23 July 2026
EMADOC-1700519818-3015851
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimpat

Lacosamide UCB

International non-proprietary name: Lacosamide

Procedure No. EMA/VR/0000321459

Note

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission deadline	06 Mar 2026	27 Feb 2026	☐
☐	Validation	22 Mar 2026	22 Mar 2026	☐
☐	Start date	23 Mar 2026	23 Mar 2026	☐
☐	CHMP Rapporteur AR	21 Apr 2026	21 Apr 2026	☐
☐	PRAC Rapporteur AR	24 Apr 2026	21 Apr 2026	☐
☐	PRAC comments	29 Apr 2026	N/A	☐
☐	Updated PRAC Rapporteur AR	30 Apr 2026	04 May 2026	☐
☐	PRAC outcome	07 May 2026	07 May 2026	☐
☐	CHMP comments	11 May 2026	N/A	☐
☐	Updated CHMP Rapporteur AR	13 May 2026	13 May 2026	☐
☐	Request for Supplementary Information (RSI)	21 May 2026	21 May 2026	☐
☐	Submission deadline	23 Jun 2026	22 Jun 2026	☐
☐	Re-start date	24 Jun 2026	24 Jun 2026	☐
☐	PRAC Rapporteur AR	29 June 2026	26 June 2026	☐
☐	PRAC comments	01 Jul 2026	N/A	☐
☐	Updated PRAC Rapporteur AR	02 Jul 2026	N/A	☐
☐	CHMP Rapporteur JAR	08 July 2026	26 June 2026	☐
☐	PRAC outcome	09 Jul 2026	09 Jul 2026	☐
☐	CHMP comments	13 Jul 2026	N/A	☐
☐	Updated CHMP Rapporteur AR	16 Jul 2026	N/A	☐
☒	CHMP Outcome	23 Jul 2026	23 Jul 2026	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma submitted to the European Medicines Agency on 27 February 2026 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(s) requested		**Type**
C.4	C.4 Change(s) in the summary of product characteristics, labelling or package leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Variation type II

Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to update clinical information based on final results from study SP0968. SP0968 was a phase 2/3, multicenter, open-label, randomized, active comparator study that evaluated the PK, efficacy, safety, and tolerability of lacosamide in neonatal study participants with repeated electroencephalographic neonatal seizures compared with an Active Comparator chosen based on standard of care per the local practice and treatment guidelines. In addition, study EP0223 report is included in this submission in compliance with Art. 46 of the EU Paediatric Regulation. EP0223 is a comparative study on long-term neurodevelopmental outcomes in neonates treated with lacosamide versus other antiseizure medications for neonatal seizures. The RMP version 18.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to implement corrections in some local languages in both Vimpat and Lacosamide UCB Product Information.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

Proposed changes

The proposed changes are mainly based on study SP0968: a Phase 2/3, multicenter, open-label, randomized, active comparator study that evaluated the PK, efficacy, safety, and tolerability of lacosamide in neonatal study participants with repeated ENS compared with an Active Comparator chosen based on StOC per the local practice and treatment guidelines. The MAH considers the available data from the small number of neonates treated in SP0968 insufficient to establish a positive benefit/risk balance in this population. Thus, no new dosing recommendations are being made for lacosamide in the neonatal patient population. While data are considered insufficient to support a new indication or a new dosing regimen, proposed updates to the EU SmPC for Vimpat/lacosamide include the addition of key SP0968 findings in Sections 4.2, 5.1 and 5.2.

Additionally, a population PK model of lacosamide was updated throughout the neonatal developmental program. CL0447-Part V, a modelling and simulation study, is considered the final retrospective population PK model of lacosamide in children from birth to <18 years of age, combining all available data at the end of the paediatric program (including data from orally and iv dosed studies) in study participants with epilepsy. CL0447-Part V is an update of the lacosamide paediatric PK model developed in CL0447 Part IV, aimed to use iv administration data in neonatal study participants from SP0968 and to perform simulations evaluating the exposure in neonates compared with the exposure in adults. The CL0447-Part V population PK modelling report was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation) (procedure EMA/PAM/0000303848).

Data included in this Application are 1) SP0968 final data, 2) a summary of key results from the final lacosamide CL0447-Part V population PK modelling report for patients from birth to <18 years of age, 3) a cumulative evaluation of postmarketing reports of lacosamide exposure in neonates (from birth to 27 days) for the period of 29 Aug 2008 to 31 Aug 2025 performed in the frame of completion of SP0968, 4) completed RWE studies that were conducted to support the design of SP0968 within the lacosamide neonatal development program are presented including the final results from the comparative RWE study (EP0223) that investigated long-term neurodevelopmental outcomes of lacosamide treatment compared to other AEDs in neonatal seizures. The EP0223 final study report is also being submitted together with the current application.

The proposed updates to the EU SmPC reflect the newly available data for lacosamide in neonates from SP0968 without making an indication claim. Inclusion of this information is expected to be clinically meaningful for prescribers, supporting an evidence-based approach to the management of neonates with epilepsy.

Relevant background information

At the time of this submission, lacosamide had a marketing authorization in 58 countries worldwide, including the US and EU. The specific indication statement and approved formulation(s) for lacosamide may differ depending on the country. In the US, dosing recommendations for the treatment of partial-onset seizures (POS) are available and locally approved down to the age of 1 month. In the EU, Vimpat is currently indicated as (1) monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy and (2) adjunctive therapy in the treatment of primary generalised tonic-clonic seizures (PGTCS) in adults, adolescents, and children from 4 years of age with IGE. Lacosamide does not have an indication for neonatal seizures. Currently available data from multicenter, randomized, controlled studies only support the use of 1 antiepileptic drug (AED; phenobarbital) to treat neonatal seizures (Sharpe et al, 2020). More than 25% of paediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). Due to substantial evidence that neonatal seizures contribute to increased morbidity (including adverse neurodevelopmental outcomes) and mortality, physicians are increasingly focused on the diagnosis and treatment of this condition (Glass et al, 2012). However, there is a data gap for clinicians in terms of a lack of newer data or clinical experience with other AEDs for this condition.

The PIP for lacosamide (Vimpat) for the condition of "treatment of paediatric epilepsy syndromes" (EMEA-000402-PIP03-17) aimed at addressing the unmet need in the treatment of paediatric epilepsy syndromes in paediatric patients. The components of the neonatal development program are presented in Table 1 and include 1 clinical study (SP0968), the CL0447-Part V population PK modelling report, and 5 supportive RWE studies (EP0147, EP0148, EP0149, EP0155, and EP0223). All studies have been completed at the time of submission. Studies EP0147, EP148, EP0149 and EP0155 are not assessed in detail here as they have been assessed in previous procedures.

The following are assessed in this application:

1) ***The final results from the comparative RWE study EP0223 submitted by the MAH.***

EP0223 was a retrospective matched cohort study of long-term neurodevelopmental outcomes in neonates treated with lacosamide versus other nonbenzodiazepine AEDs for neonatal seizures. The primary objective was to compare the incidence rate of overall prespecified neurodevelopmental outcomes in neonates treated with lacosamide versus other AEDs for neonatal seizures up to 2 years post index date.

EHR data from the PEDSnet database, incorporating patient data from Year 2009 to 2024, were used to evaluate the study objectives. The study population consisted of 2 mutually exclusive cohorts of neonates

(⩽28 days of age) within the lacosamide cohort and the other AEDs cohort. Neonates in the lacosamide cohort were treated with at least 1 dose of either iv or oral lacosamide and had at least 1 code for seizures identified from 01 Jan 2009 to 31 Dec 2022 in the PEDSnet database. There were no further restrictions on the neonates in this cohort. Each neonate from the lacosamide cohort was potentially matched with neonates in the other AEDs cohort having at least 1 seizure code and being treated with other nonbenzodiazepine AEDs. Both cohorts were defined by their initial treatment with lacosamide versus matched other AEDs, and neonates remained in that cohort thereafter until the end of the Follow-up Period. Switching of the cohorts was not allowed at any time during the ⩽28 days of age.

Of the 15,239,809 patients available from the PEDSnet database, 11,956 neonates (0.078%) had 1 or more AED administrations in the first 28 days of life. After applying the study selection criteria in EP0223, 5680 neonates (0.037%) aged ⩽28 days were eligible for the study, consisting of 103 neonates in the lacosamide cohort and 5577 neonates in the other AEDs cohort.

Of the 103 neonates treated with at least 1 dose of lacosamide identified in the initial eligible cohort, 100 neonates were successfully matched to 567 neonates treated with other AEDs using propensity score matching. The sample size of the lacosamide cohort is very small, most probably related to the fact that neonatal seizures are not part of the indication.

In EP0223, many neonates had developmental and neurodevelopmental delay outcomes (overall or of any kind) during the Follow-up Period, with a total of 14 outcomes in the lacosamide cohort (N=26) at an incidence rate of 2.2 outcomes per 1000 patient days (95% CI: 1.2 to 3.7) and 77 outcomes in the other AEDs cohort (N=138) at an incidence rate of 2.0 outcomes per 1000 patient days (95% CI: 1.6 to 2.5). Cox regression analysis showed no statistically significant difference in the association between lacosamide and other AEDs cohorts with the risk of developmental or neurodevelopmental delay in children up to 2 years after the index date (weighted HR: 1.12; 95% CI: 0.55 to 2.24; p=0.76).

Baseline demographic and disease characteristics were similar between the lacosamide and other AED cohorts. The incidence rate of developmental and neurodevelopmental delay outcomes was high, probably related to the underlying disease, but was similar between the lacosamide and other AEDs cohort.

It is acknowledged in agreement with the MAH that this study does not raise any concerns. However, it should be noted that due to the extremely limited sample size of the lacosamide cohort, it is not possible to draw conclusions with any appreciable degree of certainty.

No changes to the approved SmPC for lacosamide are proposed following the results of study EP0223.

2) *The postmarketing data provided by the MAH.*

The MAH conducted a review of postmarketing data for neonates exposed to lacosamide in the frame of completion of Study SP096. This review involved a cumulative search of the UCB Global Safety database up to 31 August 2025, which identified 140 cases of postmarketing exposure (excluding UCB-sponsored interventional clinical study reports) that were considered for detailed evaluation. Additionally, a literature review was performed.

The analysis of these postmarketing data and literature review revealed evidence of off-label use of lacosamide in treating neonatal seizures, suggesting that information from Study SP0968 could be relevant to healthcare professionals. However, the inherent characteristics of these postmarketing data, including differences in the causes, treatment, and comorbidities of neonatal seizures compared to seizures in older children, preclude any definitive interpretations regarding efficacy or safety.

The conclusion that "the safety profile in neonates is consistent with the safety profile of lacosamide in older children" is not supported. This statement would require not only qualitative consistency but also quantitative consistency in terms of adverse event (AE) frequencies. Given the limitations and variability in the postmarketing data, such a conclusion cannot be reliably drawn, and therefore, it is not agreed upon. However, no changes to the approved SmPC for lacosamide are proposed with regard to this matter.

3) ***The proposed updates to the SmPC aimed to reflect the newly available data for lacosamide in neonates from SP0968.***

The primary objective of SP0968 was to evaluate the efficacy of lacosamide versus an Active Comparator chosen based on StOC in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that were not adequately controlled with previous AED treatment. The primary efficacy variable was the reduction in seizure burden measured in the Evaluation video-EEG compared with the Baseline video-EEG. The 2-hour evaluation for efficacy started 1 hour after initiation of randomized study treatment. Participants randomized to lacosamide received iv infusions of lacosamide 15mg/kg/day (5mg/kg tid without titration). The treatment groups in the FAS, therefore, included 15 participants in the lacosamide group and 9 participants in the Active Comparator group. Descriptive statistics for the primary outcome have been provided and the mean (SD) reduction in seizure burden was 6.64mins/h (6.55) in the lacosamide group and 2.45mins/h (14.83) in the Active Comparator group.

The study design including choice of endpoints is acceptable. However, it is concurred with the MAH that the interpretation of efficacy results in SP0968 is constrained by the very limited number of study participants, thereby rendering the data inadequate for providing information about the benefit in this population.

The safety database is small and based on 14 patients in the lacosamide group and 12 patients in the active comparator group which consisted of phenobarbital (5 patients), levetiracetam (2 patients) and fosphenytoin (5 patients). The mean (SD) durations of lacosamide and Active Comparator exposure were 199.367 (92.292) hours and 34.450 (40.187) hours, respectively. The longer duration of lacosamide exposure compared was largely attributed to the fact that more study participants receiving lacosamide entered the Extension Period.

Overall, 14 study participants (53.8%) reported 42 TEAEs: 9 participants (64.3%) in the lacosamide group (21 TEAEs) and 5 participants (41.7%) in the active comparator group (21 TEAEs). No major differences in the frequencies of most TEAEs (endocrine, gastrointestinal, metabolism, nervous system, convulsions) were observed between the two groups.

Four participants (15.4%) experienced severe TEAEs. In the lacosamide group, 3 participants (21.4%) experienced a single severe TEAE each (congenital CNS anomaly which was fatal, cerebral infarction, and pulmonary oedema). In the Active Comparator group, 1 participant (8.3%) experienced a severe TEAE (cerebral ischaemia); the event was considered not related to the study treatment by the Investigator and resolved. None of these were considered related to lacosamide by the Investigator. Looking at the narrative of these cases, this is agreed. Total bilirubin >1.5xULN was more frequent in the lacosamide group (8/14 patients) compared to the active comparator group (2/12 patients). However, due to the limited sample size, heterogeneity regarding underlying conditions and longer exposure in the lacosamide group no conclusions can be derived.

In summary, although interpretation of safety data is hindered by the very small sample size, no new safety concerns seem to emerge.

4) *The updated RMP version submitted by the MAH.*

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

The RMP is updated to include the following:

- Part II Module SI updated to reflect the most recent data in line with the DLP of 31 Aug 2025
- Part II SIII updated to reflect the status of studies SP0968 and EP0151 as completed. Study SP0968 moved under indications no longer pursued in Table PartII-2 and Table Part II-3 was updated accordingly to reflect the change

- Part II SIII and Part II SV updated to reflect the current clinical (including pooled data) and postmarketing exposure data

- Part II SIII, Part II SIV, and Part II SVII, Part III, Part V, Part VI, Part VII Annex 2, and Annex 3 updated to reflect the status of study EP0012 as completed.

The RMP was thus updated to reflect the status of completed studies and the current clinical and postmarketing exposure data. Regarding the missing information of "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population", the only additional pharmacovigilance activity planned to characterize it (study EP0012) has been eliminated from the RMP, and no other required specific pharmacovigilance activity or additional risk minimization measure is included for this safety concern, beyond routine pharmacovigilance activities of adverse reaction reporting and signal detection. This is therefore eliminated from the RMP, while continued monitoring of this risk will be done in PSUR procedures. No other updates on the summary of safety concerns and risk minimization measures are proposed by the MAH and this is agreed.

Acceptability of the proposed changes or possible modifications thereof

- It is agreed that no changes to the approved SmPC for lacosamide are proposed following the results of study EP0151.
- According to EMA/551202/2010 Rev 1, when considered relevant to healthcare professionals, information relating to an indication not authorised in any population could be summarised in the SmPC. The off-label use of lacosamide in neonates as described in the postmarketing data (section 8.3) supports that data from study SP0968 might be relevant to healthcare professionals. The proposed additions in sections 4.2, 5.1 and 5.2 of the SmPC are acceptable.
- The RMP was updated to reflect the status of completed studies and the current clinical and postmarketing exposure data. In the SoSC, the missing information of "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population" was removed, since the only additional pharmacovigilance activity planned to characterize it (study EP0012) was eliminated from the RMP. This is agreed. No other updates on the summary of safety concerns and risk minimization measures are proposed by the MAH and this is also agreed.

The benefit-risk balance of Vimpat and Lacosamide UCB remains positive.

3. Recommendations

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

Variation(s) requested		**Type**
C.4	C.4 Change(s) in the summary of product characteristics, labelling or package leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Variation type II

Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to update clinical information based on final results from study SP0968 and study EP0223. SP0968 was a phase 2/3, multicenter, open-label, randomized, active comparator study that evaluated the PK, efficacy, safety, and tolerability of lacosamide in neonatal study participants with repeated electroencephalographic neonatal seizures compared with an Active Comparator chosen based on standard of care per the local practice and treatment guidelines. EP0223 is a comparative study on long-term neurodevelopmental outcomes in neonates treated with lacosamide versus other antiseizure medications for neonatal seizures. The RMP

version 18.1 has also been agreed. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to implement corrections in some local languages in both Vimpat and Lacosamide UCB Product Information.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion EMA/VR/0000321459

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

5. Introduction

At the time of this submission, lacosamide had a marketing authorization in 58 countries worldwide, including the US and EU. The specific indication statement and approved formulation(s) for lacosamide may differ depending on the country. In the US, dosing recommendations for the treatment of partial-onset seizures (POS) are available and locally approved down to the age of 1 month. In the EU, Vimpat is currently indicated as (1) monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy and (2) adjunctive therapy in the treatment of primary generalised tonic-clonic seizures (PGTCS) in adults, adolescents, and children from 4 years of age with IGE.

Lacosamide is a functionalized amino acid. The precise mechanism by which lacosamide exerts its antiepileptic effect in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.

Therapeutic context related to the current application

Seizures occur more often during the neonatal period than at any other time during life (Volpe, 2008). The most common cause of neonatal seizures is hypoxic-ischemic encephalopathy (HIE) as a result of perinatal asphyxia (van Rooij et al, 2013). A population-based study suggested that 42% of neonatal seizures were observed following HIE (van Rooij et al, 2013). Other causes include intracranial haemorrhage and stroke, infections of the CNS, congenital malformations, inborn errors of metabolism, transient metabolic disturbances, maternal drug abuse, or rare neonatal epilepsy syndromes (e.g., benign familial neonatal-infantile seizures or fifth-day seizures) (Volpe, 2008; Ronen et al, 1999).

Most neonatal seizures do not comply with the usual term epilepsy because they are symptomatic seizures commonly caused by HIE, cerebral infarction, or infection. Clinical recognition of seizures in newborns is not always simple due to a highly variable clinical expression (Volpe, 2008; Mizrahi and Kellaway, 1987). As demonstrated by prolonged video EEG recordings, especially following AED treatments, electroencephalographic neonatal seizures (ENS) patterns are not always accompanied by clinical signs (Scher et al, 2003; Boylan et al, 2002; Clancy et al, 1988; Mizrahi and Kellaway, 1987).

Currently available data from multicenter, randomized, controlled studies only support the use of 1 antiepileptic drug (AED; phenobarbital) to treat neonatal seizures (Sharpe et al, 2020). More than 25% of paediatric patients have inadequate seizure control on currently available AEDs or experience significant adverse drug effects (Hadjiloizou and Bourgeois, 2007). Due to substantial evidence that neonatal seizures contribute to increased morbidity (including adverse neurodevelopmental outcomes) and mortality, physicians are increasingly focused on the diagnosis and treatment of this condition (Glass et al, 2012). However, there is a data gap for clinicians in terms of a lack of newer data or clinical experience with other AEDs for this condition.

Overview of the lacosamide neonatal development program

The PIP for lacosamide (Vimpat) for the condition of "treatment of paediatric epilepsy syndromes" (EMEA-000402-PIP03-17) aims at addressing the unmet need in the treatment of paediatric epilepsy syndromes in paediatric patients. The components of the neonatal development program are presented in Table 1 and include 1 clinical study (SP0968), the CL0447-Part V population PK modelling report, and 5 supportive RWE studies (EP0147, EP0148, EP0149, EP0155, and EP0223). All studies have been completed at the time of submission.

Table 1. Development program for use of LCM in neonatal seizures

Study number/ Status/ Article 46 submission	Brief description	Type	Efficacy/ Effectiveness data	Safety data	PK data
EP0147/ Complete/ Complete	Loading dose safety of iv LCM in neonates (<30 days) and paediatric patients ≥30 days to <17 years of age	RWE[a]	-	X	-
EP0148/ Complete/ Complete	AED treatment patterns in neonates (<30 days)	RWE[a]	-	X	-
EP0149/ Complete/ Complete	Retrospective chart review of safety and possible effectiveness of LCM for neonatal seizures (<44 weeks postmenstrual age)	RWE/ collaborative	X	X	-
EP0155/ Complete/ Complete	Safety and EEG response to LCM for neonatal seizures (<30 days)	RWE[a]	X	X	X[b]
SP0968/ Complete/ Complete	≥2nd line treatment in neonates	Clinical/PK	X	X	X
CL0447-Part V/ Complete/ Complete	PK model dosage in neonates	PK modeling	-	-	X
EP0223/ Complete/ Ongoing[c]	Retrospective neurocognitive outcome study following LCM treatment in neonatal seizures (≤28 days)	RWE[a]	-	X	-

AED=antiepileptic drug; EEG=electroencephalogram; iv=intravenous; LCM=lacosamide; PK=pharmacokinetic(s); RWE=real-world evidence

[a] RWE study was sponsored by UCB.

[b] PK data were not available for most patients. Only 3 patients, all at the same site, had any PK laboratory data. Given the small number of values, a meaningful analysis of PK data was not possible and PK data were not reported for EP0155.

[c] The final results of EP0223 are being submitted together with the current submission.

Rationale for the proposed changes

The proposed changes are mainly based on study SP0968: a Phase 2/3, multicenter, open-label, randomized, active comparator study that evaluated the PK, efficacy, safety, and tolerability of lacosamide in neonatal study participants with repeated ENS compared with an Active Comparator chosen based on StOC per the local practice and treatment guidelines. The MAH considers the available data from the small number of neonates treated in SP0968 insufficient to establish a positive benefit/risk balance in this population. Thus, no new dosing recommendations are being made for lacosamide in the neonatal patient population. While data are considered insufficient to support a new indication or a new dosing regimen, proposed updates to the EU SmPC for Vimpat/lacosamide include the addition of key SP0968 findings in sections 4.2, 5.1 and 5.2.

Additionally, a population PK model of lacosamide was updated throughout the neonatal developmental program. CL0447-Part V, a modelling and simulation study, is considered the final retrospective population PK model of lacosamide in children from birth to <18 years of age, combining all available data at the end of the paediatric program (including data from orally and iv dosed studies) in study

participants with epilepsy. CL0447-Part V is an update of the lacosamide paediatric PK model developed in CL0447 Part IV, aimed to use iv administration data in neonatal study participants from SP0968 and to perform simulations evaluating the exposure in neonates compared with the exposure in adults. The CL0447-Part V population PK modelling report was submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation) (procedure EMA/PAM/0000303848).

Data included in this Application are 1) SP0968 final data, 2) a summary of key results from the final lacosamide CL0447-Part V population PK modelling report for patients from birth to <18 years of age, 3) a cumulative evaluation of postmarketing reports of lacosamide exposure in neonates (from birth to 27 days) for the period of 29 Aug 2008 to 31 Aug 2025 performed in the frame of completion of SP0968, 4) completed RWE studies that were conducted to support the design of SP0968 within the lacosamide neonatal development program are presented including the final results from the comparative RWE study (EP0223) that investigated long-term neurodevelopmental outcomes of lacosamide treatment compared to other AEDs in neonatal seizures. The EP0223 final study report was also submitted together with the current application.

The proposed updates to the EU SmPC reflect the newly available data for lacosamide in neonates from SP0968 without making an indication claim. Inclusion of this information is expected to be clinically meaningful for prescribers, supporting an evidence-based approach to the management of neonates with epilepsy.

Assessment comment:

In the EU, Vimpat is currently indicated as (1) monotherapy and adjunctive therapy in the treatment of POS with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy and (2) adjunctive therapy in the treatment of primary generalised tonic-clonic seizures (PGTCS) in adults, adolescents, and children from 4 years of age with IGE.

Data included in this Application are 1) SP0968 final data, 2) a summary of key results from the final lacosamide CL0447-Part V population PK modelling report for patients from birth to <18 years of age, 3) a cumulative evaluation of postmarketing reports of lacosamide exposure in neonates (from birth to 27 days) for the period of 29 Aug 2008 to 31 Aug 2025 performed in the frame of completion of SP0968, 4) completed RWE studies that were conducted to support the design of SP0968 within the lacosamide neonatal development program including the final results from the comparative RWE study (EP0223) that investigated long-term neurodevelopmental outcomes of lacosamide treatment compared to other AEDs in neonatal seizures. The EP0223 final study report is also being submitted together with the current application.

Updates to the SmPC are proposed based on data from study SP0968. An updated RMP version has also been submitted by the MAH. In addition, the list of local representatives in the PL is revised.

The following are assessed in this application:

- The proposed updates to the SmPC aimed to reflect the newly available data for lacosamide in neonates from SP0968.

- The population PK model analysis and simulations, including data from SP0968 (CL0447 – Part V).

- Studies EP0147, EP148, EP0149 and EP0155 are not assessed in detail here as they have been assessed in previous procedures.

- The final results from the comparative RWE study (EP0223) submitted by the MAH.

- The postmarketing data provided by the MAH.

- The updated RMP version submitted by the MAH.

6. Clinical Pharmacology aspects

6.1. Population PK modelling analysis and simulations (CL0447-Part V)

The PK of lacosamide was studied through a population PK model (CL0447-Part V), which included data from 10 orally dosed studies (EP0008, SP754, SP755, SP847, SP1047, SP848, SP0969, SP0966, SP0982, and SP0967) and 2 iv dosed studies (EP0060 and SP0968) in study participants with epilepsy.

The current analysis is an update of the analysis in CL0447-Part IV, provided in procedure EMEA/H/C/WS2049/G, with the addition of data from study SP0968 (previously reported in procedure EMA/PAM/0000303848).

Data

For the PK model update, the final analysis data file from CL0447-Part IV was combined with PK and dosing data from study SP0968. The full lacosamide CL0447-Part V PK data file contained a total of 7179 lacosamide concentration records from 1898 study participants. After application of the data exclusion flags (same as applied in CL0447-Part IV), 6554 quantifiable lacosamide concentration records remained in the PK analysis data selection from 1669 study participants. Study SP0968 had 64 concentration records in the analysis from 14 neonates, of which 4 study participants underwent hypothermia treatment.

In the NONMEM datafile, a total of 109 study participants had iv infused lacosamide with associated observations (95 participants in EP0060 and 14 participants in SP0968); of these, 28 participants in EP0060 provided information on both oral and iv administration, allowing a proper within-individual estimate of bioavailability and associated IIV.

Software

The population analyses and simulations were performed in the non-linear mixed effect modelling software NONMEM (version 7.5.0), supplemented with the Pearl-speaks-NONMEM toolkit (version 5.6.0) for SIR analysis (to assess parameter precision and derive CIs).

Model

The developed final population PK model comprised first order absorption, single compartment distribution, and first order elimination components, where clearance (CL), volume of distribution of the central compartment (V_c), and absorption rate constant (k_a) were estimated with exponential IIV. The effect of body weight on CL and V_c was quantified using allometric equations where the exponent for CL was freely estimated while the exponent for V_c was fixed to 1. The effect of postmenstrual age (PMA) on CL was described using a sigmoid E_{max} model. Further effects of covariates, estimated on CL, were inducer antiepileptic drug (AED) coadministration, Chinese and Japanese population. The final model parameter estimates are presented in Table 2, and a visual predictive check (VPC) for the final model, stratified by neonates, children, and adults, is presented in Figure 1.

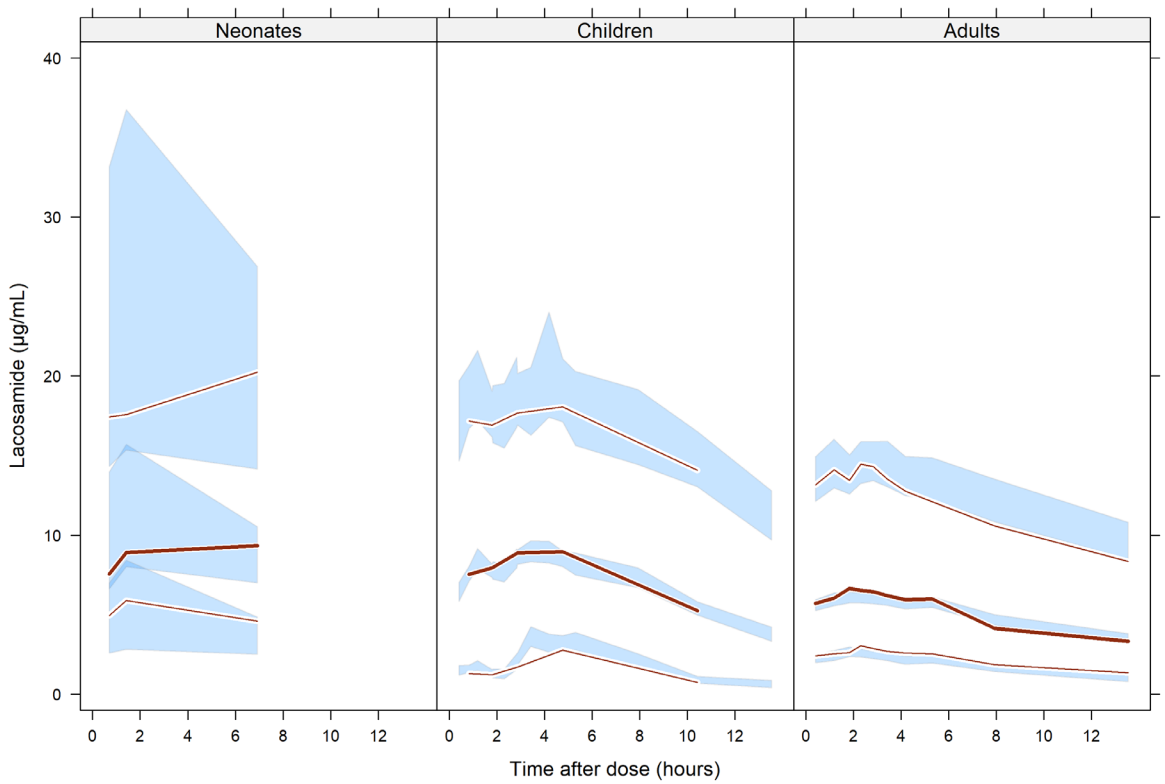
Table 2. NONMEM parameter estimates for the final lacosamide population PK model.

Parameter	Estimate (95% CI)	IIV	Shrinkage
CL (L/h at 70kg)	1.63 (1.44/1.83)	26.2%	15.6%
V_c (L at 70kg)	45.7 (40.9/50.4)	47.1%	52.0%
k_a (1/h)	1.50 (1.27/1.72)	66.2%	74.0%
F (fraction)	0.850 (0.724/0.924)	-	-

Parameter	Estimate (95% CI)	IIV	Shrinkage
Allometric scaling CL	0.577 (0.546/0.607)	-	-
Allometric scaling V_c	1.00 Fixed	-	-
Hill coefficient PMA on CL	6.93 (1.98/24.3)	-	-
PMA at 50% maturation on CL (years)	0.854 (0.757/0.963)	-	-
Change in CL (%) with China on CL	-13.4% (-16.6%/-10.1%)	-	-
Change in CL (%) with Japan on CL	-9.3% (-13.6%/-4.8%)	-	-
Change in CL (%) with IND on CL	28.3% (24.4%/32.3%)	-	-
Proportional RUV (fraction)	0.211 (0.197/0.226)	-	12.8%
Additive RUV (µg/mL)	0.337 (0.201/0.473)	-	12.8%

AED=antiepileptic drug; CI=confidence interval; CL=clearance; F=bioavailability; IIV=interindividual variability; IND=inducer AED coadministration; k_a=absorption rate constant; OFV=objective function value; PK=pharmacokinetic(s); PMA=postmenstrual age; RUV=residual unexplained variability; V_c=central volume
Note: Shrinkage is calculated using the standard deviation.
Note: OFV=14056.421; condition number=414.3

Figure 1. Visual predictive check for the final population PK model stratified by age group.



PK=pharmacokinetic(s); VPC=visual predictive check
Note: Red lines are the 5th, 50th (median), and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles using run119.

Parameter estimates for the final population PK model were quite close to the results obtained in CL0447 Part IV, with the exception of the Hill coefficient describing the relationship between PMA and CL maturation. The value of the Hill coefficient (PMA on CL) changed from 0.732 (CL0447-Part IV) to 6.93 (CL0447-Part V), resulting in a much steeper relationship due to greatly reduced CL in neonates.

The estimated changes in CL were translated to associated changes in steady state exposure, resulting in an estimated 22.1% decrease in exposure due to inducer AED coadministration, 10.3% increase in exposure for study participants from Japan, and 15.5% increase in exposure for study participants from China. PMA-dependent maturation in CL reached 50% at a PMA of 10.2 months (or 32 days after term birth).

Oral bioavailability was estimated to 85.0% (95% CI: 72.4%/92.4%) indicating a close correspondence in exposure between oral and iv dosed study participants.

Simulations

Simulations were performed to assess if predicted lacosamide paediatric average concentration at steady state (C_{ss}) fell within the range of adult values, and if these values were comparable between oral and iv dosing as well as monotherapy and add-on therapy in children for the same dosing regimen. The 1999-2023 CDC (Centers for Disease Control and prevention) NCHS (National Center for Health Statistics) National Health and Nutrition Examination Survey (Nhanes) database [34] was used to provide linked demographic variables (age and weight) to drive the simulations. Additionally, the file contains distribution of weight at birth. 1000 subjects were randomly sampled (without replacement) from each of the following groups:

- At birth (neonates)
- At 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 months
- At 1 ,2 ,3 ,4 ,5 ,6 ,7 ,8 ,9 ,10 ,11 ,12 ,13 ,14 ,15 ,16, and 17 years
- Adults (≥18 years)

Simulations were performed by sampling from the estimated IIV distributions, without additionally incorporating parameter uncertainty for population parameters.

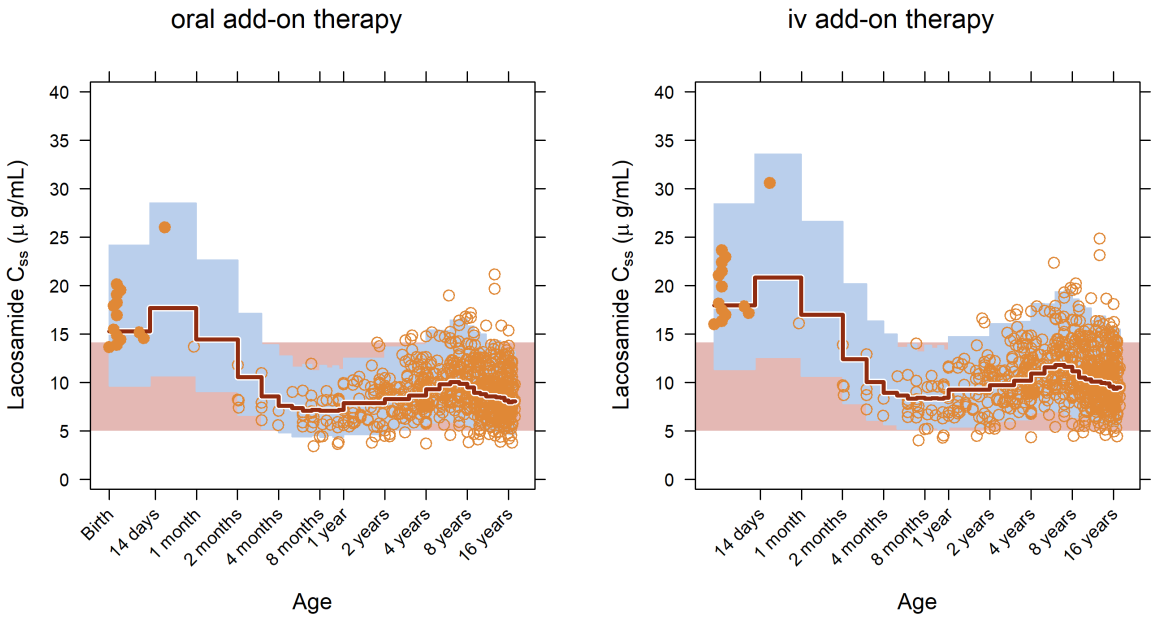
The population estimates from the final population PK model were used to simulate C_{ss} values for all sampled records with the following dosing schedule:

- 7.5 mg/kg bid oral or 5 mg/kg tid iv for weight <6 kg, including neonates
- 6 mg/kg bid for weight ≥6 kg and weight <30 kg
- 4 mg/kg bid for weight ≥30 kg and weight <50 kg
- 200 mg bid for weight ≥50 kg

The results for adults were used to derive the median and 90% of the predicted C_{ss} concentrations. To ensure that the predictions to compare adults and children were not distorted by a potentially different background AED profile between adults and children, no inducer AED coadministration effects were used in generating the reference adult PK population. These results were graphically compared for oral and iv dosing with the median and 90% of the concentrations for children, by body weight, and age classes.

The simulated lacosamide C_{ss} for the above-mentioned dosing schedules for children (by age), using the final population PK model is provided in Figure 2.

Figure 2. Add-on therapy: Predicted lacosamide C_{ss} for the recommended oral and iv dosing schedule for children (by age) using the final population PK model.



bid=twice a day; C_{ss}=average steady state concentrations over 24 hours; iv=intravenous; PK=pharmacokinetic(s); tid=3 times a day

Note: Recommended dosing schedule: a 7.5mg/kg bid oral dose or a 5mg/kg tid iv dose for weight <6kg; a 6mg/kg bid dose for 6kg≤weight<30kg; a 4mg/kg bid dose for 30kg≤weight<50kg; and a 200mg bid dose for weight ≥50kg.

Note: Age on logarithmic scale. *Red line and blue area:* Median and 90% of simulated lacosamide C_{ss} values for participants <18 years of age sampled from the Nhanes database for oral dosing (left column) and iv dosing (right column). *Orange circles:* Individual predicted lacosamide C_{ss} values, solid markers: neonates. *Pink horizontal bar:* 90% of simulated lacosamide C_{ss} values for adult participants ≥18 years of age sampled from the Nhanes database for oral dosing of 200mg bid without inducer AED coadministration.

6.2. Discussion

The MAH has updated the lacosamide population PK model, including data from study SP0968 in neonates. The analysis report (CL0447-Part V) was provided (however, not assessed) in the preceding P46 procedure (EMA/PAM/0000303848). In this procedure, the MAH suggests an update of the text on PK in the paediatric population in section 5.2 of the SmPC, to also include information on PK in neonates.

During assessment of the previous population PK model (CL0447-Part IV), which was provided in procedure EMEA/H/C/WS2049/G, it was pointed out that the estimated oral bioavailability was 84% (in the current model 85%) whereas the oral bioavailability previously established based on clinical pharmacology studies is approaching 100%. By then it was concluded that the lower oral bioavailability estimated in the population PK model was an artefact, likely caused by very limited information in the dataset (the estimate is informed by only 28 patients with very sparse data (study EP0060)). Furthermore, it was concluded that other estimates in the model have compensated for the misspecification, and thus all parameter estimates, in particular CL, should be interpreted with caution. This was not considered a major issue when the focus was on orally administered lacosamide only; however, in neonates the doses were administered IV, and hence the erroneously decreased oral bioavailability will have an impact on the model estimates and the simulations from the model.

The Applicant proposed to include the following text in section 5.2 of the SmPC:

In the study in newborns treated with 15 mg/kg lacosamide per day, a steady state exposure was observed that partly overlapped with the exposure in adults receiving 400 mg/day. The plasma clearance was estimated to be 0.26 L/h (3 kg body weight).

Given the misspecification of bioavailability, information on the estimated clearance in neonates should not be included in the SmPC. To substantiate the remaining information, it was suggested to include further information on the dosing regimens compared and clearly state that the exposure in newborns appeared to be higher than the exposure in adults.

The following amendments of the text were proposed (~~crossed out~~ text to be deleted and **bold** text to be added):

*In ~~the~~ **a** study in newborns treated with ~~15 mg/kg~~ lacosamide **administered IV as 5 mg/kg tid** ~~per day~~, **the** a**verage** steady state exposure **appeared to be higher than** ~~was observed that partly overlapped with~~ the exposure in adults receiving **lacosamide administered orally as** ~~400~~ **200** mg **bid**~~/day. The plasma clearance was estimated to be 0.26 L/h (3 kg body weight).~~*

7. Clinical Efficacy aspects

7.1. Study SP0968

Methods – analysis of data submitted

Study design

Study SP0968 was a Phase 2/3, multicenter, open-label, randomized, active comparator study that evaluated the PK, efficacy, safety, and tolerability of lacosamide in neonatal study participants with repeated electroencephalographic neonatal seizures (ENS) compared with an Active Comparator chosen based on StOC per the local practice and treatment guidelines.

Study SP0968 included participants that were ≥34 weeks of CGA, <46 weeks of CGA, and <28 days of PNA at the time the informed consent was obtained. Neonates who had confirmation on video-EEG of ≥2 minutes of cumulative ENS or ≥3 identifiable ENS prior to entering the Treatment Period could be enrolled in the study. ENS was defined as a seizure lasting for at least 10 seconds on video-EEG, despite receiving previous AED treatment (phenobarbital, levetiracetam, or midazolam in any combination; additional benzodiazepines were allowed). Only those study participants who did not have adequate seizure control with previous AED treatment were permitted to enrol in SP0968.

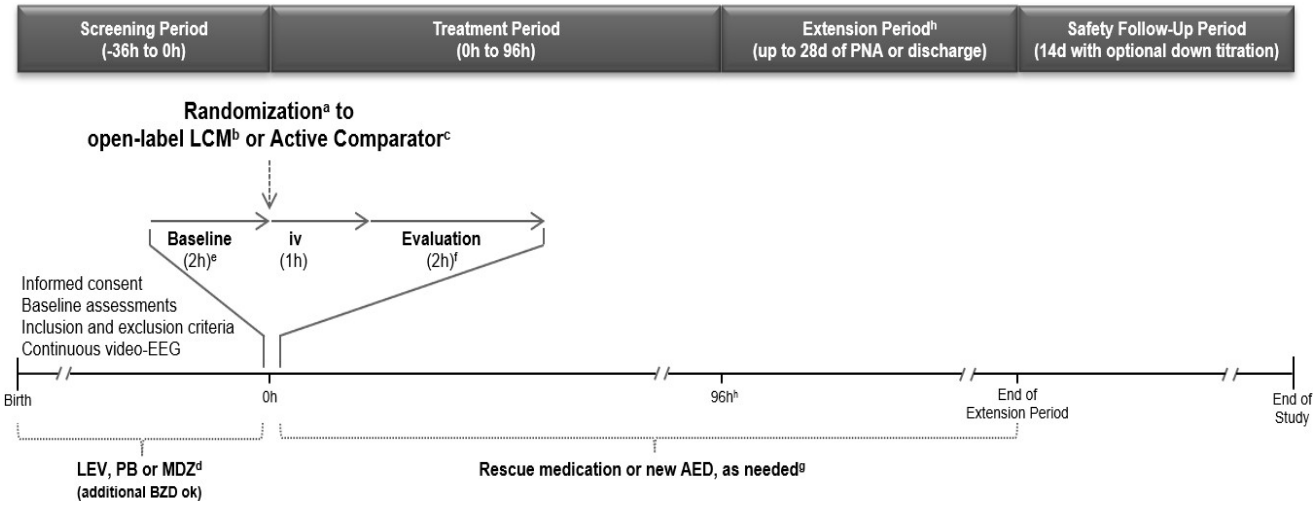
The primary objective (and secondary objective) of SP0968 was to evaluate the efficacy of lacosamide versus an Active Comparator chosen based on StOC in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that were not adequately controlled with previous AED treatment. Other secondary objectives were to evaluate (1) the short-term safety and tolerability of lacosamide in neonates (included as other objective) and (2) the PK of lacosamide in neonates who had seizures that were not adequately controlled with previous AED treatment.

The total duration of the study for an individual study participant was a maximum of 42 days and consisted of the following defined periods:

- Screening Period: Up to 36 hours (-36 hours to 0 hour)
- Treatment Period: 96 hours (0 hour to 96 hours)
- Extension Period: Up to 28 days of PNA

- SFU Period (with optional down titration): 14 days

Figure 3. Schematic overview of the study



Following the Baseline assessments, study participants were randomized 1:1 to either the lacosamide or Active Comparator (StOC, based on local practice and treatment guidelines) treatment group; the randomization was stratified by seizure severity at Baseline. During the Treatment Period, study participants randomized to lacosamide received iv infusions of lacosamide 15mg/kg/day (5mg/kg tid without titration), with each dose infused over 30 minutes. The daily dose of lacosamide (15mg/kg/day) was intended to yield approximately the same plasma concentrations as in an adult receiving lacosamide 400mg/day, the maximum dose approved for adjunctive therapy in adults.

Following the Treatment Period, all study participants who remained in the inpatient unit and continued to receive the randomized treatment (lacosamide or Active Comparator) entered the Extension Period. Some study participants in the lacosamide group continued receiving the same lacosamide dose administered at the end of the Treatment Period; the lacosamide dose was not increased, but could be decreased, at the discretion of the Investigator. Participants on lacosamide were switched to oral dosing of lacosamide (15mg/kg/day [7.5mg/kg bid]) as soon as medically possible during the Extension Period. If study participants did not benefit from lacosamide treatment after 96 hours of lacosamide administration, lacosamide administration was to be stopped, and the study participant was to be treated as per StOC.

Study participants who discontinued randomized treatment at any time, completed the Extension Period, were discharged from the inpatient unit, or reached 28 days PNA entered the 14-day SFU Period. Study participants were to return to the site for the SFU Visit at the end of the 14-day SFU Period.

Primary efficacy variable analysis

The primary efficacy variable was the reduction in seizure burden measured in the Evaluation video-EEG compared with the Baseline video-EEG. The 2-hour evaluation for efficacy started 1 hour after initiation of randomized study treatment. Baseline seizure burden was defined as seizure burden measured on the continuous video-EEG (total ENS in minutes per hour) during a period of up to 2 hours immediately prior to the first administration of study treatment. For this study, an ENS was defined as an EEG seizure lasting for at least 10 seconds on video-EEG. The video-EEGs were evaluated by an independent central reader. The independent central reader was blinded from the study participant's medical history and randomized treatment. Given the scarcity of prior evidence in randomized controlled studies in the chosen indication and line of treatment, SP0968 was considered exploratory with no formal sample size

calculation. A total of 32 study participants was planned to be enrolled. The first SP0968 study sites were opened for recruitment in Jan 2021, and the last investigative site was activated in Jan 2022. The study ended prematurely on 17 Apr 2025.

The primary efficacy variable was originally planned to be analyzed at the end of the study using Bayesian methodology, a model based on the assumption that data are normally distributed. However, based on data reviewed at an internal DEM, the data were demonstrated not to be normally distributed due to the high number of participants with a complete cessation of seizures. Consequently, the SP0968 SAP Amendment 3 (dated 04 May 2023) was amended to allow for a descriptive analysis if the study was ended early (i.e., with fewer than 32 participants randomized and dosed). Since the study concluded earlier than expected and the final data were not normally distributed, the planned Bayesian analysis could not be performed. Instead, the primary efficacy analysis was conducted using descriptive statistics to summarize the absolute reduction in seizure burden from Baseline in the Evaluation Period.

Results

A total of 29 study participants were randomized at 19 sites. Of these, 26 study participants entered the Treatment Period and were treated with at least 1 dose of study treatment (SS), 14 participants in the lacosamide group and 12 participants in the Active Comparator group; all 26 participants (100%) completed the Evaluation Period. All 26 participants (100%) completed 30 minutes of video-EEG and 21 participants (80.8%) completed 48 hours of video-EEG, 12 participants (85.7%) in the lacosamide group and 9 participants (75.0%) in the Active Comparator group. A total of 25 participants (96.2%) attended the SFU Visit and completed the study, 14 participants (100%) in the lacosamide group and 11 participants (91.7%) in the Active Comparator group.

The study treatments in the Active Comparator group included phenobarbital and fosphenytoin (5 participants [41.7%] each) and levetiracetam (2 participants [16.7%]).

Overall, 24 participants (92.3%) were included in the FAS, 14 participants (100%) in the lacosamide group and 10 participants (83.3%) in the Active Comparator group. Of note, 1 participant randomized to lacosamide received Active Comparator instead. The treatment groups in the FAS, therefore, included 15 participants in the lacosamide group and 9 participants in the Active Comparator group. No study participant discontinued in the lacosamide group; 1 participant discontinued in the Active Comparator group and reported the reason of consent withdrawn. No participant discontinued in the study due to adverse events.

Overall, the mean PNA was 3.7 days (range: 0 to 18 days) with a generally similar proportion of male and female study participants (46.2% and 53.8%, respectively). Overall, mean weight, body length, and head circumference were 3.21kg (range: 2.4 to 4.4kg), 50.75cm (range: 46.5 to 54.0cm), and 34.10cm (range: 29.5 to 39.5cm), respectively. The majority of participants were White (73.1%) with a generally similar proportion of ethnicity. The majority of participants were from the United States (96.2%). The demographics of study participants in the lacosamide group and the Active Comparator group were generally similar. Overall, the mean (SD) Apgar scores of study participants at 1 minute, 5 minutes, and 10 minutes after birth were 5.0 (3.0), 7.0 (2.8), and 5.8 (2.9), respectively. The most common primary cause of seizures, based on the most recent assessment available at Baseline, was HIE, haemorrhage, or infarctions (17 participants [65.4%]), with the majority of seizures being nonsevere (61.5%). The majority of participants did not have concomitant hypothermia treatment (76.9%). For 6 participants (50.0%) in the lacosamide group and 11 participants (78.6%) in the Active Comparator group, the primary cause of seizures was HIE, haemorrhage, or infarctions.

Efficacy results

Primary efficacy variable

During the Evaluation Period (1 to 3 hours), the mean (SD) reduction in seizure burden was 6.64mins/h (6.55) in the lacosamide group and 2.45mins/h (14.83) in the Active Comparator group.

Secondary efficacy variables

- During the Evaluation Period (1 to 3 hours), the responder proportions in the lacosamide and Active Comparator groups were similar, 60.0% and 66.7%, respectively. In the Treatment Period, between 47 to 48 hours, responder proportions were 76.9% and 66.7% in the lacosamide and Active Comparator groups, respectively.

- During the Evaluation Period, 60% of participants in the lacosamide group and 44.4% of participants in the Active Comparator group had at least 80% reduction in seizure burden regardless of seizure severity.

- The median time to response across the 48 hours was 3.0 hours for both the lacosamide and Active Comparator groups with 33.3% and 11.1% of the events censored in the lacosamide group and the Active Comparator group, respectively.

- The median time to seizure freedom was 3.0 hours for the lacosamide group and 8.0 hours for the Active Comparator group with 33.3% of the events censored in both groups.

- The mean (SD) percent reduction in seizure burden at 3 hours was 84.41 (36.42) in the lacosamide group and 30.26 (114.17) in the Active Comparator group and remained higher in the lacosamide group through 16 hours.

- At 24 hours following the administration of study treatment, 64.3% of participants in the lacosamide group and 75.0% of participants in the Active Comparator group were seizure free.

- Three hours after the administration of study treatment, 81.8% of participants in the lacosamide group and 44.4% in the Active Comparator group achieved at least 80% reduction in seizure burden.

Discussion

The interpretation of efficacy results in SP0968 is limited by the small number of study participants; 15 and 9 participants in the lacosamide and the Active Comparator groups, respectively. Therefore, it is agreed with the MAH that the currently available data from the small number of neonates treated in SP0968 are insufficient to establish a positive benefit/risk balance in this population. Thus, no new dosing recommendations are being made for lacosamide in the neonatal patient population.

Assessment comment:

The primary objective of SP0968 was to evaluate the efficacy of lacosamide versus an Active Comparator chosen based on StOC in severe and nonsevere seizure burden (defined as total minutes of ENS per hour) in neonates with seizures that were not adequately controlled with previous AED treatment. The primary efficacy variable was the reduction in seizure burden measured in the Evaluation video-EEG compared with the Baseline video-EEG. The 2-hour evaluation for efficacy started 1 hour after initiation of randomized study treatment. Participants randomized to lacosamide received iv infusions of lacosamide 15mg/kg/day (5mg/kg tid without titration). The treatment groups in the FAS, therefore, included 15 participants in the lacosamide group and 9 participants in the Active Comparator group. Descriptive statistics for the primary outcome have been provided and the mean (SD) reduction in seizure burden was 6.64mins/h (6.55) in the lacosamide group and 2.45mins/h (14.83) in the Active Comparator group.

The study design including choice of endpoints is acceptable. However, it is concurred with the MAH that the interpretation of efficacy results in SP0968 is constrained by the very limited number of study participants, thereby rendering the data inadequate for providing information about the benefit in this population.

8. Clinical Safety aspects

8.1. Study SP0968

Methods – analysis of data submitted

Safety assessments performed during SP0968 included AEs, SAEs, laboratory values (haematology and clinical chemistry), vital signs (blood pressure, respiration rate, pulse rate, temperature, and oxygen saturation), 12-lead ECGs (only for participants randomized to lacosamide), physical and neurological assessments, biometric parameters (body length, body weight, and head circumference), Sarnat scale, and other assessments related to safety (hypothermia treatment and mother's use of AEDs).

Table 3. Schedule of Activities - Extension and Safety Follow-up Periods

Assessments	**Extension Period**	**Safety Follow-up Period [a] (with optional down titration)**
	Up to 28 days of PNA or withdrawal	**14 days (Down titration [b] for 7 days)**
	q7d	**Day 14**
(Assessment window)	**(±2 days)**	**(±2 days)**
Vital signs	X	X
Physical and neurological examination	X	X
Biometric parameters: length, body weight and head circumference		X
LCM or Active Comparator administration or dispense	X	
Laboratory assessments (safety)	X	X
AEs	X	X
ECG	X	X
Concomitant medications	X	X

Medical procedures	X	X
AEDs	X	X

AE=adverse event; AED=anti-epileptic drug; ECG=electrocardiogram; IRT=Interactive Response Technology; iv=intravenous; LCM=lacosamide; PNA=postnatal age; q7d=every 7 days; SFU=Safety Follow-up.

Results

Exposure to study treatment

In SP0968, the mean (SD) durations of lacosamide and Active Comparator exposure were 199.367 (92.292) hours and 34.450 (40.187) hours, respectively. The longer duration of lacosamide exposure compared with the Active Comparator was largely attributed to the fact that more study participants receiving lacosamide entered the Extension Period following completion of the Treatment Period.

Adverse events

Table 4. Summary of AEs (SS)

Category	Active Comparator (StOC) N=12 n (%) [#]	Lacosamide N=14 n (%) [#]	All participants N=26 n (%) [#]
Any TEAEs	5 (41.7) [21]	9 (64.3) [21]	14 (53.8) [42]
Serious TEAEs	0	2 (14.3) [2]	2 (7.7) [2]
Nonserious TEAEs	5 (41.7) [21]	8 (57.1) [19]	13 (50.0) [40]
Participant discontinuations due to TEAEs	0	0	0
Permanent discontinuations of study treatment due to TEAEs	0	0	0
Drug-related TEAEs	0	1 (7.1) [2]	1 (3.8) [2]
Severe TEAEs	1 (8.3) [1]	3 (21.4) [3]	4 (15.4) [4]
All deaths (AEs leading to deaths)	0	1	1
Deaths (TEAEs leading to deaths)	0	1 (7.1) [1]	1 (3.8) [1]

AE=adverse event; CSR=clinical study report; SS=Safety Set; StOC=standard of care; TEAE=treatment-emergent adverse event.
Note: n=number of participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: All deaths was based on all participants screened and refers to all deaths occurring on the study.
Note: TEAEs were defined as AEs which had onset on or after the start date and time of the first dose of study treatment.

Overall, 14 study participants (53.8%) reported 42 TEAEs: 9 participants (64.3%) in the lacosamide group (21 TEAEs) and 5 participants (41.7%) in the Active Comparator group (21 TEAEs). Of these, 4 participants (15.4%) experienced severe TEAEs. In the lacosamide group, 3 participants (21.4%) experienced a single severe TEAE each (congenital CNS anomaly, cerebral infarction, and pulmonary oedema); none of these were considered related to lacosamide by the Investigator. In the Active Comparator group, 1 participant (8.3%) experienced a severe TEAE (cerebral ischaemia); the event was considered not related to the study treatment by the Investigator and resolved.

In the lacosamide group, 1 study participant experienced 2 TEAEs (convulsion and lethargy) that were considered related to lacosamide by the Investigator; both TEAEs were mild and resolved. One study participant experienced a fatal TEAE of congenital CNS anomaly; the event was considered not related to

lacosamide by the Investigator. Two study participants each experienced 1 serious TEAE (congenital CNS anomaly and cerebral infarction); both events were considered not related to lacosamide by the Investigator. The event of congenital CNS anomaly was fatal, and the event of cerebral infarction resolved with sequelae.

No study participant in the Active Comparator group experienced a drug-related TEAE, a fatal TEAE, or a serious TEAE.

Common AEs

Table 5: TEAEs reported by ≥2 participants in the All participants group (SS)

MedDRA 16.1 **SOC** **PT**	**Active Comparator (StOC)** **N=12** **n (%) [#]**	**Lacosamide** **N=14** **n (%) [#]**	**All participants** **N=26** **n (%) [#]**
Any TEAEs	5 (41.7) [21]	9 (64.3) [21]	14 (53.8) [42]
Endocrine disorders	2 (16.7) [2]	2 (14.3) [2]	4 (15.4) [4]
Adrenal insufficiency	1 (8.3) [1]	1 (7.1) [1]	2 (7.7) [2]
Gastrointestinal disorders	1 (8.3) [1]	3 (21.4) [3]	4 (15.4) [4]
Vomiting	1 (8.3) [1]	2 (14.3) [2]	3 (11.5) [3]
Metabolism and nutrition disorders	2 (16.7) [2]	1 (7.1) [1]	3 (11.5) [3]
Feeding disorder neonatal	1 (8.3) [1]	1 (7.1) [1]	2 (7.7) [2]
Nervous system disorders	3 (25.0) [8]	3 (21.4) [4]	6 (23.1) [12]
Convulsion	0	2 (14.3) [2]	2 (7.7) [2]

AE=adverse event; CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=System Organ Class; SS=Safety Set; StOC=standard of care; TEAE=treatment-emergent adverse event

Note: n=number of participants reporting at least 1 TEAE within SOC and PT.

Note: [#] is the number of individual occurrences of the TEAE.

Note: TEAEs were defined as AEs which had onset on or after the start date and time of the first dose of study treatment.

One study participant in the lacosamide group experienced a fatal TEAE of congenital CNS anomaly. This fatal event was severe in intensity and was considered not related to lacosamide by the Investigator.

No consistent or clinically relevant treatment-related changes from Baseline in haematology and clinical chemistry values were observed after lacosamide or Active Comparator treatment. In the lacosamide group, the elevated LFTs were ALT/AST/ALP (7.7%), TBL >1.5xULN (61.5%), and TBL >2xULN (53.8%). In the Active Comparator group, the elevated LFTs were ALT/AST/ALP (0%), TBL >1.5xULN and TBL >2xULN (18.2% each). No study participant met the criteria for PDILI.

No consistent or clinically relevant treatment-related changes from Baseline in vital signs values or ECG findings were observed after lacosamide or Active Comparator treatment.

Discussion

The overall conclusion of the information obtained to date from SP0968, completed RWE studies, and postmarketing data is that the safety profile of lacosamide remains unchanged and no new significant safety concerns were identified. The safety profile in neonates <1 month of age is consistent with the safety profile of lacosamide in older children and adults. The available evidence is still insufficient to support a positive benefit/risk balance in neonates. While UCB considers the data insufficient to support a new indication or a new dosing regimen, the safety, efficacy, and PK evidence gathered on lacosamide in

neonates are important information for the treating physicians. For this reason, updates to the EU SmPC for Vimpat/lacosamide UCB are being proposed, taking into account the EMA guidance for paediatric labelling updates.

Assessment comment:

The safety database is small and based on 14 patients in the lacosamide group and 12 patients in the active comparator group which consisted of phenobarbital (5 patients), levetiracetam (2 patients) and fosphenytoin (5 patients). The mean (SD) durations of lacosamide and Active Comparator exposure were 199.367 (92.292) hours and 34.450 (40.187) hours, respectively. The longer duration of lacosamide exposure compared was largely attributed to the fact that more study participants receiving lacosamide entered the Extension Period.

Overall, 14 study participants (53.8%) reported 42 TEAEs: 9 participants (64.3%) in the lacosamide group (21 TEAEs) and 5 participants (41.7%) in the active comparator group (21 TEAEs). No major differences in the frequencies of most TEAEs (endocrine, gastrointestinal, metabolism, nervous system, convulsions) were observed between the two groups.

Four participants (15.4%) experienced severe TEAEs. In the lacosamide group, 3 participants (21.4%) experienced a single severe TEAE each (congenital CNS anomaly which was fatal, cerebral infarction, and pulmonary oedema). In the Active Comparator group, 1 participant (8.3%) experienced a severe TEAE (cerebral ischaemia); the event was considered not related to the study treatment by the Investigator and resolved. None of these were considered related to lacosamide by the Investigator. Looking at the narrative of these cases, this is agreed. Total bilirubin >1.5xULN was more frequent in the lacosamide group (8/14 patients) compared to the active comparator group (2/12 patients). However, due to the limited sample size, heterogeneity regarding underlying conditions and longer exposure in the lacosamide group no conclusions can be derived.

In summary, although interpretation of safety data is hindered by the very small sample size, no new safety concerns seem to emerge.

8.2. Study EP0223

Methods – analysis of data submitted

Study design

EP0223 was a retrospective matched cohort study of long-term neurodevelopmental outcomes in neonates treated with lacosamide versus other nonbenzodiazepine AEDs for neonatal seizures. The primary objective was to compare the incidence rate of overall prespecified (ie, outcomes relevant to a biological age below 2 years) neurodevelopmental outcomes in neonates treated with lacosamide versus other AEDs for neonatal seizures up to 2 years post-index date. The secondary objective was to describe the Baseline demographic, Baseline and follow-up clinical characteristics in neonates treated with lacosamide and other AEDs for neonatal seizures. The exploratory objective was to compare the incidence rate of specific prespecified neurodevelopmental outcomes (≥5%) in neonates treated with lacosamide versus other AEDs for neonatal seizures up to 2 years post-index date.

EHR data from the PEDSnet database, incorporating patient data from Year 2009 to 2024, were used to evaluate the study objectives. The index date was defined as the first record of lacosamide or other AED administration in neonates aged ≤28 days at participating PEDSnet hospitals. The actual sample size for this study was based on the neonates available in the database.

The study population consisted of 2 mutually-exclusive cohorts of neonates (≤28 days of age) within the lacosamide cohort and the other AEDs cohort. Neonates in the lacosamide cohort were treated with at least 1 dose of either iv or oral lacosamide and had at least 1 code for seizures identified from 01 Jan 2009 to 31 Dec 2022 in the PEDSnet database. There were no further restrictions on the neonates in this cohort. Each neonate from the lacosamide cohort was potentially matched with neonates in the other AEDs cohort having at least 1 seizure code and being treated with other nonbenzodiazepine AEDs. Both cohorts were defined by their initial treatment with lacosamide versus matched other AEDs, and neonates remained in that cohort thereafter until the end of the Follow-up Period. Switching of the cohorts was not allowed at any time during the ≤28 days of age.

EP0223 consisted of the following defined periods:

- Washout Period (Birth to Day -1): No exposure to lacosamide or matched other AEDs and presence of prespecified neurodevelopmental outcomes.
- Baseline Period (Birth to Day -1): Assessed for comorbidities.
- Patient Identification Period (Day 0): Received first administration of lacosamide or other AED (index date). The start date was 01 Jan 2009, and the end date was 31 Dec 2022.
- Follow-up Period: Index date to up to 2 years from index date (or until lost to follow up or death or end of study period) for assessing the comorbidities and neurodevelopmental outcomes.

Measurements and evaluations

The feasibility study conducted from Mar to Aug 2024 relied on predefined SNOMED-coded developmental and neurodevelopmental delay outcomes in children aged ≤2 years using real-world clinical data from neonates treated with lacosamide or other AEDs. This study identified greater variability in the developmental assessment tools used across participating sites, along with differences in the timing of assessments.

EP0223 used EHR data from the PEDSnet database exclusively, with no manual chart review performed. Based on findings from the feasibility study, previously collected real world clinical data on neurodevelopmental outcomes for neonates (≤28 days) treated with lacosamide or other AEDs for neonatal seizures were utilized, providing a comparison of prespecified developmental and neurodevelopmental delay outcomes using SNOMED codes between the lacosamide cohort and the matched other AEDs cohort.

The matching and weighing were done using 3 steps: (1) Generation of initial propensity scores: Propensity scores were first generated using all predefined covariates: gestational age, sex, race/ethnicity, birth weight, PEDSnet health system/practice/study site, calendar year of index date, index age, duration of observation before index date, order of AED therapy on index date, total number of AEDs pre- and post-index up to ≤28 days of age, whether the neonate began lacosamide or other AED in the ICU, and baseline gastrointestinal and haematologic comorbidities; (2) Conversion to preference scores and identification of the equipoise region: These initial propensity scores were converted to preference scores to identify the equipoise region, and analyses were restricted to neonates within this region; and (3) Re-estimation of propensity scores and application of overlap weighting: Within the equipoise cohort, a reduced propensity score model was estimated using covariates of particular interest (gestational age, sex, PEDSnet health system/practice/study site, order of AED therapy on index date, total number of AEDs pre- and post-index up to ≤28 days of age, and calendar year of index date), along with additional covariates with p-values <0.05. The recalculated propensity scores were used to generate overlap weights to enhance covariate balance in the overlap population.

No other assessments related to safety were collected.

Results

Of the 15,239,809 patients available from the PEDSnet database, 11,956 neonates (0.078%) had 1 or more AED administrations in the first 28 days of life. After applying the study selection criteria in EP0223, 5680 neonates (0.037%) aged ≤28 days were eligible for the study, consisting of 103 neonates in the lacosamide cohort and 5577 neonates in the other AEDs cohort.

Of the 103 neonates treated with at least 1 dose of lacosamide identified in the initial eligible cohort, 100 neonates were successfully matched to 567 neonates treated with other AEDs using propensity score matching.

The overlap weighted cohort was used for the main analysis: 26 neonates in the lacosamide cohort and 138 neonates in the other AEDs cohort. Almost all neonates in the lacosamide cohort (84.6%) and other AEDs cohort (78.3%) had begun treatment in the ICU. In the lacosamide cohort, 19.2% of neonates were treated with 2 AEDs and 80.8% of neonates were treated with 3 or more AEDs up to ≤28 days of age. In the other AEDs cohort, 21.7% of neonates were treated with 2 AEDs and 78.3% of neonates were treated with 3 or more AEDs up to ≤28 days of age. Most neonates in the lacosamide cohort (73.1%) received lacosamide as a third-line treatment or later, with only a small number receiving lacosamide as a first or second-line treatment (3.8% and 23.1%, respectively). The majority of neonates in the other AEDs cohort (78.3%) received other AEDs as a third-line treatment or later, with 7.2% of neonates receiving other AEDs as a first-line treatment and 14.5% of neonates receiving other AEDs as a second-line treatment. In the lacosamide cohort, most neonates (76.9%) received lacosamide treatment after 2019, with fewer neonates being treated in earlier calendar years (3.8% of neonates before 2014 and 19.2% of neonates between 2014 and 2018). Similarly, in the other AEDs cohort, most neonates (73.9%) received other AED treatment after 2019, with a smaller proportion of neonates being treated before 2014 (3.6%) or between 2014 and 2018 (22.5%).

Demographic and clinical characteristics

The mean age at index date was 9.2 days (median: 7.0 days; IQR: 3.2 to 14.8 days) in the lacosamide cohort and 9.8 days (median: 8.5 days; IQR: 3.0 to 14.0 days) in the other AEDs cohort. The mean birth weight was 3.2kg (median: 3.1kg; IQR: 2.7 to 3.6kg) in the lacosamide cohort and 3.0kg (median: 3.0kg; IQR: 2.7 to 3.5kg) in the other AEDs cohort. In the lacosamide cohort, 19.2% of neonates either had a gestational age of 39 weeks or 40 weeks, with births occurring across earlier gestational-age categories (range: 3.8 to 7.7%); a notable proportion of neonates (26.9%) was recorded in the unknown gestational-age category. In the other AEDs cohort, 15.9% of neonates had a gestational age of 39 weeks and 13.0% of neonates had a gestational age of 38 weeks, with births occurring across other gestational-age categories (range: 1.4 to 9.4%); the highest proportion of neonates (36.2%) was recorded in the unknown gestational-age category.

The majority of neonates were male, 65.4% in the lacosamide cohort and 50.7% in the other AEDs cohort. The highest proportion of neonates were White (46.2% in the lacosamide cohort and 46.4% of the other AEDs cohort), followed by Hispanic/Latino (26.9% in the lacosamide cohort and 19.6% in the other AEDs cohort). Public insurance was the most common payer type in both cohorts (57.7% in the lacosamide cohort and 52.2% in the other AEDs cohort). The largest proportion of neonates was contributed by site F (30.8% in the lacosamide cohort and 20.3% in the other AEDs cohort) and site G (19.2% in the lacosamide cohort and 29.0% in the other AEDs cohort).

The mean Follow-up Period was 499.2 days (median: 637.5 days; IQR: 268.2 to 718.8 days) in the lacosamide cohort and 518.3 days (median: 672.0 days; IQR: 283.2 to 716.8 days) in the other AEDs

cohort. In both cohorts, most neonates were still being seen at PEDSnet health system/practice/study sites beyond the 2 years post-index date (76.9% in the lacosamide cohort and 71.7% in the other AEDs cohort) and this was the primary reason for Follow up Period censoring.

In the lacosamide cohort, the most common Baseline comorbidities between birth and the day before the index date were seizure (92.3%), respiratory condition (76.9%), infection and metabolic disturbance (38.5% each), and haematologic abnormality and hypoxic-ischemic encephalopathy (30.8% each). In the other AEDs cohort, the most common Baseline comorbidities between birth and the day before the index date were seizure (97.1%), respiratory condition (80.4%), infection (53.6%), metabolic disturbance (52.9%), cardiac condition (45.7%), and haematologic abnormality (39.9%). In the lacosamide cohort, the most common comorbidities during the Follow-up Period on and after the index date were gastrointestinal condition and infection (26.9% each), metabolic disturbance (23.1%), and haematologic abnormality (19.2%). In the other AEDs cohort, the most common comorbidities during the Follow-up Period on and after the index date were infection (16.7%) and gastrointestinal condition (15.2%).

Incidence rate

In EP0223, many neonates had developmental and neurodevelopmental delay outcomes (overall or of any kind) during the Follow-up Period, with a total of 14 outcomes in the lacosamide cohort (N=26) at an incidence rate of 2.2 outcomes per 1000 patient days (95% CI: 1.2 to 3.7) and 77 outcomes in the other AEDs cohort (N=138) at an incidence rate of 2.0 outcomes per 1000 patient days (95% CI: 1.6 to 2.5). Cox regression analysis showed no statistically significant difference in the association between lacosamide and other AEDs cohorts with the risk of developmental or neurodevelopmental delay in children up to 2 years after the index date (weighted HR: 1.12; 95% CI: 0.55 to 2.24; p=0.76).

Limitations of EP0223 included a small effective sample size (potentially due to lacosamide's off-label and late-line uses) and comparative study design.

Discussion

Findings from this study suggested that the treatment cohorts (lacosamide versus other AEDs) were comparable for overall developmental and neurodevelopmental safety profiles. Results from EP0223 suggested that there was no difference in the overall incidence rate of long-term prespecified neurodevelopmental outcomes between the lacosamide cohort and the other AEDs cohort, at 2 years post-index date.

Assessment comment:

The MAH has submitted a completed paediatric study for Lacosamide UCB/ Vimpat.

EP0223 was a retrospective matched cohort study of long-term neurodevelopmental outcomes in neonates treated with lacosamide versus other nonbenzodiazepine AEDs for neonatal seizures. The primary objective was to compare the incidence rate of overall prespecified neurodevelopmental outcomes in neonates treated with lacosamide versus other AEDs for neonatal seizures up to 2 years post index date.

EHR data from the PEDSnet database, incorporating patient data from Year 2009 to 2024, were used to evaluate the study objectives. The study population consisted of 2 mutually exclusive cohorts of neonates (≤28 days of age) within the lacosamide cohort and the other AEDs cohort. Neonates in the lacosamide cohort were treated with at least 1 dose of either iv or oral lacosamide and had at least 1 code for seizures identified from 01 Jan 2009 to 31 Dec 2022 in the PEDSnet database. There were no further restrictions on the neonates in this cohort. Each neonate from the lacosamide cohort was

potentially matched with neonates in the other AEDs cohort having at least 1 seizure code and being treated with other nonbenzodiazepine AEDs. Both cohorts were defined by their initial treatment with lacosamide versus matched other AEDs, and neonates remained in that cohort thereafter until the end of the Follow-up Period. Switching of the cohorts was not allowed at any time during the ≤28 days of age.

Of the 15,239,809 patients available from the PEDSnet database, 11,956 neonates (0.078%) had 1 or more AED administrations in the first 28 days of life. After applying the study selection criteria in EP0223, 5680 neonates (0.037%) aged ≤28 days were eligible for the study, consisting of 103 neonates in the lacosamide cohort and 5577 neonates in the other AEDs cohort.

Of the 103 neonates treated with at least 1 dose of lacosamide identified in the initial eligible cohort, 100 neonates were successfully matched to 567 neonates treated with other AEDs using propensity score matching. The sample size of the lacosamide cohort is very small, most probably related to the fact that neonatal seizures are not part of the indication.

In EP0223, many neonates had developmental and neurodevelopmental delay outcomes (overall or of any kind) during the Follow-up Period, with a total of 14 outcomes in the lacosamide cohort (N=26) at an incidence rate of 2.2 outcomes per 1000 patient days (95% CI: 1.2 to 3.7) and 77 outcomes in the other AEDs cohort (N=138) at an incidence rate of 2.0 outcomes per 1000 patient days (95% CI: 1.6 to 2.5). Cox regression analysis showed no statistically significant difference in the association between lacosamide and other AEDs cohorts with the risk of developmental or neurodevelopmental delay in children up to 2 years after the index date (weighted HR: 1.12; 95% CI: 0.55 to 2.24; p=0.76).

Baseline demographic and disease characteristics were similar between the lacosamide and other AED cohorts. The incidence rate of developmental and neurodevelopmental delay outcomes was high, probably related to the underlying disease, but was similar between the lacosamide and other AEDs cohort. It is acknowledged in agreement with the MAH that this study does not raise any concerns. However, it should be noted that due to the extremely limited sample size of the lacosamide cohort, it is not possible to draw conclusions with any appreciable degree of certainty.

No changes to the approved EU Summary of Product Information for VIMPAT are proposed following the results of study EP0151.

8.3. Postmarketing data

Methods – analysis of data submitted

The aim of the current evaluation was to review postmarketing data in neonates exposed to LCM in the frame of completion of Study SP0968. Based on marketing experience, an estimated 4,274,158 patient-years of exposure to lacosamide has been calculated during the reporting period from 01 Sep 2008 to 31 Aug 2025.

The UCB Global Safety database was cumulatively searched until 31 Aug 2025 for all postmarketing cases (excluding UCB-sponsored interventional CSRs) compatible with the use of lacosamide (any dose and formulation) in neonates.

Results

A total of 250 neonate cases reported the use of lacosamide and of these:

- One hundred seven cases reported exposure to lacosamide only via the transplacental/in utero/breastfeeding route. The review of these 107 cases did not identify any new significant safety information.

- Three cases had exposure to lacosamide after 27 days of life (outside the neonatal period) and were thus not considered for evaluation.

- The remaining 140 cases were considered for detailed evaluation. Overall, the review of these 140 cases did not reveal concerns specific to lacosamide use in neonates.

A review of the literature for the cumulative period from 29 Aug 2008 to 29 Feb 2020 (performed from PubMed and EMBASE) in the postmarketing report submitted to the US did not identify any relevant publication pertaining to the use of lacosamide in neonates. A similar literature search during the gap period from 01 Mar 2020 to 31 Aug 2025 (performed from Medline and EMBASE) identified a total of 182 articles; of these, 178 articles were further reviewed for use in neonates, and 8 articles were considered relevant for discussion based on positive efficacy/benefits and potential AEs reported with lacosamide use (monotherapy as well as adjunctive therapy).

Discussion

The cumulative review of the postmarketing lacosamide data indicated that the safety profile in neonates is consistent with the safety profile of lacosamide in older children as established in the CCDS. No new significant safety information was identified from the use of lacosamide therapy in neonates.

Assessment comment:

The MAH conducted a review of postmarketing data for neonates exposed to lacosamide in the frame of completion of Study SP096. This review involved a cumulative search of the UCB Global Safety database up to 31 August 2025, which identified 140 cases of postmarketing exposure (excluding UCB-sponsored interventional clinical study reports) that were considered for detailed evaluation. Additionally, a literature review was performed.

The analysis of these postmarketing data and literature review revealed evidence of off-label use of lacosamide in treating neonatal seizures, suggesting that information from Study SP0968 could be relevant to healthcare professionals. However, the inherent characteristics of these postmarketing data, including differences in the causes, treatment, and comorbidities of neonatal seizures compared to seizures in older children, preclude any definitive interpretations regarding efficacy or safety.

The conclusion that "the safety profile in neonates is consistent with the safety profile of lacosamide in older children" is not supported. This statement would require not only qualitative consistency but also quantitative consistency in terms of adverse event (AE) frequencies. Given the limitations and variability in the postmarketing data, such a conclusion cannot be reliably drawn, and therefore, it is not agreed upon.

9. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

- Part II Module SI updated to reflect the most recent data in line with the DLP of 31 Aug 2025

- Part II SIII updated to reflect the status of studies SP0968 and EP0151 as completed. Study SP0968 moved under indications no longer pursued in Table PartII-2 and Table Part II-3 was updated accordingly to reflect the change

- Part II SIII and Part II SV updated to reflect the current clinical (including pooled data) and postmarketing exposure data

- Part II SIII, Part II SIV, and Part II SVII, Part III, Part V, Part VI, Part VII Annex 2, and Annex 3 updated to reflect the status of study EP0012 as completed

Summary of safety concerns

Important identified risks	Cardiac adverse events that may be potentially associated with PR interval prolongation or sodium channel modulation
Important potential risks	None
Missing information	Pregnant or lactating women ~~Impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population~~

Additional pharmacovigilance activities

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				
Not applicable				
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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy Ongoing	To collect data on pregnancy	Missing information on use of lacosamide (LCM) in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs).
Participation in and sponsorship of North American Antiepileptic Drug Pregnancy Registry Ongoing	To collect data on pregnancy	Missing information on use of LCM in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in PSURs.
~~EP0012~~ ~~Open-label, multicenter extension study to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy (IGE).~~ ~~Ongoing~~	~~To document the long-term safety, tolerability, and efficacy of LCM in study participants 4 years and older with IGE~~	~~Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population.~~	~~Final study report submission~~	~~Aug 2023~~

LCM=lacosamide; ~~IGE=idiopathic generalized epilepsy;~~ PSUR=periodic safety update report

Assessment comment:

The RMP was updated to reflect the status of completed studies and the current clinical and postmarketing exposure data. No updates on the summary of safety concerns and risk minimization measures are proposed by the MAH. This is agreed.

Study EP0012 was completed and submitted previously (2023) in accordance with Article 46 of Regulation (EC) No1901/2006. It was assessed in procedure EMEA/H/C/000863/P46/047 and its removal from the PhV plan is concurred.

However, regarding the missing information of "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population", the only additional pharmacovigilance activity planned to characterize it (study EP0012) has been eliminated from the RMP, and no other required specific pharmacovigilance activity or additional risk minimization measure is included for this safety concern, beyond routine pharmacovigilance activities of adverse reaction reporting and signal detection. Two other additional pharmacovigilance activities (registries) are in place to characterize the missing information on "use of lacosamide (LCM) in pregnant or lactating women". Following this, "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population" was removed from the SoSC.

9.1. Overall conclusion on the RMP

The changes to the RMP very 18.1 are acceptable.

10. Changes to the Product Information

As a result of this variation, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated:

The following sections of the EU SmPC will be impacted by this update:

- Section 4.2 (Posology and method of administration): Text will be added within the paediatric population subsection to align with the EMA's guidance stating that due to the small number of neonates (0-28 days) with repeated ENS, the safety and efficacy of lacosamide (15mg/kg/day) in this patient population have not been fully established and no recommendation on posology can be made.
- Section 4.8 (Undesirable effects): Text will be added within the paediatric population subsection stating that the safety profile of lacosamide in neonates was consistent with the safety profile observed in the older paediatric population.
- Section 5.1 (Pharmacodynamic properties): SP0968 efficacy results will be summarized in a new subsection "Acute treatment of newborns with repeated electroencephalographic neonatal seizures."
- Section 5.2 (Pharmacokinetic properties): Details related to the steady state exposure and plasma clearance in neonates treated with 15mg/kg lacosamide per day will be added.

The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL is being revised.

Furthermore, the MAH took the opportunity to implement corrections in some local languages in both Vimpat and Lacosamide UCB Product Information.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

Assessment comment:

According to EMA/551202/2010 Rev 1, even if there is no indication in one or more subsets of the paediatric population, any available information should be presented in 4.2 with appropriate cross-references to sections 4.8, 5.1 and 5.2 if applicable.

11. Request for supplementary information

11.1. Major objections

None

11.2. Other concerns

Clinical aspects

Question 1

Based on the developed population PK model, the MAH has proposed a statement on the PK in neonates in Section 5.2 of the SmPC. However, a misspecification of bioavailability has been identified in the developed model. Information on the estimated clearance in neonates should therefore not be included in the SmPC. To substantiate the remaining information, it is suggested to include further information on the dosing regimens compared and clearly state that the exposure in newborns appeared to be higher than the exposure in adults (please see suggestions in the SmPC).

Question 2

The conclusion that "the safety profile in neonates is consistent with the safety profile of lacosamide in the older paediatric population" is not supported. This statement would require not only qualitative consistency but also quantitative consistency in terms of adverse event (AE) frequencies. Given the limitations and variability in the postmarketing data, such a conclusion, as also proposed in section 4.8 of the SmPC, cannot be reliably drawn, and therefore, it is not agreed upon.

Question 3

According to EMA/551202/2010 Rev 1, when considered relevant to healthcare professionals, information relating to an indication not authorised in any population could be summarised in the SmPC. The off-label use of lacosamide in neonates as described in the postmarketing data (section 8.3) supports that data from study SP0968 might be relevant to healthcare professionals. However:

Since most neonatal seizures do not comply with the term epilepsy because they are symptomatic seizures and the current indication of Lacosamide UCB/Vimpat is restricted to seizures for patients with epilepsy, neonatal seizures are to be considered outside of the current indication at any age range. Following this, the appropriate wording is thus not the one described in section 2.2 but in section 2.5 "If results of study(ies) in the paediatric population in an indication not authorised in any population (i.e. neither in children nor in adults)" of EMA/551202/2010 Rev 1. A rewording of the proposed change in section 4.2 is therefore recommended for the statement to comply with section 2.5.

The addition of text in 4.8 is not agreed since no conclusions on safety and adverse effects can be drawn. Also, according to EMA/551202/2010 Rev 1 (answer to question 3.1): "in case safety data have been collected in a paediatric development for an indication neither approved in children nor in adults, it may be more appropriate to summarise those safety data together with the results of the paediatric clinical

study(ies) in section 5.1".

a) The proposed text in 5.1 should be shortened, b) the proposed inclusion by the MAH of disease severity subgroup data in the table in Section 5.1 is not agreed, c) detailed numbers of patients in the treatment and active comparator arm should be presented for clarity, d) statements regarding similarity of effect cannot be made, e) it should briefly describe safety data.

Please refer to the SmPC Attachment which includes more detailed comments on proposed changes to the Product Information.

RMP aspects

Question 4

Regarding the missing information of "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population", the only additional pharmacovigilance activity planned to characterize it (study EP0012) has been eliminated from the RMP, and no other required specific pharmacovigilance activity or additional risk minimization measure is included for this safety concern, beyond routine pharmacovigilance activities of adverse reaction reporting and signal detection. Two other additional pharmacovigilance activities (registries) are in place to characterize the missing information on "use of lacosamide (LCM) in pregnant or lactating women". We suggest that justification of maintaining "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population" as missing information should be provided, for if it could be further characterized by the additional pharmacovigilance activities already in place (the registries mentioned before). If not, as no routine pharmacovigilance activities are in place beyond adverse reaction reporting and signal detection, we suggest eliminating it from the RMP, while continue monitoring the risk as missing information in PSUR procedures.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Question 1

Based on the developed population PK model, the MAH has proposed a statement on the PK in neonates in Section 5.2 of the SmPC. However, a misspecification of bioavailability has been identified in the developed model. Information on the estimated clearance in neonates should therefore not be included in the SmPC. To substantiate the remaining information, it is suggested to include further information on the dosing regimens compared and clearly state that the exposure in newborns appeared to be higher than the exposure in adults (please see suggestions in the SmPC).

Summary of the MAH's response

As part of the evaluation of the SP0968 pharmacokinetic results, serum concentration data were included in a population pharmacokinetic analysis. The results were presented in report CL0447-part V. The final model included the data of various adult and pediatric studies. The data were best described by a 1-compartment model with first order absorption (in case of oral data). Clearance was scaled to body weight using an allometric relation, and to post-menstrual age by a sigmoidal relation. Clearance was slightly lower in Chinese and Japanese participants and was increased when lacosamide was co-administered with CYP450 inducers. Volume of distribution was allometrically related to body weight.

This model was subsequently used to derive the distribution of the steady state concentration (i.e., AUC over 12 h divided by 12 h) in the population as a function of age and weight (only graphs for age shown). In Figures 4 – 6, the pink area represents the 90% range in adults (5.11 – 14.07µg/mL) receiving a dose of 400mg daily (200mg bid) without inducer AED coadministration. The blue area represents the 90% range for the various ages of pediatric participants. In neonates, the 90% range and the median extends above the adult reference range. However, except for IV monotherapy (Figure 6), the range still partially overlaps with the adult range. Furthermore, when comparing with data in participants aged 4 – 8 years, the results obtained in neonates do not deviate from results obtained in individual older paediatric participants taking approved doses.

For the reasons stated above and in order to reduce the use of acronyms, the MAH agrees to implement EMA's recommended wording, and requests the inclusion of minor but important clarifications:

"In a study in newborns treated with lacosamide administered ~~IV~~ **intravenously** as 5 mg/kg ~~tid~~ **three times a day**, the average steady state exposure appeared to be higher **but the range partly overlapped with** ~~than~~ the exposure in adults receiving lacosamide administered orally as 200 mg ~~bid~~ **twice a day**."

This clarification about the partial overlapping is intended to inform physicians that, although the average steady state of the unique neonatal dose of 5 mg/kg TID was higher than the average steady state noted in adults on 200 mg bid, the range of steady state exposures in neonates still partly overlapped with the range in adults.

The SmPC has been updated accordingly.

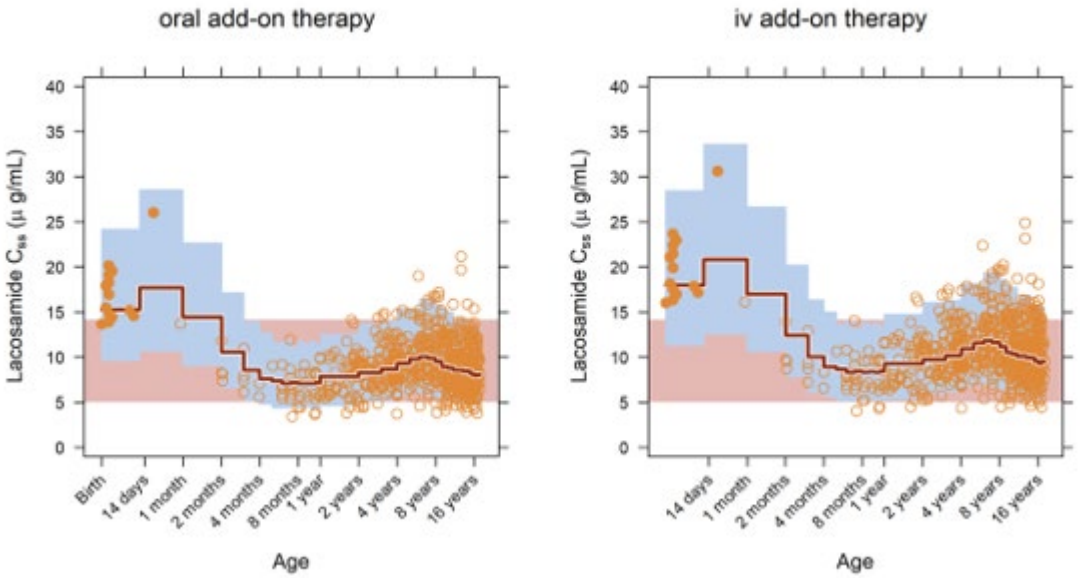


Figure 4

Add-on therapy (all study participants, with and without inducer AED coadministration): predicted LCM Css for the recommended oral and iv dosing schedule for children, using the final LCM population PK model (run119) by age

Recommended dosing schedule: a 7.5 mg/kg bid oral dose or a 5 mg/kg tid iv dose for weight <6 kg, a 6 mg/kg bid dose for 6 kg≤weight<30 kg, a 4 mg/kg bid dose for 30 kg≤weight<50 kg, and a 200 mg bid dose for weight ≥50 kg. Age on logarithmic scale. Red line and blue area: median and 90% of simulated LCM Css values for subjects <18 years sampled from the Nhanes database for oral dosing (left column) and iv dosing (right column). Orange circles: individual predicted LCM Css values, solid markers: neonates. Pink horizontal bar: 90% of simulated LCM Css values for adult subjects ≥18 years sampled from the Nhanes database for oral dosing of 200mg bid without inducer AED coadministration.

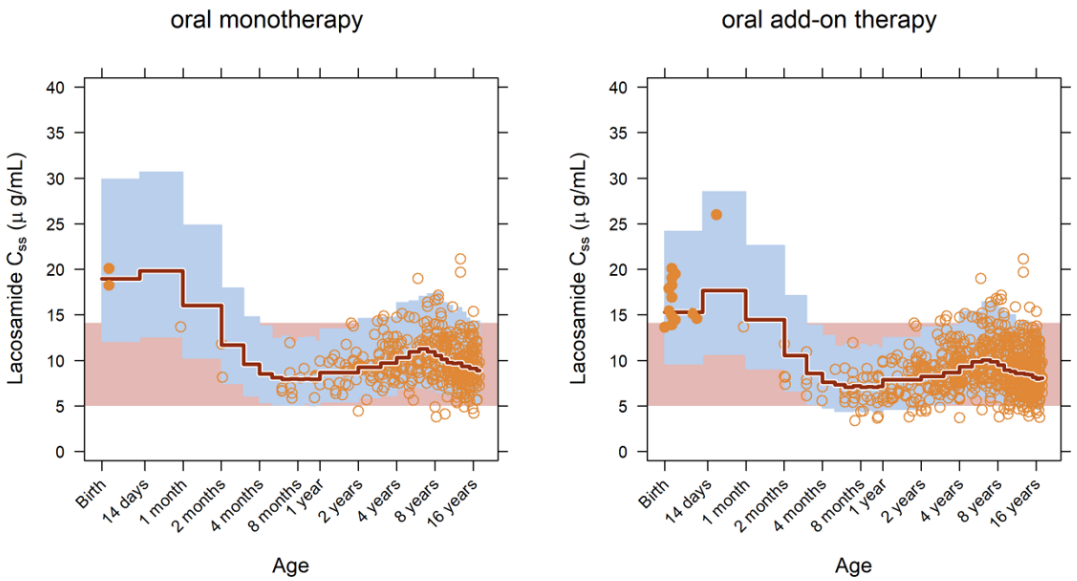


Figure 5

Predicted LCM Css after oral administration, for a monotherapy setting (without inducer AED coadministration, run119, left), and for add-on therapy (all study participants, with and without inducer AED coadministration, run119, right) for the recommended dosing schedule vs. age (top row) and vs. weight (bottom row)
Recommended dosing schedule: a 7.5 mg/kg bid dose for weight <6 kg, a 6 mg/kg bid dose for 6 kg≤weight<30 kg, a 4 mg/kg bid dose for 30 kg≤weight<50 kg, and a 200 mg bid dose for weight ≥50 kg. Weight and age on logarithmic scale. Red line and blue area: median and 90% of simulated LCM Css values for subjects <18 years sampled from the Nhanes database. Orange circles: individual predicted LCM Css values, solid markers: neonates. Pink horizontal bar: 90% of simulated LCM Css values for adult subjects ≥18 years sampled from the Nhanes database for oral dosing of 200mg bid without inducer AED coadministration. Vertical lines (bottom) correspond to weight-based dosing changes.

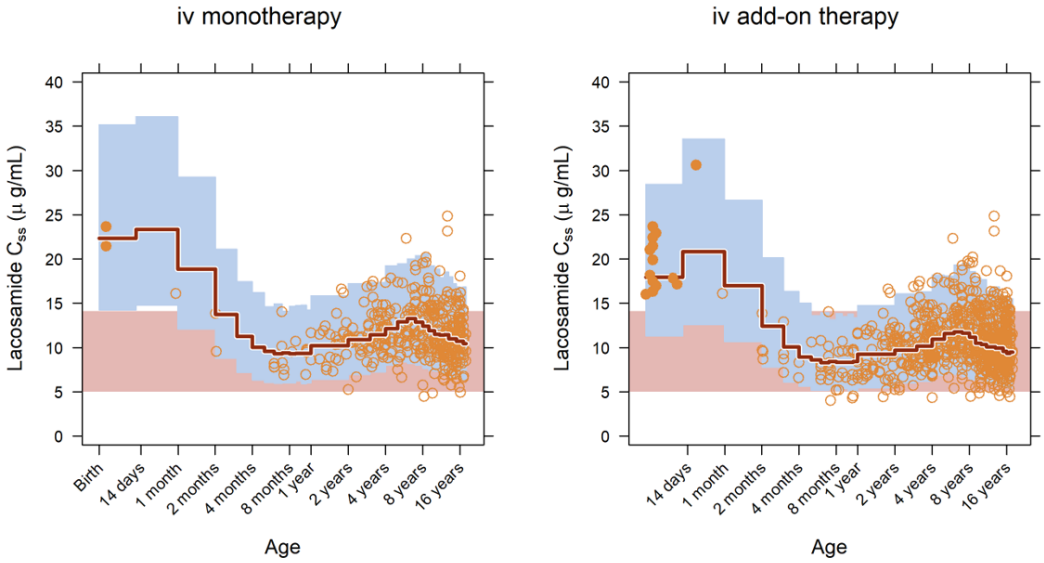


Figure 6

Predicted LCM Css after iv administration, for a monotherapy setting (without inducer AED coadministration, run119, left), and for add-on therapy (all study participants, with and without inducer AED coadministration, run119, right) for the recommended dosing schedule vs. age (top row) and vs. weight (bottom row)
Recommended dosing schedule: a 5 mg/kg tid iv dose for weight <6 kg, a 6 mg/kg bid dose for 6 kg≤weight<30 kg, a 4 mg/kg bid dose for 30 kg≤weight<50 kg, and a 200 mg bid dose for weight ≥50 kg. Weight and age on logarithmic scale. Red line and blue area: median and 90% of simulated LCM Css values for subjects <18 years sampled from the Nhanes database. Orange circles: individual predicted LCM Css values, solid markers: neonates. Pink horizontal bar: 90% of simulated LCM Css values for adult subjects ≥18 years sampled from the Nhanes database for oral dosing of 200mg bid without inducer AED coadministration. Vertical lines (bottom) correspond to weight-based dosing changes.

Assessment of the MAH's response

The MAH has agreed to update the SmPC in accordance with the proposal, but with some further amendments: acronyms are spelled out to avoid misunderstandings and the MAH would also like to state that, although the average steady state of the unique neonatal dose of 5 mg/kg TID was higher than the average steady state noted in adults on 200 mg bid, the range of steady state exposures in neonates still partly overlapped with the range in adults.

A simulation-based comparison of exposure, following IV administration in neonates and oral administration in older paediatric subjects and adults, may be affected by the identified misspecification

of oral bioavailability in the model. However, individual predictions are less likely to be affected, and it is agreed that the observed concentrations and individually predicted exposures in neonates do partly overlap with the corresponding ranges in adults. The proposed amendments are therefore agreed.

Issue considered 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

Question 2

The conclusion that "the safety profile in neonates is consistent with the safety profile of lacosamide in the older paediatric population" is not supported. This statement would require not only qualitative consistency but also quantitative consistency in terms of adverse event (AE) frequencies. Given the limitations and variability in the postmarketing data, such a conclusion, as also proposed in section 4.8 of the SmPC, cannot be reliably drawn, and therefore, it is not agreed upon.

Summary of the MAH's response

The MAH acknowledges this comment and agrees to remove the previously proposed text in the SmPC.

Assessment of the MAH's response

Issue considered 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

Question 3

According to EMA/551202/2010 Rev 1, when considered relevant to healthcare professionals, information relating to an indication not authorised in any population could be summarised in the SmPC. The off-label use of lacosamide in neonates as described in the postmarketing data (section 8.3) supports that data from study SP0968 might be relevant to healthcare professionals. However:

Since most neonatal seizures do not comply with the term epilepsy because they are symptomatic seizures and the current indication of Lacosamide UCB/Vimpat is restricted to seizures for patients with epilepsy, neonatal seizures are to be considered outside of the current indication at any age range. Following this, the appropriate wording is thus not the one described in section 2.2 but in section 2.5 "If results of study(ies) in the paediatric population in an indication not authorised in any population (i.e. neither in children nor in adults)" of EMA/551202/2010 Rev 1. A rewording of the proposed change in section 4.2 is therefore recommended for the statement to comply with section 2.5.

The addition of text in 4.8 is not agreed since no conclusions on safety and adverse effects can be drawn. Also, according to EMA/551202/2010 Rev 1 (answer to question 3.1): "in case safety data have been collected in a paediatric development for an indication neither approved in children nor in adults, it may be more appropriate to summarise those safety data together with the results of the paediatric clinical study(ies) in section 5.1".

a) The proposed text in 5.1 should be shortened, b) the proposed inclusion by the MAH of disease severity subgroup data in the table in Section 5.1 is not agreed, c) detailed numbers of patients in the treatment and active comparator arm should be presented for clarity, d) statements regarding similarity of effect cannot be made, e) it should briefly describe safety data.

Please refer to the SmPC Attachment which includes more detailed comments on proposed changes to the Product Information.

Summary of the MAH's response

The MAH acknowledges these comments and has updated the SmPC accordingly.

Please note that in section 4.2, the MAH would like to request the inclusion of a small clarification by referencing the small sample size of the study, for completeness:

"Outside its authorised indication**s**, lacosamide has been studied in newborns aged 0-28 days with repeated electroencephalographic neonatal seizures**;** ~~,~~ however**,** the results **from the small number of participants in the** ~~of~~ study did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 5.1 and 5.2".

Assessment of the MAH's response

The inclusion of the clarification is deemed acceptable, noting that this type of clarification has been previously accepted for other products (e.g. Vyxeos liposomal). Issue considered 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 4

Regarding the missing information of "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population", the only additional pharmacovigilance activity planned to characterize it (study EP0012) has been eliminated from the RMP, and no other required specific pharmacovigilance activity or additional risk minimization measure is included for this safety concern, beyond routine pharmacovigilance activities of adverse reaction reporting and signal detection. Two other additional pharmacovigilance activities (registries) are in place to characterize the missing information on "use of lacosamide (LCM) in pregnant or lactating women". We suggest that justification of maintaining "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population" as missing information should be provided, for if it could be further characterized by the additional pharmacovigilance activities already in place (the registries mentioned before). If not, as no routine pharmacovigilance activities are in place beyond adverse reaction reporting and signal detection, we suggest eliminating it from the RMP, while continue monitoring the risk as missing information in PSUR procedures.

Summary of the MAH's response

The MAH acknowledges this comment and has updated the RMP (version 18.1) by eliminating "Impact on long-term growth, long-term neurodevelopment, and puberty in paediatric population" as missing information as suggested. The MAH will continue monitoring the risk as missing information in PSUR procedures.

Assessment of the MAH's response

Issue considered 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