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Canakinumab (ILARIS®) for Cardiovascular risk reduction – Add on therapy

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LAY SUMMARY

Cardiovascular disease (CVD) is a general term that refers to all conditions affecting the heart and blood vessels (circulation). These include angina, heart attack (also known as myocardial infarction), heart failure, stroke, and a number of diseases that affect the blood vessels.

CVD is usually associated with a build-up of fatty deposits inside the blood vessels (arteries) which make the vessels become narrowed (atherosclerosis). The body also reacts to the fatty deposits by sending white blood cells to the blood vessels; this process is called inflammation. The fatty deposits along with the inflammation lead to reduction of the blood supply to the heart and significantly increase the risks of heart attack and other types of cardiovascular diseases.

Canakinumab is a medicine being developed to target inflammation. It is the first and only agent which has shown that by selectively targeting some specific biomarkers of inflammation, it significantly reduces cardiovascular risks. Canakinumab is currently being developed to be used as an add-on therapy for patients who have had a prior heart attack and have a higher risk of further cardiovascular disease.

This briefing is based on information available at the time of research 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.

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TARGET GROUP

Cardiovascular risk reduction (Post-myocardial infarction (elevated hs-CRP)) – Add on therapy

TECHNOLOGY

DESCRIPTION

Canakinumab (ILARIS®; ACZ885) is a selective, high-affinity, fully human monoclonal antibody that inhibits Interleukin 1 beta (IL-1ß), a key cytokine in the inflammatory pathway known to drive the continued progression of inflammatory atherosclerosis.[1] Inflammation contributes to all phases of the atherothrombotic process including the rupture of plaques that underlies many acute ischaemic events in the coronary and cerebral circulations. Patients with elevated inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) have increased vascular risk.[2] Canakinumab works by blocking the action of IL-1ß for a sustained period of time, therefore inhibiting inflammation that is caused by its over-production.[1]

In the phase III clinical trial (CANTOS; NCT01327846), canakinumab was given quarterly subcutaneously in three doses (50mg, 150mg, or 300mg) with standard of care therapy for the study duration (median follow up of 3.7 years).[3, 2, 4] For the 300mg dose, the regimen was 300mg every 2 weeks for the first two doses, then once every 3 months.[4]

Canakinumab is licensed in the EU for the following indications:[5]

- Four types of periodic fever syndromes (diseases marked by recurring inflammation and fever) in adults and children aged 2 and above:
  - cryopyrin-associated periodic syndromes (CAPS);
  - tumour necrosis factor receptor associated periodic syndrome (TRAPS);
  - hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD);
  - familial mediterranean fever (FMF);
- Still's disease, a rare disease causing inflammation of joints as well as rash and fever (in adults and children aged 2 and above);
- Gouty arthritis, painful inflammation of the joints caused by deposit of urate crystals (in adults).

Very common or common adverse events of canakinumab (Ilaris 150mg powder for solution for injection) reported when used for some of the above indications are:[6]

- Infections and infestations
  - Respiratory tract infections (including pneumonia, bronchitis, influenza, viral infection, sinusitis, rhinitis, pharyngitis, tonsillitis, nasopharyngitis, upper respiratory tract infection)
  - Ear infection
  - Cellulitis
  - Gastroenteritis
  - Urinary tract infection
  - Vulvovaginal candidiasis
- Nervous system disorders
  - Dizziness/vertigo
- Gastrointestinal disorders
  - Upper abdominal pain
- Skin and subcutaneous tissue disorders
  - Injection site reaction
- Musculoskeletal and connective tissue disorders

  - Arthralgia
  - Musculoskeletal pain
  - Back pain
- General disorders and administration site conditions
  - Fatigue/asthenia
- Investigations
  - Creatinine renal clearance decreased
  - Proteinuria
  - Leukopenia
  - Neutropenia

Adverse events associated with canakinumab for cardiovascular risk reduction (Post-myocardial infarction) as reported in the CANTOS trial publication include:[4]

- Serious adverse events of infections such as pneumonia, cellulitis, fatal infection or sepsis, and urinary tract infection
- Cancer
- Injection site reactions
- Arthritis: Osteoarthritis and goat (these were significantly lower with canakinumab than with placebo).
- Drug-induced liver injury
- Leukopenia
- Neutropenia
- Any haemorrhage
- Thrombocytopenia
- High levels (>3× normal value) of the of following hepatic variables: Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase.
- High level of Bilirubin (>2× normal value)

INNOVATION and/or ADVANTAGES

Canakinumab is the first and only agent which has shown that selectively targeting inflammation significantly reduces cardiovascular risk in patients who have had a prior heart attack and have an increased cardiovascular inflammatory burden.[1] If licensed, canakinumab will offer an additional add-on treatment option to reduce cardiovascular risks in patients who have had a previous heart attack and have an elevated hs-CRP.

DEVELOPER

Novartis Pharmaceuticals UK Ltd

PATIENT GROUP

BACKGROUND

Cardiovascular disease (CVD) is a general term that refers to all conditions affecting the heart and blood vessels (circulation). These include coronary heart diseases (angina, heart attack (myocardial infarction or MI)), heart failure, stroke, transient ischaemic attack, peripheral arterial disease, and aortic disease. CVD is usually associated with a build-up of fatty deposits inside the arteries which make the arteries become narrowed (atherosclerosis). CVD is also associated with an increased risk of blood clots.[7, 8]

Inflammation is commonly considered to be an important contributing factor of the pathophysiology of coronary heart disease (CHD), particularly in the atherosclerotic process. C-reactive protein (CRP) has emerged as one of the most important novel inflammatory markers. It is believed to be both a marker and a mediator of atherosclerosis and CHD. Many large-scale prospective studies demonstrate that CRP strongly and independently predicts adverse cardiovascular events, including myocardial infarction, ischemic stroke, and sudden cardiac death in individuals both with and without overt CHD. The high-sensitivity CRP (hs-CRP) assay can be used as a clinical guide to diagnosis, management, and prognosis of CHD.[9]

Risk factors for CVD can be divided into modifiable and non-modifiable risk factors.[7, 10]

Modifiable risk factors:
- High blood pressure
- Smoking
- Overweight/obesity
- Lack of physical activity
- High cholesterol
- Diabetes
- Uncontrolled stress and anger

Non-modifiable risk factors:
- Age: CVD risk increases with age
- Gender: Males have higher risk for CVD
- Family history of CVD
- Being postmenopausal
- Ethnic background: in the UK, CVD is more common in people of South Asian and African or Caribbean background

The most common symptom of CHD is chest pain (angina). Angina happens when the coronary arteries (blood supply to the heart) are partially blocked. Angina can cause discomfort, heaviness, pressure, aching, burning, fullness, squeezing, or painful feeling in the chest. These can also be felt in the shoulders, arms, neck, throat, jaw, or back. There may be other symptoms associated with angina including shortness of breath, palpitations (irregular heartbeats), tachycardia (rapid heartbeat), weakness or dizziness, nausea, and sweating. Angina is often triggered by physical activity or stressful situations. However, it can occur in restful situations as well.[11, 12, 13]

Symptoms of heart attack are usually similar to that of angina but are more severe and can occur during rest. Heart attack is a serious medical emergency in which the supply of blood to the heart is suddenly blocked completely, usually by a blood clot. A lack of blood to the heart may seriously damage the heart muscle and can be life-threatening. The symptoms of heart attack can also be similar to indigestion such as a feeling of heaviness in the chest, a stomach ache or heartburn. Sometimes heart attack can occur without any symptoms. This is known as a silent heart attack and is more common in elderly people and people with diabetes. Complications from heart attack can vary widely from mild to life-threatening complications. People with minor heart attack may have no complications. Others may have a major heart attack which may be associated with a wide range of complications.[14, 11] These include:
- Arrhythmia: (abnormal heartbeat) which can range from mild to life-threatening arrhythmia.[14]
- Heart failure: a condition in which the heart cannot pump enough blood to meet the body's needs. Heart failure causes shortness of breath and fatigue that tends to increase with physical exertion. Heart failure also can cause swelling in the feet, ankles, legs, abdomen, and veins in the neck.[13]

- Cardiogenic shock: similar to heart failure, but more serious. It develops when the heart muscle has been damaged so extensively it can no longer pump enough blood to maintain many of the body's functions.[14]
- Heart rupture: an extremely serious but relatively uncommon complication of heart attack where the heart's muscles, walls or valves rupture (split apart). It can occur if the heart is significantly damaged during a heart attack and usually happens 1 to 5 days afterwards.[14]

CLINICAL NEED and BURDEN OF DISEASE

NHS England hospital statistics for 2015/16[15]show that:

- For angina pectoris (ICD-10 code: I20), there were 47,963 hospital admissions, 67,581 finished consultant episodes (FCE), and 88,715 FCE bed days.
- For acute MI (ICD-10 code: I21), there were 79,908 hospital admissions, 153,521 FCE, and 554,999 FCE bed days.
- For subsequent MI (ICD-10 code: I22), there were 594 hospital admissions, 1,344 FCE, and 5,677 FCE bed days.
- For certain current complications following acute MI (ICD-10 code: I23), there were 98 hospital admissions, 166 FCE, and 1,063 FCE bed days.
- For other acute ischaemic heart diseases (ICD-10 code: I24), there were 15,364 hospital admissions, 26,281 FCE, and 64,222 FCE bed days.
- For chronic ischaemic heart disease (ICD-10 code: I25), there were 124,592 hospital admissions, 145,013 FCE, and 297,212 FCE bed days.
- For complications and other ill-defined conditions of heart disease (I51), there were 4,466 hospital admissions, 6,275 FCE, and 15,564 FCE bed days.[15]

CHD prevalence has remained constant at around 3% in England and 4% in Scotland, Wales, and Northern Ireland between 2004/05 and 2014/15.[16] In 2013, prevalence of CHD was highest in the North of England (4.5% in the North East) and Scotland (4.3%). Overall, around three times as many men have had a heart attack compared with women. Prevalence data for 2013 suggests that more than 915,000 people in the UK have suffered a heart attack and more than 1.3 million are living with angina. Consequently, it is estimated that almost 2.3 million people in the UK are living with some form of CHD.[17]

The annual public report of Myocardial Ischaemia National Audit Project (MINAP) shows that from April 2015 – March 2016 over 94,800 heart attack cases were submitted to the MINAP database from hospitals in England, Wales, Northern Ireland and Isle of Man. Of these 85,123 patients (90.6%) received a final diagnosis of heart attack. Approximately one quarter of all heart attacks occur in individuals who have suffered at least one such attack previously.[18]

CVD mortality declined by 70% between 1979 and 2013 in the UK, and during this period there was a 78% decrease in age-standardised premature mortality (aged <75 years).[16] In 2012, CVD was the second main cause of all deaths in the UK (28%), and was lower than cancer deaths (29%) for the first time since the middle of the 20th century.[16, 17] The decrease in mortality from heart attack over the last decade can be attributed equally to decreases in incidence and improved case fatality.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ticagrelor for preventing atherothrombotic events after myocardial infarction (TA420). December 2016

- NICE technology appraisal. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (TA317). July 2014
- NICE technology appraisal. Ticagrelor for the treatment of acute coronary syndromes (TA236). October 2011
- NICE technology appraisal. Bivalirudin for the treatment of STEMI (TA230). July 2011
- NICE technology appraisal. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010.
- NICE technology appraisal. Prasugrel for the treatment of acute coronary syndrome with percutaneous coronary intervention (TA182). October 2009.
- NICE technology appraisal. Guidance on the use of coronary artery stents (TA71). October 2003 (Updated: July 2008)
- NICE technology appraisal. Drug-eluting stents for the treatment of coronary artery disease (TA152). July 2008
- NICE technology appraisal. Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction (TA52). October 2002
- NICE Clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). July 2014
- NICE Clinical guideline. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (CG172). November 2013
- NICE Clinical guideline. Myocardial infarction with ST-segment elevation: acute management (CG167). July 2013
- NICE clinical guidance. MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction (CG48). May 2007
- NICE Quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015
- NICE Public health guideline. Cardiovascular disease prevention (PH25). June 2010
- NICE Public health guideline. Cardiovascular disease: identifying and supporting people most at risk of dying early (PH15). September 2008
- NICE Medical technologies guidance. SeQuent Please balloon catheter for in-stent coronary restenosis (MTG1). December 2010

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS standard contract for cardiology: primary percutaneous coronary intervention (PPCI) (adult). A09/S/d
- NHS England. 2013/14 NHS standard contract for cardiology: implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) (adult). A09/S/a

OTHER GUIDANCE

- The European Society of Cardiology. 2016 European guidelines on cardiovascular disease prevention in clinical practice.[19]
- Wong ND, Moran AE. The U.S. prevention of cardiovascular disease guidelines and implications for implementation in LMIC. Glob Heart. 2014.[20]
- World Health Organisation. Prevention of Cardiovascular Disease: Pocket Guidelines for Assessment and Management of Cardiovascular Risk. 2007.[21]
- JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice Heart. 2005.[22]

CURRENT TREATMENT OPTIONS

Treatment of CHD includes a combination of lifestyle changes, medicines and, sometimes surgery. The aim of medicines is to reduce blood pressure or widen the arteries. These medicines include: antiplatelets, statins, beta-blockers, nitrates, angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II receptor antagonists, calcium channel blockers, and diuretics.[23]

For the treatment of people who have had a previous heart attack, NICE pathways recommend the following medicines: ACE inhibitor, antiplatelets, beta-blockers, and statin and other lipid lowering agents. For people who had heart attack in the past 12 months, NICE pathways recommend aldosterone antagonist in addition to the above medicines. In addition to medicines, NICE also recommends cardiological assessment, cardiac rehabilitation, and lifestyle changes for the treatment of people who have had a previous heart attack.[24]

EFFICACY and SAFETY

Trial	CANTOS, NCT01327846; CACZ885M2301 (Sub-study 1 CACZ885M2301S1; Sub-study 2 CACZ885M2301S2), males and females aged ≥ 18 years, canakinumab vs placebo; phase III
Sponsor	Novartis Pharmaceuticals.
Status	Completed, open-label extension ongoing.
Source of Information	Trial registry;[3] Ridker 2011;[2] Ridker 2017[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised/placebo-controlled.
Participants	n= 10,066; aged ≥ 18 yrs; male, or female of non-child-bearing potential; spontaneous MI at least 30 days before randomization. Hs-CRP ≥ 2 mg/L. participants in sub-study 1 had to have acquisition of evaluable baseline MRI images of bilateral carotid arteries by the imaging core laboratory. Participants in sub-study 2 had to have type 2 diabetes at baseline per Main protocol criteria and be on a stable anti-hyperglycaemic medication for at least 4 weeks prior to the baseline OGTT test. They also had to be willing to have the OGTT assessment started before 10am.
Schedule	Randomised to canakinumab 50mg quarterly subcutaneous; or canakinumab 150mg quarterly subcutaneous; or canakinumab 300mg quarterly subcutaneous (with one additional dose at week 2); or placebo quarterly subcutaneous; all in combination with standard of care therapy.
Follow-up	Treatment will be given to study participants every 3 months for the study duration. The median follow-up time was 3.8 years The study ran for approximately six years
Primary Outcomes	Trial completion is anticipated to occur after the accrual of at least 1,400 primary end points

	Main: time to first occurrence of major adverse cardiovascular event, which is a composite of CV death, non-fatal MI, and stroke Sub-study 1: change from baseline in carotid plaque burden in the bifurcation region of the index carotid artery Sub-study 2: change from baseline of the insulin secretion rate (ISR) relative to glucose 0-30 min defined as Φ30 = AUCISR 0-30 /AUCGluc 0-30 averaged across the yearly visits.
Secondary Outcomes	For main study: - Time to first occurrence of the composite cardiovascular endpoint consisting of cardiovascular death, non-fatal MI, stroke and hospitalization for unstable angina requiring unplanned revascularization. - Time to new onset type 2 diabetes among patients with pre-diabetes at randomization. - Time to first occurrence of non-fatal MI, stroke and all-cause mortality composite. - Time to all-cause mortality. For Sub-study 1: - Change from baseline of the total vessel wall area at Month 3 of the index carotid artery. - Mean total vessel wall area across the left and right carotid artery at Month 3 and Month 24. - Change from baseline in corresponding total vessel wall area in the left and right carotid arteries. - The existence of a baseline total vessel wall area by treatment interaction as well as the consistency of the treatment effect across subgroups. For Sub-study 2: - Change from baseline in insulin sensitivity index. - Change from baseline in OGTT stimulated area under curve (AUC) 0-120 min of glucose concentration, insulin concentration, pro-insulin concentration, and insulin concentration/glucose concentration ratio. - Change from baseline in fasting pro-insulin concentration /insulin concentration ratio. - Change from baseline in OGTT stimulated area under the curve (AUC) 0-120 min of C-peptide concentration.
Key Results	At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group,

	0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the pre-specified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).[4]
Adverse effects (AEs)	Neutropenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, and significantly more deaths were attributed to infection or sepsis in the pooled canakinumab groups than in the placebo group (incidence rate, 0.31 vs. 0.18 events per 100 person-years; P=0.02). The patients who died from infection tended to be older and more likely to have diabetes than those who did not die from infection. Six confirmed cases of tuberculosis occurred during the trial, with similar rates in the pooled canakinumab group and the placebo group (0.06% in each group). Thrombocytopenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, but no significant difference in the incidence of haemorrhage was observed. The incidence rate of injection-site reaction did not differ significantly between any canakinumab group and the placebo group. Canakinumab resulted in significantly fewer reports of arthritis, gout, and osteoarthritis than did placebo. Cancer mortality was significantly lower with canakinumab than with placebo.[4]
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Canakinumab is already marketed in the UK. The current NHS indicative price of one vial of Canakinumab (Ilaris 150mg powder for solution for injection vials (Novartis Pharmaceuticals UK Ltd)) is £9927.80.[25]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☒ Need for new services

☐ Other:

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: hsCRP testing

☒ Other reduction in costs: Reduction in cost for MI, revascularisation

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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