CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	207620
Priority or Standard	Priority
Submit Date(s)	01 April 2019
Received Date(s)	01 April 2019
PDUFA Goal Date	01 October 2019
Division/Office	ODE1/DCaRP
Reviewer Name(s)	Shetarra Walker, MD, MSCR
Review Completion Date	19 August 2019
Established/Proper Name	Sacubitril/Valsartan
(Proposed) Trade Name	Entresto
Applicant	Novartis
Dosage Form(s)	Oral Tablet; Extemporaneous Oral Suspension
Applicant Proposed Dosing Regimen(s)	No Recommendation for Pediatric Dosing; No Change to Previously Approved Adult Dosing
Applicant Proposed Indication(s)/Population(s)	No Recommendation for a Pediatric Indication; No Change to Previously Approved Adult Indication
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

Table of Contents

Table of Tables

Table of Figures

Glossary

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
AGM	adjusted geometric mean
AGMR	adjusted geometric mean ratio
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CEC	clinical endpoint committee
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CPR	cardiopulmonary resuscitation
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CV	cardiovascular
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
FMI	final market image
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HR	hazard ratio
IA	interim analysis

IABP	intra-aortic balloon pump
IB	investigator brochure
ICU	intensive care unit
IRT	interactive response technology
IU	international units
L	liter
LLN	lower limit of normal
LLOQ	lower limit of quantification
LV	left ventricular/ventricle
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
MAED	MedDRA-based Adverse Event Diagnostics
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MTD	maximally tolerated dose
NDA	new drug application
NME	new molecular entity
NNT	number needed to treat
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PD	pharmacodynamics
PEA	pulseless electrical activity
PGIS	Patient Global Impression of Severity
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
PT	preferred term
QoL	quality of life
ROSC	return of spontaneous circulation
RS	randomized set
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan
SBP	systolic blood pressure
SoC	standard of care
SOC	system organ class
SUSAR	sudden unexpected serious adverse reaction
ULN	upper limit of normal

UNOS	United Network for Organ Sharing
URI	upper respiratory infection
US	United States
VAD	ventricular assist device
WHF	worsening heart failure
WR	Written Request

1. Executive Summary

1.1. Product Introduction

This review evaluates the efficacy and safety of LCZ696 (sacubitril/valsartan) oral tablets for treatment of HF in pediatric patients with DCM ages 1 to less than 18 years.

A first-in-class angiotensin receptor neprilysin inhibitor, sacubitril/valsartan was approved by FDA in 2015 under NDA 207620 for reduction of risk of cardiovascular death and hospitalization for HF in adult patients with chronic HFrEF. Novartis does not plan to market a new formulation of sacubitril/valsartan. However, in the study, Novartis provided an extemporaneous oral suspension or oral granules (b) (4) for use in children unable to swallow tablets. Novartis is not proposing to add a pediatric indication or pediatric dosing to labeling for sacubitril/valsartan.

1.2. Conclusions on the Substantial Evidence of Effectiveness

FDA waived pediatric study assessments under PREA but issued a WR in 2017 for a PK/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 (trial B2319, PANORAMA-HF), in 2019, we agreed to amend the WR to allow Novartis to fulfill the study requirement by submitting an IA to assess treatment effect on a bridging biomarker, NT-proBNP, in pediatric patients ages 1 to less than 18 years with HF due to DCM. We agreed to remove the infant cohort, ages 1 month to less than 1 year, from the WR because of rarity of DCM in infants. The trial is continuing after the IA, as described below.

Compared to enalapril, sacubitril/valsartan had a 15.6% greater reduction in NT-proBNP in pediatric HF patients with DCM ages 1 to less than 18 years. The primary efficacy endpoint result was not statistically significant, p=0.15. On the contrary, the sacubitril/valsartan adult HFrEF study, PARADIGM-HF, demonstrated a clinically meaningful and statistically significant reduction in risk for CV death and HF hospitalization correlated with significant NT-proBNP reduction compared to enalapril. We relied on PARADIGM-HF data to support use of NT-proBNP as a bridging biomarker assuming a true treatment effect of 30% reduction in NT-proBNP.

The IA data are not adequate to support a pediatric indication for HF treatment. However, B2319 is ongoing with plans to collect clinical outcomes data over a 52-week duration. In a resubmission to support labeling for a pediatric HF indication, Novartis must demonstrate a clinically meaningful benefit in pediatric patients based on primary efficacy endpoint data supported by secondary endpoint data including biomarkers and functional assessments. Enalapril is considered SoC therapy for pediatric HF but is not labeled by FDA for this indication.

Therefore, the expected treatment effect of enalapril on NT-proBNP in pediatric HF patients is unknown – a fact that complicates data interpretation of primary efficacy results.

Compared to the effect of sacubitril/valsartan on reduction of NT-proBNP in adults with DCM, children in the LCZ696 arm of B2319 had a similar within-group reduction in NT-proBNP. Yet, the study failed to show a statistically significant comparative reduction in NT-proBNP comparing enalapril and LCZ696. The lower than expected treatment effect of LCZ696 on NT-proBNP compared to enalapril could be explained by better than expected treatment effect by enalapril on NT-proBNP in children than observed in PARADIGM-HF. It is also plausible that LCZ696 has an inferior treatment effect on NT-proBNP in children compared to adults with DCM. Therefore, I do not believe one can determine that this product is efficacious in children by attempting to interpret results of a bridging biomarker outside the scope of pre-specified assumptions used to support use of NT-proBNP biomarker for this IA. Considering the potentially harmful risks of this combination product, I cannot conclude there is an obvious clinical benefit outweighing the potential risks of use in pediatric HF patients. I do not recommend labeling this product for use in pediatric patients based on the results of this IA.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Pediatric DCM is serious and life-threatening with one therapy approved for this indication but only for a subpopulation of pediatric DCM with HF. Unlike in adult studies, effectiveness based on 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 an IA in a pediatric study in children with DCM and HF ages 1 to less than 18 years. The results of study B2319 did not show a clinically meaningful reduction in NT-proBNP in the sacubitril/valsartan group compared to enalapril. Therefore, I cannot conclude there is a clinically meaningful benefit from treatment with sacubitril/valsartan in pediatric patients with DCM and HF. However, there were no new or unexpected safety findings in pediatric patients studied.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DCM is an intrinsic disease of heart muscle with resultant 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 American is 44 per million per year in infants, younger than 1 year, and 3.4 per million per year in children 1 to 18 years of age • Etiology, pathophysiology, and symptoms of DCM, including edema, dyspnea, and exercise intolerance, generally overlap between adults and children • Pediatric DCM patients are at 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. To date, there are no approved therapies for pediatric HF associated with DCM. Therefore, there is an unmet need for medical therapies.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td><u>Current Treatment Options</u></td><td>• Off-label use of medications with adult HF indications are typically used to treat pediatric DCM/HF including ACEI, angiotensin receptor blockers, beta-blockers, aldosterone antagonists, and diuretics</td><td>To date, there is one approved therapy for use in pediatric patients with HF due to DCM, ivabradine oral solution and tablet. However, ivabradine is labeled for use in a subgroup of pediatric HF patients with DCM, baseline elevated heart rate. There continues to be an unmet need for approved therapies.</td></tr>
<tr><td><u>Benefit</u></td><td>Primary Efficacy Endpoint – NT-proBNP Reduction
<table>
<tr><th colspan="2">LCZ696
N=55</th><th colspan="2">Enalapril
N=55</th><th colspan="3">Comparison- LCZ696 versus Enalapril</th></tr>
<tr><th>Estimate AGM RTB n=54</th><th>95% CI</th><th>Estimate AGM RTB n=54</th><th>95% CI</th><th>Estimate AGMR</th><th>95% CI</th><th>p-value</th></tr>
<tr><td>0.565</td><td>(0.48, 0.67)</td><td>0.67</td><td>(0.57, 0.79)</td><td>0.84</td><td>(0.67, 1.06)</td><td>0.15</td></tr>
</table></td><td>Sacubitril/valsartan treatment did not demonstrate a statistically significant reduction in NT-proBNP compared to enalapril in pediatric DCM patients with HF.</td></tr>
<tr><td><u>Risk and Risk Management</u></td><td>In general, AEs observed in this study are consistent with the safety profiles for both study treatments.</td><td>Compared to adult PARADIGM-HF data, there were no new safety signals identified in this pediatric study.</td></tr>
</table>

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 6.1.2
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Section 6.1.2
		☐	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 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, ECMO, or cardiac transplantation. However, neurohormonal pathophysiologic derangements are sufficiently similar between children and adults with DCM to expect similar responses to HF therapies targeting these neurohormonal pathways. To date, there are no published recommendations for differences in SoC therapeutic options based on gender or racial differences.

2.2. Analysis of Current Treatment Options

To date, there is one approved drug, ivabradine oral solution/tablet, indicated for treatment of pediatric HF due to DCM, but only for patients with sinus rhythm and baseline elevated heart rate. Drug therapeutic classes approved in adults for chronic HFrEF include diuretics, ACEIs, ARBs, aldosterone antagonists, beta blockers, digoxin, anti-arrhythmics, and anti-coagulants. Most of these drug therapies 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, sacubitril/valsartan is marketed in 109 countries for the same indication as in the US, reduction of CV death and HF hospitalization in patients with chronic HFrEF. As of July 2018, the cumulative post-marketing patient exposure is estimated to be about 0.6 million patient-treatment years. Approximately (b) (4) patients have received sacubitril/valsartan treatment in Novartis-sponsored clinical trials since 2007. Novartis's pediatric study was conducted in accordance with a WR agreement. (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 (sacubitril/valsartan) oral tablet, NME 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
- 01 April 2019: Submission of NDA 207620 efficacy supplement 13, subject of this review
- 15 May 2019: T-Con with Novartis to discuss whether the data submitted might be adequate enough to support labeling sacubitril/valsartan for a pediatric HF indication
- 29 May 2019: Novartis provided current enrollment numbers since database lock for this submission and enrollment projections for Study B2319
- 23 Jul 2019: IR response with summary information about changes in diuretic dosing in the FAS
- 25 Jul 2019: Novartis submitted a 120-day Safety Update Report

Reviewer Comments: *During the May 2019 T-Con with Novartis, we informed Novartis that, at this early stage in the review, we acknowledge that the efficacy results are not statistically significant. However, we explained to Novartis that we are open to considering if there is additional information that can be provided by Novartis or additional analyses that could support a labeled indication for treatment of pediatric HF.*

Table 1: Requirements of Pediatric Written Request

WR Section	Requirement
Required Study(ies)	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.

WR Section	Requirement
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.

WR Section	Requirement
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.

WR Section	Requirement
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.
Extraordinary Results	• If in the course of conducting the study, evidence indicating 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.

Reviewer Comments:

- *Additional requirements in the WR pertaining to timeframe for submitting reports, labeling, format, types of reports to be submitted, and response to WR are consistent with standard FDA templated language.*
- *The sponsor has reasonably fulfilled all requirements of the WR.*

3.3. Foreign Regulatory Actions and Marketing History

Sacubitril/valsartan oral tablets are not approved or marketed for children in any country.

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

4.1. Office of Biostatistics

In Dr. Zhang's review, dated 05 August 2019, she noted that both treatment groups showed that NT-proBNP decreased from baseline but there was no statistically difference between treatment groups. Dr. Zhang concluded there can be potentially different interpretations of the date with uncertainty if LCZ696 demonstrates any clinical benefit in pediatric patients given the smaller ratio reduction in NT-proBNP compared to adult HFrEF patients. Dr. Zhang recommended against approval of the pediatric indication based on the biomarker IA.

4.2. Office of Scientific Investigations (OSI)

An OSI audit was not requested.

Reviewer Comment: *The largest study site enrolled six subjects in the FAS. There was no concern that a single site drove the overall results. Novartis Global Development Quality conducted investigator site audits at seven sites, six in the US and one in Korea. The Bulgarian Drug Agency inspected one site in Bulgaria.*

4.3. Product Quality

The drug product used in the clinical drug development program is the same as the marketed product, sacubitril/valsartan 50 mg (24/26 mg), 100 mg (49/51 mg), and 200 mg (97/103 mg) film-coated tablets. For patients unable to swallow film-coated tablets or taking <25 mg of study drug, Novartis provided alternate dosage forms -- oral pellets 3.125 mg (1.52/1.61 mg) and an extemporaneous liquid suspension in 1 mg/mL (0.49/0.51 mg/mL) and 4 mg/mL (1.96/2.04 mg/mL) concentrations made from crushed sacubitril/valsartan oral tablets dispersed in commercially available vehicles i.e. OraPlus® and Ora-Sweet SF (sugar free)®. CMC sent an IR on 31 July 2019 requesting additional dissolution data to which Novartis responded on 07 August 2019. The CMC review is pending at time of this review. However, there were no major product quality issues raised during this review cycle that would affect approvability or clinical conclusions on efficacy or safety.

4.4. Clinical Microbiology

The Clinical Microbiology review is pending at time of this review. However, there were no major microbiology issues raised during this review cycle that would affect approvability or clinical conclusions on efficacy or safety.

4.5. Nonclinical Pharmacology/Toxicology

Novartis previously submitted nonclinical studies including juvenile studies under NDA 207620. Juvenile nonclinical studies were conducted only with the individual components of this combination product. Juvenile nonclinical studies could not be conducted with sacubitril/valsartan because of the dose limiting renal toxicity of valsartan. However, juvenile

nonclinical studies with valsartan were submitted to support the valsartan pediatric indication for hypertension (NDA 21283).

Juvenile nonclinical studies for sacubitril/valsartan oral tablets were previously reviewed under NDA 207620 by Dr. William Link, dated 15 May 2015. Dr. Link concluded that juvenile nonclinical study results suggest that sacubitril/valsartan may impact bone growth and impair bone and kidney development. Observed kidney changes in juvenile animals were only relevant to the valsartan component of the drug and most relevant to children under one year of age. Bone changes, most relevant to the sacubitril component, were generally transient and reversible. There were no nonclinical approvability issues discussed during this review cycle.

4.6. Clinical Pharmacology

The clinical pharmacology review is pending.

4.7. Devices and Companion Diagnostic Issues

Not Applicable.

4.8. Consumer Study Reviews/ Division of Medication Error Prevention and Analysis (DMEPA)

Not Applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Pertinent Studies

The studies included in this submission are summarized in Table 2.

Table 2: Listing of Clinical Trial(s) Relevant to this Efficacy Supplement to NDA 207620

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Study to Support Efficacy and Safety							
CLCZ696B2319 (Ongoing)	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 systolic dysfunction (Part 2) Interim Analysis to Assess for Change in NT-proBNP from baseline to Week 12 completed in pediatric patients with HF due to DCM, ages 1 to <18 years	**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 Oral Extemporaneous Suspension	**Pharmacokinetics** **Part 1** PK: Cmax,Tmax, AUC, Clearance, and T1/2. PD: Plasma cGMP, urine cGMP, BNP, NTproBNP **Part 2** Population PK and sparse PK **Efficacy** **Part 2** -change from baseline in NTproBNP, -Clinical events (Category 1: Death UNOS status 1A listing for heart transplant or equivalent; VAD / ECMO / mechanical ventilation/intraaortic balloon pump requirement	**Part 1** Open label single or two doses **Part 2** 52 weeks double blind treatment	110	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	60 centers in 19 countries (including US)

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		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	for life 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				
Other studies pertinent to this review							
CLCZ696B2314	A multicenter, randomized, double-blind, parallel group, active-controlled study to	**LCZ696** Film-coated Oral tablets: 50 mg (24/26	**Efficacy** Primary composite endpoint • CV death	Run-in: 5-10 weeks Double	8442 patients randomized	Males and females aged 18 years or older, CHF	984 centers in 47 countries

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction	mg), 100 mg (49/51 mg), 200 mg (97/103 mg) Matching placebo Target dose -- 200 mg bid given orally Enalapril Oral Tablets: 2.5mg, 5mg, 10 mg Target dose -- 10 mg bid given orally Matching placebo	• HF hospitalization **Safety** AEs, SAEs, msSBP, msDBP, PE, vital signs, height, weight, blood chemistry, hematology, urinalysis, ECG, pregnancy test, angioedema	Blind Period: event-driven until 2410 primary events reached or early termination of trial		(NYHA class II - IV), with LVEF ≤ 40%, changed to ≤ 35% by Protocol Amendment 1; BNP ≥ 150 pg/ml (or NT-proBNP ≥ 600 pg/ml) OR BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/ml) and a hospitalization for HF within the last 12 months; history of stable dose of ACEI or ARB and B-blocker (if tolerated)	
CLCZ696F2130	Open-label, randomized, two-treatment, two-period crossover, single-dose, study in healthy subjects to determine the relative bioavailability of the liquid formulation compared to	**LCZ696** 3.125 mg mini tablet and 200mg FMI tablet Treatment A: LCZ696 200mg oral liquid	PK and safety	9 days on treatment	28	Healthy adult males	1 center

Protocol Number/ Report Number	Trial Design	Dosage regimen; Route of administration	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	the final market image (FMI) tablet formulation of LCZ696 200 mg dose after single oral administration under fasting conditions	formulation Treatment B: LCZ696 200 mg oral FMI tablet **Doses** single dose on days 1 and 6					

5.2. Review Strategy

WR requirements were scrutinized to determine if Novartis met the terms of the WR. Efficacy and safety data were summarized. Analyses of AEs were performed using MAED Release Version 1.10.1. The coding from verbatim to MedDRA PTs for AEs was verified.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CLCZ696B2319 (B2319)

6.1.1. Study Design

Overview and Objective

Study B2319 is a two-part multicenter study conducted in pediatric patients with DCM and HF, ages 1 to less than 18 years, with determination of PK-PD of sacubitril/valsartan in Part 1; and randomized, double-blind, parallel group, active-controlled efficacy and safety compared to enalapril in Part 2. Efficacy data reviewed in this submission are from an IA in a subset of pediatric HF patients with DCM and baseline and Week 12 assessments for NT-proBNP, a bridging biomarker.

Reviewer Comment:

- *Enrolled patients were expected to be on optimal SoC medical and non-medical treatments for HF and comorbidities.*
- *Novartis chose enalapril as a comparator in this pediatric study because it is the most commonly used RAAS blocker in children with HF. Furthermore, Novartis considers enalapril as SoC in the treatment of chronic HF in most geographic areas and twice daily dosing of enalapril is similar to LCZ696.*
- *Sixty centers in 19 countries participated with the majority of study sites located in the US.*

Trial Design

Part 1
To be eligible for Part 1, patients must have been taking an ACEI/ARB (at any dose) prior to study.

All patients underwent a minimum 36-hour washout of their ACEI prior to receiving LCZ696 to minimize angioedema risk. Patients on baseline ARBs or renin inhibitor were required to discontinue these therapies by the morning of their single dose PK/PD visit. Age Group 3 patients (ages 1 month to less than 1 year) were to receive a single dose of 0.4 mg/kg followed

by a single dose of 1.6 mg/kg or 0.8 mg/kg followed by a single dose of 3.1 mg/kg in Age Groups 1 and 2 (ages >1 year). The low-dose phase of Part 1 was referred to as Period 1 Epoch and the high-dose phase was referred to as Period 2 Epoch.

Part 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 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. Novartis provided a copy of randomization codes in this submission. Because the study is ongoing, 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 will not be involved in other trial conduct activities.

Blinding

Because tablets, granules (minitabs), 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.

Reviewer Comment: *In the original version of the protocol, caregivers were expected to prepare the LCZ696 oral solution at home with instructions provided by the pharmacy. The protocol was subsequently modified to only allow preparation of LCZ696 oral solution at on site pharmacies.*

Dose Modification/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 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.

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

Concomitant Medication
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.

Treatment Compliance
Compliance was assessed by Investigators and/or study personnel using pill counts, liquid study medication assessment, and information provided by caregiver. Investigators and/or study personnel were to counsel patients and caregivers if compliance was below 80% at any time during the study.

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.

Administrative Structure
An external and independent DMC evaluated unblinded data during the course of the study. In addition to the IA in this submission, the DMC will review data from a futility analysis when at least 50% of patients and at least 36 patients from each age group have completed the study. The DMC and a PK/PD review committee were responsible for reviewing Part 1 PK data and dose determination for Part 2 (Efficacy).

Two adjudication committees were involved in the study: CEC and Angioedema Adjudication Committee. The CEC was responsible for adjudicating all clinical events that could potentially fulfill criteria for primary, secondary, or other endpoints including death, worsening HF, and mechanical ventilation. The Angioedema Adjudication Committee received completed CRFs for an angioedema adjudication. These CRFs were not considered substitutes for SAE reports.

Part 2 Study 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 3.

Table 3: 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 CSR for Study B2319, p46.

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 4.

Table 4: 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.

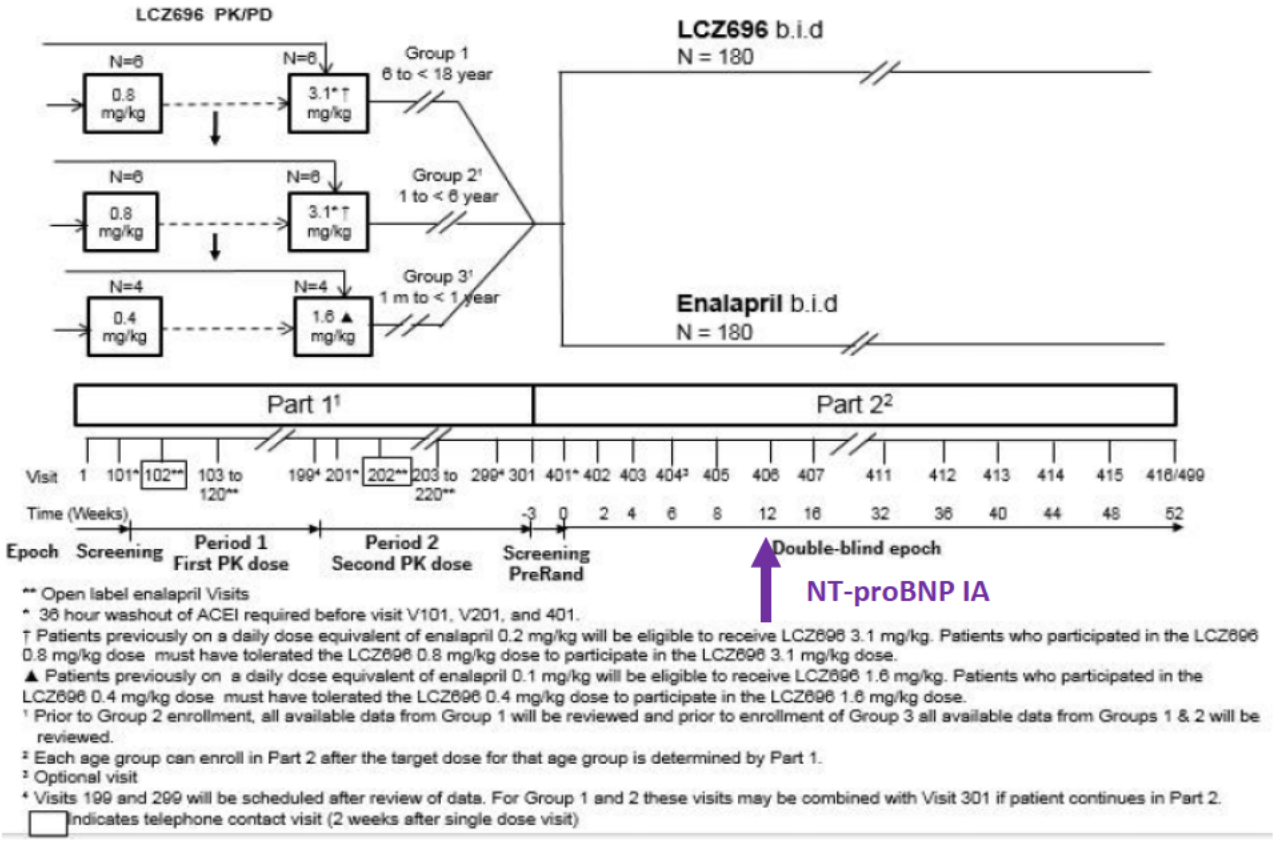
Source: Sponsor's Table 3-3 in Study Protocol (Amendment 4) for Study B2319, p37.

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.

Sparse PK sampling was performed in a cohort of 24 Age Group 2 patients.

A schematic of the study design for B2319 is shown in Figure 1 below.

Figure 1: Study Design of B2319



Source: Figure 3-1 in Protocol for Study CLCZ696B2319.

Reviewer Comments:

- *Novartis 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 renin angiotensin system inhibition compared to LCZ696 1.6 mg/kg and 3.1 mg/kg, respectively. For patients not taking enalapril, Novartis provided investigators with a chart containing the minimum required body-weight normalized daily dose of commonly prescribed ACEIs and ARBs prior to being dosed with LCZ696 1.6 mg/kg or 3.1 mg/kg.*
- *As a term in the WR, the Division reviewed Part 1 PK and safety information to agree on dosing prior to enrollment of Age Groups 1 and 2 into Part 2.*
- *Other aspects of the trial design as summarized above are acceptable.*

Study Objectives

Primary objectives of this study:

- (Part 1) To determine the PK and PD of sacubitril/valsartan in pediatric HF patients with systemic LV 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 HF in pediatric patients due to systemic LV systolic dysfunction, consistent with DCM

Secondary objectives: None.

Exploratory objectives:

- To explore the number of patients with at least one Category 1 event and with at least one Category 2 event in each treatment group
- To explore the NYHA/ROSS class change in each treatment group (a measure of functional status)
- To explore the PGIS score change in each treatment group
- To explore the PedsQL in each treatment group
- To explore the PGIC score in each treatment group
- To evaluate the safety and the tolerability of LCZ696 compared to enalapril
- To characterize the population PK of LCZ696 exposure in pediatric HF patients

Study Endpoints

Primary Efficacy: Change from baseline in NT-proBNP (log scale) at Week 12

Exploratory

- Category 1 event: death; UNOS status 1A listing for heart transplant or equivalent; VAD/ECMO/mechanical ventilation/IABP requirement for life support

  Category 2 event: WHF - defined by signs and symptoms of WHF that requires intensification of HF therapy with or without hospitalization
- Change from baseline in NYHA/ROSS class: Measure of functional status
- Change from baseline in PGIS score
- Change from baseline in PedsQL total summary score
- PGIC score
- Frequency of AEs, SAEs, and laboratory abnormalities
- PK parameters

Reviewer Comments: *Study B2319 is on ongoing study with plan for 52-week treatment duration in Part 2 and randomization of 360 patients ages 1 month to less than 18 years. A second IA is planned when at least 180 patients have completed the study and at least 40 patients have had a Category 1 or 2 event. Part 2 will stop when at least 360 patients have completed the study and, at least 80 patients have had a Category 1 or 2 event. The IA for the NT-proBNP bridging biomarker was added to Protocol Amendment 4 dated 04 Feb 2019 after agreement by the Division to amend the WR such that this IA would fulfill the study requirements.*

Statistical Analysis Plan

Refer to the statistical review by Dr. Jialu Zhang dated 05 August 2019 for detailed SAP evaluation.

The primary efficacy variable was analyzed using an ANCOVA model in which the response variable was the change from baseline in log(NT-proBNP) at Week 12. Age group, NYHA/ROSS class group at randomization, region and treatment group were included as fixed-effect factors. Baseline log(NT-proBNP) and age-group-by-baseline-log(NTproBNP) interaction were included as covariates. Based on the ANCOVA model, the estimate and the 95% CI were provided for the AGMs for ratio to baseline in NT-proBNP at Week 12 in each of the two treatment groups, and for the AGMR (LCZ696 / enalapril) at Week 12. The primary hypothesis testing was performed with a two-sided alpha of 0.05. The primary efficacy endpoint was analyzed using the FAS. All patients with missing baseline NT-proBNP values were excluded from efficacy analyses.

Handling of Missing Data

Novartis describes multiple approaches for imputation of missing data in their IA SAP submitted on 07 Feb 2019 under IND 104628. In brief, efficacy data from permanently discontinued patients due to AEs were handled by a controlled multiple imputation approach based on pattern mixture models. In this approach, patients in the LCZ696 group were assumed to behave like patients in the enalapril group after study treatment discontinuation with data imputed based on data from patients in the enalapril group according to age group. For patients without a NT-proBNP assessment at Week 12, non-missing NT-proBNP assessment obtained after Week 4 and closest to the target date of Week 12 + 84 days was used to impute the missing value at Week 12. For missing NT-proBNP data at Week 12, Novartis used a multiple imputation approach based on the MAR assumption.

Part 1 (PK/PD)

All concentrations below the LLOQ or missing were labeled as such in line listings. Concentrations below the LLOQ were treated as zero in summary statistics and for PK parameter calculations.

Part 2 (Efficacy) IA

In order to explore the robustness of the MAR assumption on the primary analysis, a sensitivity analysis was carried out which assessed cases where the data were missing not-at-random. As an additional supportive analysis, the primary analysis approach was performed using all patients with non-missing baseline NT-proBNP > 25 pg/mL.

The following analyses were performed after unblinding:

- Subgroup analyses for randomization strata variables – age group, NYHA/ROSS class
- Subset of patients with both baseline and 12-week data available (complete cases)
- Subset of patients who did not discontinue treatment before week 12

Protocol Amendments
The original protocol was finalized on 19 November 2015. The protocol was amended four 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 BNP to Part 1
  Addition of urine 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 and 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 timing
- Clarification of Visit 4A timing
- Clarification of height measurement

Amendment 4 (04 February 2019 – Part 1 Age Group 3 ongoing; Part 2 – 144 patients randomized)

- Addition of an interim biomarker analysis for NT-proBNP

Reviewer Comments:

- *These protocol amendments are appropriate and are not expected to affect the interpretation of trial results.*
- *For Japan sites, an Amendment 2 dated 05 September 2017 included changes to the protocol as required by the Japanese Health Authority. These changes included addition of an extra clinical visit to Part 2 and addition of treatment guidelines for hyperkalemia.*

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with principles of GCP, including the archiving of essential documents. Before initiation of the study, investigators and their staff were required to allow Novartis to review protocol requirements and CRFs. During the study, Novartis 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. Novartis used automatic validation procedures to check for data discrepancies during and after data entry. Furthermore, Novartis 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 Novartis reviewed Part 1 PK/PD data and dose determination for Part 2.

Financial Disclosure

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

Reviewer Comment: *No disclosable financial information was reported by any of the clinical investigators participating in the trial.*

Patient Disposition
The majority of patients described in Part 2 FAS and SAF populations below are still enrolled in the study as the study is ongoing.

Part 1
Eighteen (18) patients were enrolled with nine (9) in Age Group 1 (6 to less than 18 years) and nine (9) patients in Age Group 2 (1 to less than 6 years). In Age Group 1, there was a balanced representation of adolescents and younger children with five (5) patients at least 12 years of age and four (4) patients younger than 12 years of age.

Reviewer Comment: *As of 15 July 2019, five patients in Age Group 3 (1 month to less than 1 year) have been enrolled in Part 1. Of these five patients, four received low dose study drug, 0.4 mg/kg/dose, and two patients have received the high dose of study drug, 1.6 mg/kg/dose.*

Part 2
FAS Population

One hundred ten (110) patients ages 1 to less than 18 years of age were randomized 1:1 to either LCZ696 or enalapril. Thirteen (11.8%) of patients prematurely discontinued from the study with the most common reasons reported as death [2/55 (3.6%) and 4/55 (7.3%) patients in LCZ696 and enalapril groups, respectively] and patient/guardian decision [3/55 (5.5%) patients in each group]. Seventeen (15.5%) patients discontinued study treatment, 7 (12.7%) patients in LCZ696 group versus 10 (18.2%) patients in enalapril group. The most common reason for study treatment discontinuation was death with 6/55 (10.9%) patients in each group. Table 5 below contains a summary of patient disposition for the FAS.

Table 5: Patient Disposition (Part 2 FAS)

Overall Disposition/Reason	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Completed double-blind epoch	8 (14.5)	5 (9.1)	13 (11.8)
Discontinued double-blind epoch	5 (9.1)	8 (14.5)	13 (11.8)
Double-blind epoch ongoing	42 (76.4)	42 (76.4)	84 (76.4)
Primary reason for premature discontinuation of double-blind epoch			
Death	2 (3.6)	4 (7.3)	6 (5.5)
Physician decision	0 (0.0)	1 (1.8)	1 (0.9)
Subject/guardian decision	3 (5.5)	3 (5.5)	6 (5.5)
Received at least one dose of double-blind study treatment	55 (100)	55 (100)	110 (100)
Completed double-blind study treatment *	8 (14.5)	4 (7.3)	12 (10.9)
Discontinued double-blind study treatment	7 (12.7)	10 (18.2)	17 (15.5)
Double-blind study treatment ongoing	40 (72.7)	41 (74.5)	81 (73.6)
Primary reason for premature discontinuation of study treatment			
Adverse event	6 (10.9)	6 (10.9)	12 (10.9)
Death	0 (0.0)	1 (1.8)	1 (0.9)
Subject/guardian decision	1 (1.8)	3 (5.5)	4 (3.6)

Source: Table 14.1-1.1
The percentages are out of N.
* Includes 3 patients (2 in LCZ696, 1 in Enalapril) who completed the double-blind treatment period and had a missing End of study treatment record.

Source: Sponsor's Table 14.1-1.1 in CSR for Study B2319.

Reviewer Comment: *Patients randomized after 14 November 2018 were not included in the FAS for this IA. As of 15 July 2019, 203 patients have been randomized into Part 2 with 136 patients in Age Group 1 and 67 patients in Age Group 2. One hundred sixty-five (165) patients (116 in Age Group 1 and 49 in Age Group 2) have completed their Week 12 NT-proBNP assessment.*

Safety Set (SAF)

One hundred forty-three (143) randomized patients who received at least one dose of study drug were included in the SAF. Thirteen (9.1%) prematurely discontinued from this epoch with 5 (6.8%) and 8 (11.4%) patients in LCZ696 and enalapril groups respectively. The most common reasons for discontinuation from the epoch was death [2/73 (2.7%) and 4/70 (5.7%) patients in LCZ696 and enalapril groups, respectively] and patient/guardian decision [3 (4.1-4.3%) patients in each group]. Eighteen patients (12.6%) prematurely discontinued study treatment with 8 (11.0%) and 10 (14.3%) patients in LCZ696 versus enalapril groups. The most common reason for premature study treatment discontinuation was AE in 7 (9.6%) and 6 (8.6%) patients in

LCZ696 and enalapril groups, respectively. The disposition of patients in the SAF and reasons for discontinuation are summarized in Table 6 below. See Section 8 for a summary of AE data.

Table 6: Summary of Patient Disposition and Reasons for Discontinuation (Part 2 SAF)

Overall

Disposition/Reason	LCZ696 N=73 n (%)	Enalapril N=70 n (%)	Total N=143 n (%)
Completed double-blind epoch	8 (11.0)	5 (7.1)	13 (9.1)
Discontinued double-blind epoch	5 (6.8)	8 (11.4)	13 (9.1)
Double-blind epoch ongoing	60 (82.2)	57 (81.4)	117 (81.8)
Primary reason for premature discontinuation of double-blind epoch			
Death	2 (2.7)	4 (5.7)	6 (4.2)
Physician decision	0 (0.0)	1 (1.4)	1 (0.7)
Subject/guardian decision	3 (4.1)	3 (4.3)	6 (4.2)
Completed double-blind study treatment *	8 (11.0)	4 (5.7)	12 (8.4)
Discontinued double-blind study treatment	8 (11.0)	10 (14.3)	18 (12.6)
Double-blind study treatment ongoing	57 (78.1)	56 (80.0)	113 (79.0)
Primary reason for premature discontinuation of study treatment			
Adverse event	7 (9.6)	6 (8.6)	13 (9.1)
Death	0 (0.0)	1 (1.4)	1 (0.7)
Subject/guardian decision	1 (1.4)	3 (4.3)	4 (2.8)

Source: Table 14.1-1.2
The percentages are out of N.
* Includes 3 patients (2 in LCZ696, 1 in Enalapril) who completed the double-blind treatment period and had a missing End of study treatment record.

Source: Sponsor Table 14.1-1.2 in CSR for Study B2319.

Treatment for five (3.4%) patients were unblinded by investigational sites with three (2.1%) patients unblinded by physician for medical reasons, one (0.7%) patient unblinded due to parent request, and one (0.7%) patient unblinded in error by a site research pharmacist. For the patient unblinded in error, the CRA became unblinded but no one else at the site nor Novartis was unblinded. The site research pharmacist and the CRA were replaced with blinded personnel. The patient continued in the study in a blinded fashion.

Reviewer Comments:

- *Patients who received a first dose of study treatment after 31 January 2019 or who received no double-blind study treatment were not included in the SAF for this IA.*
- *Overall, in Part 2 FAS and SAF, slightly more patients discontinued from the study or study treatment in the enalapril treatment group. The proportion of patients among reasons for discontinuation from the study or study treatment were similar between*

treatment groups except for death that occurred up to two times more often in the enalapril group as shown in Tables 5 and 6 above. Proportional differences in reasons for study or treatment discontinuation between treatment groups are not expected to significantly affect safety or efficacy conclusions.

Protocol Violations/Deviations

Because Study B2319 is ongoing, interpretation of protocol deviation data is limited. Overall, 23 (15.2%) patients in the RS (n=151) had protocol deviations, 11 (7.3%) in the LCZ696 group and 12 (7.9%) in enalapril group. In the LCZ696 group, 8/11 (72.7%) and all in the enalapril group were in Age Group 1. Protocol deviation categories included selection criteria not met, treatment deviation, prohibited concomitant medication, and other i.e. broken blind. There were no protocol violations in this study.

Reviewer Comments: *Because there is a similar number of patients with protocol deviation between treatment groups, I would not expect a significant effect on safety conclusions. I cannot conclude whether NT-proBNP data, if collected, from patients excluded from the RS would have affected the efficacy results.*

Demographic Characteristics

As shown in Table 7, patient demographic characteristics in the FAS were similar for most characteristics. In Age Group 1 there was a higher proportion of adolescent patients compared to patients younger than 12 years of age in the enalapril group compared to LCZ696, 61.8% versus 50.9%, respectively. In the enalapril group, there was a higher proportion of males, 58.2%, compared to LCZ696 group, 45.5%. Differences in proportions of racial groups and ethnicity were observed between groups as follows: African-American patients (12.7% versus 20.0% in LCZ696 and enalapril groups, respectively), Asian patients (16.4% versus 10.9%), and Hispanic (21.8% versus 9.1%). There was a higher proportion of NYHA Class I patients in the LCZ696 group compared to enalapril, 18.2% versus 12.7%. Otherwise, there were no significant differences in baseline LVEF, LVFS, NYHA class, or hospitalization status.

Table 7: Demographic and Other Baseline Characteristics (FAS Population)

Demographic Characteristics	LCZ696 (N=55) n (%)	Enalapril (N=55) n (%)	Total (N=110) n (%)
Sex			
Male	25 (45.5)	32 (58.2)	57 (51.8)
Female	30 (54.5)	23 (41.8)	53 (48.2)
Age			
Mean years (SD)	10.9 (5.0)	11.4 (5.4)	11.2 (5.2)
Age Cohort			
12 to < 18 years	28 (50.9)	34 (61.8)	62 (56.4)
6 to 11 years	17 (30.9)	11 (20.0)	28 (25.5)
1 to < 6 years	10 (18.2)	10 (18.2)	20 (18.2)
Race			
Caucasian	32 (58.2)	31 (56.4)	63 (57.3)
Black or African American	7 (12.7)	11 (20.0)	18 (16.4)
Asian	9 (16.4)	6 (10.9)	15 (13.6)
American Indian or Alaska Native	1 (1.8)	1 (1.8)	2 (1.8)
Unknown	2 (3.6)	0 (0.0)	2 (1.8)
Other	4 (7.3)	6 (10.9)	10 (9.1)
Region			
North America	29 (52.7)	29 (52.7)	58 (52.7)
Western Europe	7 (12.7)	8 (14.5)	15 (13.6)
Central Europe	7 (12.7)	6 (10.9)	13 (11.8)
Other	12 (21.8)	12 (21.8)	24 (21.8)
Ethnicity			
Hispanic or Latino	12 (21.8)	5 (9.1)	17 (15.5)
Not Hispanic or Latino	31 (56.4)	31 (56.4)	62 (56.4)
Not Reported	9 (16.4)	11 (20.0)	20 (18.2)
Unknown	3 (5.5)	8 (14.5)	11 (10.0)
LVEF (%) Pre-Randomization			
n	55	54	109
Mean	32.5	31.0	31.7
SD	7.2	7.3	7.3
Median	35.0	32.5	34.0
LVSF (%) Pre-Randomization			
n	32	37	69
Mean	16.0	14.7	15.3
SD	4.1	4.0	4.1
Median	16.8	15.3	16.0

Demographic Characteristics	LCZ696 (N=55) n (%)	Enalapril (N=55) n (%)	Total (N=110) n (%)
NYHA/Ross Class-Baseline			
Class I	10 (18.2)	7 (12.7)	17 (15.5)
Class II	36 (65.5)	38 (69.1)	74 (67.3)
Class III	9 (16.4)	10 (18.2)	19 (17.3)
Class IV	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization Status at Randomization			
Inpatient	2 (3.6)	1 (1.8)	3 (2.7)
Outpatient	53 (96.4)	54 (98.2)	107 (97.3)

Source: Adapted from Table 10.5 from CSR for B2319. Baseline values for systolic and diastolic blood pressure are not shown.

Reviewer Comments:

- *The majority of randomized patients were adolescents, North American, and non-Hispanic Caucasians. Most patients were outpatients and had NYHA Class II heart failure, but none were NYHA Class IV.*
- *There are small numerical differences between treatment groups most notably for age cohorts, sex, race, and ethnicity. I would not expect differences for age or sex to significantly affect 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.*
- *The enalapril group had a higher proportion of adolescent patients compared to LCZ696, 61.8% versus 50.9%. The LCZ696 group had a higher a proportion of children ages 6 to 11 years than the enalapril group, 30.9% versus 20.0%.*
- The SAF included 143 patients. Overall, there were no significant differences in demographic or other baseline characteristics between the FAS and SAF except for proportionally more males than females in the LCZ696 group in the SAF. This slight numerical difference in gender distribution between the FAS and SAF would not be expected to effect interpretation of efficacy or safety results.

Pediatric Heart Failure History (FAS)

All patients had a prior history of HF. Compared to the enalapril group, the LCZ696 group had a higher proportion of patients with prior heart failure hospitalization, 58.5% versus 78.2%, and higher proportion of patients listed for heart transplant, 1.8% versus 9.1%. As shown in Table 8, the proportion of etiologies for DCM varied between the two treatment groups. In both treatment groups, the most common primary etiology for HF was "cardiomyopathy-related" (65.5% in both treatment groups).

Table 8: Pertinent Heart Failure History in Pediatric Patients (FAS)

Heart Failure Characteristics	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Prior history of HF	55 (100)	55 (100)	110 (100)
Primary HF etiology			
Ischemic	4 (7.3)	3 (5.5)	7 (6.4)
Myocarditis	5 (9.1)	7 (12.7)	12 (10.9)
Neuromuscular Disorder	1 (1.8)	4 (7.3)	5 (4.5)
Acquired/chemotherapy	4 (7.3)	3 (5.5)	7 (6.4)
LVNC	11 (20.0)	5 (9.1)	16 (14.5)
Mitochondrial Disorder	0 (0.0)	0 (0.0)	0 (0.0)
CM-related	36 (65.5)	36 (65.5)	72 (65.5)
Congenital Cardiac Malformation	6 (10.9)	8 (14.5)	14 (12.7)
Familial/genetic	13 (23.6)	11 (20.0)	24 (21.8)
Inborn Error of Metabolism	0 (0.0)	0 (0.0)	0 (0.0)
Idiopathic	18 (32.7)	17 (30.9)	35 (31.8)
Other	4 (7.3)	8 (14.5)	12 (10.9)
Prior HF hospitalization	43 (78.2)	32 (58.2)	75 (68.2)
Listed for Heart Transplant			
Yes, UNOS Status 1A or equivalent	0 (0.0)	0 (0.0)	0 (0.0)
Yes, UNOS Status 1B, 2 or equivalent	5 (9.1)	1 (1.8)	6 (5.5)
No	50 (90.9)	54 (98.2)	104 (94.5)

Source: Adapted from Table 10-6 in CSR for Study B2319.

Reviewer Comments: *Although the LCZ696 group had proportionally more patients with history of prior HF hospitalization and heart transplant listing (Table 8), there was a greater proportion of patients in the enalapril group with Class II/III HF and slightly lower baseline LVEF and LVFS (Table 7). These slight numerical differences in baseline characteristics between treatment groups would not be expected to affect efficacy or safety results.*

Treatment Compliance, Prior/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 patient and his/her parent(s)/legal guardians as appropriate. Prior to entering Part 2, the most common HF drug therapies in the SAF included ACEI (95.1%), diuretics (83.9%) including sulfonamides (62.2%), aldosterone antagonists (70.6%), and carvedilol (74.8%). About 2% of patients had a history of non-drug therapies including angiocardiograms and cardiac pacemaker evaluations.

Reviewer Comments: *There are no important imbalances among baseline CHF concomitant medications between treatment groups. In follow up to a TCon with FDA on 15 May 2019, Novartis submitted additional data tables showing the proportion of patients on diuretics at*

baseline and at each study visit leading up to and including Week 12. There were no significant changes in the proportion of patients on diuretics between treatment groups from baseline to Week 12.

In response to an IR dated 11 July 2019, Novartis submitted summary data for changes in diuretic dosing to determine if dosing changes was a confounder on the treatment effects observed in the IA. Overall, 11/110 (10%) of patients had a change in diuretic dosing including increase, decrease, added IV diuretic doses, or discontinuation with no significant difference between treatment groups as shown in Table 9.

Table 9: Patients with Diuretic Dosing Change between Baseline and Week 12 (FAS)

LCZ696	Enalapril	Total
6/55 (10.9%)	5/53 (9.4%)	11/110 (10%)

Source: Reviewer Table.

Of the patients with diuretic changes, most underwent a decrease in dose. Only one patient in the enalapril group had an increase in oral dose. Overall, there were no significant differences between treatment groups in diuretic dosing change as shown in Table 10.

Table 10: Summary of Diuretic Changes from Baseline to Week 12 (FAS)

Diuretic Change	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Number of subjects still participating in study at Week 12 vs. baseline	55	53	108
Dose increase (oral)	0 (0.0)	1 (1.9)	1 (0.9)
Dose decrease (oral)	3 (5.5)	3 (5.7)	6 (5.6)
Newly added oral	1 (1.8)	0 (0.0)	1 (0.9)
Switch to other oral diuretic	0 (0.0)	0 (0.0)	0 (0.0)
Additional IV dose(s)	2 (3.6)	1 (1.9)	3 (2.8)
Discontinuation (oral)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Adapted from Sponsor Table 14.3-1.3.6.

Efficacy Results – Primary Endpoint

The primary endpoint was change from baseline in log(NT-proBNP) at Week 12. Because of challenges enrolling pediatric patients into Study B2319, we accepted NT-proBNP as a bridging biomarker supported by extrapolation from adult development program, which included adults with non-ischemic DCM. In the sacubitril/valsartan pivotal adult HFrEF trial, PARADIGM-HF, sacubitril/valsartan was shown to reduce the risk of the combined endpoint of hospitalization for HF or CV mortality, HR 0.80 [95% CI (0.73, 0.87), $p < 0.001$; NNT 21] compared to enalapril. Based on adult data from PARADIGM-HF, we believed that changes in NT-proBNP correlated

with: HF outcomes in adults, markers of LV systolic function, and HF outcomes in pediatric patients (published literature). Moreover, we believed that reduction of NT-proBNP was a significant contributor to the treatment effect of sacubitril/valsartan on clinical outcomes in adult HFrEF patients.

As shown in Table 11 below, at Week 12, NT-proBNP decreased in both treatment groups with an AGMR for NT-proBNP (Week12/baseline) 0.565 (95% CI: 0.48-0.67) in the LCZ696 group compared to 0.67 (95% CI: 0.57-0.79) in the enalapril group. Although not statistically significant (p=0.15), there was a greater reduction in NT-proBNP reduction in the LCZ696 group compared to enalapril.

Table 11: Primary Efficacy Endpoint Results (FAS)

LCZ696 N=55		Enalapril N=55		Comparison- LCZ696 versus Enalapril		
Estimate AGM RTB n=54	95% CI	Estimate AGM RTB n=54	95% CI	Estimate AGMR	95% CI	p-value
0.565	(0.48, 0.67)	0.67	(0.57, 0.79)	0.84	(0.67, 1.06)	0.15

Source: Adapted from Table 11-1 in CSR for Study B2319, p95. AGM = adjusted geometric mean, RTB = ration to baseline, AGMR = adjusted geometric mean ration, CI = confidence interval. The ANCOVA model includes age group, NYHA/ROSS class group at randomization, region and treatment group as fixed-effect factors and baseline log(NT-proBNP) and age-group-by-baseline-log(NT-proBNP) as covariates.

Novartis performed a sensitivity analysis using imputation methods for missing NT-proBNP data at Week 12 to confirm the robustness of the primary endpoint results. Novartis observed a similar treatment effect for LCZ696 of 0.822 (95% CI 0.65-1.04). Additional post-hoc sensitivity analyses showed similar results as the primary efficacy analysis. Table 12 shows primary efficacy results stratified by age, NYHA class, and treatment discontinuation subgroups. Subgroup analyses did not reveal a statistically significant difference in LCZ696 treatment effect on NT-proBNP compared to enalapril.

Table 12: Subgroup Analyses of Primary Efficacy Endpoint (FAS)

	LCZ696 N=55			Enalapril N=55			Comparison- LCZ696 versus Enalapril		
Subgroups	n	Estimate AGM RTB	95% CI	n	Estimate AGM RTB	95% CI	Estimate AGMR	95% CI	p-value
No Treatment Discontinuation	51	0.57	(0.48, 0.67)	51	0.66	(0.56, 0.78)	0.86	(0.68, 1.09)	0.21
Age									

	LCZ696 N=55			Enalapril N=55			Comparison- LCZ696 versus Enalapril		
Subgroups	n	Estimate AGM RTB	95% CI	n	Estimate AGM RTB	95% CI	Estimate AGMR	95% CI	p-value
< 6 years	9	0.49	(0.32, 0.73)	10	0.42	(0.29, 0.61)	1.15	(0.67, 1.98)	0.22
≥ 6 years to < 18 years	45	0.59	(0.49, 0.70)	44	0.74	(0.62, 0.89)	0.79	(0.61, 1.02)	
<12 years	26	0.55	(0.43, 0.70)	21	0.60	(0.46, 0.79)	0.90	(0.63, 1.31)	0.72
≥ 12 years	28	0.58	(0.46, 0.73)	33	0.70	(0.56, 0.87)	0.83	(0.60, 1.14)	
NYHA/ROSS									
Class I/II	47	0.59	(0.50, 0.70)	47	0.73	(0.61, 0.87)	0.82	(0.64, 1.04)	0.50
Class III/IV	7	0.41	(0.25, 0.67)	7	0.39	(0.24, 0.64)	1.05	(0.53, 2.08)	

Source: Adapted from Tables 14.2-1.4.1 in CSR for Study B2319, p272. AGM = adjusted geometric mean, RTB = ration to baseline, AGMR = adjusted geometric mean ration, CI = confidence interval. The closest assessment after week 4 is used if week 12 assessment is missing. The multiple imputation approach based on the missing at random (MAR) assumption is used. The analysis is based on an ANCOVA model, in which, the response variable is the change from baseline in log(NT-proBNP) at Week 12, age subgroup, NYHA/ROSS class group at randomization, region, treatment group, and subgroup-by-treatment-group interaction are included as fixed-effect factors, baseline log(NT-proBNP) and age-subgroup-by-baseline- log(NT-proBNP) interaction are included as covariates.

Reviewer Comments: *The predicted pediatric treatment effect on NT-proBNP was 30% reduction and used to calculate sample size for a statistical power of 80% and Type I error rate 0.05. The reasons for failure of this IA are likely multifactorial. Use of enalapril as an active comparator posed a unique challenge. Although enalapril is accepted as off-label SoC therapy for pediatric HF, it is unclear what enalapril's expected treatment effect on NT-proBNP should be in a pediatric population. Therefore, we do not know if the observed treatment effect of 15.6% reduction on NT-proBNP can be explained by better than expected performance of enalapril in pediatric patients compared to adult HF patients or worse than expected performance of LCZ696.*

I considered if within-group comparisons between adult and pediatric patients or other post-hoc

analyses could provide convincing data of a clinical benefit of LCZ696 in pediatric HF patients. Moreover, I considered the potential for cofounding of the primary efficacy endpoint due to changes in diuretics or diuretic dosing during the study. However, most patients (90%) did not undergo a diuretic change during the study. Of those who had a change in diuretics, most changes involved a decrease in oral diuretic dosing or changes not temporally related to timing of Week 12 NT-proBNP sampling.

After consideration of all available efficacy data and potential limitations of this IA, I cannot conclude that LCZ696 has a clinically meaningful benefit in pediatric HF patients.

Data Quality and Integrity

OSI did not conduct site inspections. There were no significant data quality or integrity concerns noted during this review.

Efficacy Results – Exploratory endpoints

Novartis did not assess secondary endpoints in this study. However, they collected exploratory efficacy endpoint data on adjudicated clinical endpoints identified as Category 1 or 2 events, NYHA/ROSS class change, PGIS, PGIC, and QoL. Category 1 events of death, UNOS Status 1A listing for heart transplant or equivalent, VAD/ ECMO/mechanical ventilation/IABP requirement for life support were positively adjudicated in 5 patients (9.1%) in each treatment group. Category 2 events of worsening HF (signs/symptoms of HF requiring intensification of therapy with or without hospitalization) were adjudicated in 7 patients (12.7%) in each treatment group. Overall, there was no significant difference in in proportion of Category 1 or 2 events reported between treatment groups. Subgroup analysis for the exploratory endpoints showed that results were primarily driven by Age Group 1 (6 to less than 18 years) with two events, one in Category 1 and one in Category 2, reported in Age Group 2 (LCZ696 group). Table 13 shows the proportion of patients per treatment group with at least one Category or 2 event.

Table 13: Summary of Category 1 and 2 Events (FAS)

Overall	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Patients with at least one Category 1 event	5 (9.1)	5 (9.1)	10 (9.1)
Death	2 (3.6)	3 (5.5)	5 (4.5)
UNOS status 1A listing for heart transplant or equivalent	2 (3.6)	1 (1.8)	3 (2.7)
VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support	3 (5.5)	2 (3.6)	5 (4.5)
Patients with at least one Category 2 event	7 (12.7)	7 (12.7)	14 (12.7)
Worsening heart failure hospitalization with intensive care unit stay	4 (7.3)	4 (7.3)	8 (7.3)

Overall	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Worsening heart failure hospitalization without intensive care unit stay	4 (7.3)	3 (5.5)	7 (6.4)
Worsening heart failure without hospitalization	1 (1.8)	1 (1.8)	2 (1.8)

Source: Adapted from Table 11-4 in CSR for Study B2319, p98.

The clinical endpoint adjudication package included in this submission included 10 events in eight patients that had not yet been adjudicated. In Novartis' 120-day Safety Updated submitted on 25 July 2019, Novartis provides an update on the adjudication status of these events. In the LCZ696 group, three Category 1 and three Category 2 events were reported in four patients but only 4/6 events were positively adjudicated, one in Category 1 (UNOS Status 1A listing) and three in Category 2 [worsening HF with ICU stay (2) and without ICU stay (1)]. In the enalapril group, two Category 1 events and two Category 2 events were reported in four patients with 3/4 events positively adjudicated – one Category 1 (death) and two Category 2 events [worsening HF with ICU stay (1) and without ICU stay (1)]. Table 14 below contains an updated comparison of Category 1 and 2 events between treatment groups. The updated information on Category 1 or 2 events shows slightly worse performance for Category 1 and 2 events with LCZ696 compared to enalapril both overall and for most subcategories.

Table 14: Summary of Category 1 and 2 Events with Updated Positively Adjudicated Events (FAS)

Overall	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Patients with at least one Category 1 event	9 (16.4)	8 (14.5)	17 (15.5)
Death	2 (3.6)	4 (7.3)	6 (5.5)
UNOS status 1A listing for heart transplant or equivalent	3 (5.5)	1 (1.8)	4 (3.6)
VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support	3 (5.5)	2 (3.6)	5 (4.5)
Patients with at least one Category 2 event	10 (18.2)	9 (16.4)	19 (17.3)
Worsening heart failure hospitalization with intensive care unit stay	6 (10.9)	5 (9.1)	11 (10.0)
Worsening heart failure hospitalization without intensive care unit stay	5 (9.1)	4 (7.3)	9 (8.2)
Worsening heart failure without hospitalization	1 (1.8)	1 (1.8)	2 (1.8)

Source: Reviewer Table.

At Week 12, NYHA/ROSS class improved for 18.2% and 26.4% of patients in LCZ696 and enalapril groups, respectively, as shown in Table 15. NYHA/ROSS class worsened for 5.5% and

1.9% of patients in LCZ696 and enalapril groups, respectively. Most patients had no change in their NYHA/ROSS class over time.

Table 15: NYHA/ROSS Class Change by Study Week (FAS)

	LCZ696 N=55				Enalapril N=55			
Study Week	Total (n)	Improved n (%)	Unchanged n (%)	Worse n (%)	Total (n)	Improved n (%)	Unchanged n (%)	Worse n (%)
Week 4	55	5 (9.1)	49 (89.1)	1 (1.8)	55	9 (16.4)	46 (83.6)	0 (0.0)
Week 12	55	10 (18.2)	42 (76.4)	3 (5.5)	53	14 (26.4)	38 (71.7)	1 (1.9)

Source: Adapted from Table 11-5 in CSR for Study B2319, p99.

At Week 12, PGIS, assessment of HF symptom severity, improved for 36.7% and 40.0% of patients in LCZ696 and enalapril groups, respectively. PGIS worsened for 16.3% and 10.0% in LCZ696 and enalapril groups, respectively. Table 16 contains a summary of PGIS scoring results.

Table 16: PGIS Change by Study Week (FAS)

	LCZ696 N=55				Enalapril N=55			
Study Week	Total (n)	Improved n (%)	Unchanged n (%)	Worse n (%)	Total (n)	Improved n (%)	Unchanged n (%)	Worse n (%)
Week 4	51	18 (35.3)	24 (47.1)	9 (17.6)	53	20 (37.7)	28 (52.8)	5 (9.4)
Week 12	49	18 (36.7)	23 (46.9)	8 (16.3)	50	20 (40.0)	25 (50.0)	5 (10.0)

Source: Adapted from Table 11-6 in CSR for Study B2319, p99.

At Week 12, PGIC, assessment of severity of HF symptoms, was reported as "much better" in 10.4% and 20.4%, "better" in 50.0% and 51.0%, and worse in 4.2% and 0.0% of patients in LCZ696 and enalapril groups, respectively, as shown in Table 17.

Table 17: PGIC Change by Study Week (FAS)

Study Week	PGIC Change	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Week 4	Much Better	5 (10.0)	7 (13.2)	12 (11.7)
	Better	20 (40.0)	25 (47.2)	45 (43.7)
	No Change	23 (46.0)	19 (35.8)	42 (40.8)

Study Week	PGIC Change	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
	Worse	2 (4.0)	2 (3.8)	4 (3.9)
	Much Worse	0 (0.0)	0 (0.0)	0 (0.0)
	Category Event	0 (0.0)	0 (0.0)	0 (0.0)
	Total	50	53	103
Week 12	Much Better	5 (10.4)	10 (20.4)	15 (15.5)
	Better	24 (50.0)	25 (51.0)	49 (50.5)
	No Change	16 (33.3)	14 (28.6)	30 (30.9)
	Worse	2 (4.2)	0 (0.0)	2 (2.1)
	Much Worse	1 (2.1)	0 (0.0)	1 (1.0)
	Category Event	0 (0.0)	0 (0.0)	0 (0.0)
	Total	48	49	97

Source: Adapted from Table 11-7 in CSR for Study B2319, p99.

Novartis collected data from a pediatric QoL assessment tool at each study visit called PedsQL (data not shown in this review). Patients of appropriate age and parents provided responses on either a three- or five-point scale with mapping to numeric response scores ranging from 0 ["Almost always (a lot)"] to 100 ["Never (not at all)"]. Higher scores represented a better quality of life. Baseline scores for LCZ696 and enalapril groups were 71.47 and 64.99, respectively. At Week 12, there was a mean increase in patient-reported PedsQL scores of 4.93 and 2.51 in LCZ696 and enalapril groups, respectively. Mean parent-reported PedsQL scores increased by 5.36 and 3.40 in LCZ696 and enalapril groups, respectively at Week 12.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not Applicable.

7.1.1. Primary Endpoints

Refer to Section 6.1.2.

7.1.2. Secondary and Other Endpoints

Refer to Section 6.1.2.

7.1.3. Subpopulations

Refer to Section 6.1.2.

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

Novartis has an ongoing Phase 3 clinical trial to study LCZ696 in pediatric HF patients with plan to provide clinical outcome data from that 52-week study. In this NDA supplement, Novartis provided IA study results for a bridging biomarker, NT-proBNP, supported by extrapolated data from their adult HFrEF trial, PARADIGM-HF, including adults with DCM. PARADIGM-HF is a Phase 3, randomized, active-control trial comparing LCZ696 to enalapril in 8,442 adult HFrEF patients with NYHA Class II-IV. The primary efficacy endpoint was a composite of death from CV

causes or hospitalizations for HF. Based on a time-to-event analysis, sacubitril/valsartan reduced the risk of the combined endpoint [HR 0.80 (0.73, 0.87; p<0.0001)] and improved survival [HR 0.84 (0.76, 0.93), p<0.0009].

In this submission, 110 pediatric patients with DCM and HF were treated with either LCZ696 or enalapril with a primary efficacy endpoint of change in NT-proBNP from baseline to Week 12. Both treatment groups demonstrated a reduction in NT-proBNP, 43.5% with LCZ696 versus 33% with enalapril. Relative to enalapril, LCZ696 resulted in a 15.6% greater reduction in NT-proBNP, however this result was not statistically significant (p=0.15). Moreover, this relative reduction of NT-proBNP for LCZ696 is significantly lower than the predicted pediatric treatment effect of 30% reduction based on extrapolation of adult data from PARADIGM-HF.

Based on the mechanism of action of LCZ696, I would have expected pediatric patients with HF to benefit from this drug therapy. Compared to placebo, it is likely that LCZ696 would have shown a clinically meaningful benefit. But, the prespecified trial design was an active comparator superiority study that did not result in a statistically significant reduction in NT-proBNP compared to the enalapril. However, it is important to consider the following uncertainties: what is the expected treatment effect of enalapril on NT-proBNP in children?; do children respond to sacubitril/valsartan differently than adults?; are there differences in treatment effect of sacubitril/valsartan dependent on baseline NT-proBNP values in children; was the magnitude of change or absolute post-baseline NT-proBNP value more important contributor to clinical benefit seen in PARADIGM-HF?; and to what extent might non-diuretic HF therapies (used off-label) influence NT-proBNP reduction in children?

Because of lingering uncertainties in how confidently NT-proBNP is predictive of a clinically meaningful treatment effect in pediatric HF patients, the evidence of effectiveness is not substantial enough to support labeling LCZ696 for treatment of pediatric HF. To approve LCZ696 for a pediatric HF indication in a subsequent NDA supplement, the totality of evidence in that submission must substantially demonstrate a clinically meaningful benefit.

8. Review of Safety

8.1. Safety Review Approach

The SAF consisted of all randomized patients who received at least one dose of study drug on or prior to 31 January 2019. One hundred forty-three (143) patients comprised the Part 2 SAF including 108 patients who completed the Week 12 assessment. Seventy-three (73) and 70 patients in the SAF were in LCZ696 and enalapril groups respectively. Because Study B2319 is ongoing, on 25 July 2019, Novartis submitted a 120-day safety report including an updated summary of clinical endpoint and AE data collected from patients in the Part 2 SAF and

additional pediatric patients (37) enrolled in Study B2319 and Study B2319E1 (open-label extension study) since the cut-off date for this NDA supplement.

Because LCZ696 is already approved for use in adults with HFrEF, I focused on comparison of the safety profile in children to adults especially for special interest AEs of hypotension, hyperkalemia, angioedema, and renal impairment. Furthermore, I evaluated safety data for safety concerns unique to a pediatric population. Safety results are summarized for study B2319 including deaths, AEs, SAEs, and drug discontinuations/dose reduction/study withdrawal due to EAEs. AE terms used are PTs included in MedDRA.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The mean and median study duration (weeks) were 24.0 and 19.9 for LCZ696 group and 24.1 and 19.4 for enalapril group. Table 18 below shows that most patients remained in the study for at least 12 weeks (72.6% versus 70% in LCZ696 and enalapril groups, respectively). About 34-39% of patients in both treatment groups were treated for at least 26 weeks and an additional 3-8% with at least 52 weeks of treatment in both groups. Study treatment duration was shorter for Age Group 2 (1 to less than 6 years) with mean and median duration (weeks) 10.5 and 10.0 for LCZ696 group and 11.4 and 10.9 for enalapril group.

Table 18: Duration of Treatment (Part 2 SAF)

Duration of Study Treatment (weeks)	LCZ696 N=73 n (%)	Enalapril N=70 n (%)
Mean (SD)	24.0 (17.1)	24.1 (16.2)
< 12	20 (27.4)	21 (30.0)
≥ 12	53 (72.6)	49 (70.0)
≥ 26	25 (34.2)	27 (38.6)
≥ 52	6 (8.2)	2 (2.9)

Source: Adapted from Table 14.3-1.1.4 in CSR for B2319, p394.

Similar to the FAS, most patients in the SAF are in Age Group 1 (6 to less than 18 years), 104/143 (72.7%) compared to 39/143 (27.3%) in Age Group 2. The majority of subjects received weight-based rather than non-weight based/adult dosing. By Week 6, the median dose level for both LCZ696 and enalapril groups was the target dose, dose level 4, and most patients remained on the target dose throughout the study (Table 19).

Table 19: Study Drug Dose Level by Visit (Weeks 0, 6, 12)

		LCZ696 N=73 n (%)		Enalapril N=70 n (%)		Total N=143 n (%)	
Visit	Dose Level	ADL	PDL	ADL	PDL	ADL	PDL
Week 0	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	7 (13.0)	21 (38.9)	4 (7.1)	24 (42.9)	11 (10.0)	45 (40.9)
	2	10 (18.5)	16 (29.6)	9 (16.1)	19 (33.9)	19 (17.3)	35 (31.8)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Total	17 (31.5)	37 (68.5)	13 (23.2)	43 (76.8)	30 (27.3)	80 (72.7)
Week 6	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	3 (7.5)	7 (17.5)	0 (0.0)	5 (12.8)	3 (3.8)	12 (15.2)
	3	2 (5.0)	6 (15.0)	4 (10.3)	7 (17.9)	6 (7.6)	13 (16.5)
	4	3 (7.5)	18 (45.0)	6 (15.4)	17 (43.6)	9 (11.4)	35 (44.3)
	Total	8 (20.0)	31 (77.5)	10 (25.6)	29 (74.4)	18 (22.8)	60 (75.9)
Week 12	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	2 (3.6)	3 (5.5)	0 (0.0)	2 (3.9)	2 (1.9)	5 (4.7)
	3	1 (1.8)	7 (12.7)	1 (2.0)	7 (13.7)	2 (1.9)	14 (13.2)
	4	13 (23.6)	26 (47.3)	12 (23.5)	28 (54.9)	25 (23.6)	54 (50.9)
	Total	16 (29.1)	36 (65.5)	13 (25.5)	37 (72.5)	29 (27.4)	73 (68.9)

Source: Adapted from Sponsor Table 14.3-1.1.2 in CSR for Study B2319, p373.
- ADL = adult dose level, PDL = pediatric dose level.
- LCZ696: pediatric dose level 1 = 0.8 mg/kg bid.; adult dose level 1 = 50 mg bid.; pediatric dose level 2 = 1.6 mg/kg bid.; adult dose level 2 = 100 mg bid.; pediatric dose level 3 = 2.3 mg/kg bid.; adult dose level 3 = 150 mg bid.; pediatric dose level 4 = 3.1 mg/kg bid.; adult dose level 4 = 200 mg bid.;
- Enalapril: pediatric dose level 1 = 0.05 mg/kg bid.; adult dose level 1 = 2.5 mg bid.; pediatric dose level 2 = 0.10 mg/kg bid.; adult dose level 2 = 5.0 mg bid.; pediatric dose level 3 = 0.15 mg/kg bid.; adult dose level 3 = 7.5 mg bid.; pediatric dose level 4 = 0.20 mg/kg bid.; adult dose level 4 = 10.0 mg bid.;
- Dose Level 0 = no treatment (0 mg).

Reviewer Comment: *A shorter treatment duration is to be expected for the younger cohort, Age Group 2, due to the sequential enrollment into Part 2 starting with Age Group 1.*

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 except for proportionally more males than females in the LCZ696 group in the SAF. Demographic and other baseline disease characteristics are summarized in Section 6.1.

8.2.3. Adequacy of the Safety Database

The totality of safety information from PARADIGM-HF, IA for the pediatric trial (Study B2319), 120-day safety update, and approved product labeling for sacubitril/valsartan are adequate to support determination of safety in pediatric HF patients down to 1 year of age.

Reviewer Comment: *The majority of safety information in the safety database were obtained from Age Group I however, given the rarity of pediatric DCM, there is adequate representation of Age Group 2 in the SAF to make a safety determination.*

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. Novartis 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 IB. Information on known side effects of LCZ696 were included in the patient informed consent.

Serious Adverse Events
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 Novartis within 24 hours of learning of its occurrence. Any SAEs occurring after the 30-day period could be reported by Investigators to Novartis 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 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/1.73m^2. 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 Novartis within 24 hours of learning of its occurrence. A pregnancy must be followed to determine outcome of the pregnancy and fetus/infant.

Reviewer Comments: *Novartis' definitions, AE assessment strategies, reporting procedures, and follow up procedures pertaining to AEs, SAEs, SUSARs are acceptable. Novartis 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 child bearing potential females prior to enrollment in Parts 1 and 2. Novartis 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 results 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: *Study B2319 is ongoing. But, for this IA, routine clinical testing and safety assessments, include timing and procedures for handling abnormal results, are appropriate for the study population.*

8.4. Safety Results

8.4.1. Deaths

Six (4.2%) deaths occurred in the study, all in Age Group 1 (6 to less than 18 years), two (2.7%) in LCZ696 and four (5.7%) in enalapril groups. Both patient deaths in the LCZ696 group were adjudicated and due to congestive cardiac failure. In the enalapril group causes of patient death were reported as follows: cardiac death (n=1) subsequently adjudicated as such, respiratory failure (adjudicated, n=1), unknown cause of sudden death (adjudicated, n=1), and arrythmia subsequently adjudicated as congestive cardiac failure (death occurred 79 days after last dose of study drug, n=1). Two (1.4%) patients died during the screening period and prior to study drug administration.

Below are brief summaries of study deaths based on narratives provided by Novartis.

Enalapril

- 12-year-old female with NYHA Class II HF secondary to HIV infection with baseline LVEF 18% and NT-proBNP 4735 pg/mL died on Day 201 (last dose of study drug that morning) with witnessed sudden death
- 12-year-old female with NYHA Class II HF with a cardiomyopathy and history of VSD repair with baseline LVEF 20% and NT-proBNP 766 pg/mL died suddenly on Day 182 due to cardiac arrest unresponsive to CPR; last dose of study medication on Day 181
- 17-year-old male with Duchenne muscular dystrophy and NYHA Class II HF due to a familial/genetic cardiomyopathy, baseline LVEF 38%, and NT-proBNP 461 pg/mL. died on Day 47 due to respiratory failure in the setting of a viral URI; last dose of study drug on Day 46
- 17-year-old male with Duchenne muscular dystrophy and NYHA Class II HF due to familial/genetic cardiomyopathy, baseline LVEF 33%, and NT-proBNP 707 pg/mL; on Day 40 patient developed acute HF with increased NT-proBNP 1460 pg/mL resulting in hospitalization with ICU stay on Day 41; study medication initially held for hypotension on Day 42 then permanently discontinued on the same day; on Day 46 patient had sustained pulseless ventricular tachycardia with cardiac arrest with ROSC; on Day 47

patient had an episode of PEA requiring CPR; the patient continued to have a complicated hospital course and ultimately died on Day 121 (79 days after last dose of study drug) from arrythmias. However, the cause of death was subsequently adjudicated as death due to congestive heart failure

LCZ696

- 9-year-old female with NYHA class II HF due to LV non-compaction/idiopathic cardiomyopathy with baseline LVEF 25% and NT-proBNP 11720 pg/mL died on Day 124 due to congestive HF while on ECMO 15 days after last dose of study drug; prior to patient's death she experienced episodes of pyrexia then recurrent and progressively more severe episodes of acute HF exacerbations
- 15-year-old male with Duchenne muscular dystrophy and NYHA Class III HF due to familial/genetic cardiomyopathy with baseline LVEF 38% and NT-proBNP 1295 pg/mL; study drug was permanently discontinued on Day 47 due to renal impairment; On Day 58, 11 days after last dose of study medication, the patient was hospitalized for acute HF (NT-proBNP 247 pg/mL); patient died on Day 155 (108 days after last dose of study medication) due to progressively worsening congestive HF preceded by concerns for recurrent episodes of low cardiac output and worsening NT-proBNP

Reviewer Comments: *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 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, Novartis's narrative summaries, and reviewer analyses of safety data in MAED.

Forty-three (43) patients reported at least one treatment emergent SAE with lower incidence in LCZ696 group versus enalapril group, 19 (26.0%) patients versus 24 (34.2%), respectively. In Age Group 1 (6 to less than 18 years), a higher proportion of patients experienced a SAE in the enalapril group compared to LCZ696 group, 41.2% versus 24.5%. In Age Group 2 (1 to less than 6 years), a higher proportion of patients experienced a SAE in the LCZ696 group versus enalapril group, 30.0% versus 15.8%.

As shown in Table 20, the most frequently reported SAE SOCs were cardiac disorders and infections/infestations. The most frequently reported PTs were cardiac failure, pneumonia, acute cardiac failure, and syncope. For special interest AEs, there were no SAEs of hypotension or hepatotoxicity reported. However, one patient each experienced SAEs of renal failure and renal impairment in the LCZ696 group. In the enalapril group, one patient each experienced SAEs of hyperkalemia and angioedema.

Novartis provided narratives for SAEs. Most SAEs were study drug-related. However, SAEs of renal failure/impairment and angioedema were, likely, study-drug related. SAEs of syncope were rarely reported. Although both LCZ696 and enalapril can cause hypotension, it is unclear from the narratives if these episodes were study-drug related because of intercurrent conditions e.g., seizure and acute HF exacerbation could be plausible explanations for a syncopal event. Although there were numerical differences in reported SAEs between LCZ696 and enalapril groups, these differences were insignificant.

Table 20: Part 2 (SAF) SAEs by SOC and PT (≥3% of subjects in a treatment group)

	LCZ696 N = 73 n (%)	Enalapril N = 70 n (%)	Total N = 143 n (%)
Number of Patients with at least one SAE	19 (26.0)	24 (34.3)	43 (30.1)
Primary System Organ Class Preferred Term			
Cardiac Disorders	13 (17.8)	10 (14.3)	23 (16.1)
Cardiac Failure	8 (11.0)	6 (8.6)	14 (9.8)
Cardiac failure acute	1 (1.4)	3 (4.3)	4 (2.8)
Infections and Infestations	5 (6.8)	6 (8.6)	11 (7.7)
Pneumonia	2 (2.7)	3 (4.3)	5 (3.5)

Source: Reviewer's analysis based on applicant's datasets and the MAED adverse event tool. Patients with multiple SAEs during a period within a primary SOC were only counted once in the total row and multiple occurrences of an SAE by a patients were only counted once within a SAE category.

Reviewer Comments: *Compared to Age Group 1, there is a higher proportion of SAEs associated with LCZ696 compared to enalapril in Age Group 2. However, due to the small sample size in Age Group 2, it is not possible to determine if there is a differential risk for SAEs with LCZ696 in younger children. It is worth noting there were no renal impairment or renal failure SAEs reported in Age Group 2. Overall, reported SAEs did not reveal unique safety concerns in pediatric patients. Determination of the relationship between SAEs and study drug is*

complicated by underlying morbidity in these HF patients or other intercurrent events occurring at time of the SAE.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

AEs, regardless of treatment relationship, leading to permanent discontinuation of study treatment occurred in 6/73 (8.2%) patients in the LCZ696 group and 7/70 (10.0%) in the enalapril group. Of these patients, only one was in Age Group 2 (LCZ696). The most common SOC resulting in treatment discontinuation was cardiac disorders (6.8% versus 5.7% in LCZ696 and enalapril groups, respectively). The most common PTs were cardiac failure (2.7% versus 2.9% in LCZ696 and enalapril groups, respectively), cardiac arrest (0.0% versus 2.9% in LCZ696 and enalapril groups, respectively), and cardiac failure congestive (2.7% versus 0.0% in LCZ696 and enalapril groups, respectively). Other AEs leading to treatment discontinuation (occurring in ≤2% of subjects per treatment group) included bradycardia, cardiac failure acute, polyuria, renal impairment, hypoxia, death, angioedema, and viral URI.

More patients experienced dose adjustments or temporary discontinuation of study treatment with 12/73 (16.4%) and 14/40 (20.0%) in LCZ696 and enalapril groups, respectively. The most common PTs resulting in dose adjustment or temporary discontinuation were hypotension (2.7% and 5.7% in LCZ696 and enalapril groups, respectively) followed by vomiting, cardiac failure, headache, and fatigue. Other less frequent (<2% of patients) AEs leading to dose adjustment or temporary discontinuation of treatment included arrythmia supraventricular, cardiac failure acute, pyrexia, renal failure, renal impairment, acute kidney injury, nausea, presyncope, syncope, URI, and GFR decreased.

Reviewer Comments: *AEs leading to dose adjustment were nonspecific and mostly consistent with symptoms experienced by children during acute HF exacerbation. Of all AEs stated above, hypotension and renal impairment/failure are most likely to be study-drug related. Hypotension and renal impairment/failure are already included as potential adverse reactions in approved labeling for sacubitril/valsartan.*

8.4.4. Significant Adverse Events

See Section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, 106 (74.1%) subjects in the Part 2 SAF experienced at least one AE. The proportion of patients reporting AEs were similar between treatment groups, 72.6% versus 75.7% in LCZ696 and enalapril groups, respectively. Comparative percentages of AEs between treatment groups are slightly different between Age Group cohorts. Age Group 1 reported slightly less AEs in LCZ696 group compared to enalapril group, 71.7% versus 80.4%, respectively. In Age Group 2,

there were proportionally more AEs reported in the LCZ696 group compared to enalapril group, 75.0% versus 63.2%, respectively. Overall, most AEs were mild, 39.7% versus 37.1% in LCZ696 and enalapril groups, respectively, or moderate, 21.9% versus 17.1% in LCZ696 and enalapril groups, respectively. Severe AEs accounted for 11.0% versus 21.4% in LCZ696 and enalapril groups, respectively. Severity of AEs were driven by Age Group 1. Severity of AEs in Age Group 2 were, similar to Age Group1, mostly mild or moderate but with a higher proportion of mild AEs compared to Age Group 1. Overall, the most frequent reported SOC were infections and infestations followed by respiratory/thoracic/mediastinal disorders (Table 21).

Table 21: AEs by SOC Occurring in at Least 5% of Subjects

	LCZ696 (N=73)		Enalapril (N=72)	
SOC	Number of Events	n (%)	Number of Events	n (%)
Infestations and Infections	73	32 (43.8%)	62	35 (48.6%)
Respiratory, thoracic, and mediastinal disorders	54	23 (31.5%)	35	20 (27.8%)
General disorders and administration site conditions	38	21 (28.77%)	18	15 (20.8%)
Nervous system disorders	36	19 (26.0%)	44	20 (27.8%)
GI disorders	41	16 (21.9%)	50	22 (30.6%)
Cardiac disorders	23	15 (20.6%)	28	14 (19.4%)
Investigations	18	12 (16.4%)	12	11 (15.3%)
Skin and Subcutaneous tissue disorders	13	11 (15.1%)	13	9 (12.5%)
Metabolism and nutrition disorders	14	10 (13.7%)	8	8 (11.1%)
Psychiatric disorders	9	7 (9.6%)	5	4 (5.6%)
Renal and urinary disorders	9	7 (9.6%)	3	3 (4.2%)
Vascular disorders	16	7 (9.6%)	9	8 (11.1%)
Blood and lymphatic disorders	4	4 (5.5%)	1	1 (1.4%)
Injury, poisoning and procedural complications	4	4 (5.5%)	8	6 (8.3%)

Source: Reviewer's analysis based on applicant's datasets and MAED adverse event tool.

Table 22 contains the most common AEs grouped by PTs with the most frequently occurring PTs including nasopharyngitis, bronchitis, gastroenteritis, and URI.

Table 22: AEs by PT Occurring in at Least 5% of Subjects

	LCZ696 (N=73)		Enalapril (N=72)	
PT	Number of Events	n (%)	Number of Events	n (%)
Cough	19	14 (19.2%)	14	13 (18.1%)
Dizziness	16	12 (16.4%)	11	8 (11.1%)
Nasopharyngitis	20	11 (15.1%)	7	5 (6.9%)
Fatigue	11	10 (13.7%)	4	4 (5.6%)
Headache	16	10 (13.7%)	16	13 (18.1%)
Cardiac failure	11	9 (12.3%)	10	6 (8.3%)
Pyrexia	15	9 (12.3%)	4	4 (5.6%)
Vomiting	11	9 (12.3%)	17	11 (15.3%)
Hypotension	16	7 (9.6%)	9	8 (11.1%)
Diarrhea	9	6 (8.2%)	5	5 (6.9%)
URI	14	6 (8.2%)	16	11 (15.3%)
Gastroenteritis	5	5 (6.9%)	4	4 (5.6%)
Nausea	5	5 (6.9%)	9	7 (9.7%)
Abdominal pain	5	4 (5.5%)	4	4 (5.6%)
Arthralgia	4	4 (5.5%)	1	1 (1.4%)
Oropharyngeal pain	4	4 (5.5%)	1	1 (1.4%)
Pneumonia	4	4 (5.5%)	5	5 (6.9%)
Glomerular filtration rate decreased	3	3 (4.1%)	4	4 (5.6%)
Influenza	3	3 (4.1%)	5	5 (6.9%)

Source: Reviewer's analysis based on applicant's datasets and using the MAED adverse event tool.

Reviewer Comment: *In a pediatric population, particularly one that is chronically ill, infectious illnesses would be expected. Based on the mechanism of action 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 group are study-drug related. Overall, there were no new or unexpected AEs detected in this IA.*

8.4.6. Laboratory Findings

Novartis provided patient data for all urinalysis, abnormal hematology, and clinical chemistry labs collected for patients including a small proportion of patients who completed the study. 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. Novartis 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. Based on pooled central and local lab data, the most frequent biochemistry clinically significant lab results were post-baseline changes in creatinine, potassium, and sodium.

A higher proportion of patients in the enalapril group had high post-baseline potassium (local lab data) compared to LCZ696 group, 22.1% (15/68) versus 9.7% (7/73), respectively. A higher proportion of patients in the LCZ696 group had high post-baseline creatinine values (local lab data) compared to enalapril group, 9.7% (7/73) versus 4.4% (3/68). The LCZ696 group had a higher proportion of patients with post-baseline high sodium 7.0% (5/71) versus 0.0% in enalapril group. The enalapril group had a higher proportion of post-baseline low sodium compared to LCZ696, 5.9% (4/68) versus 0.0%, respectively. Most patients had normal baseline creatinine, potassium, and sodium values.

Most changes in hematology laboratory assessments were not clinically significant, I noted two patients, both in the LCZ696 group, with clinically significant hematology labs, one patients with an increase >75% from baseline in platelets to 715 x 10^9 (ULN 450 x 10^9) and one patient with decreased >50% from baseline in platelets to 59 x 10^9 (LLN 150 x 10^9).

Reviewer Comment: *Most clinically significant changes in biochemistry and hematology lab parameters were similar between treatment groups. The biochemistry changes described above are consistent with the known risk profile of both treatments. Similar biochemistry abnormalities were observed in both Age Groups 1 and 2. There were no clinically significant hematology abnormalities reported in Age Group 2.*

8.4.7. Vital Signs

Similar to lab assessment, Novartis pre-specified criteria for abnormal vital signs. Overall, 53/143 (37.1%) patients had an abnormal heart rate with most patients 51/143 (35.7%) having a high heart rate. The proportion of patients with abnormally high heart rate was slightly lower in the LCZ696 group compared to enalapril group, 32.9% versus 38.6%, respectively. About half of patients in the SAF had low systolic and/or diastolic BP. A higher proportion of patients in the LCZ696 group had low SBP and DBP compared to enalapril, 58.9% versus 38.6% and 63.0% versus 50.0%, respectively.

Reviewer Comment: *There are numerical differences in post-baseline changes in heart rate and BP between Age Groups 1 and 2. There is a slightly higher proportion of patients with high heart rate in LCZ696 group in Age Group 1 compared to enalapril and the opposite observed in Age Group 2 with slightly greater proportion with high heart rate in LCZ696 group compared to enalapril. Age Groups 1 and 2 had a higher proportion of patients with low SBP in the LCZ696 group but Age Group 2 had a slightly higher proportion of patients with low DBP in the enalapril group.*

8.4.8. Electrocardiograms (ECGs)

Novartis did not summarize ECG data in their submission. A summary of arrhythmia AEs is shown in Table 23.

Table 23: Arrhythmia Events by PT in Part 2 SAF

	LCZ696 (N=73)		Enalapril (N=72)	
PT	Number of Events	n (%)	Number of Events	n (%)
Torsades de pointes/QT prolongation	3	3 (4.1%)	9	8 (11.1%)
Supraventricular tachyarrhythmias	2	1 (1.4%)	0	0 (0.0%)
Ventricular arrhythmias	1	1 (1.4%)	7	5 (6.9%)

Source: Reviewer's analysis based on applicant's datasets and MAED adverse event tool.

Reviewer Comments: *Overall, there is a smaller proportion of patients with arrhythmias in the LCZ696 group compared to enalapril. It is unclear why there is a significantly higher proportion of patients with arrythmias in the enalapril group. However, as previously shown, there was a significantly higher proportion of patient with hyperkalemia in the enalapril group compared to LCZ696 group, which may have increased the risk for ventricular arrhythmias.*

8.4.9. Immunogenicity

Not Applicable.

8.5. Analysis of Submission-Specific Safety Issues

Based on the known risk profile of sacubitril/valsartan, Novartis identified and assessed special interest AEs including angioedema, embryo-fetal toxicity, hepatotoxicity, hyperkalemia, hypotension, and renal impairment. Tables 24, 25, and 26 show the proportions of special interest AEs in the overall SAF population and stratified by Age Group cohorts.

Table 24: Special Interest AEs in Part 2 SAF (Overall Population)

	LCZ696 N=73		Enalapril N=70		Total N=143	
AE	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**
Angioedema	5(6.8)	16.0 (5.2,37.4)	1 (1.4)	3.0 (0.1,16.6)	6 (4.2)	9.3 (3.4,20.2)
Embryo-fetal toxicity	0 (0.0)	0.0 (0.0,10.9)	1 (1.4)	3.0 (0.1,16.6)	1 (0.7)	1.5 (0.0,8.3)
Hepatotoxicity	3 (4.1)	8.9 (1.8,26.2)	2 (2.9)	6.1 (0.7,22.1)	5 (3.5)	7.5 (2.4,17.6)
Hyperkalemia	2 (2.7)	6.0 (0.7,21.6)	2 (2.9)	6.0 (0.7,21.7)	4 (2.8)	6.0 (1.6,15.4)
Hypotension	16 (21.9)	60.0 (34.3,97.4)	16 (22.9)	59.3 (33.9,96.3)	32 (22.4)	59.6 (40.8,84.2)
Renal impairment	4 (5.5)	12.1 (3.3,31.1)	2 (2.9)	5.9 (0.7,21.4)	6 (4.2)	9.0 (3.3,19.5)
Statin drug-drug interaction	1 (1.4)	3.0 (0.1,16.6)	1 (1.4)	3.0 (0.1,16.7)	2 (1.4)	3.0 (0.4,10.8)

Source: Adapted from Sponsor Table 12-5 in CSR for Study B2319, p119.
- A patient with multiple events in one topic during the period is counted only once in this topic.
- n (%): number (percentage) of patients with at least one treatment emergent event in the topic.
- EAIR (exposure adjusted incidence rate per 100 patient-year): number of patients with at least one treatment emergent event in the topic/[100 × total exposure time (year)].
- Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over patients within the treatment group.
- Safety topics of special interest are identified based on the search paths in the LCZ696 Case Retrieval Strategy (updated on 04NOV2018).

Table 25: Special Interest AEs in Part 2 SAF – Age Group 1 (Ages 6 to less than 18 years)

	LCZ696 N=53		Enalapril N=51		Total N=104	
AE	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**	**n (%)**	**EAIR (95% CI)**
Angioedema	4 (7.5)	14.7 (4.0,37.6)	1 (2.0)	3.4 (0.1,19.0)	5 (4.8)	8.8 (2.9,20.6)
Embryo-fetal toxicity	0 (0.0)	0.0 (0.0,12.5)	1 (2.0)	3.4 (0.1,18.9)	1 (1.0)	1.7 (0.0,9.4)
Hepatotoxicity	2 (3.8)	6.8 (0.8,24.5)	2 (3.9)	7.0 (0.8,25.2)	4 (3.8)	6.9 (1.9,17.6)
Hyperkalemia	2 (3.8)	6.9 (0.8,24.8)	1 (2.0)	3.4 (0.1,18.9)	3 (2.9)	5.1 (1.1,14.9)
Hypotension	13 (24.5)	56.8 (30.2,97.1)	15 (29.4)	64.6 (36.2,106.6)	28 (26.9)	60.7 (40.4,87.8)
Renal impairment	4 (7.5)	13.9 (3.8,35.7)	2 (3.9)	6.7 (0.8,24.3)	6 (5.8)	10.3 (3.8,22.3)
Statin drug-drug interaction	1 (1.9)	3.4 (0.1,18.9)	1 (2.0)	3.4 (0.1,19.0)	2 (1.9)	3.4 (0.4,12.3)

Source: Adapted from Sponsor Table 12-5 in CSR for Study B2319, p119.
- A patient with multiple events in one topic during the period is counted only once in this topic.
- n (%): number (percentage) of patients with at least one treatment emergent event in the topic.
- EAIR (exposure adjusted incidence rate per 100 patient-year): number of patients with at least one treatment emergent event in the topic/[100 × total exposure time (year)].
- Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over patients within the treatment group.
- Safety topics of special interest are identified based on the search paths in the LCZ696 Case Retrieval Strategy (updated on 04NOV2018).

Table 26: Special Interest AEs in Part 2 SAF – Age Group 2 (Ages 1 to less than 6 years)

	LCZ696 N=20		Enalapril N=19		Total N=39	
AE	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)	n (%)	EAIR (95% CI)
Angioedema	1 (5.0)	25.5 (0.6, 141.9)	0 (0.0	0.0 (0.0, 90.1)	1 (2.6)	12.5 (0.3, 69.5)
Hepatotoxicity	1 (5.0)	24.8 (0.6, 138.1)	0 (0.0	0.0 (0.0, 90.1)	1 (2.6)	12.3 (0.3, 68.5)
Hyperkalemia	0 (0.0)	0.0 (0.0, 86.8)	1 (2.0)	26.4 (0.7, 147.1)	1 (2.6)	12.4 (0.3, 69.3)
Hypotension	3 (15.0)	79.1 (16.3, 231.2)	1 (2.0)	26.6 (0.7,148.2)	4 (10.3)	53.0 (14.4, 135.6)

Source: Adapted from Sponsor Table 12-5 in CSR for Study B2319, p119.
- A patient with multiple events in one topic during the period is counted only once in this topic.
- n (%): number (percentage) of patients with at least one treatment emergent event in the topic.
- EAIR (exposure adjusted incidence rate per 100 patient-year): number of patients with at least one treatment emergent event in the topic/[100 × total exposure time (year)].
- Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over patients within the treatment group.
- Safety topics of special interest are identified based on the search paths in the LCZ696 Case Retrieval Strategy (updated on 04NOV2018).

8.5.1. Hypotension

The overall incidence of hypotension events was similar between treatment groups with minor numerical differences for hypotension-related events as shown in Table 27. Two and four hypotension events resulted in treatment interruption or dose adjustment in LCZ696 and enalapril groups, respectively. However, no episodes of hypotension resulted in permanent discontinuation of the drug.

Table 27: Hypotension and Hypotension-Related Events in Part 2 SAF

AE	LCZ696 N=73 n (%)	Enalapril N=70 n (%)	Total N=143 n (%)
Dizziness	12 (16.4)	8 (11.4)	20 (14.0)
Hypotension	7 (9.6)	8 (11.4)	15 (10.5)
Syncope	2 (2.7)	3 (4.3)	5 (3.5)
Presyncope	0 (0.0)	2 (2.9)	2 (1.4)

Source: Adapted from Sponsor Table 12-7 in CSR for Study B2319, p121.

8.5.2. Hyperkalemia

See Section 8.4.6.

8.5.3. Renal Impairment

All renal impairment events occurred in Age Group 1 with a higher incidence in the LCZ696 group compared to enalapril group, 5.5% versus 2.9%, respectively. All events were mild or moderate in severity except one event deemed serious, renal failure. The renal failure AE lead to permanent discontinuation. Most other renal events led to temporary drug discontinuation or dose reduction, mostly in the LCZ696 group, 4.1% versus 1.4% in enalapril group.

8.5.4. Angioedema

Angioedema events were adjudicated with positive adjudication in one patient (enalapril group) out of six (6) events reported by Investigators concerned for angioedema. Most reported events occurred in the LCZ696 group, 6.8% compared to 1.4% in the enalapril group. Other reported events occurring in one patient each in the LCZ696 group included skin edema, swelling face, urticaria, swelling of eyelid, and face edema.

8.5.5. Hepatotoxicity

Liver toxicity was reported in 5/143 (3.5%) patients with 3/73 (4.1%) and 2/70 (2.9%) in LCZ696 and enalapril groups, respectively. Reported hepatotoxicity events included ALT increased, hepatomegaly, AST increased, and blood bilirubin increased. Novartis reports that no hepatotoxicity event led to dose adjustment or interruption of study drug and no episodes of hepatotoxicity were deemed severe or serious. However, there was one patient in the LCZ696 group who met the criteria for Hy's Law and required permanent discontinuation of study drug.

This patient was a 9-year-old female with history of idiopathic cardiomyopathy, NYHA Class II, baseline NT-proBNP 11720 pg/mL, and LVEF 25%. She had normal AST and ALT at baseline but elevated total bilirubin of 2.99 mg/dL (ULN 1.2 mg/dL) and direct bilirubin 1.06 mg/mL (ULN 0.5 mg/dL). Pertinent medical history from patient narrative and liver function test values are summarized in Table 28.

Table 28: Hy's Law Case (Patient (b) (6))

Study Day	Medical History	Liver Function Tests
89	Hospitalized for acute HF exacerbation, NYHA Class III	AST 83 IU/L (ULN 37 IU/L) ALT 71 IU/L (ULN 26 IU/L)
96	Discharged home	
97	Readmitted with WHF	
112		direct bilirubin 1.27 mg/dL total bilirubin 2.2 mg/dL ALT 365 IU/L

Study Day	Medical History	Liver Function Tests
		AST 335 IU/L
117	Placed on ECMO	AST was 2579 U/L ALT 797 IU/L total bilirubin 4.1 mg/dL direct bilirubin 2.77 mg/dL
118		AST 18035 IU/L ALT 3327 IU/L
119		AST 4202 IU/L ALT 2024 IU/L
123		AST 207 IU/L ALT 266 IU/L
124	Death on ECMO (15 days after last dose study drug)	AST 197 IU/L ALT not reported total bilirubin 19.98 mg/dL direct bilirubin 14.14 mg/dL GGT 54 IU/L (ULN 17 IU/L)

An independent liver safety expert determined that the increase in liver enzymes were a consequence of terminal HF deterioration with no evidence of hypersensitivity or relation to study drug.

Another patient in the LCZ696 group had two liver toxicity events. This 4-year-old female has a history of Ross Class II HF with a cardiomyopathy due to chemotherapy cardiotoxicity, baseline LVEF 24% and NT-proBNP 11913 pg/mL. Baseline liver function tests were normal. On Day 27, patient reportedly had "non-serious" increases in AST and ALT but the lab values were not reported.

Reviewer Comment: *I agree with the assessment of the independent liver safety expert for the Hy's Law case. The progression of liver dysfunction is consistent with end organ failure due to worsening HF. There are no significant concerns for a drug-related liver toxicity signal. Hepatotoxicity is not listed as a safety concern in product labeling for sacubitril/valsartan, but reduced dosing recommendations are provided for hepatic impairment and a recommendation against use with severe hepatic impairment included.*

8.5.6. Change in Bone Growth and Density

No events reported.

8.5.7. Cognitive Impairment

No events reported.

8.5.8. Embryo/Fetal Toxicity

Novartis reported one patient in the enalapril group with and AE of feeding intolerance coded as the PT "Neonatal disorder" in MedDRA however the patient is 6 years old. Therefore, this event is not applicable to this special interest category. There were no pregnancies reported.

8.5.9. Hypersensitivity

There was a higher incidence of suspected hypersensitivity events reported in the LCZ696 group compared to enalapril, 12.3% versus 5.7%, respectively. AEs reported for "hypersensitivity" included "drug hypersensitivity," eczema, rash, face edema, rhinitis allergic, swelling face, swelling of eyelid, urticaria, angioedema, and infusion related reaction. There is an overlap between this category and the angioedema special interest AE evaluation described in Section 8.5.4. Except for rhinitis allergic and eczema which has 2 subjects in enalapril and LCZ696 groups, respectively. All other categories have no more than one patient each. Hypersensitivity is already listed as a safety concern in product labeling for sacubitril/valsartan. There is no concern for increased risk for hypersensitivity in this pediatric population.

8.5.10. Anaphylaxis

No events reported.

8.6. Safety Analyses by Demographic Subgroups

See Section 8.4.

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

There were no pregnancies reported during the pediatric development program.

8.8.3. Pediatrics and Assessment of Effects on Growth

See Section 8.5.6.

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

Not Applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Not Applicable.

8.9.3. Additional Safety Issues from Other Disciplines

No additional safety issues from other disciplines were raised during this review.

8.10. Integrated Assessment of Safety

The safety profile of LCZ696 in pediatric patients is similar to that reported for the approved product, sacubitril/valsartan, already marketed to adults with HFrEF. Although the study is ongoing, the 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. Although no new safety signals were identified from the pediatric safety database, the uncertain clinical benefit of LCZ696 does not adequately outweigh the potential risks of this combination product in pediatric patients with HF.

9. Advisory Committee Meeting and Other External Consultations

Not Applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information

At the time of this review, the Division is working on editing Novartis' draft labeling and, thus, has not yet obtained feedback from Novartis on our recommendations.

Other Prescription Drug Labeling

At the time of this review, the Division has not reviewed proposed changes to patient, carton, or container labeling.

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is indicated for the proposed indication.

12. Postmarketing Requirements and Commitments

Not Applicable.

13. Appendices

13.1. References

Not Applicable.

13.2. 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: 317 (173 US and 144 non-US)		
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)): 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHETARRA E WALKER
08/19/2019 12:55:09 PM

MARTIN ROSE
08/20/2019 02:29:58 PM