

HEALTH TECHNOLOGY BRIEFING MAY 2019

Inclisiran for primary hypercholesterolaemia and mixed dyslipidaemia

NIHRIO ID	12058	NICE ID	10021
Developer/Company	The Medicines Company UK Ltd	UKPS ID	647942

Licensing and market availability plans	Currently in phase III clinical trials.
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SUMMARY

Inclisiran is in clinical development for treatment of hypercholesterolaemia in patients at high risk of cardiovascular disease in addition to, or after use of, oral anti-lipidaemics including statins. Abnormal levels of lipids in the blood characterises dyslipidaemia. High levels of cholesterol in the blood (hypercholesterolemia) may be caused by inherited genetic defects as seen in familial hypercholesterolaemia, or may occur when genes and other factors such as lifestyle habits interact, as seen in non-familial hypercholesterolaemia. Elevated levels of low-density lipoprotein cholesterol (LDL-C) increase the risk of cardiovascular disease, which is responsible for many deaths and disabilities.

The current standard of care for patients with hypercholesterolaemia is primarily statins which are capable of reducing LDL-C. There is however a subset of patients who are unable to reach LDL-C goals despite maximally tolerated oral lipid lowering therapy. Inclisiran is a medicinal product that inhibits a protein called PCSK9 especially present on the liver cells leading to a decrease in circulating LDL-C. If licensed, inclisiran will offer an additional treatment option for patients with primary hypercholesterolaemia as adjunctive therapy to diet and in combination with other lipid-lowering therapies.

PROPOSED INDICATION

Treatment of primary hypercholesterolaemia (including heterozygous familial hypercholesterolemia) in adults as adjunctive therapy to diet and in combination with other lipid-lowering therapies (e.g., statins, ezetimibe).^a

TECHNOLOGY

DESCRIPTION

Inclisiran is a fully chemically modified small interference RNA (siRNA) conjugated to the triantennary N-acetylgalactosamine (GalNAc). Inclisiran is made from one 2' -deoxy, eleven 2' -fluoro, and thirty-two 2' -O-methyl modified nucleotides. Termini of the duplex are modified with phosphorothioates, and the 3' end of the passenger strand is functionalized with triantennary GalNAc. When inclisiran is delivered to the hepatocytes through GalNAc interactions with the asialoglycoprotein (ASGPR) receptor, the guide strand of the duplex enters the RNA-induced silencing complex (RISC), hybridizes to the proprotein convertase subtilisin-kexin type 9 (PCSK9) mRNA and cleaves it, preventing protein production. Down-regulation of PCSK9, a protein involved in low-density lipoprotein (LDL) receptor degradation, results in the up-regulation of LDL receptor levels on the surface of the hepatocytes, supporting more efficient clearance of LDL cholesterol from the bloodstream.¹

In the pivotal phase III clinical trials (NCT03400800, ORION-11; NCT03399370, ORION-10; NCT03397121, ORION-9), patients receive inclisiran sodium 300 milligrams (mg) (equivalent to 284 mg inclisiran) in 1.5 milliliters (mL) as a subcutaneous (SC) injection on day 1 and day 90, and then every 6 months.²⁻⁴ Treatment in these studies will continue to 18 months.⁵

INNOVATION AND/OR ADVANTAGES

Statins are the standard of care and have a proven efficacy in LDL-C lowering and in the reduction of Cardiovascular Disease (CVD) risk.⁶ However, there is considerable variability in individual responses to statins and many individuals at risk for CVD fail to achieve LDL-C goals. Furthermore, some patients demonstrate intolerance to statins, mostly due to myalgias and weakness.^{7,8} An additional subset of patients finds adherence to daily treatment challenging, occasionally forgetting to take a dose, or stopping refilling statins.⁹ There is an unmet medical need for patients who have Atherosclerotic Cardiovascular Disease (ASCVD) or who are at high risk of ASCVD and are unable to achieve sufficient and sustained reduction in LDL-C with existing treatment options and thus remain at increased risk of cardiovascular disease and the consequences thereof.¹⁰

Inclisiran is a first-in-class investigational medicine that acts by specifically targeting messenger RNA, harnessing the body's natural mechanism to prevent synthesis of PCSK9 in the liver, thus allowing the body to remove LDL-C from the bloodstream.¹¹ The mode of inhibiting PCSK9 differs from monoclonal antibodies. Advantages of inclisiran over monoclonal antibodies directed against PCSK9 include its infrequent administration (twice a year, after two initiation doses at day 1 and day 90, vs. 12–26 injections per year for PCSK9 inhibitors), as well as the fact that anti-PCSK9 monoclonal antibodies act at a plasma level, whereas inclisiran acts at the intracellular level of hepatocytes to mitigate the levels of LDL-C and PCSK9.^{7,12}

^a Information provided by The Medicines Company UK Ltd

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Inclisiran was granted orphan drug designation by the FDA in the USA in January 2018 for treatment of homozygous familial hypercholesterolaemia.¹³

Inclisiran is in phase II clinical development for homozygous familial hypercholesterolaemia.¹⁴

PATIENT GROUP

DISEASE BACKGROUND

Dyslipidaemia is a broad term describing a number of conditions, including hypercholesterolaemia, hyperlipidaemia and mixed dyslipidaemia, in which disturbances in fat metabolism lead to changes in the concentrations of lipids in the blood. Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated LDL-C.¹⁵

Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a single genetic defect (familial), or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial). In heterozygous familial hypercholesterolaemia, 1 of the pair of LDL cholesterol (LDL-C) receptor genes is defective or mutated and impairs the LDL-C receptor activity. 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.¹⁵

Dyslipidaemia, and more specifically chronically elevated LDL-C, is known to be a causal factor of ASCVD.^{16,6} Familial hypercholesterolaemia (FH) can lead to the early development of atherosclerosis and coronary heart disease, and if untreated, an estimated 50% of men and 30% of women with heterozygous FH will develop coronary heart disease by 55 years of age.^{17,18}

The majority of people with primary hypercholesterolaemia have mildly or moderately elevated cholesterol levels and exhibit few clinical symptoms. Severe hypercholesterolaemia can cause xanthomas and arcus corneae. People with hypercholesterolaemia are at increased risk of CVD because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). The narrowed arteries can cause diseases such as angina, myocardial infarction and stroke, particularly in FH.¹⁹

CLINICAL NEED AND BURDEN OF DISEASE

According to a report by Public Health England, it has been estimated that between 1 in 250 and 1 in 500 of the UK population have heterozygous FH, which means that between approximately 130,000 and 260,000 people are affected, making it a relatively common disease. Most cases of FH remain undiagnosed, and only an estimated 8-15% of cases are known (based on prevalence estimates of 1 in 250 and 1 in 500).²⁰ As of 2015, NICE estimates, primary non-familial hypercholesterolaemia affects about 4% of the adult population, totalling approximately 1.7 million people in England based on mid-year population estimates from 2017-2018.^{15,21,22}

In 2016-17, the prevalence of CVD was approximately 5.9 million in England.²³ In 2016, there were 56.7 deaths per 100,000 registered in England, for CVD in those aged 0-74 years, which equates to 28,949 deaths.²⁴ According to a report by the European Heart Network, in 2011, 14.7 per 1,000 (males) and 11.1 per 1000 (females) patients were admitted to the hospital for CVD in the UK and

total cost has been estimated at €12,000,000.²⁵ Based on the 2011 population estimates, this brings the estimated number of male and female patients admitted for CVD in 2011 to 928,775 and 701,320 respectively. Approximately 28% of ASCVD patients fail to reach the LDL-C goal of <2.5mmol, exposing them to increased risk of mortality and morbidity, resulting in substantial economic burden for the UK.^{26,27}

In 2017, 14% of adults aged 16 and over, 15% of men and 13% of women, reported having any doctor-diagnosed cardiovascular disease (CVD).²⁸ Using the 2017-18 population estimates, the number of adults with CVD equates to 6,297,404 (men: 3,304,526, women: 2,983,667).²¹

In 2017, there were 72,612,423 prescription items dispensed for lipid-regulating drugs, with a total net ingredient cost of £215,440,981 across England.²⁹ About 20-30% of statin-treated patients are suspected to be statin intolerant.⁸

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The current management of primary hypercholesterolaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. The initiation of therapy with a lipid-regulating drug is generally based on an assessment of the person's cardiovascular risk. Statins are usually the first-choice drugs.¹⁹

CURRENT TREATMENT OPTIONS

Current treatment options for hyperlipidaemia in the secondary prevention of CVD include:^{15,30}

- Start statin treatment in people with cardiovascular disease with atorvastatin 80 mg. consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.
- Evolocumab and alirocumab are recommended by NICE as options for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia if LDL-C is ≥ 3.5 mmol/L in patients at very high risk of CVD (defined as recurrent CV events or cardiovascular events in more than one vascular bed), and in patients with LDL-C ≥ 4.0 mmol/L at high risk of CVD (defined as a history of any of the following: acute coronary syndrome, (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularization procedures, coronary heart disease, ischaemic stroke, peripheral artery disease)

If a person is unable to tolerate a high-intensity statin, treat with the maximum tolerated dose.¹⁵

Current lipid modification therapy options for hyperlipidaemia in the primary prevention of CVD include:^{15,30}

- Offer atorvastatin 20 mg for the primary prevention of cardiovascular disease to people who have a 10% or greater 10-year risk of developing cardiovascular disease. For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction
- Ezetimibe as a monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults in whom initial statin therapy is contraindicated or who cannot tolerate statin therapy
- Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and
- a change from initial statin therapy to an alternative statin is being considered
- Evolocumab and alirocumab are recommended by NICE as options for treating primary heterozygous familial hypercholesterolaemia in patients with LDL-C persistently above 5 mmol/l

PLACE OF TECHNOLOGY

If licensed inclisiran will offer an additional treatment option as adjunctive therapy to diet and in combination with other lipid-lowering therapies for adult patients with primary hypercholesterolaemia (including heterozygous familial hypercholesterolemia).

CLINICAL TRIAL INFORMATION

Trial	ORION-11, NCT03400800, 2017-001846-90; inclisiran vs placebo; phase III
Sponsor	The Medicines Company
Status	Ongoing
Source of Information	Trial registry; ^{2,31} Company
Location	EU [incl UK], South Africa and Ukraine
Design	Randomised, parallel assignment
Participants	n=1,617; aged 18 years and older; ASCVD or ASCVD-risk equivalents; elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies
Schedule	Patients receive inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL as a subcutaneous (SC) injection on day 1, and day 90, then every 6 months
Follow-up	18 months
Primary Outcomes	<ul style="list-style-type: none"> • Percentage change in LDL-C from baseline to day 510 [Time frame: Baseline, day 510] • Time-adjusted percent change in LDL-C levels from baseline after day 90 and up to day 540 [Time frame: Baseline, day 90, day 540]
Secondary Outcomes	<p>Time frame: Day 510</p> <ul style="list-style-type: none"> • Absolute change in LDL-C from baseline to day 510 • Percentage change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to day 510 • Percentage change in total cholesterol from baseline to day 510 • Percentage change in apolipoprotein B (ApoB) from baseline to day 510 • Percentage change in non-HDL-C from baseline to day 510 <p>Time frame: Day 90, day 510</p> <ul style="list-style-type: none"> • Time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Primary completion date Aug 2019 ^b
Trial	ORION-10, NCT03399370; inclisiran vs placebo; phase III
Sponsor	The Medicines Company
Status	Ongoing
Source of Information	Trial registry ³
Location	USA
Design	Randomised, parallel assignment
Participants	n=1,561; aged 18 years and older; ASCVD, elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies
Schedule	Patients receive inclisiran sodium 300 mg as a SC injection on day 1, day 90 and then every 6 months
Follow-up	18 months
Primary Outcomes	<ul style="list-style-type: none"> • Percentage change in LDL-C from baseline to day 510 [Time frame: Baseline, day 510] • Time-adjusted percentage change in LDL-C levels from baseline after day 90 and up to day 540 [Time frame: Baseline, day 90, day 540]
Secondary Outcomes	<p>Time frame: Baseline, day 510</p> <ul style="list-style-type: none"> • Absolute change in LDL-C from baseline to day 510 • Percentage change in PCSK9 from baseline to day 510 • Percentage change in total cholesterol from baseline to day 510 • Percentage change in ApoB from baseline to day 510 • Percentage change in non-HDL-C from baseline to day 510 <p>Time frame: Day 90, day 540</p> <ul style="list-style-type: none"> • Time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date Oct 2019

Trial	ORION-9, NCT03397121, 2017-002472-30, inclisiran vs placebo; phase III
Sponsor	The Medicines Company
Status	Ongoing
Source of Information	Trial registry ^{4,32}
Location	EU [not incl UK], Canada, USA and South Africa
Design	Randomised, parallel assignment
Participants	n=482; aged 18 years and older; elevated LDL-C, heterozygous familial hypercholesterolaemia (HeFH) despite maximum tolerated dose of LDL-C lowering therapies

^b Information provided by The Medicines Company UK Ltd

Schedule	Patients receive inclisiran sodium 300 mg as a SC injection on day 1, day 90 and then every 6 months
Follow-up	18 months
Primary Outcomes	<ul style="list-style-type: none"> Percentage change in LDL-C from baseline to day 510 [Time frame: Baseline, day 510] Time-adjusted percentage change in LDL-C levels from baseline after day 90 and up to day 540 [Time frame: Baseline, day 90, day 540]
Secondary Outcomes	<p>Time frame: Baseline, day 510</p> <ul style="list-style-type: none"> Absolute change in LDL-C from baseline to day Percentage change in PCSK9 from baseline to day 510 Percentage change in total cholesterol from baseline to day 510 Percentage change in ApoB from baseline to day 510 Percentage change in non-HDL-C from baseline to day 510 <p>Time frame: Day 90, day 540</p> <ul style="list-style-type: none"> Time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date Sept 2019

Trial	ORION-8, NCT03814187, 2017-003092-55; inclisiran vs placebo; phase III extension
Sponsor	The Medicines Company
Status	Ongoing
Source of Information	Trial registry ^{33,34}
Location	USA
Design	Single group assignment, open label
Participants	n=3,700 (planned); aged 18 years and older; ASCVD, ASCVD-risk equivalents, or heterozygous or homozygous FH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies; participants must have completed a phase III pivotal study (ORION-9, ORION-10, ORION-11 or ORION-5)
Schedule	<p>Patients receive inclisiran sodium 300 mg as a single SC injection on day 1*, 90, then every 180 days to day 990.</p> <p>*Subjects who received blinded placebo in the feeder study will receive blinded inclisiran and subjects who received blinded inclisiran in the feeder study will receive blinded placebo on day 1 in ORION-8.</p>
Follow-up	18 months
Primary Outcomes	<p>Time frame: 1080 days</p> <ul style="list-style-type: none"> Proportion of subjects reaching on treatment LDL-C targets of <70 mg/dL Proportion of subjects reaching on treatment LDL-C targets of <100 mg/dL
Secondary Outcomes	<p>Time frame: 1080 days</p> <ul style="list-style-type: none"> Evaluate the effect of inclisiran on LDL-C levels

	<ul style="list-style-type: none"> Evaluate the effect of inclisiran on total cholesterol (TC), triglycerides, LDL-C, and HDL-C
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date Aug 2023

Trial	ORION-4, NCT03705234, 2017-005066-22; inclisiran vs placebo; phase III
Sponsor	The Medicines Company
Status	Ongoing
Source of Information	Trial registry; ³⁵ Company
Location	Europe (primarily the UK) and North America ^c
Design	Randomised, double-blind, placebo-controlled trial
Participants	n=15,000 (planned); patients aged ≥55 years, history or evidence of at least one of the following: ^d <ul style="list-style-type: none"> MI Ischemic stroke Peripheral arterial disease (evident by lower extremity artery revascularisation or aortic aneurysm repair) Absence of any exclusion criteria
Schedule	Patients receive inclisiran sodium 300 mg as a SC injection on day 1*, 90, then every 180 days ^e
Follow-up	Follow-up of all randomised participants is scheduled to continue for a median of about 5 years and until at least 1700 participants have experienced a primary outcome following randomisation.
Primary Outcomes	<ul style="list-style-type: none"> A composite of major adverse cardiovascular events defined as the time to first occurrence of: <ul style="list-style-type: none"> Coronary heart disease (CHD) death MI Fatal or non-fatal ischemic stroke Urgent coronary revascularisation procedure
Secondary Outcomes	<ul style="list-style-type: none"> A composite of CHD death or MI CV death
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date Jan 2024

^c Information provided by The Medicines Company UK Ltd

^d Information provided by The Medicines Company UK Ltd

^e Information provided by The Medicines Company UK Ltd

ESTIMATED COST

The cost of inclisiran is not known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Hypercholesterolemia - mipomersen (ID524). Expected publication date: TBC.
- NICE technology appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). June 2016.
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- NICE technology appraisal. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). February 2016.
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- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). July 2014. Last updated September 2016.
- NICE quality standard guideline. Cardiovascular risk assessment and lipid modification (QS100). September 2015.
- NICE quality standard guideline. Familial hypercholesterolaemia (QS41). August 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- European Society of Cardiology/European Atherosclerosis Society. European guidelines on cardiovascular disease prevention in clinical practice. 2016.³⁶
- American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. 2013.³⁷
- European Society of Cardiology and European Atherosclerosis Society. Guidelines on management of dyslipidaemia. 2011.¹⁶

ADDITIONAL INFORMATION

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