Darapladib for cardiovascular risk reduction in patients with coronary heart disease – add on therapy

SUMMARY

Darapladib is intended to be used as add on therapy for cardiovascular risk reduction in high-risk patients with coronary heart disease (CHD), including patients with acute coronary syndrome. If licensed, it will represent the first in a new class of treatments for this patient group. Darapladib is a selective inhibitor of lipoprotein-associated phospholipase, a key enzyme involved in lipid metabolism and inflammation which circulates with lipoprotein particles and is carried into arterial walls with low-density lipoproteins during the progression of atherosclerosis. It is not licensed for any other indication.

Diseases of the heart and circulatory system (cardiovascular disease or CVD) are the main cause of death in the UK and account for almost 191,000 deaths each year – one in three of all deaths. The main forms of CVD are CHD and stroke. The prevalence of CVD in the UK increases with age and is higher in men than in women. There are over 1.6 million men and over 1 million women in the UK with CHD, giving a total of nearly 2.7 million people. Nearly 1.6 million of these people are less than 75 years of age. In 2011-12, there were 282,569 admissions for coronary heart disease in England, resulting in 1,163,109 bed-days and 409,508 finished consultant episodes. 64,435 deaths were registered in England and Wales during 2011.

Treatment of CHD aims to prevent recurrent cardiovascular events by reducing individual patients’ cardiovascular risk. This includes lifestyle changes such as dietary modification, smoking cessation, and exercise. Current pharmacological treatment options for the prevention of cardiovascular events in high-risk patients include lipid lowering therapies, antiplatelet therapy and antihypertensive therapy. Darapladib is currently in two phase III clinical trials comparing its effect on time to first occurrence of major adverse cardiovascular events, against treatment with placebo. These trials are expected to complete in November 2014.
TARGET GROUP

- Cardiovascular risk reduction: high-risk patients with coronary heart disease (CHD), including patients with acute coronary syndrome (ACS) – add on therapy.

TECHNOLOGY

DESCRIPTION

Darapladib (SB-480848) is a selective inhibitor of lipoprotein-associated phospholipase-A₂ (Lp-PLA₂). Lp-PLA₂ is a key enzyme involved in lipid metabolism and inflammation which circulates with lipoprotein particles and is carried into arterial walls with low-density lipoproteins (LDL) during the progression of atherosclerosis. Within the vessel wall, LpPLA₂ stimulates macrophage recruitment leading to rupture of atherosclerotic plaques. Inhibition of Lp-PLA₂ may help prevent the expansion of the necrotic core of plaques, preventing rupture. Darapladib is intended to be used as add on therapy for cardiovascular risk reduction in high-risk patients with CHD, including patients with ACS. Darapladib is administered orally at 160mg once daily in combination with standard therapy. Darapladib is also in phase II clinical trials for diabetic macular oedema.

INNOVATION and/or ADVANTAGES

If licensed, darapladib will represent the first in a new class of treatments for this patient group.

DEVELOPER

GlaxoSmithKline.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

The accumulation of LDL cholesterol in the intima (inner lining) of arteries and associated inflammatory reactions gradually lead to the formation of atherosclerotic plaques within the arterial tree. Atherosclerotic plaques in the coronary arteries obstruct blood flow and reduce oxygen supply to the myocardium, which in turn produces the typical symptom of CHD, chest pain (angina pectoris). Other symptoms include exertional dyspnoea and fatigue, arrhythmias, and heart failure. Chronic stable angina and acute coronary syndrome (ACS) are clinical manifestations of CHD. ACS refers to a spectrum of clinical presentations, ranging from ST-segment elevation myocardial infarction (STEMI) to presentations found in non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The key behavioural risk factors for CHD include smoking, physically inactive lifestyles, poor diet,
excess salt, obesity and alcohol consumption. Medical risk factors include high blood pressure, high blood cholesterol, being overweight and obese, and diabetes.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to the National Service Framework for Coronary Heart Disease (2005).

**CLINICAL NEED and BURDEN OF DISEASE**

Diseases of the heart and circulatory system (cardiovascular disease or CVD) are the main cause of death in the UK and account for almost 191,000 deaths each year – one in three of all deaths. The main forms of CVD are CHD and stroke. The prevalence of CVD in the UK increases with age and is higher in men than in women. There are over 1.6 million men and over 1 million women in the UK with CHD, giving a total of nearly 2.7 million people. Nearly 1.6 million of these people are less than 75 years of age.

An estimated 233,600 people are diagnosed with ACS annually in the UK. The overall prevalence of angina in the UK is approximately 5% in men and 4% in women (8% of men and 3% of women aged 55 to 64 years and about 14% of men and 8% of women aged 65 to 74 years). It is estimated that there are around 1.5 million people who have previously suffered a myocardial infarction in the UK, and nearly 600,000 individuals of each sex who have had a stroke. Risk of CHD is directly related to blood cholesterol levels. It is estimated that around 60% of CHD is due to increased total blood cholesterol levels. The proportion of people with high cholesterol (total cholesterol levels of 5mmol/l and over) in England ranges between 54% and 64% for men and 56% and 68% for women.

In 2011-12, there were 282,569 admissions for coronary heart disease (ICD-10 I20-I25) in England, resulting in 1,163,109 bed-days and 409,508 finished consultant episodes. 64,435 deaths were registered in England and Wales during 2011. CVD is estimated to cost the UK economy around £30bn a year.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


**Other Guidance**

• European Society of Cardiology and the European Atherosclerosis Society. ESC/EAS guidelines for the management of dyslipidaemias. 2011.

**EXISTING COMPARATORS and TREATMENTS**

Treatment of CHD aims to prevent recurrent cardiovascular events by reducing individual patients’ cardiovascular risk. This includes lifestyle changes such as dietary modification, smoking cessation, and exercise. Current pharmacological treatment options for the prevention of cardiovascular events in high-risk patients include:

• Lipid lowering therapies, which include statins (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin), fibrates (bezafibrate, ciprofibrate, fenofibrate and gemfibrozil), nicotinic acid and anion exchange resins.
• Antiplatelet therapy: aspirin, clopidogrel, prasugrel, ticagrelor, abciximab, eptifibatide, tirofiban.
• Antihypertensive therapy which include, ACE inhibitors, angiotensin-II receptor antagonists, thiazides and calcium channel blockers.
• Beta blockers such as propranolol, timolol and metoprolol.

Current guidelines may also recommend revascularisation procedures in appropriate patients:
• Percutaneous coronary intervention (PCI) angioplasty with stent placement,
• Coronary artery bypass grafting (CABG).
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>SOLID-TIMI 52, NCT01000727, 480848/033; darapladib vs placebo; phase III.</th>
<th>STABILITY, NCT00799903, 100601; darapladib vs placebo; phase III.</th>
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<tr>
<td>Sponsor</td>
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<td>GlaxoSmithKline.</td>
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<td>Status</td>
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<td>Ongoing.</td>
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<td>Source of information</td>
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<td>Trial registry³⁰.</td>
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<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=13,000 (planned); adults aged ≥18 yrs; hospitalised for ACS within 30 days of study randomisation; concomitant background medication including statins, antiplatelet drugs and beta-blockers; at least one of the following: ≥60 yrs, myocardial infarction (MI) prior to qualifying ACS event, diabetes mellitus requiring pharmacotherapy, significant renal dysfunction, cerebrovascular disease or peripheral artery disease (PAD).</td>
<td>n=15,828 (planned); adults aged ≥18 yrs; chronic CHD; current treatment with statins unless study doctor deems inappropriate; at least one of the following: ≥60 yrs, diabetes mellitus requiring pharmacotherapy, HDL-C ≤50mg/dL, current smoker or smoking cessation within the last 3 months, significant renal dysfunction, cerebrovascular disease or PAD.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to darapladib 160mg once daily or placebo, in addition to standard therapy.</td>
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<tr>
<td>Follow-up</td>
<td>Study continues until approximately 1,500 primary endpoints have occurred. Median treatment duration anticipated to be approximately 3 yrs.</td>
<td>Study continues until approximately 1,500 primary endpoints have occurred. Median treatment duration anticipated to be approximately 3.5 yrs.</td>
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<td>Primary outcome/s</td>
<td>Time to the first occurrence of any component of the composite of major adverse cardiovascular events</td>
<td>Time to first occurrence of major adverse cardiovascular event.</td>
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<tr>
<td>Secondary outcome/s</td>
<td>Composite of major coronary events; composite of total coronary events; individual components of the primary end point; composite of all-cause mortality; all-cause mortality.</td>
<td>Major coronary events; total coronary events; individual components of the primary end point; all-cause mortality.</td>
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<td>Expected reporting date</td>
<td>Estimated study completion date Nov 2014.</td>
<td>Estimated study completion date Nov 2013.</td>
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<th>NCT00269048, LPL104884; darapladib vs placebo; phase II.</th>
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<td>GlaxoSmithKline.</td>
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<td>Source of information</td>
<td>Trial registry³¹.</td>
<td>Publication³², trial registry³³.</td>
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<td>Location</td>
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<td>EU, Canada, USA and other countries.</td>
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<tr>
<td>Design</td>
<td>Randomised, placebo-controlled.</td>
<td>Randomised, placebo-controlled.</td>
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</table>
| Participants  | n=300 (planned); adults aged 18 to 80 yrs; successful PCI or uncomplicated diagnostic cardiac catheterisation; antiplatelet therapy. | n=959; adults aged 18 to 80 yrs; stable CHD or CHD-risk equivalent (defined as diabetes mellitus requiring pharmacotherapy, carotid stenosis >50%, prior carotid surgery or stenting, PAD, or…
10 year risk for coronary events >20% according to Framingham Risk Score.

**Schedule**
- Randomised to darapladib 10mg once daily or placebo.
- Randomised to darapladib 40mg, 80mg or 160mg once daily, or placebo, all in combination with atorvastatin 20mg or 80mg.

**Follow-up**
- Active treatment period 1 year.
- Active treatment period 12 weeks.

**Primary outcome**
- Intravascular ultrasound (IVUS) based palpography and high-sensitivity C-reactive protein.
- Sustained inhibition of plasma Lp-PLA₂.

**Secondary outcomes**
- Endothelial function plaque volume by quantitative coronary angiography and intravascular ultrasound, circulating biomarkers.
- Other biomarkers and safety.

**Key results**

For darapladib 40mg, 80mg and 160mg respectively compared with placebo, % change (95% CI):
- Lp-PLA₂ activity, -43.0, -55.0 and -66.0 (p<0.001); high-sensitivity C-reactive protein, -6.0 (-22.0 to +13.0), -0.3 (-18.0 to +20.0), -13.0 (-18.0 to +5.0); interleukin -6, -7.8 (-18.0 to +4.0), -2.3 (-12.0 to +10.0), -12.3 (-22.0 to +1.0) (p=0.028); myeloperoxidase, +1.6 (-9.0 to +14.0), +0.9 (-10.0 to +13.0), +4.7 (-6 to +17); matrix metalloproteinase-9, -0.8 (-14.0 to +15.0), -9.8 (-22.0 to +4.0), +4.8 (-9.0 to +21.0); P-selectin, +1.0 (-6.0 to +8.0), -3.0 (-10.0 to +4.0), 0 (-7.0 to +7.0); CD40L, -3.9 (-11.0 to +14.0), -3.9 (-11.0 to +14.0), +3.4 (-13.0 to +22.0); urinary 11-dehydrothromboxane B₂, -4.5 (-16.0 to +8.0), -0.6 (-12.0 to +13.0), 0.2 (-12.0 to +13.0).

Treatment with darapladib did not modify total cholesterol, LDL-C, HDL-C or triglyceride levels compared with placebo.

**Adverse effects (AEs)**
- No AEs associated with vital signs, electrocardiograms or laboratory data were reported. Serious AEs were reported in 3% of the placebo (n=7), darapladib 40mg (n=6) and darapladib 80mg (n=7) groups and 2% of the darapladib 160mg (n=5) group. The most commonly reported AE was angina.

**Expected reporting date**
- Previously reported as August 2007.
ESTIMATED COST and IMPACT

COST

The cost of darapladib is not yet known. The cost of selected lipid-regulating drugs are summarised below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (oral)</th>
<th>Annual cost£</th>
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<tbody>
<tr>
<td>Atorvastatin (Lipitor)</td>
<td>10mg, once daily</td>
<td>£24.57</td>
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<tr>
<td>Simvastatin</td>
<td>40mg, once daily</td>
<td>£15.21</td>
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<tr>
<td>Rosuvastatin (Crestor)</td>
<td>20mg, once daily</td>
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<td>Pravastatin</td>
<td>40mg, once daily</td>
<td>£30.68</td>
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<tr>
<td>Fluvastatin</td>
<td>80mg, once daily</td>
<td>£105.82</td>
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</tbody>
</table>

IMPACT - SPECULATIVE

Impact on Patients and Carers

☑ Reduced mortality/increased length of survival
☐ Other:
☑ Reduced symptoms or disability
☐ No impact identified

Impact on Services

☐ Increased use of existing services
☐ Re-organisation of existing services
☐ Other:
☑ None identified

☐ Decreased use of existing services
☐ Need for new services

Impact on Costs

☑ Increased drug treatment costs: add on therapy.
☐ Other increase in costs:
☑ Other: uncertain unit cost compared to existing treatments.
☐ Reduced drug treatment costs
☐ Other reduction in costs:
☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified:
☑ None identified

REFERENCES

18 European Society of Cardiology. ESC/EAS Guidelines for the management of dyslipidaemias: the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European Heart Journal 2011;32:1769-1818.


