NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Inclisiran for treating heterozygous and homozygous familial hypercholesterolaemia in adolescents aged 12 to 17 years

Company/Developer	Novartis Pharmaceuticals UK

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30932	NICE ID: Not Available	UKPS ID: 672388

Licensing and Market Availability Plans

Phase III clinical trial ongoing.

Summary

Inclisiran is currently in development for the treatment of heterozygous and homozygous familial hypercholesterolaemia in adolescents aged 12 to 17 years. Familial hypercholesterolaemia is an inherited condition where differences in certain genes affect the liver's ability to process cholesterol. This can lead to premature cardiovascular diseases. Heterozygous familial hypercholesterolaemia occurs when one gene for familial hypercholesterolaemia is inherited from a single parent, while homozygous familial hypercholesterolaemia is inherited from both parents. Familial hypercholesterolaemia is associated with complications such as ischaemic heart disease, peripheral vascular disease, acute coronary syndrome, stroke and erectile dysfunction. If not treated, people with familial hypercholesterolaemia are at a greater risk of dying from heart disease. Currently, children with familial hypercholesterolaemia have limited treatment options available to them.

Inclisiran is a medicine given by an injection underneath the skin and is used to reduce cholesterol in the blood. It works by interfering with a genetic material called ribonucleic acid (RNA) to limit the production of a protein that can lead to increased levels of "bad" cholesterol. If licenced, inclisiran could provide an additional treatment option for heterozygous and homozygous familial hypercholesterolaemia in adolescents aged 12 to 17 years.

Proposed Indication

Treatment of heterozygous familial hypercholesterolaemia (HeFH) and homozygous familial hypercholesterolaemia (HoFH) and elevated low density lipoprotein cholesterol (LDL-C) in adolescents aged 12 to less than 18 years.[1-3]

Technology

Description

Inclisiran (Leqvio) is a double-stranded small interfering ribonucleic acid (siRNA) therapeutic agent that is administered subcutaneously and is specifically taken up by hepatocytes.[4] Inclisiran can lower circulating LDL-C levels by halting proprotein convertase subtilisin/kexin type (PCSK9) gene translation intracellularly, thus leading to a decreased PCSK9 generation within the hepatocytes and subsequently to an increased number of LDL receptors.[5,6] Inhibition of PCSK9 by inclisiran prevents degradation of LDL receptors, leading to increased LDL receptor recycling and thereby increased LDL-C uptake in the hepatocytes, which in turn causes a decrease in plasma LDL-C concentration. The mechanism of action of inclisiran results in a durable reduction of PCSK9 and LDL-C levels for an extended period of time after the subcutaneous injection; therefore, only a low frequency of administration is required.[4]

Inclisiran is currently in development for the treatment of HeFH and HoFH and elevated LDL-C in adolescents aged 12 to less than 18 years. In two phase III clinical trials (ORION-16, NCT04652726; ORION-13, NCT04659863), participants received a 300 mg subcutaneous dose of inclisiran sodium at days 1, 90 and 270 in the first year, followed by 300 mg subcutaneous dose of inclisiran sodium at days 450 and 630 in the second year.[1,2] In a long-term extension phase III clinical trial (VICTORION-PEDS-OLE; NCT05682378), participants received a 300 mg subcutaneous dose of inclisiran.[3]

Key Innovation

Because of the high risk of premature atherosclerotic cardiovascular disease (ASCVD) and cardiovascular death in individuals diagnosed with HeFH and HoFH, and because of improved survival linked to more intensive and earlier onset of treatment, there is a medical need to develop suitable treatment options for affected children. Inclisiran has been shown to be an effective and safe lipid-lowering treatment in adult HeFH patients, with the advantage of an infrequent twice-yearly administration schedule.[4,7] Treatment options are still limited for children with HeFH and HoFH.[4,8] If licensed, inclisiran may provide a new treatment for HeFH and HoFH in adolescents from 12 to less than 18 years of age.

Regulatory & Development Status

Inclisiran currently has Marketing Authorisation in the UK for the following indications:[8]

- for adults with primary hypercholestrolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet
- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

Inclisiran is also currently in phase II/III development for the following indications:[9]

- adults with recent acute coronary syndrome;
- adults with elevated LDL-c and at high risk of developing cardiovascular disease;
- preventing cardiovascular events in people with established cardiovascular disease; and

- in combination with maximally-tolerated statin therapy for atherosclerotic plaque progression in adults with a diagnosis of non-obstructive coronary artery disease without previous cardiovascular events.

Patient Group

Disease Area and Clinical Need

Familial hypercholesterolaemia (FH) is an inherited condition in which variants in certain genes affect the liver's ability to process LDL-C, which can lead to premature atherosclerotic cardiovascular diseases.[10] Most people with FH have inherited a defective gene for the condition from one parent only (HeFH). More rarely an affected person inherits a genetic defect from both parents (HoFH).[11] FH is caused by pathogenic changes (variants) in three main genes involved in the metabolic pathway of clearing LDL-C: the LDL-C receptor (LDLR) gene, which is the most common (accounting for 93% of cases); the apolipoprotein B (APOB) gene (5%); and the PCSK9 gene (3%). FH is generally asymptomatic until the development of ASCVD.[10] Complications arising from hypercholesterolaemia can include: ischaemic heart disease; peripheral vascular disease; acute coronary syndrome; stroke; and erectile dysfunction. If not treated, people aged 20-39 with FH have a 100-fold increased risk of death from heart disease. HeFH has a greater than 50% risk of coronary heart disease in men by the age of 50 years and at least 30% in women by the age of 60 years. HoFH is associated with early death from coronary heart disease.[11]

FH has an estimated prevalence of 1 in 270 for HeFH and 1 in 300,000 for HoFH cases.[10] In England (2022-23) there were 1,408 finished consultant episodes (FCEs) and 1,345 admissions for pure hypercholesterolaemia in people of all ages (ICD-10 code E78.0), which resulted in 1,144 day cases and 3,352 FCE bed days.[12]

Recommended Treatment Options

In children and young people with FH, the National Institute for Health and Care Excellence (NICE) recommend that lipid-modifying drug therapy and statins licensed for the appropriate age group should be considered by the age of 10 years. For those intolerant to statins, offering other lipid-modifying drug therapies capable of reducing LDL-C concentration (such as bile acid sequestrants, fibrates or ezetimibe) is recommended. In children and young people with HoFH, NICE recommend lowering LDL-C concentration through lipid-modifying drug therapy before LDL apheresis.[13] NICE also recommend evinacumab for treating HoFH in people aged 12 and over.[14]

Clinical Trial Information

Trial	**VICTORION-PEDS-OLE**, NCT05682378, EudraCT 2022-002316-23; An Open-label, Single Arm, Multicenter Extension Study to Evaluate Long-term Safety and Tolerability of Inclisiran in Participants With Heterozygous or Homozygous Familial Hypercholesterolemia Who Have Completed the Adolescent ORION-16 or ORION-13 Studies **Phase III** – Recruiting **Location(s):** Eight EU countries, UK, USA, Canada and other countries **Primary completion date:** June 2028
Trial Design	Open-label, single group assignment

Population	N=154 (estimated); participants aged 12 years and above with a diagnosis of HeFH or HoFH who completed the ORION-16 or ORION-13 studies.
Intervention(s)	Subcutaneous injection of inclisiran sodium (300 mg)
Comparator(s)	-
Outcome(s)	Primary outcome measure: Number of participants with treatment-emergent adverse events and serious adverse events [Time frame: From day 1 in the study up to the end of study visit; up to 1080 days] See the trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**ORION-16,** NCT04652726, EudraCT 2020-002757-18; Two Part (Double-blind Inclisiran Versus Placebo [Year 1] Followed by Open-label Inclisiran [Year 2]) Randomized Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of Inclisiran in Adolescents (12 to Less Than 18 Years) With Heterozygous Familial Hypercholesterolemia and Elevated LDL-cholesterol **Phase III** – Active, not recruiting **Location(s):** Eleven EU countries, UK, USA, Canada and other countries **Primary completion date:** November 2023
Trial Design	Randomised, parallel assignment, placebo-controlled, double-blind
Population	N=141 (actual); participants aged 12 to 17 years, with HeFH diagnosed either by genetic testing or on phenotypic criteria.
Intervention(s)	Subcutaneous injection of inclisiran sodium (300 mg) at days 1, 90 and 270 in the first year, a placebo subcutaneous injection on day 360 only, followed by 300 mg subcutaneous injection of inclisiran sodium at days 450 and 630 in the second year.
Comparator(s)	Placebo at days 1, 90 and 270, followed by inclisiran sodium (300 mg) at days 360, 450 and 630.
Outcome(s)	Primary outcome measure: percentage (%) change in low-density lipoprotein cholesterol from baseline to day 330 [Time frame: baseline and day 330] See the trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ORION-13,** NCT04659863, EudraCT 2020-002755-38; Two Part (Double-blind Inclisiran Versus Placebo [Year 1] Followed by Open-label Inclisiran [Year 2]) Randomized Multicenter Study to Evaluate Safety, Tolerability, and Efficacy of

	Inclisiran in Adolescents (12 to Less Than 18 Years) With Homozygous Familial Hypercholesterolemia and Elevated LDL-cholesterol **Phase III** – Active, not recruiting **Location(s):** Three EU countries, USA, Canada and other countries **Primary completion date:** October 2023
Trial Design	Randomised, parallel assignment, placebo-controlled, double-blind
Population	N=13 (actual); participants aged 12 to 17 years, with HoFH diagnosed by genetic confirmation.
Intervention(s)	Subcutaneous injection of inclisiran sodium (300 mg) at days 1, 90 and 270, in the first year, a placebo subcutaneous injection on day 360 only, followed by 300 mg subcutaneous injection of inclisiran sodium at days 450 and 630 in the second year.
Comparator(s)	Placebo at days 1, 90 and 270, followed by inclisiran sodium (300 mg) at days 360, 450 and 630.
Outcome(s)	Primary outcome measures: percentage (%) change in low-density lipoprotein cholesterol from baseline to day 330 [Time frame: baseline and day 330] See the trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Inclisiran is already marketed in the UK; a vial (189 mg per 1 ml) costs £1,987.[15]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Evinacumab for treating homozygous familial hypercholesterolaemia in children aged 5 to 11 (GID-TA11237). Expected date of issue to be confirmed.
- NICE technology appraisal. Evinacumab for treating homozygous familial hypercholesterolaemia in people aged 12 and over (TA1002). September 2024.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (NG238). December 2023.
- NICE clinical guideline. Familial hypercholesterolaemia: identification and management (CG71). October 2019.
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). May 2023.
- NICE quality standard. Familial hypercholesterolaemia (QS41). November 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 Standard Contract for Cardiology: Inherited Cardiac Conditions (All Ages). A09/S/c.

- NHS England. 2013/14 Standard Contract for Metabolic Disorders (Children). E06/S/b.
- NHS England. 2013/14 Standard Contract for Metabolic Disorders (Laboratory Services). E06/S/c.

Other Guidance

- Watts GF, Gidding SS, Hegele RA, Raal FJ, Sturm AC, Jones LK, et al. International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. 2023.[16]
- Harada-Shiba M, Arai H, Ohmura H, Okazaki H, Sugiyama D, Tada H, et al. Guidelines for the Diagnosis and Treatment of Adult Familial Hypercholesterolemia 2022. 2023.[17]

Additional Information

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