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Newcastle University

# Health Technology Briefing
# June 2022

# Sacubitril-valsartan for previously untreated chronic heart failure with reduced ejection fraction in children

| Company/Developer | Novartis Pharmaceuticals UK Ltd |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 12296 | NICE ID: 10350 | UKPS ID: 648161 |
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## Licensing and Market Availability Plans

Currently in phase III clinical development.

## Summary

Sacubitril-valsartan is currently in clinical development for the treatment of paediatric chronic heart failure (HF) with reduced ejection fraction. HF is a clinical syndrome of symptoms and signs that suggest the efficiency of the heart to pump blood around the body is impaired. The classical presenting symptoms of HF in young children are feeding difficulties, growth failure, irritability, and respiratory distress, while in older patients fatigue and exercise intolerance are more prevalent. 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. Most guidelines recommending drug therapy for paediatric HF are extrapolated from studies in adults. There remains a large unmet need for new therapies in the treatment of paediatric HFrEF.

Sacubitril-valsartan is licensed in the UK for treating adults with chronic HF with reduced ejection fraction. The combination works by increasing the actions of natriuretic peptides (a protein synthesised by the heart) which defend the heart from volume and pressure overload. Sacubitril-valsartan administered enterally, has been shown to reduce sudden cardiac death or HF hospitalisations, as well as improve quality of life. If licensed, sacubitril-valsartan could provide treatment for paediatric patients with chronic HFrEF who currently have limited treatment options.

## Proposed Indication

For the treatment of paediatric patients with chronic heart failure (HF) with reduced ejection fraction (HFrEF).[1,2]

## Technology

### Description

Sacubitril-valsartan (Entresto; LCZ696) 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.[3] 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.[3,4]

Sacubitril-valsartan is currently in clinical development for the treatment of paediatric patients with chronic HFrEF. In the phase III clinical trials (NCT02678312, NCT03785405), sacubitril-valsartan is administered via enteral route at a dose of either 0.8mg/kg or 3.1 mg/kg twice daily.[1,2]

### Key Innovation

While the benefits of pharmacotherapy in adult heart failure are well established, efficacy in paediatrics is yet to be confirmed. Sacubitril-valsartan is shown to reduce the risk of cardiovascular death and hospitalisation for HF in adult patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction.[5] Combining the angiotensin receptor blocker (ARB) valsartan with sacubitril has been found to result in significant benefit in the treatment of HFrEF, without an increased risk of angioedema. In a previous trial (PARADIGM-HF) where sacubitril-valsartan was compared to another medicine used for HF (enalapril), sacubitril-valsartan was shown to be superior in reducing the primary endpoint of death, sudden cardiac death or heart failure hospitalisations in adults with HFrEF. There was also evidence of comparable efficacy and safety profiles across all doses of drug, with similar effects in black adults compared with other races. Sacubitril-valsartan has also been shown to improve the quality of life of patients.[6] The PARADIGM-HF study was stopped early because there was compelling evidence that sacubitril-valsartan was more effective than enalapril.[4]

If licensed, sacubitril-valsartan would offer a treatment option for paediatric patients with chronic HFrEF.

### Regulatory & Development Status

Sacubitril-valsartan is currently licensed in the UK for the following indications in adults:[3,7]

- Symptomatic chronic HFrEF (in patients not currently taking an ACE inhibitor or angiotensin II receptor antagonist, or stabilised on low doses of either of these agents)
- Symptomatic chronic HFrEF (in patients currently stabilised on an ACE inhibitor or angiotensin II receptor antagonist)

Sacubitril-valsartan is currently in phase II and III clinical trials for the following indications:[8]

- Aortic valve insufficiency
- Resistant hypertension
- Hypertension with renal dysfunction

## Patient Group

### Disease Area and Clinical Need

Heart failure (HF) is a progressive clinical syndrome caused by structural or functional abnormalities of the heart, resulting in reduced cardiac output. Paediatric HF results from ventricular dysfunction, and volume or pressure overload, alone or in combination. The two most common pathophysiological categories resulting in end stage HF in children are cardiomyopathy and congenital heart disease (CHD), each contributing about half of the cases resulting in cardiac transplant.[6] HF can be defined on the basis of left ventricular ejection fraction (LVEF), as HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction.[9] LVEF is the measurement of how much blood is being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction.[9,10] In HFrEF, the left ventricle loses its ability to contract normally and therefore presents with an ejection fraction of less than 40%.[11] In young children, feeding difficulties, growth failure, irritability, and respiratory distress are the classical presenting symptoms of HF, while in older patients fatigue and exercise intolerance are more prevalent. Patients demonstrate some degree of fluid retention (congestion) which can be offset by vomiting and poor feeding in infants and young children.[6] 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.[12]

In England in 2020-21 there were 250 finished consultant episodes (FCE) for HF (ICD-10 code I50) for children aged 0 to 17 years.[13] Incidence of paediatric HF is estimated to be 0.87 per 100,000 (UK and Ireland).[6]

### Recommended Treatment Options

Treatment of paediatric HF focuses on decreasing pulmonary wedge pressure, increasing cardiac output, improving end-organ perfusion, and delaying disease progression.[14]

The following drug classes are used in the treatment of paediatric HF:[14]

- Diuretics such as spironolactone
- ACE inhibitors
- β blockers
- Inotropes
- Sympathomimetic amines
- Phosphodiesterase type III inhibitors
- Calcium sensitizer
- Vasodilators

## Clinical Trial Information

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| Trial | **PANORAMA-HF**; NCT02678312; 2015-004207-22; Multicenter, Open-label Study to Evaluate Safety, Tolerability, Pharmacokinetics, and | NCT03785405; 2018-004154-25; A Multicenter Study to Evaluate Long-term Safety and Tolerability of Open Label Sacubitril-Valsartan in Pediatric |

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| | Pharmacodynamics of LCZ696 Followed by a 52-week Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared With Enalapril in Pediatric Patients From 1 Month to < 18 Years of Age With Heart Failure Due to Systemic Left Ventricle Systolic Dysfunction<br>**Phase II/III** - Completed<br>**Location(s):** 12 EU countries, USA, Canada and other countries<br>**Study completion date:** January 2022 | Patients With Heart Failure Due to Systemic Left Ventricle Systolic Dysfunction Who Have Completed Study CLCZ696B2319<br>**Phase III –** Recruiting<br>**Location(s):** 12 EU countries, USA, Canada and other countries<br>**Primary completion date:** April 2022 |
| Trial Design | Open label, followed by randomised, double-blind, parallel assignment, active-controlled | Open label, parallel assignment |
| Population | N= 393 (actual); Subjects aged 1 month to 17 years with chronic heart failure resulting from left ventricular systolic dysfunction, and receiving chronic HF therapy (if not newly diagnosed) | N= 240 (estimated); Subjects aged 1 year to 18 years on study drug at PANORAMA-HF Part 2 end of study visit. |
| Intervention(s) | Part 1: sacubitril-valsartan administered enterally at 0.8 mg/kg or 3.1 mg/kg or both. After pharmacokinetic assessment, patients will be maintained on open-label enalapril or standard of care<br><br>Part 2: sacubitril-valsartan 3.125 mg granules and adult formulation (50, 100, 200 mg) can be given based on patient weight. | Sacubitril/valsartan at a target dose 3.1 mg/kg bid |
| Comparator(s) | Enalapril administered enterally at target dose of 0.2 mg/kg twice daily (0.4 mg/kg total daily dose) with a maximum dose of 10 mg bid (20 mg total daily dose) | No comparator |
| Outcome(s) | Pharmacokinetics of LCZ696 analytes (sacubitril, LBQ657, and valsartan): Maximum drug concentration in plasma (Cmax) [Time Frame: 0 (pre-dose), 0.5, 1, 2, 4, 8, 10, and optional 24 hours post dosing] | • Number of participants with Adverse Events (AEs) as a measure of safety and tolerability [Time Frame: to end of study, up to 3 years] |

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| | See trial record for full list of other outcomes | • Number of participants with Serious Adverse Events (SAEs) as a measure of safety and tolerability [Time Frame: to end of study, up to 3 years] |
| Results (efficacy) | - | - |
| Results (safety) | - | - |

## Estimated Cost

Sacubitril/valsartan is already marketed in the UK for the treatment of HF;[15]

- a pack of 28 x 24mg sacubitril /26mg valsartan tablets costs £45.78
- a pack of 28 x 49mg sacubitril /51mg valsartan tablets costs £45.78
- a pack of 56 x 49mg sacubitril /51mg valsartan tablets costs £91.56
- a pack of 56 x 97mg sacubitril /103mg valsartan tablets costs £91.56

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Omecamtiv mecarbil for treating chronic heart failure with reduced ejection fraction (ID3912). Expected date of issue to be confirmed.
- NICE technology appraisal. Empagliflozin for treating chronic heart failure with reduced ejection fraction (TA773). March 2022.
- NICE technology appraisal guidance. Dapagliflozin for treating heart failure with reduced ejection fraction (TA679). February 2021.
- NICE technology appraisal. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction (TA388). April 2016.
- NICE technology appraisal. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). June 2014.
- NICE technology appraisal. 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. Percutaneous implantation of pulmonary artery pressure sensors for monitoring treatment of chronic heart failure. (IPG711). November 2021.
- NICE interventional procedure guidance. Cardiac contractility modulation device implantation for heart failure (IPG655). June 2019.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Congenital heart disease standards and specifications. April 2016.

### Other Guidance

- European Society of Cardiology (ESC). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. 2021.[16]

- Scottish Intercollegiate Guidelines Network (SIGN). SIGN 147: Management of chronic heart failure. 2016.[9]

## Additional Information

## References

1 ClinicalTrials.gov. *Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LCZ696 Followed by a 52-week Study of LCZ696 Compared With Enalapril in Pediatric Patients With Heart Failure*. *Trial ID: NCT02678312*. 2016. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT02678312 [Accessed 10 May 2022].

2 ClinicalTrials.gov. *CLCZ696B2319E1 OL Extension Study to Evaluate Long-term Safety of Sacubitril/Valsartan in Pediatric Patients With HF*. *Trial ID: NCT03785405*. 2018. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03785405 [Accessed 10 May 2022].

3 Electronic Medicines Compendium (eMC). *Entresto 97 mg/103 mg film-coated tablets*. 2021. Available from: https://www.medicines.org.uk/emc/product/5074/smpc#PHARMACOLOGICAL_PROPS [Accessed 10 May 2022].

4 European Medicines Agency (EMA). *Entresto*. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/entresto [Accessed 10 May 2022].

5 Diana Ernst. *Entresto Approved to Treat Pediatric Heart Failure*. 2019. Available from: https://www.empr.com/home/news/entresto-approved-to-treat-pediatric-heart-failure/#:~:text=The%20Food%20and%20Drug%20Administration,aged%201%20year%20and%20older. [Accessed 10 May 2022].

6 Loss KL, Shaddy RE, Kantor PF. Recent and Upcoming Drug Therapies for Pediatric Heart Failure. *Frontiers in Pediatrics*. 2021;9. Available from: https://doi.org/10.3389/fped.2021.681224.

7 National Institute for Health and Care Excellence. *SACUBITRIL WITH VALSARTAN*. Available from: https://bnf.nice.org.uk/drug/sacubitril-with-valsartan.html#medicinalForms [Accessed 10 May 2022].

8 ClinicalTrials.gov. *SACUBITRIL and LCZ 696*. Available from: https://clinicaltrials.gov/ct2/results?cond=entresto&term=&cntry=&state=&city=&dist= [Accessed 17 May 2022].

9 Scottish Intercollegiate Guidelines Network (SIGN). *Management of chronic heart failure*. 2016. Available from: https://www.sign.ac.uk/assets/sign147.pdf [Accessed 10 May 2022].

10 Cleveland Clinic. *Ejection Fraction*. Available from: https://my.clevelandclinic.org/health/articles/16950-ejection-fraction [Accessed 10 May 2022].

11 National Institute for Health and Care Excellence (NICE). *Chronic heart failure*. Available from: https://bnf.nice.org.uk/treatment-summary/chronic-heart-failure.html [Accessed 10 May 2022].

12 National Institute for Health and Care Excellence (NICE). *Chronic heart failure in adults.* 2011. Available from: https://www.nice.org.uk/guidance/qs9/resources/chronic-heart-failure-in-adults-pdf-58304464837 [Accessed 10 May 2022].

13 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21#:~:text=In%202020%2D21%20there%20were%2016.2%20million%20FCEs%20recorded.&text=In%202020%2D21%20there%20were%2012.8%20million%20FAEs%20recorded.&text=There%20were%20235%2C262%20useable%20critical%20care%20records%20recorded%20in%202020%2D21. [Accessed 10 May 2022].

14 Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A, et al. Pediatric heart failure: a practical guide to diagnosis and management. *Pediatrics & Neonatology*. 2017;58(4):303-12. Avaialble from: https://doi.org/10.1016/j.pedneo.2017.01.001.

15 British National Formulary (BNF). *SACUBITRIL WITH VALSARTAN*. Available from: https://bnf.nice.org.uk/medicinal-forms/sacubitril-with-valsartan.html [Accessed 10 May 2022].

16 European Society of Cardiology (ESC). *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*. 2021. Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-and-Chronic-Heart-Failure [Accessed 10 May 2022].

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