# Office of Clinical Pharmacology Review

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| **NDA Number** | sNDA 207620 and NDA 218591 |
| **Link to EDR** | NDA207620 (eCTD 0188, \\CDSESUB1\evsprod\NDA207620\0188)<br>NDA218591 (eCTD 0000, \\CDSESUB1\evsprod\NDA218591\0000) |
| **Submission Date** | 6/14/2023 |
| **Submission Type** | • Pediatric efficacy supplement for NDA 207620 (Supplement S-25)<br>• Original NDA for NDA 218591 |
| **Brand Name** | ENTRESTO® |
| **Generic Name** | Sacubitril/Valsartan (LCZ696) |
| **Dosage Form and Strength** | Film-coated tablets and film-coated granules (new pediatric formulation, full-capsules containing film-coated granules, which come in two strengths of 4 granules (6 mg Sacubitril/6 mg Valsartan) and 10 granules (15 mg Sacubitril/16 mg Valsartan)) |
| **Route of Administration** | Oral |
| **Proposed Indication** | ENTRESTO is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker (ARB), indicated 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. ENTRESTO is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB. |
| **Applicant** | Novartis |
| **Associated INDs** | IND 104628 (sacubitril/valsartan) |
| **OCP Review Team** | Mohamed Ismail Nounou, Ph.D., Ye Yuan, Ph.D., Hao Zhu, Ph.D. & Doanh Tran, Ph.D. |
| **OCP Final Signatory** | Doanh Tran, Ph.D. |

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# 1. EXECUTIVE SUMMARY

ENTRESTO (LCZ696) is a fixed dose combination of neprilysin inhibitor, sacubitril, and angiotensin receptor blocker (ARB), valsartan, approved 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) had previously submitted a supplemental New Drug Application (sNDA) for ENTRESTO to provide the interim pediatric clinical study report at week 12 (PANORAMA-HF – study CLCZ696B2319) and received approval for treatment of pediatrics 1 year and older on 10/01/2019.

In this supplement (NDA 207620/S-25), the Applicant submits updates to labeling to include information from final study report at week 52 for study CLCZ696B2319. The Applicant also submits a new drug application (NDA 218591) for a new oral formulation of sacubitril/valsartan as film-coated granules with 2 dosage strengths, 6 mg/6 mg (4 film-coated granules) and 15 mg/16 mg (10 film-coated granules.

Review of week 52 results for study CLCZ696B2319 showed consistent response with previous results obtained at week 12. The bioavailability of sacubitril/valsartan film-coated granules and extemporaneous suspension of film-coated granules was shown to have similar bioavailability to the film-coated tablets based on results of Study B2126 and Study F2130, respectively.

## 1.1 Recommendations

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

## 1.2 Post-Marketing Requirements and Commitments

None

# 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

## 2.1 Pharmacology and Clinical Pharmacokinetics

We refer to the previous Clinical Pharmacology review for further details regarding mechanism of action and clinical pharmacokinetics parameters (*Clinical Pharmacology Review, Reference ID: 4494987, 09/20/2019*).

## 2.2 Dosing and Therapeutic Individualization

The available dosage forms and strengths are as follows:

- Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg
- Film-coated granules (loaded in capsules): 6 mg/6 mg; 15 mg/16 mg

The recommended dose for pediatric patients aged one year and older are detailed in Table 1. Dose adjustment is needed in pediatric patients based on body weight. The recommended dose is to be administered orally twice daily. Pediatric patient doses are titrated every 2 weeks, as tolerated by the patient.

(b) (4)

## 2.3 Clinical Pharmacology Review Summary

1. The safety and effectiveness of ENTRESTO for the treatment of heart failure in pediatric patients is supported by the reduction from baseline to 52 weeks in NT-proBNP in trial PANORAMA-HF Study. The response at week 52 is consistent with the previous findings at week 12.
2. The rate ($C_{max}$) and extent (AUC) of absorption of ENTRESTO analytes were found to be similar between ENTRESTO granules and film-coated tablet. In addition, the rate ($C_{max}$) and extent (AUC) of absorption of ENTRESTO analytes were comparable between granules taken under fasted condition and granules taken with a small amount of vanilla pudding.
3. Administration of ENTRESTO 200 mg granules sprinkled on pudding with high fat meal resulted in decreased rate of absorption ($C_{max}$) of sacubitril (60% decrease), sacubitrilat (19% decrease), and valsartan (57% decrease). The extent of absorption ($AUC_{inf}$) of sacubitril and

sacubitrilat were comparable while the extent of absorption of valsartan was reduced (40% decrease) when taken with a high fat meal.

## 2.4 Outstanding Issues

None

## 2.5 Summary of Labeling Recommendations

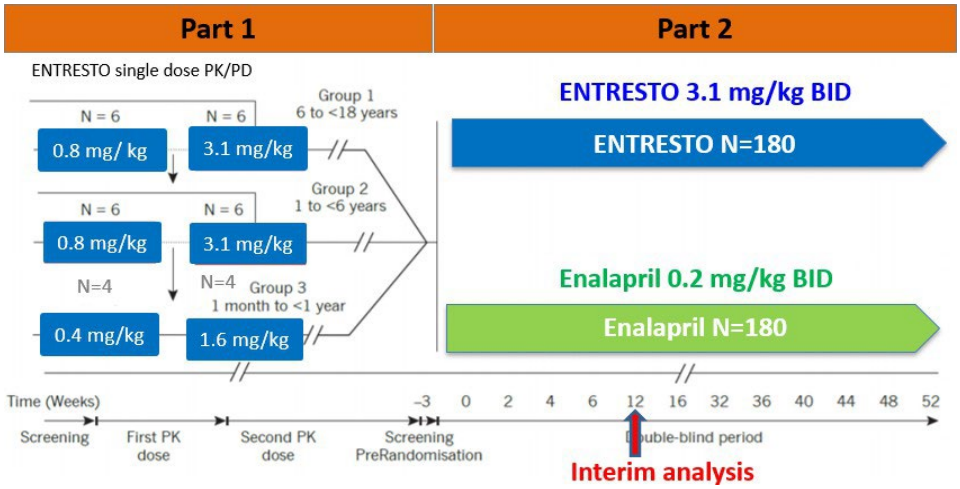
The clinical pharmacology section of the proposed label was updated to include administration instruction for the new granule's formulation.

# 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

## 3.1 Design elements of the pediatric study CLCZ696B2319 (PANORAMA-HF)

Study CLCZ696B2319 (PANORAMA-HF) is a two-part clinical trial in pediatric HF patients ages 1 month to <18 years (**Figure 1**). 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 1**: Study schematic of PANORAMA-HF clinical trial (Study CLCZ696B2319)




***Source***: Figure 7 (*Clinical Pharmacology Review, Reference ID: 4494987, 09/20/2019*, adapted from Figure 9-1 CSR Ver 2.0 Study CLCZ696B2319, NDA 207620, eCTD 0188, M 5.3.5.1)

Part 1 of PANORAMA-HF 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 equivalent to 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. In Part 1 of the study, 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). 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 Part 2 of PANORAMA-HF.

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). 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. The full demographic characteristics of the part 2 of the study participants are detailed in **Table 1**.

The Clinical Pharmacology review (*Clinical Pharmacology Review, Reference ID: 4494987, 09/20/2019*) evaluated and reviewed Part 2 of the study till week 12 (Interim analysis). Till the interim analyses, 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.

**Table 1**: Part 2 demographic characteristics (Full Analysis Set)

| **Population: Overall** | | | |
|---|---|---|---|
| **Characteristic** | **LCZ696 N=187** | **Enalapril N=188** | **Total N=375** |
| **Age at randomization (years)** | | | |
| Mean (SD) | 8.00 (5.471) | 8.26 (5.718) | 8.13 (5.590) |
| Median (Min – Max) | 7.0 (0.5, 17.0) | 8.5 (0.1, 18.0) | 8.00 (0.1, 18.0) |
| **Age group at randomization – n (%)** | | | |
| Age group 1: 6 years to < 18 years | 109 (58.29) | 111 (59.04) | 220 (58.67) |
| 12 years to < 18 years | 61 (32.62) | 68 (36.17) | 129 (34.40) |
| 6 years to 11 years | 48 (25.67) | 43 (22.87) | 91 (24.27) |
| Age group 2a: 2 years to < 6 years | 47 (25.13) | 38 (20.21) | 85 (22.67) |
| Age group 3a: 1 month to < 2 years | 31 (16.58) | 39 (20.74) | 70 (18.67) |
| Age group 2: 1 year to < 6 years | 73 (39.04) | 73 (38.83) | 146 (38.93) |
| Age group 3: 1 month to < 1 year | 5 (2.67) | 4 (2.13) | 9 (2.40) |

(*Source*: Table 14.1-3.1.2 of Study CLCZ696B2319 CSR Report Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)

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 2**). 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 2**: Study drug dose levels for double-blind enalapril and ENTRESTO in PANORAMA-HF Part 2

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

*Source*: Study CLCZ696B2319 CSR (*Source*: Table 3-5 of Study CLCZ696B2319 Protocol Ver. 7, Appendix 16.1.1 Ver. 1.0, NDA 207620, eCTD 0188, M 5.3.5.1)

This review will focus on evaluating the data generated for the treatment period of 52 weeks, as compared to the interim analysis at 12 weeks.

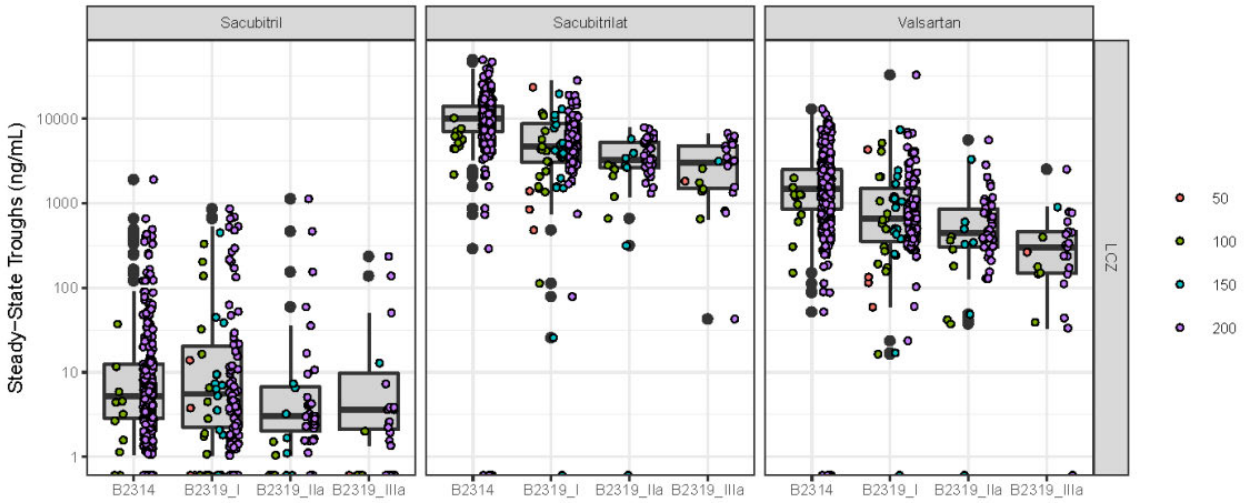
## 3.2 Clinical Pharmacology Review Questions

### *3.2.1 Is evidence of ENTRESTO effectiveness in pediatric patients in Part 2 (Week 52) of the study comparable to part 2 (Week 12)?*

#### 3.2.1.1 Pharmacokinetic Results from Study B2319 Part 2 (CLCZ696-B2319)

Part 1 results were presented by the 3 original age groups. However, Part 2 results are presented using the original Age Group 1 and modified groupings of Age Groups 2 and 3. Age Group 2a includes patients from age 2 to less than 6 years, and Age Group 3a includes patients from 1 month to less than 2 years (**Table 1**). Steady-state trough samples were collected at Week 2 or Week 4 during dose escalation, at Week 12, and Week 52. The ranges of trough levels of sacubitril, sacubitrilat, and valsartan for pediatric HF patients in Study B2319 were close to those seen in adult HF patients in Study B2314, although the mean trough concentration for sacubitrilat and valsartan tends to be lower in younger patients (**Figure 2**).

**Figure 2**: Boxplots of Steady-State Troughs of Sacubitril/Valsartan across Adults and Pediatric Patients with Heart Failure across the three pediatric age groups in studies B2314 & B2319

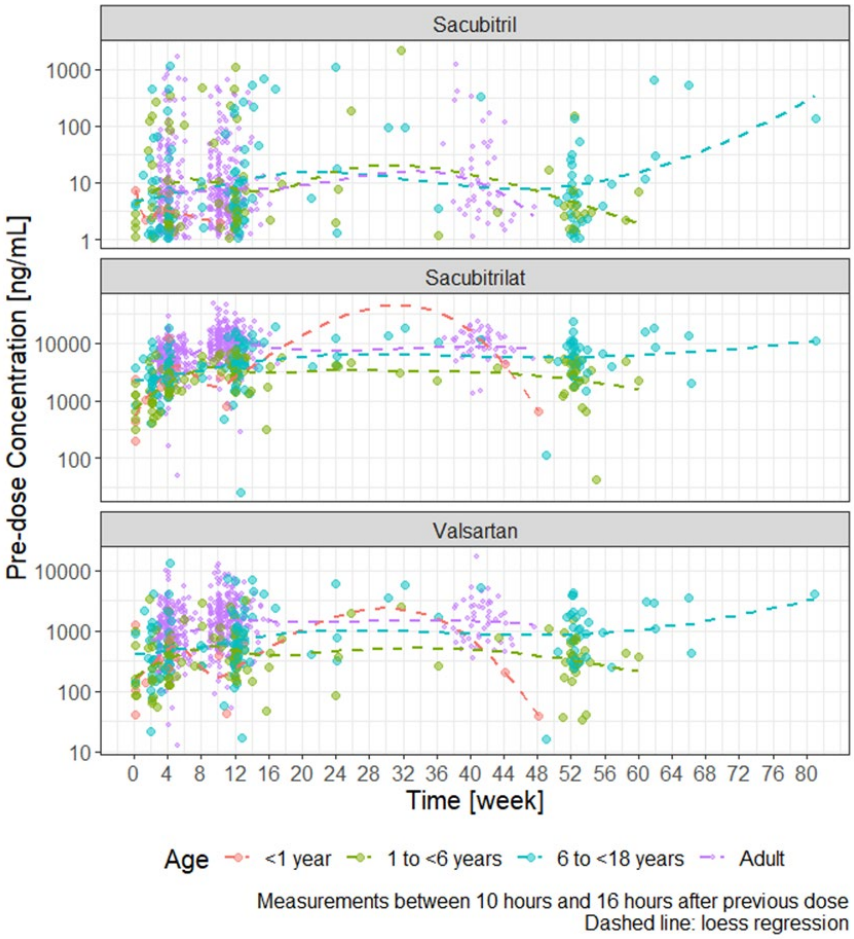



**Note**: B2319_I refers to Age Group 1 (Age 6-<18 years), B2319_IIa refers to Age Group 2a (Age 2-<6 years) and B2319_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study B2319. 50 mg=0.8 mg/kg; 100 mg =1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg.
(*Source*: Figure 4-1 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2)

As the sponsor's new analysis has different age groupings, the review team reanalyzed the data with the following age groups (based on age at demographic visit) to also focus on the <1 year group: Age Group 1 (Age 1 month - <1 year, n=8); Age Group 2 (Age 1 - <6 years, n=15) and Age Group 3 (Age 6 - <18 years, n=41). Sacubitril trough concentration for <1 year were relatively lower than the older age groups but had substantial overlap, whereas the concentrations are comparable for

sacubitrilat, the active metabolite of sacubitril, and valsartan (**Figure 3**). Interpretation is challenging as the sample size for the <1 year group is small and there is high variability in the data.

**Figure 3**: Steady-State Troughs of Sacubitril, Sacubitrilat & Valsartan across Adults and Pediatric Patients with Heart Failure across the three pediatric age groups in study B2319



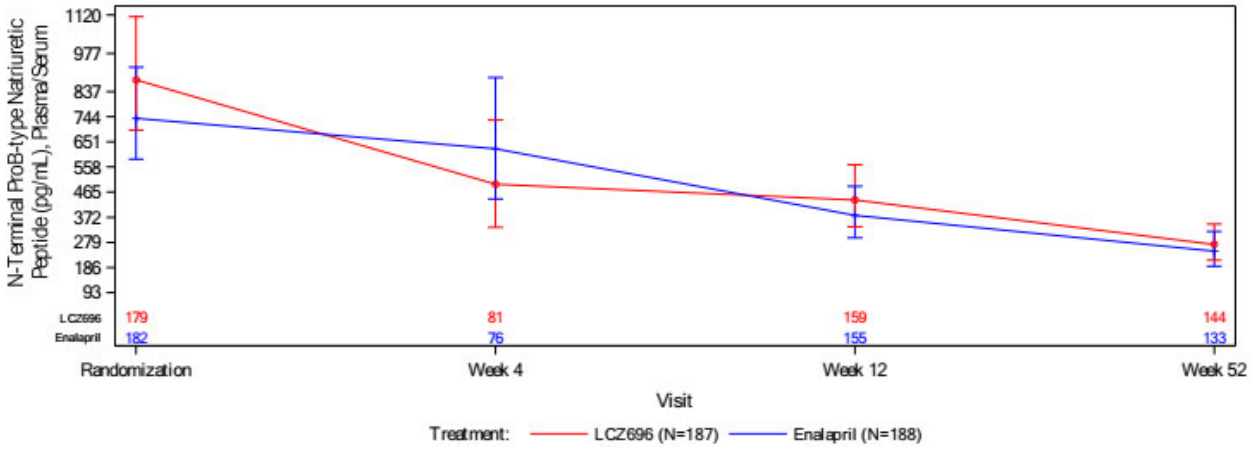

The steady state trough levels of sacubitril, sacubitrilat and valsartan at the target maintenance dose level 4 (200 mg BID or 3.1 mg/kg BID) were substantially overlapped across adult and pediatric patients. While the median steady state levels of sacubitrilat and valsartan were marginally lower in 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 observed in the steady state trough levels and the smaller sample size of the pediatric patients compared to adults. Sacubitril trough concentration for <1 year being relatively lower than the older age groups could be attributed also to the large inter-subject variability observed in the steady state trough levels and the smaller sample size of the pediatric patients. Overall, the data supports that the exposure of the main analytes, sacubitrilat and valsartan, achieved in the pediatric study was within the range that was attained in the adult PARADIGM-HF study.

### 3.2.1.2 Pharmacodynamic Results from Study B2319 Part 2 (CLCZ696-B2319, NT-proBNP change from baseline)

The safety and effectiveness of ENTRESTO for the treatment of heart failure in pediatric patients was evaluated and supported by the reduction from baseline to 52 (compared to interim portion of Part 2/Week 12) weeks in NT-proBNP (Bridging biomarker) in trial PANORAMA-HF Study.

Both treatment groups showed clinically relevant decreases in NT-proBNP levels throughout the study (**Figure 4**). The decrease was numerically greater in the sacubitril/valsartan group up to Week 52. The reduction was observed as early as 4 weeks after starting treatment, at which time the relative between-treatment difference was 27% ($p<0.05$) in favor of sacubitril/valsartan. The relative between treatment differences at both Week 12 and Week 52 were approximately 9%, which were not statistically significant. At Week 52, the reduction in NT-proBNP from baseline was 65% and 62% for the sacubitril/valsartan and enalapril groups, respectively (**Table 3**).

**Figure 4**: Part 2 NT-proBNP - geometric mean (+/- 95% CI) line plot (Full Analysis Set)




(*Source*: Figure 14.2-8.3 of Study CLCZ696B2319 Report Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)

**Table 3**: Part 2 NT-proBNP – change from baseline – Mixed Model for Repeated Measures (MMRM) (Full Analysis Set)

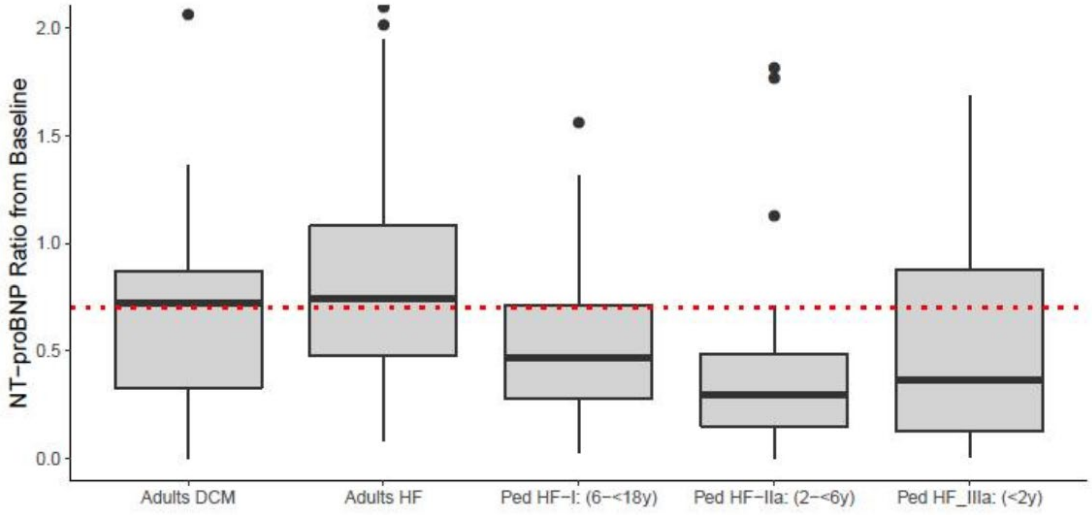
| | LCZ696 N=187 AGM RTB | | | Enalapril N=188 AGM RTB | | | Comparison (LCZ696 vs Enalapril) AGMR (LCZ696/ Enalapril) | | Nominal P-Value |
|---|---|---|---|---|---|---|---|---|---|
| Visit | n | Estimate | 95% CI | n | Estimate | 95% CI | Estimate | 95% CI | Two-sided |
| Wk4 | 81 | 0.5985 | (0.5277,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

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

(*Source*: Table 14.2-8.3 of Study CLCZ696B2319 Report Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)

Pediatric HF patients treated with the target dose of sacubitril/valsartan showed a comparable or better reduction in NT-proBNP compared to adults. There was an overlap in distribution as displayed in the boxplots at Week 52 across treatment groups with lower median ratios in pediatrics (**Figure 5**).

**Figure 5**: Boxplots of the Ratio of Plasma NT-proBNP from Baseline between Adults (at 8 months) and Pediatric Patients with Heart Failure for 200 mg (3.1 mg/kg) at 52 Weeks




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

(*Source*: Figure 5-3 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2)

**Table 4** shows the results of Applicant's primary analysis of change from baseline with respect to NT-proBNP at Weeks 12 & 52 using Mixed Model for Repeated Measures (MMRM). The decrease from baseline in NT-proBNP was not significantly different between sacubitril/valsartan and enalapril at Week 12 (adjusted geometric mean ratio: 0.9120 [95% CI: 0.7591, 1.0956]) and Week 52 (adjusted geometric mean ratio: 0.9097 [95% CI: 0.6896, 1.1999]). Results were comparable across weeks 12 and 52.

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

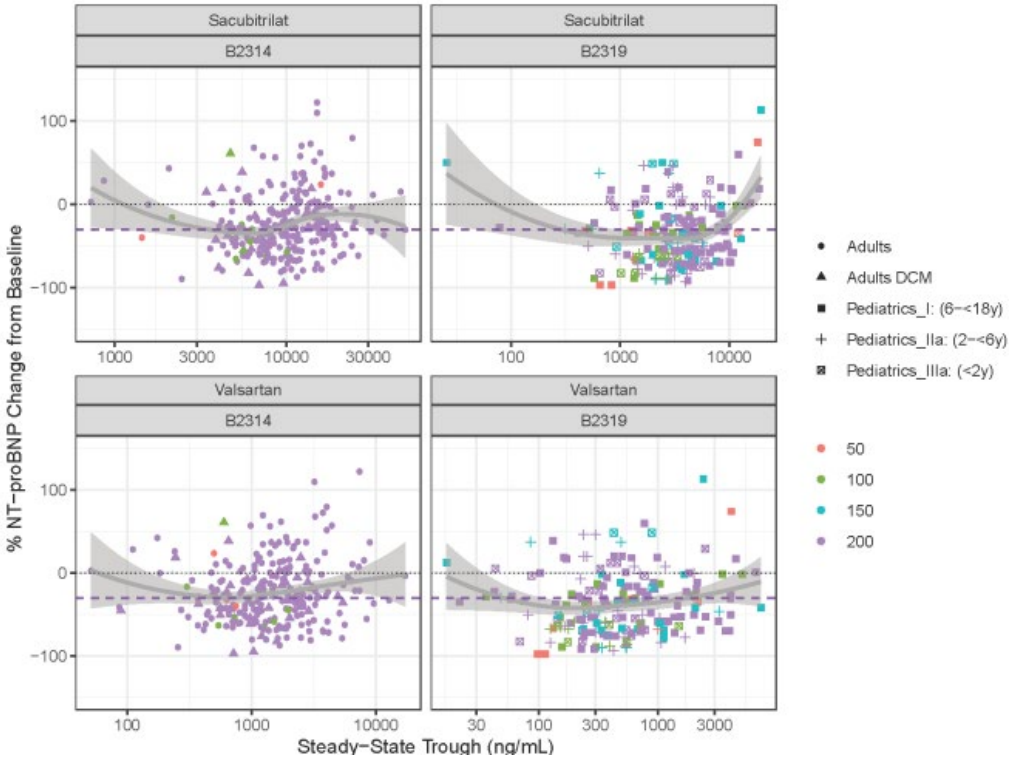
| | **Adjusted geometric mean ratio (GMR) NT-proBNP / NT-proBNP at baseline (95%CI)** | | **Adjusted geometric mean ratio (GMR) (95% CI)** |
|---|---|---|---|
| | ENTRESTO | Enalapril | ENTRESTO/ Enalapril |
| Week 12 | 0.50<br>(0.44 – 0.57)<br>(N=159) | 0.55<br>(0.48 – 0.63)<br>(N=155) | 0.91<br>(0.76– 1.10) |
| Week 52 | 0.35<br>(0.29 – 0.42)<br>(N=144) | 0.38<br>(0.31 – 0.47)<br>(N=133) | 0.91<br>(0.70– 1.20) |

*Source*: adapted from Study CLCZ696B2319- CSR Ver 2.0 Table 11-12

### 3.2.1.3 Exposure-Response (E-R) of steady-state effect of sacubitril/valsartan on plasma NT-proBNP

The ER relationship remains consistent between Week 12 and Week 52. The doses used provided sufficient exposure to achieve decreases from baseline in NT-proBNP greater than 30% as seen in adult HFrEF patients from Study B2314 (**Figure 6**).

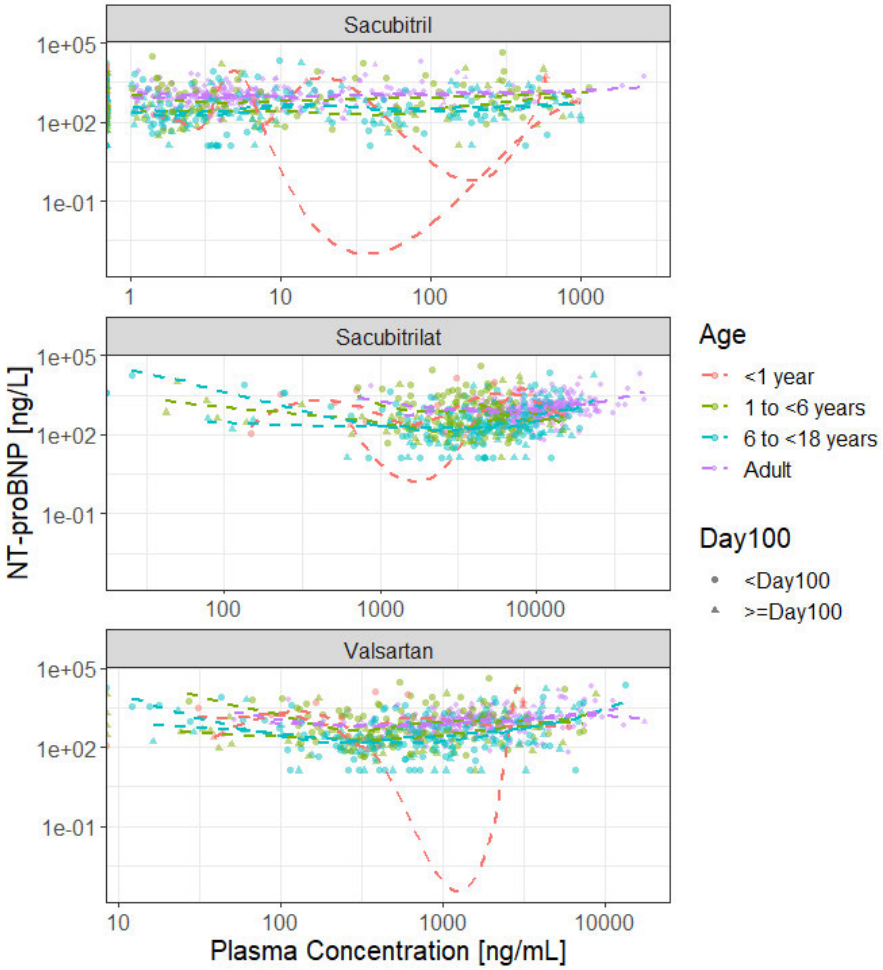
**Figure 6**: Exposure-Response Relationship of Steady-State Troughs of Sacubitril/Valsartan on Percent Change from Baseline of Plasma NT-proBNP separated by Studies.




**Note**: Dashed purple line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decrease of -30% of plasma NT-proBNP from baseline. Pediatrics_I refers to Age Group 1 (Age 6-<18 years), Pediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Pediatrics_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study B2319. DCM refers to dilated cardiomyopathy. The numbers 50 (pink symbol), 100 (green symbol), 150 (blue symbol) and 200 (purple symbol) reflects dose in mg. 50 mg=0.8 mg/kg; 100 mg=1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg.
(*Source*: Figure 6-4 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2)

The review team reanalyzed the data with the following age groups: Age Group 1 (Age 1 month - <1 years, n=8); Age Group 2 (Age 1 - <6 years, n=15) and Age Group 3 (Age 6 - <18 years, n=41). Plasma NT-proBNP response correlated with steady state trough plasma concentrations response measurements between 10 hours and 16 hours after previous dose were used. The observed E-R relationships observed within data collected before Day 100 and after Day 100 exhibited constancy (**Figure 7**), implying comparable E-R between Week 12 and Week 52. This observation was consistent across all age groups (**Figure 7**).

**Figure 7**: Exposure-Response Relationship of Steady-State Troughs concentrations of Sacubitril, sacubitrilat, and Valsartan across the three pediatric age groups in study B2319 as analyzed by the agency pharmacometrics team.




*3.3.2 Is the new formulation (film-coated granules) bioequivalent to marketed formulation (film-coated tablets)?*

ENTRESTO film-coated tablets and oral extemporaneous suspension using ENTRESTO film-coated tablets are already approved. The sponsor is seeking approval of the granule's formulation in new NDA 218591. Relative BA study CLCZ696B2126 demonstrated that the granules formulation has similar BA to that of the approved film-coated tablets under fasting conditions. Administration of the granules with a small amount of vanilla pudding does not alter the BA of the granules. Administration of the granules sprinkled on vanilla pudding with high fat meal did not alter the AUC of sacubitril or sacubitrilat but decreased the AUC of valsartan by 40%. The magnitude of food effect on the AUC of the granules is similar to that observed for the film-coated tablets and thus the current dosing recommendation (i.e., ENTRESTO can be administered with or without food) for the approved film-coated tablets can be used for the granules. Additional details are provided below.

The granules formulation is provided as 3.125 mg granules (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 granules. The capsule shell is discarded once the granules are poured onto a spoonful of soft food (b) (4).

The Applicant conducted two relative bioavailability studies in this development program**, CLCZ696B2126 *&* CLCZ696F2130**.

A. Study CLCZ696B2126*: Granules vs. Marketed Film Coated Tablets*
   - The relative bioavailability of ENTRESTO analytes (valsartan, sacubitril, sacubitrilat) following oral administration of 200 mg ENTRESTO oral granules (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 absorption of ENTRESTO analytes were found to be similar between ENTRESTO granules and film-coated tablet.
   - The rate ($C_{max}$) and extent (AUC) of absorption of ENTRESTO analytes were comparable between 200 mg granules given under fasted condition and with a small amount of vanilla pudding.
   - Administration of ENTRESTO 200 mg granules sprinkled on pudding with high fat meal resulted in decreased rate of absorption ($C_{max}$) of sacubitril (60% decrease), sacubitrilat (19% decrease), and valsartan (57% decrease). The extent of absorption ($AUC_{inf}$) of sacubitril, sacubitrilat were comparable while the extent of absorption (AUCs) of valsartan was reduced (40% decrease).
   - According to the original Clinical Pharmacology Review for the 50 mg, 100 mg and 200 mg film-coated tablets, food intake did not alter the bioavailability of sacubitril or sacubitrilat, but exposure of valsartan decreased by about 40%. The $C_{max}$ for sacubitril, sacubitrilat, and valsartan decreased approximately 54, 28, and 40%, respectively. These changes were not considered clinically significant and ENTRESTO can be taken with or without food, as done in the pivotal efficacy study (*Clinical Pharmacology Review; Luning Zhuang, Sreedharan Sabarinath, Jeffry Florian & Rajanikanth Madabushi; NDA 207620; Reference ID: 3755835; 05/2015*).

B. Study CLCZ696F2130*: Suspension from granules Vs. Marketed Film Coated Tablets*
   - The relative bioavailability of an ENTRESTO oral extemporaneous suspension prepared by dispersing granules in water compared to ENTRESTO film-coated tablet was evaluated.
   - 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 5**). The peak concentration for sacubitril is 72% (T/R Geometric Mean Ratio (GMR) of 1.72) 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 5**: Summary of PK parameters for relative bioavailability studies **CLCZ696B2126** and **CLCZ696F2130**

| Analyte | PK Parameter (Units) | T/R geometric mean ratio (%) (90% CI) | |
|---|---|---|---|
| | | Granules/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) |

### *3.3.3 Can the granules be administered with soft food?*

The Applicant proposed to allow the use of the granules with soft food. As noted above administration of the granules sprinkled on a small amount of vanilla pudding does not impact the BA of the granules. In addition, the drug can be taken without regards to meals, suggesting the type of soft food is not critical. However, it is not clear how long the granules would be stable in various soft foods. At the request of the CMC review team, the sponsor provided visual appearance data regarding the intactness of the film-coating and of the film-coated granules sprinkled on representative soft foods. For both dose strengths (12.5 & 31.25 mg capsules), the core of LCZ696 filmcoated granules sprinkled on representative soft foods (as tested, carrot puree, apple sauce, orange juice and apple juice) stayed intact for about (b) (4). At around (b) (4), the film-coating of the granules slowly started to dissolve. Although the core of the granules stayed intact, the granules became soft during the (b) (4) because of uptake of liquid from the food. The compatibility over a time period of 4 hours at room temperature was tested for samples in apple juice, orange juice, apple sauce and carrot puree. The results for appearance, assay and degradation products are presented in **Table 6**. The assay

values of LCZ696 film-coated granules in apple juice, orange juice, apple sauce and carrot puree ranged from 97.0 % to 103.8 % for valsartan and 97.4 % to 103.8 % for sacubitril, which are within the specification requirement.

**Table 6**: Chromatographic assay results for LCZ696 (sacubitril/valsartan) 6.1/6.4 [i.e., 12.5 mg] & 15.18/16.07 (i.e., 31.25 mg] film-coated granules

**Assay results for LCZ696 (sacubitril/valsartan) 6.1/6.4 mg film-coated granules**

| Vehicle name | Valsartan | Sacubitril | Valsartan | Sacubitril |
|---|---|---|---|---|
| | Initial | | After (b) (4) n contact with the vehicle | |
| Requirement | 95.0 - 105.0 % | | 95.0 - 105.0 % | |
| Control | 100.9 | 101.2 | 100.9 | 101.2 |
| Apple juice | 99.8 | 99.8 | 98.0 | 98.1 |
| Orange juice | 97.8 | 98.2 | 98.3 | 98.7 |
| Apple sauce | 103.8 | 103.8 | 102.1 | 102.2 |
| Carrot puree | 100.0 | 100.2 | 98.7 | 98.8 |

**Assay results for LCZ696 (sacubitril/valsartan) 15.18/16.07 mg film-coated granules**

| Vehicle name | Valsartan | Sacubitril | Valsartan | Sacubitril |
|---|---|---|---|---|
| | Initial | | After (b) (4) n contact with the vehicle | |
| Requirement | 95.0 - 105.0 % | | 95.0 - 105.0 % | |
| Control | 99.8 | 100.1 | 99.8 | 100.1 |
| Apple juice | 97.2 | 97.5 | 97.8 | 98.0 |
| Orange juice | 97.0 | 97.4 | 99.5 | 99.8 |
| Apple sauce | 103.4 | 103.4 | 98.5 | 98.6 |
| Carrot puree | 101.4 | 101.6 | 98.9 | 99.1 |

*Source*: LCZ696 (sacubitril/valsartan) 12.5 mg, 31.25 mg film-coated granules, pharmaceutical development – Compatibility, 6004107_SM_A_P26_975, (\\Cdsesub1\evsprod\NDA218591\0000\m3\32-body-data\32p-drug-prod\lcz696-film-coated-granules-12-5-mg--31-25-mg-01\32p2-pharm-dev, NDA 218591 eCTD 0001)

The CMC review team correspondence (Akm Khairuzzaman, November 16th, 2023) agreed and accepts the result showing that the film coat maintain its integrity (b) (4) in the soft food, after which it starts to dissolve. Subsequently, labeling should clearly indicate that once the sprinkles are mixed with soft food, it should be immediately administered (b) (4) The compatibility test results showed good physical and chemical stability of the film-coated granules mixed with soft foods (apple juice, orange juice, apple sauce and carrot puree) (b) (4) at ambient conditions. Overall, it is concluded that the granules formulation can be mixed with soft food and ingested (b) (4).

# 4. APPENDICES

## 4.1. Summary of studies reviewed

sNDA 207620 / NDA 218591consists of 3 *in-vivo* clinical and clinical pharmacology studies. In addition, 2 population pharmacokinetics and exposure-response analysis reports were submitted.

**Table 4.1.1.** Summary of clinical studies reviewed under sNDA 207620 / NDA 218591

| Study ID | Study Description | Formulation | Study population |
|---|---|---|---|
| **Phase 1 studies** | | | |
| CLCZ696B2126 | A randomized, open-label, single-dose, crossover study in healthy subjects to determine the relative bioavailability of the 200 mg LCZ696 mini-tablet compared to the 200 mg LCZ696 final market image tablet under fasted condition and also to evaluate the effect of food on the bioavailability of 200 mg LCZ696 mini-tablet | Oral mini-tablets compared to oral tablets | Healthy volunteers |
| CLCZ696F2130 | An open-label, randomized, two-treatment, two-period crossover, single-dose study in healthy subjects to determine the relative bioavailability of LCZ696 analytes following oral administration of the 200 mg LCZ696 liquid formulation compared to the 200 mg LCZ696 final market image tablet | Oral suspension from mini-tablets compared to oral tablets | Healthy volunteers |
| **Phase 2/3 studies** | | | |
| PANORAMA-HF<br>CLCZ696B2319<br>(Part 2) | Multicenter, open-label, single dose study to evaluate safety, tolerability, and pharmacokinetics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction | Oral film coated tablets & Capsules (Film coated granules) | Pediatric HF patients |
| **Pharmacometrics studies** | | | |
| Exposure-Efficacy: PK/PD analysis to evaluate the effect of steady-state trough exposures of sacubitril/valsartan on the plasma levels of NT-proBNP in adult (CLCZ696B2314) and pediatric patients (CLCZ696B2319) with heart failure: an updated report. (Studies No. CLCZ696B2314 & CLCZ696B2319). | | | |
| Population Pharmacokinetics: Population Pharmacokinetics of Sacubitril/Valsartan in healthy volunteers and Adults and Pediatric Patients (1 month to < 18 years) with Heart Failure: an updated report (Meta analysis of studies CLCZ696A2102, CLCZ696A2117, CLCZ696B2223, CLCZ696B2225, CLCZ696B2314, CLCZ696B2319). | | | |

## 4.2. 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 in two facilities (b) (4) (RCLCZ696B2319b (b) (4) (RCLCZ696B2319c (b) (4). The bioanalytical method validation summary is provided below (**Table 4.2.1**).

**Table 4.2.1**: Bioanalytical method validation summary for plasma concentration analysis

| API | sacubitril | sacubitrilat | valsartan |
|---|---|---|---|
| **Method** | **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, 30, 150, 500, 750 to 2000 | 60, 600, 3000, 10000, 15000 to 40000 | 30, 300, 1500, 5000, 7500 to 20000 |
| **Accuracy (bias, %)** | -14 to 13 | -13 to 14.75 | -13.9 to 14 |
| **Precision (%)** | QC: ≤ 6.5% | QC: ≤ 8.9% | QC: ≤ 9.39% |
| **Incurred Sample Reanalysis (ISR) within acceptance criteria (±20%) (RCLCZ696B2319b (b) (4))** | 90% | 95% | 85% |
| **Incurred Sample Reanalysis (ISR) within acceptance criteria (±20%) (RCLCZ696B2319c (b) (4))** | 82.0% | 70.6% | 84.3% |

*Source*: Final Bioanalytical Data Report - DMPK RCLCZ696B2319b, DMPK RCLCZ696B2319c (eCTD 0188, M 5.3.5.1)

**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'.

## 4.3 Individual Study Reviews

### 4.3.1. Study CLCZ696B2126 — Relative bioavailability of LCZ696 analytes in Healthy (pellets Vs. film coated tablets) Volunteers (HV)

**Title**: A randomized, open-label, single-dose, crossover study in healthy subjects to determine the relative bioavailability of the 200 mg LCZ696 mini-tablet compared to the 200 mg LCZ696 final market image tablet under fasted condition and also to evaluate the effect of food on the bioavailability of 200 mg LCZ696 mini-tablet.

**Objectives**

• Primary:

- To investigate the relative bioavailability of the LCZ696 200 mg mini-tablets compared to the LCZ696 200 mg final market image (FMI) tablet after single administration in healthy subjects under fasted condition.
- To evaluate the effect of a small amount of soft food (vanilla pudding) on the bioavailability of a single oral dose of LCZ696 200 mg mini-tablets in healthy subjects under fasted condition.
- To evaluate the effect of a high fat meal on the bioavailability of a single oral dose of LCZ696 200 mg mini-tablets sprinkled on vanilla pudding in healthy subjects.

• Secondary: To investigate the safety and tolerability of a single 200 mg oral dose of LCZ696 FMI tablet and mini-tablets in healthy subjects under fasted and/or fed conditions.

**Study population**: A total of n=40 healthy adult subjects (10 per sequence) were randomized into the study as planned in the protocol in order to have at least 32 completers. Subjects were randomized to one of the four treatment sequences in a ratio of 1:1:1:1.

**Drug product**:

- LCZ696 3.125 mg mini-tablets.
- LCZ696 200 mg oral FMI tablet.

**Study design (Table 4.3.1.1)**:

- This was an open-label, randomized, four-sequence, four-period, crossover study in healthy males and female subjects of non-childbearing potential.
- Subjects received 200 mg single oral doses of LCZ696 formulated as FMI tablets (Treatment A), mini-tablets (Treatment B), and mini-tablets sprinkled on a tablespoon of vanilla pudding (Treatment C) after an overnight fast of at least 10 h prior to dosing and remained in a fasted condition 4 h post dose.
- For Treatment D, following an overnight fast, a single oral dose of LCZ696 200 mg mini-tablets sprinkled on a tablespoon of vanilla pudding was administered 30 minutes after the start of a standard high-fat breakfast.

| Sequence | Period 1 | Washout | Period 2 | Washout | Period 3 | Washout | Period 4 |
|---|---|---|---|---|---|---|---|
| | Single dose | | Single dose | | Single dose | | Single dose |
| 1 | Treatment A | 7 to 14 days | Treatment B | 7 to 14 days | Treatment C | 7 to 14 days | Treatment D |
| 2 | Treatment B | | Treatment D | | Treatment A | | Treatment C |
| 3 | Treatment C | | Treatment A | | Treatment D | | Treatment B |
| 4 | Treatment D | | Treatment C | | Treatment B | | Treatment A |

Treatment A: single oral dose of LCZ696 200 mg FMI

Treatment B: single oral dose of LCZ696 200 mg mini-tablets

Treatment C: single oral dose of LCZ696 200 mg mini-tablets sprinkled on a tablespoon of pudding

Treatment D: single oral dose of LCZ696 200 mg mini-tablets sprinkled on a tablespoon of pudding and administered with a high fat meal

**Table 4.3.1.1** Treatment sequences (*Source*: Table 9-1 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**PK sampling:** PK blood samples are collected at 0, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr, 48 hr, 72 hr, and 96 hr post-dose for all periods.

**Results**: PK results are shown as below.

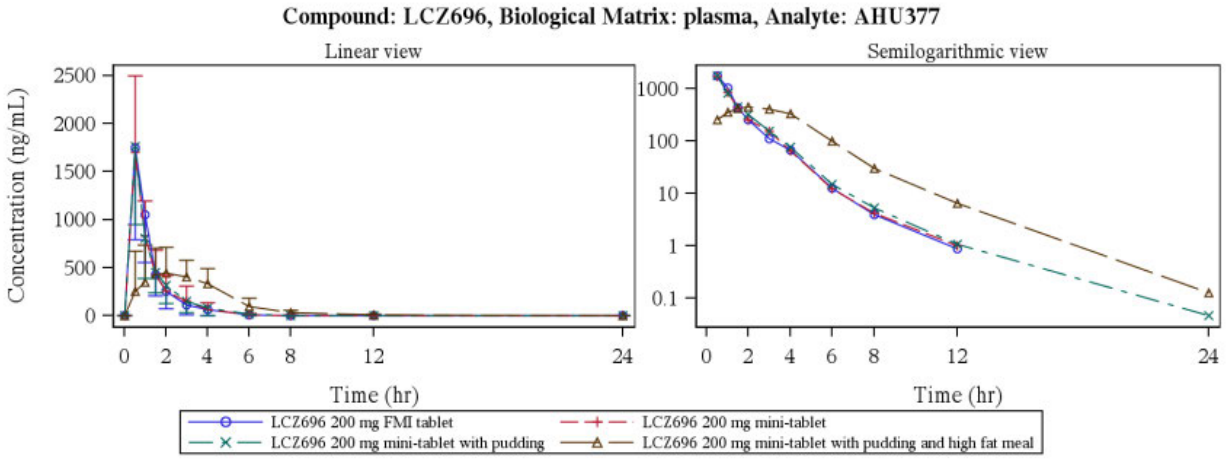



**Figure 4.3.1.1** Arithmetic mean (SD) plasma concentration-time profiles of sacubitril (AHU377) after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Figure 11-1 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

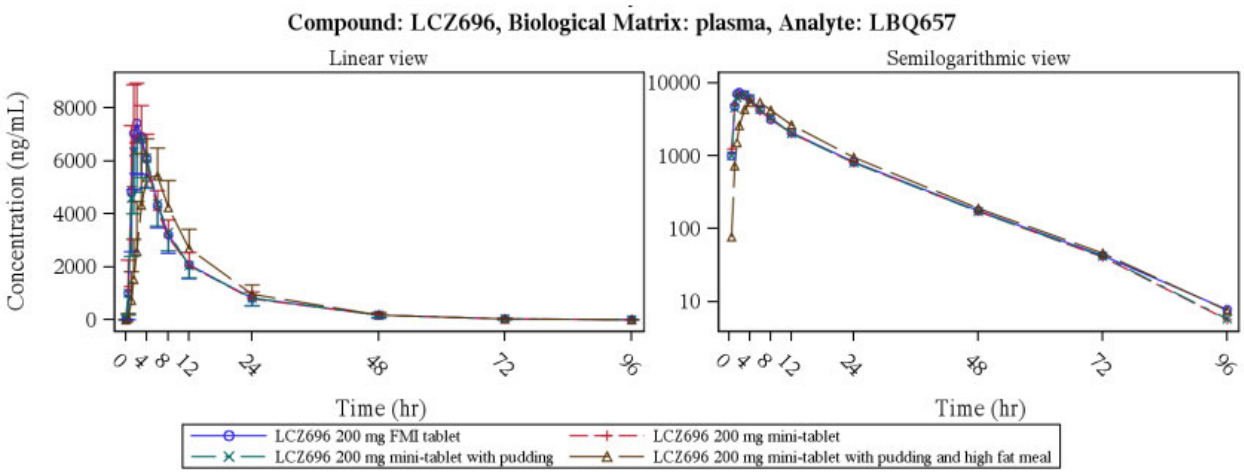



**Figure 4.3.1.2** Arithmetic mean (SD) plasma concentration-time profiles in plasma of sacubitrilat (LBQ657) after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Figure 11-2 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

| Treatment | Statistic | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) |
|---|---|---|---|---|---|---|
| FMI tablet | N | 40 | 40 | 40 | 40 | 40 |
| | Mean (SD) | 2050 (475) | 2060 (475) | 1910 (805) | - | 1.51 (0.659) |
| | CV% mean | 23.1 | 23.1 | 42.1 | - | 43.6 |
| | Geo-mean | 2000 | 2000 | 1720 | - | 1.39 |
| | CV% geo-mean | 23.9 | 23.9 | 53.2 | - | 42.4 |
| | Median | 1930 | 1930 | 1950 | 0.500 | 1.38 |
| | [Min; Max] | [1180;2990] | [1190;3000] | [497;3500] | [0.50;4.00] | [0.68;3.33] |
| Mini-tablets | N | 40 | 40 | 40 | 40 | 40 |
| | Mean (SD) | 1970 (483) | 1970 (483) | 1780 (700) | - | 1.49 (0.727) |
| | CV% mean | 24.5 | 24.5 | 39.4 | - | 48.8 |
| | Geo-mean | 1910 | 1910 | 1620 | - | 1.35 |
| | CV% geo-mean | 25.7 | 25.7 | 48.0 | - | 45.8 |
| | Median | 1970 | 1980 | 1820 | 0.50 | 1.28 |
| | [Min; Max] | [1080;2970] | [1080;2970] | [408;3390] | [0.50;1.50] | [0.74;4.02] |
| Mini-tablets with pudding | N | 39 | 39 | 39 | 39 | 39 |
| | Mean (SD) | 2070 (497) | 2080 (498) | 1810 (771) | - | 1.46 (0.679) |
| | CV% mean | 24.0 | 24.0 | 42.6 | - | 46.6 |
| | Geo-mean | 2010 | 2010 | 1630 | - | 1.33 |
| | CV% geo-mean | 26.9 | 26.9 | 51.9 | - | 44.0 |
| | Median | 2100 | 2110 | 1820 | 0.50 | 1.24 |
| | [Min; Max] | [984;3270] | [987;3280] | [425;3820] | [0.50;1.50] | [0.68;3.67] |
| Mini-tablets with pudding and high fat meal | N | 39 | 38 | 39 | 39 | 38 |
| | Mean (SD) | 2060 (519) | 2080 (528) | 713 (368) | - | 1.43 (0.601) |
| | CV% mean | 25.1 | 25.4 | 51.7 | - | 42.0 |
| | Geo-mean | 2010 | 2020 | 650 | - | 1.35 |
| | CV% geo-mean | 24.7 | 25.0 | 42.5 | - | 31.6 |
| | Median | 1910 | 1930 | 660 | 3.00 | 1.31 |
| | [Min; Max] | [1070;3710] | [1070;3740] | [334;2210] | [0.50;4.00] | [0.76;4.13] |

For Tmax: n, minimum, median and maximum are presented.

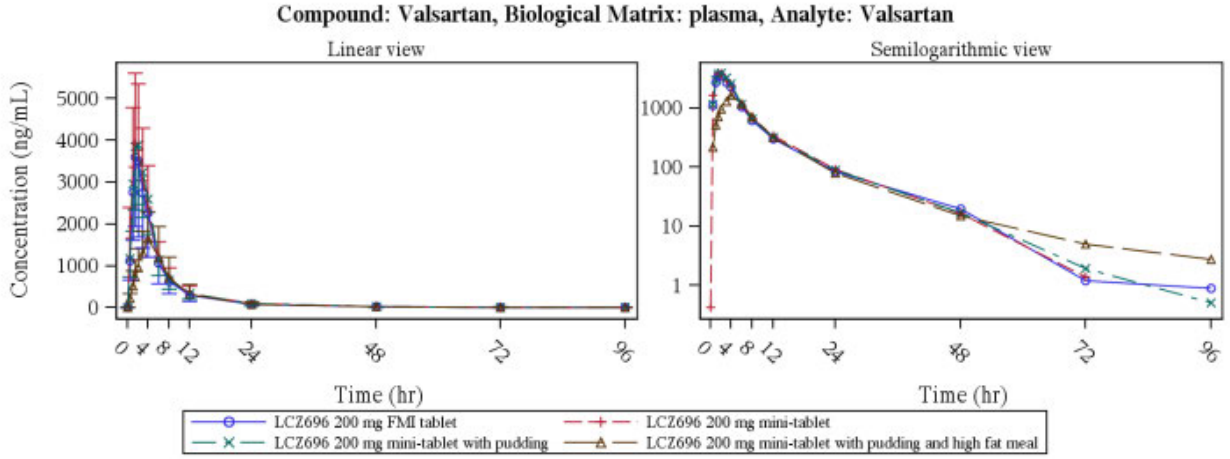
**Table 4.3.1.2** Summary statistics for PK parameters of sacubitril (AHU377) by treatment after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Table 11-3 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

| Treatment | Statistic | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) |
|---|---|---|---|---|---|---|
| FMI tablet | n | 40 | 40 | 40 | 40 | 40 |
| | Mean (SD) | 82700 (18900) | 83400 (18900) | 7920 (1540) | - | 11.0 (1.70) |
| | CV% mean | 22.8 | 22.6 | 19.5 | - | 15.4 |
| | Geo-mean | 80900 | 81600 | 7770 | - | 10.9 |
| | CV% geo-mean | 20.9 | 20.7 | 19.7 | - | 15.6 |
| | Median | 78800 | 79400 | 7600 | 2.00 | 11.2 |
| | [Min; Max] | [57200;157000] | [58000;158000] | [4680;12000] | [1.00;6.00] | [8.20;14.7] |
| Mini-tablets | n | 40 | 40 | 40 | 40 | 40 |
| | Mean (SD) | 80800 (18600) | 81500 (18600) | 7530 (1610) | - | 10.9 (2.25) |
| | CV% mean | 23.0 | 22.9 | 21.4 | - | 20.6 |
| | Geo-mean | 79000 | 79700 | 7370 | - | 10.7 |
| | CV% geo-mean | 21.4 | 21.3 | 21.0 | - | 19.6 |
| | Median | 78300 | 78900 | 7080 | 2.00 | 10.5 |
| | [Min; Max] | [51300;151000] | [52100;152000] | [4820;11400] | [1.00;4.00] | [7.31;17.9] |
| Mini-tablets with pudding | n | 39 | 39 | 39 | 39 | 39 |
| | Mean (SD) | 81600 (18800) | 82300 (18800) | 7470 (1740) | - | 11.3 (3.07) |
| | CV% mean | 23.0 | 22.8 | 23.3 | - | 27.1 |
| | Geo-mean | 79800 | 80500 | 7290 | - | 11.1 |
| | CV% geo-mean | 21.0 | 20.8 | 23.2 | - | 20.7 |
| | Median | 79700 | 80400 | 7220 | 2.00 | 10.8 |
| | [Min; Max] | [56800;153000] | [57400;154000] | [4260;12400] | [1.47;6.00] | [7.90;27.5] |
| Mini-tablets with pudding and high fat meal | n | 39 | 39 | 39 | 39 | 39 |
| | Mean (SD) | 83400 (20300) | 84100 (20300) | 5980 (1180) | - | 10.8 (2.09) |
| | CV% mean | 24.3 | 24.2 | 19.8 | - | 19.3 |
| | Geo-mean | 81400 | 82100 | 5880 | - | 10.6 |
| | CV% geo-mean | 21.5 | 21.4 | 18.9 | - | 18.3 |
| | Median | 78900 | 79500 | 5850 | 4.00 | 10.5 |
| | [Min; Max] | [59200;159000] | [60000;160000] | [3620;10500] | [2.00;6.00] | [7.41;18.5] |

For Tmax: n, minimum, median and maximum are presented.

**Table 4.3.1.3** Summary statistics for PK parameters of sacubitrilat (LBQ657) by treatment after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Table 11-4 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**Figure 4.3.1.3** Arithmetic mean (SD) plasma concentration-time profiles in plasma of valsartan after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Figure 11-3 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)



| Treatment | Statistic | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) |
|---|---|---|---|---|---|---|
| FMI tablet | n | 40 | 38 | 40 | 40 | 38 |
| | Mean (SD) | 20700 (8970) | 21000 (9210) | 3840 (1770) | - | 8.64 (2.94) |
| | CV% mean | 43.4 | 43.9 | 46.0 | - | 34.0 |
| | Geo-mean | 18800 | 19100 | 3460 | - | 8.19 |
| | CV% geo-mean | 48.0 | 48.2 | 50.6 | - | 33.9 |
| | Median | 19300 | 19300 | 3430 | 1.50 | 8.21 |
| | [Min; Max] | [4630;45400] | [4880;46000] | [849;8180] | [1.00;4.00] | [4.69;17.3] |
| Mini-tablets | n | 40 | 39 | 40 | 40 | 39 |
| | Mean (SD) | 22700 (9210) | 23300 (9090) | 4110 (1640) | - | 8.11 (2.08) |
| | CV% mean | 40.6 | 39.0 | 40.0 | - | 25.6 |
| | Geo-mean | 20800 | 21500 | 3770 | - | 7.84 |
| | CV% geo-mean | 48.0 | 45.9 | 47.2 | - | 28.0 |
| | Median | 22100 | 22400 | 3960 | 1.50 | 8.40 |
| | [Min; Max] | [4990;58400] | [5230;58500] | [822;9490] | [1.00;4.00] | [4.34;13.5] |
| Mini-tablets with pudding | n | 39 | 39 | 39 | 39 | 39 |
| | Mean (SD) | 22600 (7420) | 23000 (7430) | 4090 (1510) | - | 8.54 (3.55) |
| | CV% mean | 32.8 | 32.4 | 36.8 | - | 41.6 |
| | Geo-mean | 21400 | 21800 | 3800 | - | 7.96 |
| | CV% geo-mean | 35.7 | 35.2 | 43.4 | - | 38.4 |
| | Median | 21200 | 21500 | 3720 | 2.00 | 8.00 |
| | [Min; Max] | [6720;38700] | [6930;39000] | [722;8580] | [1.00;4.00] | [4.18;20.5] |
| Mini-tablets with pudding and high fat meal | n | 39 | 35 | 39 | 39 | 35 |
| | Mean (SD) | 14000 (6960) | 14300 (7320) | 1750 (704) | - | 7.65 (2.86) |
| | CV% mean | 49.6 | 51.1 | 40.2 | - | 37.4 |
| | Geo-mean | 12700 | 12900 | 1620 | - | 7.21 |
| | CV% geo-mean | 46.5 | 47.8 | 42.2 | - | 35.0 |
| | Median | 13100 | 13400 | 1670 | 4.00 | 7.10 |
| | [Min; Max] | [5570;39900] | [5810;40100] | [680;3980] | [1.00;6.00] | [4.08;17.5] |

For Tmax n, minimum, median and maximum are presented.

**Table 4.3.1.4** Summary statistics for PK parameters of valsartan by treatment after a single dose of 200 mg LCZ696 (PK analysis set) (*Source*: Table 11-5 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

| Analyte | Parameter | Unit | LCZ696 200 mg Treatment | N | Adjusted geometric mean* | Comparison result* Ratio (Test/ Reference) | 90% CI for ratio |
|---|---|---|---|---|---|---|---|
| AHU377 | AUCinf | ng*h/mL | Mini-tablets (Test) | 40 | 1914 | 0.96 | (0.92, 1.00) |
| | | | FMI tablet (Reference) | 40 | 2002 | | |
| | AUClast | ng*h/mL | Mini-tablets (Test) | 40 | 1910 | 0.96 | (0.92, 1.00) |
| | | | FMI tablet (Reference) | 40 | 1997 | | |
| | Cmax | ng/mL | Mini-tablets (Test) | 40 | 1623 | 0.94 | (0.80, 1.11) |
| | | | FMI tablet (Reference) | 40 | 1721 | | |
| LBQ657 | AUCinf | ng*h/mL | Mini-tablets (Test) | 40 | 79673 | 0.98 | (0.96, 0.99) |
| | | | FMI tablet (Reference) | 40 | 81590 | | |
| | AUClast | ng*h/mL | Mini-tablets(Test) | 40 | 79005 | 0.98 | (0.96, 0.99) |
| | | | FMI tablet (Reference) | 40 | 80929 | | |
| | Cmax | ng/mL | Mini-tablets (Test) | 40 | 7374 | 0.95 | (0.91, 0.99) |
| | | | FMI tablet (Reference) | 40 | 7771 | | |
| Valsartan | AUCinf | ng*h/mL | Mini-tablets (Test) | 37 | 21414 | 1.11 | (1.00, 1.24) |
| | | | FMI tablet (Reference) | 37 | 19251 | | |
| | AUClast | ng*h/mL | Mini-tablets(Test) | 40 | 20772 | 1.11 | (1.00, 1.22) |
| | | | FMI tablet (Reference) | 40 | 18798 | | |
| | Cmax | ng/mL | Mini-tablets(Test) | 40 | 3767 | 1.09 | (0.98, 1.21) |
| | | | FMI tablet (Reference) | 40 | 3459 | | |

*back transformed from log scale.

Model: The log transformed PK parameter data were analyzed using linear fixed effect model, with treatment, sequence, period and subject nested in sequence as fixed factors.

**Table 4.3.1.5** Statistical analysis of PK parameters for comparison of mini-tablets and FMI tablets of LCZ696 – Completers (PK analysis set) (*Source*: Table 11-6 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

| Analyte | Parameter | Unit | LCZ696 200 mg Treatment | N | Adjusted geometric mean* | Comparison result* Ratio (Test/ Reference) | 90% CI for ratio |
|---|---|---|---|---|---|---|---|
| AHU377 | AUCinf | ng*h/mL | Mini-tablets with pudding (Test) | 39 | 2005 | 1.04 | (1.00,1.08) |
| | | | Mini-tablets (Reference) | 39 | 1930 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding (Test) | 39 | 2001 | 1.04 | (1.00,1.08) |
| | | | Mini-tablets (Reference) | 39 | 1926 | | |
| | Cmax | ng/mL | Mini-tablets with pudding (Test) | 39 | 1627 | 1.00 | (0.85,1.18) |
| | | | Mini-tablets (Reference) | 39 | 1629 | | |
| LBQ657 | AUCinf | ng*h/mL | Mini-tablets with pudding (Test) | 39 | 80421 | 1.01 | (0.99,1.03) |
| | | | Mini-tablets (Reference) | 39 | 79831 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding (Test) | 39 | 79731 | 1.01 | (0.99,1.03) |
| | | | Mini-tablets (Reference) | 39 | 79175 | | |
| | Cmax | ng/mL | Mini-tablets with pudding (Test) | 39 | 7279 | 0.99 | (0.95,1.03) |
| | | | Mini-tablets (Reference) | 39 | 7373 | | |
| Valsartan | AUCinf | ng*h/mL | Mini-tablets with pudding(Test) | 38 | 21598 | 1.02 | (0.93,1.11) |
| | | | Mini-tablets(Reference) | 38 | 21226 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding(Test) | 39 | 21343 | 1.04 | (0.94,1.14) |
| | | | Mini-tablets(Reference) | 39 | 20598 | | |
| | Cmax | ng/mL | Mini-tablets with pudding(Test) | 39 | 3792 | 1.02 | (0.92,1.13) |
| | | | Mini-tablets(Reference) | 39 | 3720 | | |

*back transformed from log scale.

Model: The log transformed PK parameter data were analyzed using linear fixed effect model, with treatment, sequence, period and subject nested in sequence as fixed factors.

**Table 4.3.1.6** Statistical analysis of PK parameters for assessment of the effect of a small amount of soft food for LCZ696 – Completers (PK analysis set) (*Source*: Table 11-7 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

| Analyte | Parameter | Unit | LCZ696 200 mg Treatment | N | Comparison result* | | |
|---|---|---|---|---|---|---|---|
| | | | | | Adjusted geometric mean* | Ratio (Test/ Reference) | 90% CI for ratio |
| AHU377 | AUCinf | ng*h/mL | Mini-tablets with pudding and high fat meal (Test) | 38 | 2008 | 1.01 | (0.97,1.05) |
| | | | Mini-tablets with pudding (Reference) | 38 | 1992 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding and high fat meal (Test) | 39 | 2000 | 1.00 | (0.96,1.04) |
| | | | Mini-tablets with pudding(Reference) | 39 | 2001 | | |
| | Cmax | ng/mL | Mini-tablets with pudding and high fat meal (Test) | 39 | 650 | 0.40 | (0.34,0.46) |
| | | | Mini-tablets with pudding(Reference) | 39 | 1628 | | |
| LBQ657 | AUCinf | ng*h/mL | Mini-tablets with pudding and high fat meal (Test) | 39 | 81983 | 1.02 | (1.00,1.04) |
| | | | Mini-tablets with pudding(Reference) | 39 | 80425 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding and high fat meal (Test) | 39 | 81332 | 1.02 | (1.00,1.04) |
| | | | Mini-tablets with pudding (Reference) | 39 | 79734 | | |
| | Cmax | ng/mL | Mini-tablets with pudding and high fat meal (Test) | 39 | 5872 | 0.81 | (0.77,0.85) |
| | | | Mini-tablets with pudding (Reference) | 39 | 7279 | | |
| Valsartan | AUCinf | ng*h/mL | Mini-tablets with pudding and high fat meal(Test) | 35 | 13032 | 0.60 | (0.54,0.66) |
| | | | Mini-tablets with pudding(Reference) | 35 | 21878 | | |
| | AUClast | ng*h/mL | Mini-tablets with pudding and high fat meal(Test) | 39 | 12653 | 0.59 | (0.54,0.65) |
| | | | Mini-tablets with pudding(Reference) | 39 | 21376 | | |
| | Cmax | ng/mL | Mini-tablets with pudding and high fat meal(Test) | 39 | 1617 | 0.43 | (0.38,0.48) |
| | | | Mini-tablets with pudding(Reference) | 39 | 3797 | | |

*back transformed from log scale.

Model: The log transformed PK parameter data were analyzed using linear fixed effect model, with treatment, sequence, period and subject nested in sequence as fixed factors.

**Table 4.3.1.7** Statistical analysis of PK parameter for assessment of the effect of a high fat meal for LCZ696 – Completers (PK analysis set) (*Source*: Table 11-8 of Study CLCZ696F2126 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**Conclusions**:

- The rate ($C_{max}$) and extent (AUC) of absorption of LCZ696 analytes were comparable between LCZ696 200 mg mini-tablets and LCZ696 200 mg FMI tablet in healthy subjects under fasted condition (0.94-0.11-fold change range).
- The rate ($C_{max}$) and extent (AUC) of absorption of LCZ696 analytes were comparable when LCZ696 200 mg mini-tablets were administered with or without a small amount of vanilla pudding (0.99-1.04-fold change range).
- Administration of LCZ696 200 mg mini-tablets sprinkled on pudding with high fat meal resulted in decreased rate of absorption ($C_{max}$) of AHU377 (60% decrease), LBQ657 (19% decrease), and valsartan (57% decrease). The extent of absorption ($AUC_{inf}$) of AHU377 & LBQ657 were comparable while the extent of absorption (AUCinf) of valsartan was reduced (40% decrease). According to the original Clinical Pharmacology Review for the 50 mg, 100 mg and 200 mg film-coated tablets, food intake did not alter the bioavailability of sacubitril or sacubitrilat, but exposure of valsartan decreased by about 40 % from LCZ696. This change was not considered clinically significant and LCZ696 can be taken with or without food, as done in the pivotal efficacy study (*Clinical Pharmacology Review; Luning Zhuang, Sreedharan Sabarinath, Jeffry Florian & Rajanikanth Madabushi; NDA 207620; Reference ID: 3755835; 05/2015*).

### 4.3.2. Study CLCZ696F2130— Relative bioavailability of LCZ696 analytes in Healthy (Suspension from pellets vs. film coated tablets) Volunteers (HV)

**Title**: An open-label, randomized, two-treatment, two-period crossover, single-dose study in healthy subjects to determine the relative bioavailability of LCZ696 analytes following oral administration of the 200 mg LCZ696 liquid formulation compared to the 200 mg LCZ696 final market image tablet.

**Objectives**

• Primary: to determine the relative bioavailability of the LCZ696 200 mg liquid formulation compared to the 200 mg LCZ696 final market image (FMI) tablet after single oral administration in healthy subjects.

• Secondary: to assess the safety and tolerability of a single oral dose of 200 mg LCZ696 liquid formulation and FMI tablet in healthy subjects.

**Study population**: healthy subjects (n=28)

**Drug product**:

Test product, dose, and mode of administration:

- LCZ696 200 mg oral liquid formulation (64 granules 3.125 mg LCZ696 dissolved in 100 mL of water).
- LCZ696 200 mg oral FMI tablet.

Subjects fasted overnight for at least 10 hours prior to dosing and remained fasted until 4 hours post-dose. No fluid intake apart from the fluid given at the time of drug intake was allowed from 1 hour before until 1 hour after dosing.

**Study design**:

**Figure 4.3.2.1** Study design overview

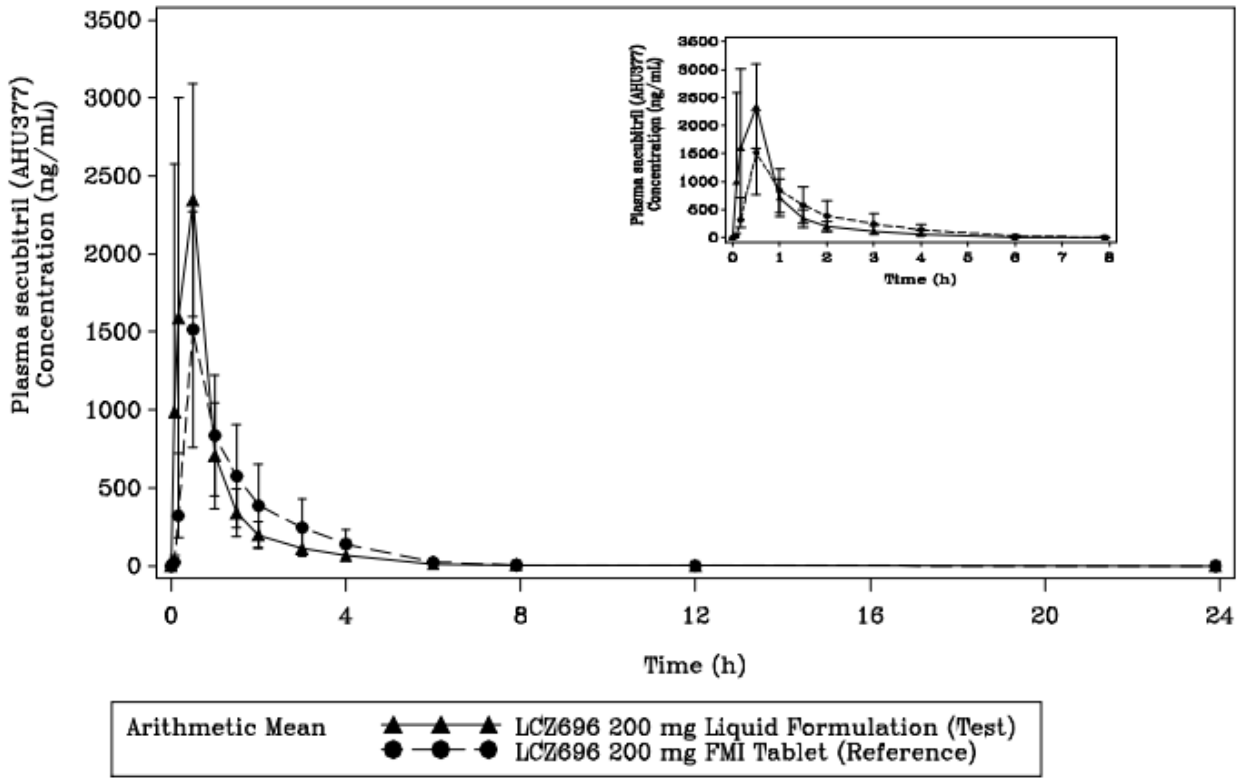
| **Study Day** | **–21 to –2** | **–1** | **1 to 4** | **5** | **6 to 9** |
|---|---|---|---|---|---|
| Period | Screening | Baseline | Treatment Period 1 | Baseline 2 | Treatment Period 2 |
| Sequence | | | | | |
| 1 | | | A | | B |
| 2 | | | B | | A |
| | | Admit to clinic | Randomization on Day 1. Pharmacokinetic profile for 72 hours after dosing. | | Pharmacokinetic profile for 72 hours after dosing. Discharge after pharmacokinetic and safety assessments on Day 9. |

(*Source*: Figure 9-1 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**PK sampling:** PK blood samples are collected at 0 and at 5 min, 10 min, 0.5 hr, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 12 hr, 24 hr, 36 hr, 48 hr, and 72 hr post-dose for all periods.

**Results**: PK results are shown as below.

**Figure 4.3.2.2** Arithmetic mean (plus minus SD) concentration-time profiles for plasma sacubitril (AHU377) by treatment (Pharmacokinetic analysis set) (*Source*: Figure 11-1 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)



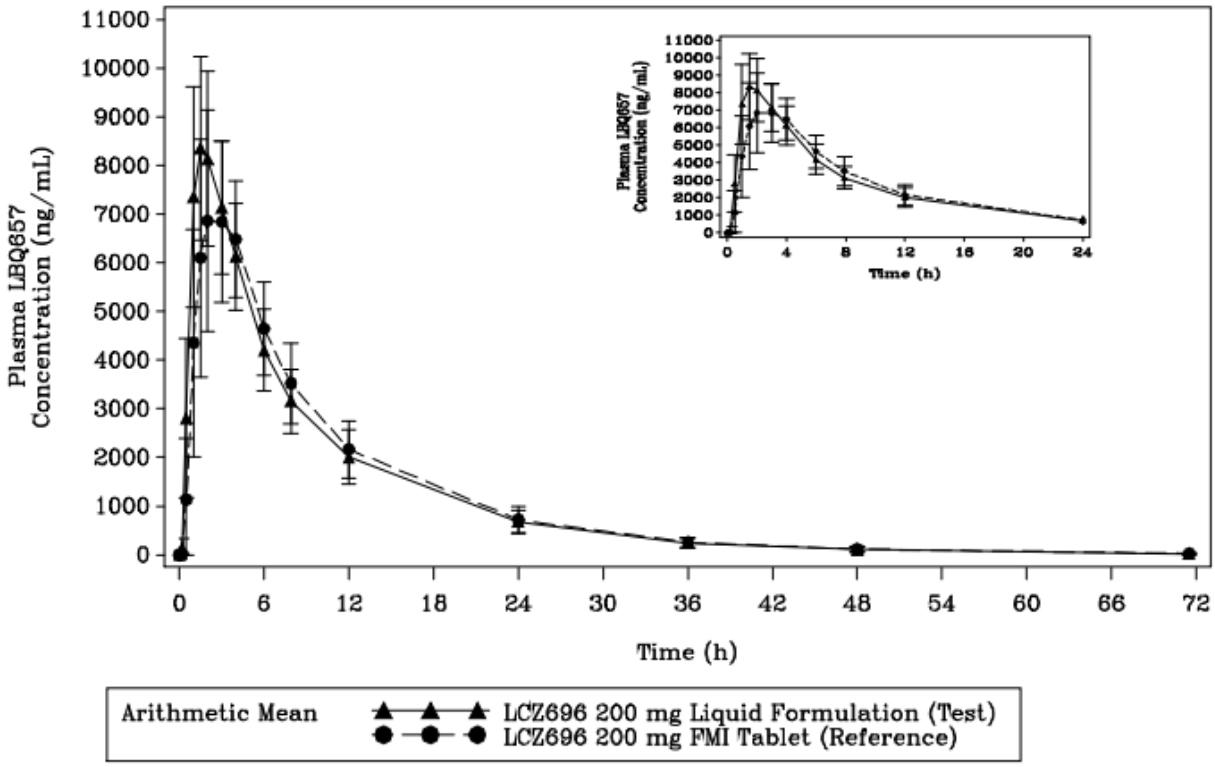

| Treatment | Statistics | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| LCZ696 200 mg liquid formulation (N=28) | n | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 2310 (592) | 2320 (591) | 2730 (1260) | NC | 1.76 (0.713) | 44.6 (11.9) | 110 (45.9) |
| | CV% mean | 25.6 | 25.5 | 46.1 | NC | 40.5 | 26.7 | 41.8 |
| | Geo-mean | 2240 | 2250 | 2530 | NC | 1.61 | 43.2 | 100 |
| | Median | 2230 | 2240 | 2490 | 0.500 | 1.86 | 43.4 | 106 |
| | [Min, Max] | [1230, 3570] | [1230, 3570] | [1220, 7880] | [0.0833, 1.00] | [0.590, 3.33] | [27.2, 79.0] | [29.4, 240] |
| LCZ696 200 mg FMI tablet (N=28) | n | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 2220 (508) | 2220 (508) | 1600 (650) | NC | 1.27 (0.367) | 46.0 (10.8) | 82.7 (25.1) |
| | CV% mean | 22.9 | 22.9 | 40.5 | NC | 28.9 | 23.4 | 30.4 |
| | Geo-mean | 2160 | 2170 | 1470 | NC | 1.22 | 44.8 | 78.6 |
| | Median | 2170 | 2180 | 1540 | 0.500 | 1.28 | 44.6 | 79.7 |
| | [Min, Max] | [1250, 3460] | [1260, 3470] | [636, 2990] | [0.500, 3.00] | [0.601, 2.00] | [28.0, 77.2] | [35.8, 129] |

CV% = coefficient of variation; FMI = final market image; geo-mean = geometric mean; max = maximum; min = minimum; n: number of subjects with nonmissing values; N = number of subjects in pharmacokinetic analysis set; NC = not calculated; SD = standard deviation

CV% = SD/mean*100.

**Table 4.3.2.1** Summary of pharmacokinetic parameters for sacubitril (AHU377) by treatment (Pharmacokinetic analysis set) (*Source*: Table 11-3 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**Figure 4.3.2.3** Arithmetic mean (plus minus SD) concentration-time profiles for plasma sacubitrilat (LBQ657) by treatment (Pharmacokinetic analysis set) (*Source*: Figure 11-2 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)



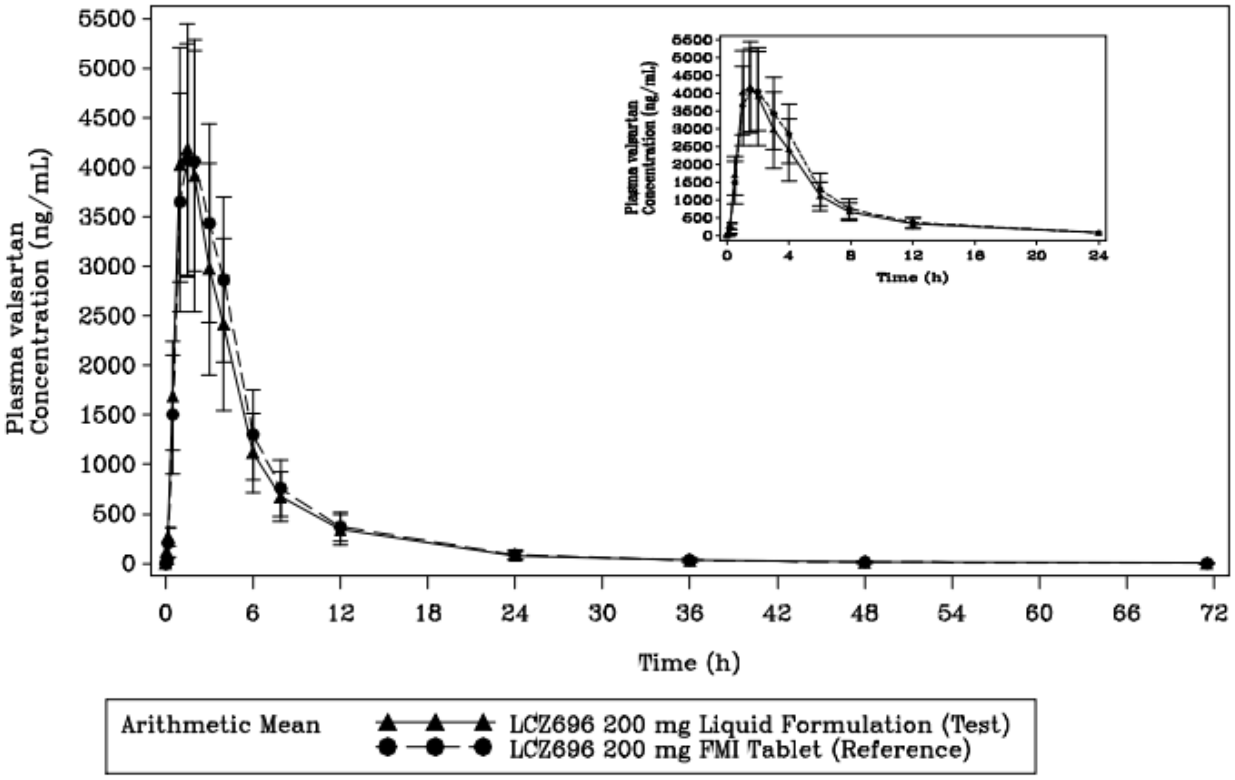

| Treatment | Statistics | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) |
|---|---|---|---|---|---|---|
| LCZ696 200 mg liquid formulation (N=28) | n | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 78200 (18000) | 78800 (18000) | 8580 (1960) | NC | 9.20 (1.49) |
| | CV% mean | 23.0 | 22.9 | 22.9 | NC | 16.2 |
| | Geo-mean | 76300 | 76900 | 8380 | NC | 9.09 |
| | Median | 75200 | 75700 | 8230 | 1.50 | 9.31 |
| | [Min, Max] | [51800, 123000] | [52700, 124000] | [5820, 14000] | [1.00, 4.00] | [6.83, 13.4] |
| LCZ696 200 mg FMI tablet (N=28) | n | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 78200 (18900) | 78800 (18900) | 7650 (1990) | NC | 9.04 (1.37) |
| | CV% mean | 24.2 | 24.0 | 26.0 | NC | 15.1 |
| | Geo-mean | 76000 | 76600 | 7410 | NC | 8.94 |
| | Median | 73200 | 73900 | 7480 | 3.00 | 9.34 |
| | [Min, Max] | [48100, 113000] | [48500, 114000] | [4470, 12300] | [1.00, 6.02] | [6.29, 11.3] |

CV% = coefficient of variation; FMI = final market image; geo-mean = geometric mean; max = maximum; min = minimum; n = number of subjects with nonmissing values; N = number of subjects in pharmacokinetic analysis set; NC = not calculated; SD = standard deviation.

CV% = SD/mean*100.

**Table 4.3.2.2** Summary of pharmacokinetic parameters for sacubitrilat (LBQ657) by treatment (Pharmacokinetic analysis set) (*Source*: Table 11-4 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**Figure 4.3.2.4** Arithmetic mean (plus minus SD) concentration-time profiles for plasma valsartan by treatment (Pharmacokinetic analysis set) (*Source*: Figure 11-3 of Study CLCZ696F2130 CSR)




| Treatment | Statistics | AUClast (ng*h/mL) | AUCinf (ng*h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2 (h) | CL/F (L/h) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|
| LCZ696 200 mg liquid formulation (N=28) | n | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 22800 (6930) | 23000 (6950) | 4430 (1350) | NC | 8.58 (3.44) | 5.04 (2.04) | 62.4 (37.3) |
| | CV% mean | 30.4 | 30.3 | 30.3 | NC | 40.1 | 40.5 | 59.8 |
| | Geo-mean | 21600 | 21800 | 4220 | NC | 8.05 | 4.73 | 54.9 |
| | Median | 23700 | 23900 | 4770 | 1.50 | 7.20 | 4.31 | 52.1 |
| | [Min, Max] | [8350, 33200] | [8550, 33600] | [1840, 6600] | [1.00, 3.00] | [5.34, 21.1] | [3.07, 12.1] | [26.5, 173] |
| LCZ696 200 mg FMI tablet (N=28) | n | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| | Mean (SD) | 24700 (6700) | 24900 (6770) | 4360 (1200) | NC | 8.61 (3.56) | 4.47 (1.32) | 52.5 (19.4) |
| | CV% mean | 27.2 | 27.2 | 27.5 | NC | 41.3 | 29.5 | 37.0 |
| | Geo-mean | 23800 | 24000 | 4200 | NC | 8.01 | 4.29 | 49.6 |
| | Median | 24800 | 25100 | 4000 | 1.50 | 8.20 | 4.11 | 47.2 |
| | [Min, Max] | [14200, 39500] | [14400, 39800] | [2340, 6590] | [1.00, 4.00] | [4.05, 19.1] | [2.59, 7.16] | [28.5, 113] |

CV% = coefficient of variation; FMI = final market image; geo-mean = geometric mean; max = maximum; min = minimum; n = number of subjects with nonmissing values; N = number of subjects in pharmacokinetic analysis set; NC = not calculated; SD = standard deviation.

CV% = SD/mean*100.

**Table 4.3.2.3** Summary of pharmacokinetic parameters for valsartan by treatment (Pharmacokinetic analysis set) (*Source*: Table 11-5 of Study CLCZ696F2130 CSR, NDA 207620, eCTD 0112, M 5.3.1.2)

**Conclusions**:

- Following oral administration, the liquid formulation provided similar total exposure ($AUC_{last}$ and $AUC_{inf}$) of LCZ696 analytes (sacubitril, LBQ657, and valsartan) compared to the FMI tablet.
- The peak concentrations ($C_{max}$) of two active analytes, LBQ657 and valsartan, were also similar between the liquid formulation and the FMI tablet; however, the Cmax of sacubitril, the inactive prodrug, was 72% higher with the liquid formulation.

**4.3.3. Study CLCZ696B2319— Clinical efficacy, safety & PK of LCZ696 for 52 weeks (Pediatric patients with heart failure, 1 month to <18 years) – Part II (Week 52 results)**

**Title**: Multicenter, open-label, single dose study to evaluate safety, tolerability, and pharmacokinetics of LCZ696 followed by a 52-week randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared with enalapril in pediatric patients from 1 month to < 18 years of age with heart failure due to systemic left ventricle systolic dysfunction.

**Objectives**

• Primary: *Part 2*: The primary objective is to determine whether LCZ696 is superior to enalapril for treatment of heart failure as assessed using a global rank endpoint in pediatric HF patients.

• Secondary:

- *Part 2*: To determine whether LCZ696 is superior to enalapril for reducing the time to first occurrence of the composite of either Category 1 and 2 events (e.g., death and worsening HF).
- *Part 2*: To determine whether LCZ696 is superior to enalapril for improving NYHA/Ross functional class.
- *Part 2*: To determine whether LCZ696 is superior to enalapril for improving the Patient Global Impression of Severity (PGIS) score.
- *Part 2*: To characterize the population PK of LCZ696 exposure in pediatric patients with HF.
- *Part 2*: To assess the safety and tolerability of LCZ696 compared to enalapril in pediatric patients with HF.

**Study population**: n=360 patients in Part 2 (Efficacy)

**Drug product**:

Test product, dose, and mode of administration:

- LCZ696
  - *Part 1*: single dose 3.1 mg/kg (using 3.125 mg granules)
  - *Part 2*: projected target dose 3.1 mg/kg (actual dose dependent on Part 1; using 3.125 mg granules, 50 mg tablets, 100 mg tablets, 200 mg tablets)
- Enalapril
  - (Open-label enalapril) and Part 2: target dose 0.2 mg/kg bid; using 1 mg/1 mL liquid formulation, 2.5 mg tablets, 5 mg tablets, 10 mg tablets.

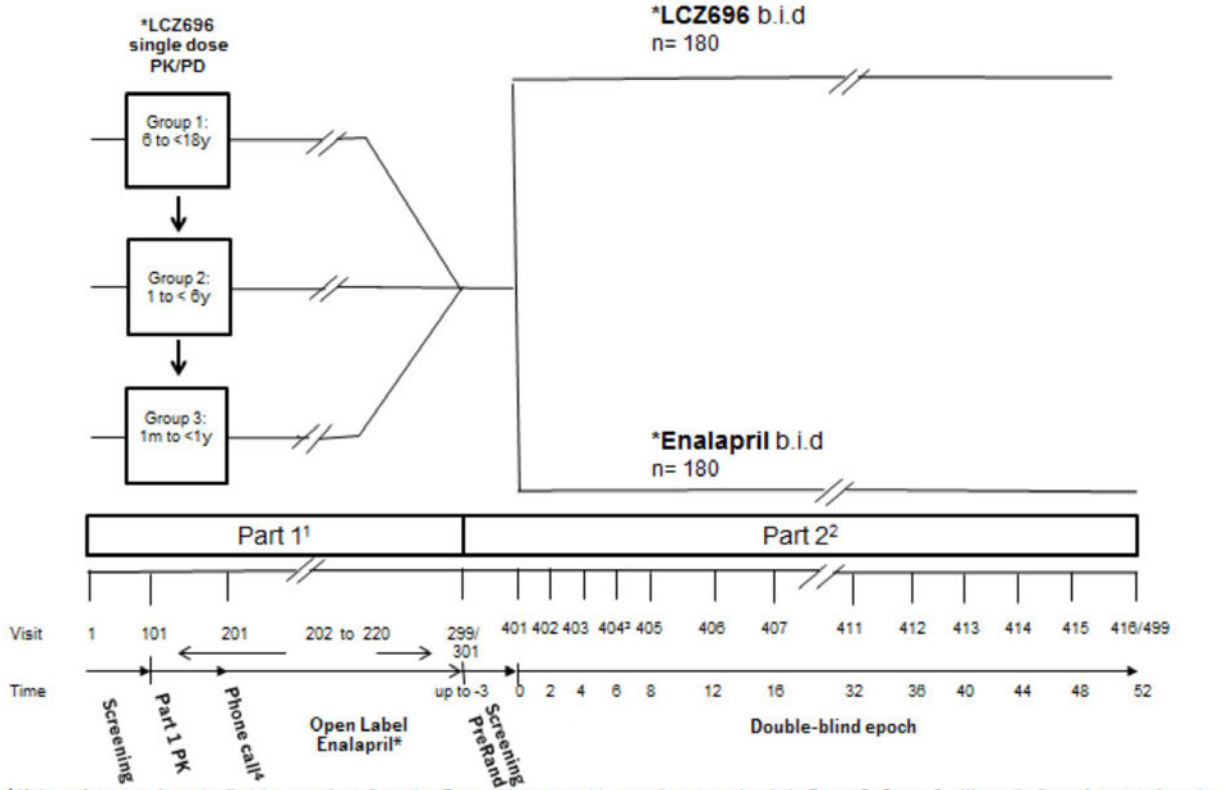
**Study design**:

This is a multi-center study in pediatric patients (1 month to <18 years) with HF (LVEF ≤ 40% or fractional shortening ≤ 20%). This study uses a seamless design which consists of two parts:

- *Part 1*: This is a multi-center, open-label study to characterize the PK and PD of LCZ696 after single dose administration. This information will enable the prediction of multiple dose PK exposure and support dosage determination for Part 2 of this study.

 *Part 2:* This is a 52-week randomized, double blind, parallel-group active controlled, study to evaluate the efficacy, safety, and tolerability of LCZ696 compared to enalapril in addition to conventional HF treatment in pediatric patients with HF.

**Figure 4.3.3.1** Study design overview

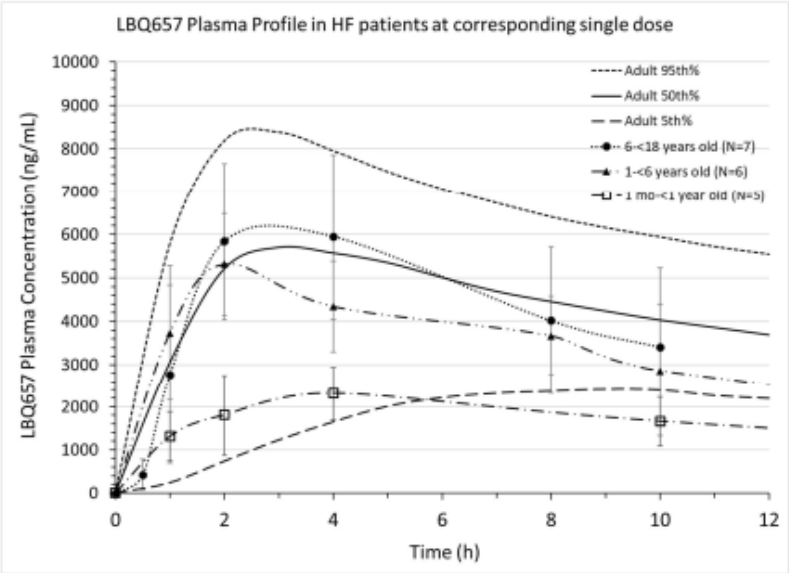



[1] If the safety data from the first three patients from the Group 1 is acceptable, enrollment can begin in Group 2. Group 3 will enroll after safety data from the first three patients in Group 2 is reviewed and considered acceptable
[2] Each age group can enroll in Part 2 after the target dose for that age group is determined by Part 1.
[3] Optional visit
[4] Visit 201-Telephone visit 2 weeks after completion of Visit 101
* Pt required to stop Enalapril/ACEI ≥ 36hrs before taking LCZ696. Open–label Enalapril starts 36 hrs after receiving LCZ696 at Visit 101.

(*Source*: Figure 3-1 of Study CLCZ696B2319 Protocol Ver. 7, NDA 207620, eCTD 0188, M 5.3.5.1)

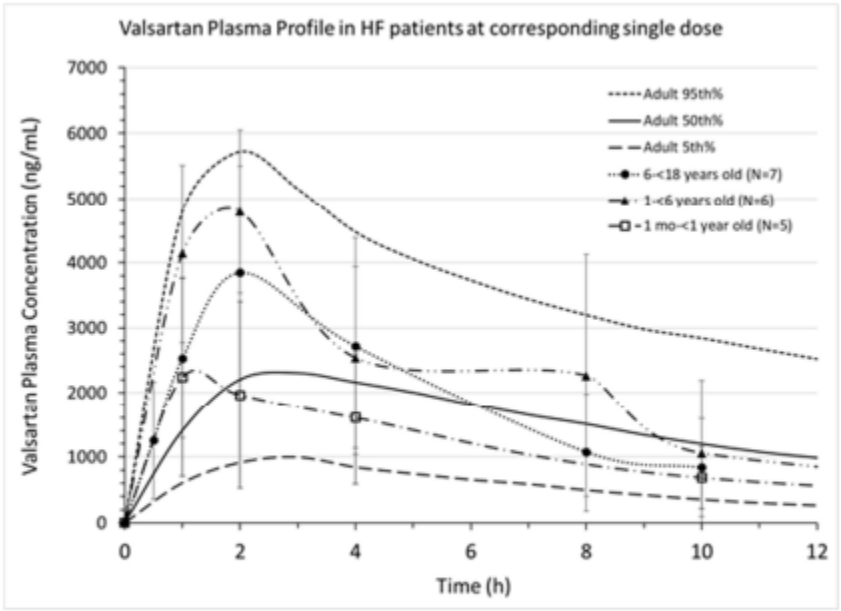
**PK sampling:** PK blood samples are collected at pre-dose, 0.5 hr, 1 hr, 2 hr, 4 hr, 8 hr, 10 hr, and 24 hr post-dose. PD biomarkers samples are collected at pre-dose, 4 hr, 8 hr, and 24 hr post-dose.

**Results**: PK, PD and E-R results are shown as below.



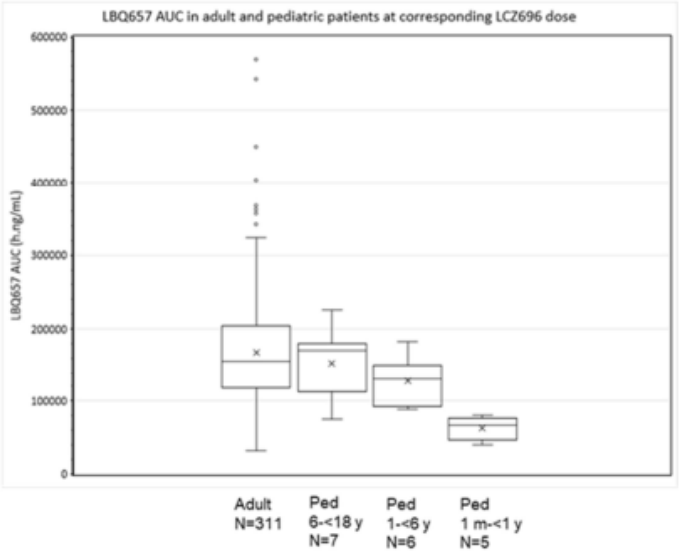

LBQ657 = sacubitrilat, the active metabolite of sacubitril
Adult data were obtained from the simulation using sacubitril/valsartan population PK model for HFrEF patients.
Doses: 200 mg for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.

**Figure 4.3.3.2** Plasma concentration vs. time profiles for sacubitrilat (Active metabolite) among adult and pediatric patients at corresponding sacubitril/valsartan single dose (*Source*: Figure 11-7 of Study CLCZ696B2319 CSR Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)




Adult data were obtained from the simulation using sacubitril/valsartan population PK model for HFrEF patients
Doses 200 mg for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.

**Figure 4.3.3.3** Plasma concentration vs. time profiles for valsartan among adult and pediatric patients at corresponding sacubitril/valsartan single dose (*Source*: Figure 11-7 of Study CLCZ696B2319 CSR Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)




LBQ657 = sacubitrilat, the active metabolite of sacubitril

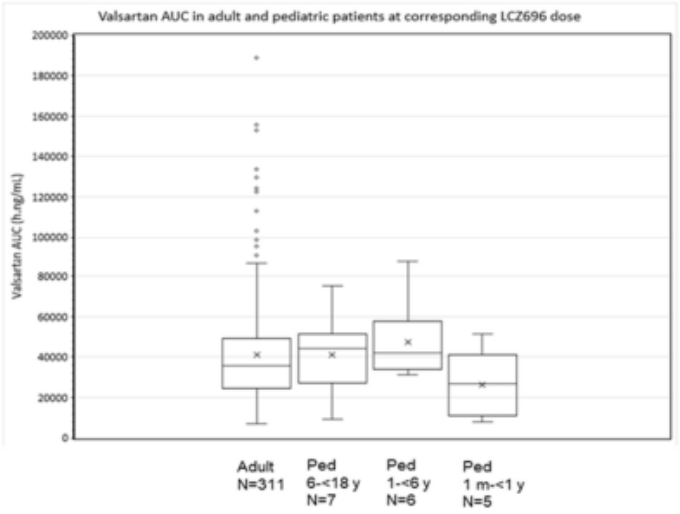
"x" inside the box represents the mean of the AUC range; solid line inside the box represents the median of the AUC range.

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

Adult data were obtained from the simulation of Study B2314 sub-Study (N=311) using sacubitril/valsartan population PK model for HFrEF patients

Doses 200 mg bid for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.

**Figure 4.3.3.4** Comparison of AUC ($AUC_{tau\_ss}$ of BID dose or $AUC_{inf}$ of single dose) among adult and pediatric patients at corresponding sacubitril/valsartan dose: sacubitrilat (*Source*: Figure 11-8 of Study CLCZ696B2319 CSR Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)

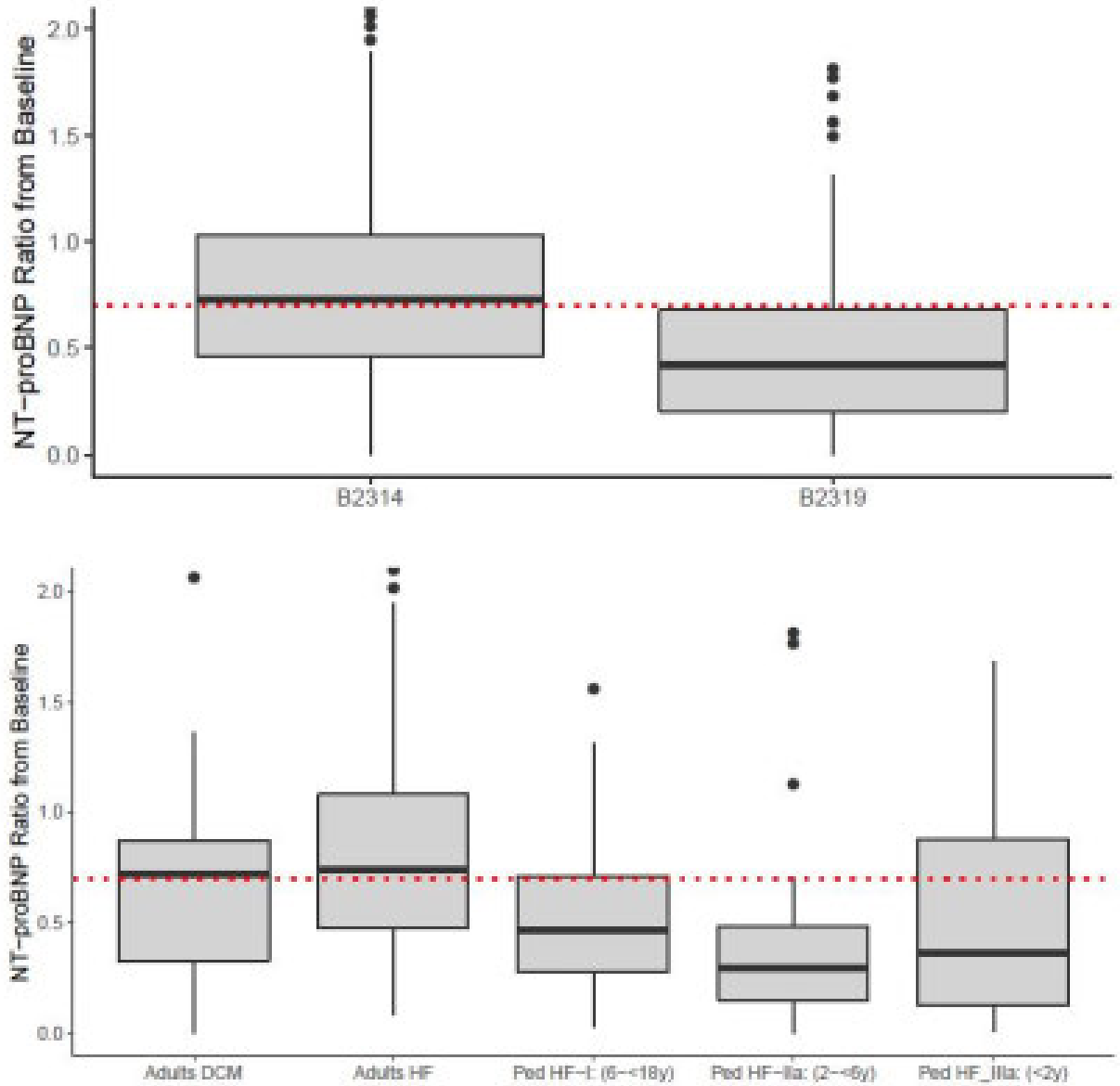



"x" inside the box represents the mean of the AUC range; solid line inside the box represents the median of the AUC range. Upper bound of the box represents 75th percentile of the AUC range; lower bound of the box represents 25th percentile of the AUC range.

Adult data were obtained from the simulation of Study B2314 sub-study (N=311) using sacubitril/valsartan population PK model for HFrEF patients

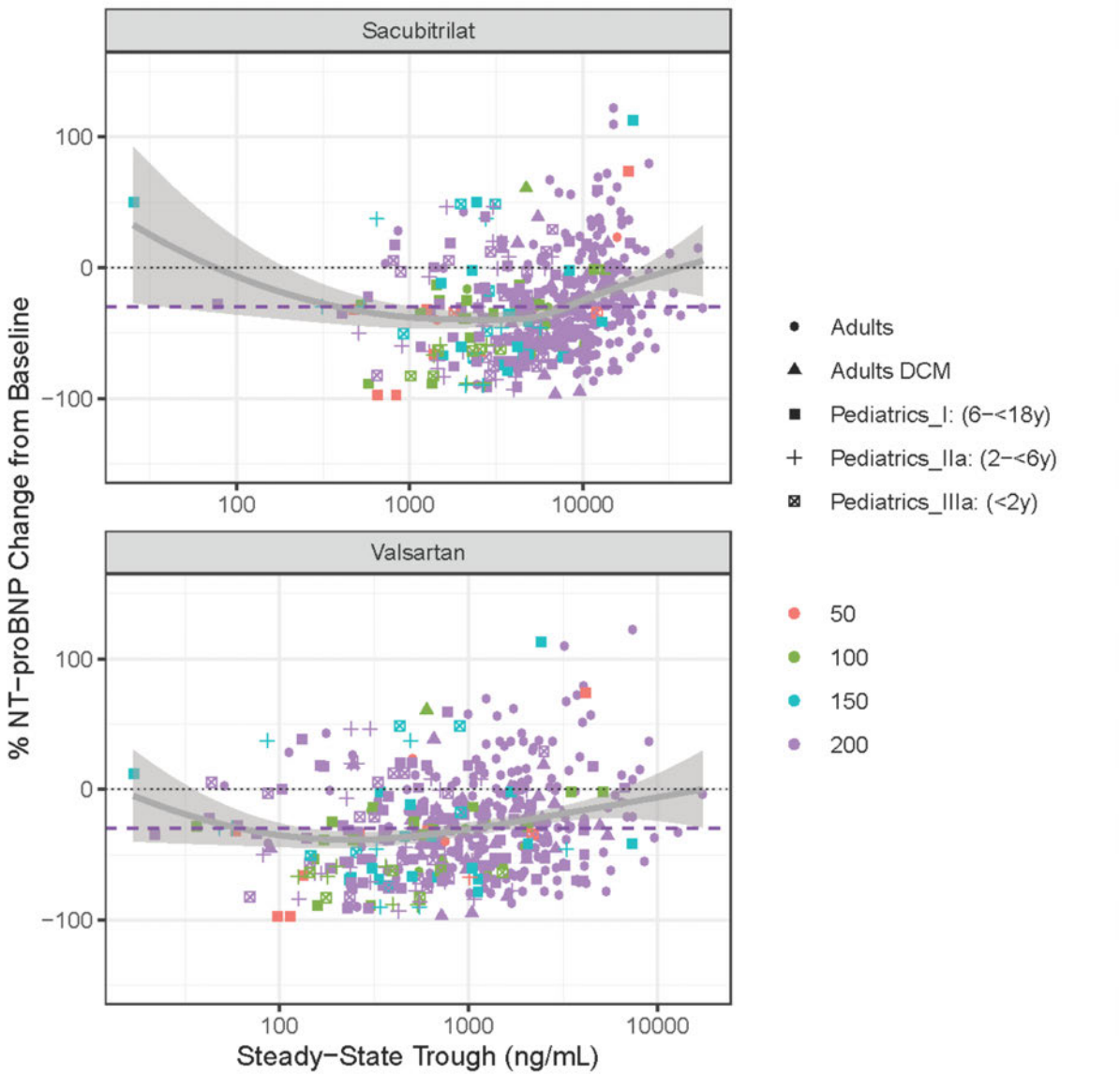
Doses 200 mg bid for adults, 3.1 mg/kg for pediatric ≥1 year old patients, 1.6 mg/kg for pediatric 1 month to <1 year old patients.

**Figure 4.3.3.5** Comparison of AUC ($AUC_{tau\_ss}$ of BID dose or $AUC_{inf}$ of single dose) among adult and pediatric patients at corresponding sacubitril/valsartan dose: valsartan (*Source*: Figure 11-8 of Study CLCZ696B2319 CSR Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)




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

**Figure 4.3.3.6** Boxplots of the Ratio of Plasma NT-proBNP from Baseline between Adults (at 8 months) and Pediatric Patients with Heart Failure for 200 mg (3.1 mg/kg) at 52 Weeks (*Source*: Figure 5-3 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2, Visit 499)

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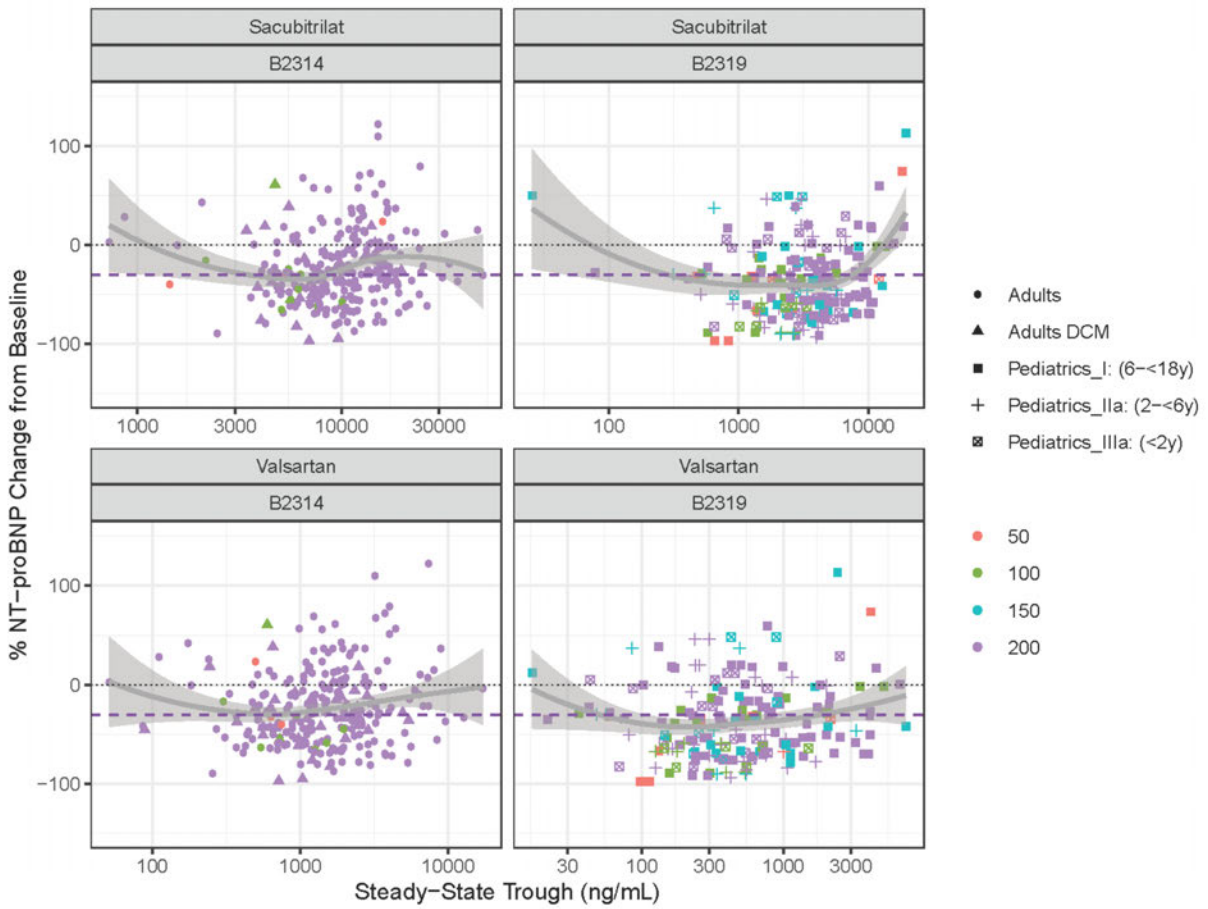
Note: Dashed purple line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decreased of -30% of plasma NT-proBNP from baseline. Note: logarithmic X-axis.
Note: Pediatrics_I refers to Age Group 1 (Age 6-<18 years), Pediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Pediatrics_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study CLCZ696B2319. DCM refers to dilated cardiomyopathy. The numbers 50 (pink symbol), 100 (green symbol), 150 (blue symbol) and 200 (purple symbol) reflects dose in mg. 50 mg=0.8 mg/kg; 100 mg=1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg.

**Figure 4.3.3.7** Exposure-Response Relationship of Steady-State Trough Levels of Sacubitril/Valsartan on Percent Change from Baseline of Plasma NT-proBNP (*Source*: Figure 6-3 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2)

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Note: Dashed purple line refers to reference reduction ratio from baseline of 0.7 that is equivalent to a decreased of -30% of plasma NT-proBNP from baseline.
Note: Pediatrics_I refers to Age Group 1 (Age 6-<18 years), Pediatrics _IIa refers to Age Group 2a (Age 2-<6 years) and Pediatrics_IIIa refers to Age Group 3a (Age 1 month-<2 years) in Study CLCZ696B2319. DCM refers to dilated cardiomyopathy. The numbers 50 (pink symbol), 100 (green symbol), 150 (blue symbol) and 200 (purple symbol) reflects dose in mg. 50 mg=0.8 mg/kg; 100 mg=1.6 mg/kg; 150 mg=2.3 mg/kg; 200 mg=3.1 mg/kg.

**Figure 4.3.3.8** Exposure-Response Relationship of Steady-State Troughs of Sacubitril/Valsartan on Percent Change from Baseline of Plasma NT-proBNP separated by Studies (*Source*: Figure 6-4 of LCZ696 Pediatric-HF PKPD Update Report Ver. 3, NDA 207620, eCTD 0188, M 5.3.4.2)

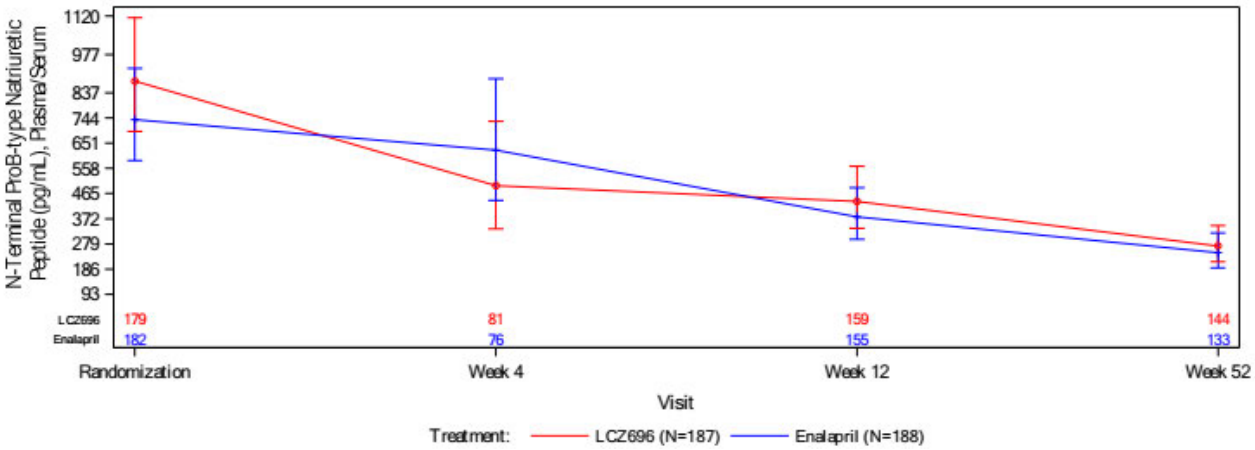


**Figure 4.3.3.9** Part 2 NT-proBNP - geometric mean line plot (Overall data set, full analysis set) (*Source*: Figure 14.2-8.3 of Study CLCZ696B2319 Report Ver. 2, NDA 207620, eCTD 0188, M 5.3.5.1)

**Conclusions**:

- The pharmacokinetics of sacubitril/valsartan were in similar range across pediatric HF age groups of 6-<18 years (n=7) and 1-<6 years (n=6) and adult HF patients (n=311) and support the proposed posology and up-titration to achieve similar exposure to the adult population for pediatric population of 1-<18 years.
- There was an overlap in distribution of the NT-proBNP ratio from baseline as displayed in the boxplots (**Figure 4.3.3.6** for Week 52 in Study CLCZ696B2319 when comparing to Week 4 and 8 months in Study CLCZ696B2314). However, the mean percent change from baseline in pediatric patients with HF showed a comparable or greater reduction in NT-proBNP (ratio ~ 0.3 to 0.5) as compared to adults HF (ratio ~ 0.7).

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