Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING OCTOBER 2018

Apabetalone in addition to high-intensity statin therapy for preventing major adverse cardiac events in high-risk cardiovascular disease patients with type 2 diabetes mellitus

NIHRIO ID	11198	**NICE ID**	9922
Developer/Company	Resverlogix Corp	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Apabetalone is in clinical development for the prevention of major adverse cardiac events (including heart attack or stroke) for patients with a high risk of cardiovascular disease, type 2 diabetes mellitus and a low high-density lipoprotein (HDL). People with type 2 diabetes have a higher risk of cardiovascular disease, as high levels of glucose in the blood can damage the walls of the arteries, making them more likely to develop fatty deposits (atheroma). These atheroma can narrow the arteries, reducing the amount of oxygen-rich blood getting to the heart, or can break off and cause a blood clot, which may result in a heart attack or stroke.

Apabetalone is the first product developed to inhibit BET proteins. These BET proteins can control the activity of cells and make them produce proteins that cause inflammation. By inhibiting the BET proteins the production of inflammatory proteins is reduced. Apabetalone also increases production of high density lipoproteins which removes excess cholesterol, reducing the risk of cardiovascular disease. Apabetalone has the potential to affect multiple processes which contribute to cardiovascular disease, with the overall result of reducing the risk of a major adverse cardiac event in diabetic patients. If licensed, apabetalone may offer an additional preventive treatment option for major adverse cardiac events in patients with type 2 diabetes mellitus, high-risk a high risk of cardiovascular disease and low HDL.

PROPOSED INDICATION

Reduction of major adverse cardiac events (MACE) in high-risk cardiovascular disease (CVD) patients with type 2 diabetes mellitus (T2DM) and low high-density lipoprotein (HDL).[1]

TECHNOLOGY

DESCRIPTION

Apabetalone (RVX-208) is in clinical development for patients with high-risk CVD, T2DM and low HDL. Apabetalone is a first-in-class, small molecule that is a selective BET (bromodomain and extra-terminal) protein inhibitor. BET bromodomain inhibition is an epigenetic mechanism that can regulate disease-causing genes. Apabetalone is a BET inhibitor selective for the second bromodomain (BD2) within the BET proteins. This selective inhibition of apabetalone on BD2 produces a specific set of biological effects with potentially important benefits for patients with conditions including high-risk CVD and diabetes mellitus, while maintaining a well described safety profile.[2]

In the phase III trial (BETonMACE; NCT02586155), apabetalone is administered orally as a 100mg capsule twice daily in addition to high-intensity statin therapy (atorvastatin or rosuvastatin).[3]

INNOVATION AND/OR ADVANTAGES

Apabetalone affects multiple processes which contribute to the onset and worsening of disease. It can regulate the expression of genes and restore the function of pathways underlying the pathogenesis of CVD. The incidence of MACE is reduced due to this epigenetic regulation, which causes:[4]

- reductions in mediators that promote inflammation of the vasculature
- reductions in mediators that promote calcium deposition in the vasculature
- reductions in the components of the coagulation cascade
- reductions in components and the function of the complement cascade
- increased apolipoprotein A-I (ApoA-I), positive effect on lipid content of HDL
- delayed and reduced oral glucose absorption and endogenous production

HDL, through activity of the main protein component ApoA-I, can reduce the risk of CVD by removing excess cholesterol from atherosclerotic plaque. Studies have shown that apabetalone increases ApoA-I gene transcription and protein production in human and primate primary hepatocytes. Accordingly, apabetalone also significantly increases levels of ApoA-I, HDL-associated cholesterol, and HDL particle number.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Apabetalone does not currently have Marketing Authorisation in the EU/UK for any indication.[6]

PATIENT GROUP

DISEASE BACKGROUND

T2DM is a long-term condition that causes the level of sugar (glucose) in the blood to become too high. In patients with T2DM the body does not produce enough insulin, or the body has become resistant to the insulin being produced.[7]

People with T2DM have an increased risk of developing CVD. High levels of glucose in the blood can damage the walls of the arteries, making them more likely to develop fatty deposits (atheroma).[7] The arteries become narrowed by the gradual build-up of atheroma, inhibiting the delivery of oxygen-rich blood to the heart. If a piece of atheroma breaks away it can cause a blood clot, which may result in a MACE such as a heart attack or stroke.[8]

CLINICAL NEED AND BURDEN OF DISEASE

The latest figures published by NHS Digital give a recorded prevalence of DM in adults at 3,116,399 in England in 2016/17.[9] It is estimated that 90% of people with DM have T2DM, which would equate to 2,804,759 adults.[10]

Multiple vascular risk factors and wide-ranging complications make diabetes care complex and time-consuming, and many areas of healthcare services must be involved for optimal management. Diabetes care is estimated to account for at least 5% of UK healthcare expenditure, and up to 10% of NHS expenditure.[11]

CVD is a major cause of death and disability in people with diabetes, accounting for 52% of fatalities in people with T2DM.[12] In patients with diabetes, women have a greater risk of developing CVD than men, and people of South Asian or African Caribbean background have an increased risk of developing T2DM and therefore an increased risk of developing CVD.[13] Recent studies suggest a MACE rate of >11% over 18 months in T2DM patients despite a baseline LDL-C of <2.1 mmol/L.[3]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

NICE guidelines recommend that clinicians should adopt an individualised approach to diabetes care that is tailored to the needs and circumstances of adults with T2DM, taking into account their personal preferences, comorbidities, risks from polypharmacy, and their ability to benefit from long-term interventions because of reduced life expectancy.[11]

Structured education is an integral part of diabetes care, and should be offered to patients at time of diagnosis, with annual reinforcement and review. Other key priorities include dietary advice, blood pressure management, blood glucose management, drug treatment, and the monitoring of complications.[11]

CURRENT TREATMENT OPTIONS

Guidelines recommend lifestyle modifications for the primary and secondary prevention of CVD, including a cardioprotective diet, physical activity, weight management, alcohol consumption and smoking cessation.[14]

NICE recommends the use of atorvastatin 20mg for the primary prevention of CVD in people with T2DM who have a 10% or greater 10-year risk of developing CVD. For patients who have CVD, atorvastatin 80mg is recommended.[14]

SIGN guidelines state:[15]

- low dose aspirin is not recommended for primary prevention of vascular disease in patients with T2DM
- Aspirin (75mg per day) should be given routinely and continued long term in patients with T2DM and coronary heart disease (CHD)
- patients with clinical MI should be maintained on long term beta blocker therapy, and should be commenced on long term ACE inhibitor therapy within the first 36 hours of MI
- intensive lipid-lowering therapy with atorvastatin 80mg should be considered for patients with T2DM and acute coronary syndromes, objective evidence of CHD on angiography or following coronary revascularisation procedures
- all patients with stable angina due to atherosclerotic disease should receive long term standard aspirin and statin therapy, and should be considered for treatment with ACE inhibitors

PLACE OF TECHNOLOGY

If licensed, apabetalone may offer an additional preventive treatment option for MACE in patients with T2DM, high-risk CVD and low HDL.

CLINICAL TRIAL INFORMATION

Trial	BETonMACE, NCT02586155, RVX222-CS-015; apabetalone vs placebo, both in addition to high-intensity statin therapy (atorvastatin or rosuvastatin); phase III
Sponsor	Resverlogix Corp
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (not UK), USA and other countries
Design	Randomised, placebo-controlled
Participants	n=2,400 (planned); aged 18+ yrs; high-risk T2DM with low HDL; coronary artery disease (CAD) event of either unstable angina or myocardial infarction 7-90 days prior to Visit 1
Schedule	Randomised to apabetalone 100mg capsule twice daily with high-intensity statin therapy (atorvastatin or rosuvastatin); or placebo capsule twice daily with high-intensity statin therapy (atorvastatin or rosuvastatin)
Follow-up	Active treatment and follow-up time periods not stated

Primary Outcomes	Time to first occurrence of adjudication-confirmed narrowly defined MACE (single composite endpoint of CV death or non-fatal MI or stroke) [Time Frame: 120 wks]
Secondary Outcomes	Time Frame 120 wks for all outcomes unless otherwise stated • Time to first occurrence of adjudication-confirmed broadly defined MACE (CV death, non-fatal MI, hospitalisation for CVD events, or stroke) • Group difference in all-cause mortality • Change over time within and between treatment groups: ○ % change in apoA-I concentration, apoB concentration, LDL-C concentration, HDL-C concentration, TG concentration ○ change in HbA1c, fasting glucose, fasting insulin, alkaline phosphatase (ALP) (including isoforms for whole pop. And quartiles of ALP baseline concentration) • Change in kidney function in pop (baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.7m^2) • Incidence of adverse events (AEs) and serious AEs within and between treatment groups • Other outcome measures: ○ % change in high-sensitivity C-reactive protein (hsCRP) within and between treatment groups ○ % change in fibrinogen within and between treatment groups ○ Transcription (messenger RNA (mRNA)) change in whole blood [Time Frame: 6 wks] ○ Health related quality of life (HRQOL) as measured using EQ-5D-5L [Time Frame: 122 wks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Sep 2018

Trial	ASSURE 1, NCT01067820, RVX222-CS-007; apabetalone vs placebo; phase II
Sponsor	Resverlogix Corp
Status	Published
Source of Information	Publication[5,16], trial registry[17]
Location	EU (not UK), Russia, Argentina and Brazil
Design	Randomised, placebo-controlled
Participants	n=324; aged 18+ yrs; CAD and low HDL-C level, scheduled to have coronary angiography for a clinical indication
Schedule	Randomised to apabetalone 100mg capsule twice daily; or placebo capsule twice daily
Follow-up	Active treatment for 26 wks, follow-up for 30 days

Primary Outcomes	Nominal change in % atheroma volume (PAV) as determined by intravascular ultrasound (IVUS) within apabetalone treated group [Time Frame: baseline to 26 wks post-randomisation]
Secondary Outcomes	• Nominal change in PAV as determined by IVUS within apabetalone treated group compared to placebo [Time Frame: baseline to 26 wks post-randomisation] • Nominal change in total atheroma volume (TAV) as determined by IVUS within apabetalone treated group compared to placebo [Time Frame: baseline to 26 wks post-randomisation] • Nominal change in TAV for the 10mm sub-segment with the greatest disease burden at baseline, with apabetalone treated group as well as compared to placebo [Time Frame: baseline to 26 wks post-randomisation] • Proportion of pts with regression of coronary atherosclerosis, defined as a change in PAV from baseline to 26 wks of <0 (i.e. any reduction in PAV) [Time Frame: baseline to 26 wks post-randomisation] • % change from baseline in HDL-C, ApoA-I and HDL-subclasses within apabetalone treated group as well as compared to placebo [Time Frame: Wks 14 and 26] • Incidence of AEs by treatment group, including MACE (death, MI, stroke, coronary revascularisation, hospitalisation for ACE or heart failure) [Time Frame: continuous]
Key Results	Pooled results for ASSURE 1 (NCT01067820), SUSTAIN (NCT01423188) and ASSERT (NCT01058018): At baseline, pts treated with apabetalone were more likely to be Caucasian, have a history of dyslipidemia, and be undertreated with ß-blocker and anti-platelet agents. Treatment with apabetalone produced the following dose-dependent changes compared with placebo: increases in ApoA-I of up to 6.7% ($P < 0.001$), increases in HDL-C of up to 6.5% ($P < 0.001$), increases in large HDL particles of up to 23.3% ($P < 0.001$), and decreases in hsCRP of − 21.1% ($P = 0.04$). Apabetalone treatment did not affect atherogenic lipoproteins compared with placebo.
Adverse effects (AEs)	Pooled results for ASSURE 1 (NCT01067820), SUSTAIN (NCT01423188) and ASSERT (NCT01058018): Pts treated with apabetalone experienced fewer major adverse cardiovascular events than those treated with placebo (5.9 vs. 10.4%; $P = 0.02$), a finding that was more prominent in patients with diabetes (5.4 vs. 12.7%; $P = 0.02$), with baseline HDL-C < 39 mg/dl (5.5 vs. 12.8%; $P = 0.01$), or with elevated hsCRP levels (5.4 vs. 14.2%; $P = 0.02$).

Trial	SUSTAIN, NCT01423188, RVX222-CS-008; apabetalone vs placebo; phase II
Sponsor	Resverlogix Corp
Status	Published
Source of Information	Publication[5,16], trial registry[18]
Location	South Africa
Design	Randomised, placebo-controlled
Participants	n=176; aged 18+ yrs; stable CAD and low HDL-C level, taking statin therapy

Schedule	Randomised to apabetalone 100mg capsule twice daily; or placebo capsule twice daily
Follow-up	Active treatment for 24 wks, follow-up for 30 days
Primary Outcomes	% change in HDL-C for apabetalone treated group compared to placebo [Time Frame: 24 wks]
Secondary Outcomes	• % change in HDL-C within treatment group from baseline to 24 wks for apabetalone treated group and placebo group [Time Frame: 24 wks] • % change in plasma ApoA-I from baseline for apabetalone compared to placebo (within and between treatment groups) [Time Frame: 4, 12 and 24 wks] • % change in LDL-C, non-HLD-C, TG and HDL sub-classes from baseline for apabetalone compared to placebo (within and between treatment groups) [Time Frame: 4, 12 and 24 wks] • Incidence of AEs by treatment group [Time Frame: pts followed for duration of study: 30 wks (2 wks screening, 24 wks active treatment, 4 wk follow-up)] • % change in HDL-C from baseline for apabetalone compared to placebo (within and between treatment groups) [Time Frame: 4 and 12 wks] • % change in hsCRP for apabetalone compared to placebo (within and between treatment groups) [Time Frame: 12 and 24 wks]
Key Results	See table above
Adverse effects (AEs)	See table above

Trial	ASSERT, NCT01058018, RVX222-CS-005; apabetalone vs placebo; phase II
Sponsor	Resverlogix Corp
Status	Published
Source of Information	Publication[16], trial registry[19]
Location	USA
Design	Randomised, placebo-controlled
Participants	n=299; aged 18+ yrs; stable CAD, taking statin therapy
Schedule	Randomised to apabetalone 50mg or 100mg or 150mg capsule twice daily; or placebo capsule twice daily
Follow-up	Active treatment for 12 wks, follow-up for 30 days
Primary Outcomes	% change in ApoA-I from baseline to 12 wks post-randomisation for each treatment arm compared to placebo [Time Frame: baseline to 12 wks post study drug treatment]
Secondary Outcomes	Compare the dose and time response relationships for major lipids (ApoA-I, total cholesterol, HDL-C, LDL-C, non-HDL-C, TG, ApoB, LDL, and HDL-subclasses) over time course [Time Frame: 4, 8 and 12 wks]
Key Results	See table above
Adverse effects (AEs)	See table above

ESTIMATED COST

The cost of apabetalone is not yet known.

ADDITIONAL INFORMATION

Resverlogix Corp 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.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Type 2 diabetes in adults: management (NG28). December 2015, updated May 2017.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). July 2014, updated September 2016.
- NICE clinical guideline. Atrial fibrillation: management (CG180). June 2014, updated August 2014.
- NICE clinical guideline. Stable angina: management (CG126). July 2011, updated August 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes (SIGN 116). March 2010, updated November 2017.[15]

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