28 November 2024
EMA/16969/2025
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

| | |
|---|---|
| Entresto | Sacubitril / Valsartan |
| Neparvis | Sacubitril / Valsartan |

Procedure No. EMEA/H/C/xxxx/WS/2738

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 27 June 2024 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I |

Update of sections 4.8 and 5.3 of the SmPC in order to update information on long-term data in paediatric patients, based on final results from study CLCZ696B2319E1(PANAROMA-HF OLE) listed as a category 3 study in the RMP (MEA/009); this is a phase 3, multicenter, uncontrolled study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319 (PANORAMA-HF); the RMP version 8 has also been submitted.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP).

# 2. Overall conclusion and impact on the benefit/risk balance

The Applicant has completed study B2319E1, an open-label long-term extension study of the core Study B2319 in pediatric patients aged ≥13 months to 18 years with Heart Failure due to Left Ventricular Systolic Dysfunction (LVSD). Of the 215 participants in this extension study, 109 had received sacubitril/valsartan in the core Study B2319. The median (IQR) duration of exposure to sacubitril/valsartan was 2.5 (1.8, 3.3) years. In core Study B2319, the median (IQR) duration of exposure was 1.0 (0.98, 1.03) year.

Overall, the frequencies of most AEs and SAEs were lower in extension Study B2319E1 than in core Study B2319. Potential reasons are better HF control due to treatment over time, or participants who were most likely to experience events may have discontinued from core Study B2319 and/or been less likely to enroll in Study B2319E1, so called ‘depletion of susceptibles’. In addition, it cannot be ruled out that the lower frequency of visits compared to core Study B2319 may have played a role in the lower exposure-adjusted rates of AEs and SAEs. In particular, there was a lower proportion of more severe and acute cardiac-related AEs/SAEs vs. a higher proportion of more chronic AEs/SAEs in extension Study B2319E1 than in core Study B2319, favoring the potential explanation that participants receiving sacubitril/valsartan long-term may have had better compensated HF.

The tolerability of sacubitril/valsartan in extension Study B2319E1 was consistent with (or somewhat better than) that observed in core Study B2319. A review of deaths in extension Study B2319E1 showed most participants had underlying contributing comorbidities and complications associated with their cardiac disease, consistent with the results of core Study B2319.

*Growth, bone growth and mineralization.*

The fracture cases from the AESI of Change in bone growth and density were low in frequency and consistently associated with accidental trauma in both extension Study B2319E1 and core Study B2319. Additionally, fractures in extension Study B2319E1 were not clustered around a particular timepoint, but rather throughout the study duration and the EAIRs between both studies are consistent, not supporting a

negative effect in bone mineralization over time with sacubitril/valsartan exposure. With that, small reversible and transient bone effects in non-clinical data are not confirmed in paediatrics. Apart from fractures, no actual mineralization data was available.

Poor growth is prevalent in children with HF (Avitzur et al 2003), and malnutrition (undernutrition) can be common in pediatric HF due to multiple factors (Bannister et al 2010, Hollander 2019, Onalo et al 2021). There was no evidence for a negative effect of sacubitril/valsartan exposure on growth in pediatric patients with HF due to LVSD. Median changes from baseline in HAZ were close to zero for all windows of observation, for the individual studies and combined analyses, suggesting no significant change in growth. The subgroup of 2-9-year-old participants, the age range expected to experience linear growth, also exhibited median changes in HAZ close to zero. There were only a few participants with clinically meaningful decreases in HAZ.

Overall, the final safety results from long-term, open-label extension Study B2319E1 were consistent with the safety results for the sacubitril/valsartan treatment arm in the core Study B2319 and with the extensively evaluated safety profile of sacubitril/valsartan in adults and pediatric patients. There was no negative effect of long-term exposure to sacubitril/valsartan in extension Study B2319E1 compared to shorter-term data from core Study B2319 on growth or bone growth and mineralization, or any other safety topic assessed. No new or unknown safety signal was observed. Updates to sections 4.8 and 5.3 of the SmPC are proposed based on the submitted data, which are acceptable.

In conclusion, 1) the safety profile of sacubitril/valsartan observed in this study is consistent with the one observed in the PANORAMA-HF core study and described in the labelling, 2) there is no evidence that the long-term exposure of children with HF to sacubitril/valsartan has negative effects on their growth, bone growth or mineralization, and 3) the benefit risk profile of sacubitril/valsartan in the pediatric population remains positive.

An updated RMP version 8.0, dated 20 June 2024 was submitted with this application to remove “Long-term effects on growth, bone growth and mineralization in the pediatric population” as an important potential risk from the RMP, based on the data from the final study report for study B2319E1. In addition to the deletion of study B2319E1, the PhV plan was updated to reflect a further 6 months delay to the end milestones for the EU Category 3 non-interventional PASS CLCZ696B2014 and CLCZ696B2015, thus constituting an overall delay of two years relative to the original plan. The due date for the submission of the final reports is now 31 Dec 2024.

The changes to the RMP are acceptable and hence RMP version 8.0 was considered acceptable.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I |

Update of sections 4.8 and 5.3 of the SmPC in order to update information on long-term data in paediatric patients, based on final results from study CLCZ696B2319E1(PANAROMA-HF OLE) listed as a category 3 study in the RMP (MEA/009); this is a phase 3, multicenter, uncontrolled study to evaluate long-term safety and tolerability of open label sacubitril/valsartan in pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed study CLCZ696B2319 (PANORAMA-HF); the RMP version 8 has also been submitted.

☒ is recommended for approval.

## *Amendments to the marketing authorisation*

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and to the Risk Management Plan are recommended.

# 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion for EMEA/H/C/WS2738

Section 4.8 of the SmPC was updated to include the information that following the completion of the long-term open-label extension study (PANORAMA-HF OLE) the safety profile of sacubitril/valsartan in paediatric patients enrolled in this study was similar to that observed in adult patients. Section 5.3 of the SmPC was updated to include the information that long-term data in paediatric patients (PANORAMA-HF OLE) showed no evidence of adverse effects of sacubitril/valsartan on (bone) growth or fracture rates.

For more information, please refer to the Summary of Product Characteristics.

# Annex: Rapporteur’s assessment comments on the type II variation

# 5. Introduction

Sacubitril/valsartan (LCZ696, Entresto®, Neparvis®) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), providing concomitant neprilysin (neutral endopeptidase) inhibition and angiotensin II type 1 (AT1) receptor blockade. Sacubitril/valsartan was first approved in 2015 for the treatment of adult patients with heart failure (HF) with reduced ejection fraction (HFrEF). Sacubitril/valsartan is also registered for the treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (LVSD) in children and adolescents aged one year or older in more than 40 countries, including the EU.

Sacubitril/valsartan has become the first and only approved therapy available to children with HF with an age-appropriate formulation (granules in capsules) to enable accurate and convenient administration for these patients and their caregivers. In the EU sacubitril/valsartan is available as granules in capsules for opening (granules in capsule) at 6 mg/6 mg and 15 mg/16 mg strengths for use in the pediatric population, i.e., an appropriate dosage form for patients with lowest body weight and/or unable to swallow tablets. Based on the final results from Study CLCZ696B2319 (PANORAMA-HF core study; hereafter Study B2319), sacubitril/valsartan was approved for the pediatric HF indication in the EU in May 2023. The efficacy basis for approval was the similar NT-proBNP reductions, similar exposure-response, and similar associations with favorable clinical response in both pediatric and adult HF populations, in line with the ICH E11A 2022 guideline. HF due to dilated cardiomyopathy (DCM) is similar between adult and pediatric populations (as described below), allowing for extrapolation from adult to pediatric patients with dilated cardiomyopathy. The safety results from Study B2319 showed consistency with the well-established safety profile in adults with HF.

# 6. Clinical Safety aspects

Juvenile toxicity studies of sacubitril/LBQ657 in rats showed reversible and transient bone effects (equivocal reductions in bone mineral density and bone length). The mechanism underlying these effects and their translatability to pediatric patients are unknown. No increased risk of fractures or altered growth were observed in the pediatric participants over a median follow-up of 1 year in Study B2319. In addition, changes in height and height z-score were comparable between sacubitril/valsartan and control (enalapril) treatment groups and age groups. Study CLCZ696B2319E1 (PANORAMA-HF open label extension study; hereafter Study B2319E1) was initiated in 2019 to evaluate long-term safety and tolerability and to provide post-trial access (prior to commercial availability) to sacubitril/valsartan to eligible participants who successfully completed the core Study B2319 Part 2 per protocol. Since the 1-year duration of completed Study B2319 was considered too short to detect long-term changes in growth (Pharmacovigilance Risk Assessment Committee 2023) and because long-term effects on growth, bone growth and mineralization in the pediatric population was included as an important potential risk in the Entresto® EU risk management plan (RMP), the ongoing Study B2319E1 became a category III post-authorization safety study (PASS) linked to this important potential risk.

## *6.1. Methods – analysis of data submitted*

Study CLCZ696B2319E1:

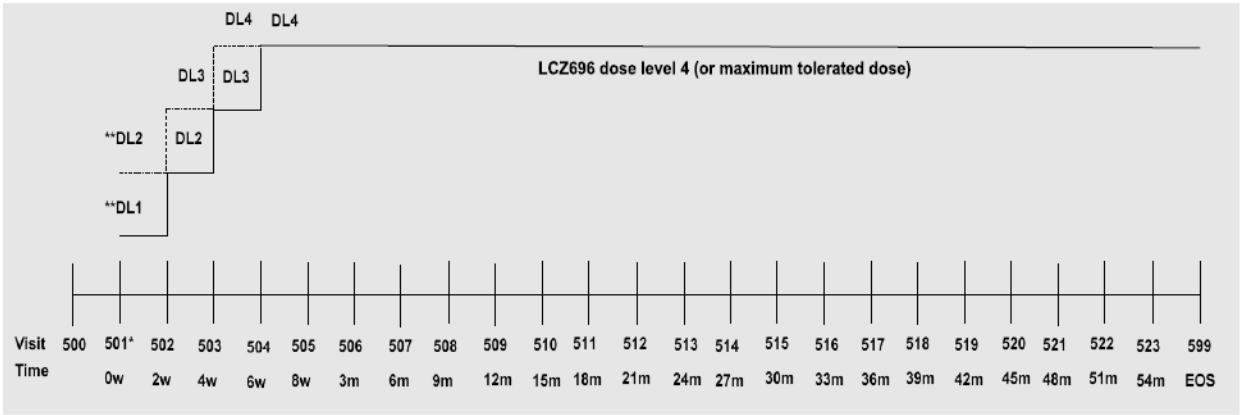
The primary source of safety data for this SCS was a post-authorization safety study, Study B2319E1.

The purpose of Study B2319E1 was to further evaluate the long-term safety and tolerability and to provide post-trial access to sacubitril/valsartan to eligible participants who successfully completed Study B2319 Part 2 by being on study medication (either sacubitril/valsartan or enalapril) at their end of study visit. It was also open to patients who had discontinued study medication early in Study B2319 Part 2 due to implementation by Novartis of an urgent safety measure related to the enalapril regimen but otherwise fulfilled protocol requirements. These participants were eligible for Study B2319E1 and were offered the option to initiate treatment with sacubitril/valsartan by enrolling into this study at the discretion of the investigator. Originally, the study duration was planned to be approximately 1 year after Last Patient Last Visit (LPLV) in Study B2319 Part 2 and approximately 3 years from the date of First Patient First Visit (FPFV) in Study B2319E1 (02-May-2019). Protocol amendment 1 extended the duration of the study to ensure that participants continued to receive age-appropriate study medication treatment (especially those requiring the pediatric formulations not currently available outside investigational use) and safety follow-up as needed. This was until the expected time when pediatric use of sacubitril/valsartan received local marketing authorization and became commercially available to patients, up to 2 years from LPLV of Study B2319 Part 2, or having reached the maximum limit allowed by local regulations, whichever occurred first.

Study design and methodology:

This trial was a multicenter, open-label long-term study for participants who have successfully completed the PANORAMA-HF core study Part 2. Participants who successfully completed the 52-week randomized double-blind, treatment period of PANORAMA-HF core study Part 2 (i.e. on dose level 1 or higher at the PANORAMA-HF End of Study visit) and were eligible for the Open-Label Extension (OLE) or who discontinued study drug treatment early in Part 2 due to the implementation of urgent safety measure (USM) of PANORAMA-HF core study, according to the protocol and in the opinion of the investigator, were offered the option to initiate treatment with sacubitril/valsartan by enrolling into this study (CLCZ696B2319E1). For all consenting participants, eligibility for the OLE was assessed at the screening visit (Visit 500) and, for participants under protocol amendment 1 or later, the study medication was initiated no later than 30 days after completion of PANORAMA HF core Part 2 End of Study (EOS) visit (Visit 416) in order to allow for a seamless transfer to the extension study. A 36-hour washout after the last dose of study medication taken in the PANORAMA-HF core study (Visit 416) was required for all participants before starting OLE study medication. A 36-hour washout before starting OLE study medication was also required for all participants that had transitioned to an Angiotensin converting enzyme inhibitors (ACEI) after completion of PANORAMA-HF core study.

Studies B2319E1 and B2319 were conducted in full compliance with current Good Clinical Practices and were closely monitored by Novartis personnel or a contract research organization for compliance to the protocol, Novartis standard operating procedures, and applicable regulatory guidance.




w=weeks; m=months; DL=LCZ696 dose level

* ≥36 hour of ACEI or double-blind study medication-free washout before starting OLE study medication at Visit 501

** The starting dose at V501 could vary according to prior dose of ACEi/ARBs or PANORAMA-HF study drug

*Figure 1: Trial design*

Inclusion criteria

Participants eligible for inclusion in this study fulfilled all of the following criteria:

• Signed informed consent as well as assent, at an appropriate age based on country regulations, had to be obtained prior to participation in the study.

• Participants were on study medication at the PANORAMA-HF core study part 2 End of Study visit (Visit 416).

Exclusion criteria

Participants meeting any of the following criteria were not eligible for inclusion in this study.

1. Participant who only participated in Part 1 of the PANORAMA-HF core study or was a screen failure in PANORAMA-HF core.

2. Use of investigational drugs within 5 half-lives of enrollment or within 30 days whichever was longer; or longer if required by local regulations – with the exception of PANORAMA-HF core study drug. For PANORAMA-HF core study drug (sacubitril/valsartan/placebo; enalapril/placebo), a minimum of 36-hour washout period was required before the initiation of study treatment (Visit 501).

3. History of hypersensitivity or allergy to any of the study treatments or its excipients or to drugs of similar chemical classes, ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to sacubitril/valsartan.

4. Renal vascular hypertension (including renal artery stenosis).

5. Participants with significant renal (eGFR calculated using the modified Schwartz formula <30% mean GFR for age) hepatic (serum aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal); gastrointestinal or biliary disorders (that could impair absorption, metabolism, or excretion of orally administered medications).

6. Participants with a history of angioedema.

7. Participants with parents or legal guardians who did not give consent or did not allow the child to give assent, or inability of the participant or the parents/legal guardians to follow instructions or comply with follow-up procedures.

8. Pregnant or nursing (lactating) women.

9. Any medical condition(s) that could put the participant at risk in the investigator's opinion, orthat the investigator deemed unsuitable for the study.

10. Participant breastfed by a mother taking ACEI.

Treatments

Similar to PANORMA HF core, Age groups 1 and 2 in the OLE had a target dose (dose level 4) of 3.1 mg/kg bid or 200 mg bid. Participants were up titrated to the target dose of sacubitril/valsartan, dose level 4 according to their tolerability. Visits 502, 503, 504 and 505, as applicable, were intended to be used for study drug up-titration and abbreviated safety follow-up at an interval of approximately 2 weeks between the visits (see figure 1). During that time, participants were required to be up titrated to the maximum tolerated oral dose of sacubitril/valsartan with a goal of reaching the target dose of 3.1 mg/kg. If a participant was unable to tolerate up-titration to a higher sacubitril/valsartan dose level or at the discretion of the investigator, participants could be maintained on lower dose levels of sacubitril/valsartan.

Safety assessment

Similar safety assessments as Study B2319 were performed, including AEs, TEAEs, SAEs, deaths, and AESI descriptions. In addition, and for the participants in Study B2319E1 and Study B2319, an analysis of growth during the exposure to sacubitril/valsartan was conducted using the collected measurements of the height in both studies. Each one of these values was subsequently used to calculate the corresponding HAZ scores. Analysis of height (i.e., absolute height value, z-score (HAZ) for height and age-adjusted percentile for height) was performed for the overall population and for participants in the 2-9 year old subgroup at each 12-month height measurement throughout Study B2319E1 and Study B2319.

Four datasets were constructed, each one composed of data points from participants in different portions of the core and/or the extension studies, as follows:

• Core LCZ696: the data points from participants who received sacubitril/valsartan during the core Study B2319 – exclusively during Study B2319.

• Core enalapril: the data points from participants who received enalapril during the core Study B2319 – exclusively during Study B2319.

• Extension only: data points from participants who received sacubitril/valsartan during the extension Study B2319E1 – exclusively during Study B2319E1.

• Core + Extension: data points from participants who received either sacubitril/valsartan or enalapril during the core Study B2319, and from participants who received sacubitril/valsartan during extension Study B2319E1. The data points from these two studies were combined.

The observation window from baseline measurement to the last valid measurement in the core study, were categorized in 12, 24 and 36 months for the core, the extension study and the combination of core and extension studies, as applicable. An additional window of observation was defined covering the entire participation of each of the participants during the study (called corresponding observation window).

For analyses of HAZ score in the 2-9 year old subgroup, the start of the observation window (baseline) was defined as the date of the first height-for-age z score value available after the participant turned 2 years old.

For analyses of the entire population, the start of the observation window for the entire population was defined as the date of the first HAZ score value available (baseline). Changes from the end of the corresponding observation window to baseline were calculated and categorized. The end was defined as the date of the last HAZ assessment available. Participants with study treatment interruptions were included in the analyses if the interruption did not exceed 10% of the treatment duration. Participants only contributed data to the analysis if there were at least 2 HAZ score measurements during the observation window. Data from Part 1 of the core study were not used in the analyses.

Summary statistics for HAZ scores by yearly visit were provided. In addition, categorical analyses of decreases in HAZ were investigated in the subpopulations and windows of observation of interest. A decrease of at least one unit of Z score was considered clinically meaningful, as it would allow a change from one category to a worse one, among the categories mentioned above.

## *6.2. Results*

Exposure:

The mean daily doses of sacubitril/valsartan were comparable between Study B2319E1 and Study B2319 and between age groups. As expected, the median duration of exposure to sacubitril/valsartan was longer in Study B2319E1 than in Study B2319. In Study B2319E1, the median duration of exposure to sacubitril/valsartan (including temporary interruptions) was 2.5 (IQR 1.8, 3.3) years and similar between the two age groups. As per protocol, the majority of participants completed the treatment greater than one year (194 participants; 90.23%). A total of 149 (69.30%) participants completed 2 years of treatment, 73 (33.95%) participants completed 3 years and 18 (8.37%) participants completed ≥4 years.

Treatment interruptions were in general short as shown by the small differences between the exposure of including and excluding treatment interruptions. In Study B2319E1, patient-years (PY) on treatment was 535.85. After week 6 in Study B2319E1, the 36 (52.94%) participants were on dose level 4 for sacubitril/valsartan (3.1 mg/kg bid). The median (interquartile range (IQR) Q1 and Q3) duration on dose level 4 was 827.50 days (498.00, 1107.50) for the entire study population.

A total of 24 (11.16%) of participants had at least one down titration. The most common reason for down titration was physician decision (12; 5.58%) and AEs (9; 4.19%). The number of participants with at least one dose interruption was 36 (16.74%) in entire study population. A total of 9 (4.19%) of participants reported at least one dose interruption exceeding 14 days. The most common reason for dose interruption was AE (23; 10.7%).

The median duration of exposure to sacubitril/valsartan (including temporary interruptions) was 911 days overall and similar between the two age groups. A total of 45 participants (20.93%) completed the oneyear treatment. A total of 76 (35.35%) participants completed 2 years of treatment, 55 (25.58%) participants completed 3 years and 18 (8.37%) participants completed ≥4 years. A total of 48 (22.33%) of participants who discontinued treatment early. Treatment interruptions were in general short as shown by the small differences between the exposure of including and excluding treatment interruptions. Overall patient-years (PY) on treatment was 535.85.

Dispositions:

From the Study B2319, 106 participants from the enalapril, and 109 participants from the LCZ groups were enrolled in Study B2319E1. Overall, 218 participants were screened of which 2 participants were screen failures and 3 participants who were re-screened. One participant was randomized into the B2319E1 (extension) study but didn't receive treatment and discontinued later from the study. Based on treatment disposition, a total of 215 participants received at least one dose of sacubitril/valsartan. Of 215 participants, 166 (77.21%) completed the study. The primary reason for discontinuing study drug were AEs in 17 (7.91%) participants, physician decision in 13 (6.05%) participants, and death in 10 (4.65%) participants.

Demographics:

In Study B2319E1, the mean age was 8.92 years. There were 106 males, 49.30% and 109 females, 50.70%. Race of participants were majority White (55.35%), Asian (21.86%), and Black or African American (13.49%). In Study B2319E1, all participants in both the age groups reported at least one relevant medical history or current medical condition. The most commonly reported relevant medical histories were, as expected by being part of core Study B2319, cardiac disorders in 211 (98.14%) followed by congenital, familial, and genetic disorders in 68 (31.63%) and infection and infestation in 49 (22.79%).The most common cardiac disorders were cardiac failure in 93 (43.26%) and dilated cardiomyopathy in 90 (41.86%) participants and the most common congenital, familial, and genetic disorders were non-compaction cardiomyopathy in 13 (6.05%) and atrial septal defect in 10 (4.65%)

participants. In Study B2319E1, most participants in both age groups reported at least one concomitant medication, 1 of the 130 participants in the ≥6 year old age group reported no concomitant medication.

Heart failure and cardiovascular medications were the most commonly used medications consistent with the trial population. The most commonly used HF and cardiovascular medications were beta blockers in 170 (79.07%) followed by aldosterone antagonists in 144 (66.98%) and diuretics other than aldosterone antagonists (including spironolactone) in 140 (65.12%) of participants.

Adverse events:

Overall, the number of participants with at least one TEAE was 187 (86.98%). At least one SAE was reported in 84 (39.07%) participants. Over the longer duration of extension Study B2319E1 compared to core Study B2319, the general overall TEAE profile of sacubitril/valsartan was consistent between extension Study B2319E1 and core Study B2319, see tables below.

*Table 1. Overall summary of treatment emergent adverse events – Study B2319E1 study period (Safety set) and Study B2319 Part 2 doubleblind period (Safety Set)*

| | LCZ696 Core N=187 | | Enalapril Core N=188 | | LCZ696 Extension N=215 | |
|---|---|---|---|---|---|---|
| Primary system organ class | n (%) | EAIR (95% CI) | n (%) | EAIR (95% CI) | n (%) | EAIR (95% CI) |
| Any TEAE(s) | 166 (88.7) | 379.849 (324.260, 442.230) | 165 (87.77) | 346.716 (295.830, 403.840) | 187 (86.98) | 126.412 (108.940, 145.890) |
| Death | 8 (4.28) | 4.286 (1.850, 8.440) | 12 (6.38) | 6.680 (3.450, 11.670) | 11 (5.12) | 2.019 (1.010, 3.610) |
| SAE(s) | 69 (36.90) | 46.588 (36.250, 58.960) | 62 (32.98) | 42.477 (32.570, 54.450) | 84 (39.07) | 19.719 (15.730, 24.410) |
| Severe AE(s) | 32 (17.11) | 18.507 (12.660, 26.130) | 40 (21.28) | 24.796 (17.710, 33.760) | 52 (24.19) | 10.599 (7.920, 13.900) |
| Dose adjustment or interruption | 38 (20.32) | 23.418 (16.570, 32.140) | 32 (17.02) | 20.097 (13.750, 28.370) | 35 (16.28) | 7.129 (4.970, 9.910) |
| Discontinued due to AE(s) | 21 (11.23) | 11.836 (7.330, 18.090) | 21 (11.17) | 12.149 (7.520, 18.570) | 18 (8.37) | 3.329 (1.970, 5.260) |

n (%): number (percentage) of patients who had any event(s) during the period of interest. EAIR (exposure adjusted incidence rate per 100 patient-year): number of patients with at least one TEAE of the risk category/[total exposure time (year)/100]. Total exposure time (year): sum(up-to-event/censoring-time in year the treatment group. MedDRA version 26.1 was used.

*Table 2. Treatment emergent adverse events regardless of study treatment - Study B2319E1 study period (Safety set) and Study B2319 Part 2 double-blind period*

| | LCZ696 Core N=187 | | Enalapril Core N=188 | | LCZ696 Extension N=215 | |
|---|---|---|---|---|---|---|
| Primary system organ class | n (%) | EAIR (95% CI) | n (%) | EAIR (95% CI) | n (%) | EAIR (95% CI) |
| Participants with at least one TEAE | 166 (88.77) | 379.849 (324.260, 442.230) | 165 (87.77) | 346.716 (295.830, 403.840) | 187 (86.98) | 126.412 (108.940, 145.890) |
| Infections and infestations | 117 (62.57) | 114.831 (94.970, 137.620) | 109 (57.98) | 107.253 (88.070, 129.380) | 127 (59.07) | 42.400 (35.350, 50.450) |
| Respiratory, thoracic and mediastinal disorders | 64 (34.22) | 45.140 (34.760, 57.640) | 65 (34.57) | 46.942 (36.230, 59.830) | 76 (35.35) | 17.764 (14.000, 22.230) |
| Gastrointestinal disorders | 73 (39.04) | 53.574 (41.990, 67.360) | 79 (42.02) | 60.575 (47.960, 75.490) | 75 (34.88) | 18.146 (14.270, 22.750) |

| | | | | | | |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 76 (40.64) | 54.385 (42.850, 68.070) | 62 (32.98) | 44.651 (34.230, 57.240) | 66 (30.70) | 15.526 (12.010, 19.750) |
| Cardiac disorders | 49 (26.20) | 30.610 (22.650, 40.470) | 47 (25.00) | 30.516 (22.420, 40.580) | 58 (26.98) | 12.032 (9.140, 15.550) |
| Investigations | 39 (20.86) | 24.429 (17.370, 33.400) | 44 (23.40) | 28.801 (20.930, 38.660) | 42 (19.53) | 8.531 (6.150, 11.530) |
| Nervous system disorders | 49 (26.20) | 32.073 (23.730, 42.400) | 43 (22.87) | 27.636 (20.000, 37.230) | 40 (18.60) | 8.450 (6.040, 11.510) |
| Metabolism and nutrition disorders | 26 (13.90) | 15.528 (10.140, 22.750) | 28 (14.89) | 16.785 (11.150, 24.260) | 30 (13.95) | 6.070 (4.100, 8.660) |
| Injury, poisoning and procedural complications | 14 (7.49) | 7.875 (4.310, 13.210) | 25 (13.30) | 15.061 (9.750, 22.230) | 26 (12.09) | 5.150 (3.360, 7.550) |
| Skin and subcutaneous tissue disorders | 33 (17.65) | 20.107 (13.840, 28.240) | 24 (12.77) | 14.598 (9.350, 21.720) | 25 (11.63) | 4.981 (3.220, 7.350) |
| Renal and urinary disorders | 19 (10.16) | 10.746 (6.470, 16.780) | 9 (4.79) | 5.109 (2.340, 9.700) | 24 (11.16) | 4.708 (3.020, 7.010) |
| Vascular disorders | 27 (14.44) | 15.917 (10.490, 23.160) | 25 (13.30) | 15.309 (9.910, 22.600) | 23 (10.70) | 4.618 (2.930, 6.930) |
| Musculoskeletal and connective tissue disorders | 19 (10.16) | 10.848 (6.530, 16.940) | 11 (5.85) | 6.348 (3.170, 11.360) | 22 (10.23) | 4.316 (2.700, 6.530) |
| Blood and lymphatic system disorders | 11 (5.88) | 6.158 (3.070, 11.020) | 8 (4.26) | 4.564 (1.970, 8.990) | 16 (7.44) | 3.067 (1.750, 4.980) |
| Reproductive system and breast disorders | 3 (1.60) | 1.620 (0.330, 4.730) | 12 (6.38) | 6.945 (3.590, 12.130) | 13 (6.05) | 2.465 (1.310, 4.210) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ear and labyrinth disorders | 3 (1.60) | 1.627 (0.340, 4.750) | 2 (1.06) | 1.114 (0.130, 4.020) | 9 (4.19) | 1.710 (0.780, 3.230) |
| Eye disorders | 6 (3.21) | 3.272 (1.200, 7.120) | 7 (3.72) | 3.955 (1.590, 8.150) | 8 (3.72) | 1.505 (0.650, 2.970) |
| Hepatobiliary disorders | 6 (3.21) | 3.261 (1.200, 7.100) | 4 (2.13) | 2.235 (0.610, 5.720) | 7 (3.26) | 1.301 (0.520, 2.680) |
| Immune system disorders | 3 (1.60) | 1.616 (0.330, 4.720) | 3 (1.60) | 1.687 (0.350, 4.930) | 7 (3.26) | 1.302 (0,520, 2.680) |
| Psychiatric disorders | 12 (6.42) | 6.676 (3.450, 11.660) | 14 (7.45) | 8.161 (4.460, 13.690) | 7 (3.26) | 1.317 (0.530, 2.710) |
| Congenital, familial and genetic disorders | 1 (0.53) | 0.537 (0.010, 2.990) | 1 (0.53) | 0.556 (0.010, 3.100) | 5 (2.33) | 0.933 (0.300, 2.180) |
| Endocrine disorders | 1 (0.53) | 0.538 (0.010, 3.000) | 1 (0.53) | 0.555 (0.010, 3.090) | 3 (1.40) | 0.554 (0.110, 1.620) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 1 (0.53) | 0.535 (0.010, 2.980) | 0 | | 2 (0.93) | 0.370 (0.040, 1.340) |
| Product issues | 0 | | 1 (0.53) | 0.557 (0.010, 3.100) | 2 (0.93) | 0.369 (0.040, 1.330) |
| Social circumstances | 1 (0.53) | 0.538 (0.010, 3.000) | 0 | | 0 | |

n (%): number (percentage) of patients who had any event(s) during the period of interest. EAIR (exposure adjusted incidence rate per 100 patient-year): number of patients with at least one TEAE of the risk category/[total exposure time (year)/100]. Total exposure time (year): sum (up-to-event/censoring-time in year the treatment group. MedDRA version 26.1 was used.

Overall, the most common PTs (≥ 15% participants) were COVID-19 in 55 (25.58%) participants, pyrexia in 41 (19.07%) participants and cough in 39 (18.14%) participants.

Age group 1 (6 to >18 years): The most common PTs (≥ 15% participants) were COVID-19 in 27 (20.77%) participants, and Cough in 20 (15.38%) participants.

Age group 2 (1 to 6 years): The most common PTs (≥ 15% participants) were COVID-19 in 28 (32.94%) participants, Pyrexia in 24 (28.24%) participants, Upper respiratory tract infection in 22 (25.88%) participants, Cough in 19 (22.35%) participants, Nasopharyngitis in 14 (16.47%) participants and Vomiting in 13 (15.29%) participants.

TEAEs by PT occurring in at least 5% of participants in any treatment group are shown for Study B2319E1 and Study B2319 below. Various TEAEs by PT had lower exposure-adjusted incidence rate (EAIR) in

B2319E1 compared to the B2319 itself, which can be due to a true improvement over time, or just a depletion of susceptibles.

*Table 3 Common treatment emergent adverse events (>=5% in any treatment arm, overall) by preferred term Study B2319E1 study period (Safety set) and Study B2319 Part 2 double-blind period*

| | LCZ696 core N=187 | | Enalapril core N=188 | | LCZ696 extension N=215 | |
|---|---|---|---|---|---|---|
| **Preferred term** | **n (%)** | **EAIR** | **n (%)** | **EAIR** | **n (%)** | **EAIR** |
| Any TEAE(s) | 166 (88.77) | 379.849 | 165 (87.77) | 346.716 | 187 (86.98) | 126.412 |
| COVID-19 | 6 ( 3.21) | 3.259 | 2 ( 1.06) | 1.114 | 55 (25.58) | 11.755 |
| Pyrexia | 39 (20.86) | 23.865 | 34 (18.09) | 21.994 | 41 (19.07) | 8.643 |
| Cough | 36 (19.25) | 22.359 | 38 (20.21) | 24.523 | 39 (18.14) | 8.117 |
| Upper respiratory tract infection | 39 (20.86) | 24.248 | 35 (18.62) | 22.286 | 30 (13.95) | 6.313 |
| Vomiting | 34 (18.18) | 20.500 | 40 (21.28) | 25.666 | 29 (13.49) | 5.862 |
| Nasopharyngitis | 29 (15.51) | 17.455 | 17 ( 9.04) | 10.142 | 25 (11.63) | 5.029 |
| Cardiac failure | 27 (14.44) | 15.687 | 27 (14.36) | 16.329 | 23 (10.70) | 4.365 |
| Hypotension | 23 (12.30) | 13.402 | 22 (11.70) | 13.279 | 22 (10.23) | 4.406 |
| Diarrhoea | 25 (13.37) | 14.654 | 23 (12.23) | 13.822 | 19 (8.84) | 3.733 |
| Gastroenteritis | 10 ( 5.35) | 5.567 | 12 ( 6.38) | 6.978 | 19 (8.84) | 3.707 |
| Headache | 22 (11.76) | 12.902 | 20 (10.64) | 11.794 | 18 (8.37) | 3.501 |
| Influenza | 13 ( 6.95) | 7.266 | 14 ( 7.45) | 8.150 | 15 (6.98) | 2.831 |
| Abdominal pain | 15 ( 8.02) | 8.435 | 11 ( 5.85) | 6.336 | 14 (6.51) | 2.689 |
| Chest pain | 7 ( 3.74) | 3.827 | 8 ( 4.26) | 4.554 | 14 (6.51) | 2.677 |
| SARS-CoV-2 test positive | 0 | 0.000 | 0 | 0.000 | 14 (6.51) | 2.653 |
| Dizziness | 23 (12.30) | 13.567 | 15 ( 7.98) | 8.732 | 13 (6.05) | 2.492 |
| Pneumonia | 8 ( 4.28) | 4.408 | 7 ( 3.72) | 3.987 | 13 (6.05) | 2.477 |
| Dyspnoea | 8 ( 4.28) | 4.391 | 5 ( 2.66) | 2.816 | 12 (5.58) | 2.268 |
| Rhinorrhoea | 7 ( 3.74) | 3.846 | 7 ( 3.72) | 4.002 | 12 (5.58) | 2.338 |
| Pharyngitis | 6 ( 3.21) | 3.270 | 5 ( 2.66) | 2.843 | 11 (5.12) | 2.081 |
| Nausea | 10 ( 5.35) | 5.544 | 9 ( 4.79) | 5.185 | 9 (4.19) | 1.708 |
| Fatigue | 19 (10.16) | 10.860 | 14 ( 7.45) | 8.094 | 8 (3.72) | 1.517 |
| Abdominal pain upper | 6 ( 3.21) | 3.279 | 10 ( 5.32) | 5.767 | 7 (3.26) | 1.306 |
| Bronchitis | 12 ( 6.42) | 6.653 | 9 ( 4.79) | 5.162 | 7 (3.26) | 1.321 |
| Epistaxis | 10 ( 5.35) | 5.479 | 6 ( 3.19) | 3.415 | 7 (3.26) | 1.314 |
| Glomerular filtration rate decreased | 9 ( 4.81) | 4.994 | 12 ( 6.38) | 6.893 | 5 (2.33) | 0.932 |
| Rhinitis | 8 ( 4.28) | 4.399 | 10 ( 5.32) | 5.785 | 2 ( 0.93) | 0.369 |

Preferred terms are sorted in descending order of frequency in the LCZ696 extension column.
EAIR exposure-adjusted incidence rate per 100 patient-years: number of participants with at least one TEAE of the risk category/[total exposure time (year)/100].
Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over participants within the treatment group.
MedDRA version 26.1 was used.

Potential relationship of adverse events to study drug

Overall, 34 (15.81%) participants reported at least one AE related to study drug. The most common AEs by PT (> 2% participants) related to study drug were Hypotension in 16 (7.44%) and Hyperkalemia in 5 (2.33%) participants

Age group 1 (6 to >18 years): The number of participants with at least one AE related to study drug was 26 (20.00%). The most common AEs by PT (> 3% participants) related to study drug were Hypotension in 13 (10.00%), Hyperkalemia in 4 (3.08%) and Dizziness in 4 (3.08%) Participants.

Age group 2 (1 to 6 years): The number of participants with at least one AE related to study drug was 8 (9.41%) in age group 2. The most common AE by PT (> 3% participants) related to study drug was Hypotension in 3 (3.53%) participants.

The number of participants with SAEs related to study drug was 5 (3.85%) in age group 1. All the SAEs by PTs related to study drug were: Acute kidney injury and Hyperkalemia in 1 participant, renal impairment in 1 participant, acute kidney injury and Hypotension in 1 participant, cardiac failure in 1 participant and presyncope in 1 participant. Only 1 (1.18%) participant in age group 2 reported SAEs (cardiac failure and hypotension) related to study drug

In the Study B2319E1, there was no indication of increased or changed rates of these AEs compared to Study B2319.

Deaths:

Overall, the number of participants with at least one TEAE leading to death was 11 (5.12%) participants. The primary cause for death during treatment period was study indication in 4 (1.86%) participants. The number of deaths was comparable between B2319E1 and B2319, see table below.

The primary cause of death across Study B2319 and Study B2319E1 combined was the study indication in 4 (1.07%) and congestive heart failure in 7 (1.87%) participants. Between the cohorts, similar AEs lead to deaths at similar rates. In both Study B2319 and Study B2319E1, there were 9 non-CV deaths, the primarily cause of which was respiratory failure, affecting 4 (1.07%) participants. Review of the deaths in extension Study B2319E1 indicated that most participants had underlying contributing comorbidities and complications associated with their cardiac disease.

*Table 4. Summary of deaths – Study B2319E1 study period (Safety set) and Study B2319 Part 2 double-blind period.*

| Primary cause of death as reported by the investigator | LCZ696 Core N=187 n (%) | Enalapril Core N=188 n (%) | LCZ696 Extension N=215 n (%) |
|---|---|---|---|
| **Number of deaths** | 8 (4.28) | 12 (6.38) | 11 (5.12) |
| **CV deaths** | 4 (2.14) | 9 (4.79) | 6 (2.79) |
| Study indication | 0 | 0 | 4 (1.86) |
| Decompensated heart failure | 0 | 0 | 1 (0.47) |
| Worsening heart failure | 0 | 0 | 1 (0.47) |
| Congestive heart failure | 3 (1.60) | 4 (2.13) | 0 |
| Sudden death <1 h[a] | 1 (0.53) | 0 | 0 |
| Arrhythmias | 0 | 2 (1.06) | 0 |
| Presumed cardiovascular death | 0 | 2 (1.06) | 0 |
| Sudden death ≥ 1 h - < 24 h[b] | 0 | 1 (0.53) | 0 |
| **Non-CV deaths** | 2 (1.07) | 2 (1.06) | 5 (2.33) |
| COVID-19 pneumonia | 0 | 0 | 1 (0.47) |
| Lower respiratory tract infection | 0 | 0 | 1 (0.47) |
| Pneumonia | 0 | 0 | 1 (0.47) |
| Respiratory distress | 0 | 0 | 1 (0.47) |
| Respiratory failure | 1 (0.53) | 2 (1.06) | 1 (0.47) |
| Gastrointestinal encephalopathy | 1 (0.53) | 0 | 0 |
| **Unknown deaths** | 2 (1.07) | 1 (0.53) | 0 |

Primary causes of death for Study B2319 are as reported by the investigator (not adjudicated confirmed).
*Manual categorization as CV or non-CV causes for Study B2319E1

[a]Sudden death witnessed or last seen alive less than 1 h

*Manual categorization as CV or non-CV causes for Study B2319E1

[b]Sudden death last seen alive greater than or equal to 1 h but less than 24 h.

Serious adverse events

Overall, the exposure-adjusted incidence rates (EAIRs) of SAEs were lower in Study B2319E1 compared to Study B2319 (Table below). In Study B2319, there was a higher proportion of more severe and acute cardiac-related AEs such as Cardiac failure, Cardiac failure acute, Cardiac arrest, Acute respiratory failure (a substantial proportion likely due to pulmonary edema due to HF worsening), Cardiac failure congestive.

*Table 5. Common treatment emergent serious adverse events (at least 1% in any treatment arm) – Study B2319E1 study period (Safety set) and Study B2319 Part 2 double-blind period*

| | LCZ696 core N=187 | | Enalapril core N=188 | | LCZ696 extension N=215 | |
|---|---|---|---|---|---|---|
| **Preferred term** | **n (%)** | **EAIR** | **n (%)** | **EAIR** | **n (%)** | **EAIR** |
| Total SAEs | 69 (36.90) | 46.705 | 62 (32.98) | 42.477 | 84 (39.07) | 19.719 |
| Cardiac failure | 24 (12.83) | 13.797 | 23 (12.23) | 13.664 | 18 (8.37) | 3.361 |
| Pneumonia | 5 (2.67) | 2.724 | 4 (2.13) | 2.254 | 9 (4.19) | 1.681 |
| COVID-19 | 0 | 0 | 0 | 0 | 8 (3.72) | 1.502 |
| Cardiac failure chronic | 0 | 0 | 0 | 0 | 6 (2.79) | 1.106 |
| Pyrexia | 4 (2.14) | 2.173 | 0 | 0 | 6 (2.79) | 1.118 |
| Chest pain | 0 | 0 | 2 (1.06) | 1.114 | 5 (2.33) | 0.928 |
| Dilated cardiomyopathy | 0 | 0 | 0 | 0 | 5 (2.33) | 0.923 |
| Gastroenteritis | 1 (0.53) | 0.537 | 1 (0.53) | 0.558 | 5 (2.33) | 0.938 |
| Vomiting | 5 (2.67) | 2.722 | 4 (2.13) | 2.256 | 5 (2.33) | 0.923 |
| Cardiac failure acute | 2 (1.07) | 1.077 | 4 (2.13) | 2.234 | 4 (1.86) | 0.737 |
| Hypotension | 4 (2.14) | 2.161 | 0 | 0 | 4 (1.86) | 0.738 |
| Acute kidney injury | 1 (0.53) | 0.537 | 2 (1.06) | 1.116 | 3 (1.40) | 0.552 |
| Dyspnoea | 3 (1.60) | 1.619 | 1 (0.53) | 0.557 | 3 (1.40) | 0.553 |
| Ventricular tachycardia | 3 (1.60) | 1.623 | 1 (0.53) | 0.558 | 3 (1.40) | 0.554 |
| Hyperkalaemia | 0 | 0 | 2 (1.06) | 1.115 | 2 (0.93) | 0.367 |
| Arrhythmia | 1 (0.53) | 0.537 | 3 (1.60) | 1.681 | 1 (0.47) | 0.184 |
| Cardiac arrest | 2 (1.07) | 1.073 | 4 (2.13) | 2.224 | 1 (0.47) | 0.184 |
| Dehydration | 0 | 0 | 2 (1.06) | 1.113 | 1 (0.47) | 0.183 |
| Hypoglycaemia | 1 (0.53) | 0.538 | 2 (1.06) | 1.113 | 1 (0.47) | 0.184 |
| Influenza | 2 (1.07) | 1.079 | 2 (1.06) | 1.117 | 1 (0.47) | 0.184 |
| Pleural effusion | 2 (1.07) | 1.078 | 1 (0.53) | 0.557 | 1 (0.47) | 0.183 |
| Upper respiratory tract infection | 4 (2.14) | 2.177 | 0 | 0 | 1 (0.47) | 0.184 |
| Viral upper respiratory tract infection | 0 | 0 | 2 (1.06) | 1.117 | 1 (0.47) | 0.184 |
| Acute respiratory failure | 2 (1.07) | 1.077 | 0 | 0 | 0 | 0 |
| Atrial thrombosis | 0 | 0 | 2 (1.06) | 1.117 | 0 | 0 |
| Bronchiolitis | 0 | 0 | 2 (1.06) | 1.119 | 0 | 0 |
| Cardiac failure congestive | 4 (2.14) | 2.164 | 3 (1.60) | 1.676 | 0 | 0 |
| Seizure | 1 (0.53) | 0.538 | 4 (2.13) | 2.236 | 0 | 0 |
| Syncope | 1 (0.53) | 0.538 | 2 (1.06) | 1.118 | 0 | 0 |

Preferred terms are sorted in descending order of frequency in the LCZ696 extension column.
EAIR exposure-adjusted incidence rate per 100 patient-years: number of participants with at least one TEAE of the risk category/[total exposure time (year)/100].
Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over participants within the treatment group.
MedDRA version 26.1 was used.

Adverse events of special interest

The adverse events of special interest for sacubitril/valsartan in pediatric patients with HF remains consistent to the previously reported safety profile with sacubitril/valsartan reported in Study B2319. In general, these safety topics presented similarly in the 2 age groups compared to the overall population. See table below for comparison between the studies.

*Table 6. Adverse events of special interest – Study B2319E1 study period (Safety set) and Study B2319 Part 2 doubleblind period*

| | LCZ696 Core N=187 | | Enalapril Core N=188 | | LCZ696 Extension N=215 | |
|---|---|---|---|---|---|---|
| Topic | n (%) (95% CI) | EAIR (95% CI) | n (%) (95% CI) | EAIR (95% CI) | n (%) (95% CI) | EAIR (95% CI) |
| Change in bone growth and density | 2 (1.07) (0.130, 3.810) | 1.080 (0.130, 3.900) | 2 (1.06) (0.129, 3.790) | 1.116 (0.140, 4.030) | 9 (4.19) (1.932, 7.797) | 1.691 (0.770, 3.210) |
| Hypotension | 43 (22.99) (17.169, 29.697) | 27.685 (20.040, 37.290) | 40 (21.28) (15.657, 27.826) | 25.735 (18.390, 35.040) | 36 (16.74) (12.011, 22.420) | 7.616 (5.330, 10.540) |
| Hyperkalaemia | 9 (4.81) (2.224, 8.939) | 4.974 (2.270, 9.440) | 10 (5.32) (2.580, 9.564) | 5.660 (2.710, 10.410) | 11 (5.12) (2.581, 8.790) | 2.076 (1.040, 3.710) |
| Renal impairment | 12 (6.42) (3.359, 10.941) | 6.681 (3.450, 11.670) | 8 (4.26) (1.855, 8.212) | 4.519 (1.950, 8.900) | 20 (9.30) (5.775, 14.001) | 3.868 (2.360, 5.970) |
| Hepatotoxicity | 15 (8.02) (4.559, 12.885) | 8.441 (4.720, 13.920) | 10 (5.32) (2.580, 9.564) | 5.699 (2.730, 10.480) | 11 (5.12) (2.581, 8.970) | 2.066 (1.030, 3.700) |
| Hypersensitivity | 22 (11.76) (7.522, 17.269) | 12.627 (7.910, 19.120) | 21 (11.17) (7.049, 16.567) | 12.597 (7.800, 19.260) | 19 (8.84) (5.405, 13.456) | 3.725 (2.240, 5.820) |
| Angioedema* | 0 | 0.000 | 1 (0.53) (0.013, 2.928) | 0.557 (0.010, 3.100) | 0 | 0.000 |
| Anaphylaxis | 1 (0.53) (0.014, 2.943) | 0.536 (0.010, 2.990) | 1 (0.53) (0.013, 2.928) | 0.555 (0.010, 3.090) | 0 | 0.000 |
| Embryo-fetal toxicity | 1 (0.53) 0.014, 2.943) | 0.537 (0.010, 2.990) | 1 (0.53) (0.013, 2.928) | 0.558 (0.010, 3.110) | 0 | 0.000 |
| Malignancy | 1 (0.53) (0.014, 2.943) | 0.537 (0.010, 2.990) | 0 | 0.000 | 0 | 0.000 |

A participant with multiple occurrences of an AE under one treatment during the period of interest is counted only once in this AE category for that treatment.

*Angioedema is AAC confirmed.
EAIR exposure-adjusted incidence rate per 100 patient-years: number of participants with at least one TEAE of the risk category/[total exposure time (year)/100].
Total exposure time (year): sum(up-to-event/censoring-time in year), where the sum is over participants within the treatment group.
MedDRA version 26.1 and Electronic Case Retrieval Strategy (eCRS) for LCZ696 as of 16-Feb-2024 were used.

Long-term effects on growth, and bone growth and mineralization in the pediatric population

*Adverse events related to change in bone growth and density*

In Study B2319E1, AEs related to change in bone growth and density were reported in 9 participants (4.19%) with exposure adjusted incidence rate (EAIR) of 1.691 (95% confidence interval [CI] 0.773, 3.211) per 100 PTY. All the AEs by PT were reported in 1 participant each.

Two participants reported severe AEs of which one participant in age group 2 had SAE. Both the severe AEs were not related to study drug.

Age group 1: AEs related to change in bone growth and density were reported in 6 (4.62%) participants with EAIR of 1.925 (95% CI 0.706, 4.189) per 100 PY. One participant reported Foot fracture which was severe but was not related to study drug.

Age group 2: AEs related to change in bone growth and density were reported in 3 participants (3.53%) in age group 2 with EAIR of 1.361 (95% CI 0.281, 3.978) per 100 PY. One participant reported Femur fracture which was severe but was not related to study drug

The review of AEs related to the risk of long-term effects on growth, bone growth, and mineralization in the pediatric population showed higher number and proportion of participants presenting with a fracture in the extension study compared to the core study (4.19% vs. 1.07%, respectively). This difference is likely due to the longer duration of follow-up of the extension study, and still represents a low fracture rate overall. The EAIR of these AE in both studies are similar: 1.080 (95% CI 0.130, 3.900) vs 1.691 (95% CI 0.770, 3.210) per 100 PY in core and extension studies respectively. Of note, most of these fractures were apparently due to accidental trauma and none of them were considered related to study drug.

*Height analyses datasets*

The height measurements collected at each 12-month height measurement throughout Study B2319E1 and Study B2319 (Part 2 only) were used to analyse height-for-age z-scores (HAZ), for the overall population and for the age subgroup of 2-9 years, an age range with linear growth. The numbers of participants contributing to the numerical and categorical analyses of HAZ change from the core + extension study populations for the observation windows, for the overall population and for the 2-9 year old subgroup are shown below. Although the longest term data for the largest population are of key interest for assessment of a potential effect on growth, the trends across the populations and observation windows are considered below.

*Table 7. Participants in Study B2319 and B2319E1 contributing to the numerical and categorical analyses of HAZ change per population and treatment observation window*

| Population<br>Window of observation | LCZ696 (core only)<br>n | LCZ696 (core and extension)<br>n | LCZ696 (extension only)<br>n | Enalapril (core only)<br>n |
|---|---|---|---|---|
| Entire population | | | | |
| Corresponding window | 146 | 245 | 186 | 132 |
| 12-month observation window | 69 | 162 | 160 | 51 |
| 24-month observation window | NA | 171 | 138 | NA |
| 36-month observation window | NA | 109 | 68 | NA |
| Participants aged 2-9 years old | | | | |
| Corresponding window | 55 | 124 | 102 | 42 |
| 12-month observation window | 22 | 87 | 92 | 12 |
| 24-month observation window | NA | 89 | 75 | NA |
| 36-month observation window | NA | 47 | 37 | NA |

The participant had to have been under study drug during the entire observation window, exception made to time before randomization in the core study.
Participant must have had at least 2 HAZ values available during the observation window.
n: number of patients of interest.
N/A =not applicable because the study concluded at 12 months.

*Height analyses numerical (Height-for-age z-scores)*

The baseline HAZ shows a slightly negative value for all cohorts, which is consistent with literature assessing similar pediatric populations. (Bannister et al 2010 and van der Meulen et al 2021). Across the windows of observation and for the overall population as well as the subgroup of 2-9 year-old participants, the median HAZ changes were close to zero.

*Table 8. Height-for-age z-score (HAZ) change on the entire population over 36-month treatment exposure in Study B2319 and B2319E1.*

| | LCZ696 (Core and extension) | | | LCZ696 (Extension only) | | |
|---|---|---|---|---|---|---|
| **Statistic** | **Base** | **Post** | **Chg** | **Base** | **Post** | **Chg** |
| n | 109 | 109 | 109 | 68 | 68 | 68 |
| Mean | -0.11 | 0.02 | 0.13 | -0.01 | 0.06 | 0.07 |
| LCI | −0.390 | -0.255 | -0.043 | -0.392 | -0.295 | -0.146 |
| UCI | 0.169 | 0.297 | 0.305 | 0.377 | 0.421 | 0.288 |
| Q1 | -1.09 | -0.82 | -0.35 | -0.87 | -0.93 | -0.47 |
| Median | -0.07 | 0.20 | 0.08 | -0.03 | 0.18 | -0.02 |
| Q3 | 0.89 | 0.92 | 0.60 | 0.88 | 0.80 | 0.43 |
| Min | -3.65 | -4.62 | -1.81 | -4.08 | -4.31 | -1.88 |
| Max | 2.92 | 3.38 | 3.57 | 3.19 | 3.73 | 3.41 |

Participants whose duration of exposure from start of observation window to EOT is less than 36 months were excluded from analysis set.
The start of the observation window is the date of the first HAZ value available (base). The end of the observation window occurs (36 months + 15 days) after its start.
Post = the last HAZ value available during the observation window.
LCZ696 (core only) and Enalapril (core only) participant data were not included in this table because the study concluded after 12 months.
n: number of participants of interest. LCI: 95% Lower Confidence. Limit. UCI: 95% Upper Confidence Limit.

The analyses based on the 36-months window of observation included 109 participants in the Core + Extension cohort including the entire population. The changes of HAZ from baseline were around zero, with the largest decline being 1.88 in the Extension only subgroup including the entire population (first quartile -0.47, n=68). The most useful of these analyses is the one conducted in the Core + Extension entire population cohort (n=109), where the median HAZ change was 0.08 (IQR -0.35, 0.60) in Table 8. This result points against the existence of a negative effect in growth in participants exposed to sacubitril/valsartan for at least 36 months.

*Table 9. Height-for-age z-score (HAZ) change on the entire population over the corresponding observation window in Study B2319 and B2319E1*

| | LCZ696 (Core only) | | | LCZ696 (Core and Extension) | | | LCZ696 (Extension Only) | | | Enalapril (Core Only) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Stats** | **base** | **post** | **chg** | **base** | **post** | **chg** | **base** | **post** | **chg** | **base** | **post** | **chg** |
| n | 146 | 146 | 146 | 245 | 245 | 245 | 186 | 186 | 186 | 132 | 132 | 132 |
| Mean | -0.27 | -0.16 | 0.11 | -0.22 | -0.08 | 0.14 | 0.00 | 0.03 | 0.02 | -0.28 | -0.22 | 0.06 |
| LCI | -0.511 | -0.393 | -0.014 | -0.404 | -0.261 | 0.020 | -0.223 | -0.185 | -0.088 | -0.558 | -0.463 | -0.083 |
| UCI | -0.020 | 0.075 | 0.227 | -0.036 | 0.102 | 0.262 | 0.225 | 0.235 | 0.136 | 0.000 | 0.024 | 0.201 |
| Q1 | -1.19 | -1.13 | -0.20 | -1.19 | -1.08 | -0.31 | -1.07 | -0.89 | -0.44 | -1.33 | -1.30 | -0.33 |
| Median | -0.19 | -0.04 | 0.02 | -0.22 | 0.01 | 0.02 | -0.03 | 0.08 | -0.04 | -0.39 | -0.43 | -0.05 |
| Q3 | 0.70 | 0.74 | 0.49 | 0.71 | 0.75 | 0.66 | 1.05 | 1.02 | 0.38 | 0.73 | 0.70 | 0.17 |
| Min | -5.59 | -4.72 | -2.46 | -5.59 | -4.72 | -3.76 | -4.08 | -4.62 | -2.33 | -7.33 | -3.15 | -1.27 |
| Max | 3.30 | 2.69 | 2.89 | 3.38 | 3.49 | 4.20 | 3.78 | 3.49 | 3.18 | 4.65 | 4.24 | 6.63 |

The start of the corresponding observation window is the date of the first HAZ value available (base).
The end of the corresponding observation window is the date of the last HAZ assessment available (post) before min (EOT + 30 days, EOS) for this participant.
The participant must be under study drug during the observation window, exception made to time before randomization in the core study
Participants must have at least 2 HAZ values available during the observation window.
n: number of participants of interest.
LCI: 95% Lower Confidence Limit.
UCI: 95% Upper Confidence Limit.

The analyses based on the 24-months window of exposure naturally included a higher number of participants than the ones based on the 36-months window of exposure. The largest contribution came from the entire population Core + Extension cohort (n=171). In this analysis, the median HAZ change from baseline was 0.08 (IQR -0.31,0.63), therefore indicating a HAZ increase.

The analysis based on the 12-months window of exposure included more participants than the 24- and 36-months windows of exposure. The entire population Core + Extension cohort included the highest number of participants (n=162). The median HAZ change from baseline for this cohort was 0.05 (IQR -0.20, 0.42), therefore indicating a slight HAZ increase.

Categorical Analysis of height change

The analyses based on the corresponding window conducted with the cohorts related exclusively to the core study showed a very limited number of cases presenting with a clinically meaningful HAZ decrease, see table below. Only 3 patients (1%) had a decrease >=2 units, representing a growth deficit according to the WHO cutoffs. Overall, all these analyses provide no evidence of an association between exposure to either enalapril or sacubitril/valsartan and the occurrence of growth deficit.

*Table 10. Decrease from base to post for height-for-age z score (HAZ) on the entire population over the corresponding observation period*

| Category | LCZ696 (Core only) N=146 n (%) | LCZ696 (Core and Extension) N=245 n (%) | LCZ696 (Extension Only) N=186 n (%) | Enalapril (Core Only) N=132 n (%) |
|---|---|---|---|---|
| Decrease of < 1 unit | 64 (43.84) | 97 (39.59) | 86 (46.24) | 72 (54.55) |
| Decrease of 1 up to < 2 units | 3 ( 2.05) | 19 ( 7.76) | 11 ( 5.91) | 2 ( 1.52) |
| Decrease of >= 2 units | 2 ( 1.37) | 3 ( 1.22) | 1 ( 0.54) | 0 |

**- The start of the corresponding observation period is the date of the first HAZ value available (base). - The end of the corresponding observation period is the date of the last HAZ assessment available (post) before min (EOT + 30 days, EOS) for this patient. - The patient must be under study treatment during the entire observation period, exception made to time before randomization in the core study. - Patients must have at least 2 HAZ values available during the observation period.- %: n/N. n: number of patients with decrease observation. N = number of SAF patients having both base and post values.**

In the analysis using a 12-month window of observation and the entire population, the proportion of participants presenting with a clinically meaningful HAZ decrease was very small across all the cohorts. These proportions increase slightly when only participants aged 2 to 9 years are considered. However, the increases are more pronounced in those cohorts with limited number of cases. Overall, those proportions are based on one to a maximum of four participants presenting with the decrease. In the analyses using a 24-month window of observation with the entire population or the subset aged 2 to 9 years, the proportions of participants presenting with a HAZ decrease from 1 to < 2 units ranged from 2.25% to 4.35%, based on 2 to 7 participants. The proportions were even smaller (0.72 to 4.49%, based on 1 or 4 participants) for HAZ decreases ≥ 2 units. In the analyses using a 36-month window of observation with the entire population or the subset aged 2 to 9 years, the proportions of participants presenting with a HAZ decrease from 1 to < 2 units ranged from 5.41% to 11.01%, based on 2 to 12 participants No participants had a HAZ decrease ≥ 2 units. See the table below.

*Table 11. Height-for-age z-score decrease from baseline to post-baseline of the entire population over 36-month treatment exposure in Study B2319 and B2319E1*

| Category | LCZ696 (Core Only) N=N/A n (%) | LCZ696 (Core and Extension) N=109 n (%) | LCZ696 (Extension Only) N=68 n (%) | Enalapril (Core Only) N= N/A n (%) |
|---|---|---|---|---|
| Participants with changes ≥ 0 | N/A | 60 (55.05) | 34 (50.00) | N/A |
| Participants with decrease <1 | N/A | 37(33.94) | 29 (42.65) | N/A |
| Participants with decrease ≥1 up to <2 | N/A | 12 (11.01) | 5 (7.35) | N/A |
| Participants with decrease ≥2 | N/A | 0 | 0 | N/A |

Participants whose duration from start of observation period to EOT is less than 36 months will be excluded from analysis set.

The start of the observation period is the date of the first HAZ value available (base) after the participant turned 2 years old.

The end of the observation period occurs (36 months + 15 days) after its start. The 36-Month exposure of study treatment must not span beyond the age of 9.

Post: The last HAZ value available during the observation period.

The participant must be under study treatment during the entire observation period, exception made to time before randomization in the core study.

Participants must have at least 2 HAZ values available during the observation period.

%: n/N. n: number of participants with decrease observation.

N = number of SAF participants having both base and post values.

Weight

At baseline, the median weight-adjusted percentile was 51.93 (IQR 18.69, 81.86) for the entire study population, 55.25 (IQR 18.94,89.18) for age group 1 and 45.49 (IQR 18.26,72.25) for age group 2. The median change from baseline of that parameter at 24 months was -0.16 (IQR - 8.92,6.24), -0.80 (IQR -11.08,3.69), and 0.67 (IQR -8.21,11.61), respectively. At EOS, those values were 0 (IQR -9.07,9.80), -0.37 (IQR -8.85,3.36), and 2.72 (IQR -9.38,14.00), respectively

Head circumference

The measurements were taken only for age group 2 for participants ≤3 years of age. At baseline, the median head circumference was 47 cm (IQR 46.00, 49.00), at month 24 the median change from baseline was 2 cm (IQR 1.65, 3.15) and at EOS the median change from baseline was 2 cm (IQR 1.00, 3.00).

## 6.3. Discussion

The Applicant has completed study B2319E1, an open-label long-term extension study of the core Study B2319 in pediatric patients aged ≥13 months to 18 years with HF due to LVSD. Of the 215 participants in this extension study, 109 had received sacubitril/valsartan in the core Study B2319. The median (IQR) duration of exposure to sacubitril/valsartan was 2.5 (1.8, 3.3) years. In core Study B2319, the median (IQR) duration of exposure was 1.0 (0.98, 1.03) year.

Overall, AEs and SAEs were lower in extension Study B2319E1 than in core Study B2319. Potential reasons for lower AEs and SAEs are better HF control due to treatment over time, or participants who were most likely to experience events may have discontinued from core Study B2319 and/or been less likely to enroll in Study B2319E1, so called 'depletion of susceptibles'. In addition, it cannot be ruled out that the lower frequency of visits compared to core Study B2319 may have played a role in the lower exposure-adjusted rates of AEs and SAEs. In particular, there was a lower proportion of more severe and acute cardiac-related AEs/SAEs vs. a higher proportion of more chronic AEs/SAEs in extension Study B2319E1 than in core Study B2319, favoring the potential explanation that participants receiving sacubitril/valsartan long-term may have had better compensated HF.

The tolerability of sacubitril/valsartan in extension Study B2319E1 was consistent with (or somewhat better than) that observed in core Study B2319. A review of deaths in extension Study B2319E1 showed most participants had underlying contributing comorbidities and complications associated with their cardiac disease, consistent with the results of core Study B2319.

*Growth, bone growth and mineralization.*

The fracture cases from the AESI of Change in bone growth and density were low in frequency and consistently associated with accidental trauma in both extension Study B2319E1 and core Study B2319. Additionally, fractures in extension Study B2319E1 were not clustered around a particular timepoint, but rather throughout the study duration and the EAIRs between both studies are consistent, not supporting a negative effect in bone mineralization over time with sacubitril/valsartan exposure. Apart from fractures, no actual mineralization data was available.

Poor growth is prevalent in children with HF (Avitzur et al 2003), and malnutrition (undernutrition) can be common in pediatric HF due to multiple factors (Bannister et al 2010, Hollander 2019, Onalo et al 2021). Few studies have investigated course of growth in children with heart diseases (Bannister et al 2010, Aguilar et al 2015, Dennis et al 2016, Castleberry et al 2018, van der Meulen et al 2021, Brief et al 2022). The use of anthropometric z scores has proved a valuable means to identify and describe children with malnutrition (Bouma 2017). Height-for-age z (HAZ) scores are generally accepted as a preferred metric for this type of analysis in comparison to absolute measures of height, allowing meaningful comparisons of values within and between individuals over time, enabling a standardization of values that cannot be derived from the use of absolute height values (Indrayan 2014). Growth deficit can be categorized adapting the criteria established by the World Health Organization and the Consensus Statement of the American Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition. Growth deficit was absent if HAZ > -2. Moderate growth deficit was defined as a HAZ ≤ -2 to > -3. Severe growth deficit was defined as a HAZ of ≤ -3 (WHO 1995, Bouma 2014, American Society for Parenteral and Enteral Nutrition 2015, Becker et al 2015). The reference for calculating HAZ in this study was the WHO growth standards (WHO 2022), which is endorsed. Analyses of changes in HAZ enabled meaningful comparisons over time of growth within and between individuals, enabling a standardization of values that cannot be derived from the use of absolute height values. Median changes from baseline in HAZ were close to zero for all windows of observation, for the individual studies and combined analyses, suggesting no significant change in growth. The subgroup of 2-9-year-old participants, the age range expected to experience linear growth, also exhibited median changes in HAZ close to zero. There were only a few participants with clinically meaningful

decreases in HAZ. Overall, there was no evidence for a negative effect of sacubitril/valsartan exposure on growth in pediatric patients with HF due to LVSD.

Overall, the final safety results from long-term, open-label extension Study B2319E1 were consistent with the safety results for the sacubitril/valsartan treatment arm in the core Study B2319 and with the extensively evaluated safety profile of sacubitril/valsartan in adults and pediatric patients. There was no negative effect of long-term exposure to sacubitril/valsartan in extension Study B2319E1 compared to shorter-term data from core Study B2319 on growth or bone growth and mineralization, or any other safety topic assessed. No new or unknown safety signal was observed.

In conclusion, 1) the safety profile of sacubitril/valsartan observed in this study is consistent with the one observed in the PANORAMA-HF core study and described in the labelling, 2) there is no evidence that the long-term exposure of children with HF to sacubitril/valsartan has negative effects on their growth, bone growth or mineralization, and 3) the benefit risk profile of sacubitril/valsartan in the pediatric population remains positive.

# 7. PRAC advice

N/A

# 8. Risk management plan

The WSA submitted/was requested to submit an updated RMP version 8.0, dated 20 June 2024 with this application. The (main) proposed RMP changes were the following:

## *8.1. Safety Specification*

### *Identified and potential risks*

Changes for RMP version 8.0 from RMP version 7.0:

In line with the GVP Module V (Rev.2) guidance and the accumulated clinical trial and post-marketing experience with sacubitril/valsartan, Novartis proposes the removal of the following risk from the list of safety concerns:

Long-term effects on growth, bone growth and mineralization in the pediatric population previously classified as important potential risk.

The rationale for the removal is provided in Table 8-1.

Table Error! No text of specified style in document.-12 Rationale for the removal of selected safety concern from the sacubitril/valsartan RMP

| **Topic**<br>**Safety concern type** | **Risk management** | **Rationale for removal** |
|---|---|---|
| Long-term effects on growth, bone growth and mineralization in the pediatric population<br>Important potential risk | Routine PV<br>No additional risk minimization activities<br>No additional PV activities | This safety concern was thoroughly assessed in Studies PANORAMA-HF and PANORAMA-HF OLE in pediatric HF patients. PANORAMA-HF (52-week study) did not show evidence that sacubitril/valsartan has an impact on body weight, height, head circumference and fracture rate. PANORAMA-HF OLE (long-term study) showed no evidence of adverse effects on (bone) growth or fracture rates associated with the exposure to sacubitril/valsartan up to 4.5 years. |

| | | |
|---|---|---|
| | | The risk is appropriately addressed in the SmPC. There are currently no additional risk minimization or PV activities in place for this safety concern.<br>It will continue to be monitored and reviewed in the next PSUR. |

PRAC Rapporteur's assessment comment

The WSA's rationale for the removal of "Long-term effects on growth, bone growth and mineralization in the pediatric population" as an important potential risk from the RMP is consistent with the CHMP Rapporteur's assessment conclusion and therefore acceptable. The RMP has been updated satisfactorily to reflect this change throughout the document.

## *8.2. Pharmacovigilance plan*

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization<br>None. | | | | |
| **Category 2 –** Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.<br>None. | | | | |
| **Category 3 -** Required additional pharmacovigilance activities | | | | |
| Noninterventional post-authorization European database safety study (CLCZ696B2014) Ongoing | To further characterize specific safety outcomes (angioedema, hypotension, hyperkalemia, renal impairment, hepatotoxicity) in HF patients newly starting treatment with LCZ696 (regardless of prior use of ACEIs or ARBs) under real-world conditions | Angioedema Use in ACEI/ARB naïve patients<br>Hypotension<br>Hyperkalemia<br>Renal impairment<br>Hepatotoxicity | Annual updates:<br><br>Final report submission | Q1 2021<br>Q1 2022<br><br>~~31-Jun-2024~~<br>31-Dec-2024 |
| Noninterventional post-authorization European database safety study (CLCZ696B2015) Ongoing | To assess the risk of statin-related events associated with concomitant exposure to LCZ696 and statins compared to statin exposure alone in HF patients | Statin drug-drug interaction | Final report submission | ~~31-Jun-2024~~<br>31-Dec-2024 |

PRAC Rapporteur's assessment comment

Following the removal of the CLCZ696B2319E1 study to evaluate Long-term effects on growth, bone growth and mineralization in the pediatric population, only two studies remain in the PhV plan, i.e. the two Category 3 non-interventional PASS CLCZ696B2014 and CLCZ696B2015.

The PhV plan was updated to reflect a further 6 months delay to the end milestones for the EU Category 3 non-interventional PASS CLCZ696B2014 and CLCZ696B2015, thus constituting an overall delay of two

years relative to the original plan. The due date for the submission of the final reports is now 31 Dec 2024.

As justification for these milestone changes, the MAH refers to a correspondence with the EMA which included an informal acceptance by PRAC Rapporteur of the further delay. Since a formal confirmation by the PRAC is still pending within this procedure, the MAH is requested to provide the pdf document, i.e., the document attached to the email sent to the EMA on 15 May 2024, with the justification for the 6 months delay to be available for assessment within this procedure. (OC)

### *8.3. Overall conclusion on the RMP*

☒ The changes to the RMP could be acceptable provided satisfactory responses to the request for supplementary information in section 5 are submitted.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

## 9. Changes to the Product Information

The Applicant proposes to update section 4.8 and section 5.3 of the SmPC. See also the PI document attached as proposed by the Applicant including the CHMP Rapporteur's assessment. The assessment is provided in the PI of Entresto. The same assessment applies to Neparvis. See separate document for comments on the proposed changes to the SmPC.

## 10. Request for supplementary information

### *10.1. Major objections*

#### *Clinical aspects*

None

#### *RMP aspects*

None.

### *10.2. Other concerns*

#### *Clinical aspects*

1. See attached SmPC assessment for comments on the changes to section 4.8.
2. For the overall summary of treatment emergent adverse events (Table 1 and 2 in this report), the frequencies are shown, but not the incidences. Considering the differing study durations, data on the incidence rates would be more useful to compare the safety results. The Applicant is therefore

requested to modify these tables to demonstrate not only the frequency but also the incidence rates.

### *RMP aspects*

3. The MAH is requested to provide the pdf document attached to the email sent to the EMA on 15 May 2024, with the justification for the 6 months delay of the two Category 3 non-interventional PASS CLCZ696B2014 and CLCZ696B2015 to be available for assessment within this procedure.

# 11. Assessment of the responses to the request for supplementary information

## *11.1. Major objections*

### *Clinical aspects*

None

### *RMP aspects*

None

## *11.2. Other concerns*

### *Clinical aspects*

Question 1

See attached SmPC assessment for comments on the changes to section 4.8.

| Summary of the WSA's response |
| --- |
| The proposed edits are accepted and the SmPC was updated accordingly. |
| Assessment of the WSA's response |
| The proposed edits were accepted. Issue resolved. |

Question 2

For the overall summary of treatment emergent adverse events (Table 1 and 2 in this report), the frequencies are shown, but not the incidences. Considering the differing study durations, data on the incidence rates would be more useful to compare the safety results. The Applicant is therefore requested to modify these tables to demonstrate not only the frequency but also the incidence rates.

Summary of the WSA's response

The tables were updated accordingly.

Assessment of the WSA's response

The Applicant has modified these concerned tables by demonstrating not only the frequency but also the incidence rates. These tables can be found in section 6.2 of this report. Issue resolved.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

## *RMP aspects*

Question 3

The MAH is requested to provide the pdf document attached to the email sent to the EMA on 15 May 2024, with the justification for the 6 months delay of the two Category 3 non-interventional PASS CLCZ696B2014 and CLCZ696B2015 to be available for assessment within this procedure.

Summary of the WSA's response

The PDF document is provided as an annex. In the document the MAH informs about a data extraction issue originating from the Spanish database, SIDIAP, as the cause of the delay.

Assessment of the WSA's response

The MAH's proposal to postpone the milestones by 6 months have been considered, and the further delay of the final reports can be accepted. We do not consider it necessary for the MAH to submit another interim report before the final reports due 31 December 2024.

Issue resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance