20 March 2023
EMA/172237/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of an extension(s) of marketing authorisation and an extension of indication variation

Neparvis

International non-proprietary name: sacubitril / valsartan

Procedure No. EMEA/H/C/004343/X/0042/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ALU	Aluminum
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the European Pharmacopoeia
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CMS	Concerned Member State
CQA	Critical Quality Attribute
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
FMEA	Failure mode effects analysis
FPM	Finished Product Manufacturer
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control
IR	Infrared
IU	International Units
KF	Karl Fischer titration
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure

PA	Polyamide
PAR	Proven Acceptable Range
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QbD	Quality by design
QC	Quality control
QOS	Quality Overall Summary
QWP	Quality Working Party
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TSE	Transmissible Spongiform Encephalopathy
TGA	Thermo-Gravimetric Analysis
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
USP/NF	United States Pharmacopoeia/National Formulary
XRD	X-Ray Diffraction

* This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Limited submitted on 21 June 2022 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of children and adolescents aged one year or older with chronic heart failure with left ventricular systolic dysfunction, based on the results of Study PANORAMA-HF (CLCZ696B2319); a multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC are being updated and the Package Leaflet is updated accordingly. In addition, an updated RMP version 4.0 was provided as part of the application. Further, the MAH requested a one year extension of the market protection.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2)

point (c) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0327/2021 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0327/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0327/2021.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Additional Data exclusivity/Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004. An assessment of this claim is appended.

1.6. Scientific advice

The MAH did not receive the Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Anette Kirstine Stark

The application was received by the EMA on	21 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	5 October 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	11 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	10 November 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	27 January 2023
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Questions to all CHMP and PRAC	28 February 2023

members on	
The PRAC Rapporteur's Assessment Report was circulated to all PRAC and CHMP members on	03 March 2023
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	10 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Neparvis on	30 March 2023
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Neparvis in comparison with existing therapies. (see Appendix on Article 14(11))	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The current combined type II variation and line extension is aimed on registering a novel pharmaceutical form, granules in capsules for opening, as well as extension of the therapeutic indication.

The proposed therapeutic indication was:

“Neparvis is indicated in children and adolescents aged one year or older for treatment of chronic heart failure with left ventricular systolic dysfunction.”

Paediatric heart failure with left ventricular systolic dysfunction

The European Society of Cardiology defined heart failure (HF) as a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise.

The International Society for Heart and Lung Transplantation defines paediatric HF as a clinical and pathophysiologic syndrome that results from ventricular dysfunction, volume, or pressure overload, alone or in combination. In children, it leads to characteristic signs and symptoms, such as poor growth, feeding difficulties, respiratory distress, exercise intolerance, and fatigue, and is associated with circulatory, neurohormonal, and molecular abnormalities.

More specifically, paediatric chronic HF with left ventricular systolic dysfunction refers to paediatric chronic HF characterized by a reduced left ventricular ejection fraction, as evidence using echocardiography.

2.1.2. Epidemiology

The incidence of paediatric heart failure is estimated to be 0.97 to 7.4 per 100,000 in the USA, whereas in Europe, incidences varied from 0.87 in the United Kingdom and Ireland to 2.0–3.0 per 100,000 in Germany [10.1016/j.cardfail.2012.03.001 & 10.1007/s00246-017-1787-2]. The prevalence of paediatric heart failure has been reported in Spain to be 83 per 100,000 children and adolescents.

2.1.3. Aetiology and pathogenesis

In the paediatric population, the major aetiologies of paediatric HF are congenital heart disease and cardiomyopathies. After birth, the major causes are fetal cardiomyopathies or extracardiac conditions (including hypoglycemia and sepsis). In the first week, congenital heart disease with ductus-dependent systemic circulation becomes the main cause, including aortic coarctation and aortic stenosis, due to the closing of the ductus arteriosus. In the following months, major causes are congenital heart diseases with left to right shunts (patent ductus arteriosus, ventricular septal defects). Later, in older children and adolescence, major causes are cardiomyopathies or myocarditis. Dilated cardiomyopathy (DCM), which is associated with abnormalities of left ventricular systolic function, is the most common myopathic process leading to paediatric HF [10.1016/j.pedneo.2017.01.001].

Regardless of the cause of paediatric HF with LVSD, the reduced systolic function leads to several compensatory mechanisms, including an activation of the sympathetic nervous system (leading to peripheral vasoconstriction) and the activation of the renin-angiotensin-aldosterone system, leading to increased concentrations of renin, angiotensin II and aldosterone. While beneficial in the short-term, on the longer term, the enhanced catecholamine leads to cardiomyocyte injury, whereas elevation of aldosterone and angiotensin promote cardiac fibrosis and apoptosis. Furthermore, an increased activation of the natriuretic peptide system has been demonstrated in paediatric HF, which partially counteracts the RAAS system.

2.1.4. Clinical presentation, diagnosis

The clinical picture of paediatric HF is strictly related to age. In infants and young children, the typical presentation is difficulty in feeding, with additional characteristics being cyanosis, tachypnea and sinus tachycardia. The major presentations in older children and adolescents include fatigue, shortness of breath, and exercise intolerance. Besides clinical investigation, additional analyses may include ECG, chest radiography, echocardiography and laboratory investigations.

Paediatric heart failure is associated with high morbidity and mortality. For example, the in-hospital mortality for patients with heart failure in 2009 was 6.7%, compared with a 0.4% in-hospital mortality rate for children without heart failure [10.1016/j.cardfail.2012.03.001].

The well-established New York Heart Association (NYHA) HF classification does not apply to most paediatric populations. The Ross HF classification was developed to assess severity in infants and has subsequently been modified to apply to all paediatric ages.

2.1.5. Management

Due to the different etiologies and the relatively low incidence of paediatric heart failure, the development of medical therapy in paediatric HF is challenging. In contrast to HF in adults, to date, few clinical trials have been conducted in paediatric patients with HF. Consequently, there are no approved therapies in the European Union (EU) for the treatment of paediatric HF, and medical recommendations are mainly based on data from adult studies. Therefore, all current medical

recommendations for peadiatric heart failure with LVSD are based on off-label usage. The mainstay of treatment consists of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, aldosterone antagonists and diuretics in case of fluid overload. Of these, ACEIs are considered the first-line treatment for paediatric HF according to The Report on the Expert Group Meeting of Paediatric Heart Failure, London, 29 November 2010 (EMA 2011) and are recommended by the International Society of Heart and Lung Transplantation (ISHLT) for the treatment of symptomatic left ventricular dysfunction (Class I recommendation, Level of Evidence B; Kirk et al. 2014). Although not approved for treating paediatric patients with HF, enalapril is the most commonly used ACEI in children with HF.

ACE inhibitors are considered the first-line treatment by the International Society for Heart and Lung Transplantation, although the evidence on which this is based is limited. A retrospective analysis of 81 patients with dilated cardiomyopathy compared ACE inhibitor treatment with conventional therapy (at that time digoxin and diuretics) and demonstrated a better survival during the first year of treatment, which became insignificant in the following years [10.1007/bf00794837]. Another retrospective analysis of 189 patients with dilated cardiomyopathy demonstrated a numerical trend toward better survival when comparing ACE inhibitor-treated patients with digoxin-treated patients, though it did not reach statistical significance [10.1016/j.jacc.2009.11.059]. A randomized, double-blind clinical trial in 57 patients with Duchenne muscular dystrophy, in which perindopril was compared to placebo, demonstrated that perindopril delayed the onset and progression of prominent left ventricle dysfunction after 3 years of treatment but did not investigate mortality [10.1016/j.jacc.2004.09.078]. A later publication of the same study demonstrated that at the end of the 10 years follow-up period, survival status was 26 (92.9%) of 28 patients in the perindopril group were alive at 10 years versus 19 (65.5%) of 29 in the placebo group (P = .02).

Given the high mortality and morbidity associated with paediatric HF, there is a significant unmet medical need for approved treatments with demonstrated benefits, acceptable safety, appropriate posology and age-appropriate formulation in paediatric patients with HF.

The main goals of HF management are to prevent the onset of symptoms related to the reduced LV ejection fraction, stabilize or improve the symptomatic patients, and increase survival.

2.2. About the product

Sacubitril/valsartan (LCZ696, Entresto®, Neparvis®) is a first-in-class angiotensin receptor and neprilysin (ARN) inhibitor that is currently approved for the treatment of adult patients with heart failure (HF) with reduced ejection fraction (HFrEF) in 117 countries, including the US and EU.

Sacubitril is a prodrug that is in vivo converted to sacubitrilat via esterases. Sacubitrilat inhibits neprilysin, a neutral endopeptidase that degrades vasoactive peptides. As a result, sacubitrilat increases the concentration of natriuretic peptides, causing blood vessel dilation and reduced ECF volume via sodium excretion. Valsartan is an angiotensin II receptor type 1 antagonist and inhibits the effects of angiotensin II.

The current indication for Neparvis as 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg film-coated tablets is as follows:

Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

The proposed indication for Neparvis was as follows:

Adult heart failure

Neparvis is indicated in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction (see section 5.1).

Paediatric heart failure

Neparvis is indicated in children and adolescents aged one year or older for treatment of chronic heart failure with left ventricular systolic dysfunction (see section 5.1).

The proposed posology for the paediatric indication is:

Paediatric heart failure
Table 1 shows the recommended dose for paediatric patients, except in the situations described below the table. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient.

Neparvis film-coated tablets are not suitable for children weighing less than 40 kg. Neparvis film-coated granules are available for these patients.

Table 1 Recommended dose titration

Patient weight		Titration step dose (twice daily)		
	Half the starting dose*	Starting dose	Second dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg#	1.6 mg/kg#	2.3 mg/kg#	3.1 mg/kg#
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg#	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients at least 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

** Half the starting dose is recommended for patients who are not currently taking an ACE inhibitor or an ARB or are taking low doses of these medicinal products, patients who have renal impairment (Estimated Glomerular Filtration Rate [eGFR] <60 ml/min/1.73 m2) and patients who have moderate hepatic impairment (see special populations).*
#0.8 mg, 1.6 mg, 2.3 mg and 3.1 mg refer to the combined weight of sacubitril/valsartan and are to be given using film-coated granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. In paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as film-coated granules) is recommended. After initiation, the dose should be increased following the recommended dose titration in Table 1 and adjusted every 3 4 weeks.

Treatment should not be initiated in patients with serum potassium level >5.3 mmol/l or with SBP <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down–titration or discontinuation of Neparvis is recommended (see section 4.4).

The agreed indication at the end of the procedure is:

Paediatric heart failure

Neparvis is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (see section 5.1).

The agreed posology for paediatric indication is:

Paediatric heart failure
Table 1 shows the recommended dose for paediatric patients. The recommended dose should be taken orally twice daily. The dose should be increased every 2-4 weeks to the target dose, as tolerated by the patient.

Neparvis film-coated tablets are not suitable for children weighing less than 40 kg. Neparvis granules are available for these patients.

Table 1 Recommended dose titration

Patient weight	To be given twice daily			
	Half the starting dose*	Starting dose	Intermediate dose	Target dose
Paediatric patients less than 40 kg	0.8 mg/kg[#]	1.6 mg/kg[#]	2.3 mg/kg[#]	3.1 mg/kg[#]
Paediatric patients at least 40 kg, less than 50 kg	0.8 mg/kg[#]	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg
Paediatric patients at least 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg	97 mg/103 mg

* Half the starting dose is recommended in patients who have not been taking an ACE inhibitor or an ARB or have been taking low doses of these medicinal products, patients who have renal impairment (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2) and patients who have moderate hepatic impairment (see special populations).
[#]0.8 mg/kg, 1.6 mg/kg, 2.3 mg/kg and 3.1 mg/kg refer to the combined weight of sacubitril and valsartan and are to be given using granules.

In patients not currently taking an ACE inhibitor or an ARB or taking low doses of these medicinal products, half of the starting dose is recommended. For paediatric patients weighing 40 kg to less than 50 kg, a starting dose of 0.8 mg/kg twice daily (given as granules) is recommended. After initiation, the dose should be increased to the standard starting dose following the recommended dose titration in Table 1 and adjusted every 3-4 weeks.

For example, a paediatric patient weighing 25 kg who has not previously taken an ACE inhibitor should start with half the standard starting dose, which corresponds to 20 mg (25 kg × 0.8 mg/kg) twice daily, given as granules. After rounding to the closest number of full capsules, this corresponds to 2 capsules of 6 mg/6 mg sacubitril/valsartan twice daily.

Treatment should not be initiated in patients with serum potassium level >5.3 mmol/l or with SBP <5th percentile for the age of the patient. If patients experience tolerability issues (SBP <5th percentile for the age of the patient, symptomatic hypotension, hyperkalaemia, renal dysfunction), adjustment of concomitant medicinal products, temporary down-titration or discontinuation of Neparvis is recommended (see section 4.4).

2.3. Type of Application and aspects on development

The present line extension is being filed for Neparvis (a separate procedure is also being filed for its duplicate marketing authorisation Entresto) (sacubitril/valsartan) to register a suitable paediatric pharmaceutical form (6 mg/6 mg granules in capsules for opening and 15 mg/16 mg granules in capsules for opening). The extension application is grouped with:

- A Type II variation (C.I.6.a) - expansion to the approved indication for the treatment of paediatric patients aged one year and above based on the results from PANORAMA-HF (Study CLCZ696B2319).

The Neparvis development program in paediatric patients for the treatment of heart failure was discussed and agreed upon with the PDCO on May 30, 2012 (EMEA-000316-PIP02-11). The Neparvis Paediatric Investigational Plan (EMEA-000316-PIP03-20) consists of quality (Study 1: Development of an age-appropriate solid oral dosage form), non-clinical (Study 2: Mechanistic in-vitro study, study 3: 4-week dose range-finding juvenile rabbit bone toxicity study and study 4: a 4-week investigative bone study in juvenile rats) and clinical measures (study 5: Open-label, randomized, single-dose, multiple treatment period study to determine the relative bioavailability of LCZ696 paediatric formulation relative to the LCZ696 200 mg Final Market Image (FMI) tablet in healthy adult subjects, study 6: Part 2 of B2319, and study 7: Part 2 of B2319). A PDCO partial compliance check procedure (EMEA-C1-000316-PIP02-11-M01) to confirm compliance of the non-clinical measures (study 2, study 3 and study 4) and one of the clinical measures (study 5) was completed prior to the submission of the original marketing authorization application. On March 08, 2022 the partial compliance check (C2-000316-PIP02- 11-M05) to confirm compliance of the quality measure (study 1) was completed. The final compliance check for the remaining clinical measures (study 6 and study 7) has received a positive opinion from the PDCO on May 20, 2022 (Procedure EMEA-C-000316-PIP02-11- M05).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as capsules filled with 4 or 10 film-coated granules containing 6 mg/6 mg (6.1 mg/6.4 mg) or 15 mg/16 mg (15.18 mg/16.07 mg) of sacubitril/valsartan sodium salt complex.

Other ingredients are:

Granule core: microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, silica colloidal anhydrous, talc

Film-coat: basic butylated methacrylate copolymer, talc, stearic acid, sodium laurilsulfate

Capsule shell (6.1 mg/6.4 mg): hypromellose, titanium dioxide (E171)

Capsule shell (15.18 mg/16.07 mg): hypromellose, titanium dioxide (E171), iron oxide, yellow (E172)

Printing ink: shellac, propylene glycol, iron oxide, red (E172), ammonia solution (concentrated), potassium hydroxide

The product is available in PA/Alu/PVC blisters as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The active substance used in the finished product (sacubitril/valsartan sodium salt complex) is the same as in the already approved film-coated tablets. Consequently, no evaluation is required for the active substance.

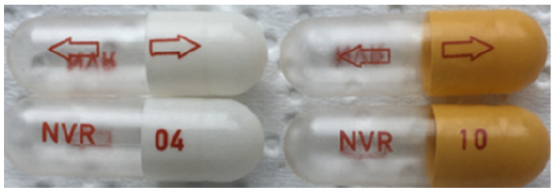
2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished products are film-coated granules filled into capsules for opening. The granules are intended to be administered by sprinkling on soft food. The capsule serves as a dosing aid and is discarded after dispensing film-coated granules.

The film-coated granules are white to almost white to slightly yellow, round, biconvex with a diameter of about 2 mm. The capsules (size 0) of both strengths have a body that is transparent with red imprints, “NVR” marking on one side, and an axial rectified unfilled arrow on the opposite site (Figure 1). The caps of the 6.1 mg/6.4 mg strength are white opaque with red imprints, “04” marking on one side, and an axial rectified unfilled arrow on the opposite side. The caps of the 15.18 mg/16.07 mg strength are yellow opaque with red imprints, “10” marking on one side, and an axial rectified unfilled arrow on the opposite side.

Figure 1: picture of commercial capsules



12.5MG **31.25MG**

Pharmaceutical development of the finished product contains QbD elements. The aim of the pharmaceutical development was to develop an oral immediate-release dosage form as an extension to the registered film-coated tablets, which is suitable for paediatric population from one year of age and enables sufficient dose flexibility.

The formulation development was initiated with the existing composition of the final blend of the 100 mg commercial adult core tablet. Batches of different compositions were manufactured to identify the final composition. Excipients used for coating are compendial and were chosen based on experience with similar products. To check the functionality of the coating, different coating levels were tested.

The manufacturing development has been evaluated through the use of risk assessment and design of experiments (DoE) to identify the critical product quality attributes (CQAs) and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes.

Based on the results of lab and pilot scale experiments, some variables were designated as potentially critical because they demonstrated a meaningful impact on finished product quality attributes. The potential critical process parameters were further investigated during full-scale manufacturing of process verification batches. The objectives of the process verification were to finalize the commercial manufacturing process, confirm the critical process parameter designations and verify the control strategy prior to process validation. The critical process parameters have been adequately identified.

Bioavailability (BA) studies were performed to bridge the proposed paediatric and commercial adult formulation. The film-coated tablets and film-coated granules formulations were demonstrated to be bioequivalent.

The finished product batches that were used in the BA studies, as well as the batches used in the pivotal clinical study, are representative of the proposed commercial product. Dissolution profiles similarity as per the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr has been demonstrated.

The development of the QC dissolution method has been described in sufficient detail and the choices made are justified. The discriminatory power of the dissolution method has been demonstrated.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The choice and ratio of the excipients used in the granule cores was based on compatibility studies and experience gained on the film-coated tablets. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

The finished product is considered adequate for use in the target paediatric population. No safety issues are foreseen with the selected excipients and their quantities for use in children. Compatibility of the film-coated granules with soft food was demonstrated. The ease of opening the capsules was confirmed in clinical practice.

The primary packaging is PA/Alu/PVC blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

At the time of CHMP opinion, there are currently no standard terms in the EDQM database deemed suitable to describe the present dosage form. After QWP consultation, the non-standard term “Granules in capsules for opening” was considered the most appropriate by majority of members. This is also in line with precedents, where for the same pharmaceutical dose form the non-standard term “Granules in capsules for opening” was included in the SmPC and packaging.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of following five main steps: dry granulation by roller compaction, screening, mixing, compression and film-coating. The film-coated granules are treated with an anti-electrostatic agent (talc) before filling into capsules. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Sufficient information on the critical process parameters and in-process controls has been provided in line with development data. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

In line with the Guideline on process validation for finished products it is acceptable that formal validation studies have not been completed yet. The manufacturing process is considered a standard process and process parameter settings are sufficiently supported by the available development data. An adequate process validation scheme has been provided in the section 3.2.R.

The critical process steps are adequately described and controlled. Proven acceptable ranges (PAR) have been defined. The available development data, the proposed control strategy and batch analysis data fully support the proposed PARs.

2.4.3.3. Product specification

The finished product release specifications shown in Table 4 and Table 5 include appropriate tests for this kind of dosage form including appearance (shell and contents), mean mass of contents, identity (IR, HPLC), water content (KF), dissolution (HPLC), uniformity of dosage units (HPLC), assay (HPLC), degradation products (HPLC) and microbiological quality.

A major objection (MO) was raised in relation to the initially proposed dissolution limit of, as the dissolution limit was not considered justified in line with clinical batch data. To ensure batch-to-batch consistency of future batches, CHMP requested to set the dissolution specification limit based on the dissolution profiles of the finished product batches that were used in the pivotal clinical study. The applicant agreed to tighten the specification limit for dissolution to in line with CHMP recommendation, resulting in MO resolution.

The limits for impurities are set in line with the ICH Q3B limits. The limit for any unspecified impurity of is acceptable based on a maximum daily dose and related identification threshold. The limit for the sacubitril related impurity exceeds the qualification threshold, however it is considered acceptable in view of the batch analysis and stability data and is also qualified from a safety point of view given the fact that the impurity is the major *in vivo*, active metabolite of sacubitril.

The absence of testing for chiral purity has been adequately justified in accordance with ICH Q6A, by demonstrating that no chiral impurities are formed during the manufacture and storage of the finished product. Control of chiral purity in the active substance alone is therefore considered sufficient.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three commercial scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A nitrosamine risk evaluation was performed considering finished product excipients, manufacturing process, packaging and storage, and no specific potential risk for nitrosamines was identified for this line-extension. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for eight pilot and three production scale batches (both strengths) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing

2.4.3.4. Stability of the product

Stability data from three commercial scale batches per strength of finished product stored for up to 12 months under long term (25 ºC / 60% RH) and intermediate conditions (30°C / 75% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. One batch of each strength was also stored at -20 °C / ambient RH (12 months) and 5 °C /

ambient RH (12 months). The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating.

In addition, one batch per dosage strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Based on available stability data, the proposed shelf-life of 24 months with storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture' as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The application concerns a line extension, therefore only the finished product part of the dossier was assessed. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The major objection related to the dissolution specification limit has been adequately addressed. The limit was tightened in line with biobatch data and CHMP recommendation. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

As at the time of CHMP opinion, there are currently no standard terms in the EDQM database deemed suitable to describe the present dosage form, the non-standard term "Granules in capsules for opening" was considered the most appropriate.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

There has been no change in the overall non-clinical safety, pharmacokinetics, and pharmacodynamics profile based on the results from non-clinical experiments included in the original MAA submission for

the treatment of adult patients with HFrEF. Since the submission of the original MAA, no additional nonclinical studies have been performed by Novartis. In both nonclinical species and humans, orally administered sacubitril/valsartan dissociates into valsartan and sacubitril (also known as AHU377), which is further metabolized to the neprilysin inhibitor sacubitrilat (also known as LBQ657).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The applicant provided an update of the literature regarding the combination sacubitril/valsartan since 2015. It was shown that the combined treatment with sacubitril/valsartan improved pharmacodynamic responses compared to valsartan treatment only in relation to cardiac function after infarction or valve insufficiency, molecular markers (such as cTnT levels, serum hsCRP, IL-6, RAAS pathway and natriuretic peptide, among others. The update and discussion provided by the applicant is considered sufficient.

2.5.3. Pharmacokinetics

No new studies or data were provided. Toxicokinetic data was discussed in the toxicology section.

2.5.4. Toxicology

Assessment of paediatric data on non-clinical aspects

Sacubitril

Sacubitril alone was tested in a rat juvenile toxicity study with exposure from PND7 through PND 70, covering the neonatal stage up to adulthood. Adverse effects on body weight were observed at all doses tested (<0.2 fold MRHD), and adverse effects on bone length (femur) and mineralization of bone (proximal tibia) were observed at higher doses, with a safety margin of 0.2 fold MRHD. After one month of recovery (PND105), femur length and bone mass at a low and mid-dose (males only) were slightly decreased compared to control (~5% decrease), but these slight decreases were proportional to body weight and were likely secondary to decreases in growth. However, at a mid dose in females and for both sexes at high doses, decreases in bone density of the proximal tibia persisted (11-15% decrease).

Gastric squamous mucosal hyperplasia and vacuolation were observed at all doses tested, which were still observed after recovery. These findings were also observed in adult rats in the repeat-dose toxicity studies.

Absolute values of bone size, bone mineral content, and bone mineral density were not affected in adult rats. Furthermore, adverse effects on the CNS and thyroid gland were observed in adult rats in the repeat-dose toxicity studies and were not observed in the sacubitril rat juvenile toxicity study.

In an investigative follow-up study, the effects of sacubitril on bone growth and mineralization were investigated further with exposure from PND7 through PND35, and a four-month recovery period. Similar findings on bone growth and mineralization were observed in this study. In addition, the greatest effects on growth were observed around PND21 (equivalent to approximately 2 years of age in humans), which was related to higher exposure to sacubitril and LBQ657 on PND7 (equivalent to human new born) compared to exposure at later time points (PND21 (weaning) and PND34 (pre-

peripubertal) and greatest body weight decreases. After four months of recovery, all bone effects were found to be reversible.

According to the applicant, the bone changes are potentially secondary to decreases in body weight gain. However, the mechanism is not well understood, as the effects observed in juvenile rats were not consistent with the on-target pharmacologic effects of Sacubitril on C-type natriuretic peptide (CNP).

In a rabbit juvenile dose range finding study, no adverse effects were observed, up to an exposure margin of 0.5-fold exposure in paediatric patients MRHD.

In conclusion, bone is a target organ together with growth retardation for sacubitril in juvenile rats with a safety margin lower than exposure in the human paediatric population. In the clinical paediatric study (B2319), no increased risk of fractures and altered growth was observed. In addition, increases in height and height Z-score were comparable between treatment and age groups. Nonetheless, the duration of this clinical study may be too short to detect long-term changes in growth. However, the mechanism behind the bone growth findings in juvenile rats is unknown; therefore, the relevance of these bone findings to the human paediatric population is also unknown.

Valsartan

In a juvenile toxicity study, rats were treated with valsartan from PND7 through PND70. Pharmacological effects of valsartan on the kidney leading primarily to juxtaglomerular cell hypertrophy/hyperplasia in adult animals, seem to be exaggerated in juvenile animals leading to tubular nephropathy, sometimes accompanied by tubular epithelial necrosis, which was not reversible. This occurred at exposures well below human exposure based on paediatric AUC values of valsartan (EM 1-6-year-old = <0.0051 fold; 6-18-year-old = <0.068 fold).

The effects on the kidney observed in this study are related to exaggerated pharmacology, as can be expected from ACE-inhibitors and angiotensin II antagonists. Until PND13, rat kidneys are not fully developed, and during this period, rats are sensitive to the observed kidney-related effects. In human, this coincides with 36 weeks of gestation, which could occasionally extend up to 44 weeks after conception. Therefore, possible effects on the development of the kidney from week 4-6 after birth cannot be excluded. As functional growth of the kidney is a gradual process one year after birth, the clinical relevance of these findings until <1 year cannot be excluded either. This is sufficiently reflected in the SmPC as the paediatric indication of Neparvis is for children >1 year.

2.5.5. Ecotoxicity/environmental risk assessment

The applicant previously submitted (EMEA/H/C/004062) a full blown ERA assessment, including the calculation of the environmental risk ratio's for the different environment compartments, which were all well below a ratio of 1. The applicant further discussed that the expected increase due to the new paediatric indication would be low due to an increase in prevalence of 1.004 as compared to the adult indication. Therefore, additional consumer usage of the paediatric population is expected to be of limited impact on the earlier calculated environmental exposures.

2.5.6. Discussion on non-clinical aspects

Sacubitril is indicated to be given chronically to paediatric patients, and therefore, long-term clinical effects on bone growth in the paediatric population are unknown. Therefore the applicant agreed to add to section 5.3 of the SmPC at the end of the proposed sacubitril section: *"However, long term paediatric data on (bone)growth and fracture rate is not available"*.

2.5.7. Conclusion on the non-clinical aspects

For the current line extension procedure, the applicant built upon the studies provided for the Neparvis marketing authorisation application (MAA). The applicant provided an updated discussion on up-to-date literature regarding the primary pharmacology of sacubitril and valsartan. No novel information was provided regarding non-clinical pharmacokinetics.

Overall the juvenile toxicology package revealed that bone is a target organ together with growth retardation for sacubitril in juvenile rats with a safety margin lower than exposure in the human paediatric population. Furthermore, in juvenile rats, valsartan-induced effects on the kidney are related to exaggerated pharmacology. The SmPC was updated to reflect that the long term paediatric data on (bone)growth and fracture rate is not available.

The application was considered acceptable from nonclinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The totality of evidence included in this submission supporting the safety and efficacy of sacubitril/valsartan for paediatric use includes 1) extrapolation of the existing adult HFrEF data from the PARADIGM-HF study to children based on the pharmacokinetic and pharmacodynamic data from PANORAMA-HF paediatric study and 2) the clinical data provided by the B2319 (PANORAMA-HF) study. A tabular listing of the reports of controlled clinical studies pertinent to the claimed indication is shown in Table 1.

Table 1. Clinical studies of the current dossier.

Study No.	Study Title
[CLCZ696B2314]	A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction
[CLCZ696B2319]	Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, 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

A more detailed tabular listing per study is shown for below study B2319 (Table 2) and B2314 (Table 3).

Table 2. Overview of Study B2319 in paediatric HF patients with left ventricle systolic dysfunction

5.1.2 Study CLCZ696B2319

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: [CLCZ696B2319] **Start**: 3-Nov-2016 **End**: 03-Jan-2022 **Countries**: Argentina, Austria, Bulgaria, Canada, China, Croatia, Czech Republic, Finland, France, Germany, Hungary, India, Israel, Italy, Japan, Jordan, Lebanon, Poland, Portugal, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United States	**Design, purpose & population**: Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, 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	**Total**: 392 **Part 1:** 26 * **Part 2**: 377 * Note: eleven (11) patients participated in both Parts 1 and 2 of the trial. **Age**: 0.10-18.00 (8.13) years **Groups**: 2 (Part 2) LCZ696: 187 Enalapril: 188	**Form(s)**: **Part 1:** LCZ696 3.125 mg granules **Part 2:** LCZ696: 3.125 mg granules; tablets: 50 mg, 100 mg, 200 mg and matching placebo. **Enalapril** 2.5 mg. 5 mg and 10 mg tablets and matching placebo **Duration**: **Part 1** Open label up to 2 single doses **Part 2**: 52 weeks of double-blind treatment	**Study Status**: complete **Report no**. [CLCZ696B2319] (full, final) **Report date**: 02-May-2022 **Other reports**: [[DMPK RCLCZ696B2319b-ch] [DMPK RCLCZ696B2319c-us] **Report no**. **Report date**: **Other reports**: [Study B2319 IA]

Table 3 Overview of Study B2314

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: [CLCZ696B2314] **Countries**: Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Denmark, Dominican Republic, Ecuador, Estonia, Finland, France, Germany, Guatemala, Hong Kong, Hungary, Iceland, India, Israel, Italy, Korea, Latvia, Lithuania, Malaysia, Mexico, Netherlands, Panama, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, United States, Venezuela **Start:** 08-Dec-2009 **End:** 21-May-2014	**Design, purpose & population**: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction	**Total**: 8,442 **Age**: 18-96 (63.8) yrs **Groups**: 2 4209 4233	**Form(s)**: tablets LCZ696 50 mg LCZ696 100 mg LCZ696 200 mg Placebo to match LCZ696 50 mg, 100 mg and 200 mg enalapril 2.5 mg enalapril 5 mg enalapril 10 mg Placebo to match enalapril 2.5 mg, 5 mg and 10 mg **Duration**: Single-blind active run-in: 5-10 weeks Double-blind treatment: up to 4.26 years **Doses**: oral, twice daily LCZ696 200 mg enalapril 10 mg	**Study Status**: terminated early by the DMC due to overwhelming efficacy results favoring LCZ696 over enalapril **Report no**. [CLCZ696B2314] Full, final **Report date**: 31-Oct-2014 **Other reports**: [dmpk-clcz696b2314]

2.6.2. Rationale for an extrapolation from adult to paediatric patients of the use of sacubitril/valsartan in HF with LVSD.

Sacubitril/valsartan, unlike any other therapy for HF, provides concomitant inhibition of neprilysin and the angiotensin type 1 (AT1) receptor. Inhibition of neprylysin with chronic oral administration of sacubitril/valsartan can promote the endogenous capacity of the body to compensate for HF exacerbations by potentiating the activity of natriuretic peptides secreted by the heart in response to cardiac stress and increased intravascular volume. Natriuretic peptides 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. The resulting increase in natriuretic peptide (NP) activity due to neprilysin inhibition and AT1 receptor blockade through RAAS inhibition have complementary effects on the CV system, improving outcomes in HF patients.

Given that the pathophysiology of HF in adult HFrEF with DCM and paediatric HF due to LVSD are similar (described and discussed in the following sections), the inhibition of the RAAS axis by sacubitril/valsartan is expected to have similar beneficial effects in children with HF due to LVSD as in adults with HFrEF. The similar pathophysiology is a key element that enables extrapolation of existing adult HFrEF data to paediatric HF patients, as highlighted in the draft ICH E11A guidance on paediatric extrapolation.

In view of this, an extrapolation plan was designed by the applicant. However, as far as currently known by the EMA, this plan has not been discussed with the PDCO.

2.6.3. Appropriateness of extrapolating sacubitril/valsartan data from adults to paediatrics

There have been ongoing efforts from regulatory agencies globally to optimize the development of treatment modalities in paediatric patients. In this context, the CHMP released in April 2022 the draft ICH guideline E11A on paediatric extrapolation (ICH E11A guideline), which aims to better leverage the use of the existing information on approved treatment in adults and enable extrapolation to paediatrics when appropriate to reduce exposure of paediatric populations to unnecessary clinical trial interventions, and to facilitate more timely access to paediatric medicines globally.

The extrapolation is based on the principles laid down in the ICH E11A guidance: similarity of the disease in the target paediatric HF patients with LVSD and the adult HFrEF patients; similar drug exposure and exposure-response demonstrated in these 2 populations; and similar reduction from baseline in NT-proBNP, a biomarker associated with clinical outcomes in both population. In Study B2314, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at baseline and changes from baseline were correlated with clinical outcomes. Changes in NT-proBNP are also associated with markers of left ventricular systolic function and heart failure outcomes in paediatric patients.

Of note, based on interim 12-week data from Study B2319 (N=110), sacubitril/valsartan was approved in the US by the FDA for the treatment of symptomatic HF with systemic LVSD in paediatric patients aged one year and older. Sacubitril/valsartan reduces N-Terminal prohormone-B-type natriuretic peptide (NT-proBNP) and is expected to improve cardiovascular outcomes. The safety and tolerability of sacubitril/valsartan in paediatric patients from the interim Study B2319 data were consistent with that observed in adult patients.

2.6.4. Key steps of the proposed extrapolation plan

The key steps of the MAHs proposed extrapolation plan are summarized below and aligned with principles laid down in the ICH E11A guidance.

1. Demonstrate disease similarity between the reference population (with established efficacy) and the target population. In this case, the applicant has defined the reference population as adult HFrEF patients with DCM and the reference population as paediatric HF patients with LVSD consistent with DCM.

2. Demonstrate similar drug pharmacology (exposure). Similar drug pharmacology will be tested by comparing the AUC of the target paediatric dose (3.1 mg/kg) in part 1 of study B2319 with the AUC of the target adult dose (200mg) in study B2314.

3. Demonstrate a similar exposure response. In this extrapolation plan, the response will be NT-proBNP change in response to treatment at an exposure-matched dose.

4. Investigate the potential of NT-proBNP as a suitable biomarker to bridge efficacy between adult and paediatric populations. To do the latter, the applicant proposed using the Prentice criteria, which are summarized below:

    1. The treatment has a significant impact on the true clinical endpoint.
    2. The treatment has a significant impact on the biomarker
    3. The biomarker is significantly associated with true clinical endpoint
    4. The effect of treatment on true clinical endpoint is explained by the biomarker

The results from the extrapolation plan are demonstrated under section 3.3.7.1 extrapolation plan (part of clinical efficacy).

2.6.5. Clinical pharmacology

2.6.5.1. Pharmacokinetics

Introduction

Sacubitril/valsartan (LCZ696, Entresto®, Neparvis®) is a first-in-class angiotensin receptor and neprilysin (ARN) inhibitor that is currently approved for the treatment of adult patients with heart failure (HF) with reduced ejection fraction (HFrEF) in 117 countries, including the US and EU. Sacubitril is a prodrug that is in vivo converted to sacubitrilat via esterases. Sacubitrilat inhibits neprilysin, a neutral endopeptidase that degrades vasoactive peptides. As a result, sacubitrilat increases the concentration of natriuretic peptides, causing blood vessel dilation and reduction of ECF volume via sodium excretion. Valsartan is an angiotensin II receptor type 1 antagonist and inhibits the effects of angiotensin II.

This application concerns an extension of the indication and a line extension for adding a new pharmaceutical form in two strengths. Where the product was initially only authorised for adults, it will now be used in children from 1-18 years as well. The new pharmaceutical form is intended to facilitate dosing in younger children.

The finished products are presented as capsules filled with 4 and 10 film-coated granules corresponding to strengths of 6 mg/6 mg (6.1 mg/6.4 mg) and 15 mg/16 mg (15.18 mg/16.07 mg) sacubitril/valsartan. The granule cores have the same composition as the commercial adult tablet, except for the disintegrant.

Bioavailability

The pivotal paediatric registration (Study CLCZ696B2319; B2319; Study 6 and 7) used three different formulations of sacubitril/valsartan: the approved FCT (50 mg, 100 mg and 200 mg); film-coated granules (3.125 mg); and extemporaneous liquid formulation prepared by using film-coated granules (3.125 mg) in Part 1 and using 100 mg FCT in Part 2, by using appropriate vehicles. To bridge the

different formulations used in the pivotal paediatric trial, Novartis conducted in-vitro dissolution tests and two relative bioavailability (rBA) studies. Study CLCZ696B2126 (Study B2126; study 5) evaluated the rBA of sacubitril/valsartan and its analytes following oral administration of 200 mg film-coated granules (64 × 3.125 mg) compared to the adult 200 mg (97/103 mg) FCT in healthy adult subjects under fasted conditions. Study CLCZ696F2130 (Study F2130) evaluated the rBA of sacubitril/valsartan oral extemporaneous liquid formulation (200 mg equivalent of 3.125 mg film-coated granules) compared to the adult 200 mg (97/103mg) FCT in healthy adult subjects.

The rate (Cmax) and extent (AUC) of sacubitril/valsartan film-coated granules absorption were similar to those of the commercially available 200 mg (97/103 mg) FCT, as the ratios of the geometric means fall in the bioequivalence boundary of 80-125%. The extemporaneous liquid formulation prepared from film-coated granules provided similar total exposure (AUC) of sacubitril/valsartan analytes (sacubitril, sacubitrilat, and valsartan) compared to the FCT. The peak concentrations (Cmax) were also similar between the extemporaneous liquid formulation and the FCT for the active sacubitril/valsartan analytes (sacubitrilat and valsartan).

The sacubitril/valsartan FCT and the film-coated granules formulations are largely similar in composition except for few differences (See Section 1.2.2), but both have been shown to provide similar BA (Study B2126). So, the preparation of the extemporaneous liquid formulation from either FCT or film-coated granules would be considered equivalent.

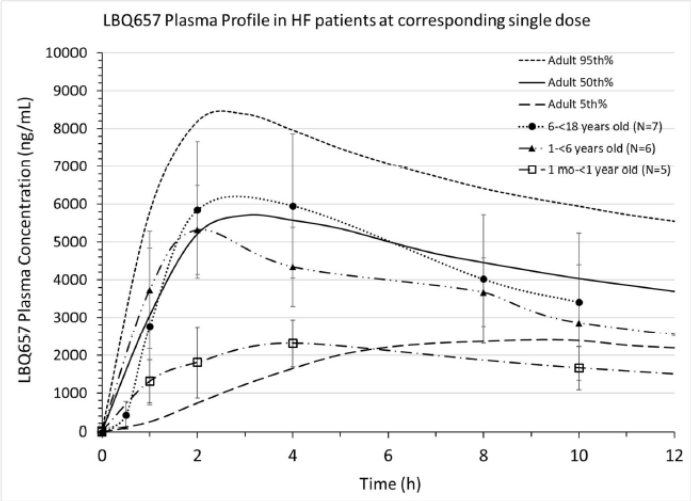
Soft food (vanilla pudding) had no significant effect on the BA, but the high-fat meal had an effect on the rate of absorption (Cmax) of sacubitril, sacubitrilat, and valsartan and the extent of absorption (AUCs) of valsartan (Study B2126). However, the effect of food on the PK of sacubitril/valsartan was comparable with previously reported results with the FCT. Hence, the food effect is independent of the formulation, and the food effect was considered clinically insignificant during the initial registration of sacubitril/valsartan. Accordingly, the three different formulations were administered without regard to meal in the current paediatric pivotal Phase III [Study B2319].

Pharmacokinetics in the paediatric population

Study B2319 was a 52-week randomized, two-part, double-blind, active-controlled paediatric clinical study to evaluate the safety and efficacy of sacubitril/valsartan compared with enalapril in paediatric patients 1 month to < 18 years of age with heart failure due to systemic left ventricular systolic dysfunction (LVSD). The study objectives and endpoints are described in [Study B2319-Section 8], and the study design is provided in [Study B2319-Section 9]. The study had 2 Parts. The sacubitril/valsartan doses used were 0.8 mg/kg and 3.1 mg/kg for Age Groups 1 and 2, and 0.4 mg/kg and 1.6 mg/kg for Age Group 3, as a single dose. The Age Group 3 dose was reduced considering the potential impact of developing the capacity of drug disposition in this very young age group on drug exposure.

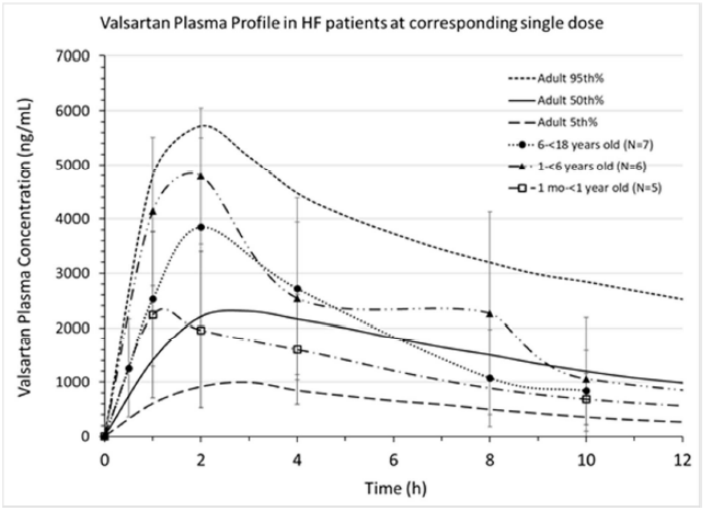
There were 26 patients enrolled in Part 1 of the study: 9 patients in Age Group 1 (6 to <18 years), 9 patients in Age Group 2 (1 to < 6 years), and 8 patients in Age Group 3 (1 month to < 1 year). Nine patients were in both Dose Cohort 1 and Dose Cohort 2; the remainder participated in one dose cohort. The results are presented below.

Figure 2-1 **Plasma concentration vs. time profiles for sacubitrilat among adult and pediatric patients at corresponding sacubitril/valsartan single dose**



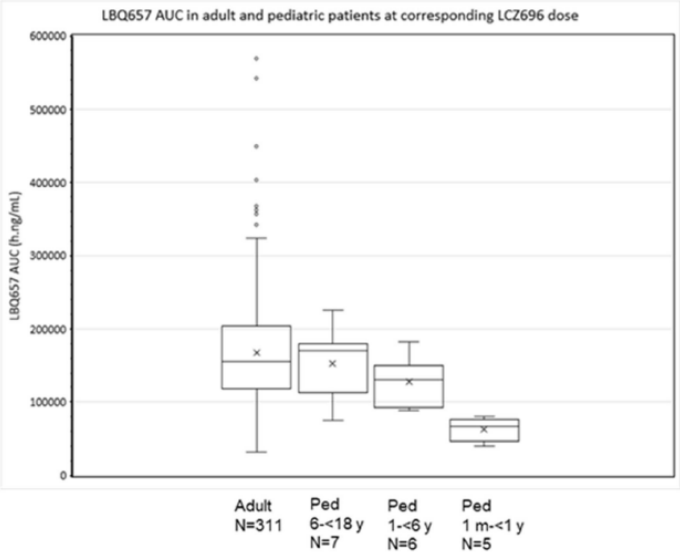
LBQ657 = sacubitrilat, the active metabolite of sacubitril
Adult data were obtained from the simulation using sacubitril/valsartan population PK model for HFrEF patients.
Doses: 200 mg for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.
Source: [Study B2319-Figure 11-7]

Figure 2-2 **Plasma concentration vs. time profiles for valsartan among adult and pediatric patients at corresponding sacubitril/valsartan single dose**



Adult data were obtained from the simulation using sacubitril/valsartan population PK model for HFrEF patients
Doses 200 mg for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.
Source: [Study B2319-Figure 11-7]

Figure 2-3 **Comparison of AUC (AUCtau_ss of BID dose or AUCinf of single dose) among adult and pediatric patients at corresponding sacubitril/valsartan dose: sacubitrilat**



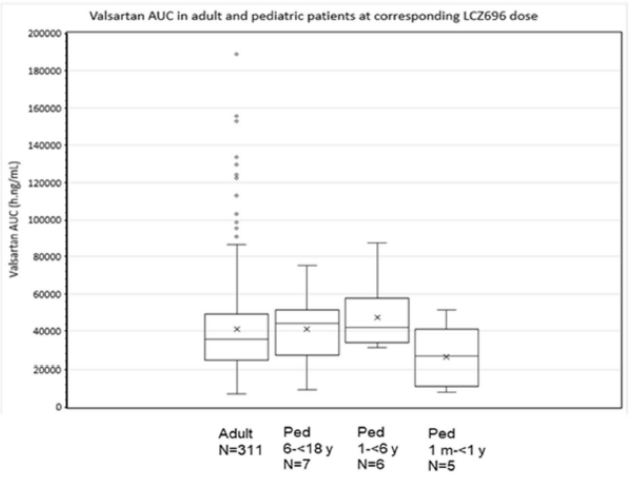
LBQ657 = sacubitrilat, the active metabolite of sacubitril

"x" inside the box represents the mean of the AUC range; solid line inside the box represents the median of the AUC range.

Upper bound of the box represents 75th percentile of the AUC range; lower bound of the box represents 25th percentile of the AUC range.

Adult data were obtained from the simulation of Study B2314 sub-Study (N=311) using sacubitril/valsartan population PK model for HFrEF patients
Doses 200 mg bid for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.
Source: [Study B2319-Figure 11-8]

Figure 2-4 **Comparison of AUC (AUCtau_ss of BID dose or AUCinf of single dose) among adult and pediatric patients at corresponding sacubitril/valsartan dose: valsartan**



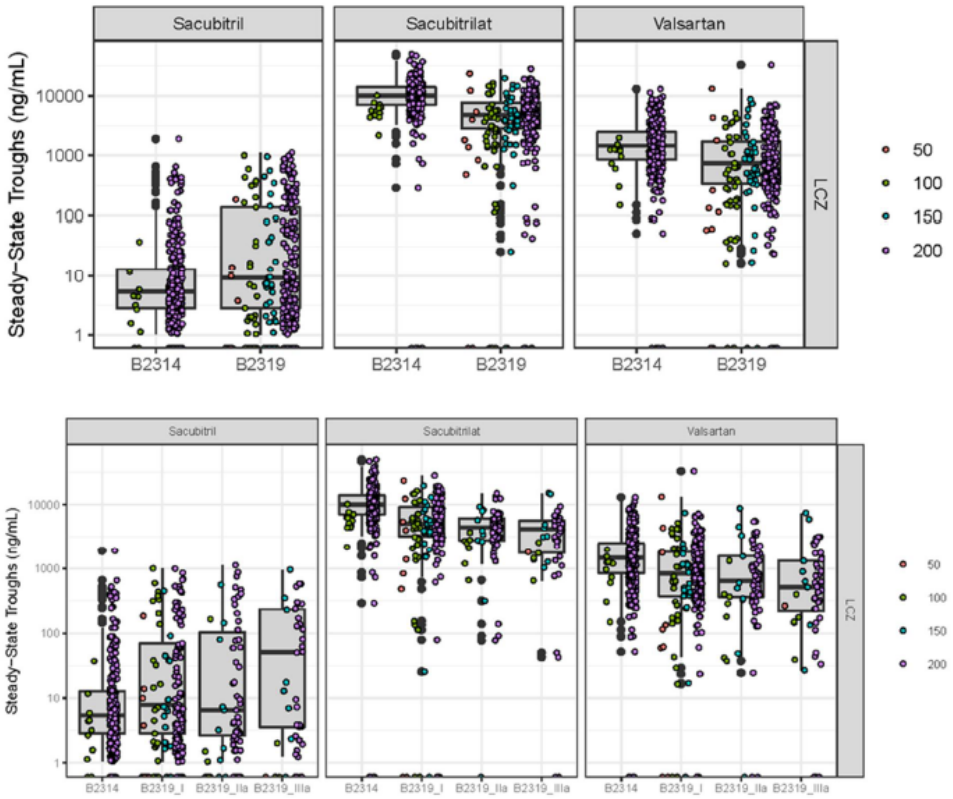
"x" inside the box represents the mean of the AUC range; solid line inside the box represents the median of the AUC range. Upper bound of the box represents 75th percentile of the AUC range; lower bound of the box represents 25th percentile of the AUC range.

Adult data were obtained from the simulation of Study B2314 sub-study (N=311) using sacubitril/valsartan population PK model for HFrEF patients
Doses 200 mg bid for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.
Source: [Study B2319-Figure 11-8]

The primary objective of Part 2 was to determine whether sacubitril/valsartan was superior to enalapril for the treatment of HF as assessed using a global rank endpoint in paediatric HF patients. Pre-dose sparse samples were collected to determine if trough exposures at steady-state were comparable to

exposures in adults with heart failure in Study B2314. PK samples were obtained from 177 paediatric patients treated with sacubitril/valsartan. The results are presented below:

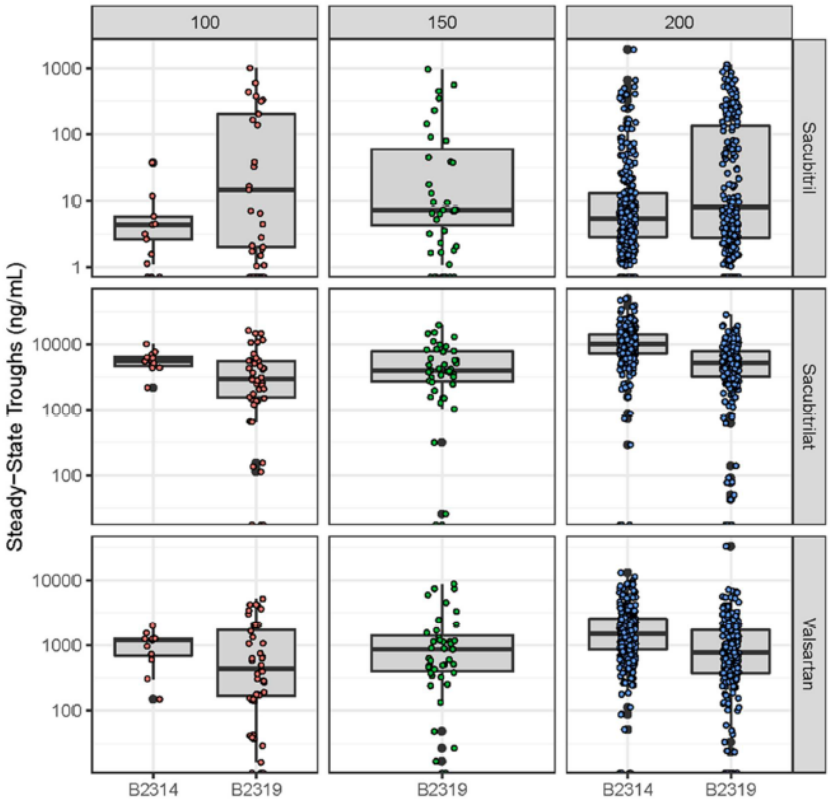
Figure 2-5 Boxplots of Steady-State Troughs of Sacubitril/Valsartan across Adults and Pediatric Patients with Heart Failure



Note: B2319_I refers to Age Group 1 (Age 6-<18 years), B2319_IIa refers to Age Group 2a (Age 2-<6 years) and B2319_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study B2319. 50 mg=0.8 mg/kg; 100 mg =1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg.

Source: [LCZ696 Pediatric-HF PKPD Update Report-Figure 4-1]

Figure 2-6 **Boxplots of Steady-State Troughs of Sacubitril/Valsartan by Dose Group for Adults and Pediatric Patients with Heart Failure**



100 mg=1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg
Source: [LCZ696 Pediatric-HF PKPD Update Report-Figure 4-2]

Sacubitrilat and valsartan drug exposure in paediatric heart failure patients is similar to exposure in adult heart failure patients at the same dose (Age Groups 1 and 2), with the ratios of geometric means of drug exposure (AUC children /AUC adults) being 0.80-0.92 and 0.99-1.29 for sacubitrilat and valsartan, respectively. Age Group 3 shows corresponding AUC changes consistent with the dose change (50% dose reduction), with the ratios of geometric means of the drug exposure (AUC children/AUC adults) being 0.39 and 0.61 for sacubitrilat and valsartan, respectively. This was confirmed in Study B2314 part 2, where comparable steady-state trough exposures at the recommended target dose of sacubitril/valsartan 97/103 mg (200 mg) in adults and the equivalent weight-based target dose 1.51/1.59 mg/kg (3.1 mg/kg) in paediatric patients were found.

In general it was shown that sacubitril/valsartan PK in paediatric heart failure patients aged 1 month to <18 years old is similar to that in adult heart failure patients.

2.6.5.2. Pharmacodynamics

Mechanism of action

Sacubitril is a prodrug that is in vivo converted to sacubitrilat via esterases. Sacubitrilat inhibits neprilysin, a neutral endopeptidase that degrades vasoactive peptides. Sacubitrilat thereby increases the concentration of natriuretic peptides, causing blood vessel dilation and reduction of ECF volume via sodium excretion. Valsartan is an angiotensin II receptor type 1 antagonist and thereby inhibits the effects of angiotensin II.

Primary and Secondary pharmacology

Study B2319

Study B2319 was a 52-week randomized, two-part, double-blind, active-controlled paediatric clinical study to evaluate the safety and efficacy of sacubitril/valsartan compared with enalapril in paediatric patients 1 month to < 18 years of age with heart failure due to systemic left ventricular systolic dysfunction (LVSD). In Part 1 of the study, multiple pharmacodynamic (PD) endpoints, including plasma B-type natriuretic peptide (BNP), plasma NT-proBNP (optional), plasma cyclic guanosine monophosphate (cGMP), urine cGMP change from baseline geometric mean ratio (GMR) after single dose treatment were assessed. An exploratory endpoint in Part 2 was NT-proBNP change from baseline through 4, 12 and 52 weeks of treatment.

Part 1
The primary objective of Part 1 of Study B2319 was to determine the pharmacokinetics (PK) and pharmacodynamics (PD) of sacubitril/valsartan in paediatric HF patients after single-dose treatment. The PK data from the paediatric patients in Part 1 were used to select doses for the same age groups in Part 2 of the clinical trial.

The PK/PD results were evaluated for the original protocol-defined age groups: Age Group 1 (6 to <18 years), Age Group 2 (1 to <6 years), and Age Group 3 (1 month to <1 year). The sacubitril/valsartan doses used were 0.8 mg/kg and 3.1 mg/kg for Age Groups 1 and 2, and 0.4 mg/kg and 1.6 mg/kg for Age Group 3. The dose for Age Group 3 dose was reduced considering the potential impact of developing the capacity of drug disposition in this very young age group on drug exposure.

A pharmacodynamic response to sacubitril/valsartan was observed for both plasma and urine cGMP in Age Group 1, which was dose-dependent (Table 4). In Age Group 2, urine cGMP results demonstrated a dose-response for the 0.8 mg/kg and 3.1 mg/kg, while an exposure-response was not observed in plasma cGMP. In Age Group 3, the increase in urine cGMP at the high dose of 1.6 mg/kg was in line with the urine cGMP findings for Age Groups 1 and 2.

Table 4. Change from baseline in PD biomarkers at 8 hours after single dose ingestion

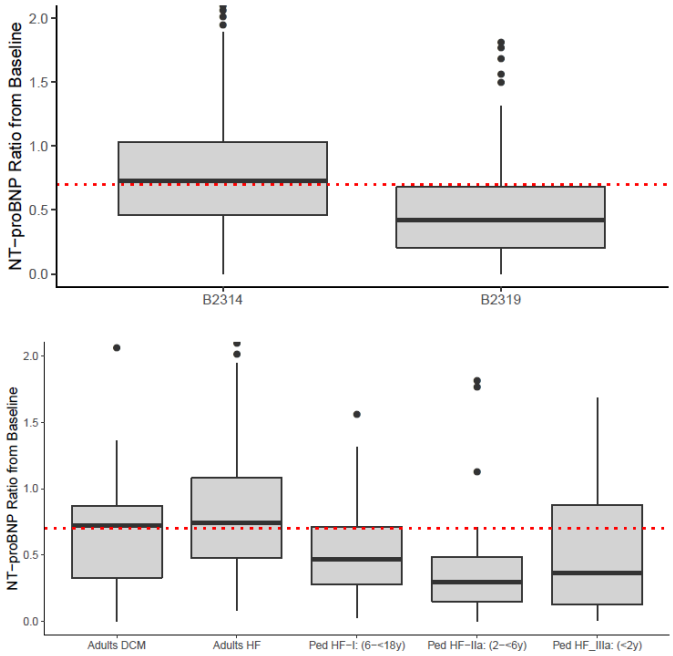
	Age group 1		Age group 2		Age group 3	
	Dose cohort 1	Dose cohort 2	Dose cohort 1	Dose cohort 2	Dose cohort 1	Dose cohort 2
BNP, pM	+44	+10	-32 *	-14 *	-11	-88
Plasma cGMP, nM	+4	+9	-3	-5	-4	-3
Urinary cGMP, nM	+138	+1469	-555	+793	+255	+683
* Only 1 participant Source: CSR Table 14.2-8.1 (Page 1 to 75)						

Part 2
In Part 2 of Study B2319, a secondary objective was to characterize the population PK of sacubitril/valsartan exposure in paediatric patients with HF (n=375). In addition, an exploratory objective was to compare sacubitril/valsartan to enalapril on change in NT-proBNP from baseline to Weeks 4, 12, and 52. The exposure-response of sacubitril/valsartan and NT-proBNP was also evaluated. Part 2 results are presented using the original Age Group 1 (6-<18 years) and modified Age Groups 2a (2-<6 years) and 3a (1 month-<2 years). Furthermore, the target dose was 3.1 mg/kg in patients aged 1 year and older and 2.3 mg/kg in a patient less than 1 year of age

The baseline NT-proBNP between adults (Study B2314) and paediatric patients (Study B2319) with HF were median 1222 ng/L vs 833 ng/L. However, when separated by specific paediatric age groups, Age Groups 2a and 3a appeared to have higher median baseline NT-proBNP than adults with HF. Off note, the physiological range of NT-proBNP is known to be higher in newborns and to decrease during childhood (Nir et al 2009).

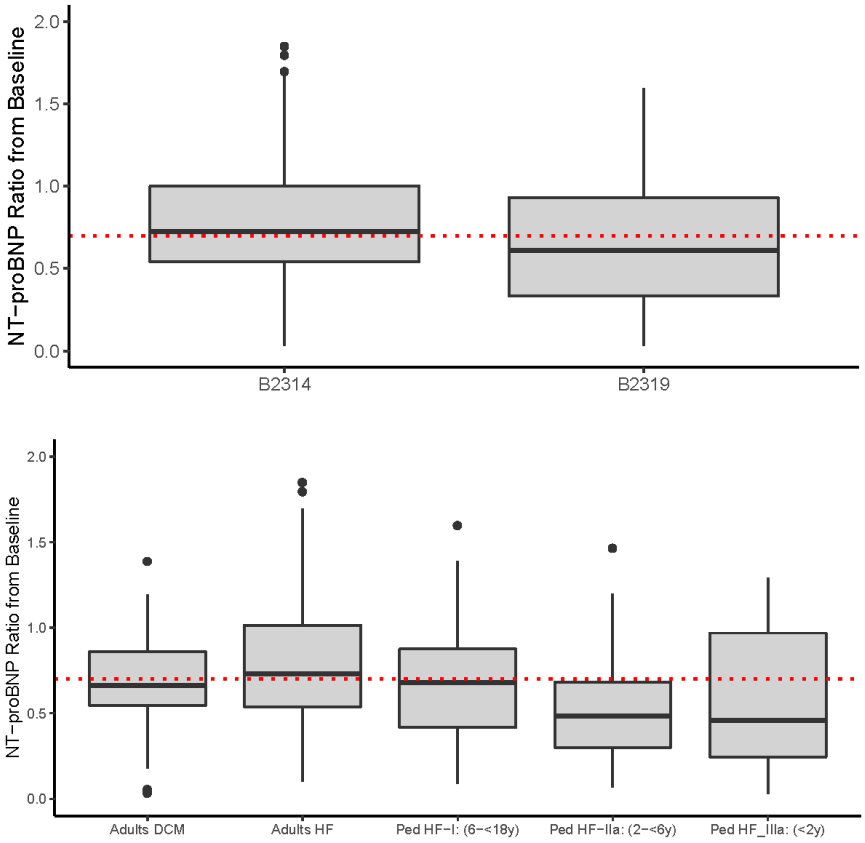
The plasma NT-proBNP levels by dose group show a consistent decrease in NT-proBNP level with increasing sacubitril/valsartan dose, supporting a similar exposure-response in adult and paediatric patients with HF. Paediatric HF patients treated with the target dose of sacubitril/valsartan showed a comparable reduction in NT-proBNP as noted in adults (median 55% vs 28%), with a substantial overlap in distribution as displayed in the boxplots at Week 52 (Figure 1). Similar results were observed at Week 12 (Figure 2).

Figure 1. Boxplots of the ratio of plasma NT-proBNP from baseline between adults (at 8 months) and paediatric patients with heart failure for 200 mg (3.1 mg/kg) at 52 Weeks



Note: Paediatrics_I refers to Age Group 1 (Age 6-<18 years), Paediatrics_IIa refers to Age Group 2a (Age 2-<6 years) and Paediatrics_IIIa refers to Age Group 3a (Age 1 month<2 years) in Study CLCZ696B2319. DCM refers to dilated cardiomyopathy. Note: Dashed red line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decreased of 30% of plasma NT-proBNP from baseline.

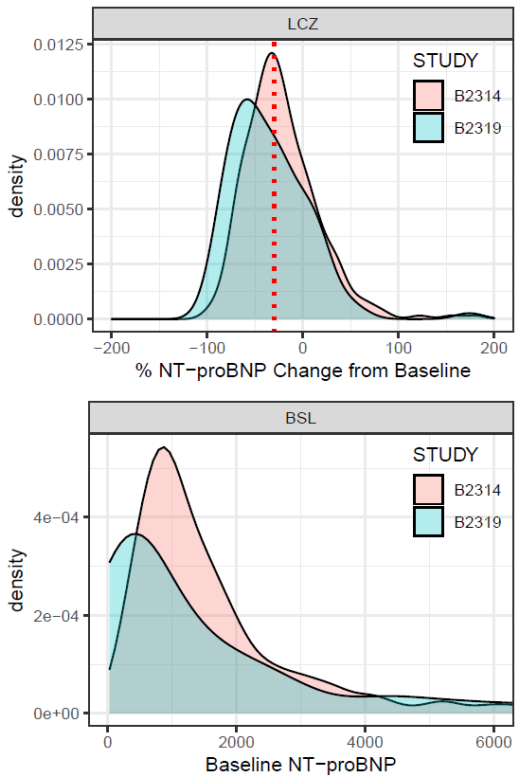
Figure 2. Boxplots of the Ratio of Plasma NT-proBNP from Baseline between Adults (at 4 weeks) and Paediatric Patients with Heart Failure for 200 mg (3.1 mg/kg) at 12 weeks



Note: Paediatrics_I refers to Age Group 1 (Age 6-<18 years), Paediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Paediatrics_IIIa refers to Age Group 3a (Age 1 month<2 years) in Study B2319. DCM refers to dilated cardiomyopathy. Note: Dashed red line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decrease of 30% of plasma NT-proBNP from baseline.

The density plot (Figure 3) further confirms that the distribution of the percent reduction of NT-proBNP between heart failure adults at Week 4 and paediatric patients at Week 12 were relatively similar since the distributions overlap each other.

Figure 3. Density Plot Comparing Distribution of Percent Change in Baseline of Plasma NT-proBNP (Week 12 for paediatrics HF and Week 4 for adults HF) and Baseline NT-proBNP for 200 mg (3.1 mg/kg)



Note: Dashed red line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decrease of 30% of plasma NT-proBNP from baseline. Unit of NT-proBNP is ng/L or pg/mL

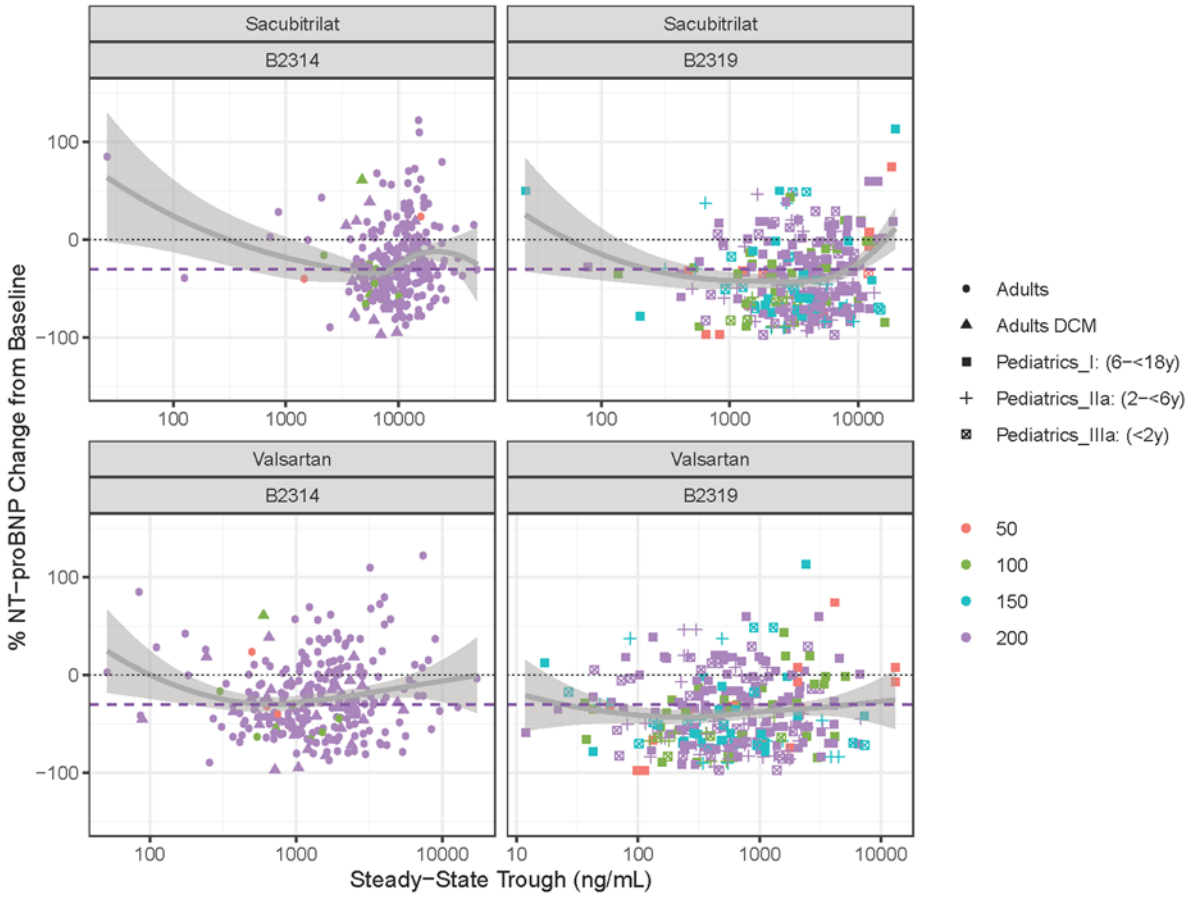
2.6.5.2.1. Relationship between plasma concentration and effect

Exposure-response of steady-state effect of sacubitril/valsartan on plasma NT-proBNP

The PK/PD analysis showed comparable NT-proBNP reductions in paediatric and adult patients treated with sacubitril/valsartan, especially in the comparison of paediatric HF with adult patients with HFrEF due to DCM. The dose-exposure-response of sacubitril/valsartan and NT-proBNP appeared to be consistent between paediatric and adult patients with HF at their equivalent dose, with greater decreases in NT-proBNP in patients who received higher doses of sacubitril/valsartan *Figure 4*. There were larger NT-proBNP reductions in paediatric HF patients compared to the overall adult HF population in Study B2314. However, this difference was marginal when comparing paediatric HF patients to adults with HFrEF due to DCM. At 52 weeks in paediatrics and 8 months in adults, the ratio of NT-proBNP relative to baseline between paediatric HF patients (3.1 mg/kg) and adult HF patients (200 mg) was 0.78 (95% CI: 0.67, 0.89), while when compared to adult HF patients with DCM it was 0.94 (95% CI: 0.74, 1.2); with approximately 50% decrease from baseline.

Taken together, the results of the PK/PD analysis support that a weight-based dose of 3.1 mg/kg in paediatric HF patients provides comparable NT-proBNP lowering (>50% decrease from baseline) and comparable sacubitril/valsartan trough exposures as in adult HFrEF patients at the equivalent target dose.

Figure 4. Exposure-Response Relationship of Steady-State Troughs of Sacubitril/Valsartan on Percent Change from Baseline of Plasma NT proBNP separated by Studies



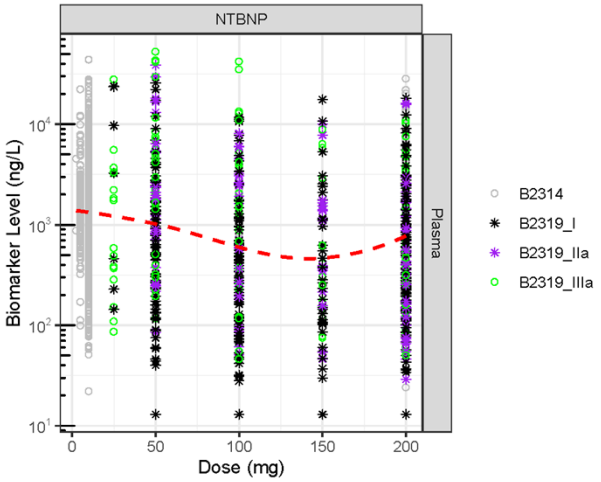
Note: Dashed purple line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decrease of -30% of plasma NT-proBNP from baseline.

Paediatrics_I refers to Age Group 1 (Age 6-<18 years), Paediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Paediatrics_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study B2319. DCM refers to dilated cardiomyopathy. The numbers 50 (pink symbol), 100 (green symbol), 150 (blue symbol) and 200 (purple symbol) reflects dose in mg. 50 mg=0.8 mg/kg; 100 mg=1.6 mg/kg; 150 mg=2.3 mg

Dose-response of steady-state effect of sacubitril/valsartan on plasma NT-proBNP

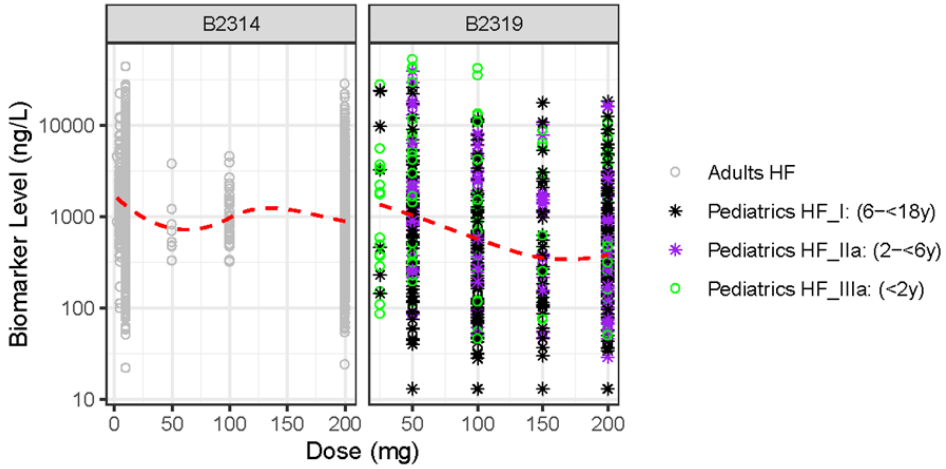
Plots of the dose-biomarker response of NT-proBNP show that the target sacubitril/valsartan 97/103 mg (200 mg) or equivalent weight-based dose 1.51/1.59 mg/kg (3.1 mg/kg) in paediatric HF patients provides greater NT-proBNP reduction (*Figure 5* and *Figure 6*) when compared to the lower dose. The dose biomarker response across studies showed lower NT-proBNP levels with increased doses of sacubitril/valsartan and indicated comparable dose-response between paediatric and adult HF patients (*Figure 6*).

Figure 5. Dose versus Plasma NT-proBNP at Steady-State



Note: Red dashed line reflects the loess curve describing the trend in the data.

Figure 6. Dose versus Plasma NT-proBNP Level at Steady-State by Studies



Note: Paediatrics_I refers to Age Group 1 (Age 6-<18 years), Paediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Paediatrics_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study B2319. Note: Red dashed line reflects the loess curve describing the trend in the data

2.6.6. Discussion on clinical pharmacology

Neparvis contains the active substances sacubitril and valsartan. The proposed beneficial effect of sacubitril is based on inhibiting the degradation of natriuretic peptides, increasing BNP. Natriuretic peptides exert their effects by activating membrane-bound guanylyl cyclase coupled receptors, resulting in increased concentrations of the second messenger, cGMP, which can be detected in plasma and urine.

The PD effects of sacubitril/valsartan were evaluated in a 52-week randomized, two-part, double-blind, active-controlled paediatric clinical study in three age categories (part 1: Age Group 1 (6 to <18 years; n=9), Age Group 2 (1 to <6 years; n=9), and Age Group 3 (1 month to <1 year; n=8); part 2:

Age Group 1 (6-<18 years) and modified Age Groups 2a (2-<6 years) and 3a (1 month-<2 years). The sacubitril/valsartan doses used were 0.8 mg/kg and 3.1 mg/kg for Age Groups 1 and 2, and 0.4 mg/kg and 1.6 mg/kg for Age Group 3.

In part 1 of study B2319, administration of sacubitril/valsartan resulted in increases in urinary cGMP in all age groups, which were dose-dependent. For plasma cGMP and plasma BNP, no clear dose-response effects were found. For age group 3, the Applicant states that a dose higher (2.3 mg/kg) than dose cohort 2 (1.6 mg/kg) was chosen after a review of data from part 1 by the FDA and DMC. From the summary of pharmacology, it is unclear how this choice was made. Since only an indication is sought for paediatric patients one year and older, this issue is not pursued.
Regarding pharmacodynamics in part 2 of study B2319, the PK/PD analysis showed comparable NT-proBNP reductions in paediatric and adult patients treated with sacubitril/valsartan, especially in comparing paediatric HF patients with adult patients with HFrEF due to DCM. Based on plots of the dose-biomarker response of the NT-proBNP at steady-state, the applicant claimed that the effect was generally consistent between paediatric and adult HF patients, with larger decreases in NT-proBNP in patients who received higher doses of sacubitril/valsartan (up to 200 mg). No clear exposure-response relationship was shown. However, this was to be expected as both B2314 (PARADIGM-HF, adult population) and B2319 (PANORAMA-HF, pediatric population) studies were designed to achieve a target maintenance dose of 200 mg (B2314) and the equivalent dose of 3.1 mg/kg (B2319). As such, the ranges for the majority of sacubitrilat and valsartan PK concentrations are relatively narrow, and the exposure-response relationships are difficult to discern for both analytes.

2.6.7. Conclusions on clinical pharmacology

Administration of sacubitril/valsartan at the target dose in paediatric patients leads to a reduction in NT-proBNP at steady state, which appears larger than the NT-proBNP reduction in adult HF patients but similar to the NT-proBNP decrease in adult HF patients with dilated cardiomyopathy (DCM). There appears to be a trend of larger NT-proBNP decreases at higher sacubitril/valsartan doses up to 200 mg. However, no clear trend between exposure and response could be ascertained. In conclusion, there is a similar decrease in NT-proBNP between adult HF with DCM and paediatrics patients with HF when treated with an equivalent dose of sacubitril/valsartan:>

2.6.8. Clinical efficacy

The totality of evidence included in this submission supporting the efficacy of sacubitril/valsartan for paediatric use includes 1) extrapolation of the existing adult HFrEF data from study B2314 (PARADIGM-HF) to children based on the pharmacokinetic and pharmacodynamic data from study B2319 (PANORAMA-HF) and 2) the clinical data provided by the PANORAMA-HF study.

2.6.8.1. Extrapolation plan

The extrapolation of sacubitril/valsartan efficacy from adults to the paediatric population

NT-proBNP is recognized as a prognostic biomarker for clinical outcomes in clinical trials in HF (Januzzi et al. 2019, Schmitt et al. 2021). NT-proBNP was used as a bridging biomarker for extrapolation from adults to the paediatric population in submission to the FDA based on an interim analysis of Week 12 data, leading to approval in the US. Using the Prentice Criteria (Prentice 1989), Novartis investigated the relationship between NT-proBNP over time and the change at Month 1 on top of baseline NT-

proBNP with the risk of CV death or HF hospitalization (Study B2314). This included the magnitude of the sacubitril/valsartan treatment effect on the clinical outcomes explained by post-randomization change from baseline in NT-proBNP over time.

The extrapolation of sacubitril/valsartan efficacy from adults to the paediatric population is predicated on the following principles, as outlined in the draft ICH E11A guideline:

1. Disease similarity
2. Similar drug pharmacology (exposure)
3. Similar exposure response
4. Predictive biomarker to bridge efficacy between adult and paediatric populations

Given the similarity between paediatric HF due to LVSD and adult HFrEF with DCM, the similar exposure between adult and paediatric HF populations, the similar magnitude of NT-proBNP reductions at exposure-matched doses of sacubitril/valsartan, and the association of NT-proBNP changes from baseline with clinical outcomes, the Applicant claimed that extrapolation from adult data using the predictive NT-proBNP marker is a reasonable approach to infer clinical efficacy in the paediatric HF population.

2.6.8.1.1. Disease similarity

Pediatric heart failure can be due to a variety of etiologies, pathophysiologies and morphologies. Morphologies include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), LV non-compaction cardiomyopathy (LVNCM). It is estimated that DCM characterizes approximately 50% of pediatric HF, 35 to 50% by HCM and < 5% by RCM. LVNCM accounts for approximately 5% of cases.

Despite the difference in etiologies between paediatric and adult HF, there are important common clinical features between adult HFrEF patients with DCM and paediatric HF patients with LVSD consistent with DCM. The major morphologic feature in both populations is dilatation of both ventricles (Dec and Fuster 1994). In both paediatric and adult HF, due to systolic dysfunction, there is a decrease in systemic cardiac output. The pathophysiologic adaptation to decreased cardiac output in both adult and paediatric HF involves increased sympathetic tone and activation of the renin-angiotensin-aldosterone system (RAAS) (Momma 2006). In addition, also similar to adult HF, paediatric HF results in increased activation of the natriuretic peptide system (Favilli et al. 2009). This pathophysiologic neurohumoral activation plays a key role in the progression of HF due to systolic dysfunction in adults and children, and this is why the clinical course and HF management in this paediatric HF subset with systemic LVSD is similar to adult HFrEF with DCM. In addition, both populations have similar physical signs and symptoms. These similarities have been highlighted in the draft ICH E11A 2022 guideline *"... heart failure due to dilated cardiomyopathy is similar between adult and paediatric populations, allowing for extrapolation from adult to paediatric patients with dilated cardiomyopathy*".

Similarities have also been noted concerning disease progression between paediatric and adult HF patients with DCM. The Ventricular Volume Variability study (VVV), designed by the National Heart, Lung, and Blood Institute (NHLBI)-funded Paediatric Heart Network, was a longitudinal observational study of children with known or suspected DCM ages 0 to 22 years from 8 paediatric clinical centres. Clinical data were collected together with 150 echocardiographic indices of left ventricle (LV) size and function. Of a total of 275 subjects with known or suspected DCM, 194 were eligible for the initial screening echocardiogram, 173 (89%) consented to participation and underwent data recording, and 131 were confirmed to have chronic DCM (Colan et al 2012). In 127 chronic DCM patients with

prospective echocardiographic and clinical data collected during the 18-month follow-up, factors that were found to be predictors of disease progression included age at diagnosis, echocardiographic evidence of larger LV size and impaired systolic and diastolic function (Molina et al 2013). Clinical progression was similar between paediatric patients in the VVV study and PARADIGM-HF patients ≤ 40 years old with DCM treated with enalapril.

PANORAMA-HF aimed to enrol a homogeneous population of pediatric HF with left ventricle systolic dysfunction (LVSD) consistent with DCM. HCM and RCM, along with uncorrected structural heart disease and single ventricle or systemic right ventricle, were excluded. Enrolment of a homogeneous pediatric HF population with LVSD consistent with DCM in PANORAMA-HF was thus achieved by defining a series of inclusion and exclusion criteria, ensuring all patients had symptomatic HF and HFrEF is defined as LVSD in pediatric patients.

More than 60% of patients in PANORAMA-HF were diagnosed with cardiomyopathy, with the cause being idiopathic in 33.6%, followed by familial/genetic conditions in 15.7% and congenital heart malformations in 13.3%. Heart failure secondary to other causes was noted in about 35% of patients. In those 35% of patients where the etiology of HF was not primarily identified as related to cardiomyopathy, it is known from the literature that all can evolve into or manifest as DCM. In particular, the most frequent cause was myocarditis-induced HF, which is the most common cause of acquired DCM in children.

In PANORAMA-HF, while there was no collection of echocardiographic data regarding ventricle volumes or diameters to confirm a diagnosis of DCM, all diseases included are known to evolve or manifest as DCM. Additionally, patients with restrictive or hypertrophic cardiomyopathy were excluded. Nonetheless, as recommended by treatment guidelines, the treatment of heart failure in children is based on pathophysiology, hence based on systolic vs. diastolic dysfunction and based on approved adult HFrEF therapies.

PANORAMA-HF evaluated a relatively homogeneous population with biventricular hearts and symptomatic HF due to a systemic left ventricle with decreased ejection fraction. All diseases included are known to possibly evolve or manifest as DCM. Such an approach resulted in a patient population that resembles the adult HF population with DCM. In conclusion, all patients enrolled in PANORAMA-HF were diagnosed with LVSD, while patients with HCM, RCM, and complex congenital heart disease with functional single ventricle or systemic right ventricle were excluded. Despite the lack of LV diameter measurement, the literature and clinical practice support that all enrolled pediatric patients with systemic LVSD had a form of DCM. Furthermore, both adult HFrEF with DCM and pediatric HF due to LVSD have similar pathophysiology, including a reduced cardiac output due to left ventricle insufficiency, which causes reduced organ perfusion, increased adrenergic tone, and RAAS activation.

2.6.8.1.2. Similar drug pharmacology (exposure)

Part 1 of study B2319 showed that sacubitrilat and valsartan drug exposure in paediatric HF patients is similar to exposure in adult heart HF at the same dose (Age Groups 1 and 2) with the ratios of geometric means of drug exposure (AUC children /AUC adults) being 0.80-0.92 and 0.99 1.29 for sacubitrilat and valsartan, respectively. Age Group 3 showed corresponding AUC changes consistent with the dose change (dose was initially 50% reduced considering the potential impact of developing the capacity of drug disposition), with the ratios of geometric means of the drug exposure (AUC children/AUC adults) being 0.39 and 0.61 for sacubitrilat and valsartan, respectively. Described in more detail in the pharmacokinetic section.

2.6.8.1.3. Similar exposure response

Part 1 of study B2319 showed a similar magnitude of NT-proBNP reductions at exposure-matched doses of sacubitril/valsartan. The ratio of NT-proBNP relative to baseline between paediatric HF patients (3.1 mg/kg) and adult HF patients (200 mg) was 0.78 (95% CI: 0.67, 0.89), while when compared to adult HF patients with DCM, it was 0.94 (95% CI: 0.74, 1.2); with approximately 50% decrease from baseline. This subject is described in more detail in the pharmacodynamic section, as well as under the following section.

2.6.8.1.4. NT-proBNP as bridging biomarker for extrapolation of efficacy

NT-proBNP has been increasingly recognized as an important biomarker in heart failure and is correlated with clinical outcomes. It is therefore proposed as a bridging biomarker between paediatric HF patients and adult patients with DCM to support extrapolation of efficacy. The Prentice criteria (Prentice 1989) provide a systematic framework to establish the adequacy of NT-proBNP as a bridging biomarker. This includes the demonstration that:

1. The treatment has a significant impact on the true clinical endpoint
2. The treatment has a significant impact on the biomarker
3. The biomarker is significantly associated with the true clinical endpoint
4. The effect of treatment on the true clinical endpoint is explained by the biomarker

Prentice criteria 1: The treatment has a significant impact on the true clinical endpoint

As reflected in the approved SmPC, in Study B2314 in adult HFrEF (FAS: N=8399), sacubitril/valsartan was superior to enalapril, reducing the risk of CV death or HF hospitalizations to 21.8% compared to 26.5% for enalapril treated patients. The absolute risk reductions were 4.7% for the composite of the CV death or HF hospitalization, 3.1% for CV death alone, and 2.8% for first HF hospitalization alone. The relative risk reduction was 20% versus enalapril. This effect was observed early and was sustained throughout the duration of the study. Both components contributed to the risk reduction. Sudden death accounted for 45% of cardiovascular deaths and was reduced by 20% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (HR 0.80, p=0.0082). Pump failure accounted for 26% of cardiovascular deaths and was reduced by 21% in sacubitril/valsartan-treated patients compared to enalapril-treated patients (HR 0.79, p=0.0338) (Neparvis SmPC). The benefit of sacubitril/valsartan was also shown for the subgroup of patients with HFrEF with DCM (N=1810), with a 25% relative risk reduction in CV death/HF hospitalization (p=0.0040) compared to enalapril. Data from B2314, therefore, meet the first criteria for both the overall HFrEF population and the DCM subgroup.

Prentice criteria 2: The treatment has a significant impact on the biomarker

In the biomarker substudy of study B2314 (N=2080), the HR (sacubitril/valsartan /enalapril) adjusted for baseline NT-ProBNP was 0.82 (95% CI 0.68, 0.98; p=0.0279) and sacubitril/valsartan treatment had a significant impact on NT-proBNP. The ratio of NT-proBNP to baseline levels was approximately 25% lower in the sacubitril/valsartan group as compared to the enalapril group both at Month 1 (Ratio: sacubitril and valsartan/enalapril 0.7376, 95% CI 0.6985 to 0.7789) and at Month 8 (Ratio: 0.7524, 95% CI 0.7003 to 0.8084) post-randomization (both p<0.0001).

In the subgroup of adult patients with HFrEF with DCM, the reduction in NT-proBNP from baseline was 43% at Month 1, and 52% at Month 8 (*Table 5*). These data show that in the overall adult HFrEF

population as well as in those with DCM, sacubitril/valsartan had a significant impact on the biomarker visible as early as 1 month and fulfils the 2nd Prentice criteria.

Table 5. Study B2314 (adult HFrEF): Change from baseline in NT-proBNP (Full Analysis Set)

	LCZ69		Enalapril		Comparison (LCZ696/ Enalapril)	
Visit	**n**	**Ratio to BL (95% CI)**	**n**	**Ratio to BL (95% CI)**	**Ratio (95% CI)**	**p-value**
Adult HFrEF (N=2080)						
Month 1	971	0.68 (0.65,0.71)	971	0.92 (0.89,0.96)	0.74 (0.70,0.78)	<0.0001
Month 8	885	0.65 (0.62,0.68)	874	0.86 (0.82,0.91)	0.75 (0.70,0.81)	<0.0001
Adult HFrEF with DCM (N=405)						
Month 1	196	0.57 (0.52,0.62)	188	0.92 (0.84,1.00)	0.62 (0.55,0.71)	<0.0001
Month 8	178	0.48 (0.42,0.56)	167	0.79 (0.68,0.91)	0.61 (0.50,0.75)	<0.0001

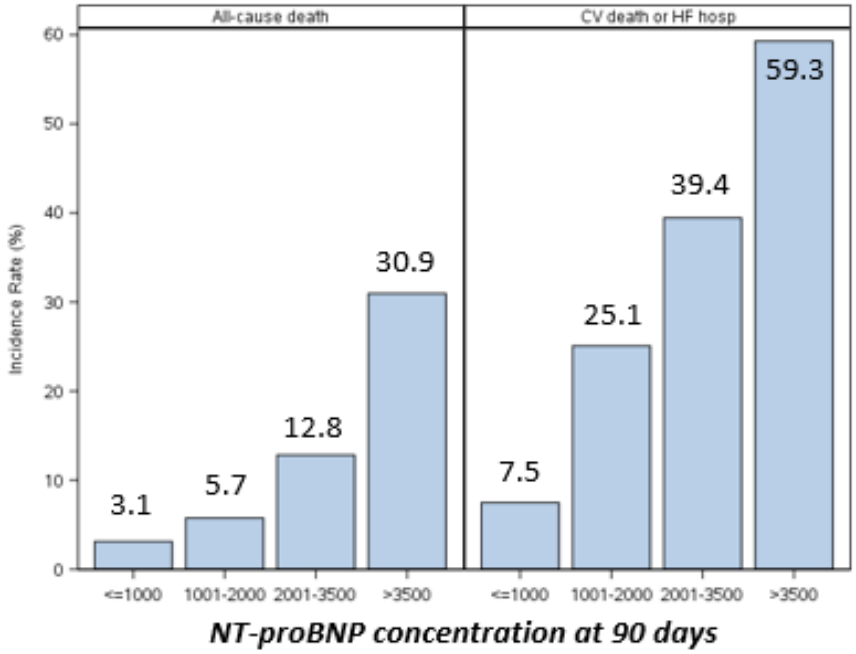
Analysis includes patients in the specified subset, who are in the Biomarker subpopulation and having non missing NT-proBNP at baseline. The analyses (repeated measurement model) uses change from baseline in log(NT-proBNP) at months 1 and 8 as response and contains treatment, region, baseline log(NT-proBNP), visit, treatment*visit and baseline log(NT-proBNP)*visit as explanatory variables assuming a common covariance for each treatment.
Source: [SCE Appendix 1-Table 14.2-3.25.1.post.02a1, Table 14.2-3.25.1.post.02a1.sub]

Prentice criteria 3: The biomarker is significantly associated with true clinical endpoint

Data in adult HFrEF demonstrate that longitudinal changes in NT-proBNP levels (measured by either absolute, relative or categorical changes) are highly predictive of risk for clinical outcomes, including mortality and hospitalization. This raises the perspective of utilizing changes in NT-proBNP to predict a drug's treatment effect.

Recent data from the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE IT) trial looking at NT-proBNP guided therapy vs usual care to achieve an NT-proBNP level <1000 pg/mL in HF patients with reduced EF and elevated NT-proBNP levels at baseline, showed a clear correlation between achieved NT-proBNP levels at 90 days and clinical outcomes (Januzzi et al 2019).

Figure 7. GUIDE-IT: Number of events per 100 patient years

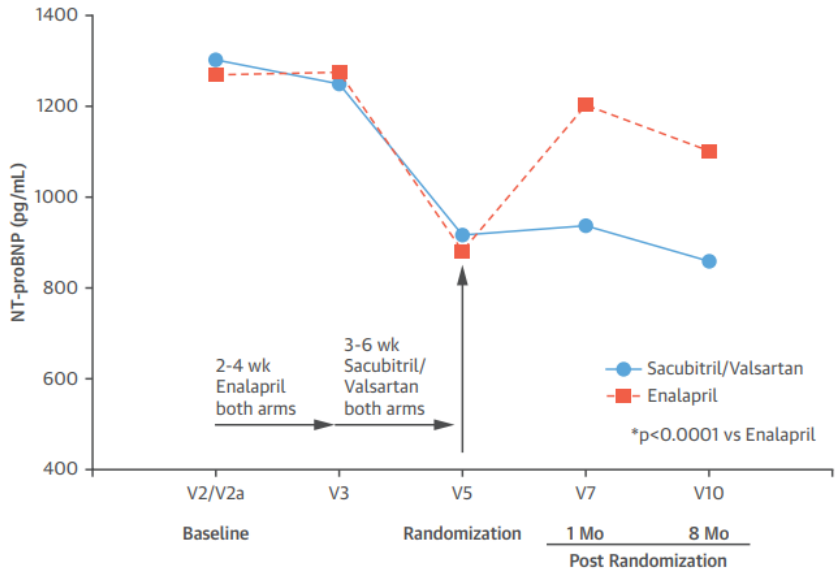


An analysis of 1742 patients from the placebo-arm of the Valsartan Heart Failure Trial (Val-HeFT), a multicenter, double-blinded, parallel-group, randomized, placebo-controlled trial of 5,010 patients with LVEF <40% revealed a progressive increase in the rate of all-cause mortality in relation to the increase in NT-proBNP analyzed in quartiles from baseline to 4 months with the rate of all-cause mortality more than doubling from 9.2% to 21.5% between the lowest and the highest quartile. The analysis of categorical changes in NT-proBNP reinforced these findings: patients whose NT-proBNP was “high” (i.e. above the optimal prognostic cutoff value (1078 pg/mL) at baseline and after 4 months had a nearly two-fold increased risk for subsequent all-cause-mortality compared to those patients with NT-proBNP values that were low at both time points. In addition, those whose values started high at baseline but fell below the threshold after 4 months had a risk for all-cause mortality similar to those who started and remained “low” (Masson et al. 2008).

Similar results were reported from the study B2314 biomarker sub-study in 2080 patients (Zile et al. 2016). In an analysis of the primary endpoint for B2314 (CV death and HF hospitalization) starting 1-month after randomization, the change of NT-proBNP from baseline to 1-month was a highly significant predictor of clinical outcomes. Median NT-proBNP at baseline was 1269 (IQR: 762 to 2184) pg/mL for enalapril-treated patients and 1303 (IQR: 781 to 2371) pg/mL for sacubitril/valsartan treated patients. The median NT-proBNP did not change significantly during the enalapril run-in but decreased significantly during the sacubitril/valsartan run-in. One month after randomization, NT-proBNP was significantly lower in the sacubitril/valsartan-treated patients (938 [IQR: 511 to 1595] pg/mL) compared with enalapril treated patients (1203 [IQR: 711 to 2,061] pg/mL; p <0.001). After adjustment for baseline NT-proBNP, the HR per doubling of NT-proBNP at 1 month was 1.46 (95% CI: 1.30 to 1.64), whereas the HR per halving of NT-proBNP at 1 month was 0.68 (95% CI: 0.61 to 0.77).

In summary, a change in plasma NT-proBNP post-randomization is associated with the CV mortality/HF hospitalization rate in adult patients with HFrEF. Whether looking at absolute, relative or categorical changes in NT-proBNP, reductions have been shown to be associated with a significantly lower morbidity and mortality rate, fulfilling the 3rd Prentice criteria.

Figure 8. NT-proBNP Values in Patients Treated With Sacubitril/Valsartan Versus Enalapril at Each Study Time Point

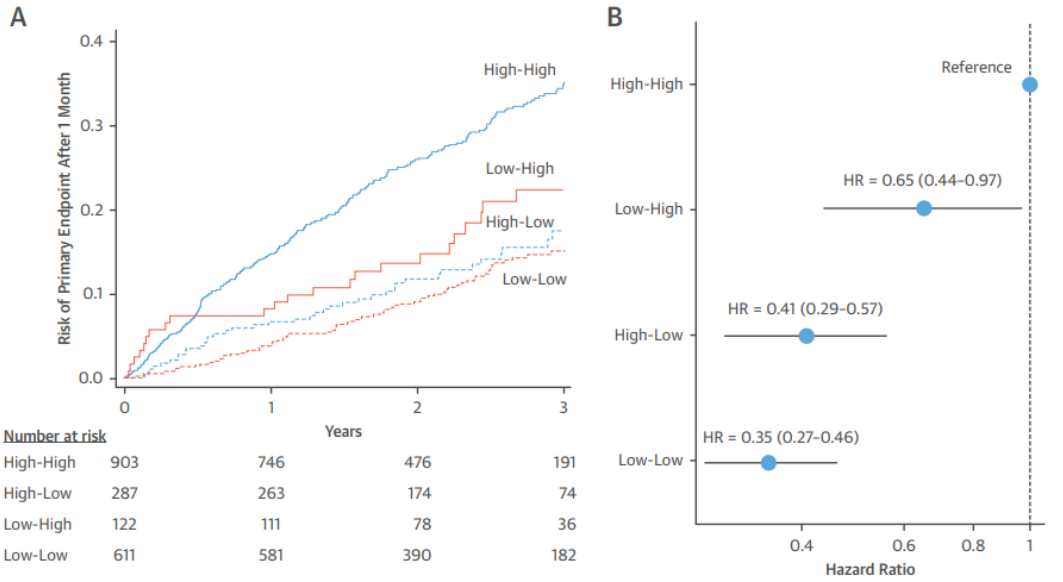


NT-proBNP (pg/mL) Median (Q1;Q3)					
	V2/V2a	V3	V5	V7	V10
Sacubitril/Valsartan n	1303 (781;2371) 1051	1251 (653;2208) 440	917 (526;1653) 1018	938 (511;1595) 971	859 (450;1708) 885
Enalapril n	1269 (762;2184) 1029	1276 (698;2186) 435	882 (517;1692) 997	1203 (711;2061) 971	1102 (610;2073) 874

Median N-terminal pro-B-type natriuretic peptide (NT-proBNP) values in the sacubitril/valsartan-treated patients **(blue circles, blue solid line)** versus enalapril-treated patients **(orange squares, orange dashed line)** at each measurement time point are shown. Numeric values for median (interquartile range: Q1;Q3) in patients with values available at each time point are presented in the table below the figure. NT-proBNP was significantly lower in the sacubitril/valsartan-treated patients than in the enalapril-treated patients at 1 and 8 months after randomization. *p < 0.05. V2/V2a = baseline before run-in; V3 = after enalapril run-in; V5 = at randomization; V7 = 1 month after randomization; and V10 = 8 months after randomization.

Source: Zile et al 2016

Figure 9. Effects on Risk of Primary Endpoint if N-Terminal Pro–B-Type Natriuretic Peptide Changed From Baseline to 1 Month After Randomization: High-High, High-Low, Low-High Analysis



Categorical analysis. Patients were divided into 4 categorical groups described in the Methods. **(A)** The lowest primary event rate occurred in the Low-Low group; the highest primary event rate occurred in the High-High group; the High-Low and Low-High groups had intermediate primary event rates. **(B)** Hazard ratio (HR) and 95% confidence intervals for each category, with High-High serving as a reference.

Additional data supporting the third prentice criteria:

As shown in *Table 6*, baseline NT-proBNP levels and change from baseline in post-baseline NT-proBNP are significantly associated with the risk of clinical events in both paediatric and adult HF patients.

In adults with HFrEF, a doubling of NT-proBNP levels at baseline or at post-baseline were both associated with a 1.6-fold increase in the risk of clinical events (composite endpoint of CV death/HF hospitalization).

The results were similar for the subpopulation of adults with HFrEF with DCM, where a doubling of NT-proBNP levels at baseline or post-baseline was associated, respectively, with a 1.6-fold and 1.5-fold increase in the risk of clinical events.

The association between NT-proBNP and risk of clinical events was similarly observed in paediatric patients: in study B2319, a doubling of NT-proBNP levels at baseline or post-baseline was associated, respectively, with a 1.8-fold and 2.1-fold increase of the risk of Category 1 or 2 events (*Table 6*). The applicant also performed sensitivity analyses that demonstrated that these analyses were not driven by outliers, supporting the robustness of the data. Results from study B2314 and study B2319 show a very similar association between the NT-proBNP level and changes in NT-proBNP to the risk of clinical outcomes events, including CV death and HF hospitalization in adult HFrEF patients with DCM and paediatric HF patients with LVSD. This supports the equal predictive value of NT-proBNP across the 2 populations

Table 6. Association between NT-proBNP and clinical outcomes in paediatric and adult HF (Full Analysis Set (1))

	Baseline log_2 (NT-proBNP)		Change from baseline log_2 (NT-proBNP)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Study B2314				
adult HFrEF (N=2080)	1.64 (1.52,1.77)	<0.0001	1.59 (1.44,1.75)	<0.0001
adult HFrEF with DCM (N=405)	1.61 (1.32,1.96)	<0.0001	1.49 (1.19,1.85)	0.0004
Study B2319				
pediatric HF (N=375)	1.79 (1.55, 2.06)	<0.0001	2.09 (1.52, 2.87)	<0.0001

(1) For Study B2314, it includes patients in the Biomarker subpopulation and having non missing NT-proBNP at baseline.
Study B2314: time to first event of CV death or HF hospitalization
Study B2319: time to first Category 1 or Category 2 event
Source: [Study B2319-Table 14.2-3.1.2.post.01], [SCE Appendix 1-Table 14.2-3.25.1.post.02a1, Table 14.2-3.25.1.post.02a1.sub]

The robustness of these analyses was improved by also performing analyses using slope rather than change from baseline. These analyses include an additional Cox's proportional hazards analysis with an average slope of available changes from baseline in log2(NT-proBNP), i.e., changes in log2(NT-proBNP) divided by time interval in a year as a covariate, and a Cox's proportional hazards analysis with slopes of log2(NT-proBNP), again, changes divided by the time interval in year, as a time-dependent covariate. Both analyses showed similar strong positive associations ($p<0.01$) between the hazards for Category 1 and/or Category 2 events and the slope of log2(NT-proBNP); see Table 7 and Table 8.

Table 7 Associations between time to first Category 1 or 2 events and the average slope of log2(NT-proBNP) and baseline log2(NT-proBNP) in PANORAMA-HF

	LCZ696 N=187	Enalapril N=188	Baseline log_2(NT-proBNP)		Average slope of log_2(NT-proBNP)	
Endpoint	n (%)	n (%)	HR (95%CI)	p-value	HR (95%CI)	p-value
Category 1 or 2	34 (18.2)	33 (17.6)	1.83 (1.58,2.12)	<0.0001	1.14 (1.07,1.21)	<0.0001
Category 1	13 (7.0)	20 (10.6)	1.71 (1.40,2.08)	<0.0001	1.13 (1.03,1.23)	0.0073
Category 2	31 (16.6)	27 (14.4)	1.85 (1.58,2.17)	<0.0001	1.16 (1.08,1.24)	<0.0001

Missing NT-proBNP at baseline is imputed within each treatment arm, gender and modified age group, discontinuation is not treated as event. CI = confidence interval.
n (%) is the number and percentage of patients with at least one event.
The adjusted hazard ratio and the p-values are based on a Cox proportional hazard model, stratified by modified age group and NYHA/ROSS class group with treatment included as a fixed-effect factor, baseline log_2(NT-proBNP) and average slope of available changes from baseline in log_2(NT-proBNP), i.e., changes divided by time interval, in year as covariates.
For USM-impacted patients, the on treatment assessments are included.
Source: [120D Responses-Table 14.2-3.1.2.haq.10]

Table 8 Associations between time to first Category 1 or 2 events and time-dependent slope of log2(NT-proBNP) and baseline log2(NT-proBNP) in PANORAMA-HF

	LCZ696 N=187	Enalapril N=188	Baseline log_2(NT-proBNP)		Slope of log_2(NT-proBNP)	
Endpoint	n (%)	n (%)	HR (95%CI)	p-value	HR (95%CI)	p-value
Category 1 or 2	34 (18.2)	33 (17.6)	1.81 (1.57,2.09)	<0.0001	1.13 (1.07,1.20)	<0.0001
Category 1	13 (7.0)	20 (10.6)	1.73 (1.42,2.10)	<0.0001	1.13 (1.05,1.21)	0.0006
Category 2	31 (16.6)	27 (14.4)	1.84 (1.58,2.16)	<0.0001	1.16 (1.09,1.24)	<0.0001

Missing NT-proBNP at baseline is imputed within each treatment arm, gender and modified age group, discontinuation is not treated as event. CI = confidence interval.

n (%) is the number and percentage of patients with at least one event.

The adjusted hazard ratio and the p-values are based on a Cox proportional hazard model, stratified by modified age group and NYHA/ROSS class group with treatment included as a fixed-effect factor and baseline log_2(NT-proBNP) as covariate and change from baseline in log_2(NT-proBNP) divided by time interval in year as time-dependent covariate.

For USM-impacted patients, the on treatment assessments are included.

Source: [120D Response Appendix-Table 14.2-3.1.2.haq.05]

Prentice criteria 4: The effect of treatment on true clinical endpoint is explained by the biomarker

The majority of the sacubitril/valsartan treatment effect on the time to the first event of CV death or HF hospitalization endpoint is captured or explained by NT-proBNP over time. The proportion of treatment effect explained on top of baseline NT-ProBNP was 85.55%, with the 95% CI (6.35%, 164.76%) excluding zero (*Table 9*).

Change from baseline in NT-proBNP, when adjusted for baseline NT-proBNP and treatment, was significantly associated with the risk of the true clinical endpoint (first event of CV death or HF hospitalization) with an HR of 1.59 (95% CI 1.44 to 1.75) for doubling post-baseline NT-proBNP (vs no change), respectively an HR of 0.825 (95% CI 0.793 to 0.860) for 25% reduction of post-baseline NT-proBNP.

Table 9. Assessment of treatment effect on the composite of cardiovascular death or heart failure hospitalization explained by NT-proBNP over time on top of baseline NT-proBNP – sacubitril/valsartan vs Enalapril (Study B2314).

			Model 1*		**Model 2***		**Proportion (%) of treatment effect explained by log_2 (NT-proBNP) (95% CI)**
Explanatory Variable	**N**	**n**	**HR (95%CI)**	**P-value**	**HR (95% CI)**	**P-value**	
Sacubitril/valsartan	1051	222	0.82 (0.68, 0.98)	0.0279	0.97 (0.81, 1.17)	0.7545	85.55 (6.35, 164.76)
Enalapril	1029	255					
Time-dependent change from baseline in log_2(NT-proBNP)					1.59 (1.44,1.75)	<0.0001	
Baseline log_2(NT-proBNP)			1.49 (1.39, 1.60)	<0.0001	1.64 (1.52,1.77)	<0.0001	

Based on patients in the B2314 FAS, who are in the Biomarker subpopulation and having non missing NT-proBNP at baseline. The analysis is performed using Cox regression.
*Model 1 contains treatment, region, and baseline log_2(NT-proBNP) as explanatory variable and Model 2 contains treatment, region, baseline log_2(NT-proBNP) and time-dependent change from baseline in log_2(NT-proBNP) as explanatory variables.
Proportion of treatment effect explained by NT-proBNP is derived as: 100 x [treatment coefficient (model 1) - treatment coefficient (model 2)] / treatment coefficient (model 1).
Source: [SCE Appendix 1-Table 14.2-3.25.1.post.02a1]

In an analysis of the primary endpoint (cardiovascular death or HF hospitalization) starting a month after randomization, the change of NT-proBNP from baseline to Month 1 was a highly significant predictor of clinical outcomes. *Table 10* demonstrates that the treatment effect of sacubitril/valsartan in study B2314 on clinical outcomes explained by the change in NT-proBNP at Month 1 on top of baseline NT-proBNP is 82.5%.

Table 10. Assessment of treatment effect on the composite of cardiovascular death or heart failure hospitalization explained by NT-proBNP change at month 1 on top of baseline NT-proBNP – sacubitril/valsartan vs Enalapril (Study B2314)

			Model 1*		Model 2*		Proportion (%) o treatment effect explained by log
Explanatory Variable	**N**	**n**	**HR (95%CI)**	**P-value**	**HR (95% CI)**	**P-value**	**(NT-proBNP) (95% CI)**
Sacubitril/valsartan	1007	197	0.81 (0.67, 0.98)	0.0302	0.96 (0.79, 1.18)	0.7169	82.50 (1.26, 163.74)
Enalapril	983	230					
Change from baseline in log_2(NT-proBNP) at Month 1					1.45 (1.29,1.63)	<0.0001	
Baseline log_2(NT-proBNP)			1.49 (1.38,1.60)	<0.0001	1.60 (1.47,1.73)	<0.0001	

Based on patients in the B2314 FAS, who are in the Biomarker subpopulation and having non missing NT-proBN at baseline. The analysis is performed using Cox regression.
*Model 1 contains treatment and region and baseline log2(NT-proBNP) as explanatory variable and Model 2 contains treatment, region, baseline log2(NT-proBNP) and change from baseline to month 1 in log2(NT-proBNP as explanatory variables.
Proportion of treatment effect explained by NT-proBNP is derived as:100 x [treatment coefficient (model 1) - treatment coefficient (model 2)] / treatment coefficient (model 1).
Source: [SCE Appendix 1-Table 14.2-3.25.1.post.09a1]

A sensitivity analysis was performed to assess the robustness of the PTE reported in the original submission using structural equation modelling and counterfactual methods. For this purpose, an Aalen additive hazard model (Lange and Hansen 2011) was performed using the same PARADIGM-HF (B2314) data. The outcome variable is the time to the first event of CV death or HF hospitalization, the mediator variable is the change from baseline to month one in log_2(NT-proBNP), and the exposure variable is the indicator of treatment (sacubitril/valsartan vs. enalapril). *Table 11* shows the percent contribution of the natural indirect effect from NT-proBNP relative change to the total effect: 81.4% (CI:24.7% to 509.3%), which is very close to the result of 82.5% (CI:1.26% to 164%) obtained with the "change in coefficients" method described above.

Table 11 Assessment of treatment effect on the first primary endpoint (cardiovascular death or heart failure hospitalization) captured or explained by change from baseline in log2(NT-proBNP) at month 1 on top of baseline log2(NT-proBNP) for LCZ696 vs Enalapril with PARADIGM-HF biomarker subset data

Treatment	DE (95%CI) (10^{-5})	IE (95%CI) (10^{-5})	TE (95%CI) (10^{-5})	IE/TE (%) (95%CI)
ENA->LCZ	−0.921 (−5.732, 4.059)	−4.033 (−5.668, −2.618)	−4.955 (−9.508, −0.232)	81.404 (24.672, 509.331)
			Aalen estimate (SE) (10^{-5})	
baseline log_2(NT-proBNP)			12.685 (1.346)	
change from baseline in log_2(NT-proBNP)			9.089 (1.585)	
Treatment: LCZ			−0.921 (2.681)	
			Regression model for mediator: estimate (SE)	
Treatment: LCZ			−0.444 (0.040)	

DE=Direct Effect, IE=Indirect Effect, TE=Total Effect.
Includes patients in the Biomarker subpopulation having non missing NT-proBNP at baseline and time to composite event ≥ 30 days from randomization.
The confidence interval for DE, IE, TE and IE/TE is calculated based on non-parametric bootstrap.
log is taken at base 2.
ENA group is the reference treatment group, ENA->LCZ refers to the treatment group change from ENA to LCZ, the estimate for reference treatment group is 0
The regression model of log2(chg(NT-proBNP)) on treatment group was adjusted for region and baseline log2(NT-proBNP).
The Aalen additive hazard Model includes log2(chg(NT-proBNP)) , region, baseline log2(NT-proBNP) and treatment group.
Source: [120D Response Appendix-Table 14.2-3.1.2.haq.04]

The assessment of the utility of NT-proBNP as a predictive marker of clinical outcome response with sacubitril/valsartan was repeated for various subgroups of HF aetiology in study B2314 to explore the consistency of the relationship across these subgroups and quantify the amount of treatment effect explained by NT-proBNP over time on top of baseline. In summary, following sacubitril/valsartan treatment, the relationship between NT-proBNP changes and clinical outcome, including the predictive value of NT-proBNP changes on outcomes, appears consistent across various aetiology subgroups. It is noted that due to reduced sample sizes, power becomes small and the focus should be on directional consistency rather than statistical significance. Results are summarized in *Table 12*.

Importantly, neutralization of the treatment effect for sacubitril/valsartan is observed after accounting for NT-proBNP change over time following treatment administration (HR=0.97, 95% CI: 0.81, 1.17, p=0.7545); All patients, Model 2) Also of note, in the DCM subgroup, the % change in NT-proBNP at Month 1 for sacubitril/valsartan vs enalapril was 38%. These analyses show that the biomarker largely explains the sacubitril/valsartan treatment effect on clinical outcome, supporting the 4th Prentice criteria. Taken together, these data support the relevance and appropriateness of NT-proBNP as a bridging biomarker for the extrapolation of efficacy benefits with sacubitril/valsartan between adults with HFrEF due to DCM and paediatric HF patients with LVSD.

The following sections focus on comparing the available data on NT-proBNP from study B2314 and study B2319 in support of extrapolating the efficacy benefits to a DCM population.

Table 12. Assessment of treatment effect on the composite of cardiovascular death or heart failure hospitalization explained by NT-proBNP over time on top of baseline NT-proBNP - sacubitril/valsartan vs enalapril, by aetiology subgroup (Study B2314)

Population	N n	Model 1 HR for treatment	Model 2 HR for treatment	Proportion (%) explained	NT-proBNP % change Month 1	NT-proBNP % change Month 8	HR for doubling post-baseline NT-proBNP
All patients	2,080 222:255	0.82 (0.68, 0.98)	0.97 (0.81, 1.17)	86 (6, 165)	-26 (-30, -22)	-25 (-30, -19)	1.59 (1.44, 1.75)
Non-Ischemic	745 61:73	0.78 (0.55, 1.09)	1.01 (0.71, 1.43)	105 (-37, 246)	-31 (-37, -25)	-33 (-42, -23)	1.76 (1.49, 2.09)
Ischemic	1,335 161:182	0.84 (0.68, 1.04)	0.96 (0.77, 1.19)	74 (-24, 172)	-23 (-28, -18)	-20 (-26, -14)	1.50 (1.33, 1.69)
DCM	**405 32:41**	**0.68 (0.43, 1.08)**	**0.91 (0.56, 1.48)**	**75 (-22, 173)**	**-38 (-45, -29)**	**-39 (-50, -25)**	**1.49 (1.19, 1.85)**
Non-DCM	1,675 190:214	0.86 (0.70, 1.04)	0.99 (0.81, 1.21)	94 (-29, 216)	-23 (-27, -18)	-21 (-27, -15)	1.62 (1.46, 1.81)
DCM ≤ median age (64 years)	**201 17:22**	**0.62 (0.33, 1.18)**	**0.96 (0.49, 1.87)**	**91 (-34, 217)**	**-41 (-52, -27)**	**-46 (-61, -25)**	**1.67 (1.26, 2.20)**
DCM > median age (64 years)	204 15:19	0.73 (0.37, 1.46)	0.83 (0.40, 1.73)	41 (-84, 166)	-35 (-43, -24)	-31 (-45, -14)	1.22 (0.84, 1.78)

N = number of patients, n = number of events, sacubitril/valsartan : enalapril. Numbers in parentheses are 95% confidence intervals
Based on patients in the B2314 FAS, who are in the Biomarker subpopulation and having non missing NT-proBNP at baseline. The analysis is performed using Cox regression.
Model 1 contains baseline log2(NT-proBNP), treatment and region as explanatory variable and Model 2 contains treatment, region, baseline log2(NT-proBNP) and time-dependent change from baseline in log2(NT-proBNP) as explanatory variables.
Proportion of treatment effect explained by NT-proBNP is derived as: 100 x [treatment coefficient (model 1) - treatment coefficient (model 2)] / treatment coefficient (model 1).
Source: [SCE Appendix 1-Table 14.2-3.25.1.post.02a1, Table 14.2-3.25.1.post.02a1.sub]

2.6.8.1.5. Summaries of the extrapolation plan

In summary, the applicant has demonstrated disease similarity between paediatric HF due to systemic LVSD and adult HFrEF with DCM. The applicant has demonstrated similar drug exposure at the target dose in both paediatric and adult populations. And the applicant has demonstrated that in both adult and paediatric populations, NT-proBNP demonstrates a large and comparable decrease during sacubitril/valsartan treatment. Using the Prentice criteria, the applicant has shown data supporting the use of NT-proBNP as a biomarker for bridging data from adult to paediatric patients.

To this end, the results demonstrate that sacubitril/valsartan treatment decreases NT-proBNP levels, and this reduction reliably predicts clinical benefits in both adult and paediatric HF patients. Based on the similar NT-proBNP reductions, similar exposure-response and similar associations with favourable clinical response in both paediatric and adult HF populations, the paediatric population is expected to experience the same benefits of sacubitril/valsartan as observed in adults.

Large decreases in NT-proBNP were observed in both treatment groups in study B2319. While the treatment difference between sacubitril/valsartan to enalapril in NT-proBNP change from baseline in study B2319 did not replicate what was observed in study B2314, the magnitude of change from baseline within the sacubitril/valsartan arm was similar to what was observed in study B2314 in adult HFrEF patient with DCM (*Table 13*). The similar large reduction in NT-proBNP from baseline, in the context of its established clinical relevance in both populations, provides a reasonable basis to extrapolate and infer clinical benefits in paediatric HF patients with LVSD.

Table 13. Change from baseline in NT-proBNP in adult and paediatric HF

	LCZ69		Enalapril		Comparison (LCZ696/ Enalapril)	
Visit	**n**	**Ratio to BL (95% CI)**	**n**	**Ratio to BL (95% CI)**	**Ratio (95% CI)**	**p-value**
Pediatric HF with LVSD (N=375)						
Week 4	81	0.60 (0.53,0.68)	76	0.82 (0.72, 0.93)	0.73 (0.61, 0.87)	0.0007
Week 12	159	0.50 (0.44,0.57)	155	0.55 (0.48,0.63)	0.91 (0.76,1.10)	0.3238
Week 52	144	0.35 (0.29,0.42)	133	0.38 (0.31,0.47)	0.91 (0.69,1.20)	0.5016
Adult HFrEF with DCM (N=405)						
Month 1	196	0.57 (0.52,0.62)	188	0.92 (0.84,1.00)	0.62 (0.55,0.71)	<0.0001
Month 8	178	0.48 (0.42,0.56)	167	0.79 (0.68,0.91)	0.61 (0.50,0.75)	<0.0001

Source: [SCE Appendix 1-Table 14.2-3.25.1.post.02a1, Table 14.2-3.25.1.post.02a1.sub], [Study B2319-Table 14.2-8.3]

2.6.8.2. Dose response studies

No specific dose-response studies were performed. Part 1 of study B2319 was used for dose-finding and is detailed below.

The doses for study B2319 part 2 were based on results from B2319 part 1. The paediatric dose selection for Part 2 of Study B2319 was based on the evaluation of safety, PK and PD response from Part 1 in children and adolescents following administration of single doses of sacubitril/valsartan: 0.8 mg/kg and 3.1 mg/kg for patients 1 year of age and above, and 0.4 mg/kg and 1.6 mg/kg for patients 1 month to <1 year old. The objective was to select a dose for Part 2 that provided similar exposures of sacubitril and valsartan to that observed in adult HF patients and that also maximized neprilysin inhibition. The PD effect of neprilysin inhibition was assessed through urine and plasma biomarkers.

Selection of doses for Study B2319 Part 1

The starting dose of sacubitril/valsartan of 0.8 mg/kg corresponds to the sacubitril/valsartan 50 mg dose for adults with a body weight of 65 kg. It delivers valsartan exposure equivalent to 0.6 mg/kg using valsartan formulation, which is below the starting dose for valsartan in paediatric hypertension (1.3 mg/kg). The target sacubitril/valsartan dose of 3.1 mg/kg corresponds to the sacubitril/valsartan 200 mg dose in adults of 65 kg. In adult HF patients, no significant impact of body weight on the PK of sacubitril/valsartan analytes was observed over a range of 41.5-157.3 kg; therefore, paediatric patients in this weight range, exposure was expected to be similar to that observed in adult HF patients. Furthermore, simulations using physiological-based PK models and allometric scaling techniques indicated similar exposure between paediatric HF patients >1 year of age and adult HF patients at an equivalent dose of sacubitril/valsartan.

The single doses for children aged 1 month to < 1 year (Age Group 3) were reduced by 50% to 0.4 mg/kg and 1.6 mg/kg, taking into consideration the potential impact of developing capacity of drug disposition in this age group on drug exposure.

Selection of doses for Study B2319 Part 2

Results from Part 1 of the study showed that the PK of sacubitril/valsartan following single-dose administration in Age Groups 1 and 2 are similar to the adult HF population based on approximately dose-proportional exposure increase, observed sacubitril T1/2, apparent total body plasma clearance for both sacubitril and valsartan, and drug exposure. Accordingly, a target dose of 3.1 mg/kg sacubitril/valsartan was selected for patients in Age Groups 1 and 2 with a maximum dose of 200 mg.

For Age Group 3 (1 month to <1 year), the mean exposure (AUC changes) of sacubitrilat and valsartan following a 1.6 mg/kg single dose were, respectively, 61% and 39% lower than the steady-state exposure in adults following sacubitril/valsartan 200 mg bid. The target dose for this age group was increased from the originally planned 1.6 mg/kg to 2.3 mg/kg to better match the exposures in adults and older paediatric patients.

2.6.8.3. Main study

Part 2 of study B2319 (PANORAMA-HF) is the pivotal source of data to support the proposed indication.

Study B2319 is a Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, 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 paediatric patients from 1 month to < 18 years of age with HF due to systemic left ventricle systolic dysfunction

Methods

Study Participants

Key inclusion criteria:
Patients eligible for inclusion in this study (Part 1 and Part 2) must fulfil all of the following criteria:
1. Written informed consent by parent(s)/legal guardian(s) for the paediatric patient must be obtained before any study-specific assessment is performed. A consent or assent may also be required for some patients depending upon their age and local requirements
2. Male or female, inpatient or outpatient, 1 month to < 18 years of age
3. Chronic heart failure resulting from left ventricular systolic dysfunction and receiving chronic HF therapy (if not newly diagnosed)
4. NYHA classification II-IV (older children: 6 to <18 years old) or Ross CHF classification II-IV (younger children: < 6 years old) any time prior to screening
5. Systemic left ventricular ejection fraction (EF) ≤ 45% or fractional shortening ≤22.5% (assessed by most recent echocardiography, MRI, MUGA or left ventricular angiogram). For Part 2, this assessment must be within 1 month from screening.[Note: The study will target enrollment of approximately 80% of patients with a systemic left ventricular ejection fraction (EF) ≤ 40% or fractional shortening ≤20% for Part 2 only].
6. Biventricular physiology with systemic left ventricle
7. For Part 1 PK/PD, patients must be treated with an ACEI (Angiotensin-converting enzyme inhibitor) or ARB (Angiotensin receptor blockers) prior to screening. For Part 1 PK/PD, patients in Group 1 and 2 must be currently treated with a daily dose equivalent of at least enalapril 0.2 mg/kg prior to the LCZ696 3.1 mg/kg single dose assessment. For Part 1 PK/PD, patients in Group 3 must be currently treated with a daily dose equivalent of at least enalapril 0.1 mg/kg.

Key Exclusion criteria:
1. Patients with single ventricle or systemic right ventricle
2. Patients listed for heart transplantation as United Network for Organ Sharing (UNOS) status 1A or hospitalized waiting for transplant while on inotropes or with ventricular assist device at time of entry into the study
3. Sustained or symptomatic dysrhythmias uncontrolled with drug or device therapy
4. For Part 2 only, patients that have had cardiovascular surgery or percutaneous intervention to palliate or correct congenital cardiovascular malformations within 3 months of the screening visit. Patients anticipated to undergo corrective heart surgery during the 12 months after entry into Part 2.
5. Patients with unoperated obstructive or severe regurgitant valvular (aortic, pulmonary, or tricuspid) disease, or significant systemic ventricular outflow obstruction or aortic arch obstruction
6. Patients with restrictive or hypertrophic cardiomyopathy

7. For Part 2 only, active myocarditis (diagnosed with presumed or acute myocarditis within 3 months of enrollment)
8. Symptomatic hypotension or blood pressures (BPs) below the calculated 5th percentile systolic BP (SBP) for age at screening visit and as described in Appendix 4
9. Renal vascular hypertension (including renal artery stenosis)
10. Severe pulmonary hypertension (defined by pulmonary vascular resistance (PVR) index >6 Wood units-m2) unresponsive to vasodilator agents (such as oxygen, nitroprusside or nitric oxide). Note measurement of PVR is not a requirement for study eligibility.
11. History or current clinical evidence of moderate-to severe obstructive pulmonary disease or reactive airway diseases (e.g. asthma)
12. Serum potassium >5.3 mmol/L at Visit 1 or at Visit 301
13. Patients with significant renal (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age,); hepatic (serum aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal); gastrointestinal or biliary disorders (that could impair absorption, metabolism, or excretion of orally administered medications)
14. Concurrent terminal illness or other severe disease (e.g. acute lymphocytic leukemia) or other significant laboratory values that, in the opinion of the Investigator, precludes study participation or survival
15. Patients with history of angioedema
16. Patients with allergy or hypersensitivity to ACEI/ARB

Treatments

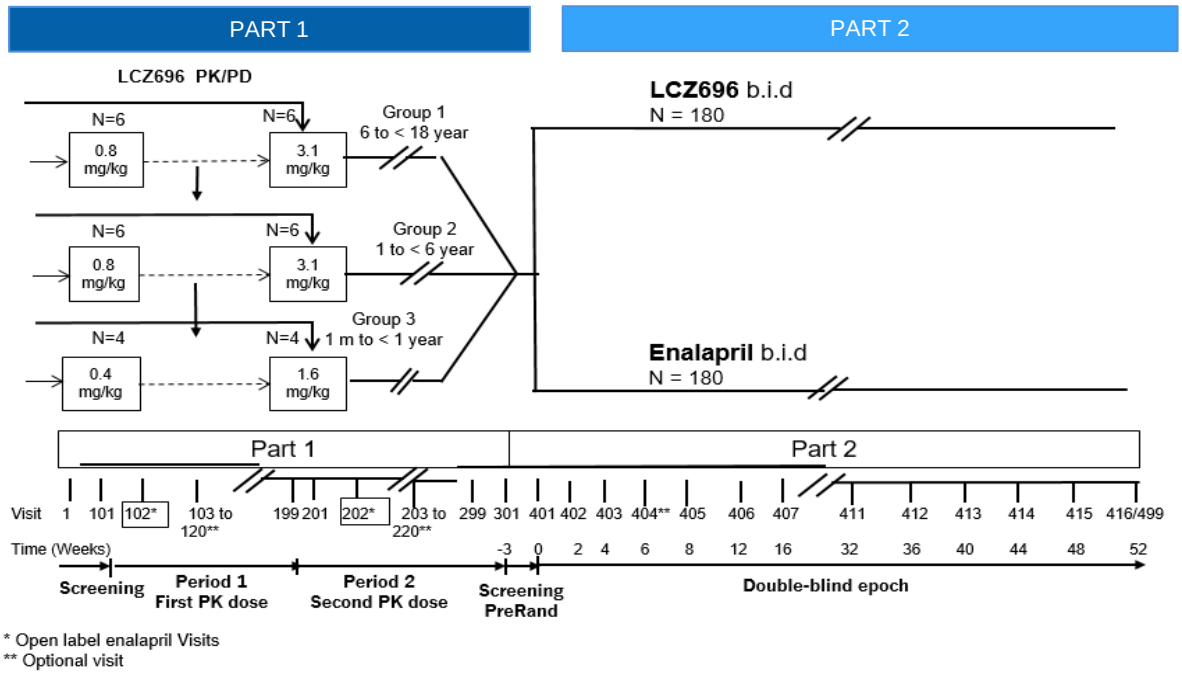
This study uses a seamless design which consists of two parts (Figure 10).
Part 1: This was an open-label study to evaluate the safety, tolerability, PK, and PD of a low and a high dose strength of sacubitril/valsartan in the following age groups: Age Group 1: 6 to <18 years; Age Group 2: 1 to <6 years; and Age Group 3: 1 month to <1 year. To ensure that patients are enrolled in both high and low end of the 6 to < 18 years of age group, approximately 50% patients will be enrolled who are 6 to 11 years of age in Group 1.

Part 2: This was a randomized, double blind, parallel-group, active controlled, 52-week study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in paediatric HF patients (1 month to < 18 years). A screening epoch of up to 3 weeks will be used to assess eligibility. Roughly 360 eligible patients will be randomized to one of the two treatment arms (LCZ696 vs enalapril) and continue treatment for 52 weeks duration.

Rationale for treatment duration
The rationale for the 52-week treatment duration is based on the positive LCZ696 treatment effect for relevant clinical endpoints that were evident as early as 4 to 6 months treatment duration in the LCZ696 adult PARADIGM-HF study. The 52-week treatment duration will also increase the number of clinical events in Categories 1 and 2.

- There was a sustained separation of Kaplan-Meier survival curves as early as 6 months for the primary composite endpoint consisting of cardiovascular death and time to first HF hospitalization.
- At four months compared to baseline, there was less worsening of HF symptoms and physical limitations compared to enalapril as measured by the KCCQ (p=0.0423).
- At four months, there were more improved patients with the Global Assessment, and fewer worsened patients for both NYHA and the Global Assessment for the LCZ696 group compared to the enalapril group (NYHA, p=0.0028; Global Assessment, p=0.0039).

Figure 10. B2319 study design



Enalapril is considered the standard of care in the treatment of chronic HF in most geographic areas (Stidham et al 2021). Enalapril doses ranging from 0.1 to 0.5 mg/kg/day are used in the treatment of paediatric HF (Das 2018). The enalapril study medication was available in two formulations: tablets or liquid formulation. The liquid formulation was not a commercially available formulation, but instead a compounded formulation, which was made using 10 mg enalapril tablets. The concentration of the liquid enalapril formulation was 1 mg/ml (compounded using 20 tablets in 200ml). The dose of 0.4 mg/kg/day was the target dose in the "Enalapril in infants with single ventricle" study published (Hsu et al. 2010), and is the target dose in the ongoing "The labelling of enalapril from neonates up to adolescents", or LENA initiative sponsored by the European Commission (http://www.lena-med.eu). In addition, enalapril has a twice-daily dosing regimen similar to sacubitril/valsartan.

Patients were randomized in a 1:1 ratio to one of the following double-blind treatments:
Sacubitril/valsartan: Projected target dose was 3.1 mg/kg bid for patients 1 year of age and older 3.125 mg granules, 50 mg tablets, 100 mg tablets, 200 mg tablets or liquid formulation. For patients less than 1 year of age, the target dose was 2.3 mg/kg bid. Patients who turned 1 year old during the study could be further up-titrated to a dose of 3.1 mg/kg bid. The study used three different formulations, e.g. film-coated tablets (50 mg, 100 mg, and 200 mg), film-coated granules (3.125 mg), and extemporaneous suspension prepared by using 100 mg film-coated tablets using appropriate vehicles.
Enalapril: Target dose was 0.2 mg/kg bid for patients 1 year of age and older. For patients less than 1 year of age, the target dose was 0.15 mg/kg bid. Patients who turned 1 year old during the study could be further up-titrated to a dose of 0.2 mg/kg bid. For this, the study uses 2.5 mg, 5 mg and 10 mg tablets and liquid formulation.

Participants in age group 1 and 2 will start on a dose of 0.8 mg/kg or 1.6 mg/kg (dose level 1 or 2, depending on prior usage of ACEi or ARB and corresponding dose). Study drug is titrated every two weeks with a target dose of 3.1 mg/kg (dose level 4).
Participants in age group 3 will start on a dose of 0.8 mg/kg or 1.2 mg/kg (dose level 1 or 2, depending on prior usage of ACEi or ARB and corresponding dose). Study drug is titrated every two weeks with a target dose of 2.3 mg/kg (dose level 4).
A summarized schedule is found in Table 14 and Table 15, the adult formulation is used by patients ≥ 57 kg.

Table 14. Part 2 (Efficacy): Study drug dose levels for double-blind enalapril and LCZ696 for age groups 1 and 2

Dose levels for pediatric formulation	**Enalapril dose**	**LCZ696 dose †**
Dose level 1	0.05 mg/kg bid.	0.8 mg/kg bid.
Dose level 2	0.1 mg/kg bid.	1.6 mg/kg bid.
Dose level 3	0.15 mg/kg bid.	2.3 mg/kg bid.
Dose level 4	0.2 mg/kg bid.	3.1 mg/kg bid.
Dose levels for adult formulation	**Enalapril dose**	**LCZ696 dose †**
Dose level 1	2.5 mg bid.	50 mg bid.
Dose level 2	5 mg bid.	100 mg bid.
Dose level 3	7.5 mg bid.	150 mg bid.
Dose level 4	10 mg bid.	200 mg bid.

†Note: LCZ696 target dose (dose level 4) and other dose levels shown in table are based on target dose of LCZ696 3.1 mg/kg bid. LCZ696 target dose has been verified by Part 1 PK/PD.

Table 15. Part 2(Efficacy): Study drug dose levels for double-blind enalapril and LCZ696 for age group 3

Dose levels for pediatric formulation	**Enalapril dose**	**LCZ696 dose †**
Dose level 1x	0.05 mg/kg bid.	0.8 mg/kg bid.
Dose level 2x	0.075 mg/kg bid.	1.2 mg/kg bid.
Dose level 3x	0.1 mg/kg bid.	1.6 mg/kg bid.
Dose level 4x	0.15 mg/kg bid.	2.3 mg/kg bid.

†Note: LCZ696 target dose 2.3 mg/kg (dose level 4x) is based on Part 1 PK/PD Safety data. The other dose levels for LCZ696 shown in table are based on target dose of LCZ696 2.3 mg/kg bid and Part 1 PK/PD Safety data. For Group 3 patients who turn 1 year old during the study, consideration should be given to up-titrate to a dose of 3.1 mg/kg bid (Dose Level 5x). See Appendix 14 for details.

All paediatric formulations of study medication (sacubitril/valsartan granules or liquid, enalapril liquid) were made available to all age groups. The adult tablet formulations of sacubitril/valsartan and enalapril were available to patients based on the patient's dose level, weight and ability to swallow adult tablets.

The proportion of patients with at least one down titration was low and similar in both sacubitril/valsartan and enalapril groups (10.16% and 9.04%, respectively). The most common reason for down titration was AE (8.02% and 6.91%, respectively).

Outcomes/endpoints

The objectives/endpoint of part 2 study B2319 are presented in Table 16. The Global Rank endpoint used in study B2319 was a composite endpoint integrating clinical outcomes, patients' function, symptoms and quality of life in a hierarchical way from worst to best. This approach leverages a broader scope of data from the trial compared to trials in adult HF to compensate for the challenges of powering a trial in paediatric HF.

Table 16. Objectives and related endpoints (generated by assessor)

OBJECTIVE	Endpoint
Primary	
To determine whether LCZ696 was superior to enalapril for the treatment of HF as assessed using a Global Rank endpoint in paediatric HF patients	Global Rank endpoint through 52 weeks of treatment based on 5 categories hierarchically ranking worst to best outcome: Category 1: Death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support at end of study. Ranking by time-to-first event of above. All Category 1 events were considered equal. ● Category 2: worsening HF, defined by signs and symptoms that require an intensification of HF therapy, ranking by hospitalization with ICU stay, without ICU stay, or without hospitalization. Within Category 2, patients were ranked first by worst worsening HF subcategory (ICU, hospitalization, none), and then by the number of events within each subcategory. Further ranking by time to first event in the worst subcategory. ● Category 3: worsened at week 52; worse NYHA/Ross or worse PGIS, and further ranking by PedsQL physical functioning domain ● Category 4: unchanged at week 52; ranking based on baseline NYHA/Ross and PGIS, and further ranking by PedsQL physical functioning domain ● Category 5: improved at week 52, as defined by improved NYHA/Ross or improved PGIS and the other at least is not worsened, and further ranking by PedsQL physical functioning domain
Secondary	
To determine whether LCZ696 was superior to enalapril in delaying time to first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF)	Time to first occurrence of Category 1 or Category 2 event through 52 weeks of treatment
To determine whether LCZ696 was superior to enalapril for improving NYHA/Ross functional class	NYHA/Ross functional class change from baseline through 52 weeks of treatment
To determine whether LCZ696 was superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score	PGIS score change from baseline through 52 weeks of treatment
To characterize the population PK of LCZ696 exposure in paediatric patients with HF, including an assessment of steady-state sparse PK data in a subset of Group 2 patients.	Population PK LCZ696 Steady-state Sparse PK data

To assess the safety and tolerability of LCZ696 compared to enalapril in paediatric patients with HF	Safety and tolerability through 52 weeks of treatment
Exploratory	
To determine whether LCZ696 was superior to enalapril as assessed using the PedsQL	PedsQL score change from baseline through 52 weeks of treatment
To compare LCZ696 to enalapril on change in NT-proBNP from baseline (randomization) to 4 and 12 weeks, and from baseline to end of study (52 weeks)	NT-proBNP change from baseline through 4, 12 and 52 weeks treatment
To determine whether LCZ696 was superior to enalapril for improving Patient Global Impression of Change (PGIC) score	PGIC score through 52 weeks of treatment
To assess whether LCZ696 was superior to enalapril in reducing the rate of Total (first and recurrent) Category 1 and 2 events (e.g. death, worsening HF)	Time to recurrent events of Category 1 and Category 2 through 52 weeks of treatment

Sample size

The assumed underlying probabilities for each category of the primary endpoint in Part 2 (Efficacy) were acquired using data from the Carvedilol Paediatric HF study data. Sample size calculations for the ordered categorical test (ordered categorical Mann-Whitney/Wilcoxon rank sum test) were determined using nQuery. A sample size of 180 patients per group (360 patients total) will provide at least 80% power for a test of the primary endpoint. The actual sample size turned out to be 375 (N=187 sacubitril/valsartan; N=188 enalapril).

Randomisation and blinding (masking)

At Visit 401, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. Patients will be stratified by age group (Age Groups 1, 2 and 3) and NYHA/Ross class group (Class I/II, Class III/IV) at randomization to ensure a balanced distribution of treatment allocation within each age strata. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller. The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

Patients, investigators and staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock.

Statistical methods

The primary endpoint comparing the distributions for patients receiving LCZ696 and patients receiving enalapril will be assessed using a stratified Wilcoxon rank-sum analysis (Kawaguchi 2011), stratifying by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years) and NYHA/Ross class group (Class I/II; Class III/IV). The overall significance level (Type 1 error) of 0.05 (2-sided) will be used. In addition, the proportion of patients falling into each of the 5 ordered categories of the primary endpoint will be presented by treatment group. These proportions will be provided both hierarchically (only the worst category counted for each patient), as the endpoint is defined, and overall, not accounting for whether a patient also had a worse event. A full analysis set will be used for these analyses.

In addition, the number and percentage of patients in each category will be provided by treatment group for each age group, each modified age group, and for overall.

The time to event endpoints will be analyzed using Cox's proportional hazards model with treatment as a fixed-effect factor stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years). The estimated hazards ratio and the corresponding two-sided confidence interval will be provided

NYHA/Ross class and PGIS will be compared for LCZ696 and enalapril at week 52, respectively. Change from baseline at week 52 for these assessments will be analyzed based on a proportional cumulative odds model, stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years) in which treatment will be included as fixed-effect factors and baseline value as a covariate. The treatment comparison between LCZ696 and enalapril for the secondary objective is to be made at week 52. This model assumes that the treatment effect sizes across measurement categories are the same. The effect size estimates and their 95% confidence intervals will also be provided.

Based on the full analysis set, the PedsQL assessment will be compared for LCZ696 and enalapril after 52 weeks of double-blind treatment. PedsQL value changed from baseline will be analyzed based on a repeated measures ANCOVA model stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years). Treatment, visit (Week 4, 12, 24, 36, and 52 visits), and treatment-by-visit interaction will be included as fixed-effect factors and baseline value as a covariate, with a common unstructured covariance matrix among visits for each treatment group. The estimated between and within treatment effects with the associated two-sided 95% confidence intervals at week 52 will be provided.
PGIC value (reflecting changes from baseline) will be analyzed by the same approach as used for PGIS, excluding baseline as a covariate in the model.

NTproBNP in this exploratory analysis will be analyzed on the full analysis set using the same method as other biomarkers. The changes from baseline in log(NTproBNP) will be analyzed using a mixed model for repeated measures (MMRM), in which the response variable will be the changes from baseline in log(NTproBNP); modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years), treatment, visit and treatment-by-visit interaction will be included as fixed-effect factors; baseline log(NTproBNP) and visit-by-baseline interactions will be included as covariates; the within-patient covariance will be modelled using an unstructured covariance matrix (a common matrix for the two treatment groups). Based on the MMRM model, the estimates and the two-sided 95% confidence intervals will be provided for the adjusted geometric means for the ratio to baseline in NTproBNP at Week 12 and Week 52 in each of the two treatment groups (LCZ696 and Enalapril), and for the ratio of the adjusted geometric means (LCZ696 / Enalapril).

Time to recurrent events of Category 1 and Category 2 will be analyzed using the proportional rates model (LWYY, Lin et al. 2000), with treatment as a fixed effect factor, stratified by modified age group (Group 1: 6 to < 18 years; Group 2a: 2 to < 6 years; Group 3a: 1 month to < 2 years). The estimated rate ratio and the corresponding two-sided confidence interval will be provided.

Results

Participant disposition and numbers analyzed

Out of 420 patients that signed written consent, a total of 43 discontinued prior to pre-randomization completion, of which 32 were screen failures. 377 patients were randomized 1:1 to receive sacubitril/valsartan (N=187) or enalapril (N=190) (Table 17). Two patients were mis-randomized (did not receive any study medication) and therefore excluded from the FAS.

The majority of patients in both treatment arms (90% in the sacubitril/valsartan arm and 86% in the enalapril arm) completed the double-blind epoch. The most frequent reason for discontinuation in both arms was death (4% vs 6% in the sacubitril/valsartan vs enalapril arms, respectively).

Table 17. overall patient disposition - double-blind epoch (Randomized Set)

Population: Overall			
Disposition/Reason	**LCZ696 N=187**	**Enalapril N=190**	**Total N=377**
Number of subjects mis-randomized	0	2 (1.05)	2 (0.53)
Full Analysis Set (FAS)	187 (100)	188 (98.95)	375 (99.47)
Completed double-blind epoch	169 (90.37)	164 (86.32)	333 (88.33)
Discontinued double-blind epoch	18 (9.63)	24 (12.63)	42 (11.14)
Primary reason for discontinuing double-blind epoch			
Adverse Event	1 (0.53)	2 (1.05)	3 (0.80)
Death	8 (4.28)	12 (6.32)	20 (5.31)
Lost to follow-up	0	2 (1.05)	2 (0.53)
Technical problems	4 (2.14)	2 (1.05)	6 (1.59)
Technical problems due to USM	3 (1.60)	2 (1.05)	5 (1.33)
Physician decision	0	0	0
Subject/guardian decision	5 (2.67)	6 (3.16)	11 (2.92)

Source: [Study B2319-Table 14.1-1.1.3]

The proportion of patients who completed double-blind treatment was 78.07% in the sacubitril/valsartan arm, and 72.63% in the enalapril arm (Table 18). In both arms, the most frequent reason for discontinuation of study treatment was AE (10.70% vs 11.05% for sacubitril/valsartan vs enalapril, respectively). Twenty patients (10 in each arm) discontinued study treatment following the implementation of the urgent safety measure (USM), described under study conduct section below.

Table 18. study treatment disposition - double-blind epoch (Randomized Set)

Population: Overall			
Disposition/Reason	**LCZ696 N=187**	**Enalapril N=190**	**Total N=377**
Received at least one dose of the study treatment during double-blind	187 (100)	188 (98.95)	375 (99.47)
Completed study treatment for double-blind epoch	146 (78.07)	138 (72.63)	284 (75.33)
Discontinued study treatment during double-blind epoch	41 (21.93)	50 (26.32)	91 (24.14)
Primary reason for discontinuing study treatment during double-blind			
Adverse Event	20 (10.70)	21 (11.05)	41 (10.88)
Death	3 (1.60)	4 (2.11)	7 (1.86)
Technical problems	11 (5.88)	10 (5.26)	21 (5.57)
Technical problems due to USM	10 (5.35)	10 (5.26)	20 (5.31)
Lost to follow-up	0	1 (0.53)	1 (0.27)
Physician decision	4 (2.14)	5 (2.63)	9 (2.39)
Subject/guardian decision	3 (1.60)	9 (4.74)	12 (3.18)

Source: [Study B2319-Table 14.1-1.3]

At Week 6, when all patients should have been up-titrated to dose level 4, 4.8% of patients were on dose level 1, 17.1% in sacubitril/valsartan vs 8.7% in enalapril were on dose level 2, 26.7% in sacubitril/valsartan vs 21.4% in enalapril group were on dose level 3, while 47.6% in sacubitril/valsartan vs 60.2% in enalapril were on dose level 4. By Week 8, 60.8% in sacubitril/valsartan group vs 66.9% in

enalapril group were on target dose level 4. The percentage of patients who reached dose level 4 at least once at any time point was 76.5% (143/187) for sacubitril/valsartan and 81.9% (154/188) for enalapril.

Conduct of the study

Urgent safety measure

An out of specification (OOS) result for an unspecified degradation product (observed: 0.3% vs requirement: ≤ 0.2%) for both enalapril maleate 5 mg and 10 mg, packaged in alu-alu blisters by Novartis for this clinical trial, was observed in representative batches during supportive stability testing. As a result, the assigned shelf-life of 24 months of enalapril 5 mg and 10 mg in alu-alu blisters can no longer be supported for the current batches in use in the study and only a shelf-life of 12 months and 18 months, respectively, is supported. This finding impacts the batches currently in use in the trial of enalapril 5 mg and 10 mg as well as one batch of enalapril 5 mg and 10 mg used earlier in the study. The current clinical trial supply of enalapril 5 mg is beyond the revised supported 12-month shelf-life (expiry date was 31 March 2021). The current supply of enalapril 10 mg has a revised supported expiry date of 18 months, lasting up to 31 October 2021. The finding only relates to enalapril 5 mg and 10 mg in alu-alu blister packs. The placebo of enalapril 5 mg and 10 mg, as well as all LCZ696/placebo and Enalapril/placebo 2.5 mg, are not impacted.

What follows outlines the safety measures that have been implemented for the 31 patients who were ongoing and receiving study medication at the time the USM was initiated. The USM includes the following:

- Investigational medicinal product (IMP) dispensation was blocked.
- All patients who were receiving study medication at the time the USM was initiated had to discontinue study treatment by 31 October 2021 and change to local standard of care, respecting any required washout periods. These patients were to attend an unscheduled visit at the site by 31 October 2021, or as soon as possible thereafter, for safety and efficacy assessments.
- It was requested that all patients return IMP in their possession by 31 October 2021.
- All IMP is to be removed from the sites for destruction per local practices.

For patients who were receiving study medication with an end-of-study visit originally planned for after

14 November 2021, were instructed to come to the study site for an unscheduled visit (or regularly scheduled visit) by 31 October 2021. During this visit, study medication was discontinued, patients were transferred to local standard of care, and additional data was assessed (Lab + clinical data).

These patients were continued to be followed in the trial until the planned end of study visit (week 52 ± 2 weeks).

The early study drug discontinuation affects a maximum of 31 patients who were on-treatment as of 26 October 2021, with a current follow-up between 297 days to 395 days. The total on-treatment follow-up time lost is expected to be <1%. Regarding CRF documentation, the reason for the treatment discontinuation is to be reported on the End of Treatment (EOT) CRF as ‘Technical problems’. If a patient withdraws from study participation after the study drug discontinuation due to the USM and before they have completed 52 weeks (± 2 weeks) of follow-up, the reason for the study phase discontinuation on the EOS CRF, is also be documented as ‘Technical problems’. Every effort is to be made to keep patients in the study until the planned 52-week follow up and to ensure study integrity. While the current statistical analysis plan (SAP) includes off-treatment data after treatment discontinuations in the primary analysis (reflecting a real-world setting), this does not seem appropriate for the study drug discontinuations in the context of this USM. The unforeseen intercurrent

events of the USM leading to study treatment discontinuations are not related to disease progression, are not related to the assigned study treatment and do not reflect a real-world setting. The exposure to the study treatment and study follow-up are reasonably long. Therefore, an on-treatment approach is considered to be more appropriate for the handling of USM-impacted patients in the primary analysis, utilizing the relevant components of the global rank endpoint including Category 1 and 2 status at the time of treatment discontinuation.

Baseline data

Baseline demographic characteristics were balanced between the treatment groups (Table 19). Overall, 48.53% were male, and the most frequent race was white (48.00%), followed by Asian (27.20%) and Black or African American (12.80%).

Age group 1 (6 to <18 years) accounted for 58.67% of all patients, age group 2a (2 to <6 years) for 22.67% of all patients, and age group 3a (1 month to < 2 years) for 18.67% of all patients.

Nine patients (2.40%) were below <1 year of age.

Table 19. Baseline characteristics FAS

Population: Overall			
Characteristic	**LCZ696 N=187**	**Enalapril N=188**	**Total N=375**
Age at randomization (years)			
Mean (SD)	8.00 (5.471)	8.26 (5.718)	8.13 (5.590)
Median (Min – Max)	7.0 (0.5, 17.0)	8.5 (0.1, 18.0)	8.00 (0.1, 18.0)
Age group at randomization – n (%)			
Age group 1: 6 years to < 18 years	109 (58.29)	111 (59.04)	220 (58.67)
12 years to < 18 years	61 (32.62)	68 (36.17)	129 (34.40)
6 years to 11 years	48 (25.67)	43 (22.87)	91 (24.27)
Age group 2a: 2 years to < 6 years	47 (25.13)	38 (20.21)	85 (22.67)
Age group 3a: 1 month to < 2 years	31 (16.58)	39 (20.74)	70 (18.67)
Age group 2: 1 year to < 6 years	73 (39.04)	73 (38.83)	146 (38.93)
Age group 3: 1 month to < 1 year	5 (2.67)	4 (2.13)	9 (2.40)
Sex – n (%)			
Male	89 (47.59)	93 (49.47)	182 (48.53)
Female	98 (52.41)	95 (50.53)	193 (51.47)
Race – n (%)			
White	87 (46.52)	93 (49.47)	180 (48.00)
Black or African American	23 (12.30)	25 (13.30)	48 (12.80)
Asian	57 (30.48)	45 (23.94)	102 (27.20)
American Indian or Alaska Native	3 (1.60)	2 (1.06)	5 (1.33)
Unknown	8 (4.28)	6 (3.19)	14 (3.73)
Other	9 (4.81)	17 (9.04)	26 (6.93)

Source: [Study B2319-Table 14.1-3.1.2]

The paediatric heart failure history was balanced between the treatment groups (Table 20). Consistent with the study requirement, all patients had a history of heart failure due to left ventricular systolic dysfunction (LVSD) and biventricular physiology. The most frequent primary aetiology for heart failure was cardiomyopathy-related (63.47% of patients), and prior heart failure-related hospitalization was reported in 68.53% of patients. The time from diagnosis to randomization was more than a year in 62.67% of patients.

Table 20. Part 2 paediatric heart failure history (Full Analysis Set)

Population: Overall			
Characteristic	**LCZ696 N=187**	**Enalapril N=188**	**Total N=375**
Prior history of heart failure	187 (100)	188 (100)	375 (100)
Primary heart failure etiology			
Ischemic	9 (4.81)	7 (3.72)	16 (4.27)
Myocarditis	20 (10.70)	28 (14.89)	48 (12.80)
Neuromuscular disorder	8 (4.28)	5 (2.66)	13 (3.47)
Acquired/chemotherapy	8 (4.28)	5 (2.66)	13 (3.47)
Left ventricular non-compaction	19 (10.16)	19 (10.11)	38 (10.13)
Mitochondrial disorder	2 (1.07)	0	2 (0.53)
Cardiomyopathy related	116 (62.03)	122 (64.89)	238 (63.47)
Congenital cardiac malformation	21 (11.23)	29 (15.43)	50 (13.33)
Familial/genetic	29 (15.51)	30 (15.96)	59 (15.73)
Inborn error of metabolism	3 (1.60)	1 (0.53)	4 (1.07)
Idiopathic	64 (34.22)	62 (32.98)	126 (33.60)
Other	7 (3.74)	7 (3.72)	14 (3.73)
Time from diagnosis to randomization date			
0 to < 3 months	25 (13.37)	26 (13.83)	51 (13.60)
3 to 12 months	42 (22.46)	46 (24.47)	88 (23.47)
> 1 year	119 (63.64)	116 (61.70)	235 (62.67)
Missing	1 (0.53)	0	1 (0.27)
Hospitalization status at pre-randomization – n (%)			
Inpatient	21 (11.23)	16 (8.51)	37 (9.87)
Outpatient	166 (88.77)	172 (91.49)	338 (90.13)
Prior heart failure hospitalization			
Yes	130 (69.52)	127 (67.55)	257 (68.53)
No	57 (30.48)	61 (32.45)	118 (31.47)
Number of heart failure hospitalizations in the last 12 months prior to screening			
0	52 (27.81)	48 (25.53)	100 (26.67)
1	53 (28.34)	52 (27.66)	105 (28.00)
2	16 (8.56)	17 (9.04)	33 (8.80)
>2	9 (4.81)	10 (5.32)	19 (5.07)
Missing	57 (30.48)	61 (32.45)	118 (31.47)
On a heart transplant list			
Yes, UNOS status 1B, 2 or equivalent	9 (4.81)	5 (2.66)	14 (3.73)
No	178 (95.19)	183 (97.34)	361 (96.27)

Time from diagnosis to randomization date = date of randomization - date of diagnosis + 1 day.
Source:, [Study B2319-Table 14.1-3.3.2, Table 14.1-3.1.2]

Baseline disease characteristics were balanced between the treatment groups (Table 21). The majority of patients (>80%) were NYHA/Ross Class II or higher at baseline (Table 22). Of note, 10 patients were randomized into the wrong NYHA/Ross class group stratum; thus, there is a slight difference between patients' NYHA/Ross class based on baseline status vs based on the randomization stratum.
The mean LVEF was 32.22%, and the mean fractional shortening 16.24%, consistent with systemic LVSD. Baseline NT-proBNP levels were higher in the sacubitril/valsartan group than the enalapril group. Within each age group, baseline disease characteristics were balanced between treatment groups, including NYHA class (age group 1) and Ross class (age groups 2a, and 3a). The baseline NT-proBNP levels were higher in the sacubitril/valsartan group than in the enalapril group across all age groups.

Table 21. Baseline disease characteristics

Population: Overall			
Characteristic	**LCZ696 N=187**	**Enalapril N=188**	**Total N=375**
NYHA/Ross class group at baseline – n (%)			
Class I	25 (13.37)	34 (18.09)	59 (15.73)
Class II	135 (72.19)	125 (66.49)	260 (69.33)
Class III	27 (14.44)	27 (14.36)	54 (14.40)
Class IV	0	2 (1.06)	2 (0.53)
NYHA/Ross class group (randomization stratum) – n (%)			
Class I/Class II	160 (85.56)	161 (85.64)	321 (85.60)
Class III/Class IV	27 (14.44)	27 (14.36)	54 (14.40)
Left ventricular ejection fraction (%) at pre-randomization			
n	186	187	373
Mean (SD)	32.80 (7.424)	31.64 (7.919)	32.22 (7.688)
Median (Min-Max)	35.00 (9.40 - 49.00)	33.00 (6.50 - 48.50)	34.00 (6.50 - 49.00)
Left ventricular shortening fraction (%) at pre-randomization			
n	119	120	239
Mean (SD)	16.21 (3.957)	16.27 (4.390)	16.24 (4.171)
Median (Min-Max)	16.50 (5.40 - 24.20)	16.00 (4.12 - 27.10)	16.20 (4.12 – 27.10)
NT-proBNP (pg/mL)			
n	179	182	361
geomean (95% CI)	879.3 (693.9, 1114.2)	737.4 (586.4, 927.3)	804.64 (682.81, 948.21)
Median (Min – Max)	900.00 (28.00 – 43187.00)	703.00 (12.50 – 25353.00)	783.00 (12.50 – 43187.00)

Source: [Study B2319-Table 14.1-3.1.2, Table 14.2-8.2]

Table 22. NYHA/Ross Class at baseline by age groupings (Full Analysis Set)

	Age group 1		**Age group 2a**		**Age group 3a**	
Parameters	**LCZ696 N=109 n (%)**	**Enalapril N=111 n (%)**	**LCZ696 N=47 n (%)**	**Enalapril N=38 n (%)**	**LCZ696 N=31 n (%)**	**Enalapril N=39 n (%)**
NYHA/Ross class at baseline – n (%)						
Class I	13 (11.93)	11 (9.91)	9 (19.15)	11 (28.95)	3 (9.68)	12 (30.77)
Class II	78 (71.56)	81 (72.97)	33 (70.21)	25 (65.79)	24 (77.42)	19 (48.72)
Class III	18 (16.51)	18 (16.22)	5 (10.64)	2 (5.26)	4 (12.90)	7 (17.95)
Class IV	0	1 (0.90)	0	0	0	1 (2.56)
NYHA/Ross class group (randomization stratum) – n (%)						
Class I/Class II	93 (85.32)	94 (84.68)	42 (89.36)	36 (94.74)	25 (80.65)	31 (79.49)
Class III/Class IV	16 (14.68)	17 (15.32)	5 (10.64)	2 (5.26)	6 (19.35)	8 (20.51)

NYHA/Ross class: NYHA class for age ≥ 6 years, Ross class for age <6 years.
Source: [Study B2319-Table 14.1-3.1.2]

Prior treatment and background treatment for heart failure

Prior heart failure and cardiovascular medication use was balanced between the two treatment groups. As expected, ACE inhibitors were used in the vast majority of patients with 91.44% vs 91.49% of patients in the sacubitril/valsartan vs enalapril groups, respectively, most frequently enalapril (45.99% vs 47.43%), captopril (22.99% vs 20.21%), lisinopril (13.37% vs 13.83%), and enalapril maleate (10.70% vs 10.11%).

The most frequent other prior heart failure and cardiovascular medications in the sacubitril/valsartan vs enalapril groups were: beta-blockers (70.59% vs 68.62%), spironolactone (64.71% vs 68.09%), furosemide (60.43% vs 67.55%), and digoxin (39.04% vs 34.57%). Aspirin (acetylsalicylic acid) was used in 39.04% (37.97%) vs 44.15% (44.15%) of patients. ARBs were used in 5.50% vs 7.21% of patients, and ivabradine, an HCN channel blocker, was used in 2.14% vs 2.13% of patients.

The use of concomitant heart failure and cardiovascular medications (i.e. medications that were ongoing or started at baseline) was balanced between the treatment groups, and, with the exception of ACE inhibitors that were prohibited during the treatment period, similar to prior use. The most frequent concomitant heart failure and cardiovascular medications used in the sacubitril/valsartan vs enalapril groups were: beta-blockers (73.26% vs 72.34%), spironolactone (68.45% vs 69.15%), furosemide (65.78% vs 69.68%) and digoxin (42.25% vs 35.64%). Aspirin (acetylsalicylic acid) was used in 43.32% (42.25%) vs 46.81% (46.81%) of patients. ARBs were used in 3.21% vs 4.26% of patients, and ivabradine was used in 4.28% vs 3.72% of patients.

ACEIs were reported as concomitant medications in 9.63% of patients in sacubitril/valsartan group and 14.36% of patients in the enalapril group. Of note, only patients who interrupted or discontinued study drug could be on ACEi or ARB treatment. The most commonly reported ACEI was enalapril (sacubitril/valsartan: 5.35%; enalapril: 6.91%) followed by lisinopril (sacubitril/valsartan: 2.67%; enalapril: 3.19%) and captopril (sacubitril/valsartan: 1.60%; enalapril: 2.66%).

Primary Outcomes and estimation

The primary endpoint analysis did not show a statistically significant difference between treatment groups (Table 23). The Mann-Whitney probability estimate numerically favoured sacubitril/valsartan (0.5244; 95% CI 0.4665, 0.5817, p=0.4238) compared to the standard of care enalapril.

The results were consistent across subgroups by age, with no significant differences observed between sacubitril/valsartan and enalapril. The interpretation is limited for patients younger than 1 year (age group 3) as only 9 patients in this age group were enrolled.

Table 23. Part 2 Global Rank endpoint – primary rank score (PACE), Mann-Whitney analysis, LOCF – Study B2319 Part 2 (FAS)

	LCZ	ENA	Total	LCZ ENA wins/loses/ties			Mann-Whitney Probability		Mann-Whitney Odds		
	n	n	n	% LCZ wins	% ENA wins	% LCZ equals ENA	Estimate	95% CI	Estimate	95% CI	Two-sided p-value
Overall	187	188	375	49.97	45.09	4.95	0.5244	(0.4665, 0.5817)	0.9069	(0.7191, 1.1438)	0.4238
Age Groups											
Group 1 6-<18 y	109	111	220	52.19	47.17	0.63	0.5251	(0.4500, 0.5990)	0.9045	(0.6687, 1.2233)	
Group 2a 2-<6 y	47	38	85	44.54	44.17	11.28	0.5019	(0.3820, 0.6210)	0.9926	(0.6091, 1.6175)	
Group 3a 1 mo-<2 y	31	39	70	49.34	39.42	11.24	0.5496	(0.4150, 0.6780)	0.8195	(0.4755, 1.4122)	
Group 2 1-<6 y	73	73	146	47.44	41.69	10.86	0.5288	(0.4350, 0.6200)	0.8912	(0.6122, 1.2975)	
Group 3 1 mo-<1 y	5	4	9	25.00	58.33	16.67	0.3333	(0.0750, 0.7560)	2.0000	(0.3224, 12.4078)	

CI = confidence interval, ENA=enalapril; LCZ=sacubitril/valsartan; PACE = positively adjudicated clinical events, LOCF = last observation carry forward prior cutoff.
For USM-impacted patients, the on treatment assessments are included.
Mann–Whitney probability > 0.5 favours LCZ696, equivalently, Mann-Whitney odds < 1.
Source: [Study B2319-Table 14.2-2.2.1, Table 14.2-2.2.4, Table 14.2-2.2.4post01]

Supportive and sensitivity analyses of the primary endpoint

Supportive analyses of the global rank endpoint (including primary rank score based on positively adjudicated clinical events (PACE) in the PPS, primary rank score based on investigator-reported clinical events (IRCE), response category based on PACE and IRCE, and primary rank score based on PACE and IRCE in the pooled strata) showed results similar to the primary analysis.

Sensitivity analysis of the global rank endpoint primary rank score based on PACE and IRCE with multiple imputations and LOCF approach without cut-off, and assessing USM impact, also showed results similar to the primary analysis. Results of a tipping point sensitivity analysis for the global rank endpoint –primary ranks score based on PACE was in agreement with the primary analysis results and demonstrated the robustness of handling the discontinuation of patients without Category 1 events

Global rank endpoint – patient allocation

Patient allocation for the Global Rank primary endpoint (based on positively adjudicated events) is shown in Table 24. This table shows the worst event per patient contributing to the global ranking: patients are hierarchically counted by their first event for the Category 1 events, and by their worst event for Category 2, and for the change in functional class (worse/unchanged/improved) for Category 3 to 5 events.

The following observation can be made:

- The proportion of patients with a Category 1 event was numerically lower in the sacubitril/valsartan group (10.16%) compared to the enalapril group (15.96%).
- The proportion of patients counted for Category 2 was numerically higher in the sacubitril/valsartan group (9.63%) compared to the enalapril group (4.79%). This difference is in part due to the higher proportion of patients on enalapril having a Category 1 event, as patients who had both a Category 1 and a Category 2 event were excluded from Category 2 (i.e. competing risks) (see also Table 2-10 below).

- A large proportion of patients, approximately 80%, in both treatment groups had no Category 1 or Category 2 event, and are counted in Category 3, 4, or 5.

Table 24. Part 2 Global Rank endpoint – patient allocation for primary analysis (Full Analysis Set)

Population: Overall		
	LCZ696 N=187 n (%)	**Enalapril N=188 n (%)**
Category 1 *	**19 (10.16)**	**30 (15.96)**
Category 2	**18 (9.63)**	**9 (4.79)**
Worsening heart failure hospitalization with ICU stay	11 (5.88)	3 (1.60)
Worsening heart failure hospitalization without ICU stay	5 (2.67)	5 (2.66)
Worsening heart failure without hospitalization	2 (1.07)	1 (0.53)
Category 3 to Category 5 - LOCF		
Category 3	20 (10.70)	15 (7.98)
Category 4	45 (24.06)	57 (30.32)
Category 5	85 (45.45)	77 (40.96)

*Category 1 includes: Death, UNOS status 1A listing for heart transplant or equivalent, VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support, and discontinued from the study during the double-blinded epoch without Category 1 event.
ICU: Intensive care unit; LOCF =last observation carry forward.
A patient with multiple events within a category is counted only once within the category.
Patients who discontinued from the study during the double-blind epoch without Category 1 event are classified into Category 1 with event date imputed by the last known alive date.
USM patients, if discontinued from the study due to USM without Category 1 event is not considered as Category 1 event. For USM impacted patients, the assessment at EOT was taken.
Source: [Study B2319-Table 14.2-2.1]

Summary of Category 1 and Category 2 events

A summary of all Category 1 and Category 2 events based on both PACE and IRCE is provided in Table 25. There were fewer events of death in the sacubitril/valsartan group (8 deaths, 4.28%) than the enalapril group (12 deaths, 6.38%). Furthermore, based on PACE, the proportion of patients with other types of Category 1 event was also lower in the sacubitril/valsartan group than in the enalapril group. A similar pattern was observed for IRCE, with the exception of the event UNOS status 1A listing for heart transplant or equivalent.

The proportion of patients with a Category 2 event was numerically higher in the sacubitril/valsartan group than in the enalapril group (16.58% vs 14.36%). The difference is less pronounced than for events allocated to Category 2 for the Global Rank primary endpoint analysis shown in Table 24, due to some patients having both a Category 1 and a Category 2 event (13 in the sacubitril/valsartan group and 18 in the enalapril group). Excluding discontinuations, there were 10 patients in the sacubitril/valsartan group and 14 patients in the enalapril group who had both a Category 1 and a Category 2 event.

Table 25. Part 2 Summary of Category 1 and Category 2 events (Full Analysis Set)

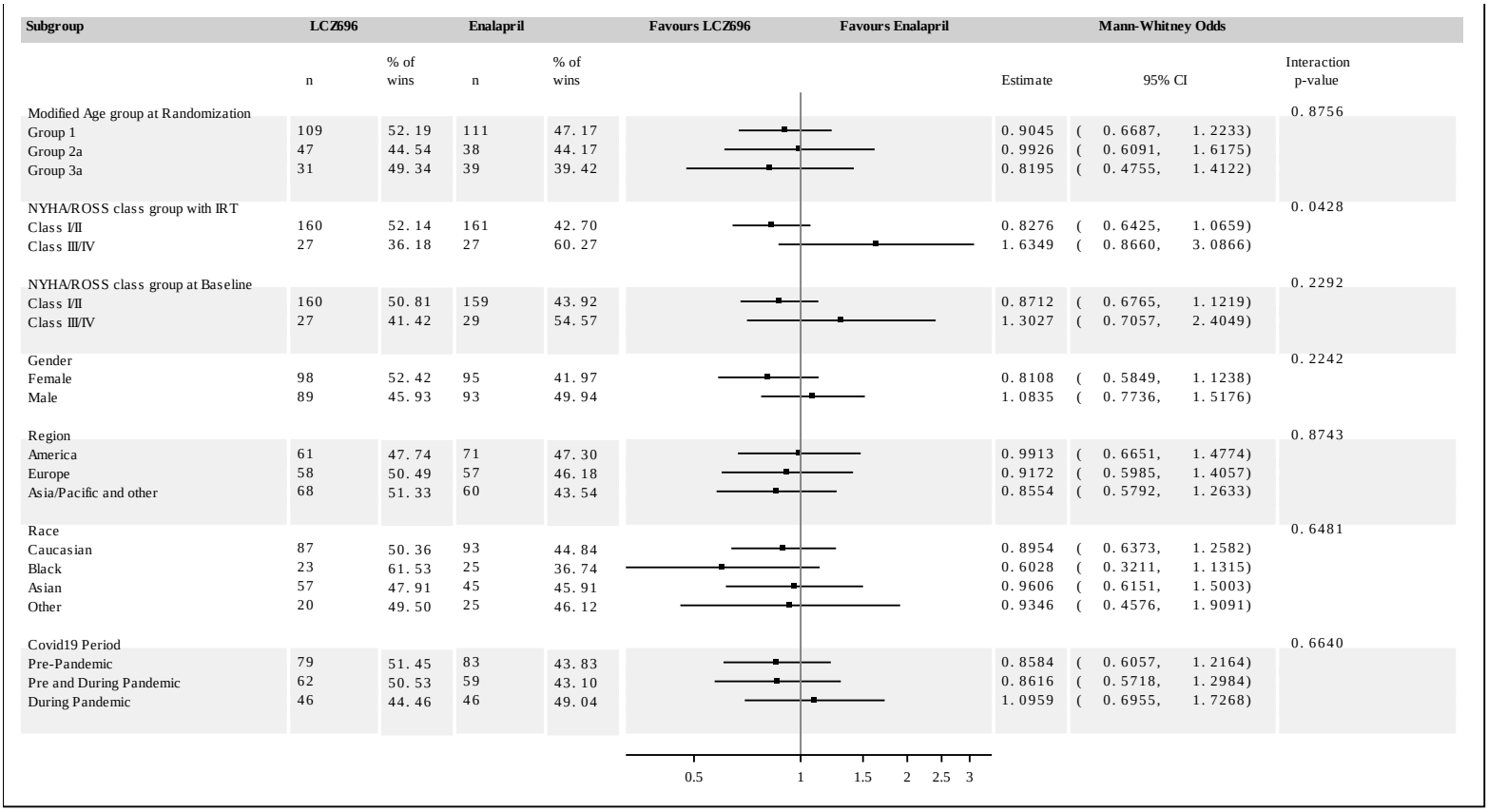
Population: Overall				
	LCZ696 N=187 n (%)		**Enalapril N=188 n (%)**	
	PACE	**IRCE**	**PACE**	**IRCE**
Category 1	**19 (10.16)**	**21 (11.23)**	**30 (15.96)**	**30 (15.96)**
Death	8 (4.28)	8 (4.28)	12 (6.38)	12 (6.38)
UNOS status 1A listing for heart transplant or equivalent	5 (2.67)	7 (3.74)	7 (3.72)	6 (3.19)
VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support	7 (3.74)	8 (4.28)	12 (6.38)	14 (7.45)
Discontinued from the study during the double-blinded epoch without Category 1 event	6 (3.21)	6 (3.21)	10 (5.32)	9 (4.79)
Category 2	**31 (16.58)**	**37 (19.79)**	**27 (14.36)**	**35 (18.62)**
Worsening heart failure hospitalization with intensive care unit stay	21 (11.23)		16 (8.51)	
Worsening heart failure hospitalization without intensive care unit stay	12 (6.42)		13 (6.91)	
Worsening heart failure without hospitalization	5 (2.67)		3 (1.60)	

PACE = positively adjudicated clinical events, IRCE = investigator reported clinical events.
A patient with multiple clinical events is counted only once for each row.
In the event a patient has more that one clinical event subcategory contributing to category 1 or category 2, the patient is counted in each applicable subcategory.
USM patients, if discontinued from the study due to USM without Category 1 event is not considered as Category 1 event.
For USM impacted patients, the assessment at EOT was taken
Source: [Study B2319-Table 14.2-2.3]

Results of subgroup analyses for the primary and secondary endpoints

The results for the primary endpoint were consistent across subgroups, with MWO numerically favouring sacubitril/valsartan in the majority of the subgroups, however with the notable exception of the small (n=27) subgroup of patients with NYHA/Ross class III/IV. As 10 patients were randomized in the wrong NYHA/Ross stratum, the subgroup analysis by “NYHA/Ross class group at baseline” should be considered; this analysis shows a less pronounced difference in treatment effect than the analysis by “NYHA/Ross class group with IRT”. The results of subgroup analyses for the secondary endpoints were generally comparable across subgroups, with no consistent trends observed.

Figure 11. Part 2 Global Rank endpoint - primary rank score (PACE) - Mann–Whitney analysis - LOCF - subgroup forest plot (Full Analysis Set)



Subgroup	LCZ696 n	LCZ696 % of wins	Enalapril n	Enalapril % of wins	Mann-Whitney Odds Estimate	95% CI	Interaction p-value
Modified Age group at Randomization							0.8756
Group 1	109	52.19	111	47.17	0.9045	(0.6687, 1.2233)	
Group 2a	47	44.54	38	44.17	0.9926	(0.6091, 1.6175)	
Group 3a	31	49.34	39	39.42	0.8195	(0.4755, 1.4122)	
NYHA/ROSS class group with IRT							0.0428
Class I/II	160	52.14	161	42.70	0.8276	(0.6425, 1.0659)	
Class III/IV	27	36.18	27	60.27	1.6349	(0.8660, 3.0866)	
NYHA/ROSS class group at Baseline							0.2292
Class I/II	160	50.81	159	43.92	0.8712	(0.6765, 1.1219)	
Class III/IV	27	41.42	29	54.57	1.3027	(0.7057, 2.4049)	
Gender							0.2242
Female	98	52.42	95	41.97	0.8108	(0.5849, 1.1238)	
Male	89	45.93	93	49.94	1.0835	(0.7736, 1.5176)	
Region							0.8743
America	61	47.74	71	47.30	0.9913	(0.6651, 1.4774)	
Europe	58	50.49	57	46.18	0.9172	(0.5985, 1.4057)	
Asia/Pacific and other	68	51.33	60	43.54	0.8554	(0.5792, 1.2633)	
Race							0.6481
Caucasian	87	50.36	93	44.84	0.8954	(0.6373, 1.2582)	
Black	23	61.53	25	36.74	0.6028	(0.3211, 1.1315)	
Asian	57	47.91	45	45.91	0.9606	(0.6151, 1.5003)	
Other	20	49.50	25	46.12	0.9346	(0.4576, 1.9091)	
Covid19 Period							0.6640
Pre-Pandemic	79	51.45	83	43.83	0.8584	(0.6057, 1.2164)	
Pre and During Pandemic	62	50.53	59	43.10	0.8616	(0.5718, 1.2984)	
During Pandemic	46	44.46	46	49.04	1.0959	(0.6955, 1.7268)	

Pre-Pandemic - end of study prior to 1-Mar-2020. Pre and During Pandemic - randomized prior to 1-Mar-2020 and end of study after 1-Mar-2020. During pandemic - randomized on or after 1-Mar-2020. For USM-impacted patients, the on-treatment assessments are included. The interaction p value was derived using meta analysis to test for heterogeneity across subgroups. The NYHA/ROSS class group at randomization referred to the data assigned in IRT when the patient was randomized. The NYHA/ROSS class group at baseline referred to the data in CRF assessed by investigator and collected at randomization visit.

Secondary endpoints

Time to Category 1 or Category 2 events

No significant difference was observed between treatment groups in time to first positively adjudicated Category 1 or 2 events (adjusted Hazard Ratio: 1.0655; 95% CI: 0.6589, 1.7232) (Table 26). The cumulative event rate was similar in both treatment groups.

The proportion of patients with a Category 1 event was lower in the sacubitril/valsartan group (6.95%) than in the enalapril group (10.64%), and the HR was numerically in favour of sacubitril/valsartan (of note, the number of events is different from the primary analysis because discontinuation was not considered an event). Conversely, for Category 2 events, the proportion of patients with a Category 2 event was slightly higher in the sacubitril/valsartan group (16.58%) than in the enalapril group (14.36%), and the HR was numerically in favour of enalapril.

Similar results were obtained using analysis based on investigator-reported Category 1 or Category 2 events (adjusted Hazard Ratio: 1.0068; 95% CI: 0.6482, 1.5638; nominal two-sided p=0.9759). Since there were no events in age group 2a with NYHA/ROSS class group III/IV, a sensitivity analysis

stratified by modified age group was conducted; the results showed a similar trend for time to first positively adjudicated Category 1 or 2 events (adjusted Hazard Ratio: 1.0559 [95% CI: 0.6531, 1.7070; nominal two-sided p=0.8245]).

The cumulative probability of both positively adjudicated or Investigator reported Category 1 or Category 2 events was similar between sacubitril/valsartan and enalapril groups.

Table 26. Part 2 time to first positively adjudicated Category 1 or Category 2 event during the double-blind epoch without cutoff - Cox proportional hazard model (Full Analysis Set)

	LCZ696 N=187		Enalapril N=188		Adjusted Hazard Ratio (LCZ696/Enalapril)		Nominal P-Value
Endpoint	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**	**Estimate**	**95% CI**	**Two-sided**
Category 1 or Category 2 event	34 (18.18)	20.133 (13.9430, 28.1344)	33 (17.55)	20.042 (13.7960, 28.1464)	1.0655	(0.6589, 1.7232)	0.7958
Category 1 event	13 (6.95)	7.074 (3.7665, 12.0963)	20 (10.64)	11.459 (6.9996, 17.6978)	0.6358	(0.3160, 1.2792)	0.2042
Category 2 event	31 (16.58)	18.357 (12.4727, 26.0562)	27 (14.36)	16.346 (10.7722, 23.7827)	1.2093	(0.7204, 2.0301)	0.4720

CI = confidence interval, n (%) is the number and percentage of patients with at least one event.
EAIR (exposure adjusted incidence rate) = number of patients with at least one event/sum of time to event/censoring.
The adjusted hazard ratio and the p-values are based on a Cox proportional hazard model, stratified by modified age group and NYHA/Ross class group with treatment included as a fixed-effect factor.
For USM-impacted patients, the on treatment assessments are included.
Discontinuation is not treated as event.
Source: [Study B2319-Table 14.2-3.1.2]

NYHA/Ross functional class change from baseline

While there was no significant difference between the treatment groups, patients experienced clinically meaningful improvements over the 52 weeks of the study in both treatment groups, based on changes in NYHA/Ross functional class from baseline. At Week 52, 37.66% of patients in the sacubitril/valsartan group and 33.96% of patients in the enalapril group had improvement at Week 52, and approximately half of all patients were stable (no change in NYHA/Ross class). The odds ratio for a favorable outcome (sacubitril/valsartan / enalapril) at Week 52 was 1.0733 (95% CI: 0.6843, 1.6832) (Table 27).

A sensitivity analysis with multiple imputations showed results similar to the main analysis above, with an adjusted odds ratio for a favourable outcome (sacubitril/valsartan/enalapril) at Week 52 of 1.0409 (95% CI: 0.6705, 1.6158).

Table 27. Part 2 NYHA/Ross classification - proportional cumulative odds model - post Category 1 event set to worsened (Full Analysis Set)

	LCZ696 N=187				Enalapril N=188				Adjusted Odds Ratio LCZ696/Enalapril		Nominal P-Value
Visit	n	Improved n (%)	Unchanged n (%)	Worsened n (%)	n	Improved n (%)	Unchanged n (%)	Worsened n (%)	Estimate	95% CI	Two-sided
Week 4	183	26 (14.21)	154 (84.15)	3 (1.64)	184	29 (15.76)	152 (82.61)	3 (1.63)	0.8516	(0.4874, 1.4879)	0.5725
Week 12	180	43 (23.89)	127 (70.56)	10 (5.56)	180	46 (25.56)	122 (67.78)	12 (6.67)	0.9200	(0.5855, 1.4455)	0.7176
Week 24	178	48 (26.97)	114 (64.04)	16 (8.99)	172	48 (27.91)	110 (63.95)	14 (8.14)	0.9077	(0.5820, 1.4158)	0.6695
Week 36	167	50 (29.94)	102 (61.08)	15 (8.98)	170	58 (34.12)	99 (58.24)	13 (7.65)	0.8162	(0.5229, 1.2742)	0.3715
Week 52	154	58 (37.66)	78 (50.65)	18 (11.69)	159	54 (33.96)	90 (56.60)	15 (9.43)	1.0733	(0.6843, 1.6832)	0.7581

For each post-baseline visit, the percentages are out of the total number of patients with baseline assessment and current visit assessment observed.
For each visit, the proportional cumulative odds model uses NYHA change (improved < unchanged < worsened) at the visit as response, and stratified by modified age group in which treatment and baseline included as fixed-effect factors.
For patients who had a Category 1 event (investigator reported or positively adjudicated),the missing NYHA/Ross scores after the first Category 1 event (investigator reported or positively adjudicated), are set to a worst category (Category 1 event).
For USM-impacted patients, the on treatment assessments are included.
Odds Ratio > 1 favors LCZ696.
Source: [Study B2319-Table 14.2-4.1]

The majority of patients (>80%) were in NYHA/Ross class II or higher at baseline. Shifts to a lower (better) NYHA/Ross functional class was observed in both treatment groups during the study. The proportion of patients with NYHA/Ross class I (i.e. had no symptoms or limitations) increased from baseline to Week 52 in both treatment groups (from 13.37% to 48.47% in the sacubitril/valsartan group and from 18.09% to 47.50% in the enalapril group). Improvements in NYHA/Ross class were observed in all age groups (Table 28).

Table 28. Part 2 NYHA/Ross classification status at baseline and Week 52 by age group (Full Analysis Set)

			NYHA/Ross classification			
			I	II	III	IV
			n (%)	n (%)	n (%)	n (%)
Overall	Sacubitril/ valsartan	Baseline (N=187)	25 (13.37)	135 (72.19)	27 (14.44)	0
		Week 52 (N=163)	79 (48.47)	75 (46.01)	6 (3.68)	3 (1.84)
	Enalapril	Baseline (N=188)	34 (18.09)	125 (66.49)	27 (14.36)	2 (1.06)
		Week 52 (N=160)	76 (47.50)	79 (49.38)	5 (3.13)	0
Group 1 6-<18 y	Sacubitril/ valsartan	Baseline (N=109)	13 (11.93)	78 (71.56)	18 (16.51)	0
		Week 52 (N=93)	38 (40.86)	50 (53.76)	4 (4.30)	1 (1.08)
	Enalapril	Baseline (N=111)	11 (9.91)	81 (72.97)	18 (16.22)	1 (0.90)
		Week 52 (N=91)	31 (34.07)	56 (61.54)	4 (4.40)	0
Group 2a 2-<6 y	Sacubitril/ valsartan	Baseline (N=47)	9 (19.15)	33 (70.21)	5 (10.64)	0
		Week 52 (N=41)	24 (58.54)	15 (36.59)	2 (4.88)	0
	Enalapril	Baseline (N=38)	11 (28.95)	25 (65.79)	2 (5.26)	0
		Week 52 (N=36)	20 (55.56)	16 (44.44)	0	0
Group 3a 1 mo-<2 y	Sacubitril/ valsartan	Baseline (N=31)	3 (9.68)	24 (77.42)	4 (12.9)	0
		Week 52 (N=29)	17 (58.62)	10 (34.48)	0	2 (6.90)
	Enalapril	Baseline (N=39)	12 (30.77)	19 (48.72)	7 (17.95)	1 (2.56)
		Week 52 (N=33)	25 (75.76)	7 (21.21)	1 (3.03)	0

Age groups: Group 1: 6 to <18 years; Group 2a: 2 to <6 years; Group 3a: 1 month to <2 years
Source: [Study B2319-Table 14.2-4.3]

Global impression of severity (PGIS) change from baseline

Consistent with the results in NYHA/Ross class, while there was no significant difference between the treatment groups on change in PGIS from baseline, a high proportion of patients in both treatment

groups experienced clinically relevant improvement, or were stable, during the study: 35.53% of patients in the sacubitril/valsartan group and 34.81% of patients in the enalapril group had improvement at Week 52, and nearly half of all patients were stable (i.e. no change in PGIS). The odds ratio for a favorable outcome (sacubitril/valsartan / enalapril) at Week 52 was 1.1498 (95% CI: 0.7349, 1.7989) (Table 29).

Similar results were obtained using a sensitivity analysis with multiple imputations to account for missing values: at Week 52, the adjusted odds ratio was 1.1251 (95% CI: 0.7266, 1.7422), numerically in favour of sacubitril/valsartan.

Table 29. Part 2 patient global impression of severity (PGIS) - proportional cumulative odds model - post Category 1 event set to worsened (FAS)

	LCZ696 N=187				Enalapril N=188				Adjusted Odds Ratio LCZ696/Enalapril		Nominal P-Value
Visit	n	Improved n (%)	Unchanged n (%)	Worsened n (%)	n	Improved n (%)	Unchanged n (%)	Worsened n (%)	Estimate	95% CI	Two-sided
Week 4	174	47 (27.01)	101 (58.05)	26 (14.94)	182	54 (29.67)	109 (59.89)	19 (10.44)	0.7687	(0.4945, 1.1949)	0.2425
Week 12	178	55 (30.90)	93 (52.25)	30 (16.85)	178	56 (31.46)	99 (55.62)	23 (12.92)	0.9224	(0.6035, 1.4100)	0.7092
Week 24	174	58 (33.33)	85 (48.85)	31 (17.82)	171	65 (38.01)	83 (48.54)	23 (13.45)	0.8266	(0.5366, 1.2734)	0.3878
Week 36	162	54 (33.33)	80 (49.38)	28 (17.28)	165	56 (33.94)	87 (52.73)	22 (13.33)	0.9893	(0.6352, 1.5407)	0.9619
Week 52	152	54 (35.53)	73 (48.03)	25 (16.45)	158	55 (34.81)	75 (47.47)	28 (17.72)	1.1498	(0.7349, 1.7989)	0.5412

For each post-baseline visit, the percentages are out of the total number of patients with baseline assessment and current visit assessment observed.
For each visit, the proportional cumulative odds model uses PGIS change (improved < unchanged < worsened) at the visit as response, and stratified by modified age group and NYHA/Ross class group in which treatment and baseline included as fixed-effect factors.
For patients who had a Category 1 event (investigator reported or positively adjudicated),the missing PGIS scores after the first Category 1 event (investigator reported or positively adjudicated), are set to a worst category (Category 1 event).
For USM-impacted patients, the on treatment assessments are included.
Odds Ratio > 1 favors LCZ696.
Source: [Study B2319-Table 14.2-5.1]

The proportion of patients who were asymptomatic (i.e. PGIS status C1 (none / good)) increased from baseline to Week 52 in both treatment groups (from 45.05% to 67.95% in the sacubitril/valsartan group, and from 38.59% to 64.94% in the enalapril group). Improvements in PGIS status were observed in all age groups. Fewer patients had moderate, severe, or very severe symptoms (PGIS classification of C3 or higher) at Week 52 than at baseline (Table 30).

Table 30. Part 2 PGIS status at baseline and Week 52 by age group (Full Analysis Set)

			PGIS classification				
			C1	C2	C3	C4	C5
			n (%)	n (%)	n (%)	n (%)	n (%)
Overall	Sacubitril/ valsartan	Baseline (N=182)	82 (45.05)	60 (32.97)	32 (17.58)	5 (2.75)	3 (1.65)
		Week 52 (N=156)	106 (67.95)	38 (24.36)	10 (6.41)	2 (1.28)	0
	Enalapril	Baseline (N=184)	71 (38.59)	71 (38.59)	33 (17.93)	9 (4.89)	0
		Week 52 (N=154)	100 (64.94)	36 (23.38)	16 (10.39)	2 (1.30)	0
Group 1 6-<18 y	Sacubitril/ valsartan	Baseline (N=106)	47 (44.34)	32 (30.19)	21 (19.81)	4 (3.77)	2 (1.89)
		Week 52 (N=90)	61 (67.78)	22 (24.44)	7 (7.78)	0	0
	Enalapril	Baseline (N=109)	36 (33.03)	45 (41.28)	20 (18.35)	8 (7.34)	0
		Week 52 (N=88)	55 (62.50)	22 (25.00)	10 (11.36)	1 (1.14)	0
Group 2a 2-<6 y	Sacubitril/ valsartan	Baseline (N=45)	23 (51.11)	16 (35.56)	5 (11.11)	0	1 (2.22)
		Week 52 (N=39)	26 (66.67)	10 (25.64)	1 (2.56)	2 (5.13)	0
	Enalapril	Baseline (N=36)	18 (50.00)	12 (33.33)	6 (16.67)	0	0
		Week 52 (N=33)	23 (69.70)	6 (18.18)	3 (9.09)	1 (3.03)	0
Group 3a 1 mo-<2 y	Sacubitril/ valsartan	Baseline (N=31)	12 (38.71)	12 (38.71)	6 (19.35)	1 (3.23)	0
		Week 52 (N=27)	19 (70.37)	6 (22.22)	2 (7.41)	0	0
	Enalapril	Baseline (N=39)	17 (43.59)	14 (35.90)	7 (17.95)	1 (2.56)	0
		Week 52 (N=33)	22 (66.67)	8 (24.24)	3 (9.09)	0	0

C1 = None (Good), C2 = Mild, C3 = Moderate, C4 = Severe, C5 = Very severe (Bad).
Age groups: Group 1: 6 to <18 years; Group 2a: 2 to <6 years; Group 3a: 1 month to <2 years
Source: [Study B2319-Table 14.2-5.3]

Exploratory Outcomes

NT-proBNP change from baseline

The sections below show data to support the relevance of NT-proBNP as an important biomarker of heart failure, with higher levels being associated with poorer outcomes in patients with HFrEF.

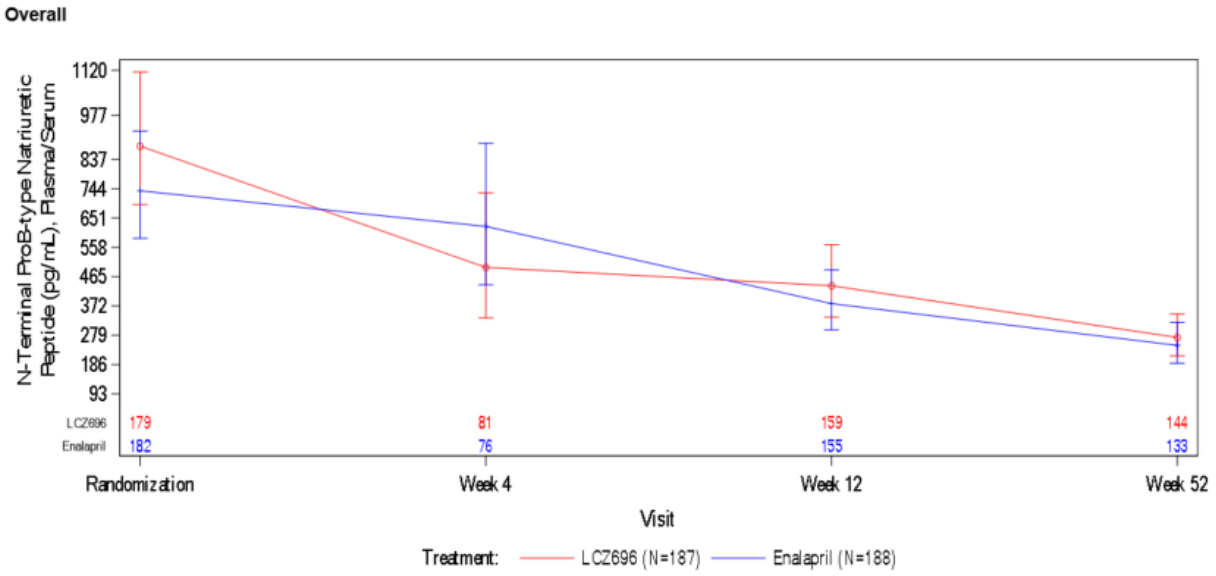
NT-proBNP change from baseline is presented for the overall population, followed by analyses conducted by the modified age group.

Change from baseline – overall population

There was an imbalance in NT-proBNP levels at baseline, with higher levels in the sacubitril/valsartan group (geomean 879.28 pg/mL) than in the enalapril group (geomean 737.42 pg/mL).

Importantly, both treatment groups showed clinically relevant decreases in NT-proBNP levels throughout the study (Figure 12). The decrease was numerically greater in the sacubitril/valsartan group up to Week 52. The reduction was observed as early as 4 weeks after starting treatment, at which time the relative between-treatment difference was 27% ($p<0.05$) in favor of sacubitril/valsartan. The relative treatment differences in both Week 12 and Week 52 were approximately 9%, which were not statistically significant. At Week 52, the reduction in NT-proBNP from baseline was 65% and 62% for the sacubitril/valsartan and enalapril groups, respectively (Table 31). Of particular note, at Week 52 the NT-proBNP values achieved with both therapies reached the upper end of the age-adjusted range reported in a healthy population by Nir et al 2009.

Figure 12. Part 2 NT-proBNP - geometric mean (+/- 95% CI) line plot (Full Analysis Set)



For the biomarkers, if the test value is below the LLOQ, the test value will be imputed by 0.5 × LLOQ; if the test value is above the ULOQ will be imputed by 1.5 × ULOQ.

Table 31. Part 2 NT-proBNP – change from baseline – Mixed Model for Repeated Measures (MMRM) (Full Analysis Set)

	LCZ696 N=187 AGM RTB			Enalapril N=188 AGM RTB			Comparison (LCZ696 vs Enalapril) AGMR (LCZ696/ Enalapril)		Nominal P-Value
Visit	**n**	**Estimate**	**95% CI**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Two-sided**
Wk4	81	0.5985	(0.5277, 0.6788)	76	0.8204	(0.7209, 0.9336)	0.7296	(0.6094, 0.8734)	0.0007
Wk12	159	0.5025	(0.4419, 0.5714)	155	0.5510	(0.4836, 0.6278)	0.9120	(0.7591, 1.0956)	0.3238
Wk52	144	0.3494	(0.2883, 0.4234)	133	0.3841	(0.3147, 0.4688)	0.9097	(0.6896, 1.1999)	0.5016

AGM = adjusted geometric mean, RTB = ratio to baseline, AGMR = adjusted geometric mean ratio, CI = confidence interval.
The MMRM model includes change from baseline in log transformed NT-proBNP as response, modified age group, NYHA/Ross class group at randomization, region, treatment (LCZ696, Enalapril), visit, and treatment-by-visit interaction as fixed-effect factors; log baseline NT-proBNP and visit-by-log-baseline interaction as covariates.
Test values below lower or above upper limit of quantification are imputed by 0.5 x LLOQ or 1.5 x ULOQ.
For USM-impacted patients, the on treatment assessments are included.
Source: [Study B2319-Table 14.2-8.3]

Association between NT-proBNP and clinical outcomes

A post-hoc analysis was performed to confirm whether baseline NT-proBNP levels and changes in NT-proBNP levels post-baseline were associated with the risk of clinical outcome events in paediatric HF, similar to earlier observations in adults with HFrEF.

The results show that similar to adults, changes in NT-proBNP post-baseline were strongly associated with the risk of Category 1 or 2 events in paediatric HF patients (Table 32). A doubling of NT-proBNP levels post-baseline was associated with an approximately 2.1-fold increased risk of a Category 1 or 2 event ($p<0.0001$). Conversely, halving NT-proBNP post-baseline levels (i.e. ratio to baseline = 0.5) is associated with a 52.2% decrease in risk (hazard) for a Category 1 or 2 event. Furthermore, a doubling of baseline NT-proBNP levels was associated with an approximately 1.8-fold increased risk of a Category 1 or 2 event.

NT-proBNP levels at baseline and changes post-baseline were also significantly associated with the risk of Category 1 event and the risk of Category 2 event when the two event categories were considered separately.

Table 32. Part 2 Association between NT-ProBNP at baseline and changes in NT-proBNP post-baseline with the risk of Category 1 or 2 events in paediatric HF patients (Full Analysis Set)

			Baseline log_2 (NT-proBNP)		Change from baseline log_2 (NT-proBNP)	
	LCZ696 n/N (%)	**Enalapril n/N (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Category 1 or 2	34/187 (18.18)	33/188 (17.55)	1.7858 (1.5509, 2.0562)	<0.0001	2.0927 (1.5245, 2.8727)	<0.0001
Category 1	13/187 (6.95)	20/188 (10.64)	1.7105 (1.4098, 2.0753)	<0.0001	2.0941 (1.3641, 3.2149)	0.0007
Category 2	31/187 (16.58)	27/188 (14.36)	1.8066 (1.5484, 2.1078)	<0.0001	2.3739 (1.6911, 3.3324)	<0.0001

Missing NT-proBNP at baseline is imputed within each treatment arm, gender and modified age group, discontinuation is not treated as event.
CI = confidence interval; n (%)=the number and percentage of patients with at least one event.
The adjusted hazard ratio and the p-values are based on a Cox proportional hazard model, stratified by modified age group and NYHA/Ross class group with treatment included as a fixed-effect factor, baseline log_2(NT-proBNP) as covariate and change from baseline log_2(NT-proBNP) as time-dependent covariate.
For USM-impacted patients, the on treatment assessments are included.
Source: [Study B2319-Table 14.2-3.1.2.post.01]

NT-proBNP levels by age group

Baseline NT-proBNP levels were consistently higher in age groups 1, 2a, and 3a than those reported for similar age groups of a healthy population by Nir et al. 2009. Conversely, clinically meaningful decreases in NT-proBNP levels were observed in all 3 age groups and both treatment groups.

MMRM analysis of change from baseline by modified age group confirmed that NT-proBNP decreased in all age groups. In the age group 1 (6 to <18 years of age), the reduction in NT-proBNP was numerically greater in the sacubitril/valsartan group throughout the study, with a relative between-treatment difference of 28% at Week 4, 15% at Week 12, and 11% at Week 52. In age group 2a (2 to <6 years of age), the change from baseline was numerically greater in the sacubitril/ valsartan group at Week 4 (relative between-treatment differences of 28%), but similar at Week 52 (relative between-treatment differences of 4%). In age group 3a (1 month to <2 years of age), the change from baseline was numerically greater in the sacubitril/valsartan group at Week 4 (relative between-treatment differences of 12%), but greater in the enalapril group at Week 52 (relative between-treatment differences of 31%).

Table 33. Part 2 NT-proBNP levels (pg/mL) at baseline and Week 52 by modified age group (Full Analysis Set)

	Age group 1		**Age group 2a**		**Age group 3a**	
	LCZ696 N=109	**Enalapril N=111**	**LCZ696 N=47**	**Enalapril N=38**	**LCZ696 N=31**	**Enalapril N=39**
Baseline						
n	105	108	44	38	30	36
Geomean	637.30	589.03	1240.73	831.75	1636.97	1274.22
Median	605.00	610.50	1749.00	791.00	2029.50	1244.00
Week 52						
n	84	79	35	30	25	24
Geomean	234.79	260.09	289.01	236.41	409.39	220.15
Median	206.00	250.00	291.00	217.50	382.00	212.50

Age group 1: 6 to <18 years; age group 2a: 2 to <6 years; age group 3a: 1 month to <2 years
Source: [Study B2319-Table 14.2-8.2]

NT-proBNP change concerning the reference change value and responder analyses

The intra-individual variability is the sum of analytical variability and biologic variability. Evaluation of biologic variability or the intra-individual between-visit-variability (sum of analytical and biological variability) in patients with CHF requires repeated NT-proBNP measurements in the same patient over time during a stable period (e.g., no progression of disease, no major changes in medications). Meijers et al 2016 reported week-to-week intra-individual coefficient of variation of 22% based on 83 CHF patients, with weekly NT-proBNP measurements over a period of 6 weeks. Bruins et al 2004 reported week-to-week intra-individual coefficient of variation of 35% based on 43 stable CHF patients, with weekly NT-proBNP measurements over a period of 6 weeks. Other relevant published reports are listed in *Table 34* below.

Similarly, most visits of the adults PARADIGM-HF study are affected by changes in treatment and potentially disease status, which would artificially inflate the visit-to-visit variation. For an estimation of the random intra-individual visit-to-visit variation, only the relatively stable enalapril run-in phase between Visits 2/2a and Visit 3 seems adequate since the two visits are in close vicinity (2-4 weeks apart) and presumably not much affected by changes in treatment (most patients were on ACEi/ARBs before participating in the study, and all patients received enalapril between Visit 2 and Visit 3). There were 835 patients with NT-proBNP measures at both visits 2/2a and 3. Based on these patients, the intra-individual coefficient of variation for NT-proBNP in PARADIGM-HF was estimated to be 34.8%.

A search of the literature was conducted to identify publications on the variability of NT-proBNP in adults or children (search terms: biological variability OR intra-patient variability OR intrapatient variability OR coefficient of variation; pediatric OR paediatric OR children; and NT-proBNP OR BNP). The publications were then reviewed and selected for relevance (e.g., assessed within-subject variability, data in HF patients, original research rather than review articles). The search did not retrieve any study of the biological variability of NT-proBNP in children. Eight relevant publications (7 original research articles and one letter to the editor), all in adults, were selected and included in the analysis (*Table 34*). Additionally, in pediatric review articles from Nir et al 2009 and Cantinotti 2016 it was reported that BNP/NT-proBNP concentrations have the highest drop in the first month of life, with a smaller reduction up to the age of 2 and then without any significant change up to 12 years of age, thus further supporting the adequacy of using the same RCV values for adults and children.

Table 34 shows the estimated RCVs based on PARADIGM (B2314) enalapril run-in dataset, PARADIGM DCM (B2314 DCM) enalapril run-in dataset and 8 published datasets. The estimated RCVs based on B2314 are around −60% which is consistent with the externally published datasets, which range from −22% to −61% with a 97.5% insurance against false positive reduction.

The RCVs corresponding to the 90% insurance against false positive reduction are also presented since, based on the argument of Fokkema et al 2006, 97.5% is probably too high of a hurdle for insurance and 90% might be clinically more appropriate for the HF population to lower the false-negative rate. The corresponding RCVs range from −16% to −46%.

Table 34 Estimated RCVs from PARADIGM-HF and external published studies – RCVs were calculated with the lognormal distribution

Study or article	Population	N	% of probability insurance	CV_t	RCV
Study B2314	Stable CHF	835	97.5%	34.8%	−60.8%
			90%		−45.8%
B2314 CM subgroup	Stable CHF	185	97.5%	31.3%	−57.2%
			90%		−42.5%
Meijier et al 2016	Stable CHF	83	97.5%	22.0%	−45.3%

Study or article	Population	N	% of probability insurance	CV_t	RCV
			90%		−32.5%
Bruins et al 2004 (w-w)	Stable CHF	43	97.5%	35.0%	−61.0%
			90%		−46.0%
Frankenstein et al 2009 (14 days)	Stable CHF	41	97.5%	17.7%	−38.5%
			90%		−27.2%
Frankenstein et al 2009 (1-month)	Stable CHF	41	97.5%	19.0%	−40.7%
			90%		−28.9%
O'Hanlon et al 2007 (1 w)	Stable CHF	45	97.5%	21.1%	−43.9%
			90%		−31.5%
Nordenskjöld et al 2013 (3 w)	Stable CAD	24	97.5%	20.4%	−42.9%
			90%		−30.6%
Tager et al 2019 (2 w)	Stable CHF	50	97.5%	9.3%	−22.7%
			90%		−15.5%
Schimmel et al 2016 (w-w)	Stable CHF	22	97.5%	30.0%	−55.7%
			90%		−41.2%

From these analyses, RCVs ranged from −16% to −61%, depending on the dataset and insurance level chosen. For the CHMP proposed responder analysis, we chose RCV thresholds −22%, −33%, −46%, and −61% from the above range. The RCV threshold of −16% was not included because it is well within the intra-subject variability from most data sources and hence might be too low to protect against false positives, i.e. to distinguish between deterioration in a patient's clinical condition and random noise. The results of the responder analysis are presented in *Table 35*. It shows reasonable proportions of patients who had reached or crossed the thresholds within treatment groups. Interestingly, especially for children in PANORAMA-HF, numerically consistently higher rates of responders in the sacubitril/valsartan group compared to the enalapril group for each threshold, for both children and adults, are observed. In addition to the odds ratios being all greater than 1.5, the lower limits of the 95% confidence intervals of the odds ratios are greater than 1 for the between treatment responder comparison for all thresholds in adults and for the −33% and −46% thresholds in children, indicating a systematic difference in favor of sacubitril/valsartan in the responder rates between the treatment groups.

Table 35 Responder rates for the selected RCV thresholds for PARADIGM-HF (B2314) and PANORAMA-HF (B2319).

		Number (%) of Responders				
	RCV threshold	LCZ696		Enalapril		OR (95% CI)
Study	(%)	N	n (%)	N	n (%)	LCZ696 vs Enalapril
B2314 (Month 8)	-22	885	495 (56.0)	874	336 (38.4)	2.05 (1.69, 2.48)
	-33		409 (46.2)		243 (27.8)	2.25 (1.84, 2.75)
	-46		301 (34.0)		174 (19.9)	2.08 (1.67, 2.60)
	-61		187 (21.1)		96 (11.0)	2.18 (1.66, 2.85)
B2314 DCM (Month 8)	-22	178	114 (64.0)	167	73 (43.7)	2.44 (1.56, 3.82)
	-33		97 (54.5)		50 (29.9)	2.97 (1.88, 4.68)
	-46		82 (46.1)		42 (25.2)	2.60 (1.64, 4.14)
	-61		60 (33.7)		26 (15.6)	2.85 (1.68, 4.83)
B2319 (Week 52)	-22	144	109 (75.7)	133	86 (64.7)	1.69 (0.98, 2.92)
	-33		103 (71.5)		74 (55.6)	2.04 (1.21, 3.44)
	-46		91 (63.2)		60 (45.1)	2.12 (1.27, 3.52)
	-61		67 (46.5)		47 (35.3)	1.56 (0.92, 2.65)

N: Number of patients in the analysis; n,%: Number and % of patients satisfying criterion

Odds ratio (OR) is derived by adjusting for baseline log(NT-proBNP), region for B2314, plus modified age group by NYHA/ROSS class for B2319.

Source: [120D Response Appendix-Table 14.2-8.2.haq.03]

Time to recurrent Category 1 and 2 events

Analysis of all Category 1 and 2 events (first and recurrent) showed a numerical trend in favour of sacubitril/valsartan but no significant difference between the treatment groups. Based on positively adjudicated Category 1 and 2 events (73 in the sacubitril/valsartan group and 79 in the enalapril group), the rate ratio (sacubitril/valsartan/enalapril) was 0.9225 (95% CI: 0.5386, 1.5800). Based on investigator-reported Category 1 and 2 events (88 in the sacubitril/valsartan group and 112 in the enalapril group, the rate ratio (sacubitril/valsartan/enalapril) was 0.7808 (95% CI: 0.4700, 1.2973).

The total number of Category 1 events was lower in the sacubitril/valsartan vs the enalapril group, based on both positively adjudicated events (25 vs 36) and investigator-reported events (31 vs 45). For Category 2 events, the total number of positively adjudicated events was higher in the sacubitril/valsartan group vs the enalapril group (48 vs 43), but for investigator-reported events, the trend was the opposite, with fewer events reported in the sacubitril/valsartan group vs the enalapril group (57 vs 67).

PedsQL score

PedsQL change from baseline

Improvements (i.e. a higher score) in both patient-reported and parent-reported total PedsQL scores were observed in both treatment groups. Patient-reported mean PedsQL scores (patients 5 to <18 years of age) increased from 72.51 at baseline to 77.12 at Week 52 in the sacubitril/valsartan group (mean increase from baseline 5.24). For enalapril, mean PedsQL scores increased from 69.90 at baseline to 72.22 at Week 52 (mean increase from baseline 2.34). Similar improvements were observed for parent-reported total PedsQL scores: in the overall population (patients 1 month to <18 years of age), mean parent-reported PedsQL scores increased from 70.91 at baseline to 77.23 at Week 52 in the sacubitril/valsartan group (mean increase 5.94), and from 72.37 at baseline to 76.09 at Week 52 in the enalapril group (mean increase 3.89). Similar results were observed in the age groups 6 to <18 years of age, 2 to <6 years of age, and 1 month to <2 years of age as in the overall populations.

The change from baseline in patient-reported and in parent-reported total PedsQL scores up to Week 52 based on the MMRM analysis was numerically higher in the sacubitril/valsartan group than in the enalapril group, but not significantly different between the treatment groups. Importantly, in the sacubitril/valsartan group, the adjusted least squares mean change from baseline exceeded the minimally clinically important difference threshold of 4.5 at Weeks 36 and 52 for both patient-reported and parent reported PedsQL, whereas the threshold was not crossed in the enalapril group (Table 36).

The change in patient-reported Physical functioning subscore, which was used for further ranking in the global rank endpoint for patients in age group 1, was also numerically higher in the sacubitril/valsartan group than in the enalapril group. The adjusted least squares mean change from baseline at Week 52 was 6.0439 (95% CI: 1.6506, 10.4372) in the sacubitril/valsartan group, and 1.7617 (95% CI: -2.5698, 6.0932) in the enalapril group.

Table 36. Part 2 paediatric quality of life (PedsQL) – patient and parent-reported total summary score – change from baseline without cutoff – Mixed Model for Repeated Measures (MMRM) (Full Analysis Set)

	LCZ696 N=187		Enalapril N=188		Comparison LCZ696 vs Enalapril	
	n	ALSM of CFB (95% CI)	n	ALSM of CFB (95% CI)	ALSM (Sac/Val - enalapril) 95% CI	Two-sided p-value
Patient-reported total summary score						
Week 12	97	3.6515 (1.23, 6.07)	100	1.0748 (-1.30, 3.45)	2.5767 (-0.81, 5.97)	0.1356
Week 24	91	3.8637 (1.33, 6.40)	94	3.0810 (0.58, 5.58)	0.7827 (-2.78, 4.35)	0.6654
Week 36	87	5.2667 (2.61, 7.93)	87	1.8897 (-0.76, 4.53)	3.3770 (-0.38, 7.13)	0.0776
Week 52	89	4.8186 (2.08, 7.56)	89	1.7246 (-1.01, 4.46)	3.0939 (-0.78, 6.97)	0.1170
Parent-reported total summary score						
Week 12	162	3.6903 (1.83, 5.55)	164	3.8811 (2.02, 5.74)	-0.1908 (-2.83, 2.45)	0.8869
Week 24	156	4.3249 (2.35, 6.30)	152	2.9577 (0.95, 4.96)	1.3672 (-1.45, 4.19)	0.3407
Week 36	146	4.9338 (2.74, 7.13)	144	4.3318 (2.11, 6.55)	0.6020 (-2.53, 3.73)	0.7052
Week 52	154	5.4962 (3.22, 7.77)	149	3.7476 (1.43, 6.06)	1.7486 (-1.50, 5.00)	0.2906

ALSM=adjusted least squares mean, CI=confidence interval, CFB= change from baseline.
The MMRM model includes change from baseline in patient and parent reported total summary score as response, age group (1 to <2 years, 2 to <6 years, 6 to <18 years), baseline NYHA/ROSS class, region, treatment, visit, and treatment by-visit interaction as fixed-effect factors; baseline patient reported total summary score and visit-by baseline interaction as covariates.
For USM-impacted patients, the on treatment assessments are included
Source: [Study B2319-Table 14.2-6.1, Table 14.2-6.2]

Proportion of patients with a 4.5 change from baseline in PedsQL

The proportion of patients with an improvement of at least 4.5 points in patient-reported PedsQL score was numerically higher in the sacubitril/valsartan group throughout the study. At Week 52, the proportion of patients with at least 4.5 point improvement was 43.43% in the sacubitril/valsartan group and 38.38% in the enalapril group; the results numerically favoured sacubitril/valsartan, with an OR of 1.5100 (95% CI: 0.8055, 2.8304; nominal 2-sided p=0.1987).

A similar pattern was observed for parent-reported PedsQL: At Week 52, the proportion of patients with at least 4.5 point improvement was 45.78% vs 42.07% for the sacubitril/valsartan and enalapril groups, respectively, with an OR of 1.1606 (95% CI: 0.7265, 1.8541; nominal 2-sided p=0.533).

Conversely, the proportion of patients with a deterioration in PedsQL of at least 4.5 points was numerically lower in the sacubitril/valsartan group than in the enalapril group in both parent-reported and patient-reported PedsQL.

PGIC score through 52 weeks

PGIC scores indicated that there was a progressive increase in the proportion of patients who felt "much better" or "better" since the start of the study in both treatment groups from Week 4 until Week 52 (Table 37). At Week 52, the proportion of patients who felt much better was 33.33% in the sacubitril/ valsartan group vs 28.24% in the enalapril group. The corresponding figures for patients who felt better were 40.94% vs 38.24% for the respective groups.

Although analysis of change from baseline showed no statistically significant difference between treatment groups for the PGIC at Week 52, the results numerically favoured sacubitril/valsartan, with an OR of 1.3510 (95% CI: 0.9134, 1.9983; nominal two-sided p=0.1320).

Table 37. Part 2 Patient Global Impression of Change (PGIC) without cutoff proportional cumulative odds model – post Category 1 event set to much worse (Full Analysis Set)

Categories	LCZ696 N=187 n (%)	Enalapril N=188 n (%)	Comparison (LCZ696/Enalapril) Adjusted Odds Ratio	95% CI	Two-sided nominal p-value
Week 4					
Observed	172	181	0.9004	(0.6054, 1.3391)	0.6045
Much better	19 (11.05)	15 (8.29)			
Better	67 (38.95)	85 (46.96)			
No change	81 (47.09)	74 (40.88)			
Worse	5 (2.91)	7 (3.87)			
Much Worse	0	0			
Week 12					
Observed	174	176	1.0541	(0.7100, 1.5650)	0.7939
Much better	27 (15.52)	30 (17.05)			
Better	88 (50.57)	82 (46.59)			
No change	53 (30.46)	57 (32.39)			
Worse	2 (1.15)	0			
Much Worse	4 (2.30)	7 (3.98)			
Week 24					
Observed	173	170	1.2285	(0.8318, 1.8143)	0.3010
Much better	44 (25.43)	36 (21.18)			
Better	72 (41.62)	73 (42.94)			
No change	45 (26.01)	46 (27.06)			
Worse	4 (2.31)	6 (3.53)			
Much Worse	8 (4.62)	9 (5.29)			
Week 36					
Observed	161	163	1.2316	(0.8265, 1.8352)	0.3061
Much better	46 (28.57)	41 (25.15)			
Better	65 (40.37)	63 (38.65)			
No change	37 (22.98)	43 (26.38)			
Worse	3 (1.86)	2 (1.23)			
Much Worse	10 (6.21)	14 (8.59)			
Week 52					
Observed	171	170	1.3510	(0.9134, 1.9983)	0.1320
Much better	57 (33.33)	48 (28.24)			
Better	70 (40.94)	65 (38.24)			
No change	29 (16.96)	42 (24.71)			
Worse	3 (1.75)	1 (0.59)			
Much Worse	12 (7.02)	14 (8.24)			

For each visit, the proportional cumulative odds model uses PGIC change (much better < better < no change < worse < much worse) at the visit as response, and stratified by modified age group in which treatment and baseline included as fixed-effect factors.
For USM-impacted patients, the on treatment assessments are included.
Source:[Study B2319-Table 14.2-7.1]

2.6.8.4. Ancillary analyses

None

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (see later sections).

Title: Multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and, 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 paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction		
Study identifier	CLCZ696B2319; EUDRACT number: 2015-004207-22	
Design	Part 1: This is a multi-center, open-label, study in paediatric patients (1 month to <18 years) with HF (LVEF = 45% or LV fractional shortening = 22.5%). Part 2: This is a randomized, multicenter, double blind, parallel-group, active controlled, 52-week study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in paediatric HF patients (1 month to < 18 years).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Part 1: not applicable, PK/PD evaluation Part 2: 52 weeks Not applicable The open label extension study (separate study CLCZ696B2319E1) will continue up to 2 years from LPLV of the part 2 of LCZ696B2319
Hypothesis	Superiority	
Treatments groups	sacubitril/valsartan	Part 1: Sacubitril / Valsartan Age Groups 1 and 2: Single dose 0.8 mg/kg, 3.1 mg/kg Age Group 3: Single dose of 0.4 mg/kg, 1.6 mg/kg N = 26 patients Part 2: Sacubitril / Valsartan Dose: 3.1 mg/kg in Group 1 and 2 Dose: 2.3 mg/kg in group 3. In addition, Group 3 patients who turned 1 year old during the study, could be further up-titrated to a dose of 3.1 mg/kg bid Duration: 52 weeks N= 187

	Enalapril		Part 1: not applicable Part 2: Enalapril Dose: 0.2 mg / kg in group 1 and 2 Dose: 0.15 mg / kg in group 3. In addition, Group 3 patients who turned 1 year old during the study, could be further up-titrated to a dose of 0.2 mg/kg bid N = 188 Duration:52 weeks
	Part 1		
	Primary endpoint	PK and PD	PK and PD of LCZ696 after single dose treatment PK: Cmax (ng/mL); Tmax (h); AUClast, AUCinf (h▪ng/mL); Cl/F (L/h); T1/2 (h); PD: plasma BNP, plasma NTproBNP, plasma cGMP, urine cGMP change from baseline geometric mean ratio (GMR) after single dose treatment
Endpoints and definitions	Secondary endpoint	Safety	To assess the safety and tolerability of LCZ696 in paediatric patients with HF
	Part 2		
	Primary endpoint	Global rank endpoint	The efficacy of LCZ696 compared to enalapril after 52-week of double-blind treatment is assessed using a global rank endpoint. The ranking was based on clinical events (such as death, listing for urgent heart transplant, mechanical life support requirement at end of study), worsening HF, NYHA/Ross class, Patient Global Impression of Severity (PGIS), and Paediatric quality of life inventory (PedsQL) physical functioning domain. Clinical events (Categories 1 and 2) are adjudicated by an external independent adjudication committee.
	Secondary endpoint	Time to recurrent events of Cat 1 and Cat 2	Time to first occurrence of Category 1 or Category 2 event through 52 weeks of treatment
	Secondary endpoint	NYHA/Ross	NYHA/Ross functional class change from baseline through 52 weeks of treatment
	Secondary endpoint	PGIS	PGIS score change from baseline through 52 weeks of treatment
	Secondary endpoint	PopPK	Population PK LCZ696
	Secondary endpoint	Safety	Safety and tolerability through 52 weeks of treatment

	Exploratory endpoint	PedsQL	PedsQL score change from baseline through 52 weeks of treatment
	Exploratory endpoint	NT-proBNP	NTproBNP change from baseline through 4,12 and 52 weeks treatment
	Exploratory endpoint	PGIC	PGIC score through 52 weeks of treatment
	Exploratory endpoint	Time to recurrent events of Cat 1 and Cat 2	Time to recurrent events of Category 1 and Category 2 through 52 weeks of treatment
Database lock	January 27th 2022		

Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full analysis 52 weeks			
Descriptive statistics and estimate variability	Treatment group		Sacubitril/valsartan	Enalapril
	Number of subjects		187	188
	Category 1 (PACE) – n (%)		19 (10.16)	30 (15.96)
	Death		8 (4.28)	12 (6.38)
	UNOS status 1A listing for heart transplant or equivalent		5 (2.67)	7 (3.72)
	VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support		7 (3.74)	12 (6.38)
	Discontinued from the study during the double-blinded epoch without Category 1 event		6 (3.21)	10 (5.32)
	Category 2 (PACE) - n (%)		18 (9.63)	9 (4.79)
	Worsening heart failure hospitalization with ICU stay		11 (5.88)	3 (1.60)
	Worsening heart failure hospitalization without ICU stay		5 (2.67)	5 (2.66)
	Worsening heart failure without hospitalization		2 (1.07)	1 (0.53)
	Category 3 (LOCF) - n (%)		20 (10.70)	15 (7.98)
	Category 4 (LOCF) - n (%)		45 (24.06)	57 (30.32)
	Category 5 (LOCF) - n (%)		85 (45.45)	77 (40.96)
Effect estimate per comparison	Primary endpoint	Comparison groups	Sacubitril/valsartan vs Enalapril	
		Mann Whitney Probability	0.5244	
		95% CI	(0.4665, 0.5817)	
		Mann-Whitney Odds	0.9069	
		Variability statistic	(0.7191, 1.1438)	

		P-value	0.4238

Results and Analysis			
Analysis description	Secondary endpoint analysis - Time to Category 1 or Category 2 events		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Neparvis	Enalapril
	Number of subjects	187	188
	Category 1 or Category 2 event n (%)	34 (18.18)	33 (17.55)
	EAIR (95% CI)	20.133 (13.9430, 28.1344)	20.042 (13.7960, 28.1464)
Effect estimate per comparison	Comparison groups	Sacubitril/valsartan vs Enalapril	
	Adjusted Hazard Ratio	1.0655	
	95% CI	(0.6589, 1.7232)	
	Nominal P-value Two sided	0.7958	

Results and Analysis			
Analysis description	Secondary endpoint analysis - NYHA/Ross functional class change from baseline		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Sacubitril/valsartan	Enalapril
	Number of patients	187	188
	Improved n (%)	Week 4: 26 (14.21) Week 12: 43 (23.89) Week 24: 48 (26.97) Week 36: 50 (29.94	Week 4: 29 (15.76) Week 12: 46 (25.56) Week 24: 48 (27.91) Week 36: 58 (34.12)
	Unchanged n (%)	Week 4: 154 (84.15) Week 12: 127 (70.56) Week 24: 114 (64.04) Week 36: 102 (61.08) Week 52: 78 (59.65)	Week 4: 152 (82.61) Week 12: 122 (67.78) Week 24: 110 (63.95) Week 36: 99 (58.24) Week 52: 90 (56.60)
	Worsened n (%)	Week 4: 3 (1.64) Week 12: 10 (5.56) Week 24: 16 (8.99) Week 36: 15 (8.98) Week 52: 18 (11.60)	Week 4: 3 (1.63) Week 12: 12 (6.67) Week 24: 14 (8.14) Week 36: 13 (7.65) Week 52: 15 (9.43)
Effect estimate per	Comparison groups	Sacubitril/valsartan vs Enalapril	

comparison	Adjusted Odds Ratio Sacubitril/valsartan /Enalapril	Week 4: 0.8516 Week 12: 0.9200 Week 24: 0.9077 Week 36: 0.8162
	95% CI	Week 4: (0.4874, 1.4879) Week 12: (0.5855, 1.4455) Week 24: (0.5820, 1.4158) Week 36: (0.5229, 1.2742)
	Nominal P-value Two sided	Week 4: 0.5725 Week 12: 0.7176 Week 24: 0.6695 Week 36: 0.3715

Results and Analysis			
Analysis description	Secondary endpoint analysis - Global impression of severity (PGIS) change from baseline		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Sacubitril/valsartan	Enalapril
	Number of subjects	187	188
	Improved n (%)	Week 4: 47 (27.01) Week 12: 55 (30.90) Week 24: 58 (33.33) Week 36: 54 (33.33) Week 52: 54 (35.53)	Week 4: 54 (29.67) Week 12: 56 (31.46) Week 24: 65 (38.01) Week 36: 56 (33.94) Week 52: 55 (34.81)
	Unchanged n (%)	Week 4: 101 (58.05) Week 12: 93 (52.25) Week 24: 85 (48.85) Week 36: 80 (49.38) Week 52: 73 (48.03)	Week 4: 109 (59.89) Week 12: 99 (55.62) Week 24: 83 (48.54) Week 36: 87 (52.73) Week 52: 75 (47.47)
	Worsened n (%)	Week 4: 26 (14.94) Week 12: 30 (16.85) Week 24: 31 (17.82) Week 36: 28 (17.28) Week 52: 25 (16.45)	Week 4: 19 (10.44) Week 12: 23 (12.92) Week 24: 23 (13.45) Week 36: 22 (13.33) Week 52: 28 (17.72)
Effect estimate per comparison	Comparison groups	Sacubitril/valsartan vs Enalapril	
	Adjusted Odds Ratio Sacubitril/valsartan /Enalapril	Week 4: 0.7687 Week 12: 0.9224 Week 24: 0.8266 Week 36: 0.9893 Week 52: 1.1498	
	95% CI	Week 4: (0.4945, 1.1949) Week 12: (0.6035, 1.4100) Week 24: (0.5366, 1.2734) Week 36: (0.6352, 1.5407) Week 52: (0.7349, 1.7989)	

	Nominal P-value Two sided	Week 4: 0.2425 Week 12: 0.7092 Week 24: 0.3878 Week 36: 0.9619 Week 52: 0.5412

Results and Analysis			
Analysis description	Exploratory endpoint analysis - NT-proBNP change from baseline		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Sacubitril/valsartan	Enalapril
	Number of subjects	187	188
	Improved n (%)	Week 4: 47 (27.01) Week 12: 55 (30.90) Week 24: 58 (33.33) Week 36: 54 (33.33) Week 52: 54 (35.53)	Week 4: 54 (29.67) Week 12: 56 (31.46) Week 24: 65 (38.01) Week 36: 56 (33.94) Week 52: 55 (34.81)
	Unchanged n (%)	Week 4: 101 (58.05) Week 12: 93 (52.25) Week 24: 85 (48.85) Week 36: 80 (49.38) Week 52: 73 (48.03)	Week 4: 109 (59.89) Week 12: 99 (55.62) Week 24: 83 (48.54) Week 36: 87 (52.73) Week 52: 75 (47.47)
	Worsened n (%)	Week 4: 26 (14.94) Week 12: 30 (16.85) Week 24: 31 (17.82) Week 36: 28 (17.28) Week 52: 25 (16.45)	Week 4: 19 (10.44) Week 12: 23 (12.92) Week 24: 23 (13.45) Week 36: 22 (13.33) Week 52: 28 (17.72)
Effect estimate per comparison	Comparison groups	Sacubitril/valsartan vs Enalapril	
	Adjusted Odds Ratio Sacubitril/Valsartan vs Enalapril	Week 4: 0.7687 Week 12: 0.9224 Week 24: 0.8266 Week 36: 0.9893 Week 52: 1.1498	
	95% CI	Week 4: (0.4945, 1.1949) Week 12: (0.6035, 1.4100) Week 24: (0.5366, 1.2734) Week 36: (0.6352, 1.5407) Week 52: (0.7349, 1.7989)	
	Nominal P-value Two sided	Week 4: 0.2425 Week 12: 0.7092 Week 24: 0.3878 Week 36: 0.9619 Week 52: 0.5412	

Results and Analysis			
Analysis description	Exploratory endpoint analysis - PedsQL score		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Sacubitril/valsartan	Enalapril
	Number of subjects	187	188

	Improved n (%)	Week 4: 47 (27.01) Week 12: 55 (30.90) Week 24: 58 (33.33) Week 36: 54 (33.33) Week 52: 54 (35.53)	Week 4: 54 (29.67) Week 12: 56 (31.46) Week 24: 65 (38.01) Week 36: 56 (33.94) Week 52: 55 (34.81)
	Unchanged n (%)	Week 4: 101 (58.05) Week 12: 93 (52.25) Week 24: 85 (48.85) Week 36: 80 (49.38) Week 52: 73 (48.03)	Week 4: 109 (59.89) Week 12: 99 (55.62) Week 24: 83 (48.54) Week 36: 87 (52.73) Week 52: 75 (47.47)
	Worsened n (%)	Week 4: 26 (14.94) Week 12: 30 (16.85) Week 24: 31 (17.82) Week 36: 28 (17.28) Week 52: 25 (16.45)	Week 4: 19 (10.44) Week 12: 23 (12.92) Week 24: 23 (13.45) Week 36: 22 (13.33) Week 52: 28 (17.72)
Effect estimate per comparison	Comparison groups	Sacubitril Valsartan vs Enalapril	
	Adjusted Odds Ratio LCZ696/Enalapril	Week 4: 0.7687 Week 12: ~~0~~ 0.9224 Week 24: 0.8266 Week 36: 0.9893 Week 52: 1.1498	
	95% IC	Week 4: (0.4945, 1.1949) Week 12: (0.6035, 1.4100) Week 24: (0.5366, 1.2734) Week 36: (0.6352, 1.5407) Week 52: (0.7349, 1.7989)	
	Nominal P-value Two sided	Week 4: 0.2425 Week 12: 0.7092 Week 24: 0.3878 Week 36: 0.9619 Week 52: 0.5412	

Results and Analysis			
Analysis description	Exploratory endpoint analysis - PGIC score through 52 weeks		
Analysis population and time point description	Full Analysis set		
Descriptive statistics and estimate variability	Treatment group	Sacubitril/valsartan	Enalapril
	Number of subjects	187	188
	Improved n (%)	Week 4: 47 (27.01) Week 12: 55 (30.90) Week 24: 58 (33.33) Week 36: 54 (33.33) Week 52: 54 (35.53)	Week 4: 54 (29.67) Week 12: 56 (31.46) Week 24: 65 (38.01) Week 36: 56 (33.94) Week 52: 55 (34.81)
	Unchanged n (%)	Week 4: 101 (58.05) Week 12: 93 (52.25) Week 24: 85 (48.85) Week 36: 80 (49.38) Week 52: 73 (48.03)	Week 4: 109 (59.89) Week 12: 99 (55.62) Week 24: 83 (48.54) Week 36: 87 (52.73) Week 52: 75 (47.47)
	Worsened n (%)	Week 4: 26 (14.94) Week 12: 30 (16.85) Week 24: 31 (17.82) Week 36: 28 (17.28) Week 52: 25 (16.45)	Week 4: 19 (10.44) Week 12: 23 (12.92) Week 24: 23 (13.45) Week 36: 22 (13.33) Week 52: 28 (17.72)
Effect estimate per	Comparison groups	Sacubitril/valsartan vs Enalapril	

comparison	Adjusted Odds Ratio LCZ696/Enalapril	Week 4: 0.7687 Week 12: 0.9224 Week 24: 0.8266 Week 36: 0.9893 Week 52: 1.1498
	95% CI	Week 4: (0.4945, 1.1949) Week 12: (0.6035, 1.4100) Week 24: (0.5366, 1.2734) Week 36: (0.6352, 1.5407) Week 52: (0.7349, 1.7989)
	Nominal P-value Two sided	Week 4: 0.2425 Week 12: 0.7092 Week 24: 0.3878 Week 36: 0.9619 Week 52: 0.5412

2.6.8.5. Clinical studies in special populations

None

2.6.8.6. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.8.7. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.8.8. Supportive study(ies)

Not applicable.

2.6.9. Discussion on clinical efficacy

Sacubitril/valsartan is approved in adult patients with heart failure with reduced ejection fraction (HFrEF) based on the results from study B2314, in which it demonstrated superiority over enalapril in reducing the risk of the primary composite endpoint of CV death or hospitalizations for heart failure (HF) by 20%.

The totality of evidence included in this submission supporting the efficacy of sacubitril/valsartan for paediatric use includes 1) extrapolation of the existing adult HFrEF data from study B2314 (PARADIGM-HF) to children based on the pharmacokinetic and pharmacodynamic data from study B2319 (PANORAMA-HF) and 2) the clinical data provided by the PANORAMA-HF study.

Extrapolation plan

Disease similarity was proposed by the applicant between adults with HFrEF based on DCM and paediatric heart failure patients with LVSD consistent with DCM. Similarities have also been highlighted in the draft ICH E11A 2022 guideline stating that *"... heart failure due to dilated cardiomyopathy is*

similar between adult and paediatric populations, allowing for extrapolation from adult to paediatric patients with dilated cardiomyopathy".

Dilated cardiomyopathy is considered a form of heart muscle disease (abnormal ventricular myocardium) whose primary abnormality is systolic dysfunction. While dilation is also a component of this disease, it can be agreed that treatment strategies in children are based on signs, symptoms, and the degree of systolic dysfunction. PANORAMA-HF aimed to enrol a homogeneous population of pediatric HF with left ventricle systolic dysfunction (LVSD) consistent with DCM. HCM and RCM, along with uncorrected structural heart disease and single ventricle or systemic right ventricle, were excluded. Enrolment of a homogeneous pediatric HF population with LVSD consistent with DCM in PANORAMA-HF was thus achieved by defining a series of inclusion and exclusion criteria, which made sure all patients had symptomatic HF and HFrEF, which is defined as LVSD in pediatric patients.

More than 60% of patients in PANORAMA-HF had a diagnosis of cardiomyopathy, with the cause being idiopathic in 33.6%, followed by familial/genetic conditions in 15.7% and congenital heart malformations in 13.3%. Heart failure secondary to other causes was noted in about 35% of patients. In those 35% of patients where the etiology of HF was not primarily identified as related to cardiomyopathy, it is known from literature, that all can evolve into or manifest as DCM. In particular, the most frequent cause was myocarditis-induced HF, which itself is the most common cause of acquired DCM in children. In PANORAMA-HF, while there was no collection of echocardiographic data regarding ventricle volumes or diameters to confirm a diagnosis of DCM, all diseases included are known to evolve or manifest as DCM, and, additionally, patients with restrictive or hypertrophic cardiomyopathy were excluded. Nonetheless, as recommended by treatment guidelines, the treatment of heart failure in children is based on pathophysiology, hence based on systolic vs. diastolic dysfunction and based on approved adult HFrEF therapies.

It can be agreed that PANORAMA-HF evaluated a relatively homogeneous population with biventricular hearts and symptomatic HF due to a systemic left ventricle with decreased ejection fraction. All diseases included are known to possibly evolve or manifest as DCM. Such an approach resulted in a patient population that resembles the adult HF population with DCM. In conclusion, all patients enrolled in PANORAMA-HF had a diagnosis of LVSD, while patients with HCM, RCM, complex congenital heart disease with functional single ventricle or systemic right ventricle were excluded. Despite the lack of LV diameter measurement, the literature and clinical practice support that all enrolled pediatric patients with systemic LVSD also had a form of DCM. Furthermore, both adult HFrEF with DCM and pediatric HF due to LVSD have similar pathophysiology, including a reduced cardiac output due to left ventricle insufficiency, which causes reduced organ perfusion, increased adrenergic tone, and RAAS activation. These translate into increased sodium retention and increased volume, which can further worsen left ventricle function.

Similar drug pharmacology was established by demonstrating that sacubitrilat and valsartan drug exposure in paediatric HF patients is similar to exposure in adult heart HF at the same dose (Age Groups 1 and 2) with the ratios of geometric means of drug exposure (AUC children /AUC adults) being 0.80-0.92 and 0.99 1.29 for sacubitrilat and valsartan, respectively. Age Group 3 showed corresponding AUC changes consistent with the dose change (dose was initially 50% reduced considering the potential impact of developing the capacity of drug disposition), with the ratios of geometric means of the drug exposure (AUC children/AUC adults) being 0.39 and 0.61 for sacubitrilat and valsartan, respectively.

Similar exposure response was established by demonstrating a similar magnitude of NT-proBNP reductions at exposure-matched doses of sacubitril/valsartan in the paediatric study B2319 and adult study B2314. The ratio of NT-proBNP relative to baseline between paediatric HF patients (3.1 mg/kg) and adult HF patients (200 mg) was 0.78 (95% CI: 0.67, 0.89), while when compared to adult HF

patients with DCM it was 0.94 (95% CI: 0.74, 1.2).
NT-proBNP as a bridging biomarker for extrapolation of effects in adults with DCM to the paediatric population was assessed using the Prentice criteria. The Prentice criteria provide a systematic framework to establish the adequacy of NT-proBNP as a bridging biomarker. This includes the demonstration that the treatment has a significant impact on the true clinical endpoint, the treatment has a significant impact on the biomarker, the biomarker is significantly associated with true clinical endpoint and that the biomarker explains the effect of treatment on true clinical endpoint.
Study B2314 in adults (n=2080) with HFrEF with DCM demonstrated that sacubitril/valsartan treatment has a significant impact on the true clinical endpoint of reducing the risk of CV death or HF hospitalizations compared to enalapril (RRR:25%) (1st Prentice criterion). In the subgroup of adult patients with HFrEF with DCM, the reduction in NT-proBNP from baseline was 43% at Month 1, and 52% at Month 8 in the sacubitril/valsartan arm (n=885), indicating that the treatment has a significant impact on the biomarker NT-proBNP (2nd Prentice criterion). Furthermore, a change in plasma NT-proBNP was associated with the CV mortality/HF hospitalization rate in adult patients with HFrEF with DCM in study B2314 (n=405), indicating that the biomarker is significantly associated with true clinical endpoint (3rd Prentice criterion). The association between NT-proBNP and risk of clinical events was similarly observed in paediatric patients (B2319), where a doubling of NT-proBNP levels at baseline or post-baseline was associated, respectively, with 1.8-fold and 2.1-fold increase of the risk of Category 1 or 2 events (n=375). Lastly, study B2314 in adults with HFrEF demonstrated that the majority of the sacubitril/valsartan treatment effect on the time to first event of CV death or HF hospitalization endpoint is explained by NT-proBNP over time (n=1990)(4th Prentice criterion). The proportion of treatment effect explained on top of baseline NT-ProBNP was 85.55%, with the 95% CI (6.35%, 164.76%) excluding zero. The applicant has performed sensitivity analyses to assess the robustness of the proportion of treatment effect explained using structural equation modelling and counterfactual methods. To this end, an Aalen additive hazard model was used, which demonstrated that the percent contribution of the natural indirect effect from NT-proBNP relative change to the total effect: 81.4% (CI:24.7% to 509.3%), which is very close to the result of 82.5% (CI:1.26% to 164%) obtained with the “change in coefficients” method presented in the original submission. This is considered acceptable.

Design and conduct of clinical study B2319

Study B2319, consisted of two parts. Part 1 was a multicenter, open-label study to evaluate the safety, tolerability, PK and PD of sacubitril/valsartan, which served to select the dose for part 2. Part 2 was a 52-week randomized, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with HF due to systemic left ventricle systolic dysfunction (LVSD). The overall design of the study was endorsed by the PDCO (000316-PIP02-11 and modifications).

Dose selection

In Part 1, PD and PK effects of sacubitril/valsartan were evaluated in three age categories (Age Group 1 (6 to <18 years; n=9), Age Group 2 (1 to <6 years; n=9), and Age Group 3 (1 month to <1 year; n=8)). The sacubitril/valsartan doses used were 0.8 mg/kg and 3.1 mg/kg for Age Groups 1 and 2, and 0.4 mg/kg and 1.6 mg/kg for Age Group 3. The objective was to select a dose for Part 2 that provided similar exposures of sacubitril and valsartan to that observed in adult HF patients and that also maximized neprilysin inhibition. The PD effect of neprilysin inhibition was assessed through urine and plasma biomarkers. Single doses of sacubitril/valsartan in patients 1 month to <18 years of age demonstrated similar PK as the adult HF patient population based on approximate dose-proportional exposure increase, observed sacubitril $T_{1/2}$, and total body plasma clearance for both sacubitril and valsartan. Furthermore, administration of sacubitril/valsartan resulted in increases in urinary cGMP in all age groups, which were dose-dependent. Overall, the results from Part 1 indicated for age group 1 and 2 that a target dose of 3.1 mg/kg achieved similar exposure to the adult dose of 200mg. For age

group 3, the dose in part 1 was reduced to 1.6mg/kg, considering the potential impact of developing capacity of drug disposition in this very young age group on drug exposure. The target dose for age group 3 (1 month to <1 year) was increased from the originally planned 1.6 mg/kg to 2.3 mg/kg, as agreed upon by the DMC and the FDA. Although the specific grounds for this decision have not been provided, this issue is not pursued since only an indication is sought for paediatric patients of one year and older.

The target dose was further confirmed by the population PK data and PK/PD analysis of NT-proBNP from Part 2. More specifically, the dose-exposure-response of sacubitril/valsartan and NT-proBNP appeared to be consistent between paediatric and adult patients with HF at their equivalent dose, especially in the comparison of paediatric HF with adult patients with HFrEF due to DCM.

Overall, the recommended target sacubitril/valsartan dose is 3.1 mg/kg twice daily for patients aged 1 to <18 years using age-appropriate dosage forms, i.e. the newly developed film-coated granules, suspension made of solid forms and the approved film-coated tablets.

Design of the main clinical study (Part 2 of B2319)

As described above, Part 2 of B2319 was a randomized, double-blind, parallel-group, active-controlled, 52-week study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in paediatric HF patients (1 month to < 18 years).

The chosen inclusion/exclusion criteria are acceptable. Key inclusion included male or female, inpatient or outpatient of 1 month to < 18 years of age with chronic HF resulting from LVSD and biventricular physiology. Furthermore, eligible patients were required to have NYHA classification II-IV (older children: 6 to <18 years old) or Ross CHF classification II-IV, systemic left ventricular ejection fraction (EF) $\leqslant$ 45% or fractional shortening $\leqslant$22.5% and receiving chronic HF therapy. Key exclusion criteria included patients listed for heart transplantation or hospitalized waiting for a transplant, patients with restrictive or hypertrophic cardiomyopathy sustained or symptomatic dysrhythmias uncontrolled with therapy, symptomatic hypotension or blood pressures, serum potassium > 5.3 mmol/L at visit 1 and patients with allergy or hypersensitivity to ACEI/ARB patients with significant renal, hepatic, gastrointestinal or biliary disorders. These inclusion/exclusion criteria lead to a more homogeneous population with biventricular hearts and HF due to systemic left ventricle with decreased ejection fraction. Such an approach will result in a patient population that resembles more closely the adult HF population in which sacubitril/valsartan has been shown to be more effective than enalapril in reducing mortality, HF hospitalization and improving symptoms in patients with HF. A disadvantage of the chosen exclusion criteria is that it will limit analyses of efficacy in subgroups of hepatic and kidney impairment. Similarly, excluding participants with hypersensitivity to ACE/ARB, while acceptable, will lead to an underestimation of the true safety profile, especially considering that most patients were not ACE/ARB naïve. Furthermore, the inclusion criterion of "*NYHA classification II-IV or Ross CHF classification II-IV*" indicates that the study is focused only on patients with symptomatic paediatric HF patients. However, it is acknowledged that at baseline, 15% had NYHA/Ross classification I (patients who had NYHA/Ross II at any time before screening). However, since PANORAMA was not able to demonstrate the anticipated superiority over enalapril, a large part of the totality of evidence relies on the extrapolation of results from B2314 in adults (described below), which also had an inclusion criterion of NYHA classification II-IV and is indicated for "symptomatic chronic heart failure with reduced ejection fraction". In alignment, the Applicant has included "symptomatic" to the proposed indication.

The study design of part 2 of B2319 is appropriate to achieve the primary objective of the study. In this study, enalapril was used as an active control. Active control of valsartan might have been more

useful for a direct comparison and understanding of the added benefit of sacubitril. However, it is acknowledged that ACE inhibitors are the first-line treatment for paediatric HF with LVSD, and the aforementioned potential design may not have led to a sufficient sample size to assess efficacy. The International Society for Heart and Lung Transplantation Guidelines for managing paediatric HF states that ACE inhibitors are a class I recommendation for managing paediatric HF with LVSD with a level B evidence. Assessment of this literature demonstrates very little evidence of ACE inhibitors affecting long-term outcomes. A retrospective analysis of 81 patients with dilated cardiomyopathy (DCM) compared ACE inhibitor treatment with conventional therapy (at that time, digoxin and diuretics) and demonstrated a better survival during the first year of treatment, which became insignificant in the following years [*DOI: 10.1007/bf00794837*]. Another retrospective analysis of 189 patients with DCM demonstrated a numerical trend towards better survival when comparing ACE inhibitor-treated patients with digoxin-treated patients, though it did not reach statistical significance [DOI: 10.1016/j.jacc.2009.11.059]. A randomized, double-blind clinical trial in 57 patients with Duchenne muscular dystrophy, in which perindopril was compared to placebo, demonstrated that perindopril delayed the onset and progression of prominent left ventricle dysfunction after 3 years of treatment but did not investigate mortality [*DOI: 10.1016/j.jacc.2004.09.078].* A later publication of the same study demonstrated that at the end of the 10 years' follow-up period, survival status was 26 (92.9%) of 28 patients in the perindopril group were alive at 10 years versus 19 (65.5%) of 29 in the placebo group (P = .02) [*DOI: 10.1016/j.ahj.2007.05.014*].

Although ACE inhibitors are a cornerstone of paediatric HF, no products have been registered for paediatric HF, making all therapy off-label. This is due primarily to the difficulties of performing paediatric HF trials. There are previous examples of paediatric cardiovascular (CV) studies that were initiated but unable to be successfully completed, such as the Paediatric Heart Network study, which aimed to test the efficacy of enalapril vs placebo in children with mitral regurgitation after atrioventricular septal defect repair. This study was terminated because only 5 of 349 patients screened were able to be enrolled over a period of 17 months (Li et al. 2011), illustrating the difficulty of conducting paediatric CV trials. Overall, while valsartan would be the ideal comparator for assessing the efficacy of sacubitril, the choice of enalapril as the active comparator is understandable and acceptable.

The primary objective of part 2 of study B2319 was to determine whether sacubitril/valsartan was superior to enalapril for the treatment of HF as assessed using a Global Rank endpoint. It is acknowledged that there is no agreement upon a validated clinical efficacy endpoint for this patient population. In addition, the low prevalence of HF in children limits the possibility of conducting large outcome trials. Therefore, using a global rank-based endpoint might be an option with the major drawback of clinical interpretability by mixing hard and soft clinical endpoints. In this study the Global Rank endpoint rank orders patients from worst to best using; (a) objective outcome events of death, listing for urgent heart transplant or mechanical support; (b) events of worsening HF; and (c) measures of functional assessment (NYHA/Ross) and patient-reported outcomes: Patient Global Impression of Severity (PGIS) and the PedsQL (a physical functioning subgroup of questions). Thus, the globally ranked endpoint encompasses clinical events grouped into broadly agreed categories of severity, from mortality to disease progression (worsening HF) to measures of symptoms and physical functioning. The use of a global rank endpoint has been endorsed and not questioned in terms of robustness, clinical relevance and interpretability by the PDCO (000316-PIP02-11-M02). Furthermore, regarding the exploratory endpoint of change in NT-proBNP from baseline, the Applicant provided data regarding the analytic method (or methods) for NT-proBNP.

The sample size was calculated based on assumed underlying probabilities for each category of the primary endpoint using data from the Carvedilol Paediatric HF study. For the analysis of an ordered categorical endpoint, there was a power of roughly 70% with a sample size of 177 patients per group

(354 total). Using a global ranked endpoint, the power under the same assumptions was expected to increase. Simulation studies have demonstrated that the power for the global rank endpoint increases 10-20% more than with the ordered categorical analysis when the power of the ordered categorical endpoint is more than 50%. Therefore the projected power using the global rank endpoint was estimated to be at least 80%. The sample size has been endorsed in the Paediatric Investigation Plan (PIP). It was acknowledged and endorsed in the PIP that the secondary endpoints are not adequately powered.

The superiority design is not explicitly discussed in the PIPs nor in modifications (1 to 5) of the PIP. However, the Applicant argued that a non-inferiority design was possible since there is no data available in the published literature to define a non-inferiority margin for such a study. The statistical analyses are adequately described.

Efficacy data and additional analyses

In part 2 of the pivotal study, 377 patients (187 patients to sacubitril/valsartan and 190 patients to enalapril) were randomized, of which 375 received at least 1 dose of the study drug, indicating that the targeted sample size had been reached. The percentage of patients who completed study treatment was relatively low; however, slightly higher in the sacubitril/valsartan group compared with enalapril (78.1% vs 72.6%, respectively). This is acceptable considering the severity of the disease and consequently the discontinuation due to clinical worsening. The main cause of study treatment discontinuation was adverse events (AEs), with an approximately similar percentage between both treatment arms (10.7 vs 11.1% for sacubitril/valsartan and enalapril, respectively). Other reasons that contributed most, however, in similar proportions, were technical problems due to urgent safety measure (USM)(5.35% vs 5.26%) and physician decision (2.1% vs 2.6%). The study appears to be well conducted, with limited patients lost to follow-up (0 vs 0.5%). Nevertheless, out of 420 patients that signed written consent, a total of 43 discontinued prior to pre-randomization completion, of which 32 were screen failures, the majority of which was related due to not reaching the inclusion criteria of reduced ejection fraction.

This study was a multicentre study (n=105). Considering that approximately 30% of the subjects were from Europe, the population is sufficiently representative for Europe.

The baseline demographic characteristics, paediatric HF history/disease characteristics and medical therapies for HF were largely comparable between the sacubitril/valsartan and enalapril arms. Age group 1 (6 to <18 years) accounted for 58.7% (n= 220) of all patients, age group 2a (2 to <6 years) for 22.7% (n=85) of all patients, and age group 3a (1 month to < 2 years) for 18.7% (n=70) of all patients. As expected, the percentage of patients < 1 year of age was very low (2.4% (n=9). Consequently, the proposed indication is limited to >1 year old. Further, the most frequent primary aetiology for HF was cardiomyopathy-related (63.5%), which, based on the exclusion criterion of restrictive and hypertrophic cardiomyopathy, will mostly be comprised of DCM. There is a representation of 69.3% of patients in NYHA/Ross Class II (69.3%) and 14.4% in NYHA/Ross Class III, allowing an adequate assessment in these specific FCs. However, there is a limited representation of patients with NYHA/Ross IV (0.5% (n= 2). Similarly, in the adult study B2314, the number of patients with NYHA IV was also very limitedly represented (n=60, <1%). Also, subgroup analyses according to NYHA/(ROSS) class demonstrated a trend toward lower efficacy in both B2319 and B2314 in patients with higher NYHA/(ROSS) class. The limited representation of NYHA IV representation is well reflected in section 4.4 of the SmPC. The Applicant has stratified by age and NYHA/Ross class at randomization to ensure a balanced distribution of treatment allocation within each age group. Nonetheless, the geometric mean of baseline NT-proBNP is higher in the sacubitril/valsartan group in each age group than enalapril (see section extrapolation for discussion). As expected, most patients used ACE-inhibitors before enrolment, with enalapril being the most used ACE inhibitor. Nevertheless, according

to the study protocol ACE- inhibitors, angiotensin receptor blockers, and renin inhibitors are all prohibited medications during the treatment phase and must be discontinued. Nonetheless, there was concomitant use of ACE-inhibitors in 45 patients, and concomitant use of angiotensin receptor blockers in 14 patients. However, according to the same protocol, only patients who interrupted or discontinued study drug could be on ACEi or ARB treatment, which is reasonable. A total of 56 patients received non-study ACEI/ARB prior to the end of the study. The Applicant performed a sensitivity analysis and demonstrated that the intercurrent use of non-study ACEI/ARB did not have a relevant impact on the results.

The analysis of the Global Rank primary endpoint did not show a statistically significant difference between the treatment groups, with a Mann-Whitney probability estimate of 0.5244 (95% CI 0.4665, 0.5817, p=0.42 (with a MWP > 0.5 being in favour of sacubitril/valsartan) compared to the standard of care enalapril. Therefore, the study failed to meet its primary objective, i.e. demonstration of the superiority of sacubitril/valsartan over enalapril. The primary results were consistent across subgroups by age, with no significant differences observed between sacubitril/valsartan and enalapril. Although the primary analysis implicates that sacubitril/valsartan is not superior, it may be non-inferior to enalapril. However, this could not be tested since non-inferiority margins are unknown for a global rank endpoint. Even if sacubitril/valsartan and enalapril are similar in efficacy, the true effectiveness over placebo remains unknown due to the lack of clinical trials investigating the efficacy of ACE inhibitors over placebo on hard clinical endpoints in paediatric HF.

Subgroup analyses of the primary rank score were consistent with the overall results, that the results for the Global Rank primary endpoint numerically favoured sacubitril/valsartan compared to enalapril in all subgroups, except for patients with NYHA/Ross Class III/IV at randomization.

Furthermore, the study failed to meet its secondary objectives, i.e., demonstrating the superiority of sacubitril/valsartan over enalapril in delaying time to the first occurrence of the composite of either Category 1 or 2 events (e.g. death, worsening HF). The patient allocation for the global rank endpoint showed that the proportion of patients with a Category 1 event (objective outcome events of death, listing for an urgent heart transplant or mechanical support) was lower in the sacubitril/valsartan group compared to the enalapril group (10% vs 16%). However, no significant difference was observed between treatment groups in time to the first category 1 event (adjusted HR: 0.64, 95% CI: 0.32 – 1.28; p=0.20). On the other hand, the proportion of patients with category 2 events (worsening of HF with/without hospitalization with/without ICU stay) was numerically higher in the sacubitril/valsartan group compared to the enalapril group (10% vs 5%). This was partially due to the higher number of patients on enalapril having a category 1 event, as patients with both category 1 and category 2 events were excluded from category 2 events. If these patients were counted, the proportion of patients with category 2 events was more similar between the groups (17% vs 14%). These data suggest that sacubitril/valsartan treatment delayed the occurrence of Category 1 events. However, similarly as for time to first category 1 events, there were no significant differences between the treatment groups in time to first category 2 event and combined category 1 or 2 event (adjusted HR: 1.21, 95% CI: 0.72-2.03; p=0.470 and adjusted HR: 1.07, 95% CI: 0.66- 1.72; p=0.78, respectively).

Clinically meaningful improvement from baseline in symptoms and functional endpoints were observed in both treatment groups. At Week 52, 37.66% of patients in the sacubitril/valsartan group and 33.96% of patients in the enalapril group had improvement, and approximately half of all patients were stable. Moreover, the proportion of patients free of HF symptoms (i.e. NYHA/Ross Class 1) increased in both groups, from 13.37% at baseline to 48.47% at Week 52 in the sacubitril/valsartan group and from 18.09% to 47.50% in the enalapril group. Improvements in NYHA/Ross class were observed in all age groups. This pattern of improvement was paralleled by the PGIS assessment: the proportion of patients who were asymptomatic (i.e. PGIS classification C1) increased from 45.05% at

baseline to 67.95% at Week 52 in the sacubitril/valsartan group, and from 38.59% to 64.94% in the enalapril group. Nevertheless, there was no significant difference between the sacubitril/valsartan and enalapril groups.

Improvements were also observed in measures of quality of life (PedsQL and PGIC). For PedsQL, the adjusted least squares mean changes from baseline exceeded the minimally clinically important difference threshold of 4.5 at Weeks 36 and 52 in the sacubitril/valsartan group, whereas the threshold was not crossed in the enalapril group. The proportion of patients with at least 4.5 point improvement in the sacubitril/valsartan vs enalapril groups at Week 52 was 43.43% vs 38.38% for patient-reported PedsQL, and 45.78% vs 42.07% for parent-reported PedsQL. PGIC scores showed a progressive increase in the proportion of patients who felt “much better” or “better” in both treatment groups. The proportion of patients who felt much better in the sacubitril/valsartan vs enalapril groups at Week 52 was 33.33% vs 28.24%; the proportion of patients who felt better was 40.94% vs 38.24% in the respective groups. The analysis of change for these secondary outcomes numerically favoured sacubitril/valsartan, yet none were statistically significant.

The improvements from baseline in disease symptoms and quality of life, though not statistically superior to enalapril, are reassuring, given the fact that paediatric HF is usually a progressive clinical and pathophysiological syndrome.

Regarding exploratory endpoints, in both the sacubitril/valsartan and enalapril arm, there was a significant decrease in NT-proBNP during study treatment. Initially, there appeared to be a larger decrease in NT-proBNP in the sacubitril/valsartan arm (at Week 4), but this difference became and remained insignificant from Week 12 onward (65% and 62% for the sacubitril/valsartan and enalapril groups at week 52, respectively; p=0.5). The Applicant calculated the reference change values (RCV) based on the intra-individual variation of NT-proBNP, described in the literature. Using several RCV thresholds (i.e. −22%, −33%, −46%, and −61%), the applicant demonstrated consistently higher rates of responders in the sacubitril/valsartan group compared to the enalapril group for each threshold. The lower limits of the 95% confidence intervals of the odds ratios were greater than 1 for the between-treatment responder comparison for all thresholds in adults and for the −33% and −46% thresholds, indicating a systematic difference in favor of sacubitril/valsartan in the responder rates between the treatment groups.

2.6.10. Conclusions on the clinical efficacy

The totality of evidence included in this submission supporting the efficacy of sacubitril/valsartan for paediatric use includes 1) extrapolation of the existing adult HFrEF data from study B2314 (PARADIGM-HF) to children based on the pharmacokinetic and pharmacodynamic data from study B2319 (PANORAMA-HF) and 2) the clinical efficacy data provided by the PANORAMA-HF study.

The Applicant adequately demonstrated similarity between adult HFrEF with DCM and pediatric heart failure with LVSD, consistent with DCM. Furthermore, the applicant demonstrated similar drug pharmacology and similar exposure-response. Lastly, the applicant demonstrated that NT-proBNP could be used bridging biomarker (using the prentice criteria) to extrapolate the efficacy between adult and paediatric populations.

In study B2319, the Global Rank primary endpoint analysis did not show a statistically significant difference between treatment groups with a Mann-Whitney probability estimate of 0.5244 (95% CI 0.4665, 0.5817, p=0.4238) compared to the standard of care enalapril. Therefore, the study failed to meet its primary objective, i.e. demonstration of the superiority of sacubitril/valsartan over enalapril. In addition, these results question the added value of sacubitril in children, however it should be noted that a direct analyses of the added value is not possible as valsartan and enalapril, while similar, are

not the same. Furthermore, it is worth noting that enalapril, although standard of care, is currently not registered for pediatric heart failure.

Given the lack of robust data supporting the efficacy of enalapril on hard outcomes, a direct assessment of the absolute efficacy is difficult. Therefore the focus is put on within-patient changes in secondary and exploratory outcomes. In these analyses, both sacubitril/valsartan and enalapril demonstrated improvements in NYHA/Ross class and PGIS, as well as measures of quality of life (PedsQL). Furthermore, both sacubitril/valsartan and enalapril lead to a large decrease in NT-proBNP.

The similar exposure response and the large reductions in NT-proBNP, which are predictive of favourable clinical outcomes, coupled with the symptomatic and functional improvements from baseline observed in paediatric HF patients in Study B2319, can be used to infer clinical benefits of sacubitril/valsartan established in adults to the paediatric HF population.

Taking into consideration the totality of the evidence, including the extrapolation of efficacy data from adults, in which the combined effect of sacubitril and valsartan has been established, to pediatric HF populations with similar pathophysiology, sacubitril/valsartan provides clinically meaningful benefits to children and adolescents with HF due to systemic LVSD.

2.6.11. Clinical safety

The totality of evidence included in this submission supporting the clinical safety of sacubitril/valsartan for paediatric use includes: 1) extrapolation of the existing adult HFrEF data from study B2314 (PARADIGM-HF) to children based on the pharmacokinetic and pharmacodynamic data from study B2319 (PANORAMA-HF) and 2) the clinical data provided by the PANORAMA-HF study.

2.6.11.1. Extrapolation of clinical safety from adult to paediatric population.

Given the similarities in disease between paediatric HF due to LVSD consistent with DCM and adult HF due to DCM and consistent with the principles of paediatric extrapolation outlined in the recent CHMP release of ICH E11A guidance, i.e. similar drug exposure at target doses and a similar decrease in NT-proBNP at exposure matched doses, the safety assessment from Study B2319 is to be considered within the context of the already adequately characterized, well-established, safety profile of sacubitril/valsartan in adults. Based on the extrapolation plan (described in full under clinical efficacy), it can be considered a reasonable approach to extrapolate the safety profile from the adult to paediatric population. In the following sections, the safety data generated in Part 2 of Study B2319 (N=375 total; N=187 sacubitril/valsartan; N=188 enalapril)) will be described and compared to the adult safety profile.

2.6.11.2. Study B2319

2.6.11.2.1. Patient exposure

The mean weight-based daily dose was 5.07 mg/kg for sacubitril/valsartan group and 0.33 mg/kg for the enalapril group.

The median duration of treatment exposure was similar between the treatment groups (365 days for sacubitril/valsartan and 364 days for enalapril). The overall exposure in Part 2 of Study B2319 was

also comparable between the treatment groups: 173.72 patient-years for sacubitril/valsartan and 164.19 patient-years for enalapril.

Study drug was to be up-titrated every 2 weeks as tolerated by the patient to the target dose (dose level 4 for Age Groups 1 and 2, and 4x for Age Group 3; see section “Treatment” for further details) guided by safety monitoring criteria. Additional safety monitoring was required for Age Group 3 patients with each initial dose level up-titration.

Results for dose levels over time showed a slower up-titration than planned in the protocol. In the overall population, at Week 6, when all patients should have been up-titrated to dose level 4, 4.8% of patients were on dose level 1, 13.0% were on dose level 2, and 24.0% were on dose level 3, while 53.9% were on dose level 4. By Week 8, 60.8% in sacubitril/valsartan group and 66.9% in enalapril group were on target dose level 4. The majority of patients reached dose level 4 at least once at any time point: 76.5% (143/187) for sacubitril/valsartan and 81.9% (154/188) for enalapril.

2.6.11.2.2. Adverse events

General frequency of adverse events

Part 2

The overall incidence of treatment-emergent AEs during Part 2 was comparable between sacubitril/valsartan (88.77%) and enalapril (87.77%) groups (Table 38). Deaths and drug-related AEs were less frequent for sacubitril/valsartan vs enalapril, while SAEs and AEs requiring adjustment or interruption were more frequent for sacubitril/valsartan vs enalapril. AEs leading to discontinuation study treatment were similar for the two treatment groups. Most of the AEs that led to study treatment discontinuation were SAEs, which tended to be lower overall with sacubitril/valsartan than enalapril. The majority of AEs were mild or moderate in severity. The incidence of severe AEs was 17.11% in sacubitril/valsartan and 21.28% in enalapril group [Study B2319-Table 14.3.1-3.2].

The safety profile of sacubitril/valsartan was consistent across the modified age groups (Table 38). The overall pattern of AEs in the age groups was generally similar to that observed for the overall population. As the sample size varied across the 3 age groups and the number of events in each age group was often small, comparisons between age groups should also be interpreted with caution. Of note, the frequency of deaths, AEs/SAEs leading to discontinuation and drug-related AEs tended to be lower in the younger groups (Age Group 2a and Group 3a) than in the oldest group (Age Group 1), regardless of study treatment. Unlike the older groups, the youngest group (Age Group 3a) had lower frequencies of AEs/SAEs leading to discontinuation and drug-related AEs in the sacubitril/valsartan group compared with the enalapril group.

Table 38. Overall summary of adverse events – Study B2319 Part 2 (Safety Set)

	Age Group 1: 6 to <18 years		Age Group 2a: 2 to <6 years		Age Group 3a: 1 month to <2 years		Overall	
	LCZ696 N=109 n (%)	Enalapril N=111 n (%)	LCZ696 N=47 n (%)	Enalapril N=38 n (%)	LCZ696 N=31 n (%)	Enalapril N=39 n (%)	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Any AE(s)	98 (89.91)	100 (90.09)	40 (85.11)	31 (81.58)	28 (90.32)	34 (87.18)	166 (88.77)	165 (87.77)
Death	5 (4.59)	9 (8.11)	2 (4.26)	0	1 (3.23)	3 (7.69)	8 (4.28)	12 (6.38)
SAE(s)	42 (38.53)	42 (37.84)	15 (31.91)	8 (21.05)	12 (38.71)	12 (30.77)	69 (36.90)	62 (32.98)
Dose adjustment or interruption[1]	24 (22.02)	20 (18.02)	9 (19.15)	7 (18.42)	5 (16.13)	5 (12.82)	38 (20.32)	32 (17.02)
Discontinued[2] due to AE(s)	16 (14.68)	15 (13.51)	3 (6.38)	2 (5.26)	2 (6.45)	4 (10.26)	21 (11.23)	21 (11.17)
Discontinued[2] due to SAE(s)	11 (10.09)	13 (11.71)	3 (6.38)	1 (2.63)	2 (6.45)	4 (10.26)	16 (8.56)	18 (9.57)
Study drug-related AEs	37 (33.94)	42 (37.84)	10 (21.28)	6 (15.79)	3 (9.68)	5 (12.82)	50 (26.74)	53 (28.19)

Most frequently occurring adverse events (Part 2)

The most commonly affected SOCs (incidence ≥ 20% in either group) were generally similar between the sacubitril/valsartan and enalapril groups (Table 39). Infections and infestations, the most frequently affected SOC, consisted primarily of upper respiratory tract infection and nasopharyngitis, with no meaningful treatment differences. The sacubitril/valsartan group had a higher incidence of AEs in SOCs of musculoskeletal and connective tissue disorders (mainly driven by pain in extremity, back pain and arthralgia) and renal and urinary disorders (mainly driven by renal impairment), while the enalapril group had a higher incidence of AEs in SOCs of injury, poisoning and procedural complications (not driven by one specific event) and reproductive system and breast disorders (not due to one specific event).

The pattern of AEs by SOCs was generally consistent between the modified age groups (Table 39). As the number of patients with AEs was low for many SOCs, particularly in the younger age groups, comparisons between age groups should be interpreted with caution.

Table 39. Adverse events by primary system organ class in at least 20% of patients in either treatment group – Study B2319 Part 2 (Safety Set)

	Age Group 1: 6 to <18 years		Age Group 2a: 2 to <6 years		Age Group 3a: 1 month to <2 years		Overall	
System organ class	LCZ696 N=109 n (%)	Enalapril N=111 n (%)	LCZ696 N=47 n (%)	Enalapril N=38 n (%)	LCZ696 N=31 n (%)	Enalapril N=39 n (%)	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Any AE(s)	98 (89.91)	100 (90.09)	40 (85.11)	31 (81.58)	28 (90.32)	34 (87.18)	166 (88.77)	165 (87.77)
Infections and infestations	58 (53.21)	57 (51.35)	37 (78.72)	26 (68.42)	22 (70.97)	26 (66.67)	117 (62.57)	109 (57.98)
General disorders and administration site conditions	48 (44.04)	35 (31.53)	19 (40.43)	11 (28.95)	9 (29.03)	16 (41.03)	76 (40.64)	62 (32.98)
Gastrointestinal disorders	47 (43.12)	45 (40.54)	15 (31.91)	17 (44.74)	11 (35.48)	17 (43.59)	73 (39.04)	79 (42.02)
Respiratory, thoracic and mediastinal disorders	33 (30.28)	37 (33.33)	21 (44.68)	10 (26.32)	10 (32.26)	18 (46.15)	64 (34.22)	65 (34.57)
Nervous system disorders	41 (37.61)	36 (32.43)	6 (12.77)	4 (10.53)	2 (6.45)	3 (7.69)	49 (26.20)	43 (22.87)
Cardiac disorders	35 (32.11)	35 (31.53)	6 (12.77)	4 (10.53)	8 (25.81)	8 (20.51)	49 (26.20)	47 (25.00)
Investigations	27 (24.77)	26 (23.42)	10 (21.28)	7 (18.42)	2 (6.45)	11 (28.21)	39 (20.86)	44 (23.40)

There were no major imbalances in AEs by preferred term between the treatment groups for most of the frequently reported AEs (Table 40). Dizziness was more frequent in the sacubitril/valsartan group compared to the enalapril group, while hypotension occurred with similar frequency between the two treatment groups. Decreased glomerular filtration rate was more frequent in the enalapril group than in the sacubitril/valsartan group.

Many of the frequently reported AEs are common in children. Pyrexia, upper respiratory tract infection, and diarrhea were more frequent in younger children (Age Groups 2a and 3a) than in older children (Age Group 1), irrespective of the treatment group. Conversely, cardiac failure, dizziness, headache, abdominal pain, nausea, and hypotension were more frequent in older children. These age-related trends are not considered to be clinically meaningful. In young children, it is not unexpected that AEs that are overtly evident to caregivers or physicians (e.g., pyrexia, vomiting, diarrhea) are more frequently reported than AEs that require the patient to self-report (e.g., dizziness, headache, nausea).

Table 40. Most frequently occurring adverse events by preferred term (at least 5% in any treatment arm overall) – Study B2319 Part 2 (Safety Set)

	Age Group 1: 6 to <18 years		Age Group 2a: 2 to <6 years		Age Group 3a: 1 month to <2 years		Overall	
Preferred term	LCZ696 N=109 n (%)	Enalapril N=111 n (%)	LCZ696 N=47 n (%)	Enalapril N=38 n (%)	LCZ696 N=31 n (%)	Enalapril N=39 n (%)	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Total AEs	98 (89.91)	100 (90.09)	40 (85.11)	31 (81.58)	28 (90.32)	34 (87.18)	166 (88.77)	165 (87.77)
Pyrexia	18 (16.51)	10 (9.01)	13 (27.66)	9 (23.68)	8 (25.81)	15 (38.46)	39 (20.86)	34 (18.09)
Upper respiratory tract infection	19 (17.43)	15 (13.51)	13 (27.66)	10 (26.32)	7 (22.58)	10 (25.64)	39 (20.86)	35 (18.62)
Cough	20 (18.35)	24 (21.62)	12 (25.53)	5 (13.16)	4 (12.90)	9 (23.08)	36 (19.25)	38 (20.21)
Vomiting	21 (19.27)	16 (14.41)	6 (12.77)	11 (28.95)	7 (22.58)	13 (33.33)	34 (18.18)	40 (21.28)
Nasopharyngitis	14 (12.84)	6 (5.41)	10 (21.28)	7 (18.42)	5 (16.13)	4 (10.26)	29 (15.51)	17 (9.04)
Cardiac failure	21 (19.27)	20 (18.02)	1 (2.13)	2 (5.26)	5 (16.13)	5 (12.82)	27 (14.44)	27 (14.36)
Diarrhoea	14 (12.84)	9 (8.11)	5 (10.64)	6 (15.79)	6 (19.35)	8 (20.51)	25 (13.37)	23 (12.23)
Dizziness	22 (20.18)	15 (13.51)	1 (2.13)	0	0	0	23 (12.30)	15 (7.98)
Hypotension	17 (15.60)	17 (15.32)	4 (8.51)	3 (7.89)	2 (6.45)	2 (5.13)	23 (12.30)	22 (11.70)
Headache	20 (18.35)	19 (17.12)	2 (4.26)	1 (2.63)	0	0	22 (11.76)	20 (10.64)
Fatigue	13 (11.93)	11 (9.91)	5 (10.64)	2 (5.26)	1 (3.23)	1 (2.56)	19 (10.16)	14 (7.45)
Abdominal pain	12 (11.01)	8 (7.21)	3 (6.38)	2 (5.26)	0	1 (2.56)	15 (8.02)	11 (5.85)
Influenza	6 (5.50)	9 (8.11)	7 (14.89)	4 (10.53)	0	1 (2.56)	13 (6.95)	14 (7.45)
Bronchitis	5 (4.59)	4 (3.60)	6 (12.77)	3 (7.89)	1 (3.23)	2 (5.13)	12 (6.42)	9 (4.79)
Epistaxis	6 (5.50)	5 (4.50)	3 (6.38)	1 (2.63)	1 (3.23)	0	10 (5.35)	6 (3.19)
Gastroenteritis	4 (3.67)	7 (6.31)	4 (8.51)	2 (5.26)	2 (6.45)	3 (7.69)	10 (5.35)	12 (6.38)
Nausea	8 (7.34)	8 (7.21)	2 (4.26)	1 (2.63)	0	0	10 (5.35)	9 (4.79)
Glomerular filtration rate decreased	4 (3.67)	5 (4.50)	4 (8.51)	2 (5.26)	1 (3.23)	5 (12.82)	9 (4.81)	12 (6.38)
Rhinitis	4 (3.67)	4 (3.60)	2 (4.26)	3 (7.89)	2 (6.45)	3 (7.69)	8 (4.28)	10 (5.32)
Abdominal pain upper	5 (4.59)	7 (6.31)	1 (2.13)	3 (7.89)	0	0	6 (3.21)	10 (5.32)

The profile of frequently reported AEs by SOC and preferred term in Part 2 of study B2319 was consistent with events typically observed in children with HF and with the safety profile of sacubitril/valsartan reported in adults with HFrEF.

2.6.11.2.3. Adverse drug reactions

No new adverse drug reactions (ADRs) were identified during Study B2319 based on a comprehensive methodology for selecting and evaluating ADRs. The ADRs in the target population of paediatric patients with HF remained consistent with those previously observed in longer-term clinical trials in adults.

A higher incidence and hence a change in the frequency category was observed for ADRs of diarrhoea, fatigue, headache, dizziness and cough in paediatric Study B2319 compared to the adult Study B2314. However, considering the small overall patient numbers and wide variability in the paediatric study, these findings should be interpreted with caution.

While the incidence of these ADRs were higher in the paediatric HF population of Study B2319 than in adults with HFrEF, there are several considerations to take into account. Some ADRs are commonly observed in children and adolescents (e.g., diarrhoea, cough) or are a common symptom of HF (e.g., fatigue). The frequencies of diarrhoea (13.4% in the sacubitril/valsartan group and 12.2% in the enalapril group) are comparable to the background rate of diarrhoea in this population (14.3% as

observed in the placebo arm of ivabradine paediatric HF study; FDA 2019). The frequency of headache (11.8% with sacubitril/valsartan and 10.6% with enalapril) was lower than the estimated prevalence of headache in children and adolescents (Abu-Arafeh et al 2010). While dizziness was more frequently reported in the sacubitril/valsartan arm of Study B2319 than in Study B2314 (12.3% vs 6.3%), the majority of cases were mild and not suspected to be related to study drug and had resolved with no change to the sacubitril/valsartan dose.

2.6.11.2.4. Serious adverse event/deaths/other significant events

Deaths

As discussed in the efficacy section, a total of 20 deaths occurred in Part 2 of Study B2319. Fewer deaths were reported in the sacubitril/valsartan group (8 deaths, 4.28%) compared with the enalapril group (12 deaths, 6.38%) (Table 41). All but 2 deaths were adjudicated as cardiovascular deaths. Of the 2 non-cardiovascular deaths, one patient in the sacubitril/valsartan arm (Age Group 2a) who entered the study with acute myeloid leukaemia died of this malignancy, and one patient in the enalapril arm (Age Group 1) died due to respiratory failure.

Table 41. Summary of deaths – Study B2319 Part 2 (Safety Set)

	Age Group 1: 6 to <18 years		Age Group 2a: 2 to <6 years		Age Group 3a: 1 month to <2 years		Overall	
	LCZ696 N=109 n (%)	Enalapril N=111 n (%)	LCZ696 N=47 n (%)	Enalapril N=38 n (%)	LCZ696 N=31 n (%)	Enalapril N=39 n (%)	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Number of deaths	5 (4.59)	9 (8.11)	2 (4.26)	0	1 (3.23)	3 (7.69)	8 (4.28)	12 (6.38)
CV deaths	5 (4.59)	8 (7.21)	1 (2.13)	0	1 (3.23)	3 (7.69)	7 (3.74)	11 (5.85)
Congestive heart failure	3 (2.75)	1 (0.90)	0	0	0	0	3 (1.60)	1 (0.53)
Cardiogenic shock	1 (0.92)	1 (0.90)	0	0	1 (3.23)	3 (7.69)	2 (1.07)	4 (2.13)
Sudden Death[a] <1 hr	1 (0.92)	3 (2.70)	0	0	0	0	1 (0.53)	3 (1.60)
CV death	0	2 (1.80)	0	0	0	0	0	2 (1.06)
Sudden death[b] ≥ 1 hr - < 24 hr	0	1 (0.90)	1 (2.13)	0	0	0	1 (0.53)	1 (0.53)
Non-CV deaths	0	1 (0.90)	1 (2.13)	0	0	0	1 (0.53)	1 (0.53)
Respiratory Failure	0	1 (0.90)	0	0	0	0	0	1 (0.53)
Malignancy	0	0	1 (2.13)	0	0	0	1 (0.53)	0

Serious adverse events

The overall incidence of SAEs in Part 2 was comparable between the sacubitril/valsartan (36.90%) and enalapril (32.98%) groups (Table 42). Cardiac failure, the most frequently reported SAE by preferred term, occurred with similar frequency in the two treatment groups. SAEs of hypotension occurred only in the sacubitril/valsartan group (4 vs 0) and conversely, SAEs of hyperkalemia occurred only in the enalapril group (0 vs 2). Syncope SAEs occurred in 2 patients in enalapril group and 1 patient in the sacubitril/valsartan group. The number of patients with SAEs other than cardiac failure was small (≤5 per group); hence comparisons of small numerical imbalances between treatment groups should be interpreted with caution. There were no meaningful differences in SAEs across the modified age groups.

Table 42. Most frequently occurring serious adverse events by preferred term (at least 1% in either treatment arm overall) – Study B2319 Part 2 (Safety Set)

	Age Group 1: 6 to <18 years		Age Group 2a: 2 to <6 years		Age Group 3a: 1 month to <2 years		Overall	
Preferred term	LCZ696 N=109 n (%)	Enalapril N=111 n (%)	LCZ696 N=47 n (%)	Enalapril N=38 n (%)	LCZ696 N=31 n (%)	Enalapril N=39 n (%)	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Total SAEs	42 (38.53)	42 (37.84)	15 (31.91)	8 (21.05)	12 (38.71)	12 (30.77)	69 (36.90)	62 (32.98)
Cardiac failure	19 (17.43)	17 (15.32)	1 (2.13)	2 (5.26)	4 (12.90)	4 (10.26)	24 (12.83)	23 (12.23)
Pneumonia	0	3 (2.70)	5 (10.64)	1 (2.63)	0	0	5 (2.67)	4 (2.13)
Vomiting	3 (2.75)	0	0	0	2 (6.45)	4 (10.26)	5 (2.67)	4 (2.13)
Cardiac failure congestive	1 (0.92)	2 (1.80)	2 (4.26)	0	1 (3.23)	1 (2.56)	4 (2.14)	3 (1.60)
Hypotension	2 (1.83)	0	1 (2.13)	0	1 (3.23)	0	4 (2.14)	0
Pyrexia	2 (1.83)	0	1 (2.13)	0	1 (3.23)	0	4 (2.14)	0
Upper respiratory tract infection	0	0	3 (6.38)	0	1 (3.23)	0	4 (2.14)	0
Dyspnoea	2 (1.83)	1 (0.90)	1 (2.13)	0	0	0	3 (1.60)	1 (0.53)
Ventricular tachycardia	3 (2.75)	1 (0.90)	0	0	0	0	3 (1.60)	1 (0.53)
Acute respiratory failure	0	0	1 (2.13)	0	1 (3.23)	0	2 (1.07)	0
Cardiac arrest	1 (0.92)	3 (2.70)	0	0	1 (3.23)	1 (2.56)	2 (1.07)	4 (2.13)
Cardiac failure acute	2 (1.83)	3 (2.70)	0	0	0	1 (2.56)	2 (1.07)	4 (2.13)
Influenza	2 (1.83)	2 (1.80)	0	0	0	0	2 (1.07)	2 (1.06)
Pleural effusion	1 (0.92)	1 (0.90)	0	0	1 (3.23)	0	2 (1.07)	1 (0.53)
Acute kidney injury	1 (0.92)	2 (1.80)	0	0	0	0	1 (0.53)	2 (1.06)
Arrhythmia	1 (0.92)	2 (1.80)	0	1 (2.63)	0	0	1 (0.53)	3 (1.60)
Hypoglycaemia	0	0	0	1 (2.63)	1 (3.23)	1 (2.56)	1 (0.53)	2 (1.06)
Seizure	0	1 (0.90)	0	2 (5.26)	1 (3.23)	1 (2.56)	1 (0.53)	4 (2.13)
Syncope	1 (0.92)	2 (1.80)	0	0	0	0	1 (0.53)	2 (1.06)
Atrial thrombosis	0	1 (0.90)	0	1 (2.63)	0	0	0	2 (1.06)
Bronchiolitis	0	0	0	0	0	2 (5.13)	0	2 (1.06)
Chest pain	0	2 (1.80)	0	0	0	0	0	2 (1.06)
Dehydration	0	2 (1.80)	0	0	0	0	0	2 (1.06)
Hyperkalaemia	0	1 (0.90)	0	0	0	1 (2.56)	0	2 (1.06)
Viral upper respiratory tract infection	0	1 (0.90)	0	1 (2.63)	0	0	0	2 (1.06)

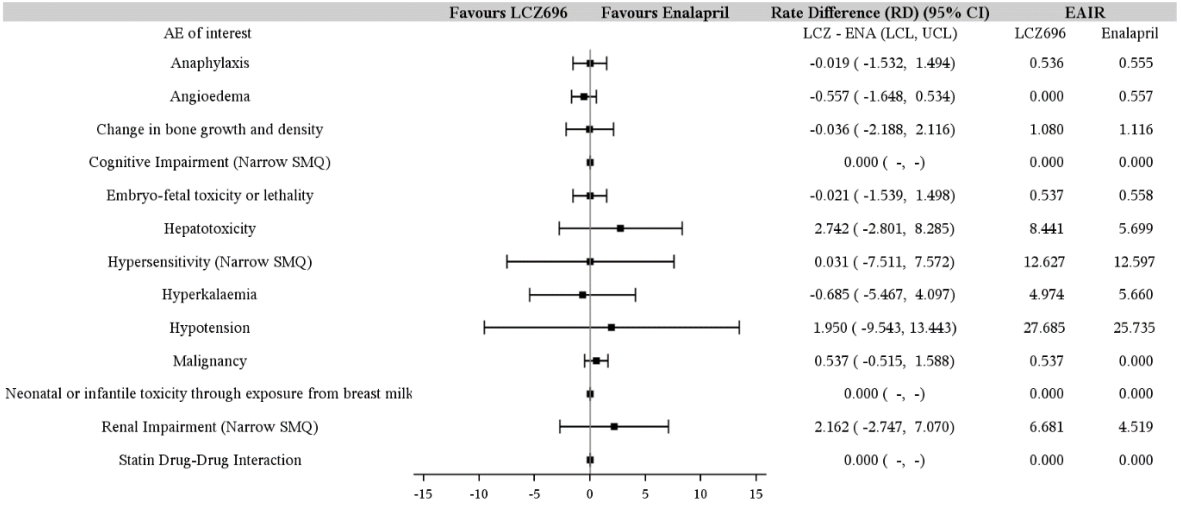
Safety topics of interest

Overall, the safety topics of interest showed largely similar frequencies between sacubitril/valsartan and enalapril groups (Figure 13 and Table 38). There were no relevant cases related to embryo-fetal toxicity or lethality, statin drug-drug interaction, cognitive impairment, neonatal or infantile toxicity through exposure to breast milk, hypersensitivity, anaphylaxis, or malignancy; hence these topics are not discussed further in this section.

Of note, cognitive impairment is a theoretical risk for sacubitril/valsartan because neprilysin is one of many enzymes involved in the metabolism of amyloid-β. The specific role of neprilysin in the pathogenesis of cognitive impairment remains unclear. There is currently no evidence of an increased risk of cognitive impairment (defined as the narrow SMQ 'Dementia') with sacubitril/valsartan

treatment from 3 large Phase III adult cardiovascular studies (PARADIGM-HF, PARAGON-HF, and PARADISE-MI) in over 18,900 HF patients.

Figure 13. Rate difference and exposure-adjusted incidence rate of adverse events by safety topic of interest - Study B2319 Part 2 (Safety Set)



AE of interest	Rate Difference (RD) (95% CI) LCZ - ENA (LCL, UCL)	EAIR LCZ696	EAIR Enalapril
Anaphylaxis	-0.019 (-1.532, 1.494)	0.536	0.555
Angioedema	-0.557 (-1.648, 0.534)	0.000	0.557
Change in bone growth and density	-0.036 (-2.188, 2.116)	1.080	1.116
Cognitive Impairment (Narrow SMQ)	0.000 (-, -)	0.000	0.000
Embryo-fetal toxicity or lethality	-0.021 (-1.539, 1.498)	0.537	0.558
Hepatotoxicity	2.742 (-2.801, 8.285)	8.441	5.699
Hypersensitivity (Narrow SMQ)	0.031 (-7.511, 7.572)	12.627	12.597
Hyperkalaemia	-0.685 (-5.467, 4.097)	4.974	5.660
Hypotension	1.950 (-9.543, 13.443)	27.685	25.735
Malignancy	0.537 (-0.515, 1.588)	0.537	0.000
Neonatal or infantile toxicity through exposure from breast milk	0.000 (-, -)	0.000	0.000
Renal Impairment (Narrow SMQ)	2.162 (-2.747, 7.070)	6.681	4.519
Statin Drug-Drug Interaction	0.000 (-, -)	0.000	0.000

EAIR (exposure adjusted incidence rate per 100 patient-year) is the number of patients with at least one TEAE of the STI category/[total exposure time (year)/100]. Rate difference (RD) is based on EAIR. Angioedema is AAC confirmed.

Table 43 Exposure-adjusted incidence rate of adverse events by AESI groupings during Study B2319 (Safety Set)

AESI	LCZ N=187 n (%) EAIR (95% CI)	ENA N=188 n (%) EAIR (95% CI)
Hypotension	43 (22.99)	40 (21.28)
	27.685 (20.036, 37.292)	25.735 (18.385, 35.044)
Hyperkalaemia	9 (4.81)	10 (5.32)
	4.974 (2.275, 9.443)	5.660 (2.714, 10.409)
Renal Impairment (Narrow SMQ)	12 (6.42)	8 (4.26)
	6.681 (3.452, 11.670)	4.519 (1.951, 8.904)
Angioedema	0	1 (0.53)
		0.557 (0.014, 3.110)
Embryo-fetal toxicity or lethality	1 (0.53)	1 (0.53)
	0.537 (0.014, 2.994)	0.558 (0.014, 3.110)
Hepatotoxicity	15 (8.02)	10 (5.32)
	8.441 (4.724, 13.922)	5.699 (2.733, 10.481)
Hypersensitivity (Narrow SMQ)	22 (11.76)	21 (11.17)
	12.627 (7.913, 19.118)	12.597 (7.798, 19.255)
Anaphylaxis	1 (0.53)	1 (0.53)
	0.536 (0.014, 2.988)	0.555 (0.014, 3.094)
Malignancy	1 (0.53)	0
	0.537 (0.014, 2.989)	
Change in bone growth and density	2 (1.07)	2 (1.06)
	1.080 (0.131, 3.901)	1.116 (0.135, 4.031)

The analyses on the following safety topics of interest revealed no cases: Cognitive impairment, Neonatal / infantile toxicity through exposure from breast milk, and Statin drug-drug interaction (Figure 2-2).
Source: [SCS Appendix 1-Table 2-8], [Study B2319-Table 14.3.1-19]

Hypotension

Hypotension is a known effect of sacubitril/valsartan based on its ARB and NEPI properties on lowering blood pressure. A higher incidence of hypotension AEs was observed in adults with HFrEF in Study B2314 (24.4% for sacubitril/valsartan vs 18.6% for enalapril). The majority of hypotension AEs in adults with HFrEF were preferred terms of hypotension and dizziness. There were no imbalances for events of greater clinical severity, such as syncope, pre-syncope, loss of consciousness, or depressed level of consciousness.

The profile of hypotension AEs in children with HF was largely consistent with that observed in adults with HFrEF. While hypotension AEs and blood pressure reductions during Part 2 of Study B2319 were more frequently reported for sacubitril/valsartan compared with enalapril across all age groups, the more severe events of syncope and pre-syncope were reported at a higher rate in the enalapril group and occurred only in the oldest age group.

The overall incidence of hypotension AEs was comparable between the two treatment groups (Table 44). By preferred term, the sacubitril/valsartan group had a comparable frequency of hypotension (12.30% vs 11.70%) but a higher frequency of dizziness (12.30% vs 7.98%), while the enalapril group had higher frequencies of syncope (1.07% vs 2.13%) and pre-syncope (0.53% vs 1.60%). Consistent with the observed effects on lowering blood pressure, greater proportions of patients in the sacubitril/valsartan group had post-baseline reductions in systolic blood pressure compared to the enalapril group (Table 44).

Most of the hypotension AEs were not serious and did not cause study treatment discontinuation. Hypotension SAEs were more frequent with sacubitril/valsartan than enalapril (Table 44). By preferred term, these SAEs consisted of hypotension (4 patients, 2.14% in the sacubitril/valsartan group vs 0 patients in the enalapril group) and syncope (1 patient, 0.53% in the sacubitril/valsartan group vs 2 patients, 1.06% in the enalapril group). One patient in the sacubitril/valsartan group discontinued study treatment due to a hypotension SAE.

Table 44. Hypotension adverse events and blood pressure changes – Study B2319 Part 2 (Safety Set)

	Statistic	LCZ696 N=187	Enalapril N=188
Hypotension AEs			
Overall AEs	n (%)	43 (22.99)	40 (21.28)
SAEs	n (%)	5 (2.67)	2 (1.06)
AEs leading to discontinuation	n (%)	1 (0.53)	0
Clinical thresholds			
Post-baseline SBP <5th percentile per age	n (%)	81 (43.32)	50 (26.60)
At least 20 mmHg drop in SBP	n (%)	79 (42.25)	50 (26.60)
Simultaneous post-baseline SBP <5th percentile per age and at least 20 mmHg drop in SBP	n (%)	36 (19.25)	18 (9.57)

Hyperkalemia

Hyperkalemia is known to occur with ACEI treatment due to RAAS blockage through inhibition of secretion of aldosterone. Hyperkalemia AEs and elevations in serum potassium were more frequently reported for the enalapril group compared with the sacubitril/valsartan group in adults with HFrEF.

The profile of hyperkalemia AEs in children with HF was consistent with that observed in adults with HFrEF. The incidence of hyperkalemia AEs was similar between the treatment groups during Part 2 of Study B2319 (Table 45). Hyperkalemia events that were serious or led to discontinuation were reported only in the enalapril group.

Mild to moderate increases in serum potassium (>20% increase and >ULN or any value >6 mmol/L, and newly occurring ≥5.5 mEq/L or >6.0 mEq/L) were comparable between the two treatment groups (Table 5-7). More severe elevations (newly occurring >6.5 mEq/L) occurred only in the enalapril group (6 patients, 3.21%).

Comparable trends were observed in oldest and youngest children (Age Groups 1 and 3a), while in children aged 2-<6 years (Age Group 2a) the sacubitril/valsartan group had more frequent hyperkalemia AEs (10.64% vs 5.26%) and newly occurring elevations of ≥5.5 mEq/L (17.39% vs 8.11%) and >6.0 mEq/L (6.52% vs 0%) than the enalapril group.

Table 45. Hyperkalemia adverse events and serum potassium elevations – Study B2319 Part 2 (Safety Set)

	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Hyperkalemia AEs		
Overall AEs	9 (4.81)	10 (5.32)
SAEs	0	2 (1.06)
AEs leading to discontinuation	0	1 (0.53)
Serum potassium elevations		
> 20% increase and > ULN or any value > 6 mmol/L	21 (11.23)	22 (11.70)
≥ 5.5 mEq/L newly occurring post-baseline	23 (12.37)	20 (10.70)
> 6.0 mEq/L newly occurring post-baseline	4 (2.15)	6 (3.21)
> 6.5 mEq/L newly occurring post-baseline	0	6 (3.21)

Renal impairment

Renal impairment has been observed with any therapy that blocks the RAAS by decreasing glomerular filtration. In Study B2314, the incidence of renal impairment AEs/SAEs was consistently lower with sacubitril/valsartan vs enalapril in adults with HFrEF. Also, the percentages of adults with categorical eGFR decreases and notably abnormal serum creatinine elevations were lower in the sacubitril/valsartan group compared with the enalapril group.

Overall, the renal profile based on AEs and laboratory parameters in the paediatric HF population was comparable between the treatment groups. In Study B2319, the incidence of renal AEs was higher for sacubitril/valsartan group compared with the enalapril group (6.42% vs 4.26%) (Table 46). This difference was driven by mild renal AEs (3.21% vs 0.53%), while the frequencies of moderate (1.60% vs 2.13%) and severe renal AEs (1.60% in both groups) showed no treatment differences. The treatment groups also had identical frequencies of renal SAEs and AEs, leading to discontinuation (Table 46).

Renal laboratory assessments further supported a comparable renal profile in the paediatric patients as seen in adults. The overall incidence of renal function abnormalities was lower for sacubitril/valsartan compared to enalapril (9.09% vs 11.70%) (Table 46). The two treatment groups had comparable frequencies of serum creatinine increases ≥25% and <50% vs baseline (7.49% vs 7.45%), while the sacubitril/valsartan group had a lower incidence of serum creatinine increase ≥ 50% vs baseline (1.07% vs 4.26%). These trends were consistent across the three age groups. Comparable frequencies of renal function abnormalities in the two treatment groups were observed in Age Group 1 (10.09% vs 10.81%) and Age Group 2a (10.64% vs 10.53%), while in the youngest group, Age Group 3a, fewer renal events were observed in the sacubitril/valsartan group vs enalapril group (3.23% vs 15.38%).

Estimated glomerular filtration rate (eGFR) data was assessed by age group taking into account the different renal development phases in children. Healthy infants < 1 year of age tend to have a lower eGFR as their kidneys are still in development and therefore were analyzed separately. In Age Groups 1 and 2 (i.e., 1-<18 years), categorical increases in creatinine and decreases in eGFR were comparable between the treatment groups throughout the study. In Age Group 3 (1 month-<1 year), a total of 7 patients (4 patients, 80% in the sacubitril/valsartan group and 3 patients, 75% in the enalapril group) had an increase in eGFR of <30% throughout the study, which is lower than expected in children of that age.

Table 46. Renal impairment adverse events and renal laboratory parameters – Study B2319 Part 2 (Safety Set)

	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Renal impairment AEs		
Overall AEs	12 (6.42)	8 (4.26)
SAEs	3 (1.60)	3 (1.60)
AEs leading to discontinuation	1 (0.53)	1 (0.53)
Renal function abnormalities		
Patients with any renal abnormalities	17 (9.09)	22 (11.70)
Serum creatinine increase ≥ 25% and < 50% vs. Baseline (confirmed)	14 (7.49)	14 (7.45)
Serum creatinine increase ≥ 50% vs. Baseline (confirmed)	2 (1.07)	8 (4.26)
New onset dipstick proteinuria (confirmed)	0	1 (0.53)
New onset dipstick glycosuria	1 (0.53)	0
New onset dipstick hematuria	1 (0.53)	0
Albumin creatinine ratio increase 2-fold vs. Baseline	0	0
Protein creatinine ratio increase 2-fold vs. Baseline	0	0

Source: [SCS-Table 2-11 and Table 2-12]

Angioedema

NEP inhibition by sacubitril/valsartan has the potential to increase levels of the substrate bradykinin and cause angioedema. Unlike omapatrilat, which has shown to increase the risk for serious angioedema by inhibiting multiple enzymes responsible for the breakdown of the angioedema-mediator bradykinin, sacubitrilat delivered by sacubitril is a highly selective NEP inhibitor, and the ARB valsartan is known to have a lower risk of angioedema compared to ACEIs (Irons and Kumar 2003, Fryer et al 2008, Toh et al 2012).

In Study B2314 (run-in and double-blind periods), the incidence of positively adjudicated angioedema was 0.31% (29 cases) in the sacubitril/valsartan group and 0.24% (25 cases) in the enalapril group. Angioedema was more frequent in Black patients compared to non-Black patients (1.79% vs 0.44%). There were no angioedema cases involving airway compromise or requiring airway support. All confirmed cases were managed with no treatment or with antihistamines, catecholamine, or steroids.

In Study B2319 (Part 1 and Part 2), no patient in the sacubitril/valsartan group had positively adjudicated angioedema compared to one (0.53%) patient in the enalapril group during Part 2. This positively adjudicated case was reported in a Black patient in Age Group 1 (6->18 years) who was hospitalized but did not need mechanical airway protection and had no airway compromise.

Hepatotoxicity

Patients with HF often experience increased liver enzymes due to liver congestion. The hepatic profile of sacubitril/valsartan does not suggest a hepatotoxic potential. In Study B2314 in adults, the incidence of AEs in the hepatotoxicity NMQ was 3.28% in the sacubitril/valsartan group and 4.35% in the enalapril group. The majority of liver-related AEs were of mild or moderate severity, and severe AEs, SAEs and AEs leading to discontinuation were infrequent and showed no differences between the treatment groups.

In Study B2319 in paediatric patients, the incidence of hepatic AEs was higher in the sacubitril/valsartan group compared with the enalapril group (8.02% vs 5.32%). All hepatic AEs were mild (4.28% vs 3.19%) or moderate (3.74% vs 1.60%), except for one severe event (preferred term: ascites) in the enalapril group. One hepatic SAE (preferred term: ascites) was reported in sacubitril/valsartan group; this event was due to an increase in hepatic congestion and resolved with drainage. Hepatic AEs leading to discontinuation were reported only in the sacubitril/valsartan group (3 patients, 1.60%) and consisted of non-serious events of increased hepatic enzyme, abnormal hepatic function, and hepatomegaly.

The incidence of newly occurring liver enzyme elevations was low and comparable between the treatment groups. One patient in each treatment group had elevated liver enzymes (ALT or AST >20×ULN). The highest categorical values in the sacubitril/valsartan group were observed in the same patient who met the criteria for biochemical Hy's law. This was a 9-year-old female patient who had a history of left ventricular non-compaction (idiopathic) and experienced worsening of cardiac failure followed by hepatomegaly due to hepatic congestion. The case was assessed by a blinded independent external liver safety expert to be consistent with heart failure deterioration and not related to study drug.

There were no major differences in liver enzyme elevations across the age groups. The majority of the elevations were reported in the oldest group and the frequencies, while low overall, were 2-3% higher in the sacubitril/valsartan group compared with the enalapril group (ALT>3×ULN: 4.26 vs 1.11%; ALT>5×ULN: 2.11% vs 0%). This oldest group also included the single patient with the highest elevation, as noted above. Liver enzyme elevations were infrequent and comparable in Age Groups 2a and 3a.

Changes in bone growth and density

There was no evidence of increased risk of fractures or altered growth in either treatment group.

Two patients in each of the sacubitril/valsartan (1.07%) and enalapril (1.06%) groups had AEs of fractures. In the sacubitril/valsartan group, there was a mild case of wrist fracture and a severe event of pathological fracture of the right femur (which resolved with surgery and no action taken with the study drug), both in the oldest age group. In the enalapril group, there was a mild event of clavicle fracture due to home injury (in Age Group 2a) and a moderate event of femur fracture in a patient with underlying osteopenia (in Age Group 3a). None of the fractures was considered related to the study drug or led to discontinuation.

The treatment groups had comparable increases in height and height Z-score during the study, and this result was consistent across the age groups

2.6.11.2.5. Laboratory findings

The safety assessment of sacubitril/valsartan treatment during Part 2 epoch included a full panel of haematology, clinical chemistry laboratory evaluations and urinalysis at screening, Week 24, Week 52, and more frequently as deemed necessary by the Investigator; a smaller chemistry panel of electrolytes and renal function was collected at all in-person visits.

Haematology

Overall, the haematology results in the paediatric Study 2319 are consistent with the results in the adult Study B2314.

Mean haematology test results, as assessed via local or central labs, as shift from baseline or to minimum or maximum values, were generally balanced by treatment group and by age groups and in-line with the known safety profile (Table 47).

Overall, clinically notable haematology parameters were infrequent (≤ 3.20%) and comparable between treatment groups. A > 50% increase in WBC count was observed in 1.60% of patients treated with sacubitril/valsartan vs 4.79% of patients treated with enalapril (Table 47). A similar trend was observed among the 3 age groups. These shifts in WBC counts were consistent with the incidence of concomitant transient infections in these paediatric patients.

Table 47. Overview of clinically notable haematology parameters during Study B2319 (Safety Set)

Hematology parameter		LCZ N=187 n (%)	ENA N=188 n (%)
RBC count	> 50% increase and > ULN	1 (0.53)	0
	> 30% decrease and < LLN	2 (1.07)	1 (0.53)
Hemoglobin	> 50% increase and >ULN	1 (0.53)	1 (0.53)
	> 30% decrease and < LLN or any value < 70 g/L	4 (2.14)	4 (2.13)
Hematocrit	> 50% increase and > ULN	1 (0.53)	0
	> 30% decrease and < LLN	1 (0.53)	0
WBC count	> 50% increase and > ULN	3 (1.60)	9 (4.79)
	> 50% decrease and < LLN	2 (1.07)	1 (0.53)
Platelet count	> 75% increase and > ULN	2 (1.07)	2 (1.06)
	> 50% decrease and < LLN	3 (1.60)	1 (0.53)

All increases and decreases are defined as compared to baseline value.
Baseline assessment is defined as the last nonmissing assessment (scheduled or unscheduled) prior to or at the time of the first double-blind study drug and after the last Part 1 dose date + 5 d. When the dose and the assessment are on the same date, and the dosing time or the assessment time is missing, the assessment is considered as pre-dose.
Local and central laboratory results.
Source: [Study B2319-Table 14.3-2.7.2]

Clinical chemistry

Overall, the clinical chemistry results in the paediatric Study B2319 are consistent with the results in the adult Study B2314.

Notable clinical chemistry values, as measured by either the central laboratory or local laboratory are shown in Table 48. There were no clinically relevant differences in the incidence of the majority of laboratory parameters between treatment groups.

Numerically lower incidence in the sacubitril/valsartan group vs enalapril group were:

- Glucose (> 50% decrease and < LLN) or any value < 3.3 mmol/L
- Potassium (> 20% decrease and < LLN), or any value < 3 mmol/L

Numerically higher incidence in the sacubitril/valsartan group vs enalapril group were:

- Uric acid 50% increase and > ULN in uric acid

The incidence of clinically notable increases in BUN (> 50% increase and > ULN) and potassium (> 20% increase and > ULN, or any value > 6 mmol/L) was higher in the youngest patients (age group 3a) compared to the older groups (age group 1 and age group 2a) irrespective of treatment. Results were comparable among the 3 age groups for all other clinically notable biochemistry events. [

Table 48. Overview of clinically notable clinical chemistries during Study B2319 (Safety Set)

Clinical chemistry parameter		LCZ N=187 n (%)	ENA N=188 n (%)
BUN	> 50% increase and > ULN	16 (8.56)	17 (9.04)
Creatinine	> 50% increase and > ULN	13 (6.95)	15 (7.98)
Albumin	< 20 g/L	6 (3.21)	4 (2.13)
Glucose	> 50% increase and > ULN	3 (1.60)	5 (2.66)
	> 50% decrease and < LLN or any value < 3.3 mmol/L	5 (2.67)	12 (6.38)
Total bilirubin	> 100% increase and > ULN	5 (2.67)	2 (1.06)
AST	> 150% increase and > ULN	3 (1.60)	2 (1.06)
ALT	> 150% increase and > ULN	6 (3.21)	3 (1.60)
Sodium	> 5% increase and > ULN or any value > 150 mmol/L	3 (1.60)	3 (1.60)
	> 5% decrease and < LLN or any value < 125 mmol/L	8 (4.28)	10 (5.32)
Potassium	> 20% increase and > ULN or any value > 6 mmol/L	21 (11.23)	22 (11.70)
	> 20% decrease and < LLN or any value < 3 mmol/L	14 (7.49)	18 (9.57)
Chloride	> 10% decrease and < LLN	1 (0.53)	3 (1.60)

Mean change from baseline of clinical chemistry test results was similar between the two treatment groups, overall and among the 3 age groups. Any shifts from normal at baseline to high or low values post-baseline were similar between the two treatment groups.

Urinalysis

Only a few cases required full microscopic analysis as the majority of urine dipsticks were negative for abnormalities.

2.6.11.3. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.11.3.1. Safety in special populations

Subgroup analyses of AEs (SOC and PT) reported during Part 2 of Study B2319 revealed no meaningful difference between sacubitril/valsartan and enalapril in the incidences of AEs or safety topics of interest across the subgroups of age, race, region, sex, and prior ACEI/ARB status.

Intrinsic factors

Analyses by factor

The following intrinsic factors were considered relevant to sacubitril/valsartan's current safety topics of interest: sex, race, ethnicity, NYHA/Ross classification at baseline, history of renal disease at baseline,

BP by quartiles at baseline, eGFR at baseline, liver disease at baseline, where applicable. These evaluations did not identify any meaningful difference. As the sample size was relatively small, the variability around frequencies of events within each category should be interpreted with caution.

The AESIs of Embryo-fetal toxicity, Anaphylaxis, Change in bone growth / density, and Malignancy reported few cases during Study B2319 and hence, no meaningful comparisons can be done for the intrinsic factor subgroups.

By AESI

The following observations were made regarding Hypotension:

AEs that belonged to Hypotension AESI presented relatively more frequently in Black enalapril-treated patients compared with sacubitril/valsartan-treated patients (11 out of 25 patients, 44.0%; 8 out of 23 patients, 34.8%, respectively).

AEs that belonged to Hypotension AESI presented relatively more frequently insacubitril/valsartan-treated patients whose baseline systolic BP was in the first tertile compared with enalapril-treated patients (20 out of 56 patients, 35.7%; 12 out of 59 patients, 20.3%, respectively) and more frequently in enalapril-treated patients whose baseline systolic BP was in the second tertile compared with sacubitril/valsartan-treated patients (18 out of 65 patients, 27.7%; 11 out of 66 patients, 16.7%, respectively).

The number of cases that reported Hyperkalemia events was low overall and, hence, no meaningful comparisons can be done for the intrinsic factor subgroups.

The following observations were made regarding Renal impairment:

AEs that belonged to Renal impairment AESI presented more frequently in sacubitril/valsartan-treated patients when NYHA/Ross was I/II at baseline compared with enalapril-treated patients (11 out of 160 patients, 6.9%; 6 out of 159 patients, 3.8%, respectively). Upon individual case evaluation, the majority of the cases presented alternate explanations (acute decompensation, worsening HF, concomitant medication, sepsis, ongoing renal impairment).

The observations regarding Hepatotoxicity were not meaningfully different. Analyses by the various intrinsic factors were similar by treatment group.

The following observations were regarding Hypersensitivity:

AEs that belonged to Hypersensitivity AESI presented relatively more frequently in Black sacubitril/valsartan-treated patients compared to enalapril-treated patients (5 out of 23 patients; 21.7%; 2 out of 25 patients, 8.0%, respectively).

Extrinsic factors

Safety during concomitant use of specific medications that are known to be related to specific risks, e.g. Statin drug-drug interaction or other medications, were investigated.

The following extrinsic factors were considered relevant to sacubitril/valsartan: ACEI, ARB, or MRA usage at screening; phosphodiesterase-5 (PDE5) inhibitor usage post-baseline, potassium-sparing diuretics at baseline; alcohol history, and smoking status, where applicable.

No clinically relevant difference was observed between sacubitril/valsartan and enalapril for AESIs and the extrinsic factors described above, except for the following:

By medication usage

AEs that belonged to Hypotension AESI presented more frequently in sacubitril/valsartan-treated patients compared to enalapril patients who did not use ACEI at screening (6 out of 19 patients; 31.6%; 3 out of 17 patients; 17.6%).

AEs that belonged to Renal impairment AESI presented more frequently in sacubitril/valsartan-treated patients compared to enalapril patients who did not use ACEI at screening (4 out of 19 patients, 21.1%; 0 out of 17 patients).

By alcohol / smoking history

Although each patient's alcohol history and substance usage was collected during Study B2319, an analysis was not considered warranted in this study population. With the exception of 1 patient who was a current smoker and 1 patient with a history of alcohol consumption, no other patient had alcohol or a smoking history.

Importantly, safety results were consistent across the three age groups as described above for the overall profile of AEs, frequently reported AEs and frequently reported SAEs, and key safety topics of interest.

2.6.11.3.2. Immunological events

No new data was generated.

2.6.11.3.3. Safety related to drug-drug interactions and other interactions

No new data have been generated in support of this dossier.

During Study B2319, prohibited drugs for concomitant use were any ACEI, any ARB, and renin inhibitors. If any concomitant use was required (Section 5.1.2), sacubitril/valsartan was temporarily discontinued prior to the start of any open-label ARB or renin inhibitor; or temporary discontinuation of study drug more than 36 hours prior to starting open-label ACEI.

There were no relevant cases related to statin drug-drug interaction.

2.6.11.3.4. Discontinuation due to adverse events

Overall, the rate of discontinuation was considered low (11.14%). However, death was the most frequent reason for treatment discontinuation (5.31%).

Overall, 21 sacubitril/valsartan-treated patients (11.23%) and 21 enalapril-treated patients (11.17%) presented an AE that led to permanent discontinuation of the study drug (Table 49). By treatment group, AEs leading to permanent discontinuation of study drug presented at a similar frequency. Cardiac failure was the most frequent event: 7 sacubitril/valsartan-treated patients (3.74%) and 11 enalapril-treated patients (5.85%). All remaining AEs presented in ≤ 2 patients (≤ 1.07%) by treatment group.

SAE leading to study drug discontinuation

There were no meaningful differences in SAE leading to study drug discontinuation by treatment group and by age group observed (16 patients (8.56%) in the sacubitril/valsartan group and 18 patients (9.57%) in the enalapril group).

Table 49. Adverse events leading to permanent study-drug discontinuation by preferred term and age group during Study B2319 (Safety Set)

AE leading to permanent study-drug discontinuation	LCZ N=109 n (%)	ENA N=111 n (%)	LCZ N=47 n (%)	ENA N=38 n (%)	LCZ N=31 n (%)	ENA N=39 n (%)	LCZ N=187 n (%)
Age group:	**Age group 1**		**Age group 2a**		**Age group 3a**		
Total no. of patients	**16 (14.68)**	**15 (13.51)**	**3 (6.38)**	**2 (5.26)**	**2 (6.45)**	**4 (10.26)**	**21 (11.23)**
Cardiac failure	6 (5.50)	9 (8.11)	0	0	1 (3.23)	1 (2.56)	7 (3.74)
Cardiac failure congestive	1 (0.92)	0	1 (2.13)	0	0	0	2 (1.07)
Cardiac arrest	1 (0.92)	0	0	0	1 (3.23)	0	2 (1.07)
Cardiac failure acute	1 (0.92)	1 (0.90)	0	0	0	0	1 (0.53)
Bradycardia	1 (0.92)	0	0	0	0	0	1 (0.53)
Hepatic enzyme increased	1 (0.92)	0	0	0	0	0	1 (0.53)
Hepatic function abnormal	1 (0.92)	0	0	0	0	0	1 (0.53)
Hepatomegaly	1 (0.92)	0	0	0	0	0	1 (0.53)
Hypotension	1 (0.92)	0	0	0	0	0	1 (0.53)
Hypoxia	1 (0.92)	0	0	0	0	0	1 (0.53)
Renal failure	1 (0.92)	0	0	0	0	0	1 (0.53)
Ventricular dysfunction	1 (0.92)	0	0		0	0	1 (0.53)
Cerebral infarction	0	0	1 (2.13)	0	0	0	1 (0.53)
Sudden death	0	0	1 (2.13)	0	0	0	1 (0.53)
Abdominal pain upper	0	1 (0.90)	0	0	0	0	0
Angioedema	0	1 (0.90)	0	0	0	0	0
Brain injury	0	0	0	0	0	1 (2.56)	0
Cardiac ventricular thrombosis	0	1 (0.90)	0	0	0	0	0
Chest pain	0	1 (0.90)	0	0	0	0	0
Circulatory collapse	0	1 (0.90)	0	0	0	0	0
Cough	0	1 (0.90)	0	0	0	0	0
Death	0	1 (0.90)	0	0	0	0	0
Dermatitis allergic	0	1 (0.90)	0	0	0	0	0
Hyperkalaemia	0	0	0	1 (2.63)	0	0	0
Hypoxic-ischaemic encephalopathy	0	1 (0.90)	0	0	0	0	0
Renal impairment	0	0	0	1 (2.63)	0	0	0
Respiratory distress	0	0	0	0	0	1 (2.56)	0
Rhabdomyolysis	0	0	0	0	0	1 (2.56)	0
Vomiting	0	0	0	0	0	1 (2.56)	0

Source: [SCS Appendix 1-Table 2-7], [Study B2319-Table 14.3.1-10.1]

Comparison with adult population

The profile of AEs leading to permanent discontinuation of the study drug was similar in adults during Study B2314. The frequencies of AEs causing permanent discontinuation of study drug in adults were low and comparable between treatment groups, as observed in the paediatric population during Study B2319.

The rate of AEs causing permanent discontinuation from the study drug was numerically lower for the sacubitril/valsartan group compared to the enalapril group (10.7% vs 12.2%). This was also the case for SAEs causing permanent discontinuation of the study drug (8.2% vs 9.4%). The most frequent AEs causing study drug discontinuation (i.e. AEs that occurred in $\geqslant$ 0.5% in either group) included cardiac failure (1.5%, each), cardiac death (0.67%, sacubitril/valsartan; 0.76%, enalapril), hypotension (0.62% vs 0.54%), sudden cardiac death (0.59% vs 0.52%), renal impairment (0.43% vs 0.78%), and sudden death (0.34% vs 0.50%). Discontinuation due to renal impairment was lower in the sacubitril/valsartan group compared to the enalapril group (0.4% vs 0.8%).

2.6.12. Discussion on clinical safety

The safety profile of sacubitril/valsartan is adequately characterized in adults with more than 28,000 patients in clinical studies and 6.0 million patient-treatment years of exposure in the post-marketing setting.

Given the similarities in disease between paediatric HF due to LVSD consistent with DCM and adult HF due to DCM and consistent with the principles of paediatric extrapolation outlined in the recent CHMP release of ICH E11A guidance, i.e. similar drug exposure at target doses and a similar decrease in NT-proBNP at exposure matched doses, the safety assessment from study B2319 is to be considered within the context of the already adequately characterized, well-established, safety profile of sacubitril/valsartan in adults. It is considered a reasonable approach to extrapolate the safety profile of adults to paediatrics, given the disease similarity, similar pharmacology and similar drug exposure.

The primary safety database to support registration of sacubitril/valsartan in paediatric patients aged 1 month to < 18 years with symptomatic HF due to LVSD is provided by Part 2 of Study B2319 (N=375 total; N=187 sacubitril/valsartan; N=188 enalapril)) in which the exposure to treatment was approximately 52 weeks at the end of the trial. The safety profile of sacubitril/valsartan in study B2319 is also assessed against the known safety profile of the HFrEF adult population (study B2314) with respect to key safety topics of interest.

Patient exposure. The overall sample size of the safety database is acceptable and exceeds the minimal requirement of 100 patients exposed for a minimum of one-year, as stated in ICH Topic E 1, which is reassuring. The overall patient-years on-treatment was similar between groups (173.72 for sacubitril/valsartan and 164.19 for enalapril). Most patients in both treatment groups had exposure ≥ 6 months (87.20% (n=168) and 89.84% (n=159) for sacubitril/valsartan and enalapril, respectively). Although up-titration occurred slower than planned, the proportion of patients reaching the target dose level at one point in time was 77% for sacubitril/valsartan and 82% for enalapril. The mean weight-based daily dose was 5.07 mg/kg for sacubitril/valsartan group and 0.33 mg/kg for the enalapril group.

Adverse events. The overall incidence of AEs during study B2319 was comparable between the sacubitril/valsartan and enalapril groups (88.8% and 87.8%, respectively). The majority of AEs were mild or moderate in severity. Deaths and drug-related AEs were less frequent for sacubitril/valsartan vs enalapril (4.3% vs 6.4% and 26.7% vs 28.2%, respectively), while SAEs and AEs requiring adjustment or interruption were more frequent for sacubitril/valsartan vs enalapril (36.9% vs 33.0% and 20.3% vs 17.0%, respectively). The safety profile of sacubitril/valsartan was consistent across the modified age groups, with minor differences (i.e. less death and drug-related AE in youngest age groups). Infections and infestations were the most frequently affected system organ class. These consisted mostly of upper respiratory tract infection and nasopharyngitis, with no meaningful treatment differences.

The most common AEs (at least 10%) were pyrexia (20.9% vs 18.1% for sacubitril/valsartan vs enalapril, respectively), upper respiratory tract infection (20.9% vs 18.6%), cough (19.3% vs 20.2%), vomiting (18.1% vs 21.3%), nasopharyngitis (15.5% vs 9.0%), cardiac failure (14.4% vs 14.4%), diarrhoea (13.4% vs 12.2%), dizziness (12.3% vs 8.0%), hypotension (12.3% vs 11.7%), headache (11.8% vs 10.6%), and fatigue (10.2% vs 7.5%). A higher incidence and hence a change in the frequency category was observed for adverse drug reactions (ADRs) of diarrhoea, fatigue, headache, dizziness and cough in paediatric Study B2319 compared to the adult Study B2314. It should be noted that most of these AE are commonly observed in children and adolescents (e.g., diarrhoea, cough) are a common symptom of HF (e.g., fatigue). The frequencies of diarrhoea (13.4% in sacubitril/valsartan group and 12.2% in enalapril group) are comparable to the background rate of diarrhoea in this

population, and the frequency of headache (11.8% with sacubitril/valsartan and 10.6% with enalapril) was lower than the estimated prevalence of headache in children and adolescents. While dizziness was more frequently reported in the sacubitril/valsartan arm of Study B2319 than in Study B2314 (12.3% vs 6.3%), the majority of cases were mild and not suspected to be related to the study drug and had resolved with no change to the sacubitril/valsartan dose.

Deaths. The proportion of reported deaths is relatively low, with fewer deaths in the sacubitril/valsartan group (4.3% (n=8)) compared with the enalapril group (6.4% (n=12)), which is reassuring. All but 2 deaths were adjudicated as cardiovascular deaths.

Serious AEs. The incidence of SAE was relatively high and slightly higher in the sacubitril/valsartan group compared with the enalapril group (36.9% vs 33.0%, respectively). Sacubitril/valsartan is known to have a larger effect on blood pressure than enalapril, which partially explains why the SAEs of hypotension only occurred in the sacubitril/valsartan group (n=4). Nevertheless, no other pattern indicative for a safety signal could be identified. The majority of serious adverse events were cardiac failures, which is in line with the progressive nature and poor prognosis of paediatric heart failure, and occurred with similar frequency in the two treatment groups. The number of patients with SAEs other than cardiac failure was small (≤5 per group), which is reassuring.

Safety topics of interest. Overall, the safety topics of interest showed largely similar frequencies between the sacubitril/valsartan and enalapril groups. There were no relevant cases related to embryo-fetal toxicity or lethality, statin drug-drug interaction, cognitive impairment, neonatal or infantile toxicity through exposure to breast milk, anaphylaxis, or malignancy.

The frequency of *hypotension*-based AEs was similar between the treatment groups in study B2319 and comparable to the incidence of hypotension-based AEs in the sacubitril/valsartan group of study B2314. The profile of *hyperkalaemia* AEs in paediatric HF was consistent with that observed in adults with HFrEF. The incidence of hyperkalemia AEs was also similar between the treatment groups in the paediatric study B2319. In Study B2319, the *incidence of renal AEs* was slightly higher for sacubitril/valsartan group compared with the enalapril group (6.4% vs 4.3%), yet lower than the incidence in the adult population (which was 10.1 vs 11.5%). No patient in the sacubitril/valsartan group had positively adjudicated *angioedema*.

Hepatic AEs were reported in higher frequency in the paediatric study B2319 compared with the adult study B2314 (3.3% vs 8.0%). Furthermore, in study B2319, the incidence of hepatic AEs was higher for sacubitril/valsartan as compared to enalapril (8.0% vs 5.3%). The individual hepatic PTs reported in the sacubitril/valsartan group were heterogeneous in nature and none showed evidence of causality to study treatment. Thus it is considered reasonable and acceptable that it is not included in the SmPC.

There is preclinical evidence suggesting a possible risk of *growth retardation* and *decreased bone mineral density* in the paediatric population. However, there was no increased risk of fractures or altered growth in either treatment group in B2319. The treatment groups had comparable increases in height and height Z-score during the study, and this result was consistent across the age groups.

Laboratory findings. Overall, both the *hematology* and *clinical chemistry* results in the paediatric study B2319 are consistent with the results in the adult study B2314. No large treatment differences were found between sacubitril/valsartan and enalapril, besides uric acid. For serum uric acid concentration the incidence of 50% increase was 6% in the sacubitril/valsartan arm and 2% in the enalapril arm, with the highest incidence in age group 1. Elevated serum uric acid concentration has been associated with an increased risk of cardiovascular disease, but this may be due to unmeasured confounders. Hyperuricemia is common in many forms of cardiovascular disease, including HF. In patients with HF, higher serum uric acid concentration has been associated with worse clinical outcomes. Interestingly, in B2314, during the run-in period, serum uric acid decreased when switching

from enalapril to sacubitril/valsartan and remained lower in the sacubitril/valsartan group than in the enalapril group at 4, 12, and 24 months after randomization. No causal relationship was found between >50% increase in uric acid levels and sacubitril/valsartan use. Furthermore, the PT hyperuricemia was reported in 0 patients in the sacubitril/valsartan arm and 1 (0.53%) in enalapril arm and PT Blood uric acid increased was reported in 1 patient (0.53%) in sacubitril/valsartan and 2 patients (1.06%) in enalapril arm.

Safety in special populations. Analyses of adverse events of special interest by intrinsic and extrinsic factors demonstrated that in paediatric patients, hypersensitivity was more frequently reported in black patients. Evaluation of the 5 cases of hypersensitivity in black patients revealed that these were all mild or moderate, recovered with no change to study treatment and were evaluated to be not related to sacubitril/valsartan by the investigator. Given the benign nature of the events reported and the lack of causality relationship to sacubitril/valsartan based on the individual case review, the finding that hypersensitivity PTs were more frequently reported in Black pediatric patients is not considered to be clinically meaningful.

The safety of sacubitril/valsartan in paediatric patients with *renal or hepatic impairment* could not be investigated adequately due to exclusion criterion (Patients with significant renal (eGFR calculated using the modified Schwartz formula < 30% mean GFR for age); hepatic (serum aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal); gastrointestinal or biliary disorders (that could impair absorption, metabolism, or excretion of orally administered medications). The limited safety data are available in paediatric patients with moderate hepatic impairment or moderate to severe renal impairment has been adequately reflected in the SmPC.

Discontinuations due to AEs. The proportion of AEs leading to discontinuations was comparable between the sacubitril/valsartan and enalapril groups (11.2% each). Most of the AEs that led to study treatment discontinuation were SAEs, which tended to be lower overall with sacubitril/valsartan than enalapril (8.6% vs 9.6%).

Post marketing experience. The additional assessment of post-marketing data, with a cut-off of 31 Jan 2022, revealed no new safety signals and/or substantial change to the safety profile of sacubitril/valsartan in adults. The known important identified risks with sacubitril/valsartan are Hypotension, Renal impairment, Hyperkalemia, Angioedema, and Embryo-fetal toxicity / Lethality. The important potential risks with sacubitril/valsartan are: Neonatal / infantile toxicity through exposure from breast milk, Hepatotoxicity, Cognitive impairment, and Statin drug-drug interaction.

2.6.13. Conclusions on the clinical safety

In conclusion, the safety profile of sacubitril/valsartan in paediatric patients aged 1 month to < 18 years with symptomatic HF due to systemic LVSD is generally consistent with the well-established safety profile in adults with HF. No new safety signal was observed in the paediatric population of Study B2319. The ADRs in paediatric patients were generally consistent with those already identified in adults.

Safety data on important safety topics of interest, such as hypotension, hyperkalemia, renal impairment, angioedema, and hepatotoxicity, were consistent with extensive prior experience in adults, with only hepatotoxicity having a higher incidence in the paediatric population. In addition, there was no evidence of any embryo-fetal toxicity/lethality or any growth-related impact in paediatric patients treated with sacubitril/valsartan.

The safety profile observed in Study B2319 was broadly consistent across the age groups,

encompassing children aged 1 month to < 18 years of age. However, as there were only 9 patients aged 1 year or less, there is insufficient information on the safety of sacubitril/valsartan in this youngest patient population.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Hypotension • Renal impairment • Hyperkalaemia • Angioedema • Embryo-foetal toxicity / lethality
Important potential risks	• Neonatal / infantile toxicity through exposure from breast milk • Hepatotoxicity • Cognitive impairment • Statin drug-drug interaction • Long-term effects on growth, bone growth and mineralisation in the paediatric population
Missing information	• Long-term use of LCZ696 in HF patients • Use in ACEI / ARB naïve HF patients

The section “juvenile toxicity” in the table in module SI was updated to reflect the current data, which indicates that bone is a target organ together with growth retardation for sacubitril in juvenile rats with a safety margin lower than exposure in the human paediatric population. In the clinical paediatric study (B2319) no increased risk of fractures and altered growth was observed. In addition, increases in height and height Z-score were comparable between treatment and age groups. Nonetheless, the duration of this clinical study may be too short to detect long-term changes in growth.

In addition, module SII was updated to reflect that the risk of long-term effects on growth, bone growth and mineralisation observed in the rat juvenile toxicity studies is considered important for inclusion to the RMP as an important potential risk. The important potential risk was phrased as “long-term effects on growth, bone growth and mineralisation in the paediatric population”.

2.7.2. Pharmacovigilance plan

The pharmacovigilance plan was updated to include the extension study PANOROMA-HF in the RMP as a category 3 PASS.

In the overview table 10-2 in Part III.1: Ongoing and planned additional pharmacovigilance activities, the added row under the heading Category 3 is inserted below.

Table 10-2 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None				
Category 3 - Required additional pharmacovigilance activities				
CLCZ696B2319E1 - EU PASS Category 3 Ongoing	To evaluate long- term safety and tolerability of sacubitril/valsartan in pediatric HF subjects	Long -term effects on growth, bone growth and mineralisation in the pediatric population.	Final report submission	31-Jul-2024

The PANORAMA-HF extension study (CLCZ696B2319E1) was considered relevant for inclusion in the RMP as additional PhV activity. The study will provide robust information to further characterise the important potential risk 'Effects on growth, bone growth and mineralization'.

2.7.3. Risk minimisation measures

The Table Part V.1: "Description of routine risk minimization measures by safety concern" was updated with the following information with regard to the newly added important potential risk:

Long -term effects on growth, bone growth and mineralisation in the pediatric population	**Routine risk communication:** To convey the relevant findings from preclinical and clinical studies. SmPC section: 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** None **Legal status:** Prescription only medicine. Medicinal product subject to restricted medical prescription

For the new important potential risk "long-term effects on growth, bone growth and mineralisation in the paediatric population" routine RMM are considered sufficient, given that the Applicant added at the end of Section 5.3 of the SmPC a statement: "*However, long term paediatric data on (bone)growth and fracture rate is not available*."

2.7.4. Conclusion

The CHMP considered that the risk management plan version 4.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

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3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Sacubitril/valsartan is a fixed-dose combination of a neprilysin inhibitor (sacubitril) and an angiotensin receptor blocker (ARB)(valsartan). The resulting increase in natriuretic peptide (NP) activity due to neutral endopeptidase (NEP) inhibition and suppression of the renin-angiotensin-aldosterone system (RAAS) activity through angiotensin II type-1 (AT1) receptor blockade have complementary effects on the cardiovascular system potentiating vasodilation, enhancing natriuresis, and promoting antihypertrophic/antifibrotic effects.

Regulatory status and proposed indication
Sacubitril/valsartan is currently approved for the treatment of adult patients with heart failure (HF) with reduced ejection fraction (HFrEF). The registration of sacubitril/valsartan in adults was based on results from study B2314 (PARADIGM-HF), a multicenter, randomized, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction. Compared with enalapril, sacubitril/valsartan reduced the risk of the composite of CV death or first HF hospitalization by 20% (HR 0.80, 1-sided $p<0.001$); reduced the risk of CV death by 20% (HR 0.80, 1-sided $p<0.001$); and reduced the risk of first HF hospitalization by 21% (HR 0.79, 1-sided $p<0.001$).

The current application is a grouped variation for extension of indication (type II variation) and a line extension. Aligned with the grouping examples laid out in Article 7.2 (b) of the Variation Regulation (Reg. 1234/2008), the line extension of the marketing authorization is being grouped with the type II variation as both changes are linked. The Applicant aims to provide evidence supporting the extension of sacubitril/valsartan use for the treatment of paediatric patients with HF with left ventricular systolic dysfunction (LVSD) in children and adolescents 1 year of age and older based on a paediatric extrapolation plan in conjunction with the results of the pivotal clinical trial B2319 (PANORAMA-HF). Furthermore, the Applicant has developed a novel pharmaceutical form, i.e. granules in capsules for opening, used within study B2319 to enable accurate and convenient administration of sacubitril/valsartan to the paediatric HF population.

Paediatric heart failure and treatment goals
Paediatric HF is a chronic condition associated with significant morbidity and mortality, frequent hospitalization and medical care, and poor quality of life. The reported prevalence was up to 83.3 per 100,000 children and adolescents in Spain. The two most common causes of paediatric HF are congenital heart disease and dilated cardiomyopathy. Treatment goals are similar to those for adult patients with heart failure, minimize morbidity and mortality and improve functional status and quality of life.

3.1.2. Available therapies and unmet medical need

In contrast to adult HF, there is no therapy approved for the treatment of paediatric HF in the European Union. Paediatric HF patients are treated with angiotensin-converting enzyme inhibitors (ACEIs) (often enalapril), beta-blockers, and spironolactone, which represents off-label use. ACEIs are considered as the first line therapy in paediatric chronic HF, which was also recognized by the World health organization and also the EMA in the Report on the Expert Group Meeting of Paediatric Heart Failure in 2010. These recommendations for paediatric HF treatment are based predominantly on small, single-centre, open-label studies of ACEIs in children with HF caused by LVSD. The efficacy of the off-label treatment on hard outcomes such as mortality is unknown, given the difficulties in adequately powering such trials. Due to the heterogeneity in clinical presentation and aetiologies, developing therapeutic strategies in paediatric HF is extremely challenging. Due to the lack of these randomized controlled studies, there also are no age-appropriate formulations of this off-label medication, i.e. enalapril. Based on the morbidity and mortality associated with paediatric HF, the absence of approved therapy and corresponding paediatric formulations, there is a significant unmet medical need for well-studied efficacious treatments with acceptable safety in this population.

3.1.3. Extrapolation plan

In line with ICH E11A, the Applicant proposes that the results from study B2314 (PARADIGM-HF, adult study, shortly described above) can be extrapolated to the paediatric population based on disease similarity, similar drug pharmacology (exposure), similar exposure-response and a predictive biomarker to bridge efficacy between adult and paediatric populations.
Disease similarity was proposed by the applicant between adults with HFrEF based on DCM and paediatric heart failure patients with LVSD consistent with DCM. This has also been highlighted in the draft ICH E11A 2022 guideline *"... heart failure due to dilated cardiomyopathy is similar between adult and paediatric populations, allowing for extrapolation from adult to paediatric patients with dilated cardiomyopathy*". Dilated cardiomyopathy is considered a form of heart muscle disease (abnormal ventricular myocardium) whose primary abnormality is systolic dysfunction. While dilation is also a component of this disease, it can be agreed that treatment strategies in children are based on signs, symptoms, and the degree of systolic dysfunction. PANORAMA-HF aimed to enrol a homogeneous

population of pediatric HF with left ventricle systolic dysfunction (LVSD) consistent with DCM. HCM and RCM, along with uncorrected structural heart disease and single ventricle or systemic right ventricle, were excluded. Enrolment of a homogeneous pediatric HF population with LVSD consistent with DCM in PANORAMA-HF was thus achieved by defining a series of inclusion and exclusion criteria, ensuring all pediatric patients had symptomatic HF and HfrEF defined as LVSD. More than 60% of patients in PANORAMA-HF were diagnosed with cardiomyopathy, with the cause being idiopathic in 33.6%, followed by familial/genetic conditions in 15.7% and congenital heart malformations in 13.3%. Heart failure secondary to other causes was noted in about 35% of patients. In those 35% of patients where the aetiology of HF was not primarily identified as related to cardiomyopathy, it is known from literature, that all can evolve into or manifest as DCM. In particular, the most frequent cause was myocarditis-induced HF, which itself is the most common cause of acquired DCM in children. In PANORAMA-HF, while there was no collection of echocardiographic data regarding ventricle volumes or diameters to confirm a diagnosis of DCM, all diseases included are known to evolve or manifest as DCM. Additionally, patients with restrictive or hypertrophic cardiomyopathy were excluded. Nonetheless, as recommended by treatment guidelines, the treatment of heart failure in children is based on pathophysiology, hence based on systolic vs. diastolic dysfunction and based on approved adult HFrEF therapies.

In conclusion, all patients enrolled in PANORAMA-HF were diagnosed with LVSD, while patients with HCM, RCM, and complex congenital heart disease with functional single ventricle or systemic right ventricle were excluded. Despite the lack of LV diameter measurement, the literature and clinical practice support that all enrolled pediatric patients with systemic LVSD also had a form of DCM. Furthermore, both adult HFrEF with DCM and pediatric HF due to LVSD have similar pathophysiology, including a reduced cardiac output due to left ventricle insufficiency, which causes reduced organ perfusion, increased adrenergic tone, and RAAS activation. These translate into increased sodium retention and increased volume, which can further worsen left ventricle function.

Similar drug pharmacology was established by demonstrating that sacubitrilat and valsartan drug exposure in paediatric HF patients is similar to exposure in adult heart HF at the same dose (Age Groups 1 and 2) with the ratios of geometric means of drug exposure (AUC children /AUC adults) being 0.80-0.92 and 0.99 1.29 for sacubitrilat and valsartan, respectively. Age Group 3 showed corresponding AUC changes consistent with the dose change (dose was initially 50% reduced considering the potential impact of developing capacity of drug disposition), with the ratios of geometric means of the drug exposure (AUC children/AUC adults) being 0.39 and 0.61 for sacubitrilat and valsartan, respectively.
Similar exposure response was established by demonstrating a similar magnitude of NT-proBNP reductions at exposure-matched doses of sacubitril/valsartan in the paediatric study B2319 and adult study B2314. The ratio of NT-proBNP relative to baseline between paediatric HF patients (3.1 mg/kg) and adult HF patients (200 mg) was 0.78 (95% CI: 0.67, 0.89), while when compared to adult HF patients with DCM it was 0.94 (95% CI: 0.74, 1.2).
NT-proBNP as a bridging biomarker for extrapolation of effects in adults with DCM to the paediatric population was assessed using the Prentice criteria. The Prentice criteria provide a systematic framework to establish the adequacy of NT-proBNP as a bridging biomarker. This includes a demonstration that the treatment has a significant impact on the true clinical endpoint, the treatment has a significant impact on the biomarker, the biomarker is significantly associated with the true clinical endpoint and that the biomarker explains the effect of treatment on the true clinical endpoint. Study B2314 in adults with HFrEF with DCM demonstrated that sacubitril/valsartan treatment significantly impacts the true clinical endpoint of reducing the risk of CV death or HF hospitalizations compared to enalapril (RRR:25%) (1st Prentice criterion). In the same subgroup of adult patients with HFrEF with DCM, the reduction in NT-proBNP from baseline was 43% at Month 1, and 52% at Month 8 in the sacubitril/valsartan arm, indicating that the treatment has a significant impact on the biomarker

NT-proBNP (2nd Prentice criterion). Furthermore, a change in plasma NT-proBNP was associated with the CV mortality/HF hospitalization rate in adult patients with HFrEF with DCM in study B2314, indicating that the biomarker is significantly associated with true clinical endpoint (3rd Prentice criterion). The results were similar for the subpopulation of adults with HFrEF with DCM. The association between NT-proBNP and risk of clinical events was similarly observed in paediatric patients (B2319), where a doubling of NT-proBNP levels at baseline or post-baseline was associated, respectively, with 1.8-fold and 2.1-fold increase in the risk of Category 1 or 2 events. Lastly, study B2314 in adults with HFrEF demonstrated that most of the sacubitril/valsartan treatment effect on the time to first event of CV death or HF hospitalization endpoint is explained by NT-proBNP over time (4th Prentice criterion). The proportion of treatment effect explained on top of baseline NT-ProBNP was 85.55%, with the 95% CI (6.35%, 164.76%) excluding zero. Robustness of these analyses was confirmed using sensitivity analyses.

3.1.4. Main clinical studies

Study B2319 (PANORAMA-HF) is a multicenter, open-label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan (part 1) followed by a 52-week randomized, double-blind, parallel-group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with HF due to systemic LVSD (part 2). Patients were required to have NYHA classification II-IV (older children: 6 to <18 years old) or Ross CHF classification II-IV, systemic left ventricular ejection fraction (EF) ⩽ 45% or fractional shortening ⩽22.5%, and receive chronic HF therapy. In part 2, 377 patients were randomized 1:1 to sacubitril/valsartan or enalapril. The target sacubitril/valsartan dose was 3.1 mg/kg twice daily for patients >1 year and 2.3 mg/kg twice daily for patients <1 year. The target enalapril dose was 0.2 mg/kg twice daily for patients >1 year and 0.15 mg/kg for patients <1 year. The efficacy of sacubitril/valsartan compared to enalapril after 52-week of double-blind treatment was assessed using a global rank primary endpoint. The ranking was based on clinical events (such as death, listing for urgent heart transplant, mechanical life support requirement at the end of study), worsening HF, NYHA/Ross class, Patient Global Impression of Severity (PGIS), and paediatric quality of life inventory (PedsQL) physical functioning domain. Key secondary/exploratory endpoints included individual components of the global rank primary endpoint and change in NT-proBNP from baseline.

3.2. Favourable effects

Study B2319

The analysis of the Global Rank primary endpoint was numerically in favour of sacubitril/valsartan over enalapril, with a Mann-Whitney probability (>0.5 indicates numerically in favour of sacubitril/valsartan) estimate of 0.5244 (95% CI 0.4665, 0.5817, p=0.42) compared to the standard of care enalapril.

Secondary outcomes:

Compared to baseline, both the sacubitril/valsartan and enalapril arm significantly improved in NYHA/Ross functional class. At Week 52, 37.7% of patients in the sacubitril/valsartan group and 34.0% of patients in the enalapril group had improvement, and approximately half of all patients were stable (no change in NYHA/Ross class). The odds ratio for a favourable outcome (sacubitril/valsartan over enalapril) at Week 52 was 1.07 (95% CI: 0.68, 1.68). Improvements in NYHA/Ross class were observed in all age groups.

Regarding the change in the patient global impression of severity (PGIS) from baseline, a high proportion of patients in both treatment groups experienced clinically relevant improvement or were stable during the study. At week 52, 35.53% of patients in the sacubitril/valsartan group and 34.81%

of patients in the enalapril group had improvement at Week 52, and nearly half of all patients were stable (i.e. no change in PGIS). The odds ratio for a favourable outcome (sacubitril/valsartan over enalapril) at Week 52 was 1.15 (95% CI: 0.73, 1.80). Improvements in PGIS status were observed in all age groups. The results of subgroup analyses for the secondary endpoints were generally comparable across subgroups, with no consistent trends observed.

Exploratory outcomes
During 52 weeks of treatment, both the sacubitril/valsartan and the enalapril group demonstrated significant decreases in NT-proBNP from baseline. The adjusted geometric mean ratio to baseline was 0.35 (95% CI: 0.29 – 0.42) in the sacubitril/valsartan group and 0.38 (95% CI: 0.31 – 0.47) in the enalapril group.

The Applicant calculated the reference change values (RCV) based on the intra-individual variation of NT-proBNP, described in the literature. Using several RCV thresholds (i.e., 22%, −33%, −46%, and −61%), the applicant demonstrated numerically consistently higher rates of responders in the sacubitril/valsartan group compared to the enalapril group for each threshold. For the thresholds of -33% and -46%, the odds ratio (95% CI) (sacubitril/valsartan over enalapril) were 2.04 (1.21; 3.44) and 2.12 (1.27; 3.52), respectively.

Paediatric quality of life (PedsQL) change from baseline demonstrated improvements (i.e. a higher score) in both patient-reported and parent-reported total PedsQL scores in both treatment groups. Patient-reported mean PedsQL scores increased to 4.8 for the sacubitril/valsartan group and 1.72 for the enalapril group. Similarly, parent-reported total PedsQL scores increased by 5.5 and 3.7, respectively.

3.3. Uncertainties and limitations about favourable effects

Study B2319
Primary outcome
The analysis of the Global Rank primary endpoint did not show a statistically significant difference between the sacubitril/valsartan and enalapril groups, with a Mann-Whitney probability (>0.5 indicates numerically in favour of sacubitril/valsartan) estimate of 0.5244 (95% CI 0.4665, 0.5817, p=0.42) compared to the standard of care enalapril. Therefore, the study failed to meet its primary objective, i.e., demonstrating the superiority of sacubitril/valsartan over enalapril. The primary analyses were consistent across age groups and in sensitivity analyses of the primary endpoint, including per protocol analyses. In addition, the results for the primary endpoint were consistent across subgroups, including gender, region, race and COVID-19 impacted period.

Secondary outcomes
The study also failed to meet its secondary objectives, i.e. demonstration of superiority of sacubitril/valsartan over enalapril over the relevant secondary endpoints were the (time to) category 1 or category 2 events, NYHA/Ross functional class change from baseline and global impression of severity change from baseline.

The proportion of patients with a Category 1 events (Death; UNOS status 1A listing for a heart transplant; VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement) was numerically lower in the sacubitril/valsartan group (10.2%) compared to the enalapril group (16.0%). However, no significant difference was observed between treatment groups in time to the first category 1 event (adjusted HR: 0.64, 95% CI: 0.32 – 1.28; P=0.20).

The proportion of patients with category 2 events (worsening of heart failure with/without hospitalization with/without ICU stay) was numerically higher in the sacubitril/valsartan arm compared to the enalapril arm (10% vs 5%). This was partially due to the higher number of patients on enalapril having a category 1 event, as patients with both category 1 and category 2 events were excluded from category 2 events. If these patients were counted, the proportion of patients with category 2 events was more similar between the groups (17% vs 14%). Similarly, as for time to first category 1 events, there were no significant differences between the treatment groups in time to first category 2 event and combined category 1 or 2 events (sacubitril/valsartan over enalapril adjusted HR: 1.21, 95% CI: 0.72-2.03; p= 0.470 and sacubitril/valsartan over enalapril adjusted HR: 1.07, 95% CI: 0.66- 1.72; p=0.78, respectively).

NT-proBNP changes. Analyses of change in NT-proBNP during study B2319 demonstrated that besides sacubitril/valsartan, enalapril also demonstrated a 62% decrease in NT-proBNP. Therefore, in contrast to adults, there was no significant difference between sacubitril/valsartan and enalapril in the percentage of NT-proBNP decrease. It is unknown whether this reflects a higher efficacy of enalapril in paediatrics or a lack of added value of sacubitril, given the similar mechanism between valsartan and enalapril. However, a direct analyses on the added value of sacubitril cannot be made, as valsartan and enalapril, while similar, are not the same.
Overall, for patients younger than 1 year (age group 3), the interpretation is very limited as only 9 patients in this age group were enrolled (should be noted that the proposed indication is for children >1 year based on this lack of data)

3.4. Unfavourable effects

Adverse events. The overall incidence of AEs during study B2319 was comparable between the sacubitril/valsartan and enalapril groups (88.8% and 87.8%, respectively). Infections and infestations was the most frequently affected system organ class. These consisted mostly of upper respiratory tract infection and nasopharyngitis, with no meaningful treatment differences. The most common AEs (at least 10%) were *pyrexia* (20.9% vs 18.1% for sacubitril/valsartan vs enalapril, respectively), *upper respiratory tract infection* (20.9% vs 18.6%), *cough* (19.3% vs 20.2%), *vomiting* (18.1% vs 21.3%), *nasopharyngitis* (15.5% vs 9.0%), *cardiac failure* (14.4% vs 14.4%), *diarrhoea* (13.4% vs 12.2%), *dizziness* (12.3% vs 8.0%), *hypotension* (12.3% vs 11.7%), *headache* (11.8% vs 10.6%), and *fatigue* (10.2% vs 7.5%). No new adverse drug reactions (ADRs) were identified during Study B2319.

Adverse events of special interest. The frequency of *hypotension*-based AEs was slightly higher in the sacubitril/valsartan than in the enalapril group (23% vs 21%); however, comparable to the incidence of hypotension-based AEs in the sacubitril/valsartan group (24%) of the adults study B2314.

The frequency of *hyperkalaemia*-based AEs was similar between the sacubitril/valsartan and enalapril group (5% vs 5%) and lower than in sacubitril/valsartan group (12%) of the adults study B2314.

The frequency of *renal impairment*-based AEs was higher in the sacubitril/valsartan group than in the enalapril group (6.4% vs 4.3%) but lower than in the sacubitril/valsartan group of study B2314 (10%).

The frequency of *hepatic AEs* was higher for the sacubitril/valsartan group than in the enalapril group (8.0% vs 5.3%) and occurred in a higher frequency in the paediatric study B2319 compared with the adult study B2314 (3.3%).

Hypersensitivity occurred in 12% of the sacubitril/valsartan arm and 11% of the enalapril arm. The frequency of hypersensitivity was higher in the paediatric population as compared to study B2314

(8%). Deaths. The proportion of reported deaths is relatively low, with fewer deaths in the sacubitril/valsartan group (4.3% (n=8)) compared with the enalapril group (6.4% (n=12)). All but 2 deaths were adjudicated as cardiovascular deaths.

SAEs. The incidence of SAE was relatively high and slightly higher in the sacubitril/valsartan group compared with the enalapril group (36.9% vs 33.0%, respectively). Sacubitril/valsartan is known to have a larger effect on blood pressure than enalapril, which partially explains why the SAEs of hypotension only occurred in the sacubitril/valsartan group (n=4). Nevertheless, no other pattern indicative for a safety signal could be identified. The majority of serious adverse events were a cardiac failure, which is in line with the progressive nature and poor prognosis of paediatric heart failure, and occurred with similar frequency in the two treatment groups. The number of patients with SAEs other than cardiac failure was small (≤5 per group).

Discontinuations due to AEs. The proportion of AEs leading to discontinuations was comparable between the sacubitril/valsartan and enalapril group (11.2% each). Most of the AEs that led to study treatment discontinuation were SAEs, which tended to be lower overall with sacubitril/valsartan than enalapril (8.6% vs 9.6%).

Age subgroups. The general safety profile of sacubitril/valsartan was consistent across all 3 age groups studied during Study B2319.

Post marketing experience. The additional assessment of post-marketing data, with a cut-off of 31 Jan 2022, revealed no new safety signals and/or substantial change to the safety profile of sacubitril/valsartan in adults.

3.5. Uncertainties and limitations about unfavourable effects

Adverse events of special interest.
Although the absence of *angioedema* in study B2319 appears reassuring, it should be noted that the incidence of angioedema was 0.5% in the sacubitril/valsartan group of study B2314. Therefore, the absence of angioedema in study B2319 may be due to the roughly 20 times lower sample size rather than a true absence in the paediatric population.

Preclinical evidence suggests a possible *risk of growth retardation* and *decreased bone mineral density* in the paediatric population. These bone findings do not appear to be related to the on-target effects of neprilysin inhibition in the bone. The absence of an increased risk of fractures or altered growth in either treatment group is reassuring. Nonetheless, the duration of the study may be too short to detect long-term changes in growth.

Monocomponent sacubitril. The neprilysin inhibitor (NEPi) component sacubitril of sacubitril/valsartan is not separately investigated in the target population, and its safety profile as a single component remains unknown.

Renal and hepatic impairment. The safety of sacubitril/valsartan in paediatric patients with renal or hepatic impairment could not be investigated adequately since these patients were excluded.

3.6. Effects Table

Table 50. Effects table for sacubitril/valsartan for the treatment of paediatric HF patients with LVSD

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
Primary endpoint	Global rank based endpoint ranking according to multiple clinical outcomes	probability of the patient of having a having a better outcome than the other treatment group, i.e. % wins per treatment group.	49.97%	45.09%	SoE: consistent across subgroups including age Unc: Mann Whitney Probability sacubitril/valsartan: 0.52 (95% CI: 0.47 – 0.58) Mann Whitney Odds sacubitril/valsartan: 0.91 (95 CI%: 0.72 – 1.14) p= 0.42 In favour of sacubitril/valsartan, yet not statistically significant
	Category 1 events	n (%)	19 (10)	30 (16)	Unc: In favour of sacubitril/valsartan, yet not statistically significant
	Category 2 events	n (%)	31 (17)	27 (14)	Unc: Uncertain whether the proportions are fully adjusted for competing risks of category 1 events. In favour of enalapril, yet not statistically significant.
Secondary endpoints	NYHA/Ross functional class change from baseline to week 52 Improved Unchanged Worsened	n (%)	58 (37.7) 78 (50.7) 18 (11.7)	54 (34.0) 90 (56.6) 15 (9.4)	Unc: Adjusted Odds Ratio (sacubitril/valsartan over enalapril) for favourable outcome: 1.07 (95% CI: 0.68, 1.68); p=0.76 SoE: Similar effect of improvement from baseline was demonstrated using the “Global impression of severity” and “Paediatric quality of life”.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Exploratory endpoints	Nt-proBNP Change from baseline to week 52	Estimate (95% CI)	0.35 (0.29-0.42)	0.38 (0.31-0.47)	SoE: Comparable decrease from baseline in sacubitril/valsartan group as seen in adults with HFrEF and DCM. Higher number of responders (change > reference change value) for sacubitril/valsartan as compared to enalapril (for multiple values of reference change values) UnC: p= 0.50 No statistical difference between sacubitril/valsartan and enalapril on change in NT-proBNP from baseline.
Unfavourable Effects					
AEs of special interest	Renal impairment	Incidence, n (%)	12 (6%)	8 (4%)	SoE: Lower than incidence in adults
	Hepatic AEs	Incidence, n (%)	15 (8%)	10 (5%)	Unc: Higher than incidence in adults
	Hypersensitivity	Incidence, n (%)	22 (12%)	21 (11%)	Unc: Higher than incidence in adults

Notes: The Global Rank endpoint rank orders patients from worst to best using: Category 1 objective outcome events of death, listing for urgent heart transplant or mechanical support; Category 2 worsening of HF with/without hospitalization with/without ICU stay; and measures of functional assessment (NYHA/Ross) and patient reported outcomes: Patient Global Impression of Severity (PGIS) and the PedsQL (physical functioning subgroup of questions) in which worsening, unchanged or improved at week 52 is ranked as Category 3, 4, and 5, respectively.

Abbrevaitions: PACE= positively adjudicated clinical events, LOCF = las observation carry forward prior cut-off, MWP= man-Whitney probability, MWO= Mann-Whitney odds; Mann-Whitney probability > 0.5 favours sacubitril/valsartan, equivalently, Mann-Whitney odd < 1

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the high mortality and morbidity associated with paediatric HF and the absence of approved paediatric HF therapy, there is a significant unmet medical need for approved treatments with demonstrated benefits, acceptable safety, appropriate posology and age-appropriate formulation in this specific population.
This extension of indication application for the use of sacubitril/valsartan in paediatric HF patients is based on an extrapolation of the results in adult patients with HFrEF of study B2314 (PARADIGM-HF) to the paediatric population using the principles for paediatric extrapolation as stated in the ICH E11A, as well as efficacy and safety data generated from study B2319 (PANORAMA-HF).

Extrapolation plan

The Applicant conducted an extrapolation of the results in adults of study B2314 (PARADIGM) to the paediatric population, based on the principles for paediatric extrapolation ICH E11A. In the extrapolation, the applicant adequately demonstrated disease similarity, similar drug pharmacology (exposure), and a similar exposure-response (NT-proBNP decrease) in the reference and target population. Furthermore, the applicant demonstrated that the Prentice criteria were fulfilled (with sufficient robustness) and that NT-proBNP can be considered as a bridging biomarker to extrapolate the results from study B2314 to the paediatric population. It should be noted that we deliberately chose to speak about a bridging biomarker rather than a surrogate biomarker (which is used in the original Prentice article) because N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a well-established biomarker in heart failure (HF) but remains controversial as a potential surrogate marker in HF trials.

The similar large reductions in NT-proBNP from baseline with sacubitril/valsartan in both paediatric and adult populations, in the context of its established clinical efficacy in adult HFrEF, provide a reasonable basis to extrapolate clinical benefits to paediatric HF patients with LVSD.

Study B2319

Efficacy

Treatment goals in paediatric heart failure are similar to those for adult patients with HF, including minimizing morbidity and mortality and improving functional status and quality of life. Ideally, study B2319 would be a large study investigating the effects on cardiovascular mortality and HF hospitalization, as was done in study B2314 in adults. However, the low prevalence of HF in children limited the possibility of conducting large outcome trials. This is shown by study B2319, conducted at 105 sites in 30 countries to enable the enrolment of 375 patients over a 4-year period, making it the largest paediatric HF study ever conducted. Nonetheless, the study was not powered to investigate the effects on hard clinical outcomes. Therefore, a Global Rank endpoint was used, which orders patients from worst to the best-using outcome, including both hard and soft clinical outcomes, ranging from mortality to disease progression (worsening HF) to measures of symptoms and physical functioning. The Global Rank primary endpoint analysis did not show a statistically significant difference between the treatment groups, with a Mann-Whitney probability estimate of 0.52 (95% CI 0.47, 0.58, p=0.42) compared to the standard of care enalapril. Therefore, the study failed to meet its primary objective, i.e., demonstrating the superiority of sacubitril/valsartan over enalapril. According to the Applicant,

a non-inferiority design was not possible since no data is available in the published literature to define a non-inferiority margin for such a study. Unfortunately, the lack of established efficacy of enalapril on hard outcomes in this paediatric population (literature described under clinical efficacy) makes it difficult to determine the true benefits (i.e., sacubitril/valsartan over placebo or no treatment) based on the primary analyses. Therefore, the results of the primary endpoint analyses of B2319 showing that sacubitril/valsartan is as least as efficacious as enalapril, with a small numerical advantage, does not directly translate to the efficacy with regards to this outcome. Analyses of the number of type 1 and 2 category events also do not directly help assess the benefit of sacubitril/valsartan over a lack of treatment, as the background incidence of these events is not well known.

The secondary and exploratory outcomes that compare changes from baseline within patients are more insightful. The beneficial effects of sacubitril/valsartan on NYHA/Ross functional class change from baseline, patient global impression of severity (PGIS) change from baseline, and paediatric quality of life change from baseline, as well as the decrease in NT-proBNP over time, are highly relevant, especially because paediatric heart failure is a progressive syndrome. Although none of these prespecified endpoints reached superiority over enalapril, it can be argued that without treatment, deterioration is expected with regards to NYHA/Ross class, PGIS score, quality of life, and NT-proBNP levels rather than improvement. These endpoints thereby support that sacubitril/valsartan treatment, albeit not superior to enalapril, improves disease severity, symptoms and quality of life in paediatric HF patients with LVSD. Furthermore, post-hoc responder analysis in which the NT-proBNP changes were analysed concerning the reference change value (reflecting clinically relevant change) demonstrated consistently higher rates of responders in the sacubitril/valsartan group compared to the enalapril group for each threshold. In addition to the odds ratios being all greater than 1.5, the lower limits of the 95% confidence intervals of the odds ratios are greater than 1 for the between treatment responder comparison for all thresholds in adults and for the −33% and −46% thresholds in children, indicating a systematic difference in favour of sacubitril/valsartan in the responder rates between the treatment groups.

New pharmaceutical form

The lack of an age-appropriate formulation for treating paediatric HF patients has been recognized as a major unmet need to ensure safe and accurate dosing in paediatric patients. The new pharmaceutical form, film-coated granules (in capsules for opening), used within the paediatric B2319 study, provides an important benefit in both accuracy and convenience of dosing sacubitril/valsartan in young children with lower body weight or who may be unable to swallow tablets. This is especially important because no other age-specific pharmaceutical forms are available for the current standard of care, i.e. ACE inhibitors (see additional considerations for a note on other current procedures).

Safety

Overall, the safety data from B2319 demonstrated that the safety profile of sacubitril/valsartan in paediatric HF patients was comparable to enalapril and consistent across all paediatric age groups. Further, the safety profile was generally consistent with the extensive data in adults both from clinical trials and post-marketing experience. No new signals or adverse drug reactions were identified in B2319. However, further safety evaluation and discussion is needed with respect to several subgroups and the potential effect of sacubitril/valsartan on hypersensitivity and hepatotoxicity. Further, it is likely that the AE profile from study B2319 may underestimate the true incidence of AE, given the low number of ACEi/ARB- naïve patients and of vulnerable patients (hypotension, hepatic and renal dysfunction or hyperkalaemia). Management of hypotension, hyperkalaemia and renal impairment does require careful clinical monitoring. For the clinician, this is expected to be comparable to other RAAS-acting products like ACEis or ARBs.

The lack of fractures or altered growth is reassuring, even though the study duration is limited in this sense. The absence of angioedema also appears reassuring but may be related to the relatively small sample size, given that the incidence was 0,5% in adults.

3.7.2. Balance of benefits and risks

The Applicant has based the totality of evidence on both a paediatric extrapolation plan using NT-proBNP as a biomarker to bridge the results in adults from study B2314 (reduction mortality and morbidity over enalapril) to the paediatric population, as well as benefits found in study B2319. Based on the disease similarity, similar drug pharmacology, similar drug exposure-response (NT-proBNP) and the demonstrated validity of NT-proBNP as a bridging biomarker in this scenario (Prentice criteria), the extrapolation of sacubitril/valsartan efficacy from adults to the pediatric population is considered a reasonable approach to infer clinical efficacy in the pediatric HF population.

Study B2319 did not demonstrate the superiority of sacubitril/valsartan over enalapril regarding the primary outcome. However, secondary and exploratory outcomes analyses demonstrated that both sacubitril/valsartan and enalapril led to clinically relevant improvements in NYHA/Ross functional class, PGIS assessment and patient-reported and parent-reported quality of life through 52 weeks. Similarly, sacubitril/valsartan and enalapril led to a substantial decrease in NT-proBNP over time. As such, it is acknowledged that the aforementioned reflects a delay in the progression of the disease and potentially a better long-term outcome, especially given that paediatric heart failure has a progressive nature without treatment.

It is also acknowledged that a new age-appropriate formulation, which has been shown to be equivalent to the approved FCT, offers an easier and safe dosing option in younger patients with lower body weight or unable to swallow tablets. Additionally, the risks of sacubitril/valsartan appear manageable and comparable to the adult population's risks.

In conclusion, sacubitril/valsartan addresses the significant unmet need in the paediatric HF population for a registered therapy that can be administered using a new age-appropriate formulation. Taking into consideration the totality of the evidence, including the NT-proBNP-based extrapolation plan, the clinically relevant improvements from baseline in symptom and quality of life measures coupled with a consistent and manageable safety profile, it can be concluded that sacubitril/valsartan provides clinically meaningful benefits to children and adolescents with symptomatic HF due to systemic LVSD

3.7.3. Additional considerations on the benefit-risk balance

Given the high mortality and morbidity associated with paediatric HF, there is a significant unmet medical need for approved treatments with demonstrated benefits, acceptable safety, appropriate posology and age-appropriate formulation in paediatric patients with HF.

As mentioned before, there are no approved therapies in the European Union for the treatment of paediatric HF, and medical recommendations are mainly based on data from adult studies. Current medical recommendations for peadiatric heart failure with LVSD are based on off-label usage. Of these, ACEIs are considered the first-line treatment for paediatric HF. Although not approved for treating paediatric patients with HF, enalapril is the most commonly used ACEI in children with HF. The lack of an age-appropriate formulation for the treatment of paediatric HF patients has been recognized as a major unmet need to ensure safe and accurate dosing in paediatric patients.

3.8. Conclusions

The overall benefit/risk balance of Neparvis is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Neparvis 6 mg/6 mg and 15 mg/16 mg granules in capsules for opening is favourable in the following indication(s):

Paediatric heart failure

Neparvis is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (see section 5.1).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Neparvis subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.*

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Additional Data exclusivity / Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Novartis Europharm Limited, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that

the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix on Article 14(11)).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0327/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension application to introduce a new pharmaceutical form associated with two new strengths (6 mg/6 mg and 15 mg/16 mg granules in capsule for opening), grouped with a type II variation (C.I.6.a) in order to extend the indication to include treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction in children and adolescents aged one year or older, based on the results from Study PANORAMA-HF (CLCZ696B2319); a multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of sacubitril/valsartan followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of sacubitril/valsartan compared with enalapril in paediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are being updated and the Package Leaflet is updated accordingly. Further, the MAH applied for an additional year of market protection. In addition, an updated RMP version 4.2 has also been submitted.