dL on treatment with a high-intensity statin therapy
Intervention(s)	• 5 mg obicetrapib oral tablet • 10mg obicetrapib oral tablet
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome(s): • Mean percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group [Friedewald formula] • Median Percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group [Friedewald formula] • Mean Percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group. LDL-C level was measured by PUC. See trial record for full list of other outcomes
Results (efficacy)	Obicetrapib 5mg and 10mg each significantly reduced LDL-C compared with placebo (P<0.0001), using Friedewald formula to calculate LDL-C, LDL-C was reduced from baseline by 42.9% and 45.7% for 5mg and 10mg obicetrapib, respectively, compared with 0.0% for placebo. Results for LDL-C measured by PUC, were comparable to those from the Friedewald formula: −41.5% and −50.8% for 5mg and 10mg obicetrapib, respectively, compared with −6.50% for placebo[30]
Results (safety)	Treatment-emergent adverse events were reported by a total of 42 (35.0%) of the 120 subjects in the safety population: 15 subjects (37.5%) and 8 subjects (20.0%) in the obicetrapib 5mg and 10mg groups, respectively, compared with 19 subjects (47.5%) in the placebo group. The most prevalent adverse events were gastrointestinal disorders (primarily nausea) and nervous system disorders (primarily headache). A majority of events were classified as mild or moderate in severity[30]

Estimated Cost

The cost of obicetrapib or obicetrapib-ezetimibe is not yet known

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia. (TA733). October 2021
- NICE technology appraisal. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). April 2021
- NICE technology appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). June 2016
- NICE technology appraisal. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394). June 2016
- NICE technology appraisal. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). February 2016.
- NICE guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (NG238) December 2023
- NICE clinical guideline. Familial hypercholesterolaemia: identification and management (CG71). August 2008. Last updated October 2019
- NICE quality standard guideline. Familial hypercholesterolaemia (QS41). August 2013. Last updated November 2017

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified

Other Guidance

- National Guidance for Lipid Management for Primary and Secondary Prevention of Cardiovascular Disease 2024[31]
- European Society of Cardiology. Guidelines on cardiovascular disease prevention in clinical practice.2021[32]
- European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. 2019[15]

Additional Information

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