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HEALTH TECHNOLOGY BRIEFING
APRIL 2021

Sacubitril/valsartan for the treatment of post-acute myocardial infarction patients with left ventricular systolic dysfucntion and/or pulmonary congestion – first line

NIHRIO ID	13270	**NICE ID**	9616
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	643041

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

SUMMARY

Sacubitril/valsartan is currently in clinical development for the treatment of patients who have suffered a heart attack (acute myocardial infarction (AMI), and who have evidence of left ventricular systolic dysfunction (LVSD) and/or pulmonary congestion. LVSD means that the heart muscle does not contract effectively and therefore, less oxygen-rich blood is pumped out to the rest of the body. Patients who develop LVSD following an AMI have a higher risk of complications and sudden cardiac death. There remains a large unmet need for new therapies for these patients.

Sacubitril/valsartan is a dual combination drug targeting the RAAS and neprilysin systems. It is given orally in the form of a tablet. It contains two different active ingredients sacubitril and valsartan, that work independently to reduce blood pressure, protect the heart from developing scar tissue and reduce the strain on the heart. If licensed, sacubitril/valsartan may offer an additional treatment option for post-acute AMI patients with evidence of LVSD and/or pulmonary congestion.

PROPOSED INDICATION

First line treatment of post-acute myocardial infarct (AMI) patients with evidence of left ventricular systolic dysfunction (LVSD) and/or pulmonary congestion, without a known prior history of chronic heart failure (HF).[1]

TECHNOLOGY

DESCRIPTION

Sacubitril/valsartan (Entresto, LCZ696) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that reduces strain on the failing heart. It contains two active components sacubitril and valsartan.[2] Sacubitril blocks the breakdown of natriuretic peptides produced in the body. Natriuretic peptides cause sodium and water to pass into the urine thereby reducing the strain on the heart. Natriuretic peptides also reduce blood pressure and protect the heart from developing fibrosis (scar tissues) that occurs in heart failure. Valsartan is an angiotensin-II-receptor antagonist, which means that it blocks the action of a hormone called angiotensin II. The effects of angiotensin II can be harmful in patients with HF. By blocking the receptors to which angiotensin II normally attaches, valsartan stops the hormone's harmful effects on the heart and it also reduces blood pressure by allowing blood vessels to widen.[3]

Sacubitril/valsartan is currently in phase III clinical development for the treatment of post-AMI patients with evidence of LVSD and/or pulmonary congestion, without a known prior history of chronic HF to delay cardiovascular death. In the phase III trial PARADISE-MI (NCT02924727, EudraCT 2016-002154-20) participants are orally administered sacubitril/valsartanin doses titrated from 50mg up to 100mg and 200mg twice daily.[1,4]

INNOVATION AND/OR ADVANTAGES

Despite substantial progress in the diagnosis and treatment of AMI, about 40% of patients with AMI develop LVSD, with or without signs of HF which adversely influences quality of life, hospitalisation rates, and mortality.[5] Current treatments focus on blocking neurohormonal pathways, such as the renin-angiotensin aldosterone system (RAAS).[6]

Sacubitril/valsartan is a first-in class compound that has a unique mode of action by targeting both the RAAS and natriuretic peptide system pathways which is thought to confer benefits in HF, whereas activation of the RAAS and of the sympathetic nervous system has detrimental effects. The binding of natriuretic peptides to type A (NRP-A) and type B (NPR-B) receptors induces natriuresis, diuresis, vasodilation and inhibition of the RAAS system and the sympathetic nervous system, as well as antifibrotic, anti-proliferative and antithrombotic effects.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Sacubitril/valsartan is already licensed in the EU/UK for the treatment of adult patients with symptomatic heart failure with reduced ejection fraction (HFrEF). The most frequently reported adverse events (≥10%) were hyperkalaemia, hypotension and renal impairment.[7]

Sacubitril/valsartan is currently being studied in 56 phase II or III clinical trials for the treatment of, for example: cardiomyopathy; HFrEF; resistant or severe hypertension; prevention of cardiac

dysfunction during breast cancer therapy; heart failure in patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).[8]

PATIENT GROUP

DISEASE BACKGROUND

AMI is a serious medical emergency in which the supply of blood to the heart is suddenly blocked, usually by a blood clot.[11] About 40% of patients who have had an AMI develop LVSD, with or without signs of HF.[5] LVSD, otherwise known as HFrEF, occurs when the left ventricle of the heart cannot contract completely and the amount of blood pumped out of the left ventricle, known as ejection fraction (EF), is ≤ 40%.[10] These patients have a higher risk of cardiac rupture, longer hospitalisations, ventricular arrhythmias, recurrent myocardial infarction (MI), and death, including sudden cardiac death.[12-14] In LVSD following AMI, the AMI itself is the leading cause of the deterioration of contractility and the decrease of EF.[5] The results from the VALLIANT trial showed that LVSD after an AMI is correlated to a higher incidence of sudden death. More than half of deaths classified as sudden death or cardiac arrest happened among survivors of AMI with an EF ≤ 30%.[23]

Several overlapping mechanisms contribute to HF following AMI. HF during the index MI occurs due to a combination of myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction. HF during hospitalisation may also be due to any of the above, compounded by fluid or contrast overload, renal dysfunction, or complications such as ventricular septal defect or cardiac tamponade. Late HF reflects the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodelling.[15]

CLINICAL NEED AND BURDEN OF DISEASE

In England, in 2019-20, there were 82,181 admissions for AMI.[16] Primary care data from 2013 in the UK suggests that the prevalence of AMI in men is about three-fold greater than for women, and that overall 915,000 people in the UK have had an AMI.[17] Applying the figure that 40% of patients who have had an AMI have reduced LVEF, this would equate to around 366,000 patients in the UK.[5]

AMI-induced myocardial injury triggers ventricular remodelling leading to an increased risk of HF.[15] Compared with no history of AMI by age 60, 65, 70 or 75 having had one previous AMI was associated wth an adjusted hazard of mortality of 1.80, 1.71, 1.50 and 1.45 respectively.[2]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The current therapeutic approach to the preservation of left ventricular function in AMI consists of reducing infarct size through administration of acetylsalicylic acid (ASA), and decelerating or preventing left ventricular remodelling and the deterioration of left ventricular ejection fraction (LVEF) through the administration of angiotensin converting enzyme (ACE) inhibitors and β-blockers.[5]

The optimisation of secondary prevention medication is crucial in improving outcomes for post-MI patients, especially in those with LVSD.[14] The effectiveness of drug treatments depends on the left

ventricular function. The assessment of left ventricular function after an MI informs the type, titration and duration of drug treatment and the type of cardiac rehabilitation that is appropriate.[18]

CURRENT TREATMENT OPTIONS

For secondary prevention and rehabilitation in patients who have had an MI and who have reduced LVSD, NICE currently recommends the following treatment options:[19]

- ACE inhibitors
- aldosterone antagonists
- anti-platelet therapy
- β-blockers
- calcium channel blockers such as diltiazem or verapamil may be considered if β-blockers are contraindicated
- statins

PLACE OF TECHNOLOGY

If licensed, sacubitril/valsartan will offer an additional first-line treatment option for patients who have LVSD following an AMI.[4]

CLINICAL TRIAL INFORMATION

Trial	**PARADISE-MI, NCT02924727, EudraCT 2016-002154-20;** A Multi-center, Randomized, Double-blind, Active-controlled, Parallel-group Phase 3 Study to evaluate the Efficacy and Safety of LCZ696 Compared to Ramipril on Morbidity and Mortality in High Risk Patients Following an AMI **Phase III –** Active, not recruiting **Locations:** 19 EU countries (incl UK), USA, Canada and other countries **Estimated primary completion date:** 12 February 2021	**PARADISE-MI, NCT04637555, EudraCT 2020-12-29;** A Multi-center Study to Evaluate the Long-term Safety and Tolerability of Open-label LCZ696 in Patients With Acute Myocardial Infarction Who Previously Participated in CLC696G2301 (PARADISE-MI) **Phase III** – Not yet recruiting **Locations:** 18 EU countries (incl UK), USA, Canada and other countries **Estimated primary completion date:** 01 June 2023
Trial design	Randomised, parallel assignment, double-blind, active-controlled	Single group assignment, open-label, extension study
Population	N=5669; adults aged 18 years and older; diagnosis of spontaneous AMI based on the universal MI definition with randomisation to occur between 12 hours and 7 days after event presentation; evidence of LV systolic dysfunction and/or pulmonary congestion requiring intravenous treatment associated with the MI event; haemodynamically stable.	N=2000; adults aged 18 years and older; participant received study treatment (either LCZ696 or ramipril treatment arm) in PARADISE-MI.

Intervention(s)	Sacubitril/valsartan (oral administration)	Sacubitril/valsartan (oral administration)
Comparator(s)	Ramipril (oral administration)	No comparator
Outcome(s)	Primary outcome measure: • Time to the first occurrence of a confirmed composite endpoint [Time frame: time from randomisation to first occurrence (up to approximately 43 months)] See trial record for full list of other outcome measures	Primary outcome measures: • Number of participants with adverse events leading to permanent study drug discontinuation, temporary study drug interruption, or study drug dose adjustment will be reported and summarized [Time frame: up to 24 months] • Number of participants with Serious adverse events [Time frame: up to 24 months] • Vital signs (blood pressure and pulse) [Time frame: baseline and up to 24 months]
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

Sacubitril/valsartan (as sacubitril/valsartan sodium salt complex) is avaiable in the UK as the following:[22]

- Level 1, 50mg; 24mg/26mg white f-c tab marked NVR and LZ, 28=£45.78.
- Level 2, 100mg; 49mg/51mg yellow f-c tab marked NVR and L1, 28=£45.78; 56=£91.56.
- Level 3, 200mg; 97mg/103mg pink f-c tab marked NVR and L11, 56=£91.56.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE clinical guideline. Acute coronary syndromes (NG185). November 2020.
- NICE quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cardiology: Inherited Cardiac Conditions (All Ages). A09/S/c.
- NHS England. 2013/14 NHS Standard Contract for Cardiology: Primary Percutaneous Coronary Intervention (PPCI) (Adult). A09/S/d.

OTHER GUIDANCE

- British Journal of General Practice. Secondary prevention following myocardial infarction: a clinical update. 2018.[20]

ADDITIONAL INFORMATION

REFERENCES

1 EU Clinical Trials Register. *PARADISE-MI: Prospective ARNI versus ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction. A multi-center, randomized, double-blind, active-controlled, parallel-group Phase 3 study to evaluate the efficacy and safety of LCZ696 compared to ramipril on morbidity and mortality in high risk patients following an acute myocardial infarction*. *Trial ID:* EudraCT-2016-002154-20. 2016. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-002154-20/GB [Accessed 31 March 2021].

2 Clinical Trials Arena. *Entresto (Sacubitril / Valsartan) for the Treatment of Heart Failure.* 2021. Available from: https://www.clinicaltrialsarena.com/projects/entresto-sacubitril-valsartan-heart-failure/#:~:text=Entresto's%20mechanism%20of%20action&text=Valsartan%20inhibits%20the%20effects%20of,of%20angiotensin%20II%2Ddependent%20aldosterone. [Accessed 31 March 2021].

3 Europeans Medicines Agency (EMA). *EPAR summary for the public: Entresto.* 2015. Available from: https://www.ema.europa.eu/en/documents/overview/entresto-epar-summary-public_en.pdf [Accessed 31 March 2021].

4 Clinicaltrials.gov. *A Multi-center, Randomized, Double-blind, Active-controlled, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Ramipril on Morbidity and Mortality in High Risk Patients Following an AMI*. *Trial ID: NCT02924727*. 2016. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02924727 [Accessed 31 March 2021].

5 Ajello, L., Coppola G., Corrado E., La Franca E., Rotolo A., Assennato P. *Diagnosis and Treatment of Asymptomatic Left Ventricular Systolic Dysfunction after Myocardial Infarction*. ISRN Cardiology. 2013:731285. Available from: https://doi.org/10.1155/2013/731285

6 Menendez, J. T. *The Mechanism of Action of LCZ696*. Cardiac failure review. 2016;2(1):40-6. Available from: https://doi.org/10.15420/cfr.2016:1:1

7 Electronic Medicines Compendium (EMC). *Entresto 97 mg/103 mg film-coated tablets.* 2020. Available from: https://www.medicines.org.uk/emc/product/5074/smpc#gref [Accessed 31 March 2021].

8 Clinicaltrials.gov. *Search for Entresto clinical studies: Phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=entresto&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 31 March 2021].

9 American Heart Association. *Ejection Fraction Heart Failure Measurement.* 2017. Available from: https://www.heart.org/en/health-topics/heart-failure/diagnosing-heart-failure/ejection-fraction-heart-failure-measurement [Accessed 30 March 2021].

10 Michigan Medicine University of Michigan. *Heart Failure With Reduced Ejection Fraction (Systolic Heart Failure).* 2020. Available from: https://www.uofmhealth.org/health-library/tx4090abc#tx4090abc-sec [Accessed 30 March 2021].

11 National Health Service (NHS). *Heart Attack: Overview.* 2019. Available from: https://www.nhs.uk/conditions/heart-attack/ [Accessed 30 March 2021].

12 Jernberg, T. J., Omerovic E. O., Hamilton E. H., Lindmark K. L., Desta L. D., Alfredsson J. A., et al. *Prevalence and prognostic impact of left ventricular systolic dysfunction after acute myocardial infarction*. European Heart Journal. 2020;41(Supplement_2). Available from: https://doi.org/10.1093/ehjci/ehaa946.1796

13 Minicucci, M. F., Azevedo P. S., Polegato B. F., Paiva S. A. R., Zornoff L. A. M. *Heart Failure After Myocardial Infarction: Clinical Implications and Treatment.* Clinical Cardiology. 2011. Available from: https://doi.org/10.1002/clc.20922

14 Forsyth, P., Moir L., Speirits I., McGlynn S., Ryan M., Watson A., et al. *Improving medication optimisation in left ventricular systolic dysfunction after acute myocardial infarction*. BMJ Open Quality. 2019;8(3):e000676. Available from: http://bmjopenquality.bmj.com/content/8/3/e000676.abstract

15 Cahill, T. J., Kharbanda R. K. *Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk*. World journal of cardiology. 2017;9(5):407-15. Available from: https://doi.org/10.4330/wjc.v9.i5.407

16 NHS digital. *Hospital Admitted Patient Care Activity 2019-20: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Downloaded 17 September 2020].

17 British Journal of Cardiology. *Acute coronary syndrome in adults: scope of the problem in the UK.* 2017. Available from: https://bjcardio.co.uk/2017/09/acute-coronary-syndrome-in-adults-scope-of-the-problem-in-the-uk/ [Accessed 31 March 2021].

18 National Institute for Health and Care Excellence (NICE). *Secondary prevention after a myocardial infarction* (*QS99)*. Last Update Date: 04 Septeber 2015. Available from: https://www.nice.org.uk/guidance/qs99/chapter/quality-statement-1-assessment-of-left-ventricular-function [Accessed 31 March 2021].

19 National Institute for Health and Care Excellence (NICE). *Acute coronary syndromes: secondary prevention and rehabilitation – everything NICE says in an interactive flowchart.* 2021. Available from: https://pathways.nice.org.uk/pathways/acute-coronary-syndromes-secondary-prevention-and-rehabilitation#path=view%3A/pathways/acute-coronary-syndromes-secondary-prevention-and-rehabilitation/acute-coronary-syndromes-drug-therapy-for-secondary-prevention.xml&content=view-index [Accessed 06 April 2021].

20 Isted, A., Williams R., Oakeshott P. *Secondary prevention following myocardial infarction: a clinical update*. British Journal of General Practice. 2018;68(668):151. Available from: http://bjgp.org/content/68/668/151.abstract

21 Gitsels LA, Kulinskaya E, Steel N. *Survival prospects after acute myocardial infarction in the UK: a matched cohort suty 1987-2011*. BMJ Open. 2017;7;e013570. Available from: https://doi.org/10.1136/bmjopen-2016-013570

22 National Institute for Health and Care Excellence (NICE). *Sacubitril with valsartan.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/sacubitril-with-valsartan.html

23 Solomon, D.S., Zelenkofske, S., McMurray, J.J.V., Finn, P.V., et al. *Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure or both.* New England journal of medicine. 2005;23352(25):2581-8. Available from: https://doi.org/10.1056/NEJMoa043938

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