U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	207620
Supplement #:	# 13
Drug Name:	ENTRESTO® (sacubitril and valsartan)
Indication(s):	pediatric patients from1 (b) (4) to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction.
Applicant:	Novartis
Date(s):	Submission Date: April 1, 2019
	PDUFA due date: October 1, 2019
Review Priority:	6-month review period for Pediatric Written Request
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Keywords:

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EXECUTIVE SUMMARY

The application included a single study PANORAMA-HF. CLCZ696B2319 (PANORAMA-HF) is an ongoing pediatric study to evaluate the efficacy and safety of LCZ696 (sacubitril/valsartan, also called Entresto) compared with enalapril in pediatric patients with heart failure (HF) due to systemic left ventricle systolic dysfunction. The study has two parts. Part 1 of the study is an open-label study to evaluate pharmacokinetics and pharmacodynamics of LCZ696. Part 2 of the study is a randomized, double-blind, parallel-group, active-controlled, 52-week study. The sponsor planned to randomize 360 patients in Part 2 and collect clinical events at Week 52 to evaluate the safety and efficacy of LCZ696 compared with enalapril for treatment of heart failure using a global rank endpoint.

A bridging biomarker interim analysis using NT-proBNP as endpoint was introduced in Protocol Amendment 4 and Pediatric Written Request Amendment 1 in March 2019 after the sponsor had extensive discussion with the Division about demonstrating efficacy of LCZ696 in pediatric population by using NT-proBNP. The Full Analysis Set (FAS) in the interim analysis included 110 patients who had Week 12 visit. This is the focus of this review.

The adjusted geometric mean ratio for NT-proBNP was 0.84 in the comparison of LCZ696 group and enalapril group with 95% confidence interval (0.67, 1.06). Both groups showed that NT-proBNP decreased from the baseline. But the comparison was not statistically significant (p-value=0.147) and the ratio reduction was much smaller than in adult patients with chronic heart failure with reduced ejection fraction (HFrEF). Various sensitivity analyses including complete case analysis, pattern mixture model and ANCOVA models adjusting for the imbalanced baseline covariates all appeared to show consistent ratio estimates on the change from baseline in NT-proBNP as the primary analysis result. The much smaller ratio reduction in change from baseline NT-proBNP in pediatric patients adds uncertainty of using the relationship established in adult patients for predicting the likely treatment effect in pediatrics.

There were 5 patients in each treatment arm with at least one Category 1 event and 7 patients in each arm with at least one Category 2 event. The clinical events, although not many, showed no difference between two treatment arms in the ongoing pediatric study.

It is not clear whether LCZ696 may demonstrate any clinical benefit in pediatric patients given the much smaller ratio reduction in NT-proBNP compared with the adult HFrEF patients. There can be potentially different interpretations. It is difficult to conclude at this point that LCZ696 is efficacious in treating pediatric patients with HF. The study does not have a placebo arm in the trial and enalapril was never approved for treating pediatric patients with HF. There is uncertainty about the efficacy of enalapril in this population. We therefore should not overinterpret the change from baseline in NT-proBNP in each individual arm.

The reviewer recommends not to approve the indication based on the biomarker interim analysis results. The clinical benefit should be evaluated after the trial is fully completed and enough data on clinical primary endpoint at Week 52 is collected.

INTRODUCTION

1.1 Overview

The application included a single study PANORAMA-HF. CLCZ696B2319 (PANORAMA-HF) is an ongoing pediatric study to evaluate the efficacy and safety of LCZ696 (sacubitril/valsartan) compared with enalapril in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction. The study has two parts. Part 1 of the study is an open-label study to evaluate pharmacokinetics and pharmacodynamics of LCZ696. Part 2 of the study is a randomized, double-blind, parallel-group, active-controlled, 52-week study. The sponsor planned to randomize 360 patients in Part 2 and collect clinical events at Week 52 in order to evaluate the safety and efficacy of LCZ696 compared with enalapril for treatment of heart failure using a global rank endpoint.

A bridging biomarker interim analysis using NT-proBNP as endpoint was introduced in Protocol Amendment 4 and Pediatric Written Request Amendment 1 in March 2019 after discussion with the Division. The sponsor would conduct the bridging biomarker interim analysis after at least 100 patients (1 to <18 years of age) had Week 12 visit, which is the focus of this review.

The interim analysis included 110 patients in the Full Analysis Set (FAS) and 143 patients in the Safety Analysis Set (SS).

Table 1: List of all studies included in review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
CLCZ696B2319	Post-market	12 weeks (this is an interim analysis of a 52-week study)	NA (this is the interim analysis)	N=55 in LCZ696 arm; N=55 in enalapril arm	pediatric patients 1- <18 years of age with heart failure due to systemic left ventricular systolic dysfunction

[Source: Reviewer's Table]

1.2 Data Sources

The pediatric study data used for this review is located at \\CDSESUB1\evsprod\NDA207620\0112\m5\datasets\lcz696b2319\analysis\adam\datasets

The review also used NT-proBNP data from biomarker sub-study in the adult trial PARADIGM-HF, which can be found at \\CDSESUB1\evsprod\NDA207620\0121\m5\datasets\lcz696b2314\analysis\legacy\datasets\

Other additional data from PARADIGM-HF trial that was used in the review is located at \\CDSESUB1\evsprod\NDA207620\0002\m5\datasets\lcz696b2314\analysis\legacy\datasets

STATISTICAL EVALUATION

1.3 Data and Analysis Quality

The reviewer was able to reproduce the results from main analyses conducted by the sponsor. The largest site enrolled 6 FAS subjects. No single site drives the overall results. In addition, the trial will continue to enroll patients and collect clinical endpoint at Week 52. The team determined not to conduct site inspection for this interim analysis.

The sponsor and the Division had several rounds of discussions on the bridging biomarker NT-proBNP. Please refer to the meeting minutes for details. Following the fact-to-face meeting on January 18, 2019, the sponsor submitted Protocol Amendment 4 and NT-proBNP Interim Statistical Analysis Plan on February 7, 2019 to include an interim biomarker analysis when at least 100 patients achieved the Week 12 visit.

1.4 Evaluation of Efficacy

1.4.1 Study CLCZ696B2319

1.4.1.1 Study Design and Endpoints

This study is a two-part pediatric study to determine the clinical treatment benefit of LCZ696 compared to enalapril over 52-week treatment duration.

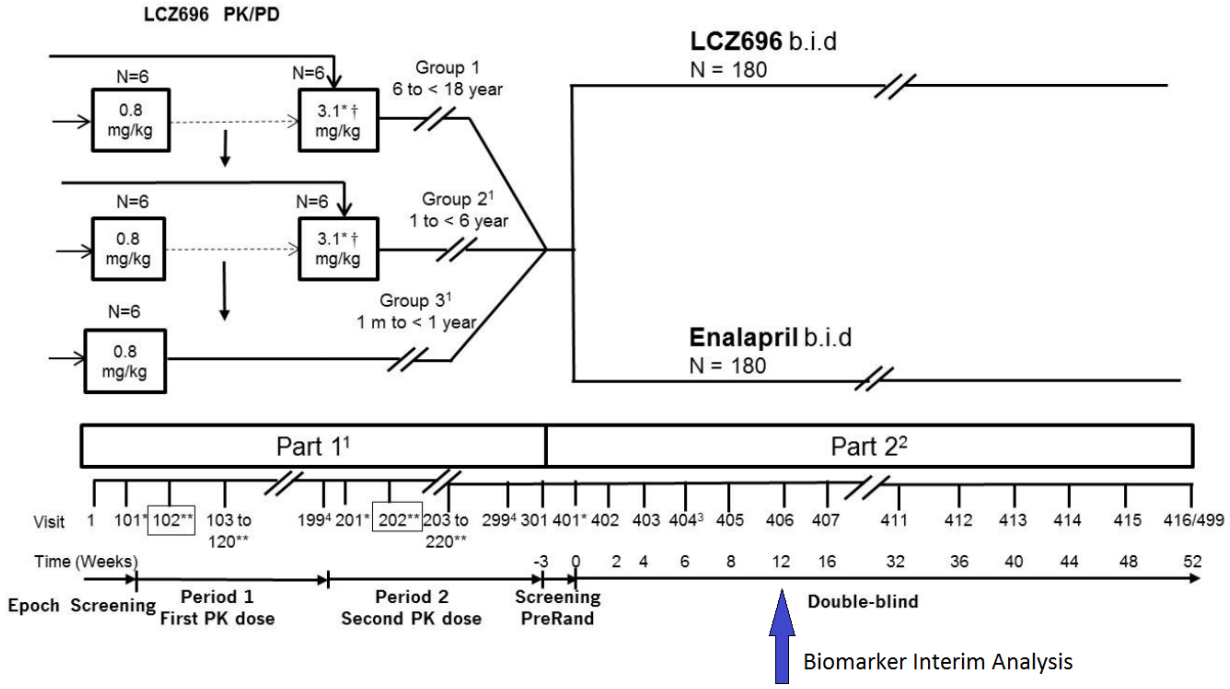
Part 1 of the study is to confirm the dose for Part 2. This part is multicenter and open-label. Eligible patients were placed into three age groups (Age Group 1: 6 years to < 18 years, Age Group 2: 1 year to < 6 years, and an extra Age Group 3: 1 month to < 1 year). For each age group, PK/PD and safety data were reviewed to confirm or modify the doses. Patients in each age group can enroll in Part 2 after the target dose for that age group was determined based on Part 1 data for the corresponding age cohort.

Part 2 is a double-blind, randomized, multicenter, 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 dilated cardiomyopathy (DCM). Per protocol, 360 patients were planned to be randomized to LCZ696 or enalapril arm for 52-week treatment. The primary endpoint is a global rank endpoint through 52 weeks of treatment, which was constructed through two steps within each of the six strata. The strata were defined by combination of age at randomization and baseline NYHA/ROSS class group.

The sponsor later proposed a bridging biomarker interim analysis in Part 2 to evaluate efficacy in patients (age 1 to <18 years) by the NT-proBNP change from baseline at Week 12. The changes were included in Protocol Amendment 4 and Written Request Amendment 1. The sponsor was required to have at least 100 patients with Week 12 assessment of NT-proBNP. Infants < 1 year old were no longer required in the study anymore due to the rarity of this age group.

Figure 1: Study Design



[Source: Figure 9-1 in Sponsor's clinical study report]

The primary endpoint for the whole study is the global rank endpoint derived from 5 categories including clinical events and functional status. For details about how the endpoint is derived, please refer to the sponsor's statistical analysis plan. The primary endpoint was not computed in this bridging biomarker interim analysis. The sponsor's current clinical study report and this review focused on the NT-proBNP change from baseline at Week 12. Descriptive statistics for endpoints such as Category 1 events, Category 2 events, NYHA/ROSS class change, patient global impression of severity (PGIS) change, patient global impression of change (PGIC) score,

and pediatric quality of life (PedsQL) were provided for the interim analyses as exploratory analyses.

1.4.1.2 Statistical Methodologies

The primary efficacy variable, change from baseline in log(NT-proBNP) at Week 12, was analyzed by ANCOVA. Age, NYHA/ROSS class group at randomization, region and treatment group were included in the model as fixed-effect factors. Baseline log(NT-proBNP) and age-by-baseline log(NT-proBNP) interaction were included as covariates.

For the NT-proBNP, if the scheduled assessment at Week 12 was not done or the assessment value was missing, the following procedure was used for missing data imputation. The number of imputations was 100.

1. For each patient, among all non-missing NT-proBNP assessments (scheduled or unscheduled) after Week 4, the assessment closest to the target date (Week 12) were used to impute the missing assessment value at Week 12. The target date (Week 12) is defined as randomization date plus 84 days.

2. After step 1, the missing NT-proBNP value at Week 12 was imputed using a multiple imputation approach based on the missing at random (MAR) assumption. The imputation model is a linear regression model specified using fully conditional specifications, in which, the response variable is the log(NTproBNP) at Week 12; NYHA/ROSS class group at randomization and region are included as fixed-effect factors, baseline log(NTproBNP) is included as covariates. For each age group and each arm, the imputation model was fitted separately based on the data from all patients in the corresponding treatment group within the age group. For each imputed data set, the primary analysis ANCOVA model was fitted. The results were combined using Rubin's rules.

To explore the robustness of the MAR assumption on the primary analysis, a sensitivity analysis based on pattern mixture model was performed to assess the case where the data are missing not at random (MNAR).

1. For each patient, among all non-missing NT-proBNP assessments (scheduled or unscheduled) after Week 4, the assessment closest to the target date (Week 12) was used to impute the missing assessment value at Week 12.

2. After step 1, a multiple imputation approach based on pattern mixture models was applied (Carpenter and Kenward 2013), whereby all missing data of patients in the LCZ696 group who permanently discontinue the double-blind study treatment due to adverse events, were assumed to behave like patients in the Enalapril group after the study treatment discontinuation and were imputed based on the data from patients in the

Enalapril group. The imputation model was a linear regression model with log (NT-proBNP) at Week 12 as response variable, NYHA/ROSS class group at baseline and region as fixed-effect factors, baseline log (NT-proBNP) as covariate. The imputation model was fitted separately for each age group.

3. After step 2, for each imputed data set from the step 2, the imputed values of the NT-proBNP at the Week 12 were multiplied by a penalty factor (range from 1 to 2), if the patient had a Category 1 event (death, listing for heart transplant, or requiring VAD/ECMO/mechanical ventilation/intra-aortic balloon pump for life support) prior to Week 12.

4. For each penalty factor and each penalized imputed data set, the primary analysis ANCOVA model was fitted based on the imputed data set. The results were combined using Rubin's rules for each penalty factor.

1.4.1.3 Patient Disposition, Demographic and Baseline Characteristics

There were 143 patients who were randomized and received at least one dose of study drug by January 31, 2019. 110 of these patients were included in the Full Analysis Set. These patients were randomized on or before November 14, 2018. The study is still ongoing. The sponsor reported that as of June 30th, 198 patients have been randomized (Age group 1= 134 Age Group 2= 64). 159 patients have completed week 12 visit (Age group 1= 113 and Age Group 2= 46).

Table 2: Patient Disposition (Full Analysis Set)

	LCZ696	Enalapril	Total
Total N	55	55	110
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%)
Death	2	4	6
Physician decision	0	1	1
Subject/guardian decision	3	3	6
Double-blind epoch ongoing	42 (76.4%)	42 (76.4%)	84 (76.4%)

[Source: review's table]

Majority of FAS patients continue in the double-blind epoch. Thirteen (11.8%) patients prematurely discontinued from the study (Table 2).

The FAS included 110 patients. There were 10 patients in each treatment group who were between 1 to 6 years of age. Demographic and baseline characteristics were mostly balanced but LCZ 696 group had fewer male patients and black patients than in the enalapril group. LCZ696 group had more patients with prior heart failure hospitalization or on a heart transplant list (Table 3).

Table 3: Patient Demographics and Baseline Characteristics

		LCZ696	Enalapril	Total
Total N		55	55	110
Age	Mean (SD)	10.9 (5.0)	11.4 (5.4)	11.2 (5.2)
	12 years to <18 years	28 (51%)	34 (62%)	62 (56%)
	6 years to <12 years	17 (31%)	11 (20%)	28 (26%)
	1 year to <6 years	10 (18%)	10 (18%)	20 (18%)
Gender	Male	25 (46%)	32 (58%)	57 (52%)
	Female	30 (45%)	23 (42%)	53 (48%)
Region	North America	29 (53%)	29 (53%)	58 (53%)
	Other	26 (47%)	26 (47%)	52 (47%)
Race	White	32 (58%)	31 (56%)	63 (57%)
	Black	7 (13%)	11 (20%)	18 (16%)
	Asian	9 (16%)	6 (11%)	15 (14%)
	Other	7 (13%)	7 (13%)	14 (13%)
NYHA/ROSS class at baseline	Class I	10 (18%)	7 (13%)	17 (16%)
	Class II	36 (66%)	38 (69%)	74 (67%)
	Class III	9 (16%)	10 (18%)	19 (17%)
	Class IV	0	0	0
Prior heart failure hospitalization		43 (78%)	32 (58%)	75 (68%)
On a heart transplant list		5 (9%)	1 (2%)	6 (6%)

[Source: Reviewer's table]

1.4.1.4 Results and Conclusions

The adjusted geometric mean ratio for NT-proBNP was 0.84 in the comparison of LCZ696 group and enalapril group with 95% confidence interval (0.67, 1.06). Both groups showed that NT-proBNP decreased from the baseline. But the comparison was not statistically significant (p-value=0.147).

Table 4: Main Analysis on NT-proBNP

LCZ696 AGM RTB		Enalapril AGM RTB		AGMR	
Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
0.57	(0.48, 0.67)	0.67	(0.57, 0.79)	0.84	(0.67, 1.06)

* AGM=adjusted geometric mean, RTB=ratio to baseline, AGMR=adjusted geometric mean ratio

[Source: Reviewer's Table]

Six patients had Week 12 NT-proBNP imputed in the primary analysis using multiple imputations (2 patients in LCZ696 and 4 patients in enalapril). Sensitivity analyses included completed case only and pattern mixture model with penalty factor (see Section 1.4.1.2 for details) and showed consistent results. Missing data at Week 12 did not have significant impact on the results or conclusion.

Table 5: Sensitivity Analyses on NT-proBNP

Model	Geometric Mean Ratio Estimate (95% CI)
Multiple imputation (Primary analysis)	0.84 (0.67, 1.06)
Complete cases	0.84 (0.67, 1.06)
Pattern mixture model (penalty factor=2)	0.82 (0.65, 1.04)

[Source: Reviewer's table]

The imbalanced demographic and baseline characteristics were included in the original ANCOVA model as covariates to evaluate the impact. The results showed that covariate adjustment did not appear to affect the conclusion and the adjusted geometric mean ratios were consistent with the original analysis (**Table 6**).

Table 6: Geometric Mean Ratio for NT-proBNP Adjusted for Selected Covariates

Model	Geometric Mean Ratio Estimate (95% CI)
Original	0.84 (0.67, 1.06)
Adjusted for Gender	0.84 (0.67, 1.07)
Adjusted for Race	0.86 (0.68, 1.08)
Adjusted for prior HF hospitalization	0.86 (0.68, 1.09)
Adjusted for transplantation list	0.86 (0.68, 1.08)

[Source: Reviewer's Table]

In the biomarker sub-study of adult heart failure trial PARADIGM-HF, the ratio of reduction in NT-proBNP was 0.73 with 95% CI (0.70, 0.77). The larger sample size resulted in a much narrower confidence interval but the reduction in NT-proBNP ratio in the PARADIGM-HF sub-study was almost double the reduction in the pediatric study.

Table 7 provides the descriptive summary on the clinical events. There were 5 patients in each treatment arm with at least one Category 1 event and 7 patients in each arm with at least one Category 2 event. Category 1 events include death, UNOS Status 1A listing for heart transplant or equivalent, and ventricular assist device (VAD)/extracorporeal membrane oxygenation (ECMO)/mechanical ventilation/intraaortic balloon pump requirement for life support. Category 2 events include worsening heart failure (defined by signs and symptoms of WHF that require an intensification of HF therapy with or without hospitalization), measures of functional status (NYHA/ROSS class change) and quality of life assessments (PGIS, PGIC, PedsQL). The clinical events, although not many, showed no difference between two treatment arms.

Table 7: Category 1 and Category 2 Events

	LCZ696 (N=55)	enalapril (N=55)
Patients with Category 1 events	5 (9%)	5 (9%)
Death	2 (4%)	3 (6%)
UNOS status 1A listing for heart transplant or equivalent	2 (4%)	1 (2%)
VAD/ECMO/mechanical ventilation/intra-aortic balloon pump requirement for life support	3 (6%)	2 (4%)
Patients with Category 2 events	7 (13%)	7 (13%)
Worsening heart failure hospitalization with intensive care unit stay	4 (7%)	4 (7%)
Worsening heart failure hospitalization without intensive care unit stay	4 (7%)	3 (6%)
Worsening heart failure without hospitalization	1 (2%)	1 (2%)

[Source: Reviewer's table]

1.5 Evaluation of Safety

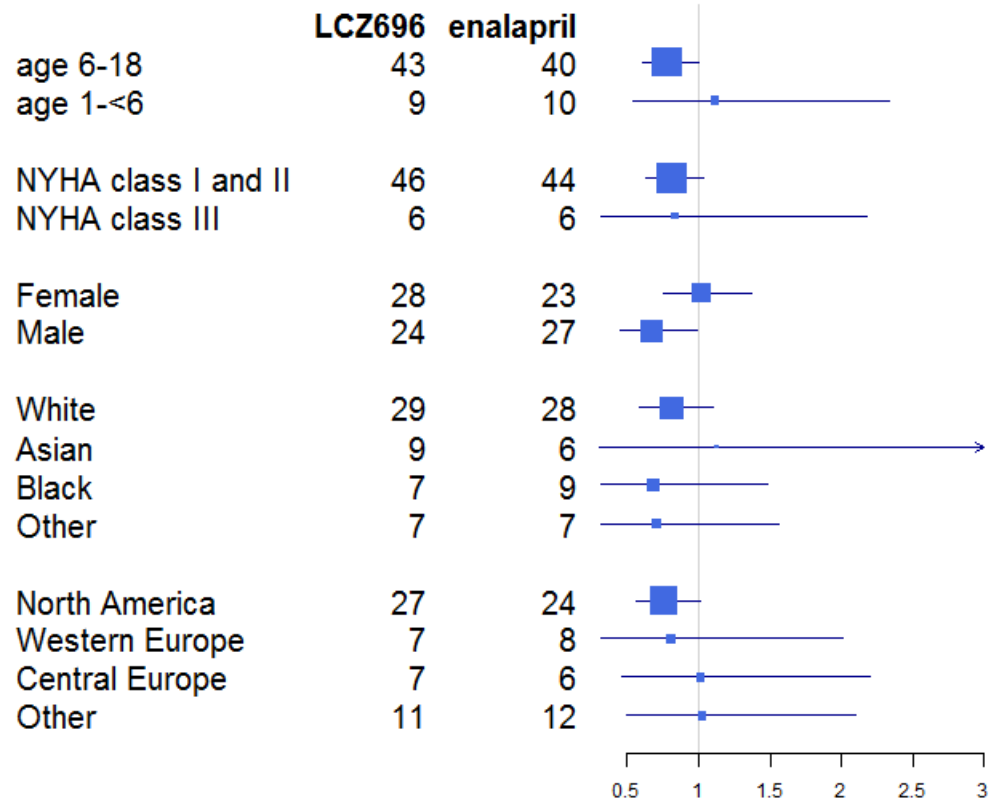
Please refer to the clinical review.

FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

1.6 Gender, Race, Age, and Geographic Region

Subgroup analyses were conducted by gender, race, region, NYHA/ROSS class and age groups (**Figure 2**). The analyses were based on observed cases only. Given that some subgroup had extremely small sample size and the results need to be interpreted with caution. We should avoid over-interpreting the results based on subgroup.

Figure 2: Forest plot from Subgroup Analyses



[Source: Reviewer's graph]

1.7 Other Special/Subgroup Populations

No other subgroups were analyzed.

SUMMARY AND CONCLUSIONS

1.8 Statistical Issues

Several sensitivity analyses, such as completed case analysis and pattern mixture model, showed consistent results with the primary analysis result in NT-proBNP. Missing data at Week 12 did not have any significant impact on study results or conclusion. The imbalanced demographic and baseline characteristics, such as gender, prior HF hospitalization, were included in the original ANCOVA model as covariates. The estimates on the ratio reduction in NT-proBNP after adjusting baseline covariates were also consistent. The conclusion remained the same.

The sponsor had extensive discussion with the Division about demonstrating efficacy of LCZ696 in pediatric population through extrapolation by using NT-proBNP. The Division agreed that based on the totality of evidence, NT-proBNP can be used to bridge the clinical efficacy of Entresto in adult patients with similar pathophysiology to pediatric patients with HF.

One key issue is what conclusion we can make on the efficacy of LCZ696 compared with enalapril in pediatric population based on the NT-proBNP results in pediatric study. This pediatric study now showed a much smaller ratio reduction in change from baseline NT-proBNP than in the adult HFrEF patients.

Is the relationship between NT-proBNP and primary clinical outcome still the same in pediatric patients as in adult HFrEF patients? Can we still bridge the efficacy results between two populations? Can children respond differently to the treatment? The fact that this pediatric study showed a much smaller ratio reduction in change from baseline NT-proBNP than in the adult HFrEF patients adds uncertainty of using the relationship established in adult patients for predicting the likely treatment effect in pediatrics. If we consider the treatment effect of LCZ696 is no better than enalapril in the pediatric patients, can we still safely conclude that LCZ696 is better than placebo? The study does not have a placebo arm in the trial and enalapril was never approved for treating pediatric patients with HF. There is uncertainty about the efficacy of enalapril in this population. We therefore should not overinterpret the change from baseline in NT-proBNP in each individual arm.

1.9 Collective Evidence

The basis for approval is that pediatric patients showed similar treatment effect in NT-proBNP as in adult HFrEF (heart failure reduced ejection fraction) patients with similar pathophysiology so that we can reasonably conclude that LCZ696 likely can show clinical benefit in the pediatric patients. Various sensitivity analyses including complete case analysis, pattern mixture model and ANCOVA models adjusting for the imbalanced baseline covariates all led to consistent ratio estimates on the change from baseline in NT-proBNP as the primary analysis result (ratio=0.85), which is a much smaller ratio reduction in NT-proBNP compared with the adult HFrEF patients. It is not clear whether LCZ696 may show any clinical benefit given the much smaller treatment effect in NT-proBNP in pediatric patients. The clinical events collected in the study so far, although not very many, did not indicate any difference between LCZ696 and enalapril arms. It is difficult to conclude at this point that LCZ696 is efficacious in treating pediatric patients with HF.

On the other hand, over 50 additional patients were randomized between January 2019 and June 2019, indicating a reasonable recruitment rate. It seems feasible to enroll 360 patients and collect sufficient number of clinical events at Week 52 to evaluate the efficacy and safety of LCZ696 in this pediatric population.

1.10 Conclusions and Recommendations

Various analysis showed a ratio around 0.85 between LCZ696 and enalapril in NT-proBNP change from baseline in the pediatric study. But there is insufficient information to conclude that LCZ696 has clinical benefit in pediatric patients. The reviewer recommends not to approve the indication based on the biomarker interim analysis results. The clinical benefit should be evaluated after the trial is fully completed and enough data on clinical primary endpoint at Week 52 is collected.

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/s/

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