CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 207620/S-025
Priority or Standard	Standard
Submit Date(s)	June 14, 2023
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PDUFA Goal Date	April 14, 2024
Division/Office	DCN/ OCHEN
Reviewer Name(s)	Jordan Pomeroy, MD, PhD William Koh, PhD
Review Completion Date	April 9, 2024
Established/Proper Name	Sacubitril and Valsartan
Trade Name	Entresto
Applicant	Novartis Pharmaceuticals Corporation
Dosage Form(s)	Oral Tablet; Sprinkle (Oral Pellets); Extemporaneous Oral Suspension
Applicant Proposed Dosing Regimen(s)	(b) (4)
Approved Indication(s)/ Population(s)	• to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. • for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/ Population(s)	Not Applicable

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Glossary

ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
BNP	brain natriuretic peptide
BP	blood pressure
CDTL	Cross-Discipline Team Leader
CEC	clinical endpoint committee
cGMP	cyclic guanosine monophosphate
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DCN	Division of Cardiology and Nephrology
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
ECHO	echocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
IA	interim analysis
IB	investigators brochure
IRT	interactive response technology
LLOQ	lowest limit of quantitation
LV	left ventricle
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed model repeated measure
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
MW	Mann Whitney
NDA	new drug application
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life
PeRC	Pediatric Review Committee
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PTY	patient treatment years
PVR	pulmonary vascular resistance
USPI	United States packaging insert
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
RAAS	renin-angiotensin-aldosterone system
REMS	risk evaluation and mitigation strategies
SAE	serious adverse event
SAF	safety sety
SAP	statistical analysis plan
SBP	systolic blood pressure
SoC	standard of care
SUSAR	suspected unexpected severe adverse reaction
ULOQ	upper limit of quantification
UNOS	United Network for Organ Sharing
USM	urgent safety measure
VAD	ventricular assist device
WR	written request

1. Executive Summary

1.1. Summary of Regulatory Action

The favorable benefit-risk profile of Entresto (interchangeably named LCZ696 or sacubitril-valsartan) for treatment of symptomatic heart failure (HF) with left ventricular systolic dysfunction (LVSD) in pediatric patients aged 1 year and older was previously established in 2019 (NDA 207620/S-013). The regulatory approval was based on a 12-week interim analysis (IA) of PANORAMA-HF (Study B2319), a 52-week trial comparing Entresto to enalapril in a pediatric HF population. PANORAMA-HF was designed under a Written Request (WR) and amended because of enrollment issues to permit evaluation of the treatment effect on a bridging biomarker, N-terminal pro-brain natriuretic peptide (NT-proBNP) from a 12-week interim analysis (IA). The results showed an Entresto-mediated 50% reduction from baseline of NT-proBNP. This reduction was similar to that observed in a subset of adults with dilated cardiomyopathy (DCM) in PARADIGM-HF (Study B2314). The association between reduction in NT-proBNP and reduction in clinical endpoints from PARADIGM-HF, coupled with a similar reduction of NT-proBNP in PANORAMA-HF, inferred a similar clinical benefit in the pediatric HF population.

The applicant has now submitted an SE-8 efficacy supplement (NDA 207620/S-025), detailing the full 52-week results of PANORAMA-HF for evaluation of the primary endpoint of global rank clinical events and key secondary endpoints. The primary global rank result of Entresto was not statistically significantly superior at Week 52 from enalapril. However, in an exploratory analysis of the NT-proBNP bridging biomarker, there was a 65% reduction from baseline at Week 52, similar in both arms, thus showing a persistence of treatment effect for this bridging biomarker. Despite no difference between the arms of PANORAMA-HF for the reduction in NT-proBNP, such reduction for Entresto remained analogous to that of the adult trial PARADIGM-HF.

The 52-week NT-proBNP results are considered observational but are consistent with the 12-week dataset that precipitated the initial regulatory action to approve Entresto for the pediatric population. The recommended regulatory action from tis sNDA is to update the USPI to include NT-proBNP data at 52 weeks.

Background

A first-in-class angiotensin receptor-neprilysin inhibitor (ARNI), Entresto is a combination drug product containing an angiotensin receptor blocker (ARB), valsartan, and a neprilysin inhibitor, sacubitril. Based on the results of the pivotal phase 3 study, PARADIGM-HF, Entresto was initially approved by the United States Food and Drug Administration (FDA) in 2015 (New Drug Application [NDA] 207620) for: *reduction of risk of cardiovascular death and hospitalization for*

HF in adults with chronic HFrEF. In 2021 (NDA207620/S-018), the FDA approved a heart failure indication for an expanded range of left ventricular ejection fraction based on the results of PARAGON-HF: *to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.*

In 2019 (NDA 207620/S-013), FDA approved Entresto as a first-in-class treatment for heart failure in pediatric patients with the following indication: *for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes*. The approved pediatric claim was based on a 12-week IA of PANORAMA-HF, in which NT-proBNP was used as a bridging biomarker to extrapolate to clinical efficacy and safety of Entresto in an analogous DCM adult population from PARADIGM-HF.

PANORAMA-HF was a global multi-center, adaptive, seamless trial with a two-part design evaluating superiority of Entresto over enalapril. Part 1 assessed the pharmacokinetics / pharmacodynamics of single ascending doses of Entresto in pediatric (1 month to <18 years) HF patients with reduced left ventricular systolic function stratified into 3 age groups (Group 1: 6 to <18 years; Group 2: 1 to <6 years; Group 3: 1 month to <1 year). Part 2 was a 52-week, efficacy and safety study where the plan was to randomize 360 eligible patients to Entresto or enalapril. The primary efficacy endpoint was a global rank of events evaluated through 52 weeks, derived by ranking patients (worst-to-best outcome) based on Category 1 events (i.e., death, listing for heart transplant, ventricular assist device, extra-corporeal membrane oxygenation, intra-aortic balloon pump) and Category 2 events (i.e., worsening of heart failure). Secondary efficacy endpoints included time to first occurrence of category 1 and 2 events, change in NYHA /Ross functional class through 52 weeks, and change in patient global impression of severity score from baseline through 52 weeks.

Concurrent to NDA 207620/S-025, the applicant filed NDA 218591 for registration of a new dosage form: Entresto Sprinkle (oral pellets). The approved Entresto (oral tablet) formulation, along with the Entresto Sprinkle formulation and an extemporaneous oral suspension described in the Entresto USPI, were tested in PANORAMA-HF.

Results

The final results for PANORAMA-HF, based on 110 subjects, did not support superiority for Entresto versus enalapril for the primary global rank endpoint at Week 52. In exploratory analyses of the change from baseline in logarithm of NT-proBNP bridging biomarker, there was continued reduction in levels of NT-proBNP from baseline: Week 12 (50%) and Week 52 (65%). As concluded in the NDA 207620/S-013 cross-discipline team leader review, and also based on the completed results of NT-proBNP at Week 52 in PANORAMA-HF, the effect on NT-proBNP

served as the basis to infer improved cardiovascular outcomes in pediatric patients. Thus, the review team recommends updating the Entresto USPI to reflect the results of the NT-proBNP bridging biomarker at 52 weeks. (b) (4)

Clinical Pharmacology Review Considerations

The Office of Clinical Pharmacology reviewed the results from the completed part 2 of PANORAMA-HF and supported the prior conclusion that it is reasonable to translate the clinical benefit on HF outcomes for ENTRESTO from adults to pediatric patients 1 year to <18 years of age. This conclusion was based on a similar percent change in NT-proBNP from baseline to Week 52 observed between pediatric patients with left ventricular systolic dysfunction and adult DCM HF patients. Additionally, the new oral formulation of Entresto as film-coated granules (oral pellets) with 2 dosage strengths, 6 mg/6 mg (4 film-coated oral pellets) and 15 mg/16 mg (10 film-coated oral pellets) was acceptable. The clinical pharmacology section of the proposed label was updated (b) (4) for the new granule formulation.

Medication Error Considerations with New Entresto Sprinkle (oral pellets) Dosage Form

The Division of Medication Error Prevention and Analysis (DMEPA) identified potential usage errors arising from:

1) The need to open and administer the contents of the Entresto Sprinkle capsule strengths (capsules are not to be swallowed) - and -
2) Insufficient guidance to achieve the recommended weight-based dose(s) with the Entresto Sprinkle (oral pellets) dosage form, inclusive of potential errors arising from mixing the two dosage strengths

Consensus was achieved between DMEPA, Clinical, and Clinical Pharmacology to produce a posology table (see Table 2 in this review) to reduce potential medication errors with use of the Entresto Sprinkle (oral pellets) dosage form.

1.2. Fulfillment of the Written Request

In 2017, FDA waived pediatric study assessments for Entresto under the Pediatric Research Equity Act (PREA) but issued a Written Request (WR) for a pharmacokinetics (PK)/pharmacodynamics (PD), efficacy, and safety study in children ages 1 month to less than 18 years with HF. Because of enrollment difficulties in the trial conducted to satisfy the WR (Study B2319; PANORAMA-HF), in 2019, the Agency agreed to amend the WR to allow the applicant to fulfill the study requirement by submitting an IA to assess the treatment effect on a

bridging biomarker, NT-proBNP. The Agency agreed to remove the infant cohort, ages 1 month to less than 1 year, from the WR because of rarity of HF/DCM in infants. At the time of initial approval of Entresto for the pediatric HF with a LVSD indication on October 1st, 2019, the Agency granted pediatric exclusivity to the Applicant because they met the terms of the WR.

With completion of the PANORAMA-HF trial, which studied an appropriate pediatric dosage form (granules; oral pellets) as required by the WR, the Applicant has concurrently submitted NDA 218591 to register the age appropriate Entresto Sprinkle (oral pellets) dosage form. This dosage form triggered the Pediatric Research Equity Act (PREA). On February 20th, 2024, the Division of Cardiology and Nephrology (DCN) met with the Pediatric Review Committee (PeRC) to discuss NDA 218591 PREA considerations. As a result of that meeting, a partial waiver was granted for pediatric patients <1 month of age because studies are impossible or highly impracticable because of the small number of pediatric patients in that age group. Furthermore, the results of PANORAMA-HF were deemed to be an adequate assessment of the new dosage form in pediatric patients aged 1 month to less than 18 years old; thus no new studies or assessments were required to fulfill PREA.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The favorable benefit-risk profile of Entresto (LCZ696; sacubitril/valsartan) for treatment of symptomatic HF with systemic LVSD in pediatric patients aged 1 year and older was previously established in 2019 (NDA 207620/S-013). Initial regulatory approval was based on a 12-week interim analysis (IA) of PANORAMA-HF (Study B2319) that demonstrated treatment with Entresto resulted in a substantial reduction from baseline of a bridging biomarker, N-terminal pro-brain natriuretic peptide (NT-proBNP), in a pediatric HF population. The reduction was similar to the reduction in NT-proBNP observed in a subset of adults with dilated cardiomyopathy (DCM) in PARADIGM-HF (Study B2314).

The applicant has now submitted an SE-8 efficacy supplement (NDA 207620/S-025), in which the full 52-week results of PANORAMA-HF were submitted for the primary global rank and key secondary endpoints. The primary global rank endpoint result was not statistically significant at Week 52 and was not supportive of a conclusion of superiority of Entresto over enalapril despite numerical trends towards Entresto in Category 1 or 2 events. Key secondary endpoints also were not nominally statistically significant. In exploratory analyses of the NT-proBNP bridging biomarker, there was a reduction from baseline at Week 12 and 52, absent a nominally statistically significant difference between Entresto and enalapril. However, the treatment effect on NT-proBNP at Week 12 and 52 in the completed 52-week study continued to show reduction from baseline. The rationale for the initial regulatory approval (NDA207620/S-013) was based on a treatment effect on NT-proBNP shown in a 12-week IA of PANORAMA-HF, in which reduction in NT-proBNP inferred a large portion of the beneficial effect of Entresto on CV outcomes in PARADIGM-HF in an adult DCM population. In the completed PANORAMA-HF study, we continue to observe this treatment effect on NT-proBNP in the completed study at Week 52. Therefore, this provides additional support for us to infer an effect of similar direction on the efficacy of Entresto for the treatment of pediatric HF patients.

Pediatric DCM is a serious and life-threatening condition with only two treatments approved for this indication: 1) Entresto based on the NT-proBNP bridging biomarker paradigm to infer efficacy and safety of Entresto in an analogous adult DCM population and 2) Corlanor (ivabradine oral solution and tablet) approved for a subpopulation of pediatric patients with HF due to DCM and baseline elevated heart rate. Unlike in adult studies, effectiveness based on cardiovascular (CV) clinical outcomes typically cannot be established in pediatric studies due to small sample sizes for comparable CV conditions. NT-proBNP is strongly correlated with reduction of risk for CV death and HF hospitalization in the adult HFrEF study, PARADIGM-HF, thereby supporting use of NT-proBNP as a bridging biomarker for a pediatric study in children with DCM and HF. While sacubitril/valsartan and enalapril demonstrated similarly strong reduction in NT-proBNP, the complete results of study B2319 did not show a nominally clinically significant treatment effect in change from baseline in logarithm of NT-proBNP in the sacubitril/valsartan group compared to enalapril at Week 12 or later. Therefore, it is not possible to conclude there is a clinically meaningful benefit from treatment with

sacubitril/valsartan in pediatric patients with DCM and HF versus enalapril. However, the demonstrated substantial reduction in NT-proBNP with Entresto treatment through 52 weeks provides additional support for us to infer an effect of similar direction on the efficacy of Entresto for the treatment of pediatric HF patients, as was concluded in the original full approval based on the 12-week IA of PANORAMA-HF. Additionally, there were no new or unexpected safety findings in pediatric patients studied in PANORAMA-HF, which supports an ongoing favorable benefit-risk profile of Entresto for the treatment of pediatric HF patients.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DCM is an intrinsic disease of heart muscle that results in myocyte dysfunction and impaired ability of the myocardium to generate contractile force • DCM typically results in HF and LV dysfunction • Incidence of DCM in a pediatric population in North America is 44 per million per year in infants, younger than 1 year, and 3.4 per million in children 1 to 18 years of age • Etiology, pathophysiology, and symptoms of DCM, generally overlap between adults and children • Pediatric DCM patients are at high risk for hospitalization, cardiac transplant, and death	Pediatric DCM is a serious and life-threatening condition with poor prognosis; 1- and 5-year rates of death or transplantation are 31% and 46%, respectively.
Current Treatment Options	• Entresto (LZC696; sacubitril/valsartan) and Corlanor (ivabradine) remain the only approved treatments for pediatric HF associated with DCM; the latter is limited to a stable pediatric HF with DCM subpopulation with elevated baseline heart rate	Given limited medical treatment options for pediatric HF associated with DCM (Entresto/Corlanor), there remains an unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Initial regulatory approval of Entresto for treatment of pediatric HF (NDA 207620/S-013; 2019) was based on a 12-week interim analysis (IA) of PANORAMA-HF (Study B2319), in which treatment with sacubitril/valsartan in subjects with pediatric HF resulted in a substantial reduction from baseline of a bridging biomarker, N-terminal pro-brain natriuretic peptide (NT-proBNP) ○ The reduction was similar to the reduction in NT-proBNP observed in a subset of adults with dilated cardiomyopathy (DCM) in PARADIGM-HF (Study B2313), and was the basis to infer improvement in CV outcomes in patients with pediatric HF • The full results of study B2319 (NDA 207620/S-025) are comparable to the 12-week IA with substantial NT-proBNP reduction observed over a 52-week treatment course with sacubitril/valsartan • A statistically significant treatment effect difference between sacubitril/valsartan and enalapril treatment was not demonstrated for NT-proBNP reduction or for the global rank primary composite endpoint	In 2019, Entresto for the treatment of pediatric HF received full approval (NDA 207620/S-013) based on a 12-week IA of PANORAMA-HF using reduction in NT-proBNP as a bridging biomarker. The current SE-8 efficacy supplement (NDA 207620/S-025) provides the full results of PANORAMA-HF. The primary endpoint of PANORAMA-HF, a global rank primary composite endpoint at Week 52, was not statistically significant. Both sacubitril/valsartan and enalapril were observed to have substantial reduction from baseline in NT-proBNP at 52 weeks in a pediatric population with HF associated with DCM (65% and 62%, respectively). However, the observed difference in treatment effect between sacubitril/valsartan and enalapril for the change from baseline in logarithm NT-proBNP at Week 52 was not nominally statistically significant. Given that treatment with sacubitril/valsartan substantially reduced NT-proBNP levels from baseline after 52 weeks of treatment in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		pediatric subjects with HF associated with DCM, with an overall percentage reduction greater than that demonstrated in clinical studies of adults with HF associated DCM, we continue to find that NT-proBNP represents a reasonable bridging biomarker on which to infer the clinical efficacy and safety of Entresto from adults to pediatric patients.
Risk and Risk Management	• In general, AEs observed in this study are consistent with the safety profiles for both study treatments.	Compared to adult PARADIGM-HF data, there were no new safety signals identified in this pediatric study. Current safety descriptions in the Entresto USPI are sufficient to identify potential risk of treatment with Entresto in pediatric patients with HF.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Section 6.2
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.2
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Pediatric cardiomyopathies are rare diseases resulting from various etiologies that may differ

between adults and children. The most common form of pediatric cardiomyopathy is DCM. DCM is characterized by a dilated left ventricle (LV) and systolic dysfunction, sometimes accompanied by diastolic dysfunction. Clinical presentation and disease progression may differ between adults and children and among pediatric patients depending on the underlying etiology for DCM and age at presentation. Compared to adults, pediatric patients with DCM are more likely to experience severe morbidity and mortality and require advanced heart failure therapies such as inotropic support, extracorporeal membrane oxygenation (ECMO), or cardiac transplantation. However, neurohormonal pathophysiologic derangements are sufficiently similar between children and adults with DCM with the expectation for similar responses to HF pharmacologic treatments targeting these neurohormonal pathways. To date, there are no published recommendations for differences in standard of care (SoC) medical treatment options based on gender or racial differences for pediatric patients.

2.2. Analysis of Current Treatment Options

To date, Entresto (sacubitril/valsartan) and Corlanor (ivabradine) remain the only approved treatments for pediatric HF associated with DCM; the latter is limited to a stable pediatric HF with DCM subpopulation with sinus rhythm and elevated baseline heart rate. Drug treatment classes approved in adults for chronic HFrEF include diuretics, angiotensin converting enzyme inhibitors (ACEIs), ARBs, aldosterone antagonists, beta blockers, digoxin, anti-arrhythmics, and anti-coagulants. Most of these drug treatments are used off-label to treat pediatric HF patients based on published guidelines. There continues to be an unmet for approved therapies for pediatric HF.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

To date, Entresto (LCZ696; sacubitril/valsartan) is marketed in 122 countries for the same indication as approved in the US, reduction of CV death and HF hospitalization in patients with chronic HFrEF. As of July 2023, the cumulative post-marketing patient exposure is estimated to be about (b) (4) million patient-treatment years (PTY). Approximately (b) (4) patients have received sacubitril/valsartan treatment in Novartis-sponsored clinical trials since 2007. Novartis's pediatric study, PANORAMA-HF (Study B2319), was conducted in accordance with a WR agreement (March 5th, 2019). (b) (4) However, enrollment of children under 1 year of age was not required to fulfill the WR.

3.2. Summary of Presubmission/Submission Regulatory Activity

The timeline of major regulatory milestones for this WR is below. Terms of the pediatric WR are summarized in Table 1.

- July 2015: FDA approval of Entresto (LCZ696; sacubitril/valsartan) oral tablet, new molecular entity under NDA 207620 for treatment of chronic HFrEF in adults
- March 2017: FDA issued a WR
- March 2019: FDA issued a revised WR to include a plan for an interim efficacy analysis of NT-proBNP in a pediatric DCM subgroup, revised statistical plan, and removal of age cohort 1 month to less than 1 year
- April 1st, 2019: Applicant T-con to discuss whether the data submitted with NDA 207620/S-013 might be adequate to support labeling sacubitril/valsartan for a pediatric HF indication
- May 29th, 2019: Applicant provided current enrollment numbers for PANORAMA-HF since database lock for NDA 207620/S-013
- October 1st, 2019: FDA approval of Entresto (sacubitril/valsartan) for pediatric HF with LVSD indication based on NT-proBNP bridging biomarker data from IA of PANORAMA-HF
- June 14th, 2023: Applicant filed NDA 207620/S-025 to submit final CSR for PANORAMA-HF to update the label with completed study results
- June 14th, 2023: Applicant filed NDA 218591 to register the Entresto Sprinkle (oral pellet) dosage form to fulfill WR requirement for a reasonable pediatric dosage form

Reviewer Comment: *The revised Written Request (dated March 5th, 2019) was fulfilled at time of initial Entresto approval for the pediatric HF with LVSD indication (October 1st, 2019). The NDA 218591 submission for the new Entresto Sprinkle (oral pellet) dosage form triggered Pediatric Research Equity Act (PREA) requirements. On February 20th, 2024, the Division of Cardiology and Nephrology (DCN) met with the Pediatric Review Committee to discuss NDA 218591; a partial waiver was granted for study of pediatric patients <1 month of age and the results of PANORAMA-HF were deemed to be a valid Assessment of the new dosage form in pediatric patients age 1 month to 18 years old and that no new studies or assessments were required to fulfill PREA.*

Table 1: Requirements of Pediatric Written Request

WR Section	Requirement
Required Studies	**Part 1:** A multi-center, open-label study in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM to assess the PK and PD of more than one dosage strength of sacubitril/valsartan. **Part 2:** A double-blind, randomized, multi-center, active-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of

	sacubitril/valsartan compared to enalapril in pediatric patients with heart failure due to systemic left ventricular systolic dysfunction, consistent with DCM.
Study Objectives	**Part 1:** to determine the PK and PD of sacubitril/valsartan in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM. **Part 2:** to evaluate efficacy by determining the NT-proBNP change from baseline at Week 12 of sacubitril/valsartan versus enalapril for the treatment of heart failure in pediatric heart failure patients due to systemic left ventricular systolic dysfunction, consistent with DCM.

Study Population	• The study must enroll pediatric patients aged 1 to < 18 years.
	  ○ Group 1: 6 to less than 18 years
	  ○ Group 2: 1 to less than 6 years
	• **Part 1** must enroll a minimum of 16 subjects with at least six subjects in Group 1 and six subjects in Group 2. Half of the minimum required subjects in Group 1 must be 6 to 11 years of age. Enrollment must be staggered starting with Group 1. Results from Part 1 must be reported to and reviewed by the Agency and agreement must be reached with the Agency on doses to be used in Part 2 before sequential initiation of each successively younger age group in Part 2. If the information from an age group in Part 1 is insufficient to inform dosing for Part 2, additional subjects from that age group must be enrolled in Part 1.
	• **Part 2** must enroll at least 100 subjects (1 to less than 18 years old) with balanced distribution in each treatment arm.
	• Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study Endpoints	**Pharmacokinetic/Pharmacodynamic Endpoints:** **Part 1:** pharmacokinetic and pharmacodynamic endpoints after single dose treatment will include: • PK: Cmax (ng/mL); Tmax(h); AUClast, AUCinf (h▪ng/mL); Cl/F (L/h); T1/2 (h) • PD: plasma cyclic guanosine monophosphate (cGMP), urine cGMP,

	plasma B-type natriuretic peptide (BNP), plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) **Efficacy Endpoints:** **Part 2:** the biomarker interim analysis efficacy endpoint will be NT-proBNP change from baseline at Week 12. Descriptive efficacy, including data on the following events: death; UNOS Status 1A listing for heart transplant or equivalent; ventricular assist device (VAD)/extracorporeal membrane oxygenation (ECMO)/mechanical ventilation/intra-aortic balloon pump requirement for life support; worsening heart failure; and measures of functional status will be provided. **Safety Endpoints:** The study must be well-designed to actively monitor for and capture safety outcomes of interest including hypotension, hyperkalemia, renal impairment, angioedema, and liver toxicity. A Data Monitoring Committee (DMC) must be included because findings at an interim analysis may require termination of the study before its planned completion.
Statistical Assessments	• In **Part 1** of the study, descriptive statistics will be provided for the specified pharmacokinetic and pharmacodynamic endpoints. • In **Part 2** of the study, the NT-proBNP interim analysis method must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance of the NT-proBNP change from baseline to Week 12, relative to control. The interim analysis is designed with at least 80% statistical power with a Type 1 error rate of 0.05 (two-sided), if the true effect size is 30%. • The statistical analysis plan (SAP) must be submitted to the FDA for review and agreement prior to the interim analysis. The SAP must prespecify methods to handle missing data for the biomarker interim analysis efficacy endpoint.
Drug Safety Monitoring	Based on the safety concerns identified in studies of sacubitril/valsartan in adults, subjects must be monitored for hypotension, hyperkalemia, renal impairment, and angioedema. Based on potential safety concerns identified in studies of valsartan in children, subjects must be monitored for liver toxicity.
	• If in the course of conducting the study, evidence indicating

Extraordinary Results	unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results; there may be a need to deviate from the requirements of this Written Request. • For any scenario described above, the sponsor must contact the Agency to seek an amendment; although, it is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.
Drug Information	• Dosage form: the dosage form must include an age-appropriate formulation. • Route of administration: the route of administration will be oral. • Regimen: the regimen will be agreed upon in the protocol. • Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Source: Clinical Reviewer

3.3. Foreign Regulatory Actions and Marketing History

On March 31st, 2023, the European Medicines Agency Committee for Medicinal Products for Human Use adopted a positive opinion recommending the approval of Entresto (sacubitril/valsartan) for a new indication to treat symptomatic chronic HF with LVSD in pediatric patients aged from 1 to <18 years. The opinion was based on final data from PANORAMA-HF and used the NT-proBNP bridging biomarker paradigm to extrapolate to demonstrated efficacy and safety of Entresto in adults in PARADIGM-HF.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No OSI audits were requested for the clinical data submitted with NDA 207620/S-025.

4.2. Product Quality

Considerations for product quality and chemistry, manufacturing, and controls were addressed as part of NDA 218591 submitted to register the Entresto Sprinkle (oral pellet) dosage form developed to fulfill the age-appropriate dosage form requirement of the WR. Reference is made to the NDA 218591 Office of Pharmaceutical Quality (OPQ) integrated review filed on March

18th, 2024.

Key issues included:

- The Entresto Sprinkle (oral pellets) dosage form was recommended for approval with a 36-month shelf life when stored at 20°C to 25°C.
- The drug product is administered by sprinkling on soft foods (b) (4) only, the capsules are never to be taken whole.
- It is also intended to replace, where feasible, the preparation of suspensions from the currently marketed tablet formulation
- Final alignment on appropriate dosage form description (granules vs. oral pellets) was not a result of consensus agreement between individual subdiscipline reviewers and required secondary reviewer and team lead consensus for approval

4.3. Clinical Pharmacology

Per the finalized review dated March 1st, 2024:

> *The Office of Clinical Pharmacology has reviewed the results of complete part 2 of study CLCZ696B2319 submitted to sNDA207620 and the results support the prior conclusion that it is reasonable to translate the clinical benefit on HF outcomes for ENTRESTO from adults to pediatric patients 1 year to < 18 years of age based on a similar percent change in NT-proBNP from baseline to Week 52 observed between pediatric patients with left ventricular systolic function and adult DCM HF patients. Additionally, the new oral formulation of sacubitril/valsartan as film-coated granules with 2 dosage strengths, 6 mg/6 mg (4 film-coated granules) and 15 mg/16 mg (10 film-coated granules) is acceptable as a new formulation.*

4.4. Division of Medication Error Prevention and Analysis

While the age-appropriate Entresto Sprinkle (oral pellet) dosage form was the subject of the concurrent NDA 218591 registration submission, label considerations for appropriate use of the Entresto Sprinkle dosage form were jointly held with NDA 207620/S-025. The Division of Medication Error Prevention and Analysis (DMEPA) identified potential usage errors arising from:

1) The need to open and administer the contents of the Entresto Sprinkle capsule strengths (capsules are not to be swallowed) - and -
2) Insufficient guidance to achieve the recommended weight-based dose(s) with the Entresto Sprinkle (oral pellets) dosage form, inclusive of potential errors arising from mixing the two dosage strengths

After discussion, DMEPA and the Clinical and Clinical Pharmacology review disciplines from DCN aligned on the Section 2.3 Table 1label description (Table 2) to reduce potential medication errors with use of the Entresto Sprinkle (oral pellets) dosage form.

Table 2: Recommended Dose and Titration for Pediatric Patients using ENTRESTO SPRINKLE[†]

Weight (kg)	Dose (twice daily)		
	Starting	**Second step**	**Final**
<13 (use oral suspension[‡])	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
13 to 19	**12 mg/12 mg** (Two 6 mg/6 mg capsules)	**18 mg/18 mg** (Three 6 mg/6 mg capsules)	**24mg/24 mg** (Four 6 mg/6 mg capsules)
19 to 26	**18 mg/18 mg** (Three 6 mg/6 mg capsules)	**24mg/24 mg** (Four 6 mg/6 mg capsules)	**30 mg/32 mg** (Two 15 mg/16 mg capsules)
26 to 34	**24mg/24 mg** (Four 6 mg/6 mg capsules)	**30 mg/32 mg** (Two 15 mg/16 mg capsules)	**45 mg/48 mg** (Three 15 mg/16 mg capsules)
34 to 50	**30 mg/32 mg** (Two 15 mg/16 mg capsules)	**45 mg/48 mg** (Three 15 mg/16 mg capsules)	**60 mg/64 mg** (Four 15 mg/16 mg capsules)

[†] When using capsules, more than one capsule may be needed to achieve recommended doses. Oral pellets are contained within each capsule. Use the entire contents of oral pellet strength to achieve the dose.
[‡] Recommended mg/kg doses are of the combined amount of sacubitril and valsartan.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies included in this submission are summarized in Table 3.

Table 3: Listing of Clinical Trial(s) Relevant to this Efficacy Supplement to NDA 207620

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
CLCZ696B2319 (PANORAMA-HF)	International, multicenter, open-label, study to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of LCZ696 (Part 1) 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	**LCZ696** Film-coated Oral tablets: 50 mg (24/26 mg), 100 mg (49/51 mg), 200 mg (97/103 mg) Oral Pellet 3.125mg (1.52/1.61 mg) Oral Extemporaneous Suspension OR matching placebo **Enalapril** Oral tablets: 2.5 mg, 5 mg and, 10 mg tablets	**Pharmacokinetics** **Part 1** PK: Cmax, Tmax, AUC, Clearance, and T1/2. PD: Plasma cGMP, urine cGMP, BNP, NT-proBNP **Part 2** Population PK and sparse PK **Efficacy** **Part 2** -change from baseline in NT-proBNP at Week 12, -Clinical events <u>Category 1</u>: Death UNOS status 1A listing for heart transplant or equivalent; VAD / ECMO / mechanical ventilation/intra-aortic balloon pump requirement for life	**Part 1** Open label single or two doses **Part 2** 52 weeks double blind treatment	N=375 LCZ696 (n=187) Enalapril (n=188)	Male and female children 1 month to less than 18 years with HF, inpatient or outpatient, Class II to IV NYHA/Ross HF, LVEF ≤ 45% or Fractional shortening ≤22.5%, biventricular physiology with systemic LV	105 centers in 30 countries (including US)

	systolic dysfunction (Part 2)	Oral Extemporaneous Suspension **Doses** **Part 1** 1) LCZ696 0.8 mg/kg or 2) LCZ696 3.1 mg/kg or Both **Part 2 (double blind)** **LCZ696:** Pediatric formulation – 0.8 to 3.1 mg/kg bid Tablet – 50 to 200 mg bid **Enalapril:** Pediatric formulation – 0.05 to 0.2 mg/kg bid Tablet – 2.5 to 10 mg bid	support at end of study Category 2: Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy, NYHA/Ross classification, PGIS score, PGIC score, PedsQL total summary score **Safety** AEs, SAE, physical exam, vital signs, height, weight, head circumference, laboratory evaluations, ECG, pregnancy, angioedema				

Abbreviations: PK, pharmacokinetics; Cmax, serum concentration maximum; Tmax, time of maximum serum concentration; AUC, area under the curve; PD, pharmacodynamics; cGMP, cyclic guanosine monophosphate; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; UNOS, United Network for Organ Sharing; VAD, ventricular assist device; ECMO, extracorporeal membrane support; HF,

heart failure; WHF, worsening heart failure; NYHA, New York Heart Association; PGIS, patient global impression of severity; PGIC, patient global impression of change; PedsQL, pediatric quality of life inventory; AE, adverse event; SAE, severe adverse event; ECG, electrocardiogram; LV, left ventricle
Source: Clinical Reviewer

5.2. Review Strategy

This review is jointly written by the Clinical (Jordan Pomeroy) and Biostatistics (William Koh) review disciplines. Matters pertaining to trial design and efficacy are jointly reviewed. Matters pertaining to safety are reviewed by the Clinical review discipline. Given that this efficacy supplement (SE-8) for NDA 207620/S-025 primarily serves to update the complete results of PANORAMA-HF (Study CLCZ696B2319; also referred to as Study B2319), review issues related to the original PANORAMA-HF interim analysis (IA) and the resulting Entresto full pediatric approval based on the NT-proBNP bridging biomarker paradigm are referenced to the clinical and cross-discipline team leader (CDTL) reviews for NDA 207620/S-013 (dated August 20th, 2019 and September 16th, 2019, respectively).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study CLCZ696B2319

6.1.1. Study Design

Overview and Objective

Study CLCZ696B2319 consists of two parts. The review is focused on study results obtained from Part 2. The primary objective in Part 2 is to determine whether LCZ696 is superior to enalapril for the treatment of HF as assessed using a global rank endpoint in pediatric HF patients.

Reviewer Comment: *Enrolled patients were expected to be on optimal SoC medical and non-medical treatments for HF and comorbidities. As previously commented (NDA 207620/S-013 primary review), the Applicant chose enalapril as a comparator in Study B2319 because it is the most commonly used renin-angiotensin aldosterone system (RAAS) blocker in children with HF. Furthermore, the Applicant considers enalapril as Soc in the treatment of chronic HF in most geographic areas and twice daily dosing of enalapril is similar to LCZ696. Overall, 105 centers in 30 countries participated with the US having the highest enrollment of each country.*

Trial Design

Study CLCZ696B2319 (PANORAMA-HF) consists of two parts (Figure 1).

Part 1

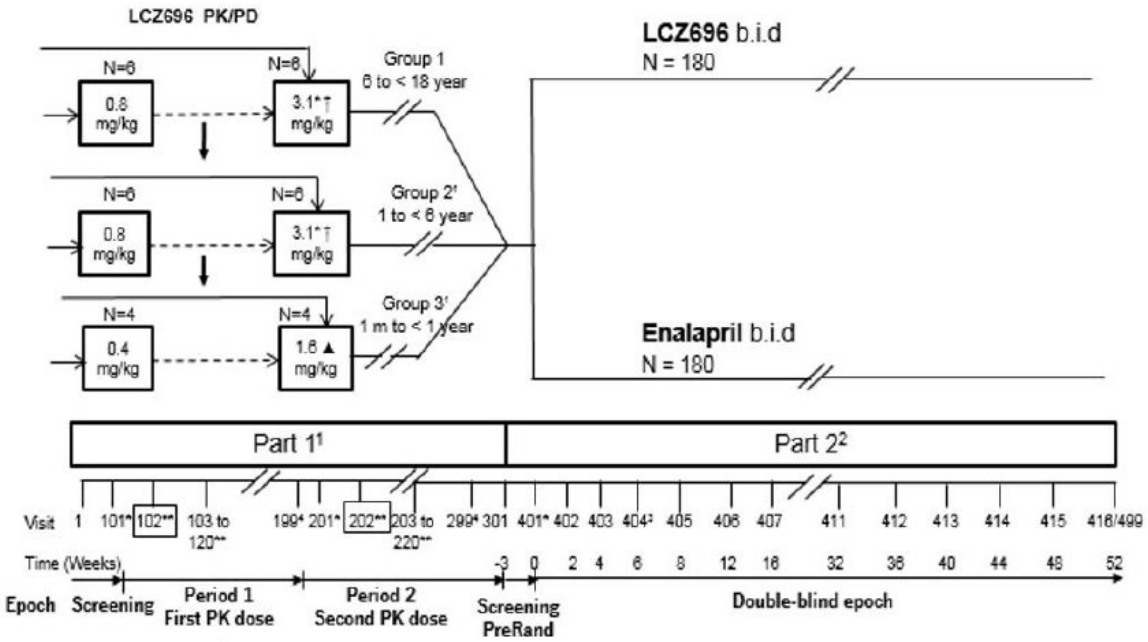
Part 1 of the study was an open-label, multicenter investigation to confirm the dose for Part 2. Eligible patients were placed into three age groups (Age Group 1: 6 years to < 18 years, Age

Group 2: 1 year to < 6 years, and an extra Age Group 3: 1 month to < 1 year). For each age group, PK/PD and safety data were reviewed to confirm or modify the doses. Patients in each age group can enroll in Part 2 after the target dose for that age group was determined based on Part 1 data for the corresponding age cohort. Part 1 of this study was previously reviewed.

Part 2

Part 2 of the study was a randomized, double-blind, parallel-group, active-controlled, 52-week study. The objective was to determine the efficacy, safety, and tolerability of sacubitril/valsartan compared to enalapril over 52 weeks in pediatric heart failure (HF) patients 1 month to < 18 years, inpatient or outpatient, with systemic left ventricle systolic dysfunction (LVEF ≤ 45% or a fractional shortening ≤ 22.5%).

Figure 1 Study Design, CLCZ696B2319 PANORAMA-HF



** Open-label enalapril visits
* 36 hour washout of ACEI required before V101, 201 and 401
† Patients previously on a daily dose equivalent of enalapril 0.2 mg/kg were eligible to receive LCZ696 3.1 mg/kg. Patients who participated in the LCZ696 0.8 mg/kg dose must have tolerated the 0.8 mg/kg dose to participate in the LCZ696 3.1 mg/kg dose
▲ Patients previously on a daily dose equivalent of enalapril 0.1 mg/kg were eligible to receive LCZ696 1.6 mg/kg. Patients who participated in the LCZ696 0.4 mg/kg dose must have tolerated the 0.4 mg/kg dose to participate in the LCZ696 1.6 mg/kg dose
[1] Prior to Group 2 enrollment, all available data from Group 1 were reviewed and prior to enrollment of Group 3, all available data from Group 1 and Group 2 were reviewed.
[2] Each age group could enroll in Part 2 after the target dose of that age group was determined in Part 1
[3] Optional Visit
[4] Visit 199 and 299 were scheduled after review of data. For Groups 1 and 2, these visits could be combined with Visit 301 if patient continued in Part 2
☐ Indicates telephone contact visit (2 weeks after single dose visit)

Source: Figure 9-1 of Module 5.3.5.1 Clinical Study Report

Study Population

The study population consisted of pediatric HF patients 1 month to < 18 years, inpatient or outpatient, with systemic left ventricle systolic dysfunction (LVEF ≤45% or a fractional shortening ≤ 22.5%).

Key Inclusion/Exclusion Criteria

The following inclusion/exclusion criteria for Part 2 are as listed.

Inclusion:

1. Written informed consent by parent(s)/legal guardian(s) for the pediatric patient had to be obtained before any study-specific assessment is performed.[1] A consent or assent could also be required for some patients depending upon their age and local requirement.
2. Male or female, inpatient or outpatient, 1 month (≥44 weeks post-conception for pre-term infants) to < 18 years of age.
3. Chronic HF resulting from left ventricular systolic dysfunction and receiving chronic HF therapy (if not newly diagnosed).
4. NYHA classification II-IV (older children: 6 to less than 18-year-old) or Ross HF classification II-IV (younger children: less than 6-year-old) any time prior to screening.
5. [Note: Age Group 1 patients may be NYHA class I at time of screening if there was a prior history of NYHA class II-IV. Age Group 2 patients were required to be Ross class II or higher at time of randomization].
6. Systemic left ventricular ejection fraction (LVEF) ≤ 45% or fractional shortening ≤22.5% (assessed by echocardiogram (ECHO), magnetic resonance imaging (MRI), multi gated acquisition scan (MUGA) or left ventricular angiogram within 1 month before patient begins Part 2). [Note: The study targeted enrollment of approximately 80% patients with a systemic left ventricular ejection fraction (EF) ≤ 40% or fractional shortening ≤20% for Part 2 only].
7. Biventricular physiology with systemic left ventricle. HF etiologies include: Congenital Cardiac Malformation with systemic ventricular systolic dysfunction; Idiopathic Cardiomyopathy; Familial/Inherited and/or Genetic Cardiomyopathy; History of Myocarditis; Neuromuscular Disorder; Inborn Error of Metabolism; Mitochondrial Disorder; Acquired (Chemotherapy, Iatrogenic, Infection, Rheumatic, Nutritional); Ischemic (e.g., Kawasaki Disease, post-operative); Left ventricular noncompaction

[1] *Assessments of HF (e.g. ECHO) in patients that were done according to current local institutional/hospital standard protocol or that were part of routine clinical care could be used to support patient screening and could have taken place before signing informed consent. An informed consent had to be obtained from a patient once they became 18 years old during the study.*

Exclusion:

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 16.1.1-Protocol-Appendix 4.
9. Renal vascular hypertension (including renal artery stenosis)
10. Severe pulmonary hypertension (defined by pulmonary vascular resistance (PVR) index >6 Wood units-m^2) 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 (estimated glomerular filtration rate (eGFR) calculated using the modified Schwartz formula < 30% mean glomerular filtration rate (GFR) for age, Appendix 16.1.1-Protocol-Appendix 10); 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 a history of angioedema
16. Patients with allergy or hypersensitivity to ACEI or ARB
17. Patients who had parents or legal guardians who did not give consent or allow the child to give assent, or inability of the patient or the parents/legal guardians to follow instructions or comply with follow-up procedures

18. Pregnant or nursing (lactating) women
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception during dosing of investigational drug and for 7 days after study drug discontinuation. Highly effective contraception is defined in Appendix 16.1.1-Protocol-Section 4.2.
20. Use of other investigational drugs within 5 half-lives or within 30 days of enrollment, whichever is shorter
21. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes
22. Any major solid organ transplant recipient
23. History of malignancy of any organ system, treated or untreated, within the past year with a life expectancy less than 1 year
24. Any advanced severe or unstable disease that may interfere with the primary or secondary study outcome evaluations or put the patient at special risk
25. Any other medical conditions that may put the patient at risk or influence study results in the Investigator's opinion, or that the Investigator deems unsuitable for the study
26. Patient breastfed by a mother taking ACEi

Part 1/2: Screening Failures

Patients who failed screening could be rescreened if the investigator believed the patient's condition had changed and would be subsequently eligible. Screen failures could be rescreened for study enrollment up to two times with a minimum of 2 weeks between rescreening. Patients who discontinued from Part 1 would be allowed to screen and enroll for participation in Part 2.

Randomization Procedure

Patients were randomized via interactive response technology (IRT) to one of two treatment arms with stratification by age group and NYHA/ROSS class at randomization to ensure a balanced distribution. Randomization numbers automatically generated by the IRT remained confidential during the study and concealed from patients and investigators. The randomization process was not changed during this study. The Applicant provided a copy of randomization codes with this submission. At the time of the IA leading to initial full pediatric approval, unblinded randomization codes were made accessible to an independent and unblinded statistician, programmer, and data personnel involved in preparing the efficacy IA reports. The unblinded data analytical team was not to be involved in other trial conduct activities.

Blinding

Because tablets, oral pellets, and a liquid formulation were used in the study, the identity of the investigational drug could not be disguised. Therefore, a double-dummy design was used to conceal the identity of study treatments by using identical packaging, labeling, schedule of maintenance, appearance, taste, and odor. Unblinding was to only occur in case of

patient emergencies, at time of IA, and at study conclusion. Matching placebo was provided for enalapril and all dosage forms of LCZ696. Both enalapril and LCZ696 liquid formulations were compounded by the on-site pharmacy.

Study Drug Dose Adjustment, Interruption or Discontinuation

Patients or caregivers were instructed to take or administer any missed dose as soon as possible unless it was almost time for the next scheduled dose. In that instance, patients or caregivers were to skip the missed dose and resume the regularly scheduled dosing schedule. Dose uptitration was planned for every 2 weeks as tolerated based on safety monitoring criteria -- hyperkalemia, symptomatic hypotension, and renal dysfunction. Following uptitration, patients were maintained on the target dose or maximum tolerated dose (MTD) for study duration. Changes to the protocol-specified dosing scheme were permitted for AEs, persistent "side effects" despite adjustments to or elimination of concomitant medications, to permit rechallenging with a higher dose of study drug, or for temporary or permanent discontinuation of study drug. Down titration was permitted at any time. Newly discovered pregnant patients were to have study drug discontinued immediately however, to date, no pregnancies have been reported.

Study Dosing Scheme

In Part 2, the target dose (dose level 4) was based on PK/PD data from Part 1. Dose levels for uptitration are shown below in Table 4.

Table 4: Study Drug Dosing Levels for Enalapril and LCZ696 for Age Groups 1 and 2

Dose levels for extemporaneous suspension	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 film-coated tablet 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.

Source: Sponsor's table 9-3 in IA CSR for Study B2319 (NDA 2017620/S-013)

The starting dose for either LCZ696 or enalapril was based on the baseline dose of the patient's ACEi/ARB as defined in the study protocol. Patients that were either ACEI/ARB naïve or on low dose ACEi/ARB started at dose level 1 of study treatment after randomization. Patients taking higher doses of ACEi/ARB started at dose level 2 of study treatment. All patients underwent a minimum 36-hour washout of their ACEi prior to receiving LCZ696 to minimize angioedema risk.

Patents on baseline ARBs or renin inhibitor were required to discontinue these therapies on the day of randomization. Otherwise, patients were to continue their HF background therapy. Study drug was titrated every 2 weeks as tolerated to dose level 4. Tolerability of dose titration was based on safety criteria listed in Table 5.

Table 5: Safety Monitoring Criteria for Initiation/Uptitration of Study Drug

Parameter	Description
Potassium level	K ≤ 5.4 mmol/L (mEq/L)
Kidney function	eGFR (calculated using the modified Schwartz formula) ≥ 30% mean GFR for age (Appendix 10, Table 22-1)
Kidney function	eGFR reduction < 35% compared to randomization Visit 401 (Part 2).
Blood pressure	SBP > than the calculated 5th percentile SBP for age as described in Appendix 4
AEs or conditions	No conditions that preclude continuation according to Investigator's judgment, including hypotension.

Abbreviations: mEq, milli-equivalents; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure
Source: Applicant Table 3-3 in Study B2319 Protocol (Amendment 4)

Furthermore, investigators could adjust non-disease modifying medications for study drug tolerability issues if the investigator believed that reduction of drug doses might remedy the situation. If modification of non-disease modifying drugs was not possible or could not alleviate side effects of concerns, Investigators were permitted to adjust or interrupt study drug for tolerability issues. An Investigator could adjust doses of disease-modifying medications if believed to be the most likely cause of an AE. Guidance on handling renal dysfunction, hypotension, and hyperkalemia were provided to Investigators.

Reviewer Comment: *The Applicant chose enalapril doses of 0.1 mg/kg and 0.2 mg/kg for Age Groups 1/2 and 3, respectively, because these doses provide similar RAAS inhibition compared to LCZ696 1.6 mg/kg and 3.1 mg/kg, respectively. For patients not taking enalapril, the Applicant provided investigators with a chart containing the minimum required body weight normalized daily dose of commonly prescribed ACEi and ARBs prior to being dosed with LCZ696 1.6 mg/kg or 3.1 mg/kg.*

Rescue Medication

Investigators were permitted to prescribe medications and/or supportive care during the study based on clinical needs.

Concomitant Cardiovascular Medications

Patients were allowed to be treated with SoC therapies except ACEI, ARBs, or renin inhibitor (aliskeren). However, if an Investigator believed the addition of an ACEI, ARB, or renin inhibitor was required, the study drug was to be temporarily discontinued. Study drug had to be stopped at least 36 hours prior to starting an ACEI. If study drug was restarted, the ACEI was stopped at least 36 hours prior to resuming study drug. Any ARBs or renin inhibitor was stopped before resuming study drug.

Study Completion/Discontinuation/Withdrawal

A patient was considered to have completed the study when the patient completed the last visit planned in the protocol. Patients could voluntarily discontinue study drug for any reason at any time. Permanent discontinuance may occur for the following reasons:

- Withdrawal of informed consent
- Investigator believes that continuation would be detrimental to the patient's well-being
- Suspected occurrence of angioedema; a patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the Investigator

Temporary or permanent discontinuation may occur when:

- Use of an open-label ACEI, ARB or renin inhibitor
- Pregnancy and post-pregnancy during lactation period (Section 7.7)

Study drug may be discontinued at the Investigator's discretion if any of the following occurs:

- Any severe or suspected drug-related AE
- Any other protocol deviation that results in significant risk to the patient's safety

The appropriate personnel from the study site and Novartis assessed whether study drug should be discontinued for any patient whose treatment code had been broken inadvertently for any reason. After study treatment discontinuation, the following minimum data were collected at clinic visits or via telephone visits: new/concomitant treatments and AEs/SAEs.

Parents/Guardians may voluntarily withdraw consent at any time. Any child's request to be withdrawn from the study was to be respected and discussed in detail with parents/guardians and local Investigator before acting upon the request.

Patients discontinued from Part 2 were not replaced.

Reviewer Comment: *As previously commented in the NDA 207620/S-013 primary clinical review and CDTL summary, the overall Study B2319 trial design was acceptable and fulfilled the requirements of the WR.*

Study Committees

Data Monitoring Committee

An external and independent data monitoring committee (DMC) evaluated the unblinded data during the course of study, which was provided by an independent and external Statistical Data Analysis Center.

Clinical Endpoint Committee

All clinical events, which could potentially fulfill the Category 1 or 2 endpoints were assessed during the study and reported to the Clinical Endpoint Committee (CEC) for adjudication. The CEC reviewed and adjudicated events including but not limited to deaths (CV and non-CV death), circulatory and/or respiratory mechanical assistance for life support, listing for heart transplantation, and clinical worsening of HF (with or without hospitalization) for endpoint determination. The detailed definitions of the endpoints, the required documentation, and the adjudication process was included in a separate CEC Manual.

Angioedema Adjudication Committee

If an angioedema or angioedema-like event occurs, the Investigator will complete case report forms for angioedema adjudication. Details on the process of reporting angioedema and angioedema-like events are outlined in a manual provided to Investigators. As specified in the protocol, the Angioedema Adjudication Committee charter describes the responsibilities of the committee members (*not submitted for review*).

Study Endpoints

Primary Endpoint

The primary endpoint was the global rank endpoint evaluated through 52 weeks. Patients were first classified into the five ordinal categories, then within each of the above category, patients were then ranked from worst to best based on the first subcategory when applicable (See ranking algorithm column in Table 6). The reader is referred to the Appendix (Section 1.1) for further details of the ranking. The response category for the global rank endpoint is defined as the category which the patient is classified into.

Table 6: Primary Endpoint Ranking Algorithm, Study CLCZ696B2319 PANORAMA-HF

Category	Sub-category	Description	Ranking algorithm
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		
	A	• 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.	Rank within this category by time to first event. All Category 1 events are considered equal.

Category	Sub-category	Description	Ranking algorithm
2	Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy.		
	B	Worsening heart failure hospitalization with intensive care unit stay.	Within Category 2, the patients will be ranked first by event subcategory, and then by number of events within each sub-category. Further ranking by time to first event in the worst subcategory
	C	Worsening heart failure hospitalization without intensive care unit stay.	
	D	Worsening heart failure without hospitalization.	
3	Worsened; worse NYHA/Ross or worse PGIS; and further ranking by PedsQL physical functioning domain.		
	E	NYHA/Ross or PGIS worsened based on last available assessment compared to baseline.	Rank by combination of NYHA/Ross and PGIS degree of change. Within a group of the same degree of NYHA/Ross and PGIS change, further rank by PedsQL (physical functioning domain) change from baseline.
4	Unchanged; unchanged NYHA/Ross and unchanged PGIS; and further ranking by PedsQL physical functioning domain.		
	F	NYHA/Ross and PGIS unchanged based on last available assessment compared to baseline.	Worst baseline combination of NYHA/Ross functional class and PGIS without change is ranked worse than a better baseline NYHA/Ross functional class and PGIS. Within a group of the same baseline NYHA/Ross and PGIS, further rank by PedsQL (physical functioning domain) change from baseline.
5	Improved; improved NYHA/Ross or improved PGIS (neither can be worse); and further ranking by PedsQL physical functioning domain).		
	G	NYHA/Ross or PGIS improved (neither worsened) based on last available assessment compared to baseline	Rank by combination of NYHA/ Ross and PGIS degree of change. Within a group of the same degree of NYHA/ROSS and PGIS change, further rank by PedsQL (physical functioning domain) change from baseline.

Source: Statistical Reviewer adapted details based on Table 2-7 of the SAP
Abbreviations: UNOS, United Network for Organ Sharing; NYHA, New York Heart Association; PedsQL, Pediatric Quality of Life Inventory; PGIS, Patient Global Impression of Severity; VAD/ECMO, Ventricular assist device/ Extracorporeal membrane oxygenation

Key Secondary Endpoints

- Time to first occurrence of Category 1 or Category 2 event through 52 weeks of treatment;
- NYHA/Ross functional class change from baseline through 52 weeks of treatment;
- Patient global impression of severity (PGIS) score change from baseline through 52 weeks of treatment;
- Population PK of sacubitril/valsartan

The same analysis cutoff date was used for key secondary endpoints evaluated up through 52 weeks.

Table 7: NYHA/ROSS Investigator Classification for Pediatric Age Groups at Randomization, Study CLCZ696B2319 PANORAMA-HF

Class	Age of 1 month to < 6 years old (Modified Ross HF Classification)	6 – 18 years old (NYHA Classification)
Class I	No limitation or symptoms.	No limitation - ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
Class II	No growth failure. Mild tachypnea with feeds in infants and/or Mild diaphoresis with feeds in infants and/or Dyspnea on exertion in older children.	Slight limitation of physical activity - comfortable at rest, ordinary physical activity results in fatigue, palpitation, dyspnea, or angina
Class III	Growth failure. Prolonged feeding time in infants. Marked tachypnea with exertion or with feeding. Marked diaphoresis with exertion or with feeding	Marked limitation of physical activity - comfortable at rest, less than ordinary activity will lead to symptoms
Class IV	Symptomatic at rest with the following sign/symptom(s): • Tachypnea and/or • Retractions and/or • Grunting and/or • Diaphoresis	Inability to carry on any physical activity without discomfort - symptoms of congestive failure present even at rest; with any physical activity, increased discomfort is experienced

Source: Reviewer compiled information from Appendix 7 of the protocol version 7.0
Abbreviations: NYHA, New York Heart Association; HF=heart failure

Exploratory Endpoints

- Pediatric quality of life inventory (PedsQL) score change from baseline through 52 weeks of treatment
- NT-proBNP change from baseline through 52 weeks treatment
- Patient Global Impression of Change (PGIC) score through 52 weeks of treatment
- Time to recurrent events of Category 1 and Category 2 through 52 weeks of treatment

Statistical Analysis Plan

The statistical analysis plan (SAP) (Combined Part 1 and Part 2 Amendment 2) was finalized on October 29, 2021 prior to initial database lock on January 27, 2022. An SAP addendum was added on November 02, 2022 to address issues related to USM. Due to a conversion issue that impacted central and local laboratory values, the database was relocked on November 21, 2022. The SAP was further modified after the first database lock to address conversion issues with the laboratory values with post-hoc sensitivity analyses.

In general, the revisions to the SAP were considered adequate. We reported the planned

statistical analysis based on SAP Addendum 1 dated November 02, 2022. SAP Addendum 2 of the addendum did not differ substantially from Addendum 1 for the primary statistical analyses of the major primary and key secondary endpoints. Evaluation of missing data was not conducted since the study results were not planned to be included in the label since the primary endpoint was not statistically significant.

Primary Global Rank Endpoint

The week 52 cutoff date was specified up to day 406 after date of randomization (Week 58). This cutoff date was applied to the primary and key secondary endpoints that were evaluated up to Week 52.

The Applicant specified that the primary global rank endpoint was evaluated using the stratified Mann Whitney (MW) probability. This is defined as the probability of the patient from the LCZ696 group having better outcome than the patient from the Enalapril group plus half of the probability of the patient from the LCZ696 group having equal outcome to the one from the Enalapril group, when the two patients are independently sampled from the LCZ696 group and the Enalapril group. The MW odds is defined as (one minus the MW probability) divided by the MW probability was reported.

The test statistic was based on the stratified Wilcoxon rank-sum test evaluated on the stratum combination generated.[2] To claim superiority of LCZ696 over enalapril based on the global rank endpoint, the p-value from the stratified Wilcoxon rank-sum test must be statistically significant at 0.05 and the point estimate for the MW probability was greater than 0.5 with 95% confidence interval (CI) excluding 0.5 (or equivalently the point estimate of the MW odds being less than 1 and the 95% CI excluding 1). The estimated MW probability, respective 95% CI, p-value based on the stratified Wilcoxon rank-sum test. In addition, the MW odds, and respective 95% CI were reported.

The Applicant's approach to handling missing values or censoring or discontinuations for the global rank endpoint was as such.

1. Patients were classified into the worst possible category, based on available and retrievable information for the patient. Within Categories 1 and 2, patients were further ranked according to the day of the last reliable information (for example, last day of contact). If the

[2] The stratified Wilcoxon rank-sum test statistic was based on the weighted sum of the within-stratum rank-sum statistics, in which, the weight for stratum was the reciprocal of (one plus the total sample size of the stratum), the mean and the variance was estimated under the null hypothesis that the MW odds in all strata were equal to one. Technical details for the computation were described in the Appendix XXX.

patient was not classified as Categories 1 or 2 (e.g., patient is alive and is documented to not have any worsening HF (WHF) events), the same principle was followed for ranking the patient

2. For patients with missing values in Category 3 to 5, the last observation carry forward (LOCF) approach post-baseline value was used for the NYHA/ROSS class, PGIS, and PedsQL ranking items. For patients who were impacted by Urgent Safety Measure (USM) and were missing values in Category 3 to 5 at Week 52, the last on-treatment non-missing value was used. When ranking patients with incomplete information at Week 52, the ranking algorithm placed the patients at the median for the missing assessment component(s).

The Applicant pre-specified several supportive and sensitivity analyses. The relevant sensitivity analyses were as follows:

1. Inclusion of off-treatment values for USM-impacted patients for the primary endpoint
2. A multiple imputation approach, under a missing at random assumption within each arm and within each stratum, was used to impute the degree of change in NYHA/ROSS class, degree of change in PGIS, and change from baseline in PedsQL ranking score. This approach was noted to exclude off-treatment values for USM-impacted patients in the imputation process.

Subgroup analyses were planned for the following baseline characteristics.

1. Modified age group at randomization (6 years to < 18 years, 2 years to < 6 years, 1 month to < 2 years)
2. Gender (Male, Female)
3. Region (America, Europe, Asia/Pacific, and Others)
4. Baseline NYHA/ROSS class group (at time of randomization as well as at baseline)
5. Coronavirus Disease 2019 (COVID-19) Impacted Period (Pre-pandemic, Pre and during Pandemic, During Pandemic)

The primary analysis approach was used to analyze each subgroup based on the full analysis set. The stratified MW probability and odds were calculated within each subgroup category using the strata obtained at time of randomization. For baseline NYHA/ROSS class group defined at baseline, the stratum was revised using the baseline derivation instead. Strata consisting of only one treatment arm or fewer than 2 patients were excluded from the analysis.

Key Secondary Endpoints

The time to first adjudicated Category 1 or 2 event was fit using a Cox proportional hazard model, stratified by modified age group, and adjusting for treatment (LCZ696, Enalapril). The estimated hazard ratio, and corresponding Wald-based 95% CI were reported, along with two-sided p-value. Annualized event rates for each arm were presented. The investigator reported Category 1 or 2 event was analyzed with the same approach and reported as supplementary

analysis. Similar Cox PH model with similar covariates was used to analyze each of the individual category regardless of the other.

The NYHA/ROSS class change response (order specified as "improved" < "unchanged" < "worsened") at Week 52 and change from baseline in PGIS response (order specified as "improved" < "unchanged" < "worsened") at Week 52 were each fit using the proportional cumulative odds model. The regression model included categorical treatment, baseline endpoint categories, and modified age group (6 years to < 18 years, 2 years to < 6 years, 1 month to < 2 years). The baseline NYHA/ROSS class category were ordered as Class I to Class IV, with lower Class indicating less severity. The baseline PGIS category were ordered as None [Good], Mild, Moderate [Neither good nor bad], Severe, Very severe [Bad]. The adjusted odds ratio, respective 95% CI, along with two-sided p-values were reported for the comparison between LCZ696 and Enalapril. The same regression model was fit to the other visit weeks and similar results were reported.

Because NT-proBNP was used to support the bridging results, we reported the results for this endpoint. The exploratory endpoint, change from baseline in log NT-proBNP, was fit using a mixed model repeated measure (MMRM), adjusting for modified age group (6 years to < 18 years, 2 years to < 6 years; 1 month to < 2 years), treatment (LCZ696, Enalapril), visit, and treatment-by-visit interaction will be included as fixed-effect factors; log baseline NT-proBNP and visit by-log-baseline interaction. An unstructured covariance matrix was used to model the within-patient covariance. For each arm, the geometric mean of the ratio of NT-proBNP with baseline, and 95% CI were reported. For the comparison between LCZ696 and Enalapril, the adjusted ratio of geometric mean ratios was reported. For purposes of interpretation, we expressed the ratio of geometric mean ratios in the form of relative percentage reduction comparing LCA696 with Enalapril.

For the any of the NT-proBNP values, if the test value is below the lowest limit of quantitation (LLOQ), the test value will be imputed by 0.5 × LLOQ; if the test value is above the upper limit of quantitation (ULOQ), the test value will be imputed by 1.5 × ULOQ.

Protocol Amendments

The original protocol was finalized on 19 November 2015. The protocol was amended seven times with key changes summarized below.

Amendment 1 (08 August 2016 – no subjects enrolled)

- Addition of second dose to Part 1 study design with plan for six patients per dose per age group; two doses were to be assessed in Age Groups 1 and 2 with one dose to be assessed in Age Group 3
- Addition of plasma brain natriuretic peptide (BNP) to Part 1

- Addition of urine cyclic guanosine monophosphate (cGMP) collection at baseline (pre-dose) for PD assessment in Part 1
- Added information that study will stop when at least 80 patients have a Category 1 or 2 event

Amendment 2 (10 July 2017 – subject enrollment number not specified)
- Removal of technical details pertaining to preparation of liquid formulation of study drugs, LCZ696 and enalapril

Amendment 3 (01 October 2018 – Part 1 Age Groups 1/2 completed; Part 2 – 86 subjects enrolled)
- For Part 1 Age Group 3 patients, removed the single dose level of LCZ696 0.8 mg/kg and replaced it with two dose levels: LCZ696 0.4 mg/kg and LCZ696 1.6 mg/kg. Total of approximately 4 observations per dose (approximately 8 in total) and a minimum of 4 patients planned for Age Group 3 enrollment in Part 1
- Added the target dose level for Age Group 3 in Part 2
- Added sparse PK assessment at steady state in a subset of patients in Part 2 Age Group 2 to further confirm the target dose for this age group
- Modified the LVEF and the LVFS inclusion threshold to expand the eligibility range for patients
- Added a Palatability and Acceptability Sub-study for the two LCZ696/placebo pediatric formulations (liquid and granules) to Part 2 of the main study
- Addition of exclusion criterion for exclusion of person committed to an institution
- Addition of individual withdrawal criteria for patients
- Clarification of Visit 2 procedures and timing
- Clarification of Visit 4A timing
- Clarification of height measurement

Amendment 4 (04 February 2019 – Part 1 Age Group 3 ongoing; Part 2 – 144 subjects randomized)
- Addition of an interim biomarker analysis for NT-proBNP

Amendment 5 (18 September 2020 – Part 1 Age Group 1/2/3 completed; Part 2 Age Group 1/2 recruitment ongoing – 325 subjects enrolled)
Allowed Age Group 3 subjects to turn 1 year old during the study
- Added recurrent events analysis to Part 2 exploratory endpoints
- Removed enrollment target of 25% ACEi/ARB naïve patients
- Removed requirement for 20% of the total n of 360 (72 patients) to be randomized and included for analysis in each age group
- Added safety monitoring requirements for Part 2 Age Group 3 patients

Amendment 6 (15 September 2021 – Part 1 Age Group 1/2/3 completed; Part 2 Age Group 1/2 recruitment ongoing – 335 subjects enrolled)

- Clarified total daily dose levels of commonly prescribed ACEi/ARBs to guide selection of the study medication starting dose
- Exclusion criterion: expanded contraception requirements per the current LCZ696 Investigator's Brochure (i.e., contraception to continue for 7 days after discontinuation of study drug).
- Pregnancy reporting: added revised follow-up requirement (12 months) after birth of the baby for participants who become pregnant during the study

Amendment 7 (15 November 2021 – Recruitment closed January 2021 – 375 subjects randomized)

- Urgent safety measure (USM) effective 26 October 2021, in consideration of a quality event affecting the active comparator (Enalapril) used in the study in order to maintain the safety of the patients and the integrity of the study
    - 339/375 subjects had completed or were discontinued at time of USM issue.
    - 36 patients remained in active follow-up (5 had discontinued enalapril)
    - 31 October 2021 all patients had to discontinue study drug treatment and be changed to local standard of care
    - Statistical model, missing values, sensitivity analyses, efficacy values, biomarkers and exploratory analyses updated to reflect the USM

Reviewer Comment: *The protocol amendments are appropriate and are not expected to affect the interpretation of trial results.*

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with principles of good clinical practices (GCP), including the archiving of essential documents. Before initiation of the study, investigators and their staff were required to allow the Applicant to review protocol requirements and case report forms (CRFs). During the study, the Applicant employed several methods of surveillance to ensure protocol and GCP compliance and data quality/integrity. Such methods included periodic field monitor visits to study sites and remote monitoring of each site's data. The applicant used automatic validation procedures to check for data discrepancies during and after data entry. Furthermore, the Applicant's staff reviewed CRFs for completeness and accuracy.

An external and independent Statistical Data Analysis Center provided data to an external and independent DMC. The DMC and the Applicant reviewed Part 1 PK/PD data and dose determination for Part 2.

Financial Disclosure

The Applicant provided a statement regarding financial certification (FDA Form 3454).

Reviewer Comment: *The Applicant submitted to m1 a document entitled "financial-cert.pdf" which demonstrated no disclosable financial information for any of the clinical investigators participating in Study B2319.*

Patient Disposition

Table 8 showed the disposition of subjects in the full analysis set (FAS) for the 52-week study. Three hundred seventy-seven (N=377) subjects were randomized 1:1 to receive either LCZ696 (N=187) or enalapril (N=190). Two patients were mis-randomized (did not receive and study medication) and therefore excluded from the FAS. In total, 41 subjects (22%) in the LCZ696 arm and 50 subjects (27%) in the enalapril arm discontinued treatment. The main reason for discontinuation of randomized treatment was due to an adverse event and this proportion was similar across arms. The most common reason for study discontinuation was death (8 subjects [4%] from the LCZ696 arm and 12 subjects [6%] from the enalapril arm).

Table 8 Subject Disposition, FAS, Study CLCZ696B2319, Part 2

Disposition, n (%)	LCZ696 N=187	Enalapril N=190
Part 2 Randomized	187 (100)	188 (100)
Safety Analysis Set	187 (100)	188 (100)
Per Protocol Set	182 (97)	177 (94)
Initiated Treatment	187 (100)	188 (100)
Completed Treatment	146 (78)	138 (73)
Discontinued Treatment	41 (22)	50 (27)
Adverse Event	20 (11)	21 (11)
Death	3 (2)	4 (2)
Lost To Follow-Up	-	1 (<1)
Physician Decision	4 (2)	5 (3)
Technical Problems	11 (6)	10 (5)
Withdrawal By Parent/Guardian	3 (2)	9 (5)
Completed Study	169 (90)	164 (87)
Discontinued Study	18 (10)	24 (13)
Adverse Event	1 (<1)	2 (1)
Death	8 (4)	12 (6)

Disposition, n (%)	LCZ696 N=187	Enalapril N=190
Lost To Follow-Up	-	2 (1)
Technical Problems[1]	4 (2)	2 (1)
Withdrawal By Parent/Guardian	5 (3)	6 (3)

[1] Issues due to USM
Abbreviations: USM, urgent safety measure; LCZ696, sacubitril/valsartan; N, included all randomized and two whom were mis-randomized to enalapril and never receive study medication
Source: Statistical Reviewer

Protocol Violations/Deviation

The Applicant's final CSR for Study B2319 summarized protocol deviations for Part 2 as follows:

> *The incidence of protocol deviations during the double-blind epoch was higher in the sacubitril/valsartan group compared to the enalapril group (41.71% vs. 36.84%). This difference was mostly due to a higher incidence of "Other" protocol deviations (33.69% in sacubitril/valsartan group vs. 25.79% in enalapril group). These deviations were mostly "extended period between safety and efficacy assessments" or "assessment/procedure changed" due to COVID-19 (Listing 16.2.2-1.3). The second most commonly reported protocol deviation was treatment deviation (sacubitril/valsartan: 9.63% vs. enalapril: 11.05%). These deviations were mostly overall drug compliance >110% (in 14 patients) or <80% (in 3 patients). Eight patients did not follow instruction regarding study drug administration while four patients took incorrect treatment during randomization period. Two patients were randomized in error and did not receive study medication. Site did not follow the IRT instructions regarding dosing regimen based on review of source documentation for one patient. Study medication was not administered as per protocol for 10 patients (Table 14.1-1.6.2)…*
>
> *In total, 16 patients were excluded from the per protocol set (PPS): Incorrect treatment taken during randomized treatment period (4 patients), blind was broken (5 patients), overall drug compliance <80% (1 patient), blind was broken along with overall drug compliance <80% (2 patients), blind was broken in error (2 patients), and Patient enrolled despite not having systemic LVEF ≤45% or fractional shortening ≤22.5% (2 patients). Two patients were randomized in error, did not receive study drug, and were excluded from the FAS, the PPS and the Part 2 safety set (Listing 16.2.3-1.2).*

Reviewer Comment: *Review of the listed protocol deviations for Study B2319 Part 2 demonstrates a slight imbalance with a higher incidence in the LCZ696 treatment arm. However, most of the imbalance is attributable to clinic site challenges secondary to the COVID-*

19 pandemic. Overall, I would not expect the protocol deviation results to have a significant impact on the efficacy and safety considerations addressed in this review.

Demographic Characteristics

Baseline demographics were balanced in the two treatment groups (Table 9). Overall, 48% of the subjects were male, and 48% identified race as White, followed by Asian (27%), and Black or African American (13%). Age Group 1 (6 to <18 years old) had the highest percentage of randomized subjects (59%), with 23% in age Group 2 (2 to <6 years old), and 19% in age Group 3 (1 month to <2 years old). Eleven subjects (3%) were age <1 year old at randomization.

Table 9: Baseline Demographics, FAS, Study CLCZ696B2319

Baseline Variable	LCZ696 N=187	Enalapril N=188	Total N=375
Age (years)			
Mean (SD)	8 (5.5)	8 (5.7)	8 (5.6)
Median	7	8	8
Min, Max	0, 17	0, 17	0, 17
Age Group			
Age Group: 12 Years to < 18 Years	61 (33)	67 (36)	128 (34)
Age Group: 6 Years to 11 Years	48 (26)	43 (23)	91 (24)
Age Group: 1 Month to < 6 Years	78 (42)	78 (41)	156 (42)
Age Group 1: 6 Years to < 18 Years	109 (58)	112 (59)	221 (59)
Age Group 2a: 2 Years to < 6 Years	47 (25)	38 (20)	85 (23)
Age Group 3a: 1 Month to < 2 Years	31 (17)	39 (21)	70 (19)
Age Group 2: 1 Year to < 6 Years	72 (39)	72 (38)	144 (38)
Age Group 3: 1 Month to < 1 Year	6 (3)	5 (3)	11 (3)
Sex, n (%)			
Male	89 (48)	93 (49)	182 (49)
Female	98 (52)	95 (51)	193 (51)
Race, n (%)			
White	87 (47)	93 (49)	180 (48)
Black or African American	23 (12)	25 (13)	48 (13)
Asian	57 (30)	45 (24)	102 (27)
American Indian or Alaska Native	3 (2)	2 (1)	5 (1)
Unknown	8 (4)	6 (3)	14 (4)
Other	9 (5)	17 (9)	26 (7)
Original Race, n (%)			
Caucasian	87 (47)	93 (49)	180 (48)
Asian	57 (30)	45 (24)	102 (27)
Black	23 (12)	25 (13)	48 (13)
Native American	3 (2)	2 (1)	5 (1)
Unknown	8 (4)	6 (3)	14 (4)
Other	9 (5)	17 (9)	26 (7)
Ethnicity, n (%)			

Baseline Variable	LCZ696 N=187	Enalapril N=188	Total N=375
Not Hispanic or Latino	134 (72)	125 (66)	259 (69)
Hispanic or Latino	25 (13)	15 (8)	40 (11)
Not Reported	22 (12)	28 (15)	50 (13)
Unknown	6 (3)	20 (11)	26 (7)
NYHA Class at Randomization, n (%)			
Class I	13 (7)	11 (6)	24 (6)
Class II	78 (42)	81 (43)	159 (42)
Class III	18 (10)	18 (10)	36 (10)
Class IV	0 (0)	1 (1)	1 (0)
Missing	78 (42)	77 (41)	155 (41)
ROSS Class at Randomization, n (%)			
Class I	12 (6)	23 (12)	35 (9)
Class II	57 (30)	44 (23)	101 (27)
Class III	9 (5)	9 (5)	18 (5)
Class IV	0 (0)	1 (1)	1 (0)
Missing	109 (58)	111 (59)	220 (59)
NYHA Class/ROSS Group at Baseline, n (%)			
Class I/II	160 (86)	159 (85)	319 (85)
Class III/IV	27 (14)	29 (15)	56 (15)
Missing	0 (0)	1 (1)	1 (0)
Left ventricular ejection fraction (%)			
Mean (SD)	33 (7.4)	32 (7.9)	32 (7.7)
Median	35	33	34
Min, Max	9, 49	6, 48	6, 49
Left ventricular shortening fraction (%)			
Mean (SD)	16 (4.0)	16 (4.4)	16 (4.2)
Median	16	16	16
Min, Max	5, 24	4, 27	4, 27
Region, n (%)			
America (USA, Canada, and Argentina)	61 (33)	71 (38)	132 (35)
US Only	57 (30)	68 (36)	125 (33)
Europe	58 (31)	57 (30)	115 (31)
Asia/Pacific and Other	68 (36)	60 (32)	128 (34)

Abbreviations: LCZ696, sacubitril/valsartan; NYHA, New York Heart Association; SD, standard deviation; FAS, full analysis set
Source: Statistical Reviewer

Reviewer Comment: *Similar to the reported demographic characteristics of the Study B2319 IA (NDA 207620/S-013), the majority of subjects were adolescents, North American or European, and identified race as White. The overall demographics were well-balanced with small numerical differences most appreciable for Ross Class. I would not expect the small numerical differences to significantly impact the efficacy or safety conclusions. Regarding race and ethnicity, there are insufficient data in the published literature to consider the possibility that*

racial or ethnic differences could explain differences in efficacy or safety between treatment groups.

Pediatric Heart Failure History (FAS)

The pediatric heart failure history was balanced between the LCZ696 and enalapril treatment arms (Table 10). Cardiomyopathies secondary to congenital cardiac malformation, familial/genetic, and idiopathic were the dominant etiology of LVSD (63%) and most subjects had a prior heart failure hospitalization (68%).

Table 10: Pediatric Heart Failure History, FAS, Study CLCZ696B2319

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)

Source: Applicant Table 2-5, Section 2.2.2.2.1, Study B2319 Summary of Clinical Efficacy

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

If at any time during the study, compliance was below 80%, the Investigator and/or study personnel were to counsel the trial subject and their parent(s)/legal guardians as appropriate. Overall, prior cardiovascular and heart failure medication use was well-balanced between the

two groups. As per expected clinical practice, ACEi medications were used in the majority of patients in the LCZ696 (91%) and enalapril (91%) treatment arms with enalapril the most common ACEi drug (46% and 47%, respectively). Beta blockers were the next most common (71% and 69%, respectively), followed by spironolactone (65% and 68%, respectively), furosemide (60% and 68%, respectively), digoxin (39% and 35%, respectively), ARBs (6% and 7%, respectively), and ivabradine (2% in both arms).

Reviewer Comment: *Given the well-balanced distribution of prior medications for heart failure medical management, I do not expect the small demonstrated numerical differences to significantly affect interpretation the efficacy and safety results for Study B2319.*

Efficacy Results – Primary Endpoint

The primary endpoint for Study B2319, the global rank endpoint, did not meet the pre-specified level of significance (p=0.4). Treatment with LCZ696 did not result in a statistically significant difference between arms in the primary global rank endpoint (Table 11) despite trends towards benefit for LCZ696. Results within each stratum are presented. Table 12 showed the summary of patients who experienced at least one Category 1 or Category 2 events regardless of adjudication.

Table 11: Primary Results for the Global Rank Endpoint, FAS, Study CLCZ696B2319

Primary Endpoint	LCZ696 N=187 n (%)	Enalapril N=188 n (%)	Total N=375 n (%)	% of LCZ696 wins	% of ENA wins	% of Ties	MW Prob (95% CI)	MW Odds (95% CI)
Global Rank Endpoint	187 (100)	188 (100)	375 (100)	50	45	5	52 (47, 58)	0.9 (0.7, 1.1)
6 years to < 18 years								
Class I/II	93 (50)	94 (50)	187 (50)	56	44	<1	56 (48, 64)	0.8 (0.6, 1.1)
Class III/IV	16 (9)	17 (9)	33 (9)	31	68	<1	31 (12, 50)	2.2 (0.9, 5.3)
2 years to < 6 years								
Class I/II	42 (22)	36 (19)	78 (21)	45	44	11	50 (37, 63)	1.0 (0.6, 1.7)
Class III/IV	5 (3)	2 (1)	7 (2)	40	40	20	50 (11, 89)	1.0 (0.2, 4.8)
1 month to < 2 years								
Class I/II	25 (13)	31 (16)	56 (15)	50	37	13	56 (41, 71)	0.8 (0.4, 1.4)
Class III/IV	6 (3)	8 (4)	14 (4)	48	48	4	50 (19, 81)	1.0 (0.3, 3.4)

Outcomes based on on-treatment assessments were included for patients impacted by USM. LOCF was specified as the primary analysis.
Abbreviations: LCZ696, sacubitril/valsartan; ENA, enalapril; CI, confidence intervals; FAS, full analysis set; MW, Mann-Whitney; Prob, probability
Source: Statistical Reviewer

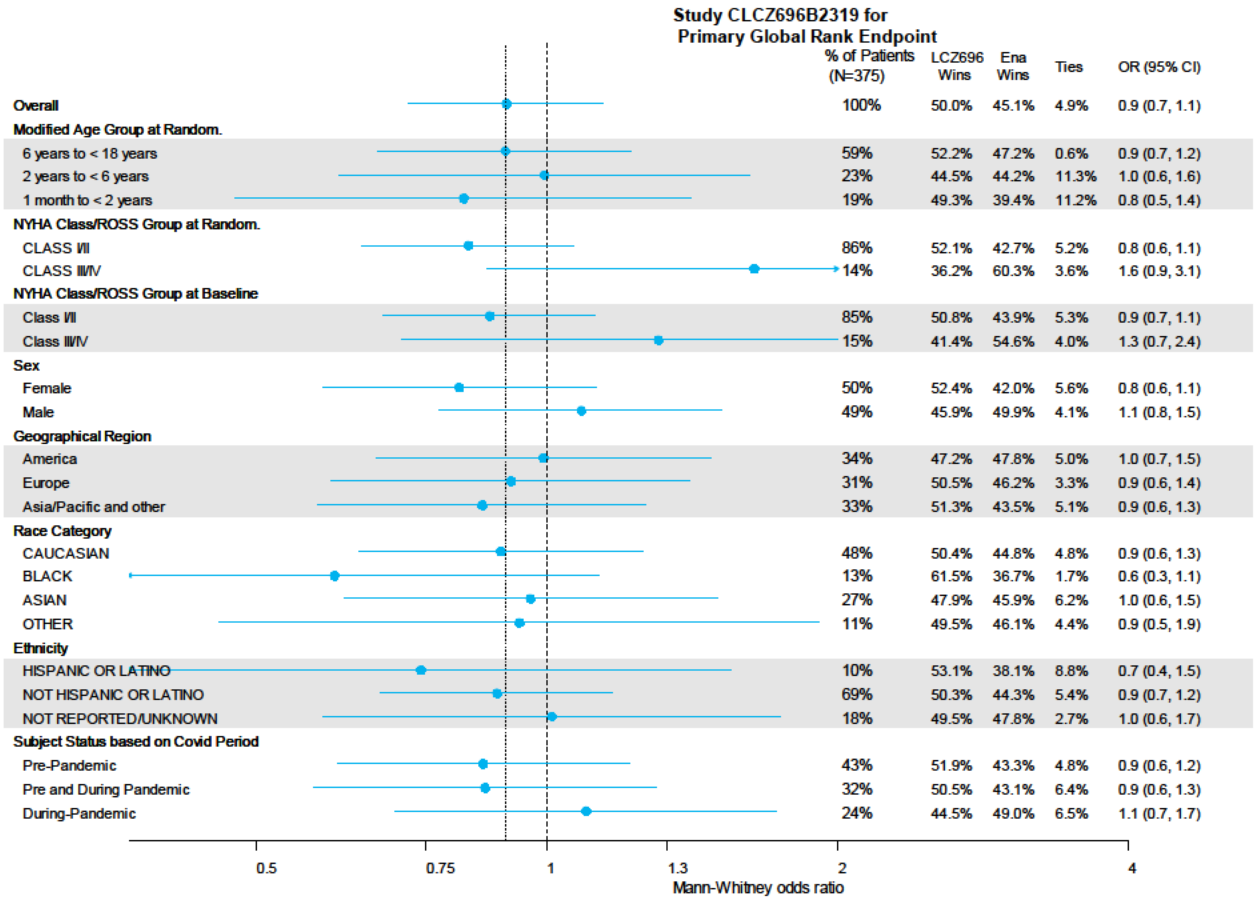
Table 12 Summary of Category 1 and 2 Events, FAS, Study CLCZ696B2319

	LCZ696 N=187 n (%) PACE	LCZ696 N=187 n (%) IRCE	Enalapril N=188 n (%) PACE	Enalapril N=188 n (%) IRCE
Category 1				
Death	8 (4)	8 (4)	12 (6)	12 (6)
UNOS status 1A listing for heart transplant or equivalent	5 (3)	7 (4)	7 (4)	6 (3)
VAD/ECMO/MV/intra-aortic balloon pump requirement for life support	7 (4)	8 (4)	12 (6)	14 (7)
Category 2	38 (20)	37 (20)[1]	32 (17)	35 (19)[1]
Worsening HF hospitalization with ICU stay	21 (11)	-	16 (9)	-
Worsening HF hospitalization without ICU stay	12 (6)	-	13 (7)	-
Worsening HF without hospitalization	5 (3)	-	3 (2)	-

Patients with at least one clinical event are reported.
[1] Categories of worsening were not reported by the Applicant for investigator reports
Abbreviations: PACE, positively adjudicated clinical events, IRCE, investigator reported clinical events; MV, mechanical ventilation; HF, heart failure, UNOS, United Network for Organ Sharing; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation; FAS, full analysis set; ICU, intensive care unit
Source: Statistical Reviewer

Subgroup results were shown in Figure 2. The findings were generally consistent with primary efficacy findings, with numerical trends towards benefit for LCZ696 except for subgroups of NYHA/Ross Class.

Figure 2 Subgroup Analysis for Primary Global Rank Endpoint, FAS, Study CLCZ696B2319



OR values above 1 is in favor of Enalapril, while OR values below 1 is in favor of LCZ696.
For Ethnicity, patients in the not reported and unknown category were combined. Ethnicity was not part of the pre-specified subgroup analysis.
Abbreviations: Random, randomization; NYHA, New York Heart Association; LCZ696, sacubitril/valsartan; ENA, enalapril; CI, confidence intervals; FAS, full analysis set; OR, Mann-Whitney Odds Ratio
Source: Statistical Reviewer

Reviewer Comment: *Study B2319 did not demonstrate superiority of LCZ696 versus enalapril (p=0.4) for the global rank primary composite endpoint. While there were numerical trends of benefit towards LCZ696, inclusive of fewer deaths (8 vs. 12) compared to enalapril, these data do not inform conclusions for efficacy* (b) (4)

Data Quality and Integrity

No site inspection was planned for the study.

An interim efficacy analysis was planned to be conducted when at least 180 patients (at least 36

patients from each age group) had completed the study (i.e., reached a terminal endpoint or completed the 1 year study visit), and at least 40 patients had an event in Category 1 or 2. However, this planned interim analysis was not performed as 36 patients could not be recruited in each age group as required for conducting this IA for efficacy. Based on review of the data, since this determination is based on recruitment into each age group, dropping the interim efficacy analysis was considered reasonable and done blinded to any accruing study results. As such, no alpha is considered to have been spent.

The data quality of the application for study CLCZ696 was considered adequate. The statistical reviewer was able to reproduce the primary study findings based on the data submitted for review.

Efficacy Results – Secondary and other relevant endpoints

Because the primary global rank endpoint comparing LCZ with enalapril did not meet statistical significance, the prespecified secondary endpoints were descriptive. P-values reported in the tables are nominal. In summary, none of the key secondary endpoints were nominally statistically significant in favor of LCA compared to enalapril.

Time to first Category 1 or Category 2 Event

The key secondary endpoint, time to first Category 1 or Category 2 Event, was not nominally significantly different between arms (Hazard ratio 1.1; 95% CI 0.7, 1.7) (Table 13). Additional supportive analyses for the time to event key secondary based on investigator reported Category 1 or 2 events regardless of positive adjudication were included in Table 13.

Table 13: Time to First Category 1 or Category 2 Event, FAS, Study CLCZ696B2319

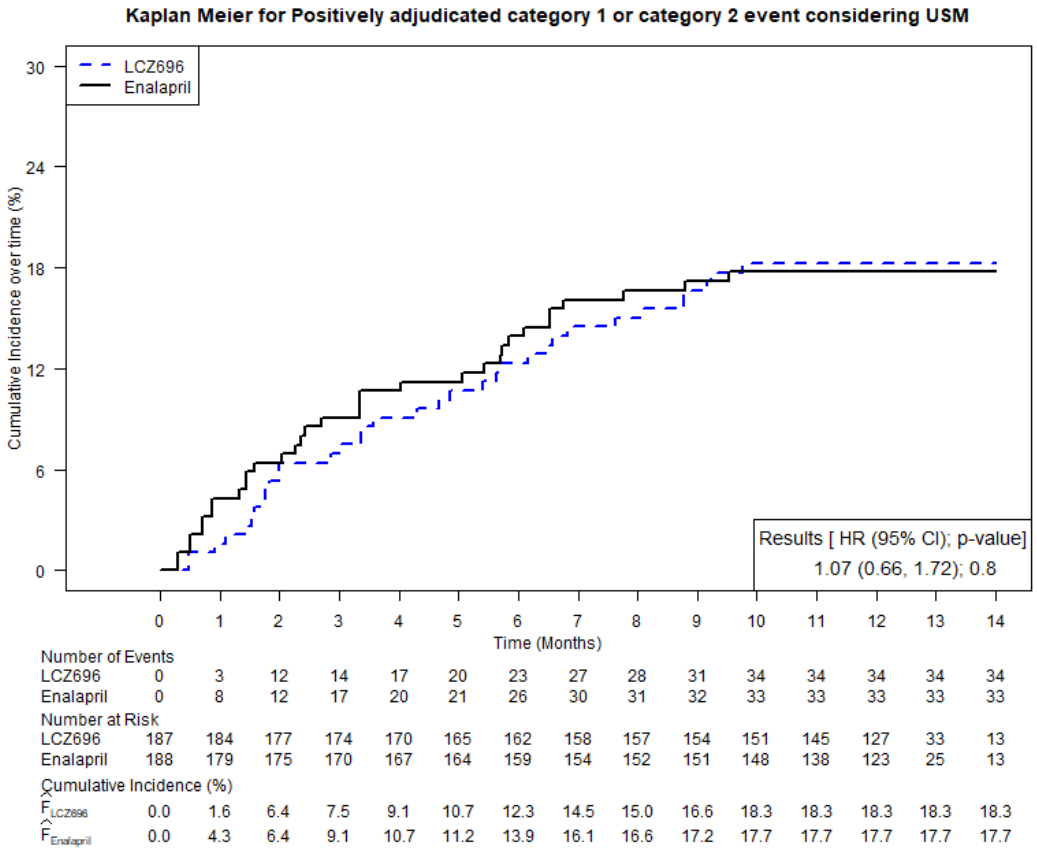
Endpoint	LCZ696 (n=187) Events (IR)	Enalapril (n=188) Events (IR)	HR (95% CI)	Nominal P-Value[1]	Difference in Rates (95% CI)
Adjudicated Category 1 or 2	34 (20.1)	33 (20.0)	1.1 (0.7, 1.7)	0.8	0.1 (-9.5, 9.7)
Category 1 event	13 (7.1)	20 (11.5)	0.6 (0.3, 1.3)	0.2	-4.4 (-10.7, 1.9)
Category 2 event	31 (18.4)	27 (16.3)	1.2 (0.7, 2.0)	0.5	2.0 (-6.9, 10.9)
Investigator reported Category 1 or 2	40 (24.0)	40 (24.9)	1.0 (0.6, 1.6)	1	-0.9 (-11.6, 9.8)
Category 1 event	15 (8.2)	21 (12.1)	0.7 (0.4, 1.4)	0.3	-3.8 (-10.5, 2.8)
Category 2 event	38 (22.8)	36 (22.4)	1.1 (0.7, 1.7)	0.8	0.4 (-9.9, 10.7)

Abbreviations: LCZ696, sacubitril/valsartan; USM, urgent safety measure; HR, hazard ratio; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

Across the study period, even though the Kaplan Meier (KM) curves for LCZ and Enalapril did not separate, the KM curve for LCZ was below the KM curve for Enalapril through Month 10

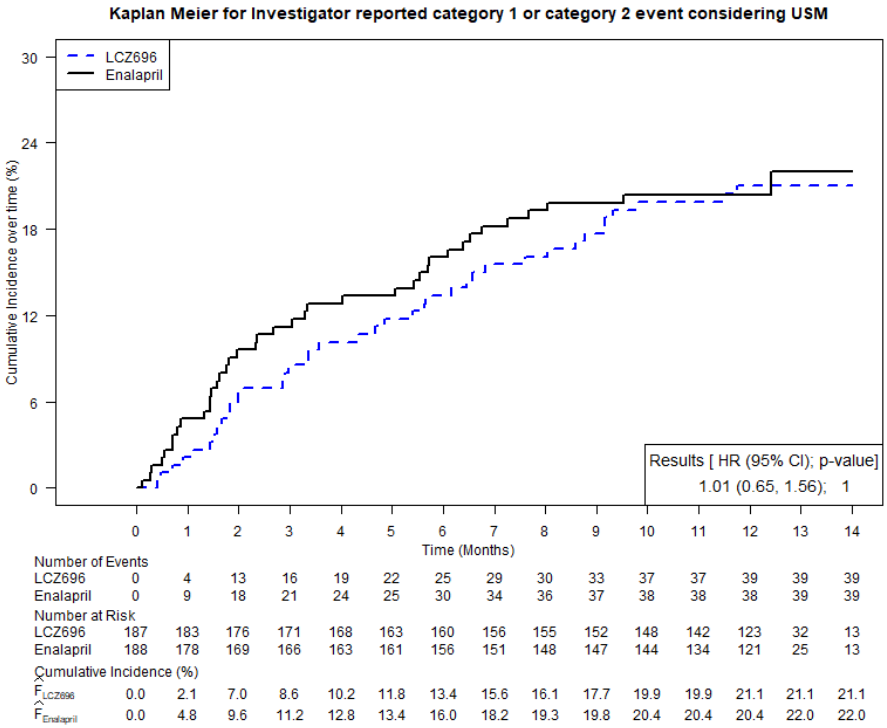
(Figure 3). Similar trends were observed based on investigator reported Category 1 or 2 events regardless of positive adjudication (Figure 4).

Figure 3: Kaplan Meier Curves for Time to First Positively Adjudicated Category 1 or Category 2 Events Considering USM, FAS, Study CLCZ696B2319



Abbreviations: LCZ696, sacubitril/valsartan; USM, urgent safety measure; HR, hazard ratio; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

Figure 4: Kaplan Meier Curves for Time to First Investigator Reported Category 1 or Category 2 Events Considering USM Regardless of Adjudication, FAS, Study CLCZ696B2319



Abbreviations: LCZ696, sacubitril/valsartan; USM, urgent safety measure; HR, hazard ratio; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

Improvement in NYHA/Ross functional class from baseline to Week 52

There was no difference between arms in the proportion of patients who had an improvement in NYHA/Ross functional status from baseline to Week 52 (Table 14). At Week 52, the proportion of patients on LCZ who has improvement, no change, and worsened in NYHA/Ross functional class from baseline were 37%, 46%, and 10% respectively. At Week 52, the proportion of patients on Enalapril arm who has improvement, no change, and worsened in NYHA/Ross functional class from baseline were 32%, 53%, and 7% respectively.

Table 14: Change from Baseline in NYHA/Ross Functional Class Across Study Visits – post Category 1 Event Set to Missing, FAS, Study CLCZ696B2319

Endpoint	LCZ (N=187)	Enalapril (N=188)
Week 4		
Improved, n (%)	26 (14)	29 (16)
Unchanged, n (%)	154 (84)	152 (83)
Worsened, n (%)	3 (2)	3 (2)
Total Observations	183	184
Estimate (95% CI)	0.9 (0.5, 1.5)	
Week 12		
Improved, n (%)	43 (24)	46 (26)
Unchanged, n (%)	127 (71)	122 (68)
Worsened, n (%)	10 (6)	12 (7)
Total Observations	180	180
Estimate (95% CI)	0.9 (0.6, 1.4)	
Week 24		
Improved, n (%)	48 (27)	48 (28)
Unchanged, n (%)	114 (64)	110 (64)
Worsened, n (%)	16 (9)	14 (8)
Total Observations	178	172
Estimate (95% CI)	0.9 (0.6, 1.4)	
Week 36		
Improved, n (%)	50 (30)	58 (34)
Unchanged, n (%)	102 (61)	99 (58)
Worsened, n (%)	15 (9)	13 (8)
Total Observations	167	170
Estimate (95% CI)	0.8 (0.5, 1.3)	
Week 52		
Improved, n (%)	70 (40)	60 (35)
Unchanged, n (%)	86 (49)	99 (57)
Worsened, n (%)	19 (11)	14 (8)
Total Observations	175	173
Estimate (95% CI)	1.1 (0.7, 1.7)	
Nominal p-value	0.8	

Percentages presented are relative to the total observations.
Abbreviations: LCZ696, sacubitril/valsartan; n, number of subjects with available observation; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

Improvement in Patient Global Impression of Severity (PGIS) score from baseline to Week 52

There was no difference between arms in the proportion of patients who had an improvement in PGIS score change from baseline to Week 52 (Table 15). At Week 52, the proportion of patients on LCZ who had improvement, no change, and worsened in PGIS score from baseline

were 29%, 39%, and 13% respectively. At Week 52, the proportion of patients on Enalapril arm who had improvement, no change, and worsened in PGIS score from baseline were 29%, 40%, and 15% respectively.

Table 15: Change in Patient Global Impression of Severity from Baseline across Study Visits, (Post Category 1 Event Set to Worsened), FAS, Study CLCZ696B2319

Endpoint	LCZ696 (N=187)	Enalapril (N=188)
Week 4		
Improved, n (%)	47 (27)	54 (30)
Unchanged, n (%)	101 (58)	109 (60)
Worsened, n (%)	26 (15)	19 (10)
Total Observations	174	182
Estimate (95% CI)	0.8 (0.5, 1.2)	
Week 12		
Improved, n (%)	55 (31)	56 (31)
Unchanged, n (%)	93 (52)	99 (56)
Worsened, n (%)	30 (17)	23 (13)
Total Observations	178	178
Estimate (95% CI)	0.9 (0.6, 1.4)	
Week 24		
Improved, n (%)	58 (33)	65 (38)
Unchanged, n (%)	85 (49)	83 (49)
Worsened, n (%)	31 (18)	23 (13)
Total Observations	174	171
Estimate (95% CI)	0.8 (0.5, 1.3)	
Week 36		
Improved, n (%)	54 (33)	56 (34)
Unchanged, n (%)	80 (49)	87 (53)
Worsened, n (%)	28 (17)	22 (13)
Total Observations	162	165
Estimate (95% CI)	1.0 (0.6, 1.5)	
Week 52		
Improved, n (%)	54 (36)	55 (35)
Unchanged, n (%)	73 (48)	75 (47)
Worsened, n (%)	25 (16)	28 (18)
Total Observations	152	158
Estimate (95% CI)	1.2 (0.7, 1.8)	
Nominal p-value	0.6	0

Percentages presented are relative to the total observations.
Abbreviations: LCZ696, sacubitril/valsartan; n, number of subjects with available observation; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

Change from baseline in logarithm of NT-proBNP to Week 52

Results based on NT-proBNP was presented in Table 16. At Week 4, the adjusted ratio of geometric mean ratio comparing LCZ696 with Enalapril is 0.7 (95% CI: 0.6, 0.9; p<0.001), translating to a 27% significant relative reduction. However, at Week 52, this relative ratio was numerically greater for LCZ696 compared to Enalapril.

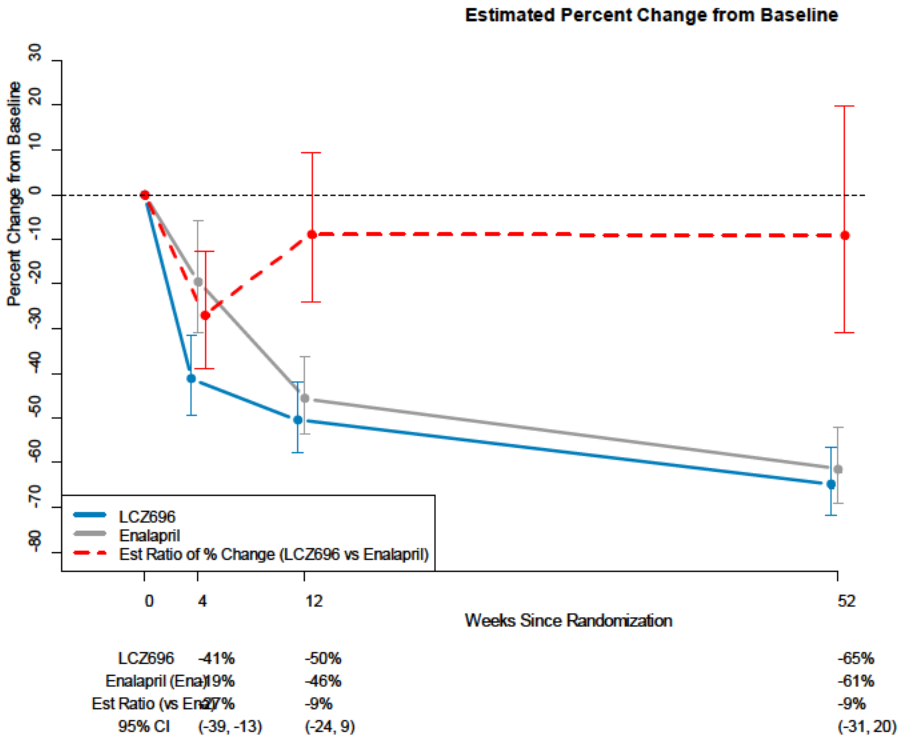
Table 16: Change from Baseline in Log NT-proBNP across Study Visits, FAS, Study CLCZ696B2319

Description	LCZ696 (N=187) GMR (SE)	Enalapril (N=188) GMR (SE)	Adjusted Ratio of GMR (95% CI)	Percent Reduction (95% CI)	p-value
Baseline, geomean (SD[1])	879 (1.6)	737 (1.6)			
Estimated Results[2]					
Week 4	0.6 (0.08)	0.8 (0.08)	0.73 (0.61, 0.87)	27% (13%, 39%)	<0.001
Week 12	0.5 (0.08)	0.5 (0.08)	0.91 (0.76, 1.09)	9% (-9%, 24%)	0.32
Week 52	0.4 (0.11)	0.4 (0.11)	0.91 (0.69, 1.20)	9% (-20%, 31%)	0.5

[1] Standard deviation is obtained from standard deviation of the logarithm of NT-proBNP.
[2] Adjusted geometric mean ratio of NT-proBNP with baseline and standard error from the MMRM model are presented in parenthesis.
Abbreviations: LCZ696, sacubitril/valsartan; NT-proBNP, N-terminal pro-brain natriuretic peptide; GMR, geometric mean ratio; SE, standard error; CI, confidence interval; FAS, full analysis set
Source: Statistical Reviewer

The adjusted percent change from baseline across study visits is shown in Figure 5. Both arms show similar trajectory in decline in NT-proBNP. Across all visit weeks, the decline in reduction in NT-proBNP from baseline is numerically larger for LCZ696 compared to Enalapril.

Figure 5: Estimated Percent Change from Baseline Across Study Visits, FAS, Study CLCZ696B2319



Estimated ratio of % change from baseline at each week was expressed as percentage change by using 100* (1 – adjusted ratio of geometric mean ratio) where adjusted ratio of geometric mean ratio is obtained from the MMRM regression model.
Abbreviations: LCZ696, sacubitril/valsartan; Est, estimated; CI, confidence interval; MMRM, mixed model repeated measures; FAS, full analysis set
Source: Statistical Reviewer

Table 17: Change from Baseline in NT-proBNP in Adult and Pediatric HF

	LCZ696		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

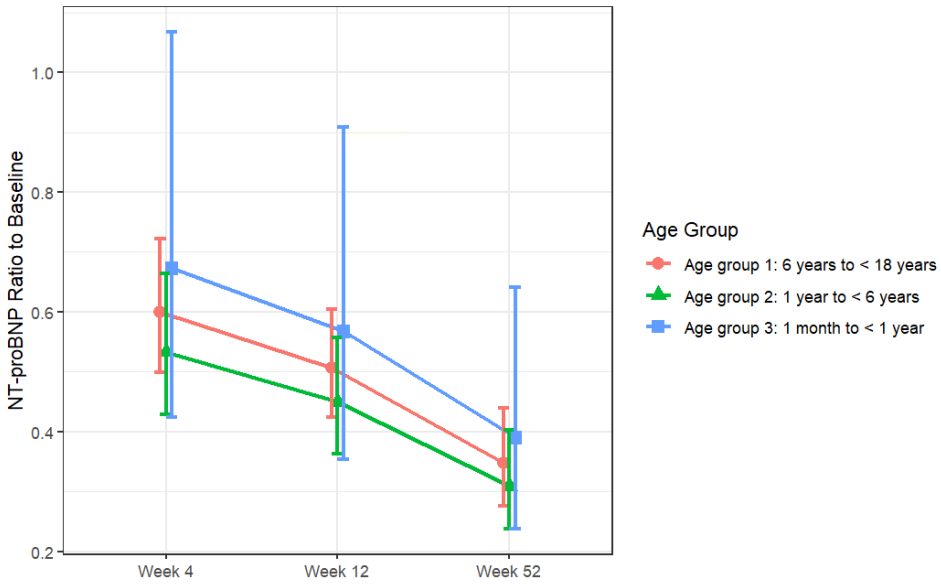
Source: Table 3-6, applicant Summary of Clinical Efficacy, Pg. 66

Reviewer Comment: *Our rationale for the use of the NT-proBNP bridging biomarker paradigm, to extrapolate to a pediatric DCM population in PANORAMA-HF the efficacy and safety demonstrated in an analogous adult DCM population in PARADIGM-HF (Study B2314), is well-described in the NDA 207620/S-013 primary clinical review and CDTL review (dated August 20th, 2019 and September 16th, 2019, respectively). The 12-week IA for PANORAMA-HF (NDA 207620/S-013) that led to the initial full approval of Entresto for the pediatric HF indication was based on demonstration of a 43% reduction for NT-proBNP at Week 12 with LCZ696 treatment. For comparison, in the PARADIGM-HF adult DCM population, Entresto demonstrated NT-proBNP reductions of 43% at Month 1 and 52% at Month 8. The final CSR for Study B2319 (NDA 207620/S-025) now reports a 50% adjusted geometric mean reduction in NT-proBNP at Week 12 and 65% reduction at Week 52 with LCZ696 treatment. Additionally, treatment with enalapril led to substantial reduction in adjusted geometric mean NT-proBNP from baseline at Week 12 (45%) and Week 52 (62%).* Table 17 *describes the comparative NT-proBNP treatment effects from baseline between pediatric DCM and adult DCM subjects treated with LCZ696 or enalapril from PANORAMA-HF and PARADIGM-HF. Overall, we recommend updating the Entresto USPI to reflect the NT-proBNP treatment effect demonstrated by the full 52-week results of PANORAMA-HF.*

Additional Analyses Conducted on the Individual Trial

The reviewer conducted an exploratory analysis on the biomarker NT-proBNP by age groups (6 to 18 years, 1 to 6 years, and 1 month to 1 year) on the LCZ696 treatment arm. The mixed model for repeated measures (MMRM) includes change from baseline in log transformed NT-proBNP [Δlog(NTProBNP)] as response, age group, NYHA/Ross class group at randomization, region, and visit as fixed-effect factors; log(baseline) and visit*log(baseline) interaction as covariates. NT-proBNP continuously decreased from baseline from Week 4 to Week 52 for all age groups (Figure 6). The decrease was significant for age groups of 6-18 years and 1-6 years at all visits. Data from the 1 month to 1 year age group showed large variability due to the limited number of subjects.

Figure 6. Geometric Mean and 95% Confidence Interval NT-proBNP Change from Baseline with LCZ696 Treatment – Mixed Model for Repeated Measures (MMRM) – (Full Analysis Set)



Reviewer Comment: *The approved Entresto pediatric HF indication has a lower age range of 1 year. However, Study B2319 studied pediatric heart failure subjects down to 1 month of age. The intent of the above exploratory analysis was to evaluate the NT-proBNP treatment effect of LCZ696 in pediatric HF subjects aged 1 month to <1 year old. While the analysis indicates a comparatively similar NT-proBNP reduction for all age ranges, the small sample size (N=9) and large variability in the 1 month to <1 year old age group did not support consideration of expanding the pediatric HF with LVSD indication to a lower age range of 1 month. An additional consideration was such that the small sample size would not provide an adequate safety database for determination of an acceptable risk-benefit profile.*

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not Applicable

7.1.1. Primary Endpoints

Refer to Section 8.1.1

7.1.2. Secondary and Other Endpoints

Refer to Section 8.1.1

7.1.3. Subpopulations

Refer to Section 8.1.1

7.1.4. Dose and Dose-Response

Refer to Clinical Pharmacology Review

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Refer to Clinical Pharmacology Review

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Not Applicable

7.2.2. Other Relevant Benefits

Not Applicable

7.3. Integrated Assessment of Effectiveness

The efficacy of Entresto for treatment of pediatric patients with HF and LVSD was previously established in 2019 (NDA 207620/S-013). Initial regulatory approval was based on a 12-week interim analysis (IA) of PANORAMA-HF (Study B2319) that demonstrated treatment with Entresto resulted in a substantial reduction from baseline of a bridging biomarker, N-terminal pro-brain natriuretic peptide (NT-proBNP), in a pediatric HF population. The reduction was similar to the reduction in NT-proBNP observed in a subset of adults with dilated cardiomyopathy (DCM) in PARADIGM-HF (Study B2314).

The applicant has now submitted an SE-8 efficacy supplement (NDA 207620/S-025), in which the full 52-week results of PANORAMA-HF were submitted for the primary global rank and key secondary endpoints. The primary global rank endpoint result was not statistically significant at Week 52 and was not supportive of a conclusion of superiority of Entresto over enalapril despite numerical trends towards Entresto in Category 1 or 2 events. Key secondary endpoints were also not nominally statistically significant. In exploratory analyses of the NT-proBNP bridging biomarker, there was a reduction from baseline at Week 12 and 52, absent a nominally statistically significant difference between Entresto and enalapril. The treatment effect on NT-proBNP at Week 12 and 52 in the completed 52-week study continued to show reduction from

baseline. The rationale for the initial regulatory approval (NDA207620/S-013) was based on a treatment effect on NT-proBNP shown in a 12-week IA of PANORAMA-HF, in which reduction in NT-proBNP inferred a large portion of the beneficial effect of Entresto on CV outcomes in PARADIGM-HF in an adult DCM population. In the completed PANORAMA-HF study, we continue to observe this treatment effect on NT-proBNP in the completed study at Week 52. Therefore, this provides additional support for us to infer an effect of similar direction on the efficacy of Entresto for the treatment of pediatric HF patients.

Per prior review of the PANORAMA-HF 12-week IA (NDA 207620/S-013), FDA concluded that the NT-proBNP bridging biomarker paradigm facilitated extrapolation to efficacy and safety data from PARADIGM-HF, which was a clinical trial of Entresto (LCZ696) in adults with HFrEF, inclusive of an analogous population of adults with DCM. PARADIGM-HF was a phase 3, randomized, active-control trial comparing LCZ696 to enalapril in 8,442 adult HFrEF subjects with NYHA Class II-IV functional status. The primary efficacy endpoint was a composite of death from CV causes or hospitalization for HF. Based on a time-to-event analysis, sacubitril/valsartan reduced the risk of the combined endpoint (HR 0.80 [95% CI: 0.73-0.87]; p<0.0001) and improved survival (HR 0.84 [95% CI: 0.76-0.93]; p<0.0009). Treatment of adults with HF and DCM with LCZ696 reduced NT-proBNP 43% at Month 1 and 52% at Month 8 (Table 17). Notably, the observed reductions in NT-proBNP in PARADIGM-HF were shown to statistically explain >80% of the observed clinical benefit of LCZ696 in adults with HF. Additionally, there is a strong biological rationale for believing that the reductions in NT-proBNP are linked to the drug's effects on HF and improvements in the rates of death and hospitalization.

With the full results of PANORAMA-HF (N=375 subjects), 187 pediatric HF subjects were treated with LCZ696 and 188 subjects were treated with enalapril. The Mann-Whitney Odds Ratio for the primary global rank endpoint was not statistically significant (p=0.4), despite numerical trends towards LCZ696 for Category 1 or 2 events. The key secondary endpoints were not nominally statistically significant, despite numerical trends towards LCZ696. In an exploratory analysis at Week 52, there were 144 subjects treated with LCZ696 and 133 subjects treated with enalapril with a post-baseline assessment of NT-proBNP. The estimated least squares mean percent reduction from baseline in NT-proBNP at Week 52 was 65% and 62% in the LCZ696 and enalapril groups, respectively. In comparison to the adult HF with DCM population in PARADIGM-HF, acknowledging the limitations of cross-study comparisons, treatment with LCZ696 in pediatric HF subjects was observed to have a larger reduction from baseline for NT-proBNP at similar timepoints (Table 17). Overall, the large and continued reduction of NT-proBNP from baseline observed in pediatric HF patients treated with LCZ696 for 52 weeks is consistent with the use of the bridging biomarker paradigm for this pediatric DCM population.

Based on the complete results of PANORAMA-HF, the applicant has proposed to update Section 14.2 of the Entresto USPI with a description of (b) (4) the NT-proBNP bridging biomarker results. The applicant has not proposed a change to the

pediatric HF indication statement. (b) (4) treatment with LCZ696 was observed to reduce NT-proBNP from baseline with continued reduction at Weeks 12 and 52. The observations of findings in NT-proBNP were consistent with the adult subgroup from PARADIGM-HF. These data further support the use of the NT-proBNP bridging biomarker in a pediatric HF population through extrapolation to safety and efficacy demonstrated in an analogous population of adults with HF and DCM. Overall, our evaluation of efficacy supports a recommendation to update Section 14.2 of the Entresto USPI to reflect the results of the NT-proBNP bridging biomarker (b) (4)

8. Review of Safety

8.1. Safety Review Approach

The safety set (SAF) consists of all randomized patients who received at least one dose of study drug. Three hundred seventy-five (375) subjects comprised the Part 2 SAF, including 187 subjects treated with LCZ696 and 188 subjects treated with enalapril. Given the prior full approval of Entresto indicated for the treatment of pediatric patients with HF and LVSD based on the Study B2319 12-week IA data (NDA 207620/S-013), and well-known safety profile of Entresto in adults with HF, this review primarily focuses on updating safety information for adverse events of special interest (AESIs; inclusive of hypotension, hyperkalemia, angioedema, and renal impairment), along with narratives for key severe adverse events (SAEs), drug discontinuations/withdrawals, and deaths. AE terms used are preferred terms (PTs) included in the Medical Dictionary for Regulatory Activities (MedDRA).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

During Part 2 of Study B2319, the median duration of exposure to study drug, including temporary interruptions was similar for both treatment arms: 365 days for LCZ696 and 364 days for enalapril. The majority of study subjects had ≥26 weeks of exposure to study drug with 168 (89.8%) subjects for LCZ696 and 159 (84.6%) subjects for enalapril meeting this threshold (Table 18). Duration of study drug exposure was comparable across all three pre-specified age groups.

Table 18: Duration of Treatment Exposure (Part 2 SAF)

Duration of Treatment Exposure	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
Mean Days (SD)	339.3 (95.6)	319.0 (110.7)
<2 Weeks	2 (1.1)	2(1.1)
2 to <8 Weeks	5 (2.7)	9 (4.8)
8 to <26 Weeks	12 (6.4)	18 (9.6)
≥26 Weeks	168 (89.8)	159 (84.6)

Source: Adapted from Table 14.3-1.2 in Study B2319 CSR v2, p1321

Similar to the FAS, the SAF dataset demonstrated that age Group 1 (6 years to <18 years) had the highest number of randomized subjects (N=220), while age Group 2 (2 to <6 years) and age Group 3 (1 month to <2 years) had a similar number of subjects: N=77 for age Group 2 and N=70 for age Group 3. The majority of subjects received weight-based dosing rather than non-weight-based/adult dosing. By Week 20, most study subjects had reached dose Level 4 (LCZ696 pediatric dose 3.1 mg/kg twice daily versus enalapril pediatric dose 0.20 mg/kg twice daily; adult doses 200 mg twice daily and 10 mg twice daily, respectively), which remained generally consistent through the Week 52 visit (See Table 4 for description of all dosing levels). The number and percentage of subjects who reached target-dose Level 4 at least once at any timepoint was 143/187 (76.5%) for LCZ696 and 154/188 (81.9%) for enalapril (Table 19).

Table 19: Study Drug Dose Level by Visit (Week 20 and Week 52)

		LCZ696 N=187 n (%)		Enalapril N=188 n (%)		Total N=375 n (%)	
Visit	Dose Level	ADL	PDL	ADL	PDL	ADL	PDL
Week 20	1	0	6 (4.2)	0	3 (2.1)	0	9 (3.2)
	2	4 (14.8)	8 (5.6)	3 (13.0)	6 (4.3)	7 (14.0)	14 (4.9)
	3	1 (3.7)	29 (20.1)	2 (8.7)	19 (13.5)	3 (6.0)	48 (16.8)
	4	22 (81.5)	101 (70.1)	18 (78.3)	113 (80.1)	40 (80.0)	214 (75.1)
Week 52	1	0	1 (0.9)	0	2 (1.7)	0	3 (1.3)
	2	6 (22.2)	8 (6.8)	0	1 (0.8)	6 (13.6)	9 (3.78)
	3	0	20 (17.0)	2 (11.8)	17 (14.2)	2 (4.6)	37 (11.6)
	4	21 (77.8)	89 (75.4)	15 (88.2)	100 (83.3)	36 (81.8)	189 (79.4)

Abbreviations: ADL, adult dose level; PDL, pediatric dose level
Source: Adapted from Table 14.3-1.4 in Study B2319 CSR v2.0, Pg. 2233-2243

Reviewer Comment: *Overall exposure to, and duration of, study treatment was reasonable in both treatment arms for Study B2319. Most study subjects reached the target highest dose*

titration step at some point in the study suggesting that tolerability to study treatment(s) was reasonable and adequate to justify the approved pediatric dosing paradigm.

8.2.2. Relevant characteristics of the safety population:

There were no significant differences in demographic or other baseline characteristics between the FAS and SAF (Demographic and other baseline characteristics are summarized in Section 8.1.2.)

8.2.3. Adequacy of the safety database:

As previously reviewed for initial full approval under NDA 207620/S-013, the totality of safety information obtained from the PARADIGM-HF adult HFrEF population, the now completed results of the PANORAMA-HF pediatric HF study, and approved product labeling for Entresto are adequate to support a determination of safety in a pediatric HF with LVSD population age 1 year to <18 years old.

Reviewer Comment: *The majority of safety information in the safety database were obtained from age Group 1 and Group 2. However, given the rarity of pediatric DCM, there is adequate representation of age Group 3 in the SAF to make a safety representation down to 1 year old.*

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Not Applicable

8.3.2. Categorization of Adverse Events

An AE was defined as any untoward medical occurrence [e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease] in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. All reports of intentional misuse and abuse of the product were considered an AE irrespective if a clinical event occurred.

Abnormal laboratory values or test results were considered AEs only if they fulfilled at least one of the following criteria:

- they induced clinical signs or symptoms
- they were considered clinically significant
- they required therapy

Clinically significant abnormal laboratory values or test results were to be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

baseline or the previous visit, or values considered to be non-typical in patients with underlying disease. The applicant provided "alert ranges" for laboratory and other test abnormalities in the study protocol.

AEs were recorded in the AE CRF under the signs, symptoms or diagnosis associated with them, accompanied by the severity grade as follows:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

All AEs were treated by one of more of the following methods, as deemed appropriate:

- no action taken (e.g. further observation only)
- investigational treatment dosage adjusted/temporarily interrupted
- investigational treatment permanently discontinued due to an AE
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

All AEs were followed until resolution or until judged to be permanent with assessment made at each visit (or more frequently if needed) of any changes in severity, suspected relationship to study drug, interventions required to treat the AE, and outcome. Information about common side effects already known for LCZ696 were documented in the investigators brochure (IB). Information on known side effects of LCZ696 were included in the patient informed consent.

<u>Serious Adverse Events</u>

A SAE was defined as any AE [appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)] which met any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition not associated with that is unrelated to the indication under study and has not worsened since signing the informed consent

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention

Every SAE, regardless of causality, occurring after patient informed consent and until 30 days after last study visit was reported to the applicant within 24 hours of learning of its occurrence. Any SAEs occurring after the 30-day period could be reported by Investigators to the applicant if deemed study drug-related. SAEs not previously documented in the IB or package insert and deemed study drug-related were to be reported as SUSARs to health regulatory authorities and relevant ethics committees.

Special Considerations

AEs or SAEs commonly seen in the study population such as WHF, edema, hypotension, and renal impairment were not reported as suspected unexpected severe adverse reactions (SUSARs). However, these SAEs were reviewed by the DMC to assess for clinically important imbalances in AEs or SAEs. Moreover, SUSARs were not unblinded if they could represent one of the following pre-specified disease related endpoints: death (all-cause, CV, non-CV), VAD/ECMO/mechanical ventilation/IABP, or WHF (with and without hospitalization).

Hepatotoxicity and renal impairment were closely monitored to identify special interest AEs during the study. Investigators were provided an algorithm for investigation of and follow up requirements for abnormal liver tests or liver toxicity AEs. For renal monitoring, serum and urine events were pre-specified. A serum event was defined as confirmed (after ≥24 hours) decrease in eGFR (Schwartz equation) of ≥25% compared to baseline during normal hydration status and eGFR <90mL/min/1.73m2. A urine event was defined as new onset (≥1+) proteinuria, hematuria, or glucosuria with confirmation of new onset proteinuria by urinary protein creatinine ratio. Novartis provided renal "alert" criteria and actions to be taken by Investigators.

Pregnancy occurring after informed consent must be reported to the applicant within 24 hours of learning of its occurrence. A pregnancy must be followed to determine outcome of the pregnancy and fetus/infant.

Reviewer Comment: *The applicant's definitions, AE assessment strategies, reporting procedures, and follow-up procedures pertaining to AEs, SAEs, and SUSARs are acceptable. The applicant included treatment guidelines for elevated potassium/hyperkalemia, symptomatic hypotension, and management of renal dysfunction in their study protocol.*

8.3.3. Routine Clinical Tests

Hematology, blood chemistry, and urine laboratory evaluations were performed in Parts 1 and 2 with local and central laboratories used for analyses depending on the timing of study visits. Pregnancy testing was performed for childbearing potential females prior to enrollment in Parts 1 and 2. The applicant provided a reference table in their study protocol for maximum blood volumes permitted in one blood draw and total drawn in a 28-day period.

Investigators were allowed to proceed with study visit procedures based on local laboratory results while awaiting central lab results. Local and central laboratory results did not need to agree for the Investigator to enroll a patient in the trial or make a dose titration decision. A patient enrolled in the study based on local laboratory results and subsequently determined to be outside the pre-specified limits of an exclusion criterion based on central laboratory results could be continued or discontinued from the study at the discretion of the Investigator. Moreover, Investigators could use his/her clinical judgment on how best to manage the study drug dose level in the event a dose titration decision based on a local laboratory result is subsequently found to be discrepant with central laboratory results.

Other safety assessments included physical examinations, vital signs, anthropometric assessments, and ECG. Of note, supine and sitting SBP and DBP were measured.

Reviewer Comment: *The routine clinical testing and safety assessment, including timing and procedures for handling abnormal test results, are appropriate for the pediatric study population.*

8.4. Safety Results

8.4.1. Deaths

20 (5.3%) deaths occurred during Study B2319, with the primary cause of death determined by the adjudication committee to be CV in all but 2 subjects (7 and 11 CV deaths for LCZ696 and enalapril, respectively). Congestive HF (n=4), cardiogenic shock (n=6), witnessed sudden death (n=4), presumed CV death (n=2), and unwitnessed CV death (n=2) were the adjudicated etiologies. The non-CV deaths were attributable to 1 subject with malignancy treated with LCZ696 and 1 subject with respiratory failure treated with enalapril.

Below are brief summaries of study subject deaths based on narratives provided by the applicant:

LCZ696

- 10-year-old female with NYHA Class II HF secondary to an ischemic etiology with Baseline LVEF 35% and NT-proBNP 2037 pg/mL died on Day 244 (study drug had been

discontinued on Day 218 secondary to hepatomegaly). The cause of death was adjudicated as congestive heart failure (*cardiogenic shock*).

- 14-year-old female with NYHA Class II HF secondary to an ischemic etiology with Baseline LVEF 30% and NT-proBNP 6959 pg/mL died on Day 309 (last dose of study drug on Day 196 secondary to ventricular dysfunction). The cause of death was adjudicated as cardio-respiratory failure (*cardiogenic shock*).
- 9-year-old female with NYHA Class II HF secondary to idiopathic cardiomyopathy with Baseline LVEF 25% and NT-proBNP 11720 pg/mL died on Day 124 (last dose of study drug on Day 97 secondary to worsening heart failure). The cause of death was adjudicated as cardiac failure (*congestive heart failure*).
- 11-month-old male with Ross Class II HF secondary to idiopathic cardiomyopathy with Baseline LVEF 28% and NT-proBNP 41638 pg/mL died on Day 310 (last dose of study drug on Day 293 secondary to cardiac arrest). The cause of death was adjudicated as cardiac failure (*cardiogenic shock*).
- 15-year-old male with NYHA Class II HF secondary to a neuromuscular disorder with Baseline LVEF 38% and NT-proBNP 1295 pg/mL died on Day 151 (last dose of study drug on Day 43 secondary to renal impairment). The cause of death was adjudicated as cardiac failure (*congestive heart failure*)
- 2-year-old male with Ross Class II HF secondary to acquired (chemotherapy) cardiomyopathy with Baseline LVEF 34% and NT-proBNP 2419 pg/mL died on Day 262 (last dose on Day 262 secondary to congestive heart failure). The cause of death was adjudicated as non-CV secondary to progression of malignancy (acute myeloid leukemia)
- 11-year-old female with NYHA Class II HF secondary to left ventricular non-compaction with Baseline LVEF 39% and NT-proBNP 783 died on Day 100 (last dose of study drug was on the same day). The cause of death was adjudicated as *sudden cardiac arrest*.
- 3-year-old male with Ross Class II HF secondary to idiopathic cardiomyopathy with Baseline LVEF 27% and NT-proBNP 6417 pg/mL died on Day 47 (last dose of study drug was on the same day). The cause of death was adjudicated as *sudden cardiovascular death*.

Enalapril

- 8-year-old female with NYHA Class II HF secondary to congenital cardiac malformation with Baseline LVEF 25% and NT-proBNP 2456 pg/mL died on Day 21 (last dose of study drug on the same day). The cause of death was adjudicated as arrhythmia and cardiac failure (*sudden cardiac death – witnessed*).
- 6-year-old female with NYHA Class I HF secondary to familial/genetic cardiomyopathy with Baseline LVEF 28% and NT-proBNP 1671 pg/mL died on Day 191 (last dose of study drug on Day 170 secondary to parent/guardian withdrawn consent to participate in the study). The cause of death was adjudicated as cardiac failure (*cardiogenic shock*).
- 10-year-old male with NYHA Class III HF secondary to myocarditis with Baseline LVEF 20% and NT-proBNP 687 pg/mL died on Day 49 (last dose of study medication on Day 43

secondary to circulatory collapse). The cause of death was adjudicated as circulatory collapse with hypoxic ischemic encephalopathy (*sudden cardiovascular death*).

- 12-year-old female with NYHA Class II HF secondary to acquired (chemotherapy) cardiomyopathy with Baseline LVEF 18% and NT-proBNP 4735 pg/mL died on Day 201 (last dose of study medication on the same day). The cause of death was adjudicated as *sudden cardiovascular death – witnessed*.
- 12-year-old female with NYHA Class II HF secondary to congenital cardiac malformation with Baseline LVEF 20% and NT-proBNP 766 pg/mL died on Day 182 (last dose of study medication was Day 181). The cause of death was adjudicated as *sudden cardiac death – witnessed*.
- 12-month-old male with Ross Class II HF secondary to idiopathic cardiomyopathy with Baseline LVEF 37% and NT-proBNP 1350 pg/mL died on Day 117 (last dose of study drug on Day 85 secondary to worsening HF). The cause of death was adjudicated as respiratory distress secondary to cardiac failure (*cardiogenic shock*).
- 17-year-old female with NYHA Class I HF secondary to idiopathic cardiomyopathy with Baseline LVEF 26% and NT-proBNP 1322 pg/mL died on Day 230 (last dose of study medication was Day 70 secondary to angioedema. The cause of death was adjudicated as cardiac failure (*sudden cardiac death - unwitnessed*).
- 16-month-old female with Ross Class I HF secondary to familial/genetic cardiomyopathy with Baseline LVEF 21% and NT-proBNP 712 pg/mL died on Day 196 (last dose of study medication on Day 188 secondary to rhabdomyolysis). The cause of death was adjudicated as cardiac failure (*cardiogenic shock*).
- 17-year-old male with NYHA Class II HF secondary to neuromuscular disorder with Baseline LVEF 38% and NT-proBNP 461 pg/mL died on Day 47 (last dose of study drug was Day 46). The cause of death was adjudicated as no-CV (*respiratory failure secondary to viral respiratory infection*).
- 17-year-old male with NYHA Class II HF secondary to neuromuscular disorder with Baseline LVEF 33% and NT-proBNP 707 pg/mL died on Day 121 (last dose of study drug on Day 42 secondary to cardiac failure). The cause of death was adjudicated as cardiac failure (*congestive heart failure*).
- 16-month-old male with Ross Class IV HF secondary to left ventricular non-compaction with Baseline LVEF 29% and NT-proBNP 5486 pg/mL died on Day 393 (last dose of study drug on Day 293 secondary to vomiting). The cause of death was adjudicated as cardiac failure (*cardiogenic shock*).
- 12-year-old male with NYHA Class II HF secondary to idiopathic cardiomyopathy with Baseline LVEF 27% and NT-proBNP 10545 pg/mL died on Day 152 (last dose of study drug on the same day). The cause of death was adjudicated as *presumed CV death* in the setting of cardiac failure.

Reviewer Comment: *Reported deaths do not reveal new safety concerns unique to pediatric patients. Moreover, there was no obvious evidence of study drug directly contributing to death.*

All CV-related patient deaths can be attributed to consequences of chronic HF typically due to either a precipitating illness or acute exacerbation of HF.

8.4.2. Serious Adverse Events

Review of SAE data included select CRFs and the applicant's narrative summaries.

One-hundred-thirty-one (34.9%) of study subjects reported at least one treatment emergent SAE with comparable incidence between both the LCZ696 (36.9%) and enalapril (33.0%) treatment arms (Table 20). The small numerically higher incidence of SAEs for the LCZ696 treatment arm was not driven by a particular SAE class with overall difference of 1 or 2 patients contributing to the observed incidence differences. As shown in Table 20, the most frequently reported SAE PTs (≥1% in any treatment arm) were cardiac failure, pneumonia, and vomiting. For special interest AEs, there were 4 hypotension SAEs in the LCZ696 treatment arm and none in the enalapril treatment arm. For renal impairment, there was 1 SAE in the LCZ696 treatment arm and 2 SAEs in the enalapril treatment arm. For hyperkalemia, there were no SAEs for LCZ696 and 2 SAEs in the enalapril treatment arm. For other AESIs (hepatotoxicity and angioedema), none met the ≥1% threshold so likely represented 1 or fewer events.

Table 20: SAEs by SOC and PT (≥1% of subjects for any treatment), Study B2319, Part 2 SAF

Preferred Term	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
TOTAL	69 (36.9)	62 (33.0)
Cardiac Failure	24 (12.8)	23 (12.2)
Pneumonia	5 (2.7)	4 (2.1)
Vomiting	5 (2.7)	4 (2.1)
Cardiac Failure Congestive	4 (2.1)	3 (1.6)
Hypotension	4 (2.1)	0
Pyrexia	4 (2.1)	0
Upper Respiratory Infection	4 (2.1)	0
Dyspnoea	3 (1.6)	1 (0.5)
Ventricular Tachycardia	3 (1.6)	1 (0.5)
Acute Respiratory Failure	2 (1.1)	0
Cardiac Arrest	2 (1.1)	4 (2.1)
Cardiac Failure Acute	2 (1.1)	4 (2.1)
Influenza	2 (1.1)	2 (1.1)
Pleural Effusion	2 (1.1)	1 (0.5)
Acute Kidney Injury	1 (0.5)	2 (1.1)
Arrhythmia	1 (0.5)	3 (1.6)

Hypoglycemia	1 (0.5)	2 (1.1)
Seizure	1 (0.5)	4 (2.1)
Syncope	1 (0.5)	2 (1.1)
Atrial Thrombosis	0	2 (1.1)
Bronchiolitis	0	2 (1.1)
Chest Pain	0	2 (1.1)
Dehydration	0	2 (1.1)
Hyperkalemia	0	2 (1.1)
Viral Upper Respiratory Infection	0	2 (1.1)

Source: Adapted from Table 2-6, Study B2319 Integrated Summary of Safety, SCS Appendix 1a, Pg. 54

Reviewer Comment: *Review of the applicant's narratives for SAEs indicated most likely were not study drug related. However, determination of the relationship between SAEs and study drug is complicated by underlying morbidity from a diagnosis of HF and other intercurrent events occurring at the time of the reported SAE. Most SAEs of special interest (e.g., hypotension, renal impairment, and angioedema) were likely study drug-related, although these events were numerically small and do not suggest a significant safety signal for pediatric patients treated with LCZ696 versus enalapril. Furthermore, no pattern for an age-related dependence for reported SAE imbalances could be established from the limited dataset.*

8.4.3. Discontinuations, Interruptions, and Changes Due to Adverse Effects

AEs, regardless of treatment relationship, leading to permanent discontinuation of study treatment occurred in 21/187 (11.2%) subjects in the LCZ696 treatment arm and 21/188 (11.2%) subjects in the enalapril treatment arm. The most common PTs resulting in treatment discontinuation were cardiac failure (3.7% versus 5.9% in LCZ696 and enalapril arms, respectively), cardiac arrest (1.1% vs. 0% in LCZ696 and enalapril arms, respectively), cardiac failure congestive (1.1% and 0% in LCZ696 and enalapril arms, respectively), and cardiac failure acute (0.5% in both arms). One discontinuation event each was reported for hepatic enzyme increased, hepatic function abnormal, hepatomegaly, hypotension, and renal failure leading to LCZ696 discontinuation. For enalapril discontinuation, one event each was reported for angioedema, hyperkalemia, and renal failure.

For AEs leading to dose interruption and change, 38 (20.3%) LCZ696 treated subjects and 32 (17.0%) enalapril treated subjects had a relevant AE. Hypotension was the most frequent event for 7 (3.7%) subjects treated with LCZ696 and 6 (3.2%) subjects treated with enalapril. Cardiac failure was the next most common for 5 (2.7%) subjects treated with LCZ696 and 6 (3.2%) subjects treated with enalapril. All remaining AEs leading to study drug interruption of change presented in ≤4 (≤2.1%) subjects in either treatment arm. No significant age-dependent treatment-emergent incidence differences were reported.

Reviewer Comment: *AEs leading to discontinuation, interruption, or dose changes were non-*

specific and mostly consistent with symptoms experienced by pediatric HF patients during and acute HF exacerbation. Of all AEs stated above, hypotension and renal impairment/failure are most likely to be study drug related, but these reported events are too numerically small to inform a concerning safety signal. Hypotension and renal impairment/failure are already included as potential adverse reactions in approved labeling for Entresto.

8.4.4. Significant Adverse Events

See Section 10.4.2

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, 331 (88.2%) subjects in the Study B2319, Part 2 SAF experienced at least one AE. The proportion of subjects reporting AEs were similar between treatment groups with 166 (88.8%) subjects in the LCZ696 treatment arm and 165 (87.8%) subjects in the enalapril treatment arm (Table 21). Comparative AE incidence by age Group 1/2/3 was similar.

Table 21: AEs by SOC Occurring in ≥5% of Subjects, Study B2319, Part 2 SAF

SOC	LCZ696 N=187 n (%)	Enalapril N=188 n (%)
TOTAL	166 (88.8)	165 (87.8)
Infections and Infestations	117 (62.6)	109 (58.0)
General Disorders and Administration Site Considerations	76 (40.6)	62 (33.0)
Gastrointestinal Disorders	73 (39.0)	79 (42.0)
Respiratory, Thoracic and Mediastinal Disorders	64 (34.2)	65 (34.6)
Cardiac Disorders	49 (26.2)	47 (25.0)
Nervous System Disorders	49 (26.2)	43 (22.9)
Investigations	39 (20.9)	44 (23.4)
Skin and Subcutaneous Tissue Disorders	33 (17.7)	24 (12.8)
Vascular Disorders	27 (14.4)	25 (13.3)
Metabolism and Nutrition Disorders	26 (13.9)	28 (14.9)
Musculoskeletal and Connective Tissue Disorders	19 (10.2)	11 (5.9)
Renal and Urinary Disorders	19 (10.2)	9 (4.8)
Injury, Poisoning and Procedural Complications	14 (7.5)	25 (13.3)
Psychiatric Disorders	12 (6.4)	14 (7.5)
Blood and Lymphatic System Disorders	11 (5.9)	8 (4.3)

Source: Adapted from Table 2-2, Study B2319 Integrated Summary of Safety, SCS Appendix 1a, Pg. 10-11

Reviewer Comment: *In a pediatric population, particularly one that is chronically ill, infectious*

illnesses would be expected. Based on the mechanism of LCZ696 and no concerns for increased risk for immunosuppression in either nonclinical or prior human studies, it seems unlikely that observed infections in the LCZ696 treatment arm are study drug related. Overall, there were no new or unexpected AEs detected in the full PANORAMA-HF study results.

8.4.6. Laboratory Findings

The applicant provided patient data for all abnormal hematology, clinical chemistry, and urinalysis labs collected for all study subjects. Central lab samples were collected at Baseline, Week 24, and Week 52. However, local lab sampling occurred more frequently and earlier in the study at pre-screening, Weeks 4, 8, and 12 and optional at Weeks 2 and 6. The applicant provided criteria for "clinically notable" lab results (e.g., xx% increase or decrease from baseline). Central and local lab data differed primarily due to less timepoints for central lab assessments compared to scheduled local lab assessments.

Hematology
Based on pooled central and local lab data, the most frequent abnormal hematology clinically significant lab results were post-baseline white blood cell count. In general, most subjects had normal hematology values at baseline and these values remained normal post-baseline for most subject in both treatment arms. Any shifts from normal at baseline to high or low values post-baseline were similar between the two treatment groups.

Clinical Chemistry
Based on pooled central and local lab data, the most frequent biochemistry clinically significant lab results were post-baseline blood urea nitrogen, creatinine, and potassium. In general, most subjects had normal biochemistry values at baseline and these values remained normal post-baseline for most patients in both treatment arms. Any shifts from normal at baseline to high or low values post-baseline were similar between the two treatment groups.

Serum Potassium
The incidence of clinically notable increase (>20% increase in Potassium and >ULN [or any value >6 mmol/L]) in serum potassium was comparable between LCZ696 (10.7%) and enalapril (11.7%). No patient in LCZ696 and enalapril had serum potassium >6.5 mEq/L at baseline; however, post-baseline serum potassium >6.5 mEq/L was assessed in 6 patients (3.21%) in the enalapril group and none in the LCZ696 group.

Liver Enzymes
Newly occurring liver enzyme elevations were mostly observed in Age Group 1 and were more frequent in the sacubitril /valsartan compared to enalapril. ALT>3xULN or AST>3xULN was reported in 4 (4.26%) patients treated with sacubitril/valsartan compared to 1 (1.11%) patient treated with enalapril. In the same age group, TBL>1.5xULN was reported in 5 (5.62%) patients in the LCZ696 group compared to 2 (2.20%) patients in the enalapril group.

Renal Parameters
The proportion of patients with renal events was lower in the LCZ696 group compared to the enalapril group (9.09% vs. 11.70%). Confirmed serum creatinine increase ≥50% versus baseline was noted in a lower proportion of subject in the LCZ696 group (1.07%) compared to the enalapril group (4.26%) and increase ≥25% and <50% versus baseline was noted in a similar proportion of subject in both the LCZ696 (7.49%) and enalapril (7.45%) groups. A similar trend in renal function assessment was observed in the three age groups.

Reviewer Comment: *Most clinically significant changes in biochemistry and hematology lab parameters were consistent between treatment groups. There were numerically more significant liver enzyme elevations for subjects treated with LCZ696, but the small dataset does not inform a new safety signal. Overall, the biochemistry changes described above are consistent with the known risk profile of both treatments.*

8.4.7. Vital Signs

Similar to lab assessment, the applicant pre-specified criteria for abnormal vital signs. For heart rate abnormalities, 51/150 (34.0%) of LCZ696 treated subjects and 49/139 (35.3%) of enalapril treated subjects had findings of clinically significant high or low heart rate. For systolic blood pressure (SBP), 100/164 (61.0%) of LCZ696 treated subjects and 74/172 (43.0%) of enalapril treated subjects had high or low SBP, with the imbalance primarily driven by low SBP findings for LCZ696. For diastolic blood pressure (DBP), the imbalance was also present, where 108/155 (70.0%) of LCZ696 treated subjects and 88/158 (54.4%) of enalapril subjects had high or low DBP findings. Again, low DBP measurements drove the increased incidence in the LCZ696 treated group.

Reviewer Comment: *The higher incidence of clinically significant low SBP and DBP measurements is expected based on the known strong antihypertensive effect of Entresto. Importantly, such findings did not appear to translate into a clinically significant imbalance for downstream organ dysfunction.*

8.4.8. Electrocardiograms (ECGs)

The applicant reports 3 (1.6%) LCZ696 treated subjects and 6 (3.2%) enalapril treated subjects had a clinically significant ECG abnormality, as reported by the Investigator. Further review of ECG findings in the LCZ696 treated subjects indicated no abnormality in one patient, increase in QRS duration (75 ms to 116 ms) in one patient, and a likely pre-existing QT prolongation secondary to prior congenital heart surgery.

Reviewer Comment: *No significant ECG findings with LCZ696 treatment in PANORAMA-HF.*

8.4.9. QT

Per the Entresto USPI, no cardiac repolarization abnormalities were noted in a thorough QTc clinical study in healthy male subjects. No pediatric specific abnormalities are expected.

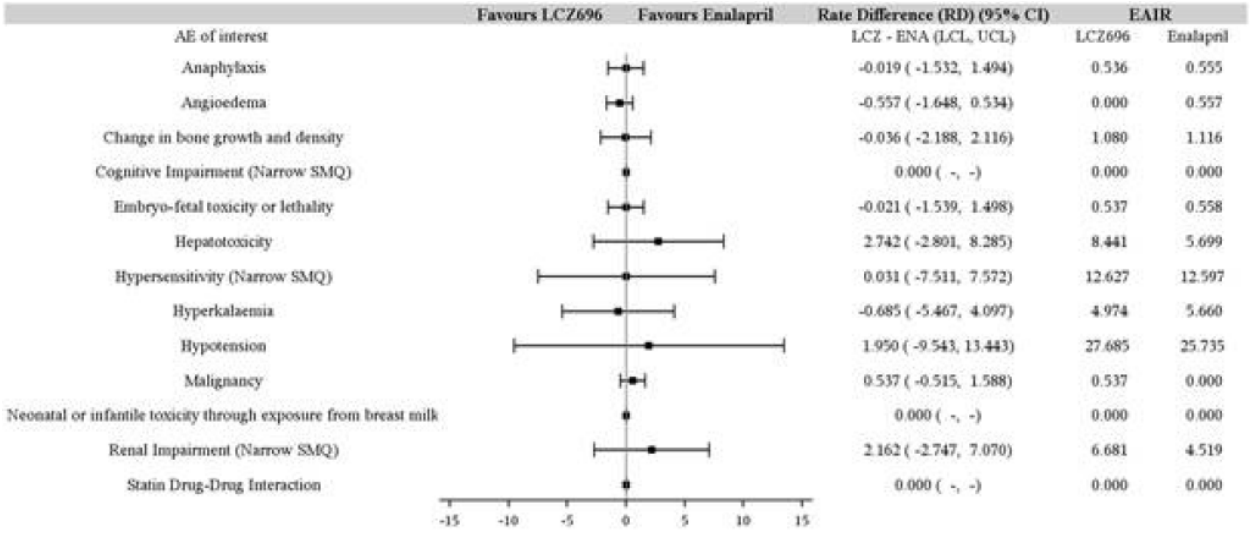
8.4.10. Immunogenicity

Not Applicable.

8.5. Analysis of Submission-Specific Safety Issues

Based on the known risk profile for Entresto, the applicant identified and assessed AESIs, inclusive of angioedema, embryo-fetal toxicity, hepatotoxicity, hyperkalemia, hypotension, and renal impairment. The applicant submitted a risk difference analysis and exposure-adjusted incidence rate (EAIR) analysis of AESIs, which shows comparatively similar rates (Figure 1Figure 7). A tabular representation of the underlying data is presented in Table 22.

Figure 7: Risk Difference (plus/minus 95% CI) and EAIR of AEs by AESI Grouping During Study B2319, Part 2 SAF



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

Source: Figure 2-2, Summary of Clinical Safety for Study B2319, Pg. 55

Table 22: Incidence and EAIR of Treatment Emergent AESIs in Study B2319, Part 2 SAF

	LCZ696 N=187		Enalapril N=188	
AESI	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**
Hypotension	43 (23.0)	27.7 (20.0, 37.3)	40 (21.3)	25.7 (18.4, 35.0)
Hyperkalemia	9 (4.8)	4.97 (2.28, 9.44)	10 (5.3)	5.66 (1.95, 8.90)
Renal Impairment (Narrow SMQ)	12 (6.4)	6.68 (3.45, 11.67)	8 (4.3)	4.52 (1.95, 8.90)
Angioedema	0	n/a	1 (0.53)	0.56 (0.01, 3.10)
Hepatotoxicity	15 (8.0)	8.44 (4.72, 13.92)	10 (5.3)	5.70 (2.733, 10.48)
Hypersensitivity	22 (11.8)	12.63 (7.91, 19.12)	21 (11.2)	12.60 (7.80, 19.26)
Change in Bone Growth and Density	2 (1.1)	1.08 (0.13, 3.90)	2 (1.1)	1.12 (0.14, 4.03)

Source: Adapted from Table 2-8, Study B2319 Integrated Summary of Safety, SCS Appendix 1a, Pg. 82-83

Reviewer Comment: *Overall, the above data suggest similar incidence of AESIs with LCZ696 and enalapril treatment. Renal impairment AESIs were predominantly mild in severity with the incidence of renal SAEs being low and comparable between the two groups (n=3, respectively, with treatment discontinuation occurring in n=1, respectively). For hepatotoxicity, most events were mild-to-moderate in severity (24/25 AEs) with one SAE in the enalapril treatment arm. However, 3 subjects treated with LCZ696 had treatment discontinuation secondary to hepatic function abnormalities; review of AE narratives lends some support for the events having potential relationship to HF disease progression. While there were numerical imbalances with more events for LCZ696 treated subjects for the AESIs of renal impairment and hepatotoxicity, the small dataset does not currently suggest a clinically significant safety signal. Furthermore, the approved Entresto USPI currently describes adverse reactions for angioedema, hypotension, impaired renal function, and hyperkalemia while recommending against use in patients with severe hepatic impairment. The lack of a significant safety signal for AESIs in PANORAMA-HF and current descriptions for adverse reactions in the Entresto USPI should be sufficient to mitigate potential risk.*

8.6. Safety Analyses by Demographic Subgroups

See Section 10.4

8.7. Specific Safety Studies/Clinical Trials

Not Applicable

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not Applicable

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported during Study B2319.

8.8.3. Pediatrics and Assessment of Effects on Growth

See Section 10.5. No differential effects on bone growth or density were reported in Study B2319.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Per the applicants Summary of Clinical Efficacy:

> *Up to the cut-off date of 31-Dec-2022, worldwide cumulative patient exposure since the International Birth Date (07-Jul-2015) is estimated to be approximately* (b) (4) *million patient treatment years. Considering pediatric patients only, 360 cases were identified worldwide, as of Periodic Safety Update Report (31 Jul 2022) and a comprehensive medical assessment of these cases revealed no new safety signal.*

8.9.2. Expectations on Safety in the Postmarket Setting

The listed adverse reactions in the current Entresto USPI are sufficient to provide guidance.

8.9.3. Additional Safety Issues From Other Disciplines

See Section 6.4.

8.10. Integrated Assessment of Safety

Per review of the full Study B2319 results, the safety profile of LCZ696 in pediatric patients remains similar to that reported for the approved product, Entresto, which is already marketed to adults with HFrEF and pediatric patients with HF and LVSD. The overall size and duration of the safety database are adequate to characterize the safety of LCZ696 in pediatric patients. Risks of hypotension, renal impairment, and hyperkalemia are not insignificant in a pediatric HF population, although these risks are well-described in adult HF patients and are adequately represented in the Entresto USPI. Per review of Study B2319 efficacy results on the NT-proBNP bridging biomarker, the clinical benefit of LCZ696 likely outweighs the potential risk of treatment in pediatric patients with HF.

9. Advisory Committee Meeting and Other External Consultations

Not Applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Proposed Label Revision

Final updates to the Entresto USPI arising from the NDA 207620/S-025 efficacy supplement (SE-8) submission are pending alignment between the applicant and DCN. However, our recommendation is to update the Section 14.2 description of the NT-proBNP bridging biomarker to describe the 52-week results of PANORAMA-HF as follows:

> *The efficacy of ENTRESTO was evaluated in a multinational, randomized, double-blind trial PANORAMA-HF comparing ENTRESTO (n = 187) and enalapril (n = 188) in pediatric patients aged 1 month to < 18 years old due to systemic left ventricular systolic dysfunction (LVEF ≤ 45% or fractional shortening ≤ 22.5%). Patients with systemic right ventricle, single ventricle, restrictive cardiomyopathy or hypertrophic cardiomyopathy were excluded from the trial.*

At Week 52, there were 144 ENTRESTO and 133 enalapril patients with a post-baseline assessment of NT-proBNP. The estimated least squares mean percent reduction from baseline in NT-proBNP was 65% and 62% in the ENTRESTO and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for ENTRESTO and enalapril were larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy.

Because ENTRESTO improved outcomes and reduced NT-proBNP in adults in PARADIGM-HF, the effect on NT-proBNP was the basis to infer improved cardiovascular outcomes in pediatric patients.

Interchangeability of ENTRESTO and ENTRESTO SPRINKLE

With the concurrent NDA 218591 submission for registration of the ENTRESTO SPRINKLE (oral pellets) dosage form, for which development of an age-appropriate dosage form was a requirement of the pediatric WR, we note that references throughout the shared Entresto/Entresto Sprinkle USPI to 'ENTRESTO' or 'ENTRESTO SPRINKLE' are considered to be interchangeable with respect to safety and efficacy. Recommended dosage as described in Section 2 of the USPI are specific to the named product/dosage form.

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is indicated for the pediatric HF with LVSD indication.

12. Postmarketing Requirements and Commitments

Not Applicable.

13. Appendices

13.1. Additional Efficacy

13.1.1. Ranking Algorithm Used to Derive the Primary Global Endpoint

Within Category 1, patients were first rank by the time first positively adjudicated Category 1 event, which was defined as the date of first positively adjudicated Category 1 event minus t the date of randomization plus one day.
If the patient did not have a positively adjudicated Category 1 event, then the patient would be evaluated to determine if the patient has at least one positively adjudicated Category 2 event occurred during the double-blind epoch.
If so, the patient would be sub-classified into three sub-categories (2-B (most severe) < 2-C < 2-D (less severe)), using the following criteria.

1. Category 2-B if the patient has at least one positively adjudicated Category 2-B event during the double-blind epoch.
2. Category 2-C if the patient has at least one positively adjudicated Category 2-C event during the double-blind epoch, and is not in Category 2-B.
3. Category 2-D if the patient has at least one positively adjudicated Category 2-D event during the double-blind epoch, and is not in Category 2-B or 2-C.

Within each patient-sub-category, patients would be ranked first by the number of positively adjudicated events in the corresponding sub-category (taking into consideration the worsening hierarchy of 2-B < 2-C < 2-D), and then by the time to first positively adjudicated event in the sub-category, which is defined as the date of the first positively adjudicated event in the subcategory minus the date of randomization plus one day.

If the patient does not have any category 1 or 2 events, they would be classified into Category 3 to 5 based on NYHA/ROSS class and PGIS at Week 52. Table 23 and Table 24 described the scores assigned to the combination of baseline score and post-baseline visit in NYHA/Ross class and PGIS respectively. Based on the combination of scores defined in each of the table,
The initial ranking score is obtained according to Table 25 using the scores from Table 23 and Table 24.

Table 23 Degree of change from baseline in NYHA/ROSS class

Degree of Change from Baseline		Post-Baseline Visit			
		Class I	Class II	Class III	Class IV
Baseline	Class I	0	-1	-2	-3
	Class II	+1	0	-1	-2
	Class III	+2	+1	0	-1
	Class IV	+3	+2	+1	0

Source: Table 2-8 of the statistical analysis plan

Table 24 Degree of change from baseline in PGIS

Degree of Change from Baseline		Post-Baseline Visit				
		None (Good)	Mild	Moderate (NGNB)	Severe	Very severe (Bad)
Baseline	None (Good)	0	-1	-2	-3	-4
	Mild	+1	0	-1	-2	-3
	Moderate (NGNB)	+2	+1	0	-1	-2
	Severe	+3	+2	+1	0	-1
	Very severe (Bad)	+4	+3	+2	+1	0

- NGNB = neither good nor bad

Source: Table 2-9 of the statistical analysis plan

Based on the degree of change defined above in Table 23 and Table 24, Table 25 defines an initial ranking score.

Table 25 Initial ranking score based on degree of change from baseline in NYHA/ROSS class and PGIS at Week 52

Initial Ranking Score		Degree of Change from baseline in PGIS at Week 52								
		-4	-3	-2	-1	0	+1	+2	+3	+4
Degree of Change from Baseline in NHYA/ROSS Class at Week 52	-3	1	2	4	7	10	14	18	22	26
	-2	3	4	6	9	13	17	21	25	28
	-1	5	7	9	12	16	20	24	27	29
	0	8	10	13	16	30	31	32	34	36
	+1	11	14	17	20	31	33	35	37	39
	+2	15	18	21	24	32	35	38	40	41
	+3	19	22	25	27	34	37	40	42	43

Source: Table 2-10 of the SAP

If the initial ranking score at Week 52 was lower than 30, the patient would be assigned into Category 3. If the initial ranking score at Week 52 was equal to 30, the patient would be assigned into Category 4. If the initial ranking score at Week 52 is higher than 30, the patient would be assigned into Category 5.

Within each of these categories, in the event of ties, a subset of the physical functioning domain based on patient reported PedsQL would be used to further rank patients at randomization from 6 years to < 18 years based on Table 26 and Table 27.

For each post-baseline visit, if there are three or more non-missing items, the PedsQL ranking score will be defined as the mean of the non-missing mapped values; if there are three or more missing items, the PedsQL ranking score will be considered as missing.

Patients with age at randomization from 1 month to < 6 years would not be further ranked by the patient reported PedsQL.

Table 26 PedsQL Ranking Items (Age at Randomization: 8 years to < 18 years)

Item ID	Item	Never	Almost Never	Some-times	Often	Almost Always
1	It is hard for me to walk more than one block	100	75	50	25	0
2	It is hard for me to run	100	75	50	25	0
3	It is hard for me to do sports activity or exercise	100	75	50	25	0
4	It is hard for me to lift something heavy	100	75	50	25	0
6	It is hard for me to do chores around the house	100	75	50	25	0

Source: Table 2-11 of the SAP

Table 27 PedsQL Ranking Items (Age at Randomization: 6 years to 7 years)

Item ID	Item	Not at All	Sometimes	A Lot
1	It is hard for you to walk	100	50	0
2	It is hard for you to run	100	50	0
3	It is hard for you to play sports activity or exercise	100	50	0
4	It is hard for you to pick up big things	100	50	0
6	It is hard for me to do chores (like pick up your toys)	100	50	0

Source: Table 2-12 of the SAP

For Category 1 and Category 2, patients will be classified into the worst possible category.

- A patient will be classified into Category 1 with event date imputed by the last known alive date (recorded on CRF page: “Survival Information”), or the date of last visit, whichever occurred later, if the patient discontinues from the study during the double-blind epoch without any positively adjudicated Category 1 event and with no available clinical endpoint information to refute classification into Category 1.
- A patient will be classified into Category 2 with event date imputed by the last known alive date (recorded on CRF page: “Survival Information”), or the date of last visit, whichever occurred later, if the patient discontinues from the study during the double-blind epoch without any positively adjudicated Category 1 and there is available and retrievable information for the patient that refutes classification into Category 1.

- Any positively adjudicated Category 2 event with its adjudicated sub-category missing will be classified into Category 2-B (Category 2-B: Worsening heart failure hospitalization with intensive care unit stay).
- If the event date of a positively adjudicated Category 1 event is missing, the event date will be imputed by the last known alive date (recorded on CRF page: "Survival Information"), or the date of last visit, whichever occurred later.
- If the event date of a positively adjudicated Category 2 event is missing, the event date will be imputed by the date of last visit.

13.1.2. Non-Standard Statistical Methodology for the Primary Endpoint

Let $N_{k,0}$ and $N_{k,1}$ be the number of patients in the Enalapril group and in the LCZ696 group in stratum k, $N_k = N_{k,0} + N_{k,1}$ be the total number of patients in stratum k, $k = 1, \ldots, K$.

Let $F_{N,k,0}$ and $F_{N,k,1}$ be the empirical cumulative distribution function for the response variable in the Enalapril group and in the LCZ696 group in stratum k, $F_{N,k} = (N_{k,0}/N_k) \times F_{N,k,0} + (N_{k,1}/N_k) \times F_{N,k,1}$ be the pooled empirical cumulative distribution function, $k = 1, \ldots, K$.

For stratum k, the Wilcoxon rank-sum statistic is

$$WRS_{N,k} = \frac{1}{2}N_{k,1} + \frac{1}{2}N_k^2 + N_{k,1}N_{k,0}\int \frac{1}{2}\left(F_{N,k,0}(x) + F_{N,k,0}(x^-)\right)dF_{N,k,1}(x)$$

With respective mean and variance under the null hypothesis

$$WRS_{N,k} = \frac{1}{2}N_{k,1} + \frac{1}{2}N_k^2 + N_{k,1}N_{k,1}\int \frac{1}{2}\left(F_{N,k,0}(x) + F_{N,k,0}(x^-)\right)dF_{N,k,1}(x)$$

where

$$Var_{N,k,0}^{NULL} = \int \left(\left(\frac{1}{2}\left(F_{N,k,1}(x) + F_{N,k,1}(x^-)\right)\right) - \frac{1}{2}\right)^2 dF_{N,k,0}(x)$$

$$Var_{N,k,0}^{NULL} = \int \left(\left(\frac{1}{2}\left(F_{N,k,1}(x) + F_{N,k,1}(x^-)\right)\right) - \frac{1}{2}\right)^2 dF_{N,k,0}(x)$$

The stratified Wilcoxon-rank-sum statistic is

$$WRS_N = \sum_{k=1}^{K} \frac{WRS_N}{N_k + 1}$$

Whose mean and variance are

$$Mean\ of\ WRS_N = \sum_{k=1}^{K} \frac{mean\ of\ WRS_{N,k}}{N_k + 1} = \frac{1}{2}\sum_{k=1}^{K} N_{k,1}$$

$$Variance\ of\ WRS_N = \sum_{k=1}^{K} \frac{variance\ of\ WRS_{N,k}}{N_k + 1} = \sum_{k=1}^{K} \left(\frac{N_{k,1}N_{k,0}}{N_k + 1}\right)^2 \left(\frac{V_{N,k,0}^{NULL}}{N_{k,0}} + \frac{V_{N,k,1}^{NULL}}{N_{k,1}}\right)$$

The test statistic is

$$WRS_N = \sum_{k=1}^{K} \frac{WRS_N}{N_k + 1}$$

Estimation of the MW probability

For stratum k, the MW probability within stratum k will be estimated by

$$MWP_{N,k} = \frac{WRS_{N,k} - N_{k,1}(N_{k,1} + 1)/2}{N_{k,1}N_{k,0}} = \int \frac{1}{2}\left(F_{N,k,0}(x) + F_{N,k,0}(x-)\right) dF_{N,k,1}(x)$$

With variance estimated by

$$MWP_{N,k} = \frac{V_{N,k,0}}{N_{k,0}} + \frac{V_{N,k,1}}{N_{k,1}}$$

Where

$$Var_{N,k,0}^{NULL} = \int \left(\left(\frac{1}{2}\left(F_{N,k,1}(x) + F_{N,k,1}(x-)\right)\right) - (1 - MWP_{N,k})\right)^2 dF_{N,k,0}(x)$$

$$Var_{N,k,1}^{NULL} = \int \left(\left(\frac{1}{2}\left(F_{N,k,0}(x) + F_{N,k,0}(x-)\right)\right) - (MWP_{N,k})\right)^2 dF_{N,k,1}(x)$$

The overall MW probability is defined as

$$MWP_N = \sum_{k=1}^{K} \frac{N_{k,1}N_{k,0}}{N_k + 1} MWP_k / \sum_{k=1}^{K} \frac{N_{k,1}N_{k,0}}{N_k + 1}$$

Whose variance is estimated by

$$Variance\ of\ MWP_N = \left[\sum_{k=1}^{K} \left(\frac{N_{k,1}N_{k,0}}{N_k + 1}\right)^2 Variance\ (MWP_{N,k})\right] / \left[\sum_{k=1}^{K} \frac{N_{k,1}N_{k,0}}{N_k + 1}\right]^2$$

The (1- α) CI for the overall MW probability is as

$$\left(\frac{1}{1+\exp\{\theta_N^U\}}, \frac{1}{1+\exp\{\theta_N^L\}}\right)$$

Where

$$\theta_N^L = \log\frac{1-MWP_N}{MWP_N} - \frac{\Phi^{-1}\left(1-\frac{\alpha}{2}\right)\left(Variance\ MWP_N\right)^{1/2}}{MWP_N(1-MWP_N)}$$
$$\theta_N^U = \log\frac{1-MWP_N}{MWP_N} + \frac{\Phi^{-1}(1-\alpha/2)\left(Variance\ MWP_N\right)^{1/2}}{MWP_N(1-MWP_N)}$$

with Φ^{-1} being the quantile function for the standard Gaussian distribution

The overall MW odds is estimated by $MWO_N = \frac{1-MWP_N}{MWP_N}$ and 1- α CI for MW odds given as $(\exp\{\theta_N^L\}, \exp\{\theta_N^U\})$.

13.2. References

Not Applicable

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): B2319

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 597 (US: 245, Non-US: 352)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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