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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Entresto for chronic heart failure with preserved ejection fraction

NIHRIO ID	7916	**NICE ID**	9554
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	603105

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Entresto (a tablet comprising a combination of the drugs sacubitril and valsartan), is in clinical development for people with chronic heart failure with preserved ejection fraction. Heart Failure (HF) is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. Symptoms include breathlessness and fatigue, and signs of the condition include swollen ankles and crackling sounds in the lungs. People with HF often have a poor quality of life, and about a third of people experience severe and prolonged depressive illness. About half of people with HF have a preserved ejection fraction (HF-PEF), meaning that over 50% of the blood in the left ventricle is pumped out with each contraction of the heart.

Entresto is licensed in the UK for treating people with HF with a reduced ejection fraction. The drug combination works by augmenting the actions of natriuretic peptides, which defend the heart from volume and pressure overload. Trials have shown that treatment with Entresto can reduce pressure and wall stress in the left ventricle. If licensed, Entresto could provide a treatment for people with HF-PEF, who currently have no effective treatments available.

PROPOSED INDICATION

Chronic heart failure (HF) with preserved ejection fraction (HF-PEF)[a]

TECHNOLOGY

DESCRIPTION

Entresto (LCZ696, sacubitril + valsartan) exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan. The complementary cardiovascular benefits of Entresto in HF patients are attributed to the enhancement of peptides that are degraded by neprilysin, such as natriuretic peptides (NP), by LBQ657 and the simultaneous inhibition of the effects of angiotensin II by valsartan. NPs exert their effects by activating membrane-bound guanylyl cyclase-coupled receptors, resulting in increased concentrations of the second messenger cyclic guanosine monophosphate (cGMP), which could result in vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and anti-fibrotic effects.[1]

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release. This prevents sustained activation of the renin-angiotensin-aldosterone system that would result in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.[1]

Entresto is in clinical development for patients with HF-PEF. In the phase III clinical trial (PARAGON-HF; NCT01920711), Entresto is administered as oral tablets at 200mg twice daily for up to 57 months.[2]

INNOVATION AND/OR ADVANTAGES

Augmentation of the actions of natriuretic peptides could offer an alternative approach to the treatment of HF-PEF. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are secreted in response to cardiac myocyte stretch as a result of increased myocardial wall tension and act to defend the heart from volume and pressure overload, a protective mechanism recently shown to be deficient early in the development of HF-PEF. Neprilysin inhibition, by blocking the breakdown of natriuretic peptides, should augment this endogenous defence mechanism and could be beneficial in HF-PEF. In addition to their vasodilatory, natriuretic, and diuretic effects, ANP and BNP inhibit the renin-angiotensin-aldosterone system, sympathetic nervous system, and release of antidiuretic hormone, improve myocardial relaxation and vagal tone, and are antifibrotic and antihypertrophic. Importantly, however, simultaneous inhibition of the generation or action of angiotensin II is needed because neprilysin also degrades angiotensin II, and inhibition of this enzyme can increase circulating and tissue angiotensin II.[3]

Raised NP concentrations are associated with adverse outcomes in patients with HF-PEF, and reductions in NT-proBNP (a marker of left ventricular wall stress) have been associated with improved outcomes in HF. Trials have found that in patients with HF-PEF Entresto reduced NT-proBNP to a greater extent than did valsartan at 12 weeks, and was associated with left atrial reverse remodelling at 36 weeks and improvements in New York Heart Association (NYHA) functional class at 36 weeks, consistent with the hypothesis that Entresto reduced left ventricular pressures and wall stress.[3]

[a] Information provided by Novartis on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Entresto is licensed in the UK for the treatment of symptomatic chronic HF with reduced ejection fraction.[1]

The most commonly reported (≥1/10) adverse reactions during treatment with Entresto are hypotension, hyperkalaemia and renal impairment.[1]

Entresto is also in phase III clinical development for the treatment of children (aged 1 month to 17 years) with chronic HF with reduced ejection fraction, and for the reduction in HF events after myocardial infarction in adults.[4,5]

PATIENT GROUP

DISEASE BACKGROUND

HF is a clinical syndrome of symptoms (e.g. breathlessness, fatigue) and signs (e.g. oedema, crepitations) resulting from structural and/or functional abnormalities of cardiac function which lead to reduced cardiac output or high filling pressures at rest or with stress. HF may arise as a consequence of a myocardial, valvular, endocardial or arrhythmic problem (or a combination of these). HF is defined on the basis of left ventricular ejection fraction (LVEF).[6] This is calculated as the percentage of how much blood in the left ventricle (LV) is pumped out with each contraction; a normal LVEF may be between 50% and 70%.[7]

The European Society of Cardiology (ESC) defines HF-PEF as the presence of signs and symptoms of HF, LVEF ≥50%, elevated NP levels, and structural heart disease and/or diastolic dysfunction. Patients with HF-PEF generally do not have a dilated LV, but instead often have an increase in LV wall thickness and/or increased left atrial size as a sign of increased filling pressures. Most have additional evidence of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients.[8]

For people with HF and their family members and carers, the condition can have adverse effects on their quality of life and be a financial burden. People with HF often experience poor quality of life because of breathlessness and fatigue, and over one-third of people experience severe and prolonged depressive illness.[9]

CLINICAL NEED AND BURDEN OF DISEASE

In England in 2017-18, 485,561 people were recorded by GPs as having heart failure (prevalence rate of 0.83%).[10] As it is estimated that HF-PEF accounts for up to half of all HF, this would equate to 242,780 people in England.[11]

Both the incidence and prevalence of HF increase with age, with an average age at first diagnosis of 76 years. The prevalence is expected to rise in the future as a result of an ageing population, improved survival of people with ischaemic heart disease and more effective treatments for HF.[9]

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.[9]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

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.[12]

No therapies have been conclusively shown to alter morbidity or mortality in patients with HF-PEF.[6] Existing recommendations focus on judicious use of diuretics to relieve congestion (when present), and optimal management of comorbidities.[13]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend that patients with HF-PEF should usually be offered a low to medium dose of loop diuretics (e.g. less than 80mg furosemide per day). People whose HF does not respond to this treatment will need further specialist advice.[14]

PLACE OF TECHNOLOGY

If licensed, Entresto will offer an additional treatment option for patients with HF-PEF, who currently have no effective treatments available.

CLINICAL TRIAL INFORMATION

Trial	PARALLAX, NCT03066804, EudraCT-2016-003410-28; Entresto vs enalapril or valsartan or placebo; phase III
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[15]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=2,500 (planned); aged 45 yrs and older; symptoms of HF requiring treatment with diuretics (NYHA class II-IV), LVEF ≥40%, NT-proBNP >220pg/mL for pts with no atrial fibrillation/flutter (AF) or >600pg/mL for pts with AF, evidence of structural heart disease
Schedule	All pts stratified before randomisation based upon prior therapy for comorbidities to 1 of 3 strata: • Angiotensin-converting Enzyme Inhibitors (ACE): pts receive Entresto or enalapril • Angiotensin II Type 1 Receptor Blocks (ARB): pts receive Entresto or valsartan • No Renin Angiotensin System Inhibitors (RAS): pts receive Entresto or matching placebo Experimental arm pts receive: • ACE stratum: Entresto in titrated doses from level 1 up to level 3 (50mg, 100mg and 200mg twice daily orally) and placebo to match enalapril in titrated doses from level 1 up to level 3 (2.5mg, 5mg and 10mg twice daily orally)

	• ARB stratum: Entresto in titrated doses from level 1 up to level 3 (50mg, 100mg and 200mg twice daily orally) and placebo to match valsartan in titrated doses from level 1 up to level 3 (40mg, 80mg and 160mg twice daily orally) • No RAS stratum: Entresto in titrated doses from level 1 up to level 3 (50mg, 100mg and 200mg twice daily orally) Comparator arm pts receive: • ACE stratum: enalapril in titrated doses from level 1 up to level 3 (2.5mg, 5mg and 10mg twice daily orally) and placebo to match Entresto in titrated doses (50mg, 100mg and 200mg twice daily orally) • ARB stratum: valsartan in titrated doses from level 1 up to level 3 (40mg, 80mg and 160mg twice daily orally) and placebo to match Entresto in titrated doses (50mg, 100mg and 200mg twice daily orally) • No RAS stratum: placebo to match Entresto in titrated doses (50mg, 100mg and 200mg twice daily orally)
Follow-up	24 wks active treatments, follow-up not stated
Primary Outcomes	• Change from baseline in NT-proBNP at wk 12 • Change from baseline in 6 minute walk distance at wk 24
Secondary Outcomes	• Mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) at wk 24 • % of pts with ≥5-points deterioration in KCCQ CSS at wk 24 [Time frame: baseline, wk 24] • % of pts with ≥5-points improvement in KCCQ CSS at wk 24 [Time frame: baseline, wk 24] • Change from baseline in NYHA functional class at wk 24 • Change from baseline in Short Form Health Survey (SF-36) physical component summary score at wk 24
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2019.

Trial	PARAGON-HF, NCT01920711, EudraCT-2013-001747-31; Entresto vs valsartan; phase III
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Publications[16,17], trial registry[2]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=4,822; aged 50 yrs and older; symptoms of HF (NYHA class II-IV), LVEF ≥45%, increased plasma concentrations of NT-proBNP, evidence of structural heart disease
Schedule	Single blind run-in period: 1-2 wks valsartan 40mg or 80mg oral tablets twice daily (bid), with those started on lower dose up-titrated to 80mg twice daily after 1-2 wks. Pts who tolerated valsartan 80mg bid were switched to Entresto 100mg bid for 2-4 wks. Pts who tolerated Entresto 100mg bid were eligible for randomisation.

	Double-blind randomisation: either valsartan 160mg bid or Entresto 200mg bid.
Follow-up	Double-blind period up to 57 mths. Study visits every 4-16 wks during first 48 wks, every 12 wks thereafter. All randomised pts followed-up until at least 1,847 total (first and recurrent) HF hospitalisations and cardiovascular (CV) deaths occur, with follow-up of ≥ 26 mths after randomisation for all non-censored pts.
Primary Outcomes	Cumulative number of primary composite events of CV death and total (first and recurrent) HF hospitalisations [Time frame: total follow-up time (up to 57 mths)]
Secondary Outcomes	• Change from baseline to mth 8 in KCCQ CCS • Change from baseline to mth 8 in NYHA functional class • Time to first occurrence of a composite renal endpoint: renal death or reaching end-stage renal disease or ≥50% decline in eGFR relative to baseline [Time frame: total follow-up time (up to 57 mths)] • Time to all-cause mortality [Time frame: total follow-up time (up to 57 mths)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as May 2019.

Trial	PARAMOUNT, NCT00887588, EudraCT-2009-010208-27; Entresto vs valsartan; phase II
Sponsor	Novartis Pharmaceuticals
Status	Published
Source of Information	Publication[3], trial registry[18]
Location	EU (not UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=308; aged 40 yrs and older; symptoms of HF (NYHA class II-IV), LVEF ≥45%, plasma NT-proBNP >400pg/ml, on diuretic therapy, controlled systolic BP (systolic BP <140mm/Hg or ≤160mm/Hg if on 3 or more blood pressure drugs at randomisation), EGFR ≥30ml/min/1.73m^2 and potassium concentration ≤5.2mmol/L at screening.
Schedule	Single blind run-in period: 2 wks on placebo, pts continued on background treatments; ACE inhibitors and ARBs discontinued 24h before randomisation. Double-blind randomisation: either Entresto 50mg bid, titrated to final dose of Entresto 200mg bid over 2-4 wks; or valsartan 40mg bid, titrated to final dose of valsartan 160mg bid over 2-4 wks. Background therapy at discretion of treating physicians.
Follow-up	Double-blind period 36 wks (12 wk main study period and 24 wk extension period)
Primary Outcomes	Change from baseline in NT-proBNP [Time frame: baseline, 12 wks]
Secondary Outcomes	Secondary endpoints included: • changes in echocardiographic measures (left ventricular volumes and ejection fraction • left atrial volume

	• measures of diastolic function) • change in blood pressure • change in NYHA class • clinical composite assessment • quality of life (KCCQ)
Key Results	In pts with HF-PEF, Entresto reduced NT-proBNP to a greater extent than did valsartan after 12 wks of treatment. The reduction in NT-proBNP in pts receiving Entresto became evident at 4 wks and appeared to be sustained to 36 wks, although the between-group difference was no longer significant. There was a reduction in left atrial size, indicative of reverse left atrial remodelling, in pts assigned to Entresto compared to those assigned valsartan. NYHA class improved significantly at 36 wks in pts on Entresto compared with those on valsartan.
Adverse effects (AEs)	Entresto was well tolerated overall, and its side-effect profile was similar to that of valsartan in the study.

ESTIMATED COST

Entresto is already marketed in the UK for the treatment of HF; a pack of 56 x 200mg tablets (sacubitril 97mg + valsartan 103mg) costs £91.56.[19]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Chronic heart failure in adults: diagnosis and management (NG106). September 2018.
- NICE quality standard. Chronic heart failure in adults (QS9). September 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No guidance identified.

OTHER GUIDANCE

- European Society of Cardiology (ESC). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. July 2016.[8]
- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. March 2016.[6]

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.