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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Neparvis

Sacubitril / Valsartan

Procedure no: EMEA/H/C/004343 -EMA/PAM/0000248986

Note

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

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Table of contents

1. Introduction

On 31 January 2025, the MAH submitted a completed paediatric study (CLCZ696B2319E2 or B2319E2) for Neparvis, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

Neparvis (sacubitril/valsartan) is a first-in-class, angiotensin receptor neprilysin inhibitor (ARNI) treatment for chronic HF that simultaneously inhibits neprilysin (NEP) via sacubitrilat, the active metabolite of the prodrug sacubitril, and blocks angiotensin II type-1 receptor via valsartan.

Neparvis (24 mg/26 mg film-coated tablets, 49 mg/51 mg film-coated tablets, and 97 mg/103 mg film-coated tablets) received marketing authorization throughout the EU in 2015 for the treatment of symptomatic chronic HF with reduced ejection fraction in adult patients. In 2023, Neparvis was granted approval for an additional pharmaceutical formulation with two new strengths (6 mg/6 mg granules in capsule for opening and 15 mg/16 mg granules in capsule for opening) for a new indication to include treatment in children and adolescents aged one year or older for treatment of symptomatic chronic HF with left ventricular systolic dysfunction (Neparvis SmPC 2024).

Background of prior clinical studies of pediatric relevance

PANORAMA-HF study (CLCZ696B2319 or B2319) was a phase 2/3, multicenter pediatric HF trial that included patients with systemic left ventricular systolic dysfunction <18 years of age. The study comprised of two parts. Part 1 was an open-label study with primary objective of characterizing PK and PD of sacubitril/valsartan to predict the optimal dose level. Part 2 was a 52-week, double-blind, randomized, parallel-group, active controlled study to assess the efficacy, safety, and tolerability of sacubitril/valsartan compared with enalapril in pediatric patients with HF. In Part 2 of the study, 377 participants were randomized to receive sacubitril/valsartan (n=187) or enalapril (n=188). The study demonstrated a favorable benefit-risk, leading to the approval in patients >1 year of age. The median duration of exposure to study treatment in 187 participants who had received sacubitril/valsartan was 365 days. The study was part of the paediatric investigation plan (PIP).

The completion of PANORAMA-HF study was followed by the PANORAMA-HF OLE (Study B2319E1). Study B2319E1 enrolled 215 patients who had successfully completed Study B2319 (who were treated with either sacubitril/valsartan or enalapril) to receive open-label sacubitril/valsartan for up to 2 years from last patient last visit (LPLV). The median duration of exposure to sacubitril/valsartan was 911 days overall. No new safety signals were identified from Study B2319E1 and the observed safety profile was consistent with the safety profile observed during Study B2319. The completion of study B2319E1 resulted in the removal of the important potential risk of "Long-term effects on growth, bone growth and mineralisation in the pediatric population". B2319E1 study was a PASS and has been assessed in procedure EMEA/H/C/WS2738.

The current review concerns the submission of the findings obtained from Study CLCZ696B2319E2 (B2319E2), an interventional open-label study designed to collect additional safety information of sacubitril/valsartan in the Japanese pediatric patients after long-term treatment of sacubitril/valsartan in study B2319E1. Study B2319E2 is not part of a PIP required by the PDCO of the EMA.

The MAH concludes that the benefit-risk balance for sacubitril/valsartan (Neparvis) remains favourable for paediatric patients and therefore no change to the product information is currently warranted.

2.2. Information on the pharmaceutical formulation used in the study

The study concerning this application is study CLCZ696B2319E2 (B2319E2), a multicenter, open-label extension study for Japanese patients who had successfully completed study B2319E1. Participants who permanently discontinued study drug treatment during study B2319E1 were not eligible for this study. The PASS B2319E1 has been assessed in procedure EMEA/H/C/WS2738.

Formulations used in study B2319E2:

- Capsules in bottles:
    - Capsule containing 4 granules (3.125 mg/granule) - strength 12.5 mg
    - Capsule containing 10 granules (3.125 mg/granule) – strength 31.25 mg
- Tablets in bottles:
    - 50 mg tablets
    - 100 mg tablets
    - 200 mg tablets
- Liquid suspension:
    - Concentration of 4 mg/mL prepared from tablets 100 mg

2.3. Clinical aspects

2.3.1. Introduction

The MAH has submitted the final report for study CLCZ696B2319E2 (B2319E2) according to the Article 46 of Regulation (EC) No. 1901/2006. This study is not part of a PIP.

Study CLCZ696B2319E2 (B2319E2)

Description

Study B2319E2 was a safety study of sacubitril/valsartan in Japanese pediatric patients with heart failure due to systemic left ventricle systolic dysfunction who have completed CLCZ696B2319E1 study.

Methods

Study participants

All patients who have completed PANORAMA-HF OLE (B2319E1) study and who meet all inclusion and exclusion criteria were eligible in the study.

Main inclusion criteria: Male or female, inpatient or outpatient, and < 18 years of age (at the time of signing informed consent).

Main exclusion criteria: Patients who permanently discontinued the study drug treatment during PANORAMA-HF OLE study; renal vascular hypertension; history of angioedema; patient breastfed by a mother taking ACEI.

Treatments

The sacubitril/valsartan study medication was available in 3 formulations: tablets, granules or liquid. The dose level at the EOS visit of the study B2319E1 could remain the same, or the dose level could be changed at the discretion of the Investigator.

Objectives

To collect additional safety information of sacubitril/valsartan in Japanese patients after long-term treatment of sacubitril/valsartan in study B2319E1. To provide patients who had been treated until the end of study B2319E1 with access to sacubitril/valsartan until its market availability in Japan.

Outcomes/endpoints

Safety outcomes, including:

- AEs (including SAEs, AESIs and deaths)
- Physical examinations
- Vital signs
- Height, weight
- Laboratory evaluations
- Pregnancy test

Sample size

There is no specific sample size required for the study. A maximum of 8 Japanese patients will be enrolled into the study.

Randomisation and blinding (masking)

Not applicable

Statistical Methods

The data collected were summarized descriptively and listed. No statistical hypotheses were tested, and no model analyses were performed for this study.

The following analysis sets were used for the statistical analyses:

• Enrolled set (ENR): All participants who signed the informed consent for the extension open-label study.

• Safety Set (SAF): All ENR participants who received at least one dose of open-label study treatment during the extension open label study B2319E2.

Results

Participant flow

Eight (8) participants were screened, enrolled, and all participants completed the study (ENR and SAF population).

Baseline data

The median age (min-max) of the participants was 5.5 (3-16) years with half (50.0%) being <6 years old. Six participants (75.0%) were females.

All participants in Study B2319 had a prior history of HF due to left ventricle systolic dysfunction with biventricular physiology, consistent with study B2319 requirements. All participants (100%) were reported at least one relevant medical history or current medical condition. The most commonly reported SOCs were “Cardiac disorders” (75.0%) followed by “Infections and infestations” and “Skin and subcutaneous tissue disorders” (50.0% each).

All participants had prior therapy with beta blocking agents, carvedilol (7/8 participants, 87.5%) and bisoprolol (1/8 participants, 12.5%) . No prior significant non-drug therapy was reported.

All participants (100%) had concomitant therapy with beta blocking agents, carvedilol (7/8 participants, 87.5%) and bisoprolol (1/8 participants, 12.5%) for HF. The other most commonly reported concomitant therapies were "antihistamines for systemic use" (5/8 participants, 62.5%), "corticosteroids, dermatological preparations", "cough and cold preparations", "diuretics", and "drugs for obstructive airway diseases" (3/8 participants, 37.5% each). As concomitant significant non-drug therapies, MRI heart for underlying HF in 1 participant (12.5%) and oxygen therapy and physiotherapy for respiratory support in another participant (12.5%) were reported.

Dosing and exposure to the medicinal product

All participants (100%) continued the study treatment until EOS. No dose interruption or down titration was reported. The majority of the participants (5/8 participants, 62.5%) were on target dose (Dose level 4: 3.1 mg/kg bid) for sacubitril/valsartan through Day 1 to EOS. There were 2/8 participants (25.0%) at Dose level 3 (2.3 mg/kg bid) and 1/8 participants (12.5%) at dose level 1 (0.8 mg/kg bid).

The median (min-max) duration of exposure to sacubitril/valsartan was 177 (166-246) days overall.

Efficacy results

Not Applicable

Safety results

There were no deaths during treatment period or fatal AEs. No AEs leading to discontinuation of study drug were reported. No participants underwent a heart transplant. One participant (12.5%) experienced SAEs. No AEs categorized as AESI were reported (Table 1)

Table 1. Overview of treatment emergent adverse events (Safety Set)

Category	All Patients N=8 n (%)
Treatment emergent adverse events	6 (75.00)
Treatment-related	0
Treatment emergent SAEs	1 (12.50)
Treatment-related	0
Treatment emergent fatal SAEs	0
Treatment-related	0
Treatment emergent adverse events leading to treatment discontinuation	0
Treatment-related	0

Numbers (n) represent counts of subjects.
MedDRA version 27.0.
Source: [Study B2319E2-Table 2-3]

Adverse events

Six participants (75.0%) had at least one AE. None of the AEs were considered related to sacubitril/valsartan (Table 1) All AEs were mild in severity, except two serious AEs that occurred in the same patient, which were assessed as severe and moderate (see '*Serious adverse events'*).

Table 2. Treatment emergent adverse events regardless of study treatment relationship, by primary system organ class and preferred term (Safety Set)

Primary system organ class Preferred term	All Patients N=8 n (%)
Number of subjects with at least one AE	6 (75.00)
Gastrointestinal disorders	1 (12.50)
Vomiting	1 (12.50)
Immune system disorders	1 (12.50)
Seasonal allergy	1 (12.50)
Infections and infestations	6 (75.00)
Nasopharyngitis	2 (25.00)
Upper respiratory tract infection	2 (25.00)
COVID-19	1 (12.50)
Gastroenteritis	1 (12.50)
Influenza	1 (12.50)
Otitis media	1 (12.50)
Streptococcal infection	1 (12.50)
Urinary tract infection	1 (12.50)
Metabolism and nutrition disorders	1 (12.50)
Hypoglycaemia	1 (12.50)
Musculoskeletal and connective tissue disorders	1 (12.50)
Muscle tightness	1 (12.50)
Respiratory, thoracic and mediastinal disorders	1 (12.50)
Asthma	1 (12.50)
Rhinitis allergic	1 (12.50)
Skin and subcutaneous tissue disorders	1 (12.50)
Eczema	1 (12.50)

- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.
- A subject with multiple occurrences of an AE under one treatment is counted only once in this AE category for that treatment.
- System organ classes are presented in alphabetical order; preferred terms are sorted within system organ class in descending frequency in All Patients column .
- MedDRA Version 27.0 has been used for the reporting of adverse events.

Source: [Study B2319E2-Table 2-4]

Serious adverse events

One participant (4 year-old female) was reported with the SAEs of upper respiratory tract infection and asthma, not considered as related to sacubitril/valsartan. Upper respiratory tract infection was considered severe and reported as recovered/resolved. Asthma was considered moderate and reported as recovering/resolving. The seriousness criteria for the events was hospitalization. There was no dose change of sacubitril/valsartan at the end of the study. The participant had a medical history of eczema at the start of the study.

Clinical laboratory and vital signs

No clinically meaningful values in vital signs, laboratory parameters, or height and weight were observed during the study.

2.3.2. Discussion on clinical aspects

This application concerns the submission of the final clinical study report for Study B2319E2 in accordance with Article 46 of Regulation (EC) No 1901/2006. This study is not part of a PIP.

B2319E2 was an extension study conducted among Japanese patients that had completed the long-term PANORAMA-HF OLE study (CLCZ696B2319E1 or B2319E1). The study was conducted with the aim of collecting additional safety data and to provide Japanese patients from study B2319E1 with access to the medicinal product until its market availability in Japan. The study did not collect efficacy data.

The study design is considered adequate to meet the objective of collecting safety data and giving access to the medicinal product. The study enrolled 8 patients. This number was pre-defined in the study protocol, although the rationale for the sample size is not clear. The study is not part of the PIP, and therefore, a justification of the sample size is not pursed.

The median age (min-max) of the participants was 5.5 (3-16) years and six participants (75.0%) were females. Patients who finished the B2319E1 OLE study were eligible for inclusion. This is agreed given the aim of the study.

Median (min-max) duration of exposure was 177 (166-246) days. The majority of patients (5/8) were on the target dose recommended in the SmPC: 3.1 mg/kg bid, and 3/8 patients were in lower doses (2 patients were on 2.3 mg/kg bid and 1 patient was on 0.8 mg/kg bid). Foe none of the patients the dose was reduced or the medicinal product was discontinued by the end of the study, which supports its tolerability.

There were no deaths or discontinuations during the study. There were 6 patients who suffered AEs, of which 1 was a SAE (upper respiratory tract infection and asthma). None of the events was considered related to sacubitril/valsartan and the AEs were considered mild in severity. The SAEs of upper respiratory tract infection was considered severe and the asthma event was considered moderate in severity. The outcomes were reported as resolved for the upper respiratory tract infection and resolving for asthma. The dose of sacubitril/valsartan was not changed, which aligns with the judgement of the treatment not being related to the SAEs. It is noticed that 6 events occurred in the SOC of Infections and Infestations, which may be considered high. However, no pattern in the type of events is identified, and it is plausible that they were unrelated to the treatment (e.g., COVID-19, gastroenteritis, or influenza). No remarkable findings in relation to vital signs, laboratory parameters, or height and weight were observed during the study.

Overall, it is agreed that the study results show no new safety signals. Given the very limited amount of patients included in the study, the lack of newly identified safety information, and that the study does not concern EU patients, it is agreed that no additional information from study B2319E2 is included in the SmPC of Neparvis.

3. Rapporteur's overall conclusion and recommendation

Study B2319E2 was an extension study conducted among Japanese patients that had completed the long-term OLE study B2319E1. B2319E2 study collected safety information in 8 patients exposed to sacubitril/valsartan, with a median (min-max) duration of exposure of 177 (166-246) days. There were no deaths or discontinuations during the study. There were 6 patients who suffered AEs, of which one suffered SAEs. None of the events was judged as related to sacubitril/valsartan. The submitted study results did not identify any new safety signals. The study results do not change the benefit-risk of sacubitril/valsartan in the currently approved paediatric population.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**