

HEALTH TECHNOLOGY BRIEFING NOVEMBER 2020

Omecamtiv mecarbil for treating chronic heart failure with reduced ejection fraction

NIHRIO ID	7606	NICE ID	10367
Developer/Company	Servier Laboratories Ltd	UKPS ID	649985

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

Omecamtiv mecarbil is currently in clinical development for the treatment of heart failure (HF) with reduced ejection fraction. HF is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart to pump blood around the body is impaired. The classic symptoms of HF are breathlessness, ankle swelling, or fatigue. More than half of people with HF have reduced ejection fraction (HFrEF) which means the heart muscle does not contract effectively and therefore less oxygen-rich blood is pumped out to the body. There remains a large unmet need for new therapies in the treatment of HFrEF.

Omecamtiv mecarbil is given by oral administration in the form of a tablet. Omecamtiv mecarbil works by interacting with a protein called cardiac myosin that is responsible for converting chemical energy into the mechanical force that results in contraction of the heart. The interaction of omecamtiv mecarbil with cardiac myosin improves the performance of the heart muscle to preserve its function. If licensed, omecamtiv mecarbil may provide an additional treatment option for people with HFrEF who currently have limited therapies available.

PROPOSED INDICATION

Treatment of adults aged 18 years and older who have chronic heart failure (HF) with reduced ejection fraction (HFrEF).¹

TECHNOLOGY

DESCRIPTION

Omecamtiv mecarbil (AMG-423, CK-1827452) is a novel, selective cardiac myosin activator that binds to the catalytic domain of myosin. Preclinical research has shown that cardiac myosin activators increase cardiac contractility without affecting intracellular myocyte calcium concentrations or myocardial oxygen consumption. Cardiac myosin is the cytoskeletal motor protein in the cardiac muscle cell that is directly responsible for converting chemical energy into the mechanical force resulting in cardiac contraction.²

Omecamtiv mecarbil is in clinical development for the treatment of chronic HFrEF. In the phase III clinical trial (GALACTIC-HF, NCT02929329, EudraCT 2016-002299-28) participants are given omecamtiv mecarbil twice daily as an oral tablet for up to 208 weeks. Dose levels range from 25mg to 50mg taken twice daily (BID), and are determined by periodic blood testing.^{1,3}

INNOVATION AND/OR ADVANTAGES

HF remains one of the leading causes of mortality and morbidity in developed countries and contributes significantly to the economic burden of modern health care systems.⁴ There remains a large unmet need for new therapies in the treatment of HFrEF.⁵

Phase I and II studies have shown that omecamtiv mecarbil, which is first-in-class, is safe and well tolerated. It produces dose-dependent increases in systolic ejection time (SET), stroke volume, left ventricular ejection fraction (LVEF) and fractional shortening. The COSMIC-HF trial showed omecamtiv mecarbil improved cardiac function and reduced ventricular diameters compared to placebo and had a similar safety profile.⁶

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Omecamtiv mecarbil does not currently have Marketing Authorisation in the EU/UK for any indication.

Omecamtiv mecarbil was granted a fast track designation by the FDA in May 2020 for the treatment of HF.⁷

Omecamtiv mecarbil is also currently in phase II development for treatment of ischemic cardiomyopathy and angina.⁸

PATIENT GROUP

DISEASE BACKGROUND

HF is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. Patients with HF may present with one or more of the classical triad of symptoms: breathlessness, ankle swelling or fatigue.⁹ HF is often the result of a number of conditions affecting the heart at the same time such as coronary heart disease, high blood pressure or cardiomyopathy.¹⁰ The risk of HF is greater in men, smokers and diabetic patients and increases with age.¹¹

HF can be defined as HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction on the basis of left ventricular ejection fraction (LVEF), how much blood in the left ventricle is pumped out with each contraction.^{12,13} In HFrEF, the left ventricle loses its ability to contract normally and therefore presents with an ejection fraction of less than 40%.¹¹ Differentiation of patients with HF based on LVEF is important due to different underlying aetiologies, demographics, co-morbidities and response to therapies. It is only in patients with HFrEF that therapies have been shown to reduce both morbidity and mortality.⁵

For people with chronic HF and their family members and carers, the condition can have adverse effects on their quality of life and can be a financial burden. People with HF often experience poor quality of life because of breathlessness and fatigue symptoms, and over one-third of people experience severe and prolonged depressive illness.¹⁴

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-18, 485,561 people were recorded by GPs as having HF (prevalence rate of 0.83%).¹⁵ In 2017, it was reported that 66.8% of HF patients are reported to have HFrEF; if applied to the 2017-18 GP figures this equates to approximately 324,355 patients with HFrEF in England.¹⁶ In England in 2019-20 there were 205,462 finished consultant episodes (FCE) for HF (ICD-10 code I50) resulting in 94,185 admissions, 7,512 day cases and 894,573 FCE bed days.¹⁷

The prevalence of HF incidence in the UK is rising due to an ageing population and an increasing rates of obesity. The prevalence and incidence of HF both increases with age, with the rise starting at age 65 and peaking between 75 and 85. The average age at diagnosis is 77.¹⁸

HF has a poor prognosis: 30-40% of people diagnosed with HF die within one year, but thereafter the mortality is less than 10% per year. Patients on GP HF registers, representing prevalent cases of HF, have a 5-year survival rate of 58%, compared with 93% in the general population.¹⁴

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For most people HF is a long-term condition that cannot be cured. The goal of treatment is to keep symptoms under control through lifestyle changes (eating a balanced diet, not smoking, regular exercise), medication or surgery.¹⁹ Implantable cardioverter defibrillators, cardiac resynchronisation therapy with defibrillator (CRT) or CRT with pacing are recommended as treatment options for people with HF who have left ventricular dysfunction with LVEF of 35% or less.²⁰

The core specialist HF multidisciplinary team should work in collaboration with the primary care team, and should include a lead physician with subspecialty training in HF, a specialist HF nurse, and a healthcare professional with expertise in specialist prescribing for HF.¹⁸

CURRENT TREATMENT OPTIONS

NICE recommends the following treatment options for patients with HFrEF:²⁰

First-line:

- Offer an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker licensed for HF to people who have HFrEF. Clinical judgement should be used when deciding which drug to start first
- Consider an angiotensin II receptor blocker (ARB) licensed for HF as an alternative to an ACE inhibitor for people who have HFrEF and intolerable side effects with ACE inhibitors
- If neither ACE inhibitors nor ARBs are tolerated, seek specialist advice and consider hydralazine in combination with nitrate for people who have HFrEF
- Offer a mineralocorticoid receptor antagonist (MRA) in addition to an ACE inhibitor (or ARB) and beta-blocker, to people who have HFrEF if they continue to have symptoms of HF

Specialist treatment:

- Specialist treatment options include ivabradine, sacubitril valsartan, hydralazine with nitrate, and digoxin

PLACE OF TECHNOLOGY

If licensed, omecamtiv mecarbil may offer an additional treatment option for patients with HFrEF who currently have few effective treatments available.¹

CLINICAL TRIAL INFORMATION

Trial	GALACTIC-HF , NCT02929329 , EudraCT 2016-002299-28 ; A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects With Chronic Heart Failure With Reduced Ejection Fraction Phase III – Completed Locations: 16 EU countries (incl UK), USA, Canada and other countries Study completion date: 14 September 2020
Trial design	Double-blind, parallel assignment, randomized, placebo-controlled
Population	N=8256; adults aged 18 to 85 years; history of chronic HF (defined as requiring treatment for HF for a minimum of 30 days before randomization); LVEF ≤35%; NYHA class II to IV
Intervention(s)	Omecamtiv mecarbil taken twice daily (oral tablet)
Comparator(s)	Placebo taken twice daily (oral tablet)
Outcome(s)	Primary outcome measure:

	<ul style="list-style-type: none"> Measure time to cardiovascular death or first heart failure event [Time Frame: Through study completion, up to 208 weeks] <p>See trial record for full list of outcome measures</p>
Results (efficacy)	Treatment with omecamtiv mecarbil achieved the primary composite efficacy endpoint and demonstrated a statistically significant reduction of cardiovascular death or HF events (heart failure hospitalization and other urgent treatment for heart failure) compared to placebo in patients treated with standard of care (p=0.0252). No reduction in the secondary endpoint of cardiovascular death was observed. ²¹
Results (safety)	Adverse events, including major ischemic cardiac events, were balanced between treatment arms. ²¹

Trial	<p>COSMIC-HF, NCT01786512; A Double-blind, Randomized, Placebo-controlled, Multicenter, Dose Escalation Study to Select and Evaluate an Oral Modified Release Formulation of Omecamtiv Mecarbil in Subjects with HF and Left Ventricular Systolic Dysfunction</p> <p>Phase II – Completed</p> <p>Locations: 10 EU countries (incl UK), USA and other countries</p> <p>Study completion date: August 2015</p>
Trial design	Randomized, Parallel Assignment, Double-blind, Placebo-controlled
Population	N=544; adults aged 18 years to 85 years; history of chronic HF, defined as requiring treatment for HF for a minimum of 4 weeks prior to screening; treated with stable pharmacological therapy for ≥ 4 weeks; history of LVEF ≤ 40%
Intervention(s)	Omecamtiv mecarbil (oral tablet) taken twice daily
Comparator(s)	Placebo
Outcome(s)	<p>Primary outcome measures: To characterize omecamtiv mecarbil pharmacokinetics.</p> <p>Dose-escalation</p> <ul style="list-style-type: none"> C_{max} (maximum observed plasma concentration) C_{min} (minimum observed plasma concentration) T_{max} (time taken to reach maximum plasma concentration) <p>[Time Frame: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 96, 120 hours after first dose; 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 168 hours following dose on day 7]</p> <ul style="list-style-type: none"> AUC_{12h} (area under the curve until 12 hours after the investigational product administration) [Time frame: 0, 0.5, 1, 2, 4, 6, 8, 12 hours after first dose; 0, 0.5, 1, 2, 3, 4, 6, 8, 12 hours following dose on day 7] <p>Expansion:</p>

	<ul style="list-style-type: none"> • C_{max} [Time frame: predose, predose, 1, 2, 4, 6 and 8 hours after morning dose on weeks 2 and 12; predose, between 1-4 hours post dose on week 20] • C_{predose} (concentration prior to investigational product administration) [Time Frame: predose before morning dose on day 1, weeks 2, 8, 12, 16 and 20] <p>See trial record for full list of outcome measures</p>
Results (efficacy)	<p>Following 20 weeks of treatment, statistically significant improvements were observed in all pre-specified secondary endpoint measures of cardiac function in the dose titration group compared to placebo. Systolic ejection time increased by 25.0 msec (p<0.0001), stroke volume increased by 3.6mL (p=0.0217) and heart rate decreased by 3.0 beats per min (p=0.0070). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.8mm (p=0.0027) and 1.3mm (p=0.0128), respectively and were associated with statistically significant reductions in left ventricular end-systolic and end diastolic volumes.²²</p>
Results (safety)	<p>Adverse events (AEs), including serious AEs, in patients on omecamtiv mecarbil were comparable to placebo. The incidence of adjudicated deaths (3 percent died on placebo, 1 percent died on omecamtiv mecarbil 25mg twice daily, 2 percent on omecamtiv mecarbil dose titration), myocardial infarction (1 percent on placebo, 0 percent on omecamtiv mecarbil 25mg twice daily, 1 percent on omecamtiv mecarbil dose titration) and unstable angina (0 percent on placebo, 1 percent on omecamtiv mecarbil 25mg twice daily, 0 percent on omecamtiv mecarbil dose titration) was similar. Other cardiac AEs were generally balanced between placebo and active treatment groups. In patients receiving omecamtiv mecarbil compared to placebo, cardiac troponin increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at week 20) in the 25mg twice daily group and dose titration group, respectively. Events of increased troponin (n=278 across all treatment groups) were independently adjudicated and none were adjudicated as an episode of myocardial ischemia or infarction.²²</p>

ESTIMATED COST

The estimated cost of omecamtiv mecarbil is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- Empagliflozin for treating chronic heart failure with reduced ejection fraction (ID3826). Expected publication date to be confirmed.

- NICE technology appraisal in development. Vericiguat for treating chronic heart failure with reduced ejection fraction (ID2731). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Dapagliflozin for treating heart failure with reduced ejection fraction (ID1656). Expected publication date: 03 February 2021.
- NICE technology appraisal. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE technology appraisal guidance. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). June 2014.
- NICE technology appraisal guidance. Ivabradine for treating chronic heart failure (TA267). November 2012.
- NICE guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE quality standard. Chronic heart failure in adults (QS9). September 2018.
- NICE interventional procedure guidance. Cardiac contractility modulation device implantation for heart failure (IPG655). June 2019.
- NICE interventional procedure guidance. Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure (IPG463). August 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England service specification. Cardiac surgery – adults. A10/S/a.
- 2013/14 NHS Standard Contract for Cardiology: Implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) (Adult). A09/S/a.
- 2013/14 NHS standard Contract for ventricular assist devices (VADS) as a bridge to heart transplantation or myocardial recovery (All ages). A18/S(HSS)/b.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Heart failure – chronic. 2017.²³
- European Society of Cardiology (ESC). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. 2016.²⁴
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ADDITIONAL INFORMATION

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