Office of Clinical Pharmacology Review

NDA or BLA Number	207620
Link to EDR	\\cdsesub1\evsprod\NDA207620
Submission Date	4/1/2019
Submission Type	Pediatric efficacy supplement
Brand Name	ENTRESTO
Generic Name	Sacubitril/ Valsartan (LCZ696)
Route of Administration	Oral
Proposed Indication	Pediatric heart failure with left ventricular systolic dysfunction
Applicant	Novartis
Associated IND	IND 104628
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Table of Contents

1. EXECUTIVE SUMMARY

ENTRESTO (LCZ696) is a fixed dose combination of neprilysin inhibitor, sacubitril, and angiotensin receptor blocker (ARB), valsartan, approved by the FDA in July 2015 (NDA 207620) to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). The Applicant (Novartis) has submitted a supplemental New Drug Application (sNDA) for ENTRESTO to provide the interim pediatric clinical study report (PANORAMA-HF – study CLCZ696B2319) in response to FDA's Written Request - Amendment-1 (March 05, 2019).

This submission provides the results of the primary efficacy analysis of biomarker NT-proBNP (N terminal fragment of B-type natriuretic peptide prohormone) and the interim safety data from the ongoing 52-week randomized, double-blind, parallel-group study (PANORAMA-HF) to evaluate the efficacy and safety of ENTRESTO compared to enalapril, an angiotensin converting enzyme inhibitor (ACEi), in pediatric patients 1 year to < 18 years of age with heart failure due to systemic left ventricular systolic dysfunction. The Division issued a Written Request (March 02, 2017) to the Applicant to conduct a clinical study to evaluate the pharmacokinetics and pharmacodynamics of ENTRESTO in pediatric patients (1 month to < 18 years) and to evaluate the efficacy, safety and tolerability of ENTRESTO compared to enalapril as determined by a Global Rank Endpoint based on death, requirement for heart transplant or life support assistance, worsening heart failure and measures of functional status and quality of life. Recognizing the disease similarity between adult HFrEF patients with dilated cardiomyopathy (DCM) and pediatric patients with left ventricular systolic dysfunction and, in conjunction with data supporting the use of NT-proBNP to bridge the clinical efficacy of ENTRESTO from adults to pediatric patients, the Division amended the Written Request (March 05, 2019) to allow for determination of the efficacy of ENTRESTO in pediatric patients from 1 to <18 years of age using NT-proBNP as a bridging biomarker. The Division waived the requirement for patients < 1 year old due to the rarity of pediatric heart failure diagnosis in this age group.

The Division agreed to the use of NT-proBNP as a bridging biomarker based on the clinical data that showed changes in NT-proBNP to be correlated with heart failure outcomes in adults and with the markers of left ventricular systolic function and heart failure outcomes in pediatric patients. Applicant's analysis demonstrating the change in NT-proBNP explaining a significant proportion of the treatment effect of ENTRESTO on the clinical outcomes in PARADIGM-HF trial, was another evidence that the Division relied upon to agree to the analysis of Week 12 change from baseline in NT-proBNP as the primary analysis to compare ENTRESTO to enalapril in PANORAMA-HF. The interim analysis for primary efficacy was designed to demonstrate a statistically significant 30% greater reduction in NT-proBNP change from baseline at Week 12 for ENTRESTO compared to enalapril in pediatric patients. Compared to enalapril, ENTRESTO demonstrated 15.6% greater reduction (adjusted geometric mean ratio 0.84 (95%CI 0.67–1.06)) for the mean ratio of NT-proBNP at Week 12 to baseline levels in pediatric patients. Although, ENTRESTO did not demonstrate superiority over enalapril in pediatric patients, mean percent reduction from baseline in NT-proBNP level at Week 12 (44%) for ENTRESTO was similar to the reduction seen for ENTRESTO in adult DCM heart failure patients (43% at Month 1 and 52% at Month 8) in the pivotal Phase 3 trial (PARADIGM-HF).

This review primarily evaluates the change in NT-proBNP within the ENTRESTO arm in pediatric patients compared to that in adults from PARADIGM-HF as an evidence of effectiveness for ENTRESTO in pediatric patients. When grouped by different levels of baseline NT-proBNP, the percent reduction in NT-proBNP within ENTRESTO remain more or less consistent, however, enalapril showed a trend for a greater effect at higher baseline, acknowledging the limitations of interpreting data with small sample size. The reason for a slightly altered response to enalapril in pediatric patients compared to adults is not well understood. It is also noted that the median baseline NT-proBNP is lower in pediatric patients compared to adults. However, as demonstrated in adults from Val-HeFT and PARADIGM-HF trials, keeping the NT-proBNP levels low is important to minimize the risk for HF outcomes and in that regard ENTRESTO's effect on NT-proBNP as seen in pediatric patients may be of clinical significance. The review also looked at the frequency and dosing of other HF treatments, particularly diuretics, and ruled out any confounding effect of those treatments on the within treatment group changes in NT-proBNP observed for ENTRESTO and enalapril.

While the primary comparison to enalapril is not statistically significant, would it be reasonable to assume that if the percent change in NT-proBNP is similar in pediatric heart failure patients with left ventricular systolic dysfunction and adult DCM heart failure patients, the clinical benefit seen for ENTRESTO in adults will translate to pediatric patients? NT-proBNP is a marker for ventricular wall stretch and simultaneous inhibition of neprilysin and angiotensin II by ENTRESTO leads to a reduction in ventricular overload and wall stretch. As shown by the Applicant, decreases or increases in NT-proBNP by Month 1 correlated well with better or worse HF outcomes, respectively, in adult HF patients. Therefore, using the totality of evidence, the assumption to translate clinical benefit from adult to pediatric patients based on a similar percent change in NT-proBNP might seem reasonable.

Making within treatment comparison certainly comes with the limitation of moving away from the pre-specified between treatment comparison for the change in NT-proBNP that was initially designed to bridge the clinical efficacy of ENTRESTO relative to enalapril from adults to pediatric patients. While a reasonable case for bridging clinical benefit from adult to pediatric patients can be made for ENTRESTO based on a similar effect seen in adult and pediatric patients, it may not support superiority to enalapril. The question then arises whether the pediatric trial has shown value for adding sacubitril to valsartan, knowing that both valsartan and enalapril have a similar action of inhibition of the RAAS pathway. However, given that both valsartan and enalapril are not currently approved for pediatric heart failure and enalapril is used off label as standard of care to treat pediatric patients, another question arises whether showing superiority over enalapril should be the requirement to demonstrate evidence of effectiveness for pediatric approval of ENTRESTO.

On April 22, 2019, FDA approved Corlanor® (ivabradine) oral solution for the treatment of stable symptomatic heart failure due to DCM in pediatric patients aged 6 months and older. The approval was based on a successful demonstration of the primary endpoint i.e., proportion of pediatric patients with a 20% reduction in heart rate for ivabradine (72%) versus placebo (16%) in the pediatric PK/PD study. If ivabradine had effects on HR in pediatric patients like those observed in the pivotal SHIFT trial of ivabradine in adult patients, it was assumed that the clinical benefit on HF outcomes observed in adult DCM patients will translate to pediatric

patients. The situation with ENTRESTO appears no different or rather more convincing compared to ivabradine. Based on the understanding that adult and pediatric DCM patients have similar pathophysiology and symptoms, reduction in heart rate was used as a bridging biomarker for ivabradine which is expected to mediate its effects on heart failure outcomes via the only known effect of reduction in heart rate. In contrast, the reduction in NT-proBNP observed with ENTRESTO is a result of ENTRESTO's effect on ventricular overload and wall stretch and not a direct marker of the mechanism of action of either valsartan or sacubitril.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the results of study CLCZ696B2319 submitted to sNDA207620 and concludes that it is reasonable to translate the clinical benefit on HF outcomes for ENTRESTO from adults to pediatric patients 1 year to < 18 years of age based on a similar percent change in NT-proBNP from baseline to Week 12 observed between pediatric patients with left ventricular systolic function and adult DCM HF patients.

1.2 Post-Marketing Requirements and Commitments

None.

2. REGULATORY BACKGROUND

ENTRESTO was approved under section 505(b)(1) of Federal Food, Drug and Cosmetic Act (FDCA) on July 7, 2015 to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). The primary evidence of efficacy and safety of ENTRESTO were supported by the pivotal Phase 3 (CLCZ696B2314: PARADIGM-HF) trial which demonstrated superiority of ENTRESTO (200 mg BID) compared to enalapril (10 mg BID) in delaying time to the first occurrence of either CV death or HF hospitalization in adults with left ventricular systolic dysfunction (HFrEF- left ventricular ejection fraction (LVEF) ≤ 40%). The Applicant submitted an initial Pediatric Study Plan (iPSP) to the Division on December 11, 2013 requesting a full pediatric waiver (under Pediatric Research Equity Act or PREA) and a final agreement was reached with the Division (June 13, 2014) as the causes and mechanisms of heart failure in pediatric patients and are different from adults. Following the results from the pivotal Phase 3 PARADIGM-HF trial, the Applicant submitted a proposed Pediatric Study Request (PPSR) on February 06, 2015 to support further evaluation of ENTRESTO for the treatment of pediatric patients from 1 month to < 18 years with Stage C heart failure (structural heart disease with prior or current symptoms of HF) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%). The Applicant proposed evaluation of a more homogeneous pediatric HF population considering the potential differential effect systemic ventricular morphology may have on outcomes and to more closely resemble the adult HFrEF population from PARADIGM-HF.

Following a succession of discussions with the Division to reach an agreement on the pediatric study design and analysis, the Applicant submitted an updated PPSR on August 19, 2016 and, the Division issued a Written Request to the Applicant on March 02, 2017 for studies to obtain needed pediatric information on the efficacy and safety of ENTRESTO to be determined by a clinical study in pediatric patients (1 month to <18 years of age, divided into three age groups: 6 to <18 years (Age Group 1); 1 to < 6 years (Age Group 2); and 1 month to < 1year (Age Group

3)) with left ventricular systolic dysfunction. The objective of open label Part 1 of the clinical study was to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of more than one dose level of ENTRESTO in pediatric patients. The objective of Part 2 of the clinical study was to evaluate the clinical efficacy and safety of ENTRESTO compared to enalapril in pediatric patients as evaluated by the primary efficacy Global Ranked Endpoint based on death, requirement for heart transplant or life support assistance, worsening heart failure, functional status and quality of life. Following completion of Age Group1 in Part 1, and as per the Written Request, the Applicant reached agreement with the Division on July 28, 2017 on the target doses for Age Group 1 in Part 2. Age Group 2 (ages 1 to < 6 years) completed Part 1 (PK/PD) on March 12, 2018. The Applicant submitted Age Group 2 Part 1 on June 12, 2018 and reached agreement on doses for Part 2 with the Division in August 2018.

At the August 30, 2018 Type C meeting the Applicant requested removal of the requirement for Age Group 3 (pediatric HF patients ages 1 month to < 1year old). They cited concerns about recruitment and completion of the study of these patients in a reasonable timeframe as Age Group 3 patients frequently have congenital heart disease and often have a cardiac transplant or a device (or are waiting to receive one) making them ineligible for recruitment into PANORAMA-HF. Based on the supportive data provided by the Applicant, the Division agreed to remove the requirement for a minimum number of subjects to be enrolled in Age Group 3.

At the August 30, 2018 Type C meeting the Applicant also expressed concern for slow enrollment in the trial because of the limited number of patients, reluctance to provide informed consent and inexperienced sites. The Applicant proposed to predict efficacy in patients ages 12 to <18 years with systemic left ventricular dysfunction by extrapolating data from adult HFrEF patients with DCM which the Applicant identified as the adult population of interest in PARADIGM-HF. At the follow-up type A meeting on November 21, 2018, the Division agreed with the Applicant's data/analyses addressing similar pathophysiology between adults with non-ischemic DCM and pediatrics with DCM ≥ 1 year old. At the Type A Meeting on January 19, 2019, an agreement was reached with the Applicant over the approach to use NT-proBNP to bridge the clinical efficacy of ENTRESTO in adults to pediatric patients to support revising the WR and fulfilling the WR with a supplemental new drug application (sNDA) submission by April 5, 2019. The Division amended the WR (Amendment -1 issued March 5, 2019), to allow determination of ENTRESTO's efficacy in pediatric patients from 1 to <18 years of age using NT-proBNP as a bridging biomarker.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

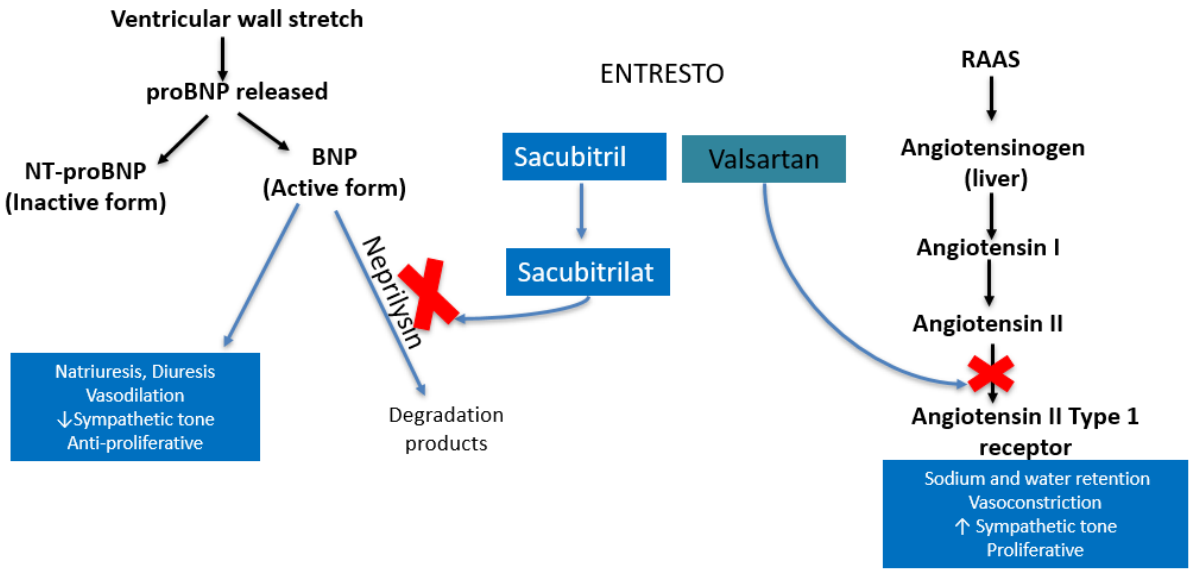
This is an abridged version of the question-based review. For review of clinical and clinical pharmacology studies supporting the approval of ENTRESTO, refer to the review associated with original NDA 207620. This section primarily reviews the pediatric sNDA supported by the interim-analysis of the pivotal pediatric clinical study PANORAMA-HF (study CLCZ696B2319). This section provides a comprehensive review of the data that the Applicant provided in support of the use of NT-proBNP as a bridging biomarker, study design of PANORAMA-HF, the primary efficacy analysis of changes in NT-proBNP, and the review team's analyses and conclusions about the evidence of effectiveness of ENTRESTO in the PANORAMA-HF.

3.1 What is the mechanism of action for the components of ENTRESTO?

ENTRESTO is combination of sacubitril (AHU377), a pro-drug, and valsartan - an angiotensin II type-1 (AT_1) receptor blocker (ARB). Following oral administration of ENTRESTO, sacubitril is metabolized by esterases to the active-metabolite sacubitrilat (LBQ657), a neprilysin inhibitor. The cardiovascular and renal effects of ENTRESTO in heart failure patients are attributed to the enhancement of beneficial effects of natriuretic peptides (NPs) that are degraded by the endopeptidase, neprilysin, via sacubitrilat and the simultaneous inhibition of deleterious cardiovascular and renal effects of angiotensin II and its effectors via valsartan.

Valsartan inhibits the renin-angiotensin-aldosterone system (RAAS) by selective and competitive blockade of the binding of angiotensin II to the AT1-receptor in many tissues, such as the vasculature, heart, kidney and the adrenal gland. Valsartan inhibits actions of angiotensin II and aldosterone, the principal effector hormones of the RAAS, associated with vasoconstriction, renal sodium and fluid retention resulting in increased blood pressure and blood volume, and activation of cellular growth and proliferation of vascular and cardiac cells.

Figure 1: Mechanism of action of ENTRESTO



NPs represent a family of peptide hormones, including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). Precursor prohormones proANP and proBNP are mainly synthesized and released into the circulation by the heart in response to myocardial stretch and other hemodynamic and inflammatory stimuli, whereas CNP is synthesized by endothelial and renal epithelial cells and acts in a paracrine manner. NPs are cleared from the circulation by neprilysin-dependent proteolytic degradation and through the natriuretic peptide clearance receptor (NPR-C). The prohormone proBNP is cleaved to the biologically active form BNP, and biologically inactive N-terminal-proBNP (NT-proBNP). Neprilysin is the principal enzyme that degrades the biologically active BNP. Neprilysin is not involved in the degradation of NT-proBNP. ANP and BNP bind to the particulate guanylyl cyclase A receptor (pGC-A), activate the second messenger 30-50-cyclic guanosine

monophosphate (cGMP) and mediate cardiovascular and renal effects including natriuresis, vasodilation, suppression of hypertrophy and fibrosis, inhibition of the renin and aldosterone release, and reduction of sympathetic activity. ENTRESTO potentiates the physiological effects of NPs by inhibiting neprilysin-dependent degradation resulting in increased levels of NPs.

As neprilysin is involved in degrading BNP while having no effect on the breakdown of NT-proBNP, one may expect that patients who are treated with ENTRESTO will have higher plasma BNP levels due to the inhibition of neprilysin activity. Conversely, NT-proBNP levels are not directly influenced by neprilysin inhibition. The combined effect on neprilysin inhibition and angiotensin II type-1 receptor blockade, is associated with decreases in NT-proBNP possibly due to reduction in ventricular wall stretch.

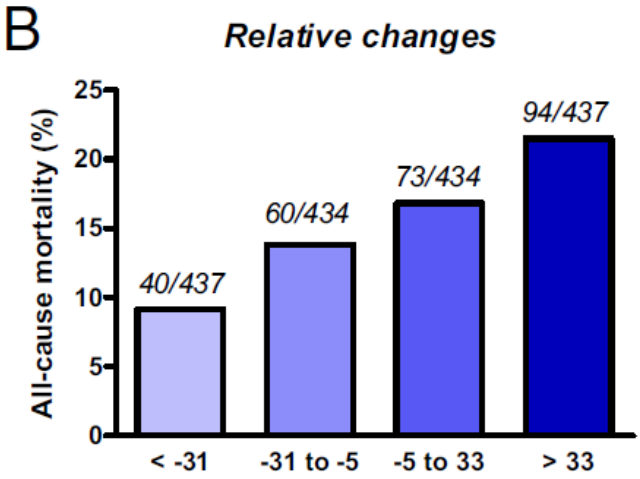
3.2. What data supports or qualifies the use of NT-proBNP as bridging biomarker?
The following section describes the information provided by the Applicant and the analysis conducted by the Applicant that the Division agreed on to support the use of NT-proBNP as a bridging biomarker.

i. Correlation of changes in NT-proBNP with heart failure outcomes in adults:
The evidence from post-hoc analysis from Valsartan HeFT trial and PARADIGM-HF trial in adult heart failure patients was used by the Applicant in support of demonstrating the correlation of changes in NT-proBNP with heart failure outcomes.

Valsartan-HeFT trial:
The Valsartan Heart Failure trial (Val-HeFT) was a randomized, placebo-controlled, double-blind, parallel-arm multicenter trial which was designed to determine whether addition of valsartan improved the outcomes of patients receiving standard-of-care therapies for heart failure. A total of 5010 patients with stable, symptomatic heart failure (New York Heart Association (NYHA) class II, III, or IV) who were on prescribed HF therapy and had left ventricular ejection fraction (LVEF) < 40% and left ventricular diameter in diastole adjusted for body surface area $\geq$ 2.9 cm/m^2 were stratified according to whether or not they were receiving a beta-blocker as background therapy and randomized to receive 160 mg of valsartan (n=2511) or placebo (n=2499) twice daily.

A post-hoc analysis of 1,742 patients from the placebo-arm of Val-HeFT was conducted to evaluate the association of changes in NT-proBNP concentration over time with primary outcome of all-cause mortality in patients with chronic and stable HF. Median (Q1 to Q3) concentrations of NT-proBNP were 861 (368 to 1,803) pg/mL at baseline and 783 (327 to 1,781) pg/mL after 4 months of follow-up (n = 1,742). Patients who died before 4 months of follow-up (n = 117) were excluded from the analysis related to changes in NT-proBNP concentration and subsequent mortality. A progressive increase in the rate of all-cause mortality was observed in relation to quartiles of percent relative changes in NT-proBNP from baseline to 4 months. For patients in quartile 1 with a reduction of NT-proBNP from baseline >31%, the rate for all-cause mortality was 9.2% whereas in quartile 4 with patients having an increase in NT-proBNP of >33%, the rate for all-cause mortality was 21.5% (**Figure 2**).

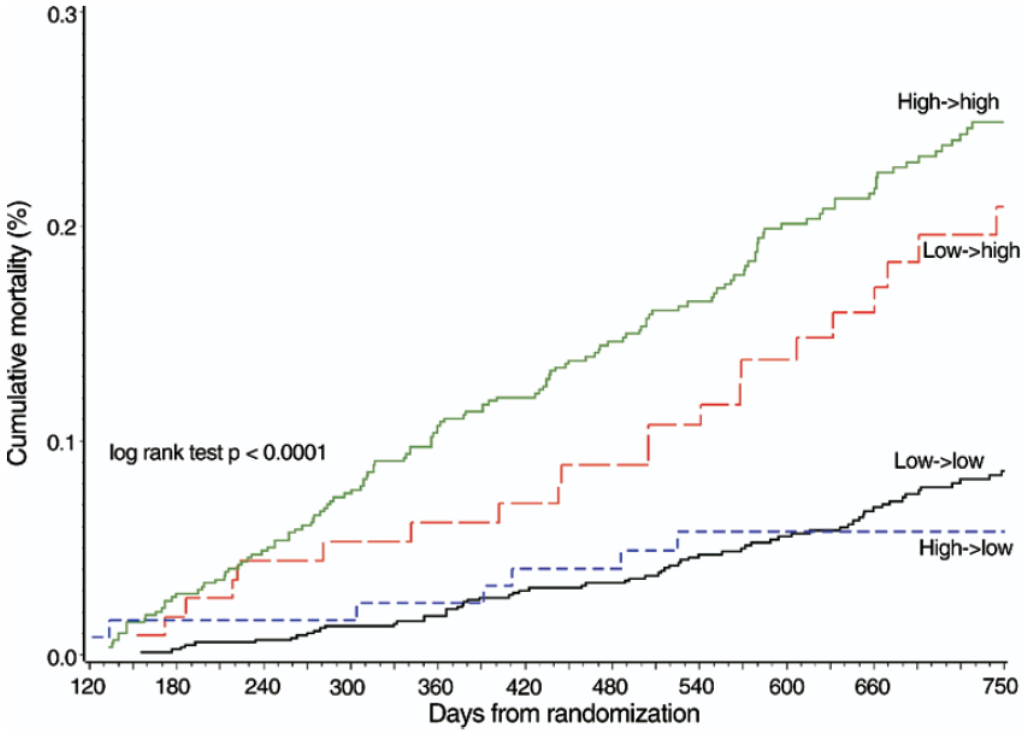
Figure 2: Association of percentage relative change in NT-proBNP to the primary outcome of all-cause mortality (Valsartan Heart Failure Trial)



Source: Figure 1B, Masson S, et al., J Am Coll Cardiol. 2008

A categorical analysis of the association of the change in NT-proBNP from baseline to month 4 was conducted by dividing patients into 4 categories according to NT-proBNP concentrations at baseline and 4 months relative to a threshold (1,078 pg/mL) determined by receiver-operator characteristic curves. A multivariate Cox regression analysis was performed in a model considering the 4 categories of NT-proBNP changes, baseline NT-proBNP, and the clinical variables associated with outcome to evaluate independent contribution of categorical NT-proBNP changes over time to outcome. Kaplan-Meier survival curves for patients classified by categorical changes are shown in (**Figure 3**). Patients whose NT-proBNP remained above threshold at baseline and 4 months (n=599, High → High) had an increased risk for all-cause-mortality (HR 1.877 [1.180-2.986]), whereas those whose values dropped below the imposed threshold after 4 months ((n=125, High → Low) had a significantly lower risk for all-cause mortality which in turn was similar to those who started and remained with NT-proBNP below threshold at baseline and 4 months (n=904, Low → Low) (HR=0.61 [0.290-1.302]). Similarly. patients whose NT-pro-BNP was initially below a specific threshold value at baseline had a significantly increased risk for all-cause mortality if their NT-proBNP was above threshold after 4 months (n=114, Low → High). These findings from Val-HeFT show that changes in NT-proBNP concentrations over time relative to baseline are associated with heart failure outcomes in patients with chronic HF.

Figure 3: Categorical analysis of the association of changes in NT-proBNP from baseline to month 4 to the primary outcome of all-cause mortality (Valsartan Heart Failure Trial)



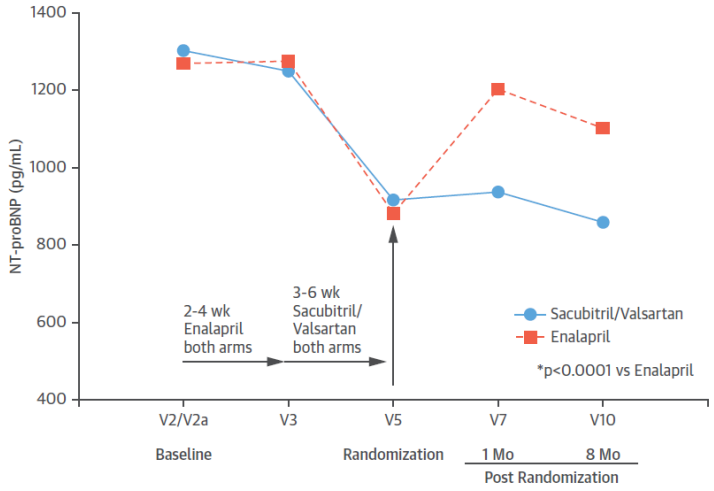
Source: Figure 3, Masson S, et al., J Am Coll Cardiol. 2008

PARADIGM-HF trial:
The Applicant provided the results of PARADIGM-HF (study CLCZ696B2314) in adults with HFrEF as an additional evidence in support of association of the change in NT-proBNP over time, as assessed by absolute, relative and categorical change, with the HF clinical outcomes. PARADIGM-HF is a randomized, double-blind, multicenter, parallel arm, active-controlled Phase 3 trial that evaluated the efficacy and safety of ENTRESTO vs. enalapril in 8442 patients with HFrEF (ejection fraction ≤ 40% (changed during the trial to ≤ 35% by amendment), New York Heart Association functional class II to IV symptoms, and elevated NPs (if no recent hospitalization for HF: BNP ≥150 ng/L or NT-proBNP ≥600 ng/L; if hospitalization for HF within 12 months: BNP ≥100 ng/L and NT-proBNP ≥400 ng/L). Following 4 to 6 weeks of single-blind enalapril run-in, followed by an additional 4 to 6 weeks single-blind ENTRESTO run-in, if both drugs were tolerated at target dose during the run-in periods, patients were then randomized in a 1:1 ratio to enalapril 10 mg BID or ENTRESTO 200 mg BID. PARADIGM-HF demonstrated a clinically and statistically significant effect of ENTRESTO (200 mg BID) on delaying the primary composite endpoint of CV death or HF hospitalization as well as CV death alone compared to enalapril (10 mg BID).

A post-hoc biomarker assessment sub-study of PRADIGM-HF (N=2080) assessed NT-proBNP at 4-weeks and 8-months post-randomization to evaluate the relationship between longitudinal

changes in NT-proBNP and clinical outcomes (morbidity and mortality) in patients with HFrEF and the influence of the treatment assigned on this relationship.

Figure 4: Median NT-proBNP in patients treated with ENTRESTO versus enalapril at each study time point



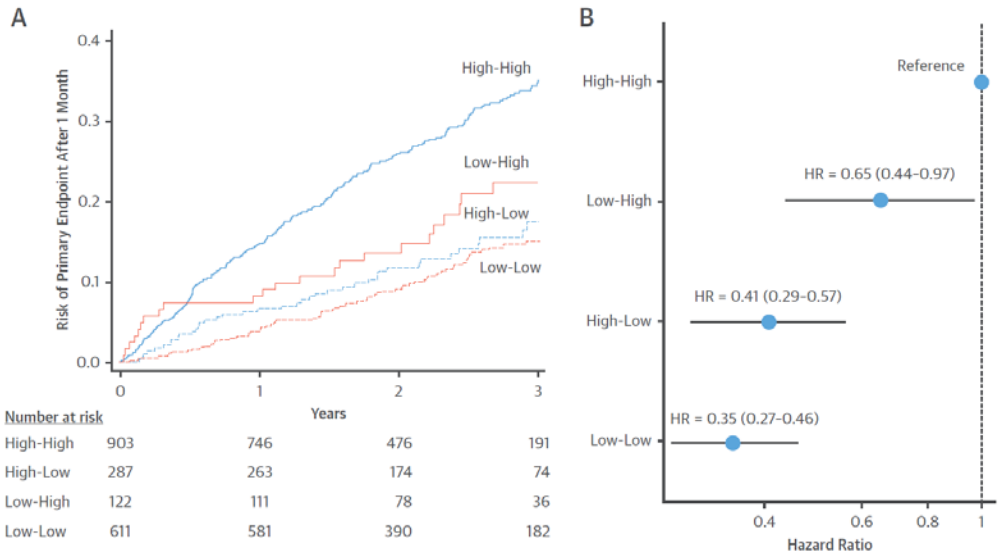
NT-proBNP (pg/mL) Median (Q1;Q3)					
	V2/V2a	V3	V5	V7	V10
Sacubitril/Valsartan n	1303 (781;2371) 1051	1251 (653;2208) 440	917 (526;1653) 1018	938 (511;1595) 971	859 (450;1708) 885
Enalapril n	1269 (762;2184) 1029	1276 (698;2186) 435	882 (517;1692) 997	1203 (711;2061) 971	1102 (610;2073) 874

Source: Type A Meeting Package IND 104628

Median NT-proBNP was similar between the two treatment arms. The median NT-proBNP did not change significantly during the enalapril run-in but decreased significantly during the ENTRESTO run-in (**Figure 4**). One month after randomization, NT-proBNP was significantly lower in the ENTRESTO-treated patients (median: 938 [Inter-quartile range: 511 to 1,595] pg/mL) compared with enalapril treated patients (median:1,203 [Inter-quartile range: 711 to 2,061] pg/mL).

Based on a threshold NT-proBNP level of 1000 pg/mL, Patients were grouped into 4 categories based on their NT-proBNP levels being High (above a threshold of 1000 pg/mL) or Low (below a threshold of 1000 pg/mL) at baseline (visit 2) and at month 1 post-randomization (**Figure 5**). Using a categorical analysis, the lowest primary event rate occurred in patients in the Low-Low group (NT-proBNP ≤1,000 pg/mL at both baseline and 1 month), and the highest primary event rate was seen in patients in the High-High group (NT-proBNP > 1,000 pg/mL at both baseline and 1 month). Patients in the High-Low group (NT-proBNP >1,000 pg/mL at baseline and ≤1,000 pg/mL at 1 month) and Low-High group (NT-proBNP ≤ 1,000 pg/mL at baseline and > 1,000 pg/mL at 1 month) had intermediate rates of the primary event.

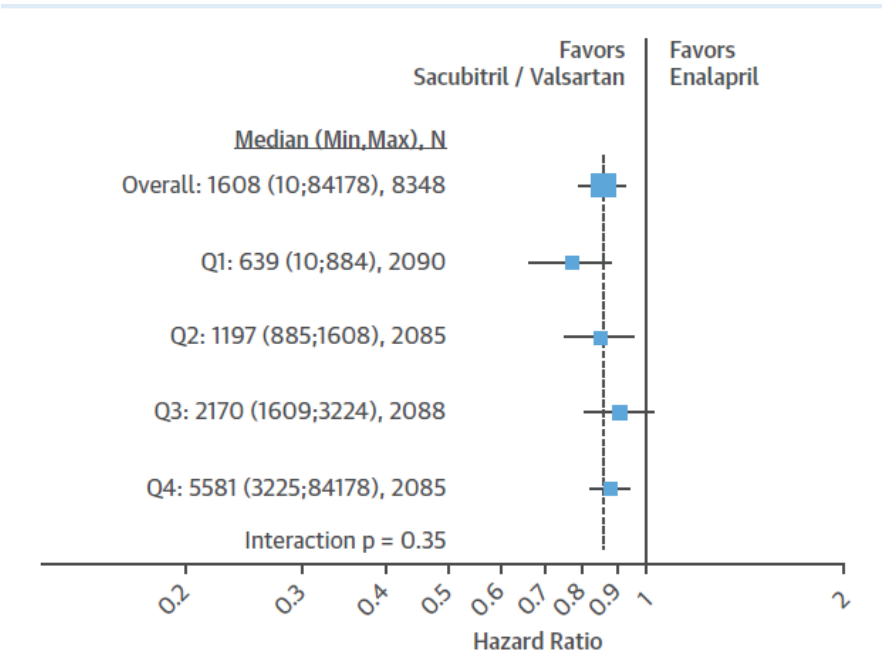
Figure 5: Effects on risk of primary endpoint if N-Terminal Pro–B-Type Natriuretic Peptide changed from baseline to 1 Month after randomization



Source: Type A Meeting Package IND 104628

Median NT-proBNP at baseline was 1,269 (IQR: 762 to 2,184) pg/mL for enalapril-treated patients and 1,303 (IQR: 781 to 2,371) pg/mL for ENTRESTO treated patients. Baseline NT-proBNP did not modify the treatment effect of ENTRESTO versus enalapril (**Figure 6**)**.** In each quartile of baseline NT-proBNP, treatment with ENTRESTO decreased the primary event rate compared to treatment with enalapril to a similar extent.

Figure 6: Effect of randomized therapy on relationship between baseline NT-proBNP and primary event rate



Source: Figure 6, Zile M, et al., J Am Coll Cardiol. 2016

ii. Proportion of the treatment effect of Entresto on the clinical outcome explained by change in NT-proBNP at Month 1 after adjustment for baseline NT-proBNP in PARADIGM-HF

The Applicant investigated the relationship between NT-proBNP and the change over time in NT-proBNP with the risk of a primary composite endpoint of CV death or HF hospitalization. The Applicant assessed the magnitude of ENTRESTO treatment effect on the primary composite endpoint that is explained by the baseline NT-proBNP and post-randomization change from baseline in NT-proBNP. Cox proportional hazards model including log transformed NT-proBNP value over time as a time-dependent covariate and log-transformed baseline NT-proBNP value and region as covariates was used (For further details on the statistical analysis refer Statistics review by Dr. Jialu).

In the biomarker sub-study of PARADIGM-HF (N=2,080), the hazard ratio (ENTRESTO/ enalapril) for the primary composite endpoint was 0.83 (95% confidence interval [CI], 0.69 to 1.00). The ratio of NT-proBNP to baseline levels was approximately 25% lower in the ENTRESTO group as compared to the enalapril group at 1 month (Ratio: ENTRESTO/Enalapril 0.74, 95% CI 0.70 to 0.78) and 8 months (Ratio: 0.752, 95% CI 0.700 to 0.808) post-randomization. About 84% (2-sided 90% CI (9.49, 165.13)) of the treatment effect on time to first event of CV death or HF hospitalization endpoint was explained by baseline and post-baseline changes in NT-proBNP (**Table 1**). The assessment was repeated for various subgroups of HF etiology in PARADIGM-HF to explore if the relationship is consistent across these

subgroups. In the DCM subgroup, the ratio of NT-proBNP to baseline levels was approximately 38% (95%CI -45%, -29%) lower in the ENTRESTO group as compared to the enalapril group at 1-month post-randomization and 39% (95%CI -50%, -25%) lower in the ENTRESTO group as compared to the enalapril group 8 months post-randomization. About 77% (2-sided 90% CI (-14, 153)) of the treatment effect on primary composite endpoint was explained by baseline and post-baseline changes in NT-proBNP in the DCM subgroup.

Table 1: Assessment of treatment effect on the composite of cardiovascular death or heart failure hospitalization explained by NT-proBNP change at month 1 on top of baseline NT-proBNP – ENTRESTO vs enalapril

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

Clinical Overview document, Table 1-2

Overall, the biomarker sub-study of PARADIGM-HF trial demonstrated that change in plasma NT-proBNP from baseline to month 1 was associated with a change in cardiovascular mortality and HF hospitalization rate in patients with HFrEF, as evaluated by both, categorical analysis and as a continuous analysis adjusted for baseline NT-proBNP. The association between changes in NT-proBNP and the clinical outcomes appeared to be consistent across the DCM-subgroup. The relationship between changes in NT-proBNP and changes in subsequent risk of a primary endpoint event was independent of treatment group assignment.

iii. Correlation of changes in NT-proBNP with markers of left ventricular systolic function and heart failure outcomes in pediatric patients

Thirty-six (36) children with HF secondary to dilated cardiomyopathy were retrospectively evaluated by Rusconi et al. for associations between NT-proBNP levels and NYHA/Ross functional class and LV remodeling using generalized linear mixed effects models. In this study, a 10-fold increase in NT-proBNP serum levels was associated ($p < .001$) with a 9.8% decrease in LVEF as well as deterioration in other function parameters and an increased-odds of being in functional class III/IV (OR 85.5; 95% CI, 10.9 to 671.0). In addition, an NT-proBNP level greater than 1000 pg/mL identified children constantly or intermittently in functional class III-IV with 95% sensitivity and 80% specificity.

The results from a retrospective study by den Boer et al in 115 children with DCM demonstrated the association of NT-proBNP change over time with clinical outcomes (den Boer et al 2016). All children (0 to 18 years) who fulfilled the criteria of DCM (median age 1.3 years (IQR 0.3-7.3 years) were selected for this study investigating the value of NT-proBNP measurements in predicting outcomes defined as death, heart transplantation and need for mechanical circulatory support. Patients were analyzed in two groups: 79 children from diagnosis up to 1 year and a second group of 68 children surviving more than 1 year and still meeting the DCM criteria. The latter group was followed for a median time of 4.2 years. All patients were up-titrated to the maximal tolerated dosages of angiotensin converting enzyme inhibitors (ACEI) and β-blockers. Any 10% increase in NT-proBNP over a 1-month period 30 days after diagnosis indicated higher risk of cardiac death HR 1.72, 95% CI 1.11 to 2.71, p = 0.01), whereas a 10% decrease indicated a lower risk (HR 0.55, 95% CI 0.33 to 0.89). A doubling over 3 months >1 year after diagnosis was associated with higher risk (HR 10, 95% CI 1.97 to 50.6) and a 50% reduction was associated with lower risk (HR 0.10, 95% CI 0.020 to 0.508). At any time during follow-up, a two-fold higher NT-proBNP resulted in a 2.9 times higher risk in the first year (p <0.001) and a 1.8 times higher risk thereafter (p <0.001).

The studies by den Boer et al and Rusconi et al, demonstrate positive correlations between NT-proBNP changes and clinical outcomes and improvements in echocardiographic measures of left ventricular systolic function, respectively, in pediatric heart failure patients with dilated cardiomyopathy.

Based on the totality of evidence summarized under i, ii, and iii, the Division agreed with the use of NT-proBNP to bridge the clinical efficacy of ENTRESTO from adult HFrEF patients to pediatric patients with HF:

- Changes in NT-proBNP are correlated with heart failure outcomes in adults (Valsartan HeFT trial)
- Changes in NT-proBNP are correlated with markers of left ventricular systolic function and heart failure outcomes in pediatric patients (Rusconi et al 2011, den Boer et al 2016)
- Change in NT-proBNP at Month 1 explains a significant proportion of the treatment effect of Entresto on the clinical outcome after adjustment for baseline NT-proBNP in PARADIGM-HF. Similar analyses in subgroups of patients, including adult subsets most relevant to the pediatric population of interest, produced consistent results.

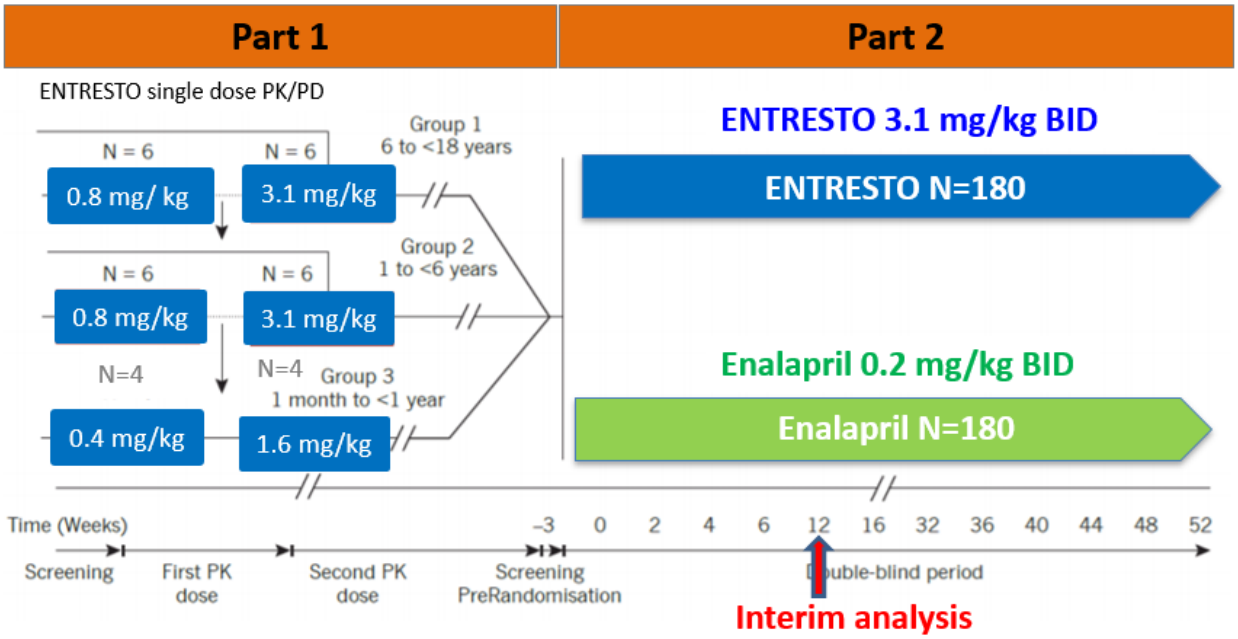
The Division further noted the wide confidence interval around the point estimate of the proportion of the treatment effect explained by ENTRESTO as basis for concern, however, the Division concluded that the evidence, in its totality, is sufficient to support the proposed use of NT-proBNP in ENTRESTO's pediatric development program. (Ref: Type A meeting minutes dated January 18, 2019).

3.3 What are the design elements of the pediatric study?

Study CLCZ696B2319 (PANORAMA-HF) is a two-part clinical trial in pediatric HF patients ages 1 month to <18 years (**Figure 7**). The PANORAMA-HF study population consists of pediatric HF patients with systemic left ventricular systolic dysfunction. This pediatric HF population has pathophysiology similar to adult HFrEF patients, particularly of DCM etiology, where sacubitril/valsartan has demonstrated a statistically significant benefit compared to

enalapril for the combined mortality and hospitalization for HF endpoint. The overall purpose of this study is to determine whether pediatric HF patients will derive greater clinical efficacy with sacubitril/valsartan compared to enalapril over a 52-week treatment duration. In PANORAMA-HF, patients were divided across three groups based on age, 6 to <18 years (Age Group 1); 1 to <6 years (Age Group 2); and 1 month to <1year (Age Group 3).

Figure 7: Study schematic of PANORAMA-HF clinical trial (Study CLCZ696B2319)



Source: Adapted from Figure 9-1 CSR Study CLCZ696B2319

Part 1 of the study was a multi-center, open-label study to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of two dose strengths of LCZ696 (0.8 mg/kg for Dose Cohort 1 and 3.1 mg/kg for Dose Cohort 2 in Age Group 1 and 2 and, 0.4 mg/kg for Dose Cohort 1 and 1.6 mg/kg Dose Cohort 2 in Age Group 3). The 0.8 mg/kg dose of ENTRESTO corresponds to the sacubitril/valsartan 24/26 mg (50 mg) dose for adult subjects with a body weight of 65 kg. 50 mg dose is the recommended starting dose for adult HF patients who are ACEI/ARB naïve, on a low dose of ACEI/ARB treatment, have severe renal impairment, or have moderate hepatic impairment. The sacubitril/valsartan 0.8 mg/kg dose delivers valsartan exposure bioequivalent of 0.6 mg/kg valsartan which is below the starting dose for valsartan in pediatric hypertension (1.3 mg/kg). The sacubitril/valsartan 3.1 mg/kg dose corresponds to the sacubitril/valsartan 97/103 mg (200 mg) dose in adult subjects of 65 kg body weight. In adult HF patients, no significant impact of body weight on the PK of sacubitril/valsartan analytes was observed over a range of 41.5 kg to 157.3 kg. Therefore, for pediatric patients in this weight range, sacubitril/valsartan 3.1 mg/kg is expected to have similar exposure to that observed in adult heart failure patients.

Target dose selection for the Part 2 of the study were based on the PK, PD and safety data obtained from Part 1. For Part 1, the PK and PD endpoints after single dose treatment were: PK: C_{max} (ng/mL); T_{max}(h); AUC_{last}, AUC_{inf} (h.ng/mL); CL/F (L/h); $T_{1/2}$ (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). In Part 1 there were 18 patients enrolled with 9 patients in Age Group 1 (6 to <18 years) and 9 patients in Age Group 2 (1 to < 6 years). Part 1 included balanced representation of patients from Age Group 1 with 5 patients between the ages of 12 to <18 years old and 4 patients between the ages of 6 to 11 years old.

Part 2 of the study was a double-blind, randomized, multi-center, active-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of ENTRESTO compared to enalapril in pediatric HF patients. The eldest age group was the first cohort of Part 1. Results for each age cohort in Part 1 was reviewed and doses for each age cohort in Part 2 were agreed upon by the Division before enrollment began for that age cohort in Part 2. The target dose for enalapril was 0.2 mg/kg BID (0.4 mg/kg total daily dose) with a maximum dose of 10 mg BID (20 mg total daily dose). The target dose for ENTRESTO was 3.1 mg/kg BID. In the Part 1 of PANORAMA-HF, single oral 3.1 mg/kg dose of ENTRESTO demonstrated similar PK in pediatric HF patients aged 6 to <18 years old and 1 to <6 years old compared to the predicted PK in adult heart failure patients at an equivalent ENTRESTO dose (200 mg). The assessment was based on 1) similar observed sacubitril elimination half-life and similar apparent total body plasma clearance for sacubitril and valsartan and, 2) similar exposure of sacubitrilat and valsartan between the pediatric and adult patients with the geometric mean ratio of the systemic exposure ($AUC_{0-\infty}$ pediatrics/$AUC_{0-tau,ss}$ adults) for sacubitrilat and valsartan being within 0.80-1.25 (**Table 2**). The single dose pharmacokinetics of ENTRESTO were also comparable between pediatric heart failure patients of 1 to <6 years old and 6 to <18 years of age. Following 200 mg single oral dose, geometric mean apparent total body plasma clearance of sacubitril in adults and pediatric patients 6 to 18 years is 38 L/h and 36 L/h, respectively. Geometric mean apparent total body plasma clearance of valsartan in adults and pediatrics patients 6 to 18 years and 1 to < 6 years of age is 3.8 L/h, 3.3 L/h and 2.6 L/h, respectively.

Part 1 PK results showed that the systemic exposures of the analytes of 3.1 mg/kg ENTRESTO in pediatric patients aged 6 to <18 years old and 1 to <6 years old is similar to that in adult patients following administration of a single dose of ENTRESTO equivalent to a 200 mg (97/103 mg sacubitril/ valsartan) adult dose. The Division agreed with Applicant's proposal to evaluate 3.1 mg/kg as the target maintenance dose of ENTRESTO in the Part 2 of PANORAMA-HF.

Table 2: Comparison of PK parameters of sacubitril and valsartan in pediatric patients from PANORAMA-HF study and population PK model-based prediction in adult HFrEF patients

Analyte	Study population	Geometric mean AUC ng.hr/mL	Geometric mean ration $AUC_{0-\infty}$ pediatrics/ $AUC_{0-tau, ss}$ adults
Sacubitril	Pediatric patients 6 to < 18 years	2660[a]	0.84
	Pediatric patients 1 to < 6 years	1000[a]	0.31
	Adult patients	3171[b]	
Sacubitrilat	Pediatric patients 6 to < 18 years	145433[a]	0.94
	Pediatric patients 1 to < 6 years	123549[a]	0.80
	Adult patients	154873[b]	-
Valsartan	Pediatric patients 6 to < 18 years	35314[a]	1.00
	Pediatric patients 1 to < 6 years	44545[a]	1.26
	Adult patients	35238[b]	-

a $AUC_{0-\infty}$ following single oral 200 mg dose of ENTRESTO
b AUC_{0-tau} at steady state following 200 mg BID of ENTRESTO
Source: Study CLCZ696B2319 Part 1 PK/PD and Safety Data for Age Group 2 (1 to <6 years old) and (6 to <18 years old) CSR- [PANORAMA_FDA Report_2], and [other-cor-ped-excel-PANORAMA-FDA-Report].

Blinded study drug was titrated to the target dose as tolerated per the safety monitoring criteria for adverse events (symptomatic hypotension, worsening renal function, or hyperkalemia, abnormal laboratory values) approximately every 2 weeks. Patients are required to discontinue enalapril, other ACEI, ARB or renin inhibitor prior to initiation of the blinded study drug at randomization. The initial study drug dose started at randomization was dose level 1 or 2 (**Table 3**). Patients who are ACEI/ARB naïve or on low dose ACEI/ARB prior to randomization should start at dose level 1 at randomization. Patients who are on higher doses of ACEI/ARB (dose levels 3 or 4;) prior to randomization should start at dose level 2. Patients continued taking their background HF therapy except for ACEIs, ARBs and renin inhibitors.

Table 3: Study drug dose levels for double-blind enalapril and ENTRESTO in PANORAMA-HF Part 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: Study CLCZ696B2319 CSR

Part 2 of the clinical study was originally designed to determine whether ENTRESTO is superior to enalapril for the treatment of HF as assessed using a Global Rank endpoint based on Category 1 event: 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 at end of study; Category 2 event of worsening heart failure; and measures of functional status and quality of life. Patients were assigned to ENTRESTO or enalapril arms in a ratio of 1:1 (180 patients each arm) for a planned treatment duration of 52 weeks. Part 2 was to continue until at least 360 patients have completed the study and 80 patients have an event in Category 1 or 2. A blinded interim efficacy analysis and futility analysis was planned to be performed when at least 180 patients (at least 36 patients from each age group) have completed the study, and at least 40 patients have had an event in Category 1 or 2.

Since initiating Part 2 for Age Group 1 on August 21, 2017 and as of mid-July 2018, there were 60 patients randomized in Part 2. Encountering challenges of recruiting pediatric HF patients, especially in the younger age groups, the Applicant proposed the use of NT-proBNP as a bridging biomarker to evaluate the clinical efficacy of ENTRESTO compared to enalapril, based on the understanding that pathophysiology between pediatric HF patients with DCM and adult HFrEF DCM patients is similar (FDA/M-CERSI pediatric workshop in October 2017). The Sponsor proposed and interim analysis to evaluate the primary clinical efficacy in pediatric patients by NT-proBNP change from baseline to Week 12, for ENTRESTO relative to enalapril. Follow-up for safety was to continue until at least 100 enrolled subjects have completed the Week 12 assessment. in pediatric HF patients. The interim analysis was 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%. Exploratory descriptive analysis of efficacy includes data on the following measures of disease severity and quality of life provide descriptive efficacy: Category 1 event: 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 at end of study; Category 2 event: Worsening HF (WHF); defined by signs and symptoms of WHF that requires an intensification of HF therapy; Change from baseline in

NYHA/ROSS class (a measure of functional status); Change from baseline in Patient Global Impression of Severity (PGIS) score; Change from baseline in PedsQL total summary score; Patient Global Impression of Change (PGIC) score. Some of the safety outcomes of interest include hypotension, hyperkalemia, renal impairment, angioedema, and liver toxicity. Trough PK samples of ENTRESTO analytes were to be collected during randomization, at Week 12 and End-of-study visit.

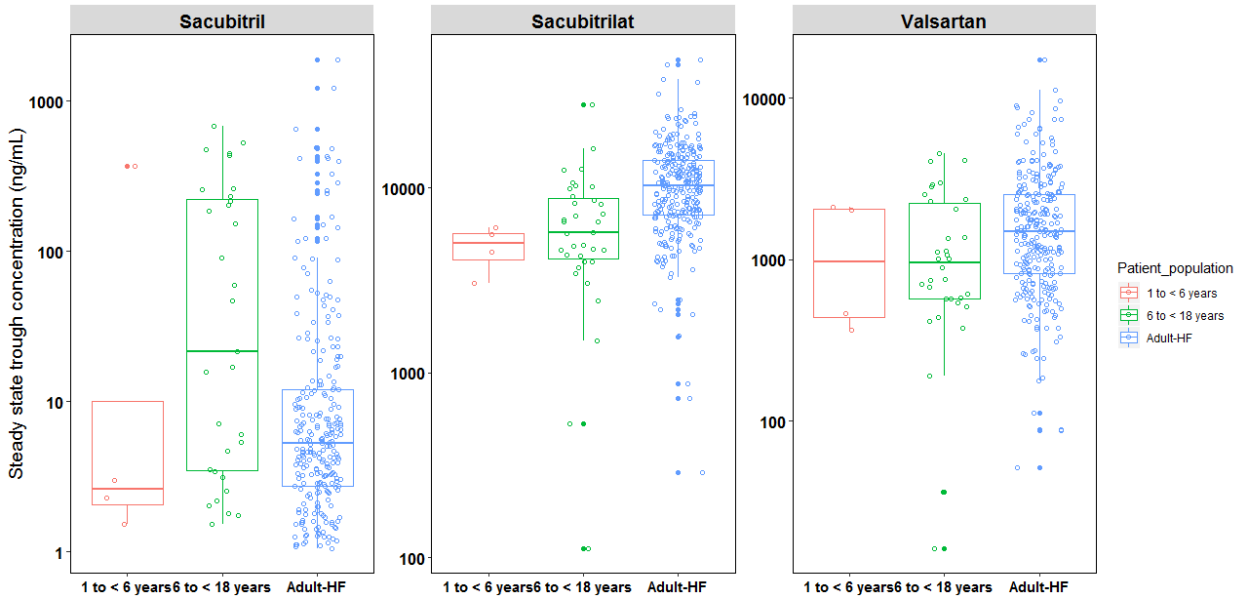
3.4 Is there evidence of effectiveness for ENTRESTO in pediatric patients?

At the time of submission of the application, there were 110 patients (55 patients in each treatment group) from 1 to <18 years of age evaluated for efficacy and 143 patients (73 and 70 patients in the LCZ696 and enalapril groups, respectively) evaluated for safety. The primary efficacy variable was evaluated at Week 12; exploratory (descriptive) efficacy variables and safety were assessed for all evaluable data up to Week 52. Efficacy was evaluated by determining the between treatment difference for NT-proBNP change from baseline to Week 12. Patients enrolled in Part 2 will continue in their assigned treatment arms for 52 weeks to characterize the treatment effect on a global rank endpoint, derived from five categories including clinical events and functional status, and long-term safety will continue to be collected.

Similarity in exposures for the analytes of ENTRESTO between adult and pediatric patients

The Applicant measured the steady state trough levels of sacubitril, sacubitrilat and valsartan in pediatric patients participating in Part 2 of the PANORAMA-HF study and evaluated whether exposures at steady state were similar to those attained in adult heart failure patients in the PARADIGM-HF study (**Figure 8**). Enalapril exposures were not measured in the study. The steady state trough levels of sacubitril, sacubitrilat and valsartan at the target maintenance dose level 4 (200 mg BID or 3.1 mg/kg BID), at the time of measurement, were similar across adult and pediatric patients. While the median steady state levels of sacubitrilat and valsartan were marginally lower in pediatric patients compared to adults, particularly in ages 1-<6 years, pediatric exposures were within the range of adult exposures, also acknowledging the large inter-subject variability (>80%) observed in the steady state trough levels and the smaller sample size of the pediatric patients compared to adults. Nevertheless, the data supports that the exposure of the main analytes, sacubitrilat and valsartan, achieved in the pediatric study was similar to that attained in the adult PARADIGM-HF study.

Figure 8: Comparison of steady state trough concentrations of sacubitril, sacubitrilat and valsartan at the target maintenance dose in adult patients in PARADIGM-HF and pediatric patients in PANORAMA-HF



Source: Reviewer's analysis
Adult-HF: Adult heart failure patients from PARADIGM-HF study, 6 to < 18 years: Pediatric patients from Part 2-PANORAMA-HF Age group 1, 1 to < 6 years: Pediatric patients from Part 2-PANORAMA-HF Age group 2

Primary analysis of NT-proBNP between ENTRESTO and enalapril groups
Baseline NT-proBNP spanned a wide range and were left-skewed for both ENTRESTO (Median: 638 (Range: 46 – 23865) pg/mL) and enalapril (Median: 663 (Range: 12 – 12116) pg/mL) arms. Overall, at Week 12 there is a decrease from baseline in NT-proBNP levels for both, ENTRESTO and enalapril arms (**Table 4**). The adjusted geometric mean (AGM) for NT-proBNP at Week 12/ NT-proBNP at baseline for ENTRESTO arm was 0.565 (95% CI for ratio 0.480 − 0.665), which corresponds to approximately 43.5% decrease in NT-proBNP from baseline to Week 12. For enalapril, a 33% decrease in NT-proBNP from baseline to Week 12 was observed with the AGM for Week 12/ baseline of 0.670 (95% CI for ratio 0.569 − 0.788).

Table 4 shows the back-transformed results of Applicant's primary analysis of change from baseline in log (NT-proBNP) at Week 12 using analysis of covariance (ANCOVA) model which 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. Relative to the enalapril arm, there was a 15.6% larger reduction in NT-proBNP from baseline in the ENTRESTO arm. The comparison between the treatment groups was not statistically significant (p=0.1466).

Table 4: Primary analysis of change from baseline in NT-proBNP at Week 12 for ENTRESTO and Enalapril - (Full Analysis Set)

Adjusted geometric mean NT-proBNP at Week 12/ NT-proBNP at baseline (95%CI)		Adjusted geometric mean ratio (95% CI)
ENTRESTO (N=54)	Enalapril (N=54)	ENTRESTO/ Enalapril
0.56 (0.48 – 0.67)	0.67 (0.57 – 0.79)	0.84 (0.67– 1.06)

Source: Study CLCZ696B2319- CSR Table 11-1

Although, not statistically significant, ENTRESTO showed a larger mean reduction for NT-proBNP from baseline to Week 12 compared to enalapril. Categorization by the two age cohorts, showed consistent result for Age group 1 (6 years to < 18 years) where mean ratio of NT-proBNP at Week 12 to baseline showed a 21% larger reduction for ENTRESTO compared to enalapril (**Table 5**).

For age group 2 (1 year to <6 years), while ENTRESTO did not show a larger reduction in NT-proBNP by Week 12 compared to enalapril, both treatments showed significant reductions in NT-proBNP compared to baseline (ENTRESTO 0.49 (95%CI 0.32 – 0.73), enalapril 0.42 (95%CI 0.29 – 0.61)). While recognizing the limitation of a comparatively smaller sample size for age group 2, it is interesting to note that the effect of ENTRESTO is similar between the two age groups with overlapping with overlapping 95% confidence intervals. However, for enalapril, the younger pediatric patients, showed a greater mean reduction in NT-proBNP from baseline compared to the older pediatric patients, without a significant overlap in the 95% confidence intervals between the two groups.

Table 5: Primary analysis of change from baseline in NT-proBNP at Week 12 for ENTRESTO and Enalapril – categorized by age subgroups (Full Analysis Set)

Pediatric-HF patient age group (N-ENTRESTO arm, N-enalapril arm)	Adjusted geometric mean NT-proBNP at Week 12/ NT-proBNP at baseline (95%CI)		Adjusted geometric mean ratio (95% CI)
	ENTRESTO	Enalapril	ENTRESTO/Enalapril
6 to < 18 years N=45, N=44	0.59 (0.49 – 0.70)	0.74 (0.61 – 0.88)	0.79 (0.61 – 1.02)
1 to < 6 years N=9, N=10	0.49 (0.32 – 0.73)	0.42 (0.29 – 0.61)	1.15 (0.67 – 1.98)

Source: CLCZ696B2319- CSR supp Table 14.2-1.4, Table 14.2-1.4.1, Study CLCZ696B2314 CSR Table 11-19.; CLCZ696B2319- CSR supp Table Table 14.2-3.28.post.03 (Study CLCZ696B2314), Clinical Overview pg 21, 23-Table 1-3

Comparison of NT-proBNP changes between pediatric patients from PANORAMA-HF and adult patients from PARADIGM-HF

In the PARADIGM-HF post-hoc biomarker assessment sub-study in adult heart failure patients, the ratio of NT-proBNP to baseline levels was approximately 25% lower for ENTRESTO compared to enalapril at 1 month (AGM Ratio: ENTRESTO/Enalapril 0.75, 95% CI 0.70 to 0.78) and 8 months (AGM Ratio: ENTRESTO/Enalapril 0.75, 95% CI 0.70 to 0.81) post-randomization (**Table 6**). In the adult-DCM sub-group, 38% (AGM Ratio: ENTRESTO/Enalapril 0.62, 95% CI 0.55 to 0.71) and 39% (AGM Ratio: ENTRESTO/Enalapril 0.61, 95% CI 0.50 to 0.75) greater reduction in the ratio of NT-proBNP to baseline levels was observed for ENTRESTO compared to enalapril at Month 1 and Month 8 post-randomization.

Table 6: Comparison of adult heart failure patients in PARADIGM-HF trial and pediatric patients from PANORAMA-HF (Full Analysis Set) trial for primary analysis of change from baseline in NT-proBNP

Patient population (N-ENTRESTO arm, N-enalapril arm)	**Time post-randomization**	**Adjusted geometric mean NT-proBNP/ NT-proBNP at baseline (95%CI)**		**Adjusted geometric mean ratio (95% CI)**
		ENTRESTO	Enalapril	ENTRESTO/ Enalapril
Pediatrics 1 to <18 years N=54, N=54	Week 12	0.56 (0.48 – 0.67)	0.67 (0.57 – 0.79)	0.84 (0.67– 1.06)
Adults-DCM subgroup N=213, 192	Month 1	0.57 (0.52 – 0.62)	0.92 (0.84 – 1.0)	0.62 (0.55 – 0.71)
Adults-DCM subgroup N=178, 167	Month 8	0.48 (0.42 – 0.56)	0.79 (0.68 – 0.91)	0.61 (0.50 – 0.75)
Adults N=971, N=971	Month 1	0.68 (0.66 – 0.71)	0.93 (0.89 – 0.96)	0.75 (0.70 – 0.78)
Adults N=885, N=874	Month 8	0.65 (0.62 – 0.69)	0.87 (0.82 – 0.91)	0.75 (0.70 – 0.81)

Source: Study CLCZ696B2319- CSR Table 11.1; Study CLCZ696B2314 CSR Table 11-19.; CLCZ696B2319- CSR supp Table 14.2-3.28.post.03 (Study CLCZ696B2314), Clinical Overview pg 21, 23-Table 1-3

Compared to adult-DCM subgroup, the between-treatment (ENTRESTO/Enalapril) mean percentage reduction in the ratio of NT-proBNP to baseline is lower (39% at Months 1 and 8 versus 15.6% at Week 12) in the pediatric patients (1 to < 18 years). However, when making a within-treatment comparison between the adult-DCM subgroup and the pediatric patients, the mean percentage reduction in NT-proBNP from baseline for ENTRESTO in pediatric patients at

Week 12 (44% (95% CI 33 - 52%)) is similar to adult-DCM subgroup at Month 1 (43% (95% CI 38 - 48%)) or marginally lower at Month 8 (52% (95% CI 44 - 56%). Whereas, for enalapril, the mean percentage reduction in NT-proBNP from baseline is relatively larger for the pediatric patients compared to adult-DCM sub group (33% (95% CI 21-43%) in pediatrics at Week 12 versus 8% (95% CI 0-16%) at Month 1 and 21% (95% CI 9-32%) at Month 8 in adult-DCM subgroup).

While the primary between treatment comparison is not statistically significant, it is noteworthy to observe a similar within treatment effect for ENTRESTO between adult and pediatric HF patients. As noted above, the magnitude of enalapril's effect on NT-proBNP in pediatric patients is greater than what is seen in adults. Analysis of the study drug dose level show that a similar proportion of patients in both ENTRESTO (72%) and enalapril (74%) groups attained target dose level 4 by Week 12 (**Table 7**). The proportion of patients at dose level 3 (14%) and lower (5-12%) were also similar between the two treatment groups. Therefore, the reason for a slightly larger effect for enalapril on NT-proBNP in pediatric patients is not well understood. It may be possible that the exposure-biomarker relationship for enalapril is slightly different in pediatric patients compared to adults. To explore the issue further, the change from baseline NT-proBNP data at Week 12 in pediatric patients were analyzed by different baseline NT-proBNP baseline groups.

Table 7: Week 12 dose levels of PANORAMA-HF study-part 2

	Patients at a Dose Level							
Age group	**ENTRESTO (n=54)**				**Enalapril (n=51)**			
Dose level	**0**	**2**	**3**	**4**	**0**	**2**	**3**	**4**
Age group 1: 6 years to < 18 years	2	3	6	33	1	2	4	35
Age group 2: 1 year to < 6 years	1	1	2	6	0	0	4	5

Source: Reviewer's analysis

Comparison of ENTRESTO and enalapril for the change in NT-proBNP relative to baseline NT-proBNP in PARADIGM-HF

Table 8 provides the descriptive statistics for the percentage change in NT-proBNP from baseline to Week 12 in the ENTRESTO and enalapril arms for 4 different groups classified based on baseline NT-proBNP: < 250 pg/mL, 250 to < 1000 pg/mL, 1000 to < 5000 pg/mL, and > 5000 pg/mL. It should be noted that this analysis is highly exploratory given the small sample size within each group and was performed to understand trends in data. In patients with baseline NT-proBNP <1000 pg/mL, ENTRESTO shows a greater median percentage reduction from baseline compared to enalapril, whereas in patients with baseline NT-proBNP between 1000 to <5000 pg/mL, both treatments show a similar percentage reduction. In the highest baseline NT-proBNP group of >5000 pg/mL, albeit the very small sample size, enalapril shows a better response compared to ENTRESTO. In comparison, ENTRESTO showed a consistently larger percent decrease in NT-proBNP when compared to enalapril across both <1000 and ≥1000 pg/mL groups in adults in the PARADIGM-HF biomarker sub study (data not shown) suggesting a differential treatment effect as a function of baseline between pediatric patients and adults.

However, the data shown in **Table 8** seem to suggest a trend for greater percent decrease in NT-proBNP for enalapril in pediatric patients with increasing baseline NT-proBNP, however, not so for ENTRESTO. Therefore, the differential treatment effect for ENTRESTO over enalapril as a function of baseline between pediatric patients and adults may be due to enalapril's response within its treatment group in the pediatric study which is not well understood. Nevertheless, the percentage reduction in NT-proBNP for ENTRESTO is more or less consistent across different baseline NT-proBNP groups both in adult and pediatric patients.

Table 8: Comparison of ENTRESTO and enalapril for the percentage change in NT-proBNP relative to baseline NT-proBNP in PANORAMA-HF

Baseline NT-proBNP (pg/mL) (N-ENTRESTO arm, N-enalapril arm)	**Parameter**	**Percentage change in NT-proBNP from baseline to week 12**	
		ENTRESTO	**Enalapril**
< 250 pg/mL N=14, N=16	Median	-47	-10
	Mean	-37	-4
	Minimum, Maximum	37, -89	68, -82
250 to < 1000 pg/mL N=15, N=14	Median	-28	-19
	Mean	-33	-18
	Minimum, Maximum	15, -77	35, -62
1000 to < 5000 pg/mL N=17, N=14	Median	-53	-53
	Mean	-34	-37
	Minimum, Maximum	74, -84	80, -90
> 5000 pg/mL N=6, N=4	Median	-23	-61
	Mean	-25	-56
	Minimum, Maximum	50, -78	-36, -65

Source: Reviewer's analysis

Conclusion

When agreeing to the use of NT-proBNP as the bridging biomarker, the hypothesis was that if the changes in NT-proBNP tracked similarly for both ENTRESTO and enalapril to what was seen in adults, the clinical benefit on HF outcomes from adults can then be translated to pediatric patients. While the biomarker results did not exactly track the way it did for comparison of ENTRESTO's effect over enalapril, it showed similar effect in the ENTRESTO group as seen in adults. This can be construed as a reasonable case for evidence of effectiveness for ENTRESTO and allow borrowing clinical benefit from adults to pediatric patients if one can assume that ENTRESTO's benefit on HF outcomes is reflected, at least partly, by decreases in NT-proBNP. Given the mechanism of action of both valsartan and sacubitril, which work to reduce cardiac pre-load and in turn the stress on ventricular wall for which NT-proBNP is a marker, making this assumption does not seem unreasonable.

Compared to the adult HFrEF patients in the PARADIGM-HF study, while the range of baseline NT-proBNP values in both age group 1 and 2 were similar, the median was lower in pediatric patients (**Table 9**). Mildly elevated BNP or NT-proBNP was an inclusion criterion in the PARADIGM-HF trial to ensure that patients enrolled were at risk for CV events to ensure a reasonable event incidence rate over the duration of the trial. Baseline NT-proBNP above a pre-specified level was not required as an inclusion criterion for PANORAMA-HF study. It is well known that higher NT-proBNP values have the worst prognosis for HF outcomes. As shown in the Val-HeFT and PARADIGM-HF biomarker-outcome correlation analyses (**Figure 3**, **Figure 5**), where a cut-off of 1078 and 1000 pg/mL for NT-proBNP were used, respectively, the risk for all-cause mortality or HF outcomes reduced significantly if NT-proBNP values by Month 1 dropped below the pre-specified threshold. While we do not know the magnitude of biomarker decrease in that group (High→Low), it gives a sense that reducing high NT-proBNP significantly may be of clinical relevance in terms of improving HF outcomes. As noted earlier, the median baseline NT-proBNP values are lower in pediatric patients compared to adults. Nevertheless, as seen again from Val-HeFT and PARADIGM-HF analyses, keeping 'low' NT-proBNP values (defined less than 1000 pg/mL) lower is also of clinical relevance as shown by the Kaplan Meir (KM) curve for Low→Low group which is similar to the High→Low group. Conversely, it can be seen by the KM curve for Low→High group, that if lower NT-proBNP values are not kept low, it may lead to an increase in the risk for HF outcomes over time. Moreover, the post-hoc analysis of PARADIGM-HF study demonstrates, that across the four quartiles of baseline NT-proBNP, the treatment effect of ENTRESTO compared to enalapril was similar (**Figure 6**), suggesting that an effect on NT-proBNP in the group of lower baseline NT-proBNP was also of clinical relevance.

Table 9: Comparison of baseline NT-proBNP for Pediatrics (study CLCZ696B2319- Full Analysis Set) and Adult-DCM (CLCZ696B2314) Patients with Heart Failure

Patient Population (N-ENTRESTO arm, N-enalapril arm)	Statistic	ENTRESTO	Enalapril
Pediatrics 1 to < 18 years N=54, N=54	Median (Minimum- maximum)	639 (46 - 23865)	664 (13-12116)
	Geometric Mean (95% CI)	823 (536 - 1264)	614 (411 - 916)
Pediatrics 1 to < 6 years N=9, N=10	Median (Minimum- maximum)	1718 (75-11913)	906 (164-5721)
	Geometric Mean (95% CI)	1197 (358-3999)	799 (354-1801)
Pediatrics 6 to < 18 years N=45, N=44	Median (Minimum- maximum)	605 (46 - 23865)	557 (13-12116)
	Geometric Mean (95% CI)	763 (475- 1227)	577 (362 – 922)
Adults-DCM N=213, 192	Median (Minimum- maximum)	1206 (64-15214)	1244 (122-8650)
	Geometric Mean (95% CI)	1307 (1165-1467)	1339 (1196-1499)

Source: Table 14.2-1.5 CSR CLCZ696B2319, CLCZ696B2319- CSR supp `Table 14.2-3.28.post.03` (Study CLCZ696B2314)

3.5 Are there any factors that may have a confounding effect on the observed changes in the NT-proBNP in the two treatment arms or in other words, can the changes in NT-proBNP post-treatment with ENTRESTO and enalapril be attributed to their respective treatments?

Concomitant medication

The Applicant assessed whether prior and concomitant medication use was balanced between treatment groups and whether there were differential changes in medications over time, which might have affected post-treatment NT-proBNP. The most commonly used concomitant medications were diuretics (85.3% of the safety set), beta blockers (78.3%), aldosterone antagonists (71.3%), plain sulfonamides (65.0%), alpha- and beta-blocking agents (58.7%) and acetylsalicylic acid (52.4%). Overall, the frequency of prior and concomitant medication or therapy use was similar between ENTRESTO and enalapril groups and between patients in Age Group 1 and Age Group 2. The number and proportion of individual patients who required the addition or discontinuation of frequently used cardiovascular medications was small and similar in each treatment group.

The Applicant assessed the diuretic dosing in PANORAMA-HF, in response to an information request sent by the Division to the Applicant to provide information to better understand if changes in diuretic drug dosing during the pediatric trial confounded with post-treatment changes in NT-proBNP. Overall, the use of diuretics was comparable between the ENTRESTO and

enalapril arms for both the age groups. During the trial, the change in diuretics was minimal and the overall pattern of diuretic use was comparable between the ENTRESTO and enalapril arms (**Table 10**).

Table 10: Pediatric patients with diuretic dose changes at week 12 vs baseline (Full analysis set-PANORAMA-HF)

Overall population Reference visit Change	LCZ696 N=55 n (%)	Enalapril N=55 n (%)	Total N=110 n (%)
Week 12 vs baseline (m)	55	53	108
Increase in dose (oral)	0 (0.0)	1 (1.9)	1 (0.9)
Decrease in dose (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 diuretic (oral)	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)

3.6 What are the formulations used in the pediatric study?

In the pediatric clinical study, three formulations of ENTRESTO were used: film-coated tablets (marketed formulation), film-coated pellets (also known as granules or [redacted] (b) (4)) and oral extemporaneous suspension formulation. ENTRESTO film-coated tablets are commercially available in the following strengths: 50 mg: sacubitril 24 mg and valsartan 26 mg, 100 mg: sacubitril 49 mg and valsartan 51 mg and 200 mg: sacubitril 97 mg and valsartan 103 mg.
The pellet formulation was provided as 3.125 mg pellets (sacubitril 1.52 mg and valsartan 1.61 mg), packaged in capsules containing 4 or 10 granules corresponding to 12.5 mg and 31.25 mg of ENTRESTO, respectively. The capsule shell is used as a dosing container only and is manually opened for dosing the pellets. The capsule shell is discarded once the pellets are poured onto a spoonful of soft food or directly into the mouth. Oral extemporaneous suspension is prepared by a pharmacist by dispersing the ENTRESTO 49/51 mg film-coated tablets in commercially available vehicles Ora-Plus® and then diluting with Ora-Sweet® SF. The extemporaneous suspension can be prepared in 2 different concentrations, as a 1 mg/mL and as a 4 mg/mL suspension using two tablets or eight tablets (for 4 mg/mL) of ENTRESTO 49/51 mg film-coated tablets, respectively. Syringes with CE marking were used for administration of the extemporaneous suspension. Enalapril was available in extemporaneous liquid formulation and as tablets of 2.5 mg, 5 mg and 10 mg strengths.

Patients weighing ≥ 57 kg used ENTRESTO film-coated tablets for titration to the target maintenance dose. For pediatric patients weighing < 57 kg, a physician determined the patient's dose based on the pediatric 'mg/kg' weight-based dose and allowed the use of ENTRESTO film-coated tablets if the determined dose was within 20% of an available tablet strength. For patients whose calculated dose was not covered by the available tablet strengths, were allowed to use the extemporaneous suspension or oral pellets. Additionally, children who have difficulties swallowing tablets may take extemporaneous suspension. During the course of the trial, some

patients switched formulations. The combination of formulations taken by patients in the Part 2 Safety Set of CLCZ696B2319 - Analysis at Week 12 are listed in **Table 11**.

Table 11: The combination of formulations taken by patients in the Part 2 Safety Set of CLCZ696B2319 - Analysis at Week 12

Formulation(s)	Number of patients (%)	
	Age group: 1 year to < 6 years N=20	Age group: 6 year to < 18 years N=53
Extemporaneous suspension	17 (85.0)	6 (11.3)
Pellet	1 (5.0)	15 (28.3)
Extemporaneous suspension, Pellet	2 (10.0)	5 (9.4)
Film-coated tablet	-	18 (34.0)
Extemporaneous suspension, Film-coated tablet	-	2 (3.8)
Pellet, Film-coated tablet	-	7 (13.2)

Source: Table 14.2-2.post.4a - CLCZ696B2319 Clinical Study Report Supplement 2
Note: Formulation is not necessarily reflective of the order in which the formulation was taken by the patient. Patients who took more than one formulation switched during the course of the study

3.7 Is there relative bioavailability data in adults to support the pediatric formulations?

(b) (4)

The Applicant conducted two relative bioavailability studies in this development program. In Study CLCZ696B2126, the relative bioavailability of ENTRESTO analytes (valsartan, sacubitril, sacubitrilat) following oral administration of 200 mg ENTRESTO oral pellets (64 x 3.125 mg) compared to the adult 200 mg film-coated tablet was assessed under fasted condition. The rate (C_{max}) and extent (AUC) of exposure of ENTRESTO analytes were found to be similar between ENTRESTO pellets and film-coated tablet (**Table 12**). In addition, study CLCZ696F2130 examined the relative bioavailability of an ENTRESTO oral extemporaneous suspension prepared by dispersing pellets in water with ENTRESTO film-coated tablet. Following oral administration, the extemporaneous suspension provided similar total exposure (AUC_{last} and AUC_{inf}) of ENTRESTO analytes compared to the film-coated tablet (**Table 12**). Although there is not a direct comparison of film-coated tablet and extemporaneous suspension made using the film-coated tablet, since the ENTRESTO tablets and the pellets are very similar in composition and manufacturing process and both have been shown to provide similar bioavailability,

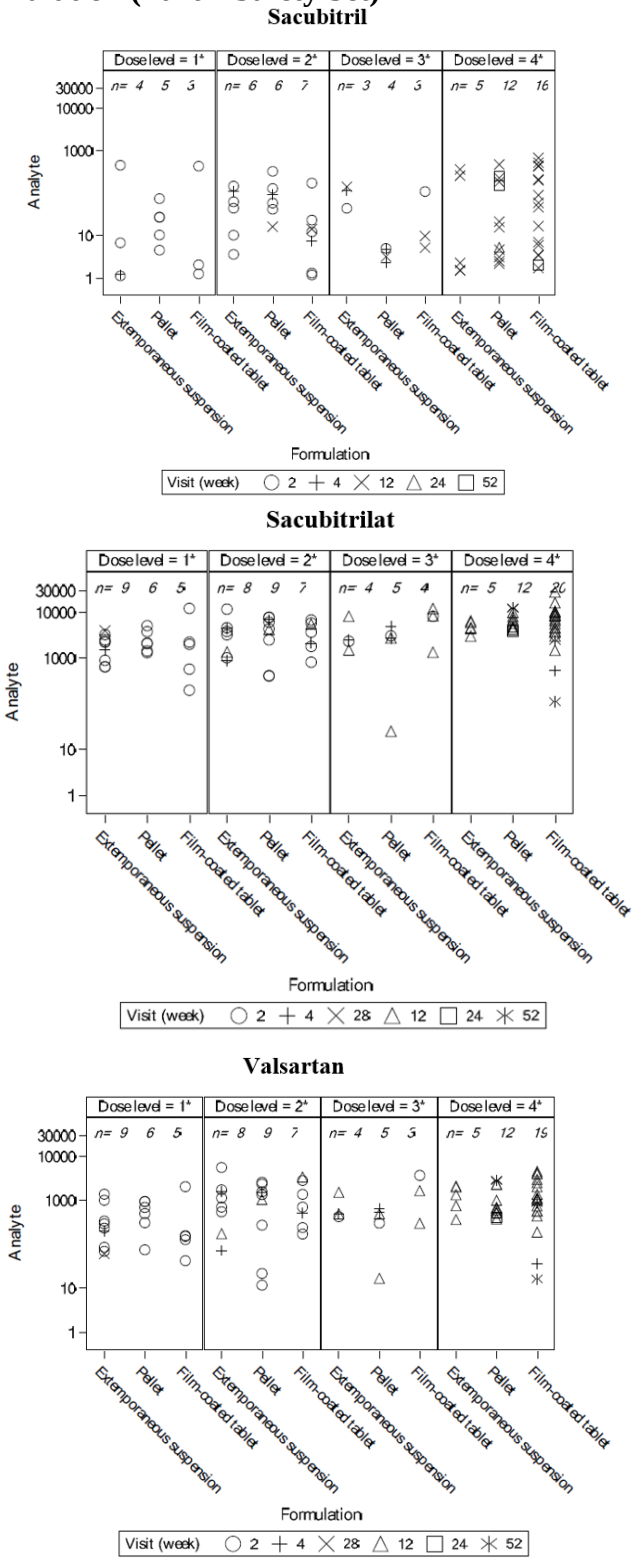
preparation of the extemporaneous suspension from either tablets or pellets can be considered equivalent. The peak concentration for sacubitril is 72% higher for extemporaneous suspension compared to film-coated tablet, however, because sacubitril is an inactive prodrug, and eliminated relatively quickly, the higher peak concentration is not clinically significant.

Table 12: Summary of PK parameters for relative bioavailability studies CLCZ696B2126 and CLCZ696F2130

Analyte	PK Parameter (Units)	T/R geometric mean ratio (%) (90% CI)	
		Pellet/film-coated tablet CLCZ696B2126	Extemporaneous suspension from pellets/film-coated tablet CLCZ696F2130
Sacubitril	C_{max} (ng/mL)	0.91 (0.83 – 1.00)	1.72 (1.48, 1.98)
	AUC_{0-t} (ng.hr/mL)	0.96 (0.92, 1.00)	1.04 (1.00, 1.07)
	$AUC_{0-\infty}$ (ng.hr/mL)	0.96 (0.92, 1.00)	1.04 (1.00, 1.07)
Sacubitrilat	C_{max} (ng/mL)	0.95 (0.91, 0.99)	1.13 (1.08, 1.18)
	AUC_{0-t} (ng.hr/mL)	0.98 (0.96, 0.99)	1.00 (0.98, 1.02)
	$AUC_{0-\infty}$ (ng.hr/mL)	0.98 0.96, 0.99)	1.00 (0.99, 1.02)
Valsartan	C_{max} (ng/mL)	1.09 (0.98, 1.21)	1.00 (0.91, 1.10)
	AUC_{0-t} (ng.hr/mL)	1.11 (1.00, 1.22)	0.91 (0.83, 1.00)
	$AUC_{0-\infty}$ (ng.hr/mL)	1.11 (1.00, 1.24)	0.91 (0.83, 1.00)

The Division also recommended the Applicant (Type A meeting, January 18th, 2019) to use all the available data to provide an adequate bridge between all the formulations used in the pediatric study. The Applicant performed steady state trough PK comparison of the ENTRESTO analytes following administration of film-coated tablets, oral pellets and extemporaneous suspension administered to the pediatric patients in Part 2 of the clinical study (**Figure 9**). The range of steady state trough levels of the ENTRESTO analytes were reasonably similar across the three formulations.

Figure 9: Steady state trough concentrations of sacubitril, sacubitrilat and valsartan by visit, dose level and formulation (Part 2 Safety Set)



3.8 What is the recommended dosing regimen for the pediatric population for which the indication is being sought? Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The Applicant's dosing proposal recommended the use of adult dosing regimen with ENTRESTO tablets in pediatric patients weighing > (b) (4) kg. For pediatric patients weighing < (b) (4) kg, the Applicant recommended a weight adjusted dosing regimen starting at 1.6 mg/kg and titrating up to 3.1 mg/kg. The recommendation allowed the use of ENTRESTO tablets as long as the weight adjusted dose was within 20% of available tablet strengths. Obviously, pediatric patients in certain weight ranges, where the weight adjust dose would fall <40 mg (b) (4) were recommended to take extemporaneous suspension. The proposed dosing recommendation may mirror closely to what was executed in the pediatric clinical trial, however, because patients in certain weight ranges have to switch between tablets and suspension, there is a potential for dose prescribing or dispensing errors. In addition, the proposal presents oral suspension as the only choice for the starting dose in certain higher weight groups who would be old enough to swallow tablets whole.

The dosing recommendation for pediatric patients was revised by the review team to simplify the dosing instructions and minimize dosing errors (**Table 13**). The revision recommends the use of oral suspension only, in patients below 40 kg. This recommendation was made to not have younger patients switch between different dosage forms as they grow and also to reduce dispensing errors. A body weight cut-off of 40 kg was chosen to maximize the use of tablets, even for the starting dose, in patients above the weight cut-off who are mostly expected to swallow the tablets whole. The proposed doses are reasonably close to what was studied in PANORAMA-HF, while keeping the dosing instructions simple.

Table 13: Recommended dosage of ENTRESTO for pediatric patients

	Titration Step Dose (twice daily)		
	Initial	**Second**	**Final**
Pediatric Patients Less than 40 kg†	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Patients At least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg‡
Pediatric Patients At least 50 kg	49/51 mg	72/78 mg‡	97/103 mg

† Use of the oral suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan
‡ Doses of 72/78 mg can be achieved using three 24/26 mg tablets

Pediatric patients with body weight less than 40 kg are recommended to be started with a twice-daily dose of 1.6 mg/kg. The dose is recommended to be titrated to 2.3 mg/kg and up to the

target maintenance dose of 3.1 mg/kg twice-daily. As per the dosing regimen followed in the pediatric clinical trial, the dose is to be titrated every 2-weeks, as tolerated by the patient.

As presented in **Table 14**, the recommended starting dose in pediatric patients weighing at least 50 kg or higher is100 (49/51) mg twice-daily followed by titrating the dose to 150 mg (three 24/26 mg tablets twice-daily) and a target maintenance dose of 200 mg twice-daily. Recommended tablet dose is 11 to 30% higher compared to the weight-based dose and will result in correspondingly greater systemic exposures of ENTRESTO. However, the exposures will still be within the range of adult exposures, as PARADIGM-HF enrolled patients down to 41.5 kg.

Table 14: Weight-based dosing recommendation for ENTRESTO film-coated tablets

Patient weight	mg/kg dose	Corresponding weight-based dose amount (mg)	Recommended ENTRESTO tablet strength	Recommended dose compared to weight-based dose
40 kg	1.6 mg/kg	64 mg	50 mg	22% lower
49 kg		78 mg		36% lower
50 kg		80 mg	100 mg	25% higher
56 kg		90 mg		11% higher
40 kg	2.3 mg/kg	92 mg	100 mg	9% higher
49 kg		113 mg		12% lower
50 kg		115 mg	150 mg	30% higher
56 kg		129 mg		16% higher
40 kg	3.1 mg/kg	124 mg	150 mg	20% higher
49 kg		152 mg		1% higher
50 kg		160 mg	200 mg	25% higher
56 kg		174 mg		15% higher

For patients weighing at least 40 kg and less than 50 kg, the recommended starting dose is 50 mg (24/26) mg twice-daily. This will result in 22 to 36% lower recommended dose than the weight-based dose of 1.6 mg/kg. However, following titration to 100 (49/51) mg the margin of difference compared to the weight-based dose of 2.3 mg/kg is reduced to 9% lower to 12% higher, which further increases to 1 to 20% higher at the target maintenance dose of 150 mg twice daily. This ensures that the pediatric patients in this weight group are not consistently under-dosed at the target maintenance dose.

Dose adjustment for patients not taking an ACE inhibitor or ARB or previously taking low doses of these agents

Consistent with the dosing recommendation followed in the pediatric trial, ENTRESTO should be initiated at half the normal recommended initial dose. For patients weighing at least 50 kg, we recommend starting ENTRESTO at a twice-daily dose of 24/26 mg oral tablet. For patients weighing less than 50 kg we recommend initiating ENTRESTO at 0.8 mg/kg twice daily using

extemporaneous oral suspension due to unavailability of an oral tablet strength lower than 50 mg.

Dose adjustment for pediatric patients with severe renal impairment and moderate hepatic impairment

Based on the PK similarity in adult and pediatric heart failure patients and, extrapolating the effect of severe renal impairment and moderate hepatic impairment on the PK in adults to that in pediatric patients, we recommend dose adjustment to the starting dose of ENTRESTO in pediatric patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) and moderate hepatic impairment. For patients weighing at least 50 kg, we recommend starting ENTRESTO at a twice-daily dose of 24/26 mg oral tablet. For patients weighing less than 50 kg, we recommend initiating ENTRESTO at 0.8 mg/kg twice daily using extemporaneous oral suspension due to unavailability of an oral tablet strength lower than 50 mg.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of sacubitril, sacubitrilat and valsartan were measured by a validated high-performance liquid chromatography-tandem mass spectrometry assay. The bioanalytical validation summary for study CLCZ696B2319 is provided below.

Table 15: Bioanalytical method validation summary for plasma concentration analysis

	Analyte		
Study	sacubitril	sacubitrilat	valsartan
Method	LC-MS/MS	LC-MS/MS	LC-MS/MS
LLOQ (ng/mL)	1.0	20.0	10.0
ULOQ (ng/mL)	1000.0	20000.0	10000.0
Concentration Range (ng/mL)	1.0 to 1000	20.0 to 20000.0	10.0 to 10000.0
QC (mg/mL)	3.0, 30.0, 150.0, 500.0, 750.0	60.0, 600.0, 3000.0, 10000.0, to 15000.0	30.0, 300.0, 1500.0, 5000.0 to 7500.0
Accuracy (bias) (%)	-4.0 to 5.5	-6.5 to 6.3	-4.1 to 5.6
QC Accuracy (bias) (%)	0.7 to 12.5	-3.5 to 9.7	0.0 to 6.7

Precision (%)	QC: ≤ 8.1%	QC: ≤ 7.2%	QC: ≤ 7.8%
Incurred sample reanalysis percentage within ±20%	80.0%	70.6%	84.3%

Source: Interim Bioanalytical Data Report - DMPK RCLCZ696B2319, DMPK RCLCZ696B2319a

Reviewer's comment: *Accuracy and precision of QC samples for the LC-MS/MS bioanalytical assay were within acceptable limits (≤15% and ≤20% at LLOQ). Greater than two-thirds of the incurred samples concentration results were within 20% of the original concentration of the respective samples and meets the acceptance criteria for incurred samples reanalysis. The bioanalytical assay methods for sacubitril, sacubitrilat and valsartan in plasma are acceptable, based on the limits specified in 'Guidance for Industry: Bioanalytical Method Validation.'*

4.2 Pharmacometrics Review

Exposure-response relationship for ENTRESTO in pediatric patients

Exploratory analyses were conducted to examine the relationship between NT-proBNP change from baseline and exposure to sacubitrilat and valsartan. The NT-proBNP change from baseline was calculated as geometric mean ratio (GMR) of week 12 to baseline NT-proBNP. **Figure 10**A and B shows week 12 to baseline NT-proBNP GMR versus sacubitrilat and valsartan plasma concentrations, respectively. In both figures, GMR is less than 1 at most exposure levels. An I_{max} model was fitted to describe the exposure-NT-proBNP GMR relationship. Table 1 shows parameter estimates from I_{max} model fitted to exposure-vs-GMR data for sacubitrilat and valsartan. For both drugs, the estimates of I_{max} were statistically significant. It suggests both moieties may have the capacity of reducing NT-proBNP assuming placebo effects are minimal. For both drugs, the IC_{50} estimates were not statistically significant, and that may be due to insufficient PK data from the "linear range" of the E-R curve. As stated earlier, this is an exploratory analysis and the results should be interpreted with caution because of the small sample size.

Figure 10: GMR of week 12 to baseline NT-proBNP versus sacubitril and valsartan plasma concentration for 43 pediatric subjects with baseline and week 12 NT-proBNP data

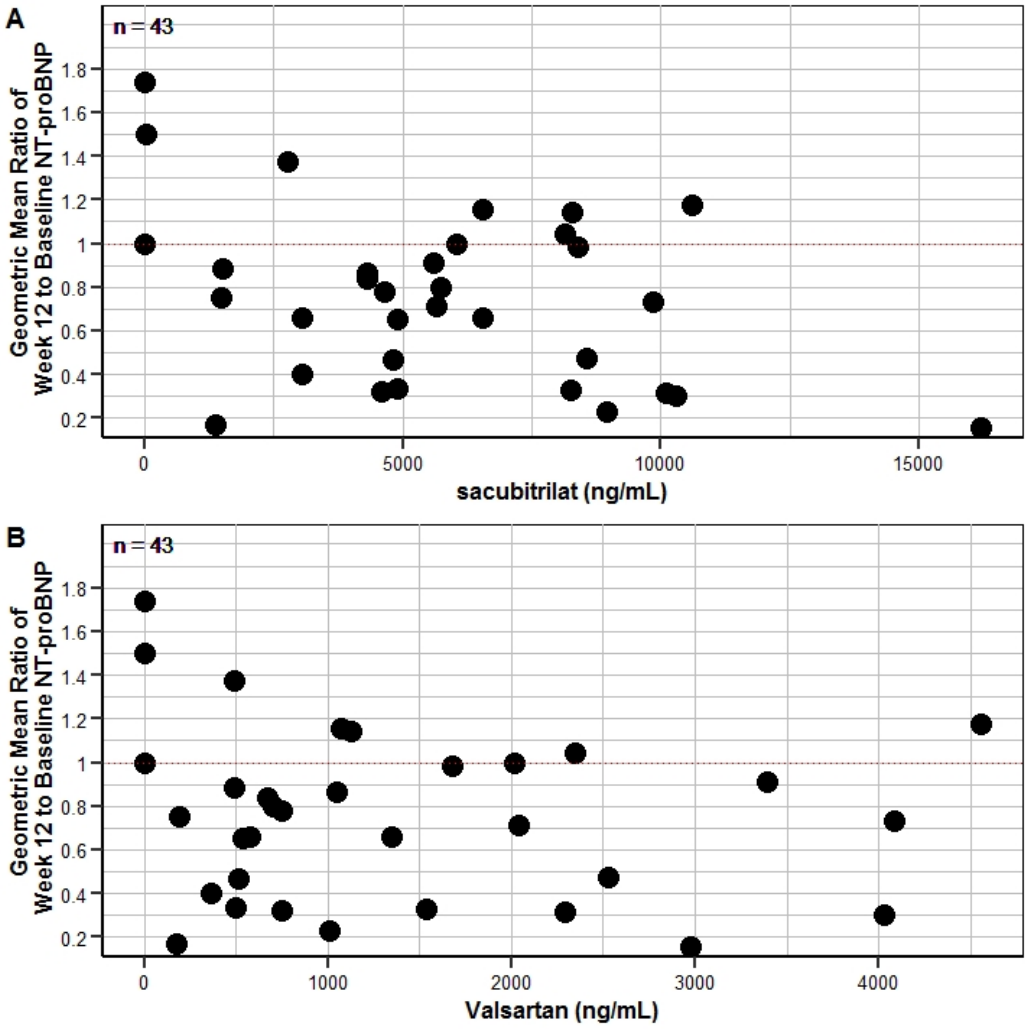


Table 16. Parameter estimates from the fitted Imax models for sacubitrilat and valsartan

Model	Parameters	Estimates	P-value
Sacubitrilat IMAX Model	Intercept	1.06	$2\times e^{-16}$
	IC_{50}	0.50	0.67
	I_{max}	0.37	$2.68\times e^{-4}$
Valsartan IMAX model	Intercept	1.02	$2\times e^{-16}$
	IC_{50}	0.0001	1
	I_{max}	0.34	$7.51\times e^{-6}$

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