

Health Technology Briefing August 2023

Evolocumab for preventing major cardiovascular events in adults with a high risk of cardiovascular events

Company/Developer Amgen Ltd

New Active Substance Significant Licence Extension (SLE)

NIHRIO ID: 27407

NICE TSID: N/A

UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Evolocumab is currently in clinical development for the prevention of major cardiovascular events in adults without prior heart attack or stroke who are at high risk of a cardiovascular event. Cardiovascular disease (CVD) is an umbrella term for all diseases of the heart and circulation. It includes everything from conditions that are inherited or that a person is born with, to those that are develop later, such as coronary heart disease (CHD), atrial fibrillation, heart failure, and stroke. Risk factors of CVD include high blood pressure, diabetes, high cholesterol, smoking, and air pollution. There is a need for safer and more effective treatment options as standard treatment options have limited efficacy.

Evolocumab is administered by subcutaneous injection. It works by binding to a molecule called proprotein convertase subtilisin kexin type 9 (PCSK9) in the liver, which prevents this molecule binding to a receptor on liver cells called low-density lipoprotein receptor (LDLR). This allows the liver cells to reduce the levels of low-density-lipoprotein (LDL) cholesterol (LDL-C; 'bad' cholesterol) that is circulating in the blood, by binding to them. Clinical trials testing PSCK9 inhibitors have shown that reducing LDL-C levels is associated with lower rates of CVD events. If licensed, evolocumab will offer an additional preventative treatment option for patients who are at risk of experiencing a major cardiovascular event.

Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Prevention of major cardiovascular events in adults aged 50 to 79 years without a prior myocardial infarction (MI) or stroke who are at high risk of a cardiovascular event.^{1,a}

Technology

Description

Evolocumab (Repatha) is a lipid modifying agent that binds selectively to proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that is mainly synthesised and secreted by the liver.^{2,3} It prevents circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on liver cells and thus prevents PCSK9-mediated LDLR degradation. The increased LDLR levels in the liver causes reductions in serum LDL-cholesterol (LDL-C) levels.³

Evolocumab is currently in clinical development for the prevention of major cardiovascular events in adults aged 50 to 79 years, who are at high risk of a major cardiovascular event, without previous MI or stroke. In the phase III clinical trial (VESALIUS-CV, NCT03872401), patients are administered evolocumab 140 mg by subcutaneous (SC) injection once every 2 weeks (Q2W).¹

Key Innovation

Human monoclonal antibodies that target PCSK9, lower LDL-C levels by effective levels in different high-risk patient groups. Evolocumab is a fully human IgG subtype that binds with an approximate 1:1 stoichiometry to circulating PCSK9 and prohibit its binding to the LDLR, thus creating a PCSK9-deficiency state that results in tremendous accumulation of LDLR on the membrane of hepatocytes, accelerated clearance of LDL particles, and large decreases in plasma LDL-C. Aggressive LDL-C lowering with fully human PCSK9 monoclonal antibodies has been accompanied by a favourable safety profile. Previous clinical trials with PCSK9 inhibitors have demonstrated profound reductions to LDL-C levels along with lower rates of cardiovascular events.⁴ If licensed, evolocumab will offer an additional preventative treatment option for patients who are at high risk of experiencing a major cardiovascular event without prior MI or stroke.

Regulatory & Development Status

Evolocumab currently has Marketing Authorisation in the UK for treating adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia; paediatric patients aged 10 years and over with heterozygous familial hypercholesterolaemia as an adjunct to diet; adults and paediatric patients aged 10 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies; and adults with established atherosclerotic cardiovascular disease (MI, stroke or peripheral arterial disease) to reduce cardiovascular risk.³

Evolocumab is in phase II and III clinical development for other indications including:⁵

- stroke patients with symptomatic intracranial atherosclerotic stenosis
- acute coronary syndrome
- cardiac allograft vasculopathy
- lung cancer
- hereditary spastic paraplegia type 5
- aortic stenosis

^a Information provided by Amgen Limited

Patient Group

Disease Area and Clinical Need

Cardiovascular disease (CVD) is an umbrella term for all diseases of the heart and circulation. It includes everything from conditions that are inherited or that a person is born with, to those that develop later, such as coronary heart disease (CHD), atrial fibrillation, heart failure, stroke, and vascular dementia. CHD is the most common type and occurs when coronary arteries become narrowed by a build-up of atheroma (a fatty material within artery walls). The pain or discomfort felt from such narrowing is called angina and if a blockage occurs it can cause a MI which can cause heart failure. Heart failure occurs when the heart is not pumping blood around the body properly. Atrial fibrillation is one of the most common forms of abnormal heart rhythm (arrhythmia) and a major cause of stroke. When blood supply to the brain is temporarily disrupted, a transient ischaemic stroke (TIA, a 'mini stroke') can happen, or if the bloody supply to an area of the brain is affected, vascular dementia can manifest. Stroke occurs when blood supply to an area of the brain is blocked. Some risk factors of CVD include high blood pressure, diabetes, high cholesterol, smoking, and air pollution.⁶

There are approximately 7.6 million people living with CVD in the UK and around 7-8 million adults in the UK are currently taking lipid-lowering drugs such as statins. The British Heart Foundation (BHF) estimate that over half the UK population will experience CVD in their lifetime. Heart and circulatory diseases (CVD) cause an estimated 25% of all deaths in the UK; that is around 168,000 deaths annually.⁶

Recommended Treatment Options

The National Institute for Health and Care excellence (NICE) currently recommends the following therapies for preventing cardiovascular events in patient with CVD risk:⁷⁻¹⁰

- lipid modification therapies, which include statins (atorvastatin, rosuvastatin)
- icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides
- alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia
- rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease

Clinical Trial Information

Trial	<p>VESALIUS-CV, NCT03872401, EudraCT 2018-004565-14; A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate the Impact of Evolocumab on Major Cardiovascular Events in Patients at High Cardiovascular Risk Without Prior Myocardial Infarction or Stroke</p> <p>Phase III: Active, not recruiting</p> <p>Location(s): 21 EU countries, UK, USA, Canada and other countries</p> <p>Primary completion date: July 2025</p>
Trial Design	Randomised, parallel assignment, quadruple-masked, double blind
Population	N=12,301 (actual); adults aged ≥50 (men) or ≥55 (women) to < 80 years; low-density lipoprotein cholesterol (LDL-C) ≥ 90 mg/dL (≥ 2.3 mmol/L) or non-high-

	density lipoprotein cholesterol (non-HDL) \geq 120 mg/dL (\geq 3.1 mmol/L), or apolipoprotein B \geq 80 mg/dL (\geq 1.56 μ mol/L); no prior MI or stroke
Intervention(s)	Evolocumab 140 mg by SC injection Q2W.
Comparator(s)	Matching placebo
Outcome(s)	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> • Time to Coronary Heart Disease Death, Myocardial Infarction, or Ischemic Stroke [Time Frame: From randomization; for approximately a median of 4.5 years] • Time to Coronary Heart Disease Death, Myocardial Infarction, Ischemic Stroke, or Any Ischemia-driven Arterial Stroke [Time Frame: From randomization; for approximately a median of 4.5 years] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price for two evolocumab 140mg/1ml pre-filled disposable injection pens are £340.20.¹¹

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (TA805). July 2022.
- NICE technology appraisal. Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (TA607). October 2019.
- NICE technology appraisal. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). June 2016.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). May 2023.

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Specialised Vascular Services (Adults). A04/S/a.

Other Guidance

- European Society of Cardiology. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. September 2021.¹²
- European Society of Cardiology & European Atherosclerosis Society. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. 2019.¹³

- Public Health England. Public Health England cardiovascular disease prevention initiatives, 2018 to 2019. November 2018.¹⁴
- Healthcare Improvement Scotland. Risk estimation and the prevention of cardiovascular disease (SIGN 149). June 2017.¹⁵

Additional Information

Amgen Ltd did not enter information about 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.

References

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