15 October 2020
EMA/23665/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimpat	lacosamide
Lacosamide UCB	lacosamide

Procedure No. EMEA/H/C/xxxx/WS/1782

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CBZ	carbamazepine
CBZ-CR	carbamazepine controlled release
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
ET	early termination
FAS	Full Analysis Set
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HR	hazard ratio
IGE	idiopathic generalized epilepsy
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IRT	interactive response technology
iv	intravenous(ly)
KM	Kaplan-Meier
LCM	lacosamide
LTG	lamotrigine
NCI CTC	National Cancer Institute Common Terminology Criteria
PB	phenobarbital
PDILI	potential drug-induced liver injury

PGTCS	primary generalized tonic-clonic seizures
PHT	Phenytoin
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
POS	partial-onset seizures
PPS	Per Protocol Set
PT	Preferred Term
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SS	Safety Set
SWAP	Scientific Advice Working Party
TEAE	treatment-emergent adverse events
TEMA	treatment-emergent markedly abnormal
VPC	visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 13 January 2020 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy for Lacosamide UCB and Vimpat. Consequently sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 15.0 has also been submitted.
Furthermore, the PI is brought in line with the latest QRD template version 10.1. The MAH also takes the opportunity to align the PI of Lacosamide UCB with the PI of Vimpat.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0059/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000402-PIP03-17 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The WSA received Scientific Advice from the CHMP on 20 September 2012 (EMA/H/SA/1570/4/2012/II). The Scientific Advice pertained to clinical aspects and was given in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Filip Josephson

Daniela Melchiorri

Timetable	Actual dates
Submission date	13 January 2020
Start of procedure:	1 February 2020
CHMP Rapporteur Assessment Report	27 March 2020
CHMP Co-Rapporteur Assessment Report	16 April 2020
PRAC Rapporteur Assessment Report	27 March 2020
PRAC members comments	6 April 2020
Updated PRAC Rapporteur Assessment Report	8 April 2020
PRAC Outcome	17 April 2020
CHMP members comments	23 April 2002
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 April 2020
Request for supplementary information (RSI)	30 April 2020
MAH's responses to RSI	19 May 2020
CHMP Rapporteur Assessment Report	23 June 2020
PRAC Rapporteur Assessment Report	23 June 2020
PRAC Outcome	9 July 2020
CHMP members comments	14 July 2020
Updated CHMP Rapporteur Assessment Report	16 July 2020
Request for supplementary information (RSI)	23 July 2020
MAH's responses to RSI	12 August 2020
CHMP Rapporteur Assessment Report	15 September 2020
PRAC Rapporteur Assessment Report	22 September 2020
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	1 October 2020
CHMP members comments	6 October 2020
Updated CHMP Rapporteur Assessment Report	8 October 2020
Opinion	15 October 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed therapeutic indication

In this procedure, the MAH applies for the following extension of the indication (New text – bold underlined):

Lacosamide UCB is indicated as monotherapy ~~and adjunctive therapy i~~n the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.

Lacosamide UCB is indicated as adjunctive therapy

- **in the treatment of partial-onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.**
- **in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy.**

Epidemiology

Epilepsy is one of the most common neurological diseases. Worldwide, about 65 million people are estimated to have epilepsy (Thurman et al, 2011). The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic seizures (23%), absence seizures (6%), and myoclonic seizures (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

The incidence and prevalence of idiopathic generalised epilepsy (IGE) was recently described by Gesche J. et al., 2019. The study included all patients (≥17 years) with IGE inhabiting Funen (496 000 inhabitants), Denmark. The average IGE incidence (2008–2017) was 2.9/100 000 inhabitants/year. The point prevalence of identifiable IGE patients was 1.0/1000 adults (juvenile myoclonic epilepsy 0.4/1000; absence epilepsy 0.3/1000, epilepsy with generalized tonic–clonic seizures alone 0.3/1000); 92.1% of the patients were diagnosed before 25 years of age.

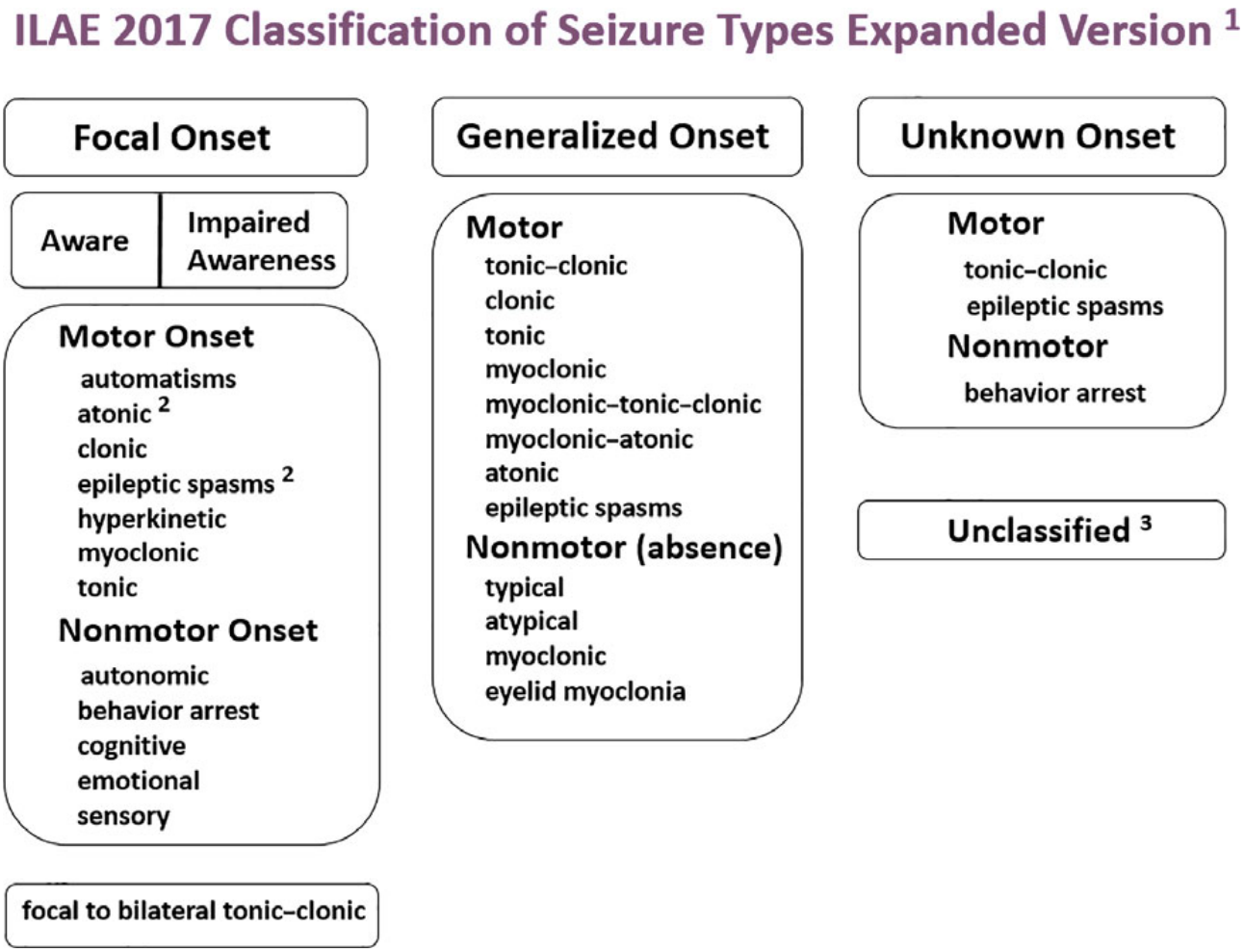
Aetiology and pathogenesis

The term idiopathic generalized epilepsy (IGE) is meant to reflect the genetic aetiology without explicitly saying so. A genetic aetiology may be suggested by clinical research in populations with the same syndrome such as Childhood Absence Epilepsy or Juvenile Myoclonic Epilepsy. Evidence for a genetic basis comes from studies such as Lennox's twin studies in the 1950s and familial aggregation studies. The onset of IGE almost always occurs during childhood or adolescence, although there are exceptions; some patients develop these kinds of epilepsies after the second decade of life or, rarely, even later.

Clinical presentation, diagnosis

According to the new ILAE classification of epilepsy from 2017, a common subgroup of the Idiopathic Generalized Epilepsies (IGEs) is well-recognized within the Generalized Epilepsies (I.E. Scheffer et al., 2017). The IGEs encompass four well-established epilepsy syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic–Clonic Seizures Alone (formerly known as Generalized Tonic–Clonic Seizures on Awakening but modified in recognition that seizures can occur at any time of day).

Generalized seizures are those in which the first clinical changes indicate initial involvement of both brain hemispheres. Consciousness may be impaired, and this impairment may be the initial manifestation. Generalized seizure types according to the new ILAE classification are presented bellow (Fisher et al., 2017).



It is noted that the MAH used the old ILAE classification from 1989. According to the authors of new ILAE classification, the classification of generalized-onset seizures is similar to that of the 1981 classification, with addition of a few new types (Fischer et al., 2017).

Typically, the onset of childhood absence epilepsy is between 4 to 8 years of age, with peak onset at ages 6 to 7 years. Approximately 40% develop generalized tonic clonic seizures as they reach adolescence.

The onset of juvenile absence epilepsy is between 10 to 17 years of age, with peak onset between 10 and 12 years. These patients may have occasional tonic-clonic seizures.

The onset of juvenile myoclonic epilepsy varies from 8 to 26 years and peaks at 12 to 14 years. Juvenile myoclonic epilepsy is characterized by myoclonic seizures that appear with tonic-clonic seizures in most patients, and absence seizures in about one-third of patients.

The onset of epilepsy with grand mal seizures on awakening is usually in the second decade of life. This syndrome typically presents as a generalized tonic clonic seizure within 2 hours after awakening but may include myoclonic and/or absence seizures.

Idiopathic generalized epilepsy with PGTCS only is considered a syndrome in the ILAE diagnostic scheme (Engel, 2006) and incorporates "epilepsy with PGTCS on awakening" (ILAE, 1989; Janz, 2000). The terminology "IGE with PGTCS only" implies that it includes only those patients with PGTCS alone (i.e. without absences and/or jerks) and that these may occur at any time. Overall, PGTCS are reported to occur on awakening (17% to 53% of patients), diffusely while awake (23% to 36%) or during sleep (27% to 44%), or randomly (13% to 26%) (Wolf, 2002). It is undetermined what proportion of these patients also has other generalized seizures (jerks or absences).

Age at onset varies from 6 to 47 years with a peak at 16 to 17 years; 80% have their first PGTCS in the second decade of life. Men (55%) slightly predominate over women, probably because of differences in alcohol exposure and sleep habits. Exact prevalence of "IGE with PGTCS only" is unknown. If strict criteria apply (PGTCS only), this may be very small (0.9% of IGE), but others give a prevalence of 13% to 15% among IGE (Roger et al, 1994; Oller-Daurella and Oller, 1994).

Management

In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation. The newer AEDs differ from older agents in several important ways, including mechanism of action, spectrum of activity, and PK characteristics (Herman and Pedley, 1998).

Between 15% and 40% of patients with generalized epilepsy remain refractory to therapy or do not tolerate the currently available AEDs (valproate, ethosuximide, phenytoin [PHT], lamotrigine [LTG], carbamazepine [CBZ], topiramate, and levetiracetam) (Bartolomei et al, 1997; Verrotti et al, 2007); some of these AEDs can induce serious, life threatening AEs (such as aplastic anemia, rash, hepatic failure). Generalized tonic-clonic seizures may respond to drugs that aggravate typical absences and/or myoclonic jerks (Genton, 2000; Verrotti et al, 2007). Two IGE seizure types, typical absences and myoclonic jerks, are particularly prone to aggravation by certain AEDs (CBZ, vigabatrin, tiagabine, PHT, phenobarbital [PB], and LTG). The pharmacodynamic aggravation is usually associated with a clear increase of interictal (and ictal) EEG changes.

Of patients with IGE experiencing PGTCS, clinical experience has shown that up to 30% of patients who are treated with currently available AEDs have insufficient seizure control or unacceptable drug tolerability according to the MAH. Thus, there is a significant unmet medical need for new treatment options in this patient population.

2.1.2. About the product

Lacosamide (LCM) is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. Electrophysiological studies have shown that LCM enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces neuronal hyperexcitability and the potential for seizures.

Lacosamide (LCM) has been approved in the EU (oral tablets, oral solution, and solution for intravenous [iv] infusion) as monotherapy or adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients 4 years of age and older.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

In this procedure, the MAH applied for the new indication for use of LCM as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients with idiopathic generalized epilepsy (IGE) from 4 years of age.

The demonstration of efficacy and safety for the indication extension is based on a pivotal study SP0982 (a Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group study designed to assess the efficacy and safety of LCM as adjunctive therapy for uncontrolled PGTCS in study participants 4 years of age and older with IGE) and is in general in agreement with the CHMP Scientific Advice issued on 20 Sep 2012 (EMEA/H/SA/1570/4/2012/II). The pivotal study SP0982 supporting the PGTCS indication is listed as study 20 in the Lacosamide UCB Pharma S.A. PIP EMEA-000402-PIP03-17-M03.

The development of LCM for use in PGTCS was initiated with SP0961 (a Phase 2, open-label pilot study to assess the safety of oral LCM as adjunctive therapy for uncontrolled PGTCS in study participants with IGE) and SP0962 (a Phase 2, open-label extension study to assess the safety and seizure frequency associated with long-term oral LCM for uncontrolled PGTCS in study participants with IGE).

2.1.4. General comments on compliance with GCP

The studies were conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved, as stated by the MAH.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application.

2.2.1. Ecotoxicity/environmental risk assessment

In line with the ERA guideline EMEA/CHMP/SWP/4447/00, an updated ERA report, evaluating the potential environmental impact of the new indication of Vimpat in the treatment of primary generalized tonic-clonic seizures (PGTCS), was provided.

Summary of fate and effect analysis

Risk Characterisation			
PEC (mg/L)	**PNEC (mg/L)**	**PEC/PNEC ratio**	**Criterion for Tier B Evaluation**
$PEC_{SURFACEWATER}$ = 0.0057	$PNEC_{WATER} \geq 1$	≤ 0.0057	PEC/PNEC Ratio ≥ 1
$PEC_{SURFACEWATER}$ = 0.0057	$PNEC_{MICROORGANISM} \geq 100$	$\leq 5.7 * 10^{-5}$	PEC/PNEC Ratio > 0.1
$PEC_{GROUNDWATER}$ = 0.0014	$PNEC_{GROUNDWATER}$ = 3.2	$4.4 * 10^{-4}$	PEC/PNEC Ratio > 1
Physico-chemical Properties, Fate Analysis			
Kow (mean) = 1.78			$K_{OW} > 10^3$
Koc (mean) = 9 L/kg			$K_{OC} > 10^4$ L/kg
Water sediment study: 14% for sediment on Day 14 (a waiver was granted by rapporteur, EMEA/CHMP/628025/2008)[6] (see Annex)			> 10%

The risk characterisation shows that the revised PEC/PNEC ratios based on worst case market penetration values are lower than the ERA guideline Tier B trigger values.

It can therefore be concluded that use of lacosamide, in the current and proposed new indications, is unlikely to present a risk to the terrestrial and aquatic environments.

2.2.2. Discussion on non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Lacosamide.

2.2.3. Conclusion on the non-clinical aspects

The CHMP agrees that the no new non-clinical data are needed to support the proposed extension of indication.

From the updated ERA data, the use of lacosamide, in the current and proposed new indications, is unlikely to present a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were

carried out in accordance with the ethical standards of Directive 2001/20/EC.>

- Tabular overview of clinical studies:

Overview of ongoing and completed studies of LCM in the treatment of PGTCS with IGE in adults and children 4 years of age and older

Study number	Study description	Study Status
SP0961	A Phase 2, open-label pilot study to assess the safety of oral LCM as adjunctive therapy for uncontrolled PGTCS in study participants with IGE	Completed
SP0962	A Phase 2 OLE study to assess the safety and seizure frequency associated with long-term oral LCM for uncontrolled PGTCS in study participants with IGE	Completed
SP0982	A Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of oral LCM as adjunctive therapy for uncontrolled PGTCS in study participants ≥4 years of age with IGE	Completed
EP0012	A Phase 3, multicenter, OLE study designed to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled PGTCS in study participants with IGE, previously enrolled in SP0982	Ongoing

2.3.2. Pharmacokinetics

In order to complement the pharmacokinetic (PK) profile of lacosamide characterized for the current indication, the MAH investigated the PK of oral LCM for primary generalized tonic-clonic seizures (PGTCS) in study participants with idiopathic generalized epilepsy (IGE) in the pivotal study SP0982.

Lacosamide is rapidly and completely absorbed after oral administration with negligible first-pass effect and has minimal protein binding properties. The high oral bioavailability of approximately 100% is not affected by food. Peak plasma concentrations occur between 0.5 and 4hours post dose. The average maximal plasma concentration following 200mg twice daily (bid) is about 10µg/mL (approximately 40µM). The PK is linear with respect to dose and exhibits low intra-and inter-study participant variability. Approximately 40% of the dose is excreted by the kidney as unchanged compound. The major metabolic pathway of LCM is demethylation. The plasma half-life of the unchanged drug is approximately 13hours and is not altered by different doses or by multiple dosing.

Several population PK analyses has been conducted during the development program. PK data from the pivotal study SP0982 were used to update the existing popPK model. The modeling data set comprised data from the prior population PK modeling project CL0447-Part I, including the adult data from CL0261, as well as new data from SP0982. Model parameters were re-estimated, and the covariate analysis was revisited, see table below. Visual predictive checks were performed for the final reduced population PK covariate model to investigate if model simulations correspond to observed medians and ranges for the entire population, stratified by adults and children (figure below).

Table 3–4: Part II: NONMEM parameter estimates for the final reduced population PK covariate model with an extra PGTCS effect

Parameter	Estimate (95% CI)	IIV (%)	Shrinkage[a] (%)
CL/F (L/hr)	1.93 (1.88, 1.98)	25.7	15.3
Vc/F (L)	52.3 (48.5, 56.1)	48.8	53.4
Ka (1/hr)	1.60 (1.35, 1.85)	64.5	73.8
Allometric scaling CL/F	0.519 (0.485, 0.553)	-	-
Allometric scaling Vc/F	1.00 Fixed	-	-
Change in CL/F (%) with China	-13.7% (-16.9%, -10.4%)	-	-
Change in CL/F (%) with Japan	-11.3% (-15.6%, -6.8%)	-	-
Change in CL/F (%) with inducer AEDs	28.3% (24.2%, 32.5%)	-	-
Change in CL/F (%) with PGTCS	-3.6% (-10.3%, 3.5%)	-	-
Proportional RUV (fraction)	0.207 (0.193, 0.221)	-	11.5
Additive RUV (µg/mL)	0.341 (0.203, 0.479)	-	11.5

AED=antiepileptic drug; CI=confidence interval; CL=clearance; CL/F=apparent clearance; F=bioavailability; IIV=inter-individual variability; Ka=absorption constant; PGTCS=primary generalized tonic-clonic seizures; PK=pharmacokinetic; RUV=residual unexplained variability; Vc=central volume; Vc/F=apparent central volume
[a] Shrinkage calculated using the standard deviation.

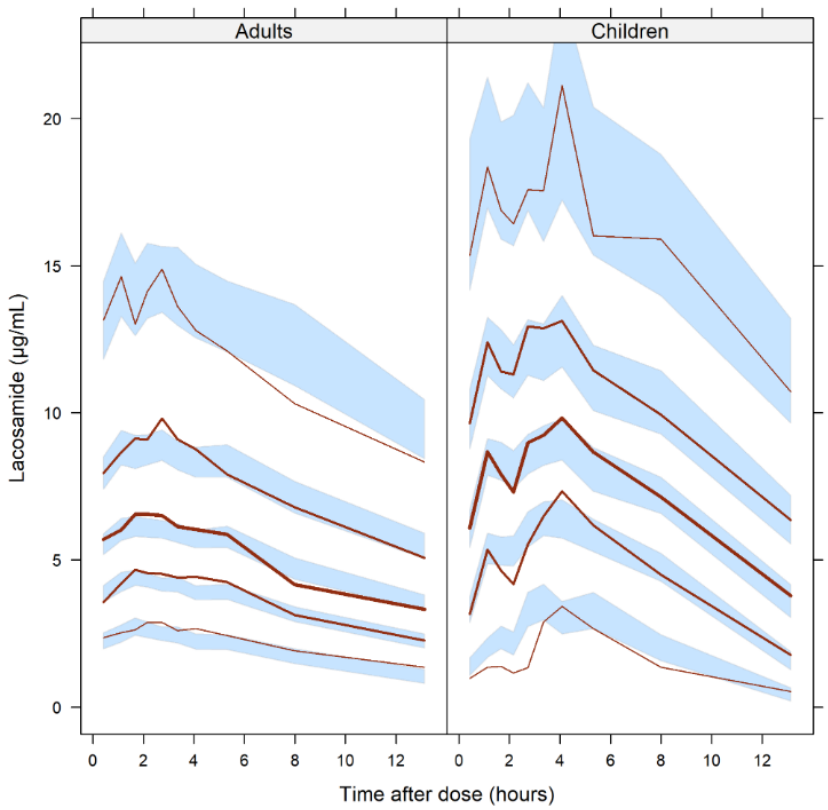
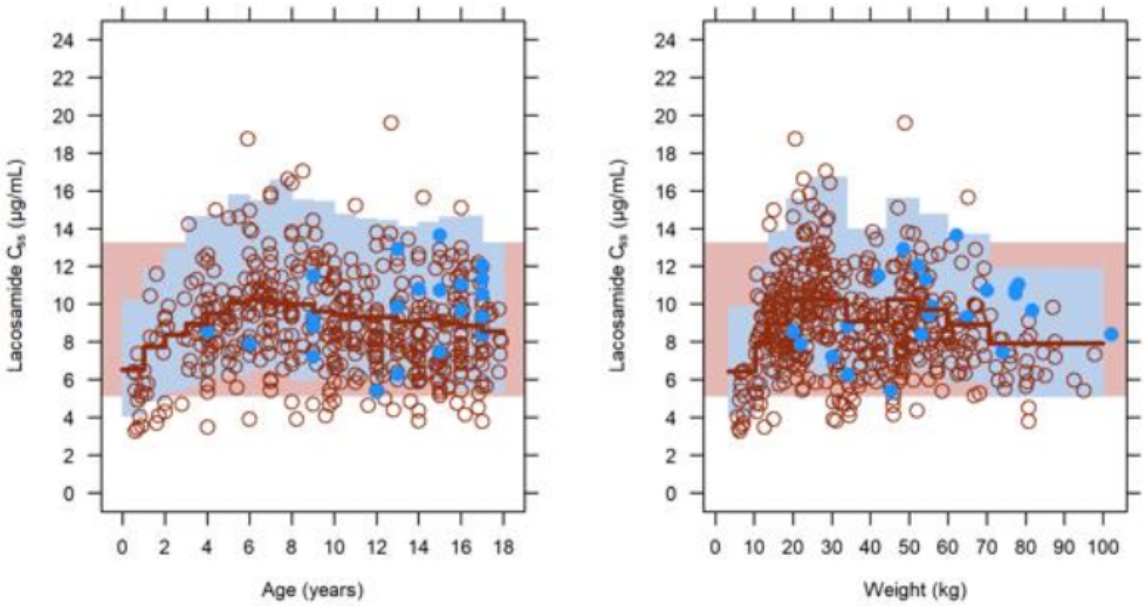


Figure 19 VPCs for the final reduced population PK covariate model split by adults and children
Red lines are the 5th, 25th, 50th (median), 75th and 95th percentiles of the observed data and the light blue areas contain 95% of the simulated quantiles using run023.

Comparison of exposures in pediatric study-participants (POS and PGTCS) and adults (POS)

In the figure below (3-3), the pink shaded area depicts 90% of the simulated adult Css values for an oral dose of LCM of 200mg bid in all panels, and the red line and blue shaded area depict the median and 90% of the simulated pediatric Css values for POS pediatric study participants (left) and PGTCS pediatric study participants (right). The red circles indicate the predicted Css values for the pediatric individuals in all studies with POS (left) and with PGTCS (right). The figure shows that the dosing regimen resulted in model-predicted pediatric Css values in the adult range for most body weights and ages for both POS and PGTCS study participants.

Figure 3-3: Exposure overlap between pediatric study participants with POS and PGTCS



AED=antiepileptic drug; bid=twice daily; C_{ss}= steady state LCM concentrations over 24 hours; LCM=Lacosamide: PK=pharmacokinetic; PGTCS=primary generalized tonic-clonic seizures; POS=partial-onset seizures;
Note: Simulations were performed using the final reduced population PK model (excluding country and inducer AED coadministration effects).
Note: Dosing was based on weight as follows: <30kg: 6mg/kg/bid; ≥30kg to <50kg: 4mg/kg bid; ≥50kg: 200mg bid.
Note: Red line and blue area: median and 90% of simulated LCM C_{ss} values for study participants <18 years sampled from the Nhanes database. Markers: individual predicted LCM C_{ss} values for POS pediatric study participants (red open markers) and PGTCS pediatric study participants (blue solid markers).

2.3.3. Pharmacodynamics

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. Electrophysiological studies have shown that LCM enhances the slow inactivation of sodium channels by attenuating the proportion of available channels in a time- and voltage-dependent manner. This leads to a reduction of sodium channel long-term availability which increases activation thresholds and reduces neuronal hyperexcitability and the potential for seizures.

2.3.4. PK/PD modelling

The MAH provided PK/PD modelling but concluded that the model relating time to second PGTCS and LCM exposure could not be reliably constructed, and simulation of alternative dosing strategies, including a monotherapy scenario, could not be performed.

2.3.5. Discussion on clinical pharmacology

The pharmacokinetics between POS and PGTCS patients are not expected to be different. The MAH has updated the previous popPK model and the results show that exposure (Css) in POS patients is similar to POS patients and also that exposure is in the adult range of exposure. The model includes estimated exponent for clearance which is not considered ideal. Goodness of fit plots of LCM concentrations vs. population predictions (PRED) and individual predictions (IPRED) showed absence of systematic model misspecification. Visual predictive checks (VPC) performed for the final reduced population PK covariate model (run023) indicate model adequacy. Just shrinkage values for Vc/F and Ka, 53.5% and 73.8% respectively are considerate too high values making the EBEs for Vc/F and Ka unsuitable for diagnostic purposes. For these parameters, also IIV values estimated using SIR for the final reduced population PK covariate model (run023) were quite high. The provided VPC, included VPCs stratified on age, look adequate.

The PK/PD modelling attempt was not deemed satisfactory by the MAH and was not used.
This is agreed by the CHMP.

2.3.6. Conclusions on clinical pharmacology

The CHMP agrees with the conclusion that PK is similar in POS and PGTCS patients, including paediatric patients from 4 years old and older.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were performed for this extension of indication.

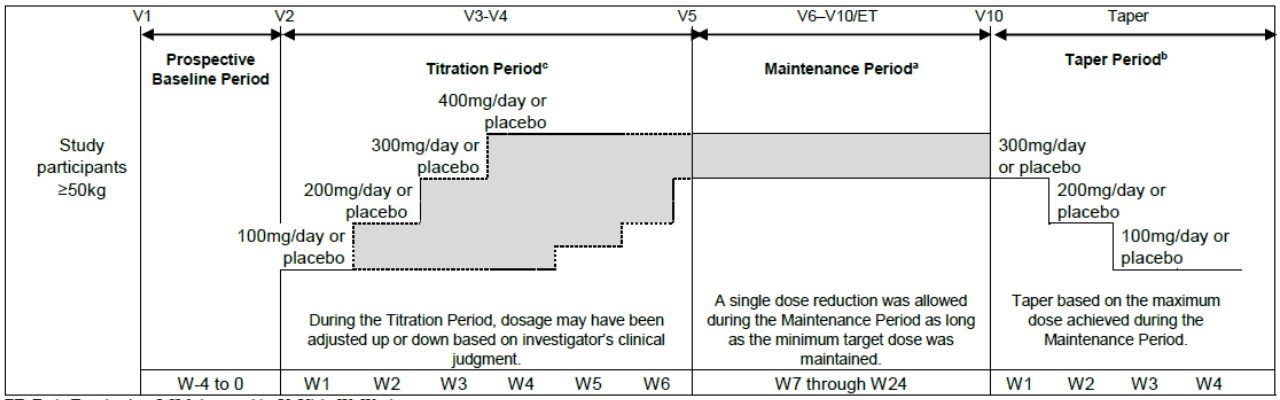
2.4.2. Main study(ies)

Title of Study

SP0982: a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM versus placebo as adjunctive therapy for PGTCS in study participants ≥4 years of age with IGE taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs.

Methods

Figure 1. SP0982 overall study design schematic diagram



ET=Early Termination; LCM=lacosamide; V=Visit; W=Week

SP0982 was a time-to-event study which enrolled study participants in order to observe 125 events (an event was defined as the occurrence of the second PGTCS during the 24-week Treatment Period). Although this was a time-to-event study, study participants were required to complete a minimum of 6 weeks of treatment; study participants could have completed 24 weeks of treatment with no event, completed at 6 weeks if an event had occurred during titration, or completed the study between 6 and 24 weeks after an event had occurred. Enrolment was discontinued once the 125th event occurred.

Study participants were randomized to receive LCM or placebo in a 1:1 fashion and stratified by Baseline PGTCS frequency (≤2 per 28 days vs >2 per 28 days for the 16-week Combined Baseline Period prior to randomization) and by age at informed consent (≥4 to <12 years of age, ≥12 to <18 years of age, and ≥18 years of age).

Study participants

To be eligible to participate in this study, the study participant must have met all inclusion criteria. The key inclusion criteria are listed below:

- Male and female ≥4 years of age.

- confirmed diagnosis at least 24 weeks prior to Visit 1 and a disease onset prior to 30 years of age, consistent with IGE experiencing PGTCS (Type IIE) that were classifiable according to the ILAE Classification of Epileptic Seizures (ILAE, 1981).

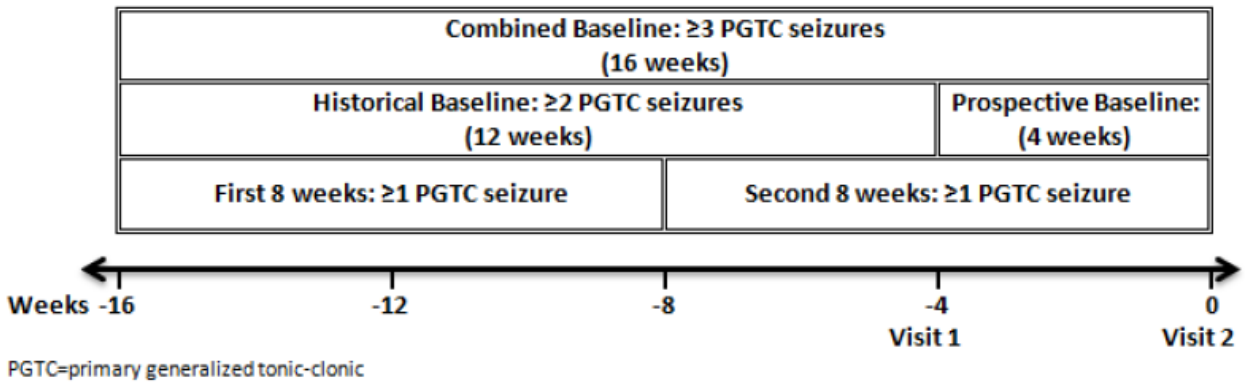
- ≥3 PGTCS during the 16-week Combined Baseline (12-week Historical Baseline plus 4-week Prospective Baseline) distributed as described below:

    - at least 3 PGTCS should have occurred during the 16-week Combined Baseline Period,

    - at least 2 PGTCS should have occurred during the 12-week Historical Baseline Period,

    - of the above seizures, at least 1 PGTCS should have occurred during the first 8 weeks and atleast 1 PGTCS should have occurred during the second 8 weeks of the 16-week Combined Baseline Period.

Figure 2. Combined Baseline Period seizure eligibility for SP0982



PGTC=primary generalized tonic-clonic

- If a brain magnetic resonance imaging (MRI)/computed tomography (CT) scan had been performed, there must have been no evidence of any progressive abnormality or any lesion likely to be associated with partial-onset seizures.

- Study participant had been maintained on a stable dose regimen of 1 to 2 non-benzodiazepine marketed AEDs with no benzodiazepine AEDs OR 1 benzodiazepine marketed AED with 1 to 2 non-benzodiazepine marketed AEDs for at least 28 days prior to Visit 1 with or without additional concurrent stable VNS.

- Vagus nerve stimulation (VNS) must have been in place for at least 6 months prior to Visit 1 with constant settings for at least 28 days prior to Visit 1 and during the Prospective Baseline and Treatment Period.

Key exclusion criteria were a history of partial-onset seizures or EEG findings indicative of partial onset seizures, symptomatic generalized epilepsy (eg, Lennox-Gastaut Syndrome typically presenting with seizures including tonic seizures), some other related syndrome like Doose's syndrome (typically presenting with myoclonic-atonic seizures), or evidence of both focal and generalized epilepsy, history of convulsive status epilepticus 1 year prior to screening, and current or previous diagnosis of pseudo seizures, conversion disorders, or other nonepileptic ictal events which could have been confused with seizures.

Treatments

Investigational medicinal product was provided as LCM oral solution (syrup) (LCM 10mg/mL), LCM tablets (LCM 50mg), and matching Placebos. Study medication was administered orally bid (at approximately 12-hour intervals in the morning and in the evening).

For study participants <30kg, the target dose for the Maintenance Period was 12mg/kg/day (oral solution). For study participants ≥30kg to <50kg, the target dose for the Maintenance Period was 8mg/kg/day (oral solution). For study participants ≥50kg, the target dose for the Maintenance Period was 400mg/day (tablets). The tablet formulation was used for adult study participants (≥18 years of age) and pediatric study participants weighing ≥50kg, while the oral solution formulation was used for pediatric study participants weighing <50kg.

Objectives

The primary study objective was to demonstrate the efficacy of oral LCM vs Placebo as adjunctive therapy for uncontrolled PGTCS in study participants with IGE currently taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs.

The secondary study objective was to assess the safety and tolerability of LCM in study participants with IGE with uncontrolled PGTCS.

Outcomes/endpoints

The primary efficacy variable was the time to the second PGTCS during the 24-week Treatment Period.

The key secondary efficacy variable was seizure freedom for PGTCS during the 24-week Treatment Period, estimated using Kaplan-Meier (KM) analysis.

The other secondary efficacy variables were time to the first PGTCS during the Treatment Period, days with seizures per 28 days, seizure-free status for PGTCS, seizure-free for all generalized seizure types, responder status for reduction in PGTCS frequency, responder status for reduction in days with absences seizures and with myoclonic seizures, PGTCS worsening and health quality related outcomes.

Sample size

Observing 125 events (study participants who had a second PGTCS during the 24-week Treatment Period) would provide 90% power to observe an HR of 0.56 at the 2-sided 5% level, assuming a dropout rate of <15%. The observed HR was based on a 25.4% survival rate for Placebo and 48.2% for lamotrigine from a previous study comparing lamotrigine and Placebo (French et al, 2007).

Randomisation

Interactive response technology (IRT) was used for assigning eligible study participants to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB. The randomization schedule was produced by the IRT vendor who was otherwise not involved in this study.

Blinding (masking)

UCB Global Clinical Trial Supply created a packaging list using a validated application. The packaging list was provided to the IRT vendor and to the packaging vendor who prepared the kits accordingly.

The treatment randomization schedule was generated by UCB (or designee) in a manner that ensured that the study team remained blinded, in accordance with current standard operating procedures (SOPs). The randomization schedule was maintained in a secure location until the study was unblinded for the final statistical analysis.

Statistical methods

The Full Analysis Set (FAS) served as the primary analysis population for assessing efficacy endpoints. The FAS was a subset of the Safety Set (SS) that consisted of all study participants with at least 1 seizure diary assessment during the Treatment Period. The primary efficacy variable was evaluated using a Cox proportional hazards regression model with an effect for treatment, using the following pooled strata:

- Stratum 1: Baseline PGTCS frequency ≤2 per 28 days and paediatric

- Stratum 2: Baseline PGTCS frequency ≤2 per 28 days and adult

- Stratum 3: Baseline PGTCS frequency >2 per 28 days and All (paediatric and adult)

The stratified hazard ratio (HR) was calculated using the placebo arm as the reference group. The 95% confidence interval (CI) for the HR was also reported.

Additionally, a KM plot for time to event, as well as the KM estimate for the median time to event and 95% CI, were provided. If the median time was not estimable, then the 25th percentile and 95% CI were provided. The number of events was reported by treatment group for the Titration Period, first 12 Weeks, and Treatment Period, as well as the percentage of study participants who were censored in the analysis.

The summary of time to event during the 166-day Treatment Period was presented by all subgroups for the FAS. A KM plot for time to second PGTCS by some subgroups was also provided.

Sensitivity analyses on the primary efficacy endpoint were conducted in order to assess the effect of dropouts, important protocol deviations, and operational bias on the primary endpoint.

Provided that the primary efficacy endpoint was statistically significant, a gatekeeping strategy was used to test the key secondary efficacy variable. For the gatekeeping strategy, if the primary endpoint was statistically significant at the 5% level, then the key secondary efficacy endpoint was also assessed at the 5% significance level. If the primary endpoint failed to reach statistical significance, then the key secondary efficacy endpoint was exploratory only. No other efficacy endpoints would be assessed for significance. Analyses of all other secondary efficacy variables were descriptive in manner and exploratory only.

Analysis of the key secondary efficacy variable was evaluated using an extended Mantel-Haenszel testing procedure which took into account that the study participants were initially stratified for the study participants' Baseline PGTCS frequency and development (adult vs paediatric). The number and percentage of study participants who experienced a PGTCS or censoring and the KM seizure-free rate from PGTCS (and 2-sided 95% CI) by Day 166 were presented by treatment group for each stratum and overall. The stratified seizure-freedom rate from PGTCS (and 2-sided 95% CI) at Day 166 for each treatment group and the difference between treatment groups were presented.

Time to first PGTCS was calculated using the same algorithm as the calculation for the time to second PGTCS endpoint. A KM plot for time to first PGTCS was provided.

Results

Participant flow

Overall, a total of 350 study participants were screened at 115 sites. A total of 110 study participants (31.4%) were considered screen failures; the most common primary reason for screen failure was ineligibility (92 study participants [26.3%]). A total of 37 study participants (10.6%) were Baseline failures due to PGTCS frequency during the Combined Baseline Period.

Overall, a total of 242 study participants started the study, including 121 study participants each in the LCM and Placebo groups, and 213 study participants (88.0%) completed the study (103 study participants [85.1%] in the LCM group and 110 study participants [90.9%] in the Placebo group). A total of 29 study participants (12.0%) discontinued the study, including 18 study participants (14.9%) in the LCM group and 11 study participants (9.1%) in the Placebo group.

Table 3. Study participant disposition and discontinuation reasons (SS)

Disposition	Placebo N=121 n (%)	LCM N=121 n (%)	All study participants N=242 n (%)
Started study	121 (100)	121 (100)	242 (100)
Completed study	110 (90.9)	103 (85.1)	213 (88.0)
Discontinued study	11 (9.1)	18 (14.9)	29 (12.0)
Primary reason for discontinuation			
Adverse event	4 (3.3)	10 (8.3)	14 (5.8)
Lack of efficacy	0	1 (0.8)	1 (0.4)
Protocol violation	1 (0.8)	2 (1.7)	3 (1.2)
Lost to follow up	2 (1.7)	3 (2.5)	5 (2.1)
Consent withdrawn	3 (2.5)	1 (0.8)	4 (1.7)
Other	1 (0.8)	1 (0.8)	2 (0.8)
Started Titration Period	121 (100)	121 (100)	242 (100)
Completed Titration Period	114 (94.2)	107 (88.4)	221 (91.3)
Completed Titration, not continuing into Maintenance	44 (36.4)	25 (20.7)	69 (28.5)
Completed Titration, continuing into Maintenance	70 (57.9)	82 (67.8)	152 (62.8)
Discontinued during Titration Period	7 (5.8)	14 (11.6)	21 (8.7)
Primary reason for discontinuation			
Adverse event	2 (1.7)	8 (6.6)	10 (4.1)
Lack of efficacy	0	1 (0.8)	1 (0.4)
Protocol violation	1 (0.8)	2 (1.7)	3 (1.2)
Lost to follow up	1 (0.8)	3 (2.5)	4 (1.7)
Consent withdrawn	2 (1.7)	0	2 (0.8)
Other	1 (0.8)	0	1 (0.4)
Started Maintenance Period	70 (57.9)	82 (67.8)	152 (62.8)
Completed Maintenance Period	66 (54.5)	78 (64.5)	144 (59.5)
Discontinued during Maintenance Period	4 (3.3)	4 (3.3)	8 (3.3)
Primary reason for discontinuation			
Adverse event	2 (1.7)	2 (1.7)	4 (1.7)
Lack of efficacy	0	0	0
Protocol violation	0	0	0

Disposition	Placebo N=121 n (%)	LCM N=121 n (%)	All study participants N=242 n (%)
Lost to follow up	1 (0.8)	0	1 (0.4)
Consent withdrawn	1 (0.8)	1 (0.8)	2 (0.8)
Other	0	1 (0.8)	1 (0.4)

The discontinuation rate was relatively low in the study.

Most patients discontinued the study due to adverse events with most patients in the LCM group (see Table above). More patients in the LCM group discontinued during titration period (11.6%) compared to the placebo group (5.8%).

Recruitment

The first study participant enrolled on 23 Apr 2015 and the last study participant completed their final on-site clinic visit on 27 May 2019, which was followed by a telephone call to the investigator on 05 Jun 2019. The study was conducted at 115 sites. The database was locked on 20 Jun 2019.

Patients were recruited in North America: US, Puerto Rico; Latin America: Brazil, Mexico; Western/Central Europe: Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain; Eastern Europe: Bulgaria, Romania, Russia, Turkey and Asia/Pacific/Other: Australia, China, Israel, Japan, South Korea, Taiwan.

Conduct of the study

The original SP0982 study protocol was dated 05 Aug 2011. Subsequently, 5 protocol amendments were implemented.

Baseline data

The baseline data are summarized in the table below:

Table 4: Study participant demographics (SS)

Variable Statistic	Placebo N=121	LCM N=121	All study participants N=242
Age (years)			
Mean (SD)	27.64 (12.45)	27.82 (13.13)	27.73 (12.77)
Min, max	5.0, 65.0	4.0, 66.0	4.0, 66.0
Age group (years), n (%) [a]			
≥4 to <12	9 (7.4)	8 (6.6)	17 (7.0)
≥12 to <18	16 (13.2)	16 (13.2)	32 (13.2)
≥18 to <65	95 (78.5)	96 (79.3)	191 (78.9)
≥65 to <85	1 (0.8)	1 (0.8)	2 (0.8)
≥85	0	0	0
Age group (years), n (%) [b]			
≤18	27 (22.3)	28 (23.1)	55 (22.7)
≥19 to <65	93 (76.9)	92 (76.0)	185 (76.4)
≥65	1 (0.8)	1 (0.8)	2 (0.8)
Age stratification category based on IRT (years), n (%)			
≥4 to <12	9 (7.4)	8 (6.6)	17 (7.0)
≥12 to <18	16 (13.2)	16 (13.2)	32 (13.2)
≥18	96 (79.3)	97 (80.2)	193 (79.8)
Gender, n (%)			
Male	45 (37.2)	55 (45.5)	100 (41.3)
Female	76 (62.8)	66 (54.5)	142 (58.7)

Weight (kg)			
Mean (SD)	72.75 (22.19)	70.42 (21.84)	71.59 (22.00)
Min, max	21.1, 154.3	15.8, 127.4	15.8, 154.3
Height (cm)			
Mean (SD)	164.75 (12.32)	165.89 (15.04)	165.32 (13.73)
Min, max	121.0, 191.5	105.0, 203.2	105.0, 203.2
BMI (kg/m^2)			
Mean (SD)	26.47 (6.78)	25.09 (6.21)	25.78 (6.52)
Min, max	14.2, 47.2	14.3, 50.0	14.2, 50.0
Race, n (%)			
American Indian/ Alaskan	1 (0.8)	1 (0.8)	2 (0.8)
Asian	25 (20.7)	18 (14.9)	43 (17.8)
Black	2 (1.7)	2 (1.7)	4 (1.7)
Native Hawaiian or other	0	0	0
White	89 (73.6)	97 (80.2)	186 (76.9)
Other/mixed	4 (3.3)	3 (2.5)	7 (2.9)
Ethnicity, n (%)			
Hispanic or Latino	18 (14.9)	10 (8.3)	28 (11.6)
Not Hispanic or Latino	103 (85.1)	111 (91.7)	214 (88.4)

The median number of PGTCS per 28 days during the Combined Baseline Period was 1.25 (range: 0.3 to 12.3) for the LCM group and 1.24 (range: 0.7 to 19.4) for the placebo group, with the majority of study participants in both groups having ≤2 PGTCS per 28 days during the Combined Baseline Period based on the IRT (95 study participants [78.5%] in each group).

A total of 241 out of 242 study participants had a history of generalized seizures, most commonly classified in both the LCM and placebo groups as tonic-clonic (120 study participants [99.2%] and 121 study participants [100%], respectively).

The ILAE seizure classification history is presented in the following table:

Table 5. ILAE seizure classification history (SS)

Seizure type	Placebo N=121 n (%)	LCM N=121 n (%)	All study participants N=242 n (%)
Partial onset seizures	0	1 (0.8)	1 (0.4)
Simple partial (IA)	0	1 (0.8)	1 (0.4)
Complex partial (IB)	0	0	0
Partial evolving to secondarily generalized (IC)	0	0	0
Generalized seizures	121 (100)	121 (100)	242 (100)
Absence (IIA1)	41 (33.9)	49 (40.5)	90 (37.2)
Atypical absence (IIA2)	2 (1.7)	2 (1.7)	4 (1.7)
Myoclonic (IIB)	48 (39.7)	46 (38.0)	94 (38.8)
Clonic (IIC)	2 (1.7)	3 (2.5)	5 (2.1)
Tonic (IID)	1 (0.8)	2 (1.7)	3 (1.2)
Tonic-clonic (IIE)	121 (100)	120 (99.2)	241 (99.6)
Atonic (IIF)	3 (2.5)	2 (1.7)	5 (2.1)
Unclassified epileptic seizures (III)	0	2 (1.7)	2 (0.8)

All pediatric study participants in the LCM and Placebo groups had a generalized seizure classification history of tonic-clonic seizures (24 study participants and 25 study participants, respectively). A greater proportion of pediatric study participants in the LCM group had a generalized seizure classification history of absence seizures compared with Placebo (58.3% [n=14] and 40.0% [n=10], respectively). The proportion of pediatric study participants with a generalized seizure classification history of myoclonic seizures was 20.8% (n=5) in the LCM group and 28.0% (n=7) in the Placebo group.

For adults, nearly all study participants had a generalized seizure classification history of tonic-clonic seizures (96 study participants [99.0%] in the LCM group and 96 study participants [100%] in the Placebo group). The proportion of adult study participants with absence seizures (35 study participants [36.1%] and 31 study participants [32.3%], respectively) and myoclonic seizures (41 study participants [42.3%] and 41 study participants [42.7%], respectively) was similar between the LCM and Placebo groups.

Table 6. Classification of epileptic syndrome (SS)

Variable	Placebo N=121 n (%)	LCM N=121 n (%)	All study participants N=242 n (%)
Generalized idiopathic	121 (100)	121 (100)	242 (100)
Benign neonatal familial convulsions	0	0	0
Benign neonatal convulsions	0	1 (0.8)	1 (0.4)
Benign myoclonic epilepsy in infancy	0	1 (0.8)	1 (0.4)
Childhood absence epilepsy	6 (5.0)	9 (7.4)	15 (6.2)
Juvenile absence epilepsy	15 (12.4)	13 (10.7)	28 (11.6)
Juvenile myoclonic epilepsy	42 (34.7)	34 (28.1)	76 (31.4)
Epilepsy with grand mal seizures on awakening	19 (15.7)	15 (12.4)	34 (14.0)
Other generalized idiopathic epilepsies not defined above	54 (44.6)	55 (45.5)	109 (45.0)
Epilepsies with seizures precipitated by specific modes of activation	6 (5.0)	6 (5.0)	12 (5.0)
Generalized symptomatic	1 (0.8)	0	1 (0.4)
Non-specific etiology	0	0	0
Early myoclonic encephalopathy	0	0	0
Early infantile epileptic encephalopathy with suppression burst	0	0	0
Other symptomatic generalized epilepsies not defined above	1 (0.8)	0	1 (0.4)
Specific syndromes	0	0	0
Situation-related seizures	4 (3.3)	1 (0.8)	5 (2.1)

LCM=lacosamide; SS=Safety Set
Note: Percentages were based on the number of study participants in the SS.
Data source: Table 4.2.1

The predominant epileptic syndrome classifications for study participants in the LCM and Placebo group were similar overall and by development (pediatric and adult).

The most common concomitant AEDs and benzodiazepines at study entry in the LCM and Placebo groups were valproate (59 study participants [48.8%] and 67 study participants [55.4%], respectively), levetiracetam (55 study participants [45.5%] and 48 study participants [39.7%], respectively), lamotrigine (36 study participants [29.8%] and 37 study participants [30.6%], respectively), and topiramate (16 study participants [13.2%] and 15 study participants [12.4%], respectively).

For the paediatric study participants, the most common concomitant AEDs and benzodiazepines in the LCM and Placebo groups at study entry were valproate (50.0% [n=12] and 56.0% [n=14], respectively), levetiracetam (54.2% [n=13] and 36.0% [n=9], respectively), lamotrigine (33.3% [n=8] and 32.0% [n=8], respectively), topiramate (12.5% [n=3] and 12.0% [n=3], respectively), and oxcarbazepine (12.5% [n=3] and 4.0% [n=1], respectively). A total of 5 paediatric study participants were taking benzodiazepines (3 study participants [12.5%] in the LCM group and 2 study participants [8.0%] in the Placebo group), which included clonazepam (1 study participant [4.2%] in the LCM group and 2 study participants [8.0%] in the Placebo group) and clobazam (2 study participants [8.3%] in the LCM group and no study participants in the Placebo group).

For adult study participants, the most common concomitant AEDs and benzodiazepines in the LCM and Placebo groups at study entry were valproate (48.5% [n=47] and 55.2% [n=53], respectively), levetiracetam (43.3% [n=42] and 40.6% [n=39], respectively), lamotrigine (28.9% [n=28] and 30.2% [n=29], respectively), topiramate (13.4% [n=13] and 12.5% [n=12], respectively), and clonazepam (10.3% [n=10] and 10.4% [n=10], respectively).

Numbers analysed

The Full Analysis Set (FAS) served as the primary population for assessing primary, secondary, and other efficacy endpoints. A total of 240 study participants (99.2%) had at least 1 seizure diary assessment during the Treatment Period and were included in the FAS, including 119 study participants (98.3%) in the LCM group and all 121 study participants (100%) in the placebo group. One study participant in the LCM group was randomized after the 125th event and was excluded from the primary and secondary endpoint analyses, resulting in a total of 118 study participants in the LCM group.

The Per-Protocol Set (PPS), which excluded study participants who completed fewer than 6 weeks of treatment or study participants with important protocol deviations affecting the interpretation of the primary efficacy analysis, included 207 study participants (85.5%) overall, with 104 study participants (86.0%) in the LCM group and 103 study participants (85.1%) in the placebo group.

The Safety Set (SS) served as the primary population for assessing the number of days with absence seizures and number of days with myoclonic seizures per 28 days (observed results and percent changes from Prospective Baseline). A total of 242 study participants (100%) received at least 1 dose of study medication (LCM or placebo) and were included in the SS, including 121 study participants each in the LCM and placebo groups.

The proportions of study participants who completed the study were similar in the LCM and placebo treatment groups. A total of 213 study participants (88.0%) completed the study (103 study participants [85.1%] in the LCM group and 110 study participants [90.9%] in the placebo group). A total of 29 study participants (12.0%) discontinued the study, including 18 study participants (14.9%) in the LCM group and 11 study participants (9.1%) in the placebo group. The most common primary reason for discontinuation in the LCM and placebo groups was AE (10 study participants [8.3%] and 4 study participants [3.3%], respectively).

Outcomes and estimation

Primary efficacy variable

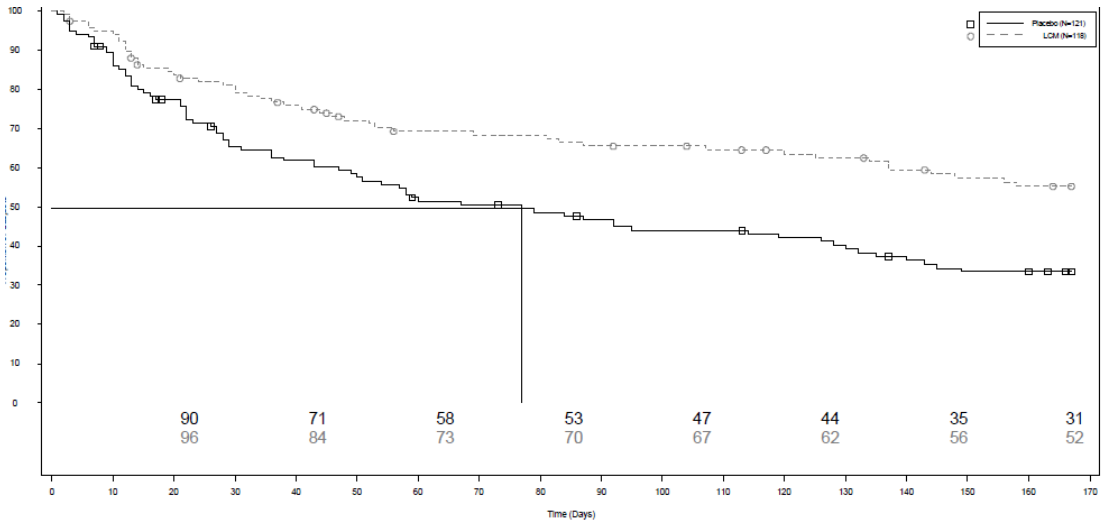
The primary efficacy variable was the time to the second PGTCS during the 24-week Treatment Period. The primary efficacy assessment was based on the Full Analysis Set (FAS).

Table 7. Analysis of time to second PGTCS (125 events) (FAS)

	Placebo N=121		LCM N=118	
	Cumulative number of events	KM survival estimate (%)	Cumulative number of events	KM survival estimate (%)
Treatment Period	76	33.37	49	55.27
KM analysis				
Time to event (days)				
Median	77.0		-	
95% CI	49.0, 128.0		144.0, -	
Study participants censored[a], n (%)	45 (37.2)		69 (58.5)	
Treatment comparison				
LCM – Placebo				
HR[b]	0.540			
95% CI of HR	0.377, 0.774			
p-value	<0.001			

[a] Study participants who completed the Treatment Period without having a second PGTCS during the Treatment Period were censored. If the study participant's Treatment Period participation was less than 166 days, they were censored on the date of the last dose of study medication. If the study participant's Treatment Period participation was greater than 24 weeks minus the visit window for Visit 10, they were censored as of Day 167 or the date after the 125th event.
[b] An HR <1 indicates time to second PGTCS was improved for LCM compared with placebo.

Figure 2–1: Kaplan-Meier estimates for time to second PGTCS (FAS)



The risk of developing a second PGTCS during the 24-week Treatment Period was statistically significantly lower in the LCM group compared with the placebo group; the survival estimates at the end of the Treatment Period were 55.27% in the LCM group and 33.37% in the placebo group (HR: 0.540 [95% CI: 0.377, 0.774]; p<0.001) (Table 9). Overall, the cumulative number of events (ie. second PGTCS) during the 24-week Treatment Period was 49 events in the LCM group and 76 events in the placebo group. The median time to second PGTCS was 77.0 days (95%CI: 49.0, 128.0) for the placebo group. For the LCM group, the median time to second PGTCS could not be estimated by KM methods because >50% of study participants did not experience a second PGTCS by Day 166.

Table 8. Subgroup analyses of time to second PGTCS during the Treatment Period (FAS)

Subgroup	Placebo (n=121)			LCM (n=119)			LCM - Placebo		
	N	Cumulative number of events	KM survival estimate (%)	N	Cumulative number of events	KM survival estimate (%)	HR [a]	95% CI of HR	p-value
Age from IRT									
≥4 to 12 years	9	5	44.44	8	2	75.00	**0.492**	0.089,	0.417
≥12 to 18 years	16	9	41.25	16	7	54.14	**0.740**	0.265,	0.564
≥18 years	96	62	31.25	94	40	53.60	**0.527**	0.354,	0.002
Development									
Paediatric	25	14	41.54	24	9	61.03	**0.650**	0.271,	0.335
Adult	96	62	31.25	94	40	53.60	**0.527**	0.354,	0.002
Race									
White	89	49	40.45	94	40	53.52	0.713	0.469,	0.113
Non-white	32	27	15.00	24	9	61.76	0.261	0.120,	<0.001
Gender									
Male	45	26	39.71	54	15	70.68	**0.397**	0.209,	0.005
Female	76	50	29.35	64	34	42.24	**0.685**	0.442,	0.090
Region									
North America	13	10	16.92	16	7	53.00	0.446	0.158,	0.128
Latin America	11	8	24.24	5	3	30.00	0.946	0.238,	0.937
Western/Central	36	16	48.30	41	21	46.22	1.298	0.671,	0.438
Eastern Europe	22	7	66.53	29	6	77.75	0.522	0.172,	0.251
Asia/Pacific/Other	39	35	10.26	27	12	52.32	0.263	0.134,	<0.001
Baseline PGTCS frequency									
≤2 per 28 days	95	56	37.45	93	34	60.31	0.501	0.327,	0.002
>2 per 28 days	26	20	17.72	25	15	37.59	0.653	0.334,	0.213
Number of concomitant AEDs at study entry									
0	0	0	-	1	0	100.00	-	-, -	-
1	44	22	44.77	34	12	63.22	0.570	0.279,	0.123
2	55	37	30.24	61	26	53.72	0.539	0.323,	0.018
≥3	22	17	19.39	22	11	44.43	0.440	0.201,	0.040

[a] An HR <1 indicates time to second PGTCS was improved for LCM compared with placebo. Wald's method was used to calculate the p-value and CIs.

The survival rates were numerically greater in the LCM group compared with the placebo group for all subgroups assessed. Of the 125 events analyzed in the primary efficacy analysis, 23 events (18.4%) were observed in pediatric study participants (including 9 events in the LCM group and 14 events in the placebo group).

All sensitivity analyses demonstrated consistent results, with the risk of developing a second PGTCS during the 24-week Treatment Period statistically significantly lower in the LCM group compared with the placebo group for all analyses.

Secondary efficacy variables

Seizure freedom for PGTCS at Day 166 of the Treatment Period

Table 9. Proportion of study participants with seizure freedom at Day 166 (FAS)

Parameter	Placebo N=121	LCM N=118
Overall		
Number of study participants	121	118
Number of study participants with a seizure, n (%)	97 (80.2)	79 (66.9)
Number of study participants censored, n (%) [a]	24 (19.8)	39 (33.1)
KM seizure free (%) (95% CI)	17.3 (10.3, 24.3)	31.0 (22.4, 39.6)
Stratum 1: Baseline PGTCS frequency ≤2 per 28 days and pediatric		
Number of study participants	21	21
Number of study participants with a seizure, n (%)	18 (85.7)	16 (76.2)
Number of study participants censored, n (%) [a]	3 (14.3)	5 (23.8)
KM seizure free (%) (95% CI)	14.3 (0.0, 29.3)	22.9 (4.4, 41.3)
Stratum 2: Baseline PGTCS frequency ≤2 per 28 days and adult		
Number of study participants	74	72
Number of study participants with a seizure, n (%)	56 (75.7)	46 (63.9)
Number of study participants censored, n (%) [a]	18 (24.3)	26 (36.1)
KM seizure free (%) (95% CI)	22.3 (12.5, 32.1)	34.2 (23.0, 45.5)
Stratum 3: Baseline PGTCS frequency >2 per 28 days		
Number of study participants	26	25
Number of study participants with a seizure, n (%)	23 (88.5)	17 (68.0)
Number of study participants censored, n (%) [a]	3 (11.5)	8 (32.0)
KM seizure free (%) (95% CI)	4.9 (0.0, 14.3)	30.0 (11.3, 48.7)
Stratified [b]		
KM seizure free (%) (95% CI)	17.2 (10.4, 24.0)	31.3 (22.8, 39.9)

Parameter	Placebo N=121	LCM N=118
LCM - Placebo		
KM seizure free (%) (95% CI)	14.1 (3.2, 25.1)	
Superiority of LCM versus placebo p-value [c]	0.011	

[a] Study participants censored prior to or at Day 166.
[b] Estimated by extended Mantel Haenszel methods.
[c] Based on a chi-square test on 1 degree of freedom.

The stratified KM estimate of the proportion of study participants who were seizure free at Day 166 was 31.3% (95% CI: 22.8%, 39.9%) in the LCM group and 17.2% (95% CI: 10.4%, 24.0%) in the placebo group. The difference in stratified seizure freedom rate at Day 166 between the LCM and placebo groups was 14.1% (95% CI: 3.2%, 25.1%); this difference was statistically significant (p=0.011).

Within the strata that evaluated Baseline PGTCS frequency ≤2 per 28 days (stratum 1 and stratum 2), the proportion of study participants who were seizure free was higher in stratum 2 (Baseline PGTCS frequency ≤2 per 28 days and adult) for both groups (34.2% and 22.3% for the LCM and placebo groups, respectively) compared with stratum 1 (Baseline PGTCS frequency ≤2 per 28 days and pediatric; 22.9% and 14.3% for the LCM and placebo groups, respectively). For stratum 3 (Baseline PGTCS frequency >2 per 28 days), the KM estimates of the proportion of study participants who were seizure free at Day 166 were 30.0% for the LCM group and 4.9% for the placebo group.

Time to first PGTCS during the 166-day Treatment Period

A summary of the analysis of time to first PGTCS is presented in the following table:

Table 10. Analysis of time to first PGTCS (FAS)

	Placebo N=121		LCM N=118	
	Cumulative number of events	KM survival estimate (%)	Cumulative number of events	KM survival estimate (%)
Treatment Period	97	17.27	79	30.97
KM analysis				
Time to event (days)				
Median	20.0		36.0	
95% CI	13.0, 34.0		25.0, 78.0	
Study participants censored [a], n (%)	24 (19.8)		39 (33.1)	
Treatment Comparison				
LCM – Placebo				
HR [b]	0.683			
95% CI of HR	0.507, 0.921			
p-value	0.012			

[a]Study participants who completed the Treatment Period without having a first PGTCS during the Treatment Period were censored. If the study participant's Treatment Period participation was less than 166 days, they were censored on the date of the last dose of study medication. If the study participant's Treatment Period participation was greater than 24 weeks minus the visit window for Visit 10, they were censored as of Day 167 or the date after the 125th event.

[b] An HR <1 indicates time to first PGTCS was improved for LCM compared with placebo.

The risk of developing a first PGTCS during the 24-week Treatment Period was lower in the LCM group compared with the placebo group; the survival estimates at the end of the Treatment Period were 30.97% in the LCM group and 17.27% in the placebo group (HR: 0.683 [95% CI: 0.507, 0.921]; p=0.012) (Table 12). Overall, the cumulative number of events (ie, first PGTCS) during the 24-week Treatment Period was 79 events in the LCM group and 97 events in the placebo group. The median time to first PGTCS was 36.0 days (95% CI: 25.0, 78.0) for the LCM group and 20.0 days (95% CI: 13.0, 34.0) for the placebo group.

Other efficacy variables

PGTCS frequency per 28 days

The median PGTCS frequency per 28 days at Combined Baseline was 1.25 (range: 0.3 to 12.3) in the LCM group and 1.24 (range: 0.7 to 19.4) in the placebo group. Greater median percent changes from Combined Baseline in PGTCS frequency per 28 days were observed in the LCM group compared with the placebo group during the Titration Period (-66.37% and -42.71%, respectively), first 12 weeks (-71.33% and -55.69%, respectively), and 24-week Treatment Period (-77.92% and -43.24%, respectively).

For pediatric study participants, the median PGTCS frequency at Combined Baseline was 1.01 (0.7 to 7.5) in the LCM group and 1.00 (range: 0.7 to 19.4) in the placebo group. Similar median percent changes from Combined Baseline in PGTCS frequency per 28 days were observed in the LCM and placebo groups during the Titration Period (-33.33% and -32.74%, respectively). However, greater median percent changes from Combined Baseline in PGTCS frequency per 28 days were observed in the LCM group compared with the placebo group during first 12 weeks (-67.06% and -56.08%, respectively) and 24-week Treatment Period (-80.64% and -31.20%, respectively).

For adult study participants, the median PGTCS frequency at Combined Baseline was 1.26 (range: 0.3 to 12.3) in the LCM group and 1.49 (range: 0.7 to 15.0) in the placebo group. Greater median percent changes from Combined Baseline in PGTCS frequency per 28 days were observed in the LCM group compared with the placebo group during the Titration Period (-100.00% and -46.67%, respectively), first 12 weeks (-77.84% and -51.80%, respectively), and 24-week Treatment Period (-77.71% and -43.96%, respectively).

The median PGTCS frequency per 28 days was rather low at the combined baseline period, (1.25 and 1.24, for LCM and PBO groups, respectively) despite the inclusion criteria requiring at least 3 PGTCS during combined baseline period. Moreover, median values were significantly lower than the corresponding mean value (1.88 and 2.02, respectively), the distribution is thus skewed to the right indicating that the scores fall toward the lower side of the frequency scale. Moreover, Baseline LCM values are lower compared to PBO and differences are observed between SD values (1.76 vs 2.42). For a time-to-event analysis, it is crucial that the baseline conditions (including the magnitude of SD) are as much similar as possible, to support the assumption that the probability to develop a second seizure is similar in the two arms.

The reduction of median PGTCS frequency from Combined Baseline per 28 days was highest at 24-week Treatment Period and similar between children and adults.

Days with seizures per 28 days

Overall, the median number of days with absence seizures during Prospective Baseline was 0.0 days (range: 0 to 28 days) for the LCM group and 1.5 days (range: 0 to 28 days) for the placebo group. Greater median percent changes (improvement) from Prospective Baseline in days with absence seizures were observed in the LCM group compared with the placebo group during the Titration Period (-24.6% and -11.1%, respectively), first 12 weeks of the Treatment Period (-30.4% and -13.3%, respectively), and 24-week Treatment Period (-30.1% and -15.3%, respectively).

For pediatric study participants, the median number of days with absence seizures during Prospective Baseline was 0.0 days (range: 0 to 18 days) in the LCM group and 1.0 days (range: 0 to 6 days) in the placebo group. Greater median percent changes from Prospective Baseline in days with absence seizures were observed in the LCM group compared with the placebo group during the Titration Period (-51.8% and-8.9%, respectively) and the first 12 weeks of the Treatment Period (-51.8% and -28.6%, respectively). The median percent change in days with absence seizures from Prospective Baseline during the 24-week Treatment Period was -51.8% for pediatric study participants in the LCM group and -44.6% for pediatric study participants in the placebo group.

For adult study participants, the median number of days with absence seizures during Prospective Baseline was 2.0 days (range: 0 to 28 days) in the LCM group and 1.5 days (range: 0 to 28 days) in the placebo group. The median percent changes from Prospective Baseline in days with absence seizures in the LCM and placebo groups were similar during the Titration Period (-21.9% and -13.2%, respectively), but were greater in the LCM group compared with the placebo group during first 12 weeks of the Treatment Period (-30.4% and -13.2%, respectively) and 24-week Treatment Period (-30.1% and -13.3%, respectively).

Overall, the median number of days with myoclonic seizures during Prospective Baseline was 2.0 days (range: 0 to 28 days) for the LCM group and 1.0 days (range: 0 to 28 days) for the placebo group. The median percent changes from Prospective Baseline in number of days with myoclonic seizures for the LCM and placebo groups were -32.5% and -51.8%, respectively, during the Titration Period; -43.8% and -65.7%, respectively, during the first 12 weeks of the Treatment Period; and -54.6% and -65.7%, respectively, during the 24-week Treatment Period.

For pediatric study participants, the median number of days with myoclonic seizures during Prospective Baseline was 3.0 days (range: 0 to 17 days) in the LCM group and 1.1 days (range: 0 to 28 days) in the placebo group. The median percent changes from Prospective Baseline in number of days with myoclonic seizures for pediatric study participants in the LCM and placebo groups were 12.4% and -42.2%, respectively, during the Titration Period; 11.5% and -41.6%, respectively, during the first 12 weeks of the Treatment Period; and 11.5% and -34.0%, respectively, during the 24-week Treatment Period. The worsening of myoclonic seizures following LCM administration in paediatric patients was also evident when treatment effect was expressed as changes in median myoclonic seizures frequency.

For adult study participants, the median number of days with myoclonic seizures during Prospective Baseline was 1.5 days (range: 0 to 28 days) in the LCM group and 0.5 days (range: 0 to 28 days) in the placebo group. The median percent changes from Prospective Baseline in number of days with myoclonic seizures for adult study participants in the LCM and placebo groups were -40.0% and -55.7%, respectively, during the Titration Period, -44.1% and -70.6%, respectively, during the first 12 weeks of the Treatment Period, and -55.9% and -70.6%, respectively, during the 24-week Treatment Period.

Number of patients with absence seizures was rather high in LCM group (40.5%) and in placebo group (33.9%). The number of days with absence seizures was relatively low during the Prospective Baseline period in both treatment groups (see above). The LCM treatment reduced frequency of days with absence seizures at higher degree compared to placebo, especially in paediatric population.

The median number of days with myoclonic seizures during Prospective Baseline was slightly higher in LCM group compared to placebo. It seems that the percent change of days with myoclonic seizures was lower in LCM group compared to placebo, especially in paediatric patients. The explanation of this observation is not obvious (LoQ).

It is noted that while frequency of PGTCS is compared to Combined Baseline period the frequency of days with absences and myoclonic seizures are compared to Prospective Baseline period. The MAH was asked to clarify the arguments for the selection of different baselines for comparison. The MAH stated that myoclonic seizures were anticipated to be more difficult to be remembered back from the 12-week Historical Baseline Period. Due to the potential for under-reporting of myoclonic seizures with the use of the Historical Baseline, the Prospective Baseline was chosen for myoclonic seizures. This potential risk is acknowledged.

Potentially under-reporting of myoclonic seizures during the historical baseline period would result in even higher apparent worsening of them during the treatment period. Since worsening of myoclonic seizures is accepted by the MAH and proposed to be considered as an adverse event, this issue is not further pursued.

Seizure-free status for PGTCS

A summary of seizure-free status for PGTCS is presented for the FAS in the following table:

Time Period Variable	Placebo N=121	LCM N=119
Titration Period		
Completion of time period, n	114	114
Seizure-free status, n (%)	39/118 (33.1)	51/116 (44.0)
First 12 weeks of the Treatment Period		
Completion of time period, n	61	77
Seizure-free status, n (%)	26/116 (22.4)	43/111 (38.7)
24-week Treatment Period		
Completion of time period, n	41	65
Seizure-free status, n (%)	15/114 (13.2)	30/109 (27.5)

The percentages of pediatric study participants who had seizure-free status for PGTCS in the LCM and placebo group were 25.0% (6 of 24) and 28.0% (7 of 25), respectively, during the Titration Period; 25.0% (6 of 24) and 16.0% (4 of 25), respectively, during the first 12 weeks of the Treatment Period; and 13.0% (3 of 23) and 8.3% (2 of 24), respectively, during the 24-week Treatment Period.

For adult study participants, the percentages of study participants in the LCM and placebo groups who had seizure-free status for PGTCS were 48.9% (45 of 92) and 34.4% (32 of 93), respectively, during the Titration Period; 42.5% (37 of 87) and 24.2% (22 of 91), respectively, during the first 12 weeks of the Treatment Period; 31.4% (27 of 86) and 14.4% (13 of 90), respectively during the 24-week Treatment Period.

It seems that more adult patients (27.5%) achieved seizure free status for PGTCS during 24-week Treatment Period compared to paediatric patients (13%).

Seizure-free status for all generalized seizure types

Overall, the percentage of study participants who had seizure-free status for all generalized seizure types was higher in the LCM group compared with the placebo group for the first 12 weeks of the Treatment Period and the 24-week Treatment Period.

The percentages of study participants who had seizure-free status for all generalized seizure types in the LCM and placebo group were 33.6% (39 of 116) and 27.1% (32 of 118), respectively, during the Titration Period; 27.9% (31 of 111) and 17.2% (20 of 116), respectively, during the first 12 weeks of the Treatment Period; and 21.1% (23 of 109) and 13.2% (15 of 114), respectively, during the 24-week Treatment Period.

For pediatric study participants, the percentages of study participants who had seizure-free status for all generalized seizure types in the LCM and placebo group were 20.8% (5 of 24) and 20.0% (5 of 25), respectively, during the Titration Period; 20.8% (5 of 24) and 8.0% (2 of 25), respectively, during the first 12 weeks of the Treatment Period; and 17.4% (4 of 23) and 4.2% (1 of 24), respectively, during the 24-week Treatment Period.

For adult study participants, the percentages of study participants who had seizure-free status for all generalized seizure types in the LCM and placebo group were 37.0% (34 of 92) and 29.0% (27 of 93), respectively, during the Titration Period; 29.9% (26 of 87) and 19.8% (18 of 91), respectively, during the first 12 weeks of the Treatment Period; and 22.1% (19 of 86) and 15.6% (14 of 90), respectively, during the 24-week Treatment Period.

It appears that proportion of LCM treated patients with seizure-free status for all generalized seizure types was reduced from the titration period (33.6%) to 24-week treatment period (21.1%). Similar trend, though, was also observed for placebo arm.

Responder status for reduction in PGTCS frequency

The 50% responder rates for study participants in the LCM and placebo groups were 54.6% and 43.8%, respectively, during the Titration Period; 68.9% and 52.1%, respectively, during the first 12 weeks of the Treatment Period; and 68.1% and 46.3%, respectively, during the 24-week Treatment Period.

For pediatric study participants, the 50% responder rates for the LCM and placebo groups were 29.2% and 28.0%, respectively, during the Titration Period; 75.0% and 60.0%, respectively during the first 12 weeks of the Treatment Period; and 70.8% and 44.0%, respectively, during the 24-week Treatment Period.

For adult study participants, the 50% responder rates in the LCM and placebo groups were 61.1% and 47.9%, respectively, during the Titration Period; 67.4% and 50.0%, respectively, during the first 12 weeks of the Treatment Period; and 67.4% and 46.9%, respectively, for the 24-week Treatment Period.

Responder status for reduction in days with absence seizures

The 50% responder rates for reduction in days with absence seizures for the LCM and placebo groups were 15.7% and 16.7%, respectively, during the Titration Period; 19.6% and 14.3%, respectively, during the first 12 weeks of the Treatment Period; and 19.6% and 16.7%, respectively, during the 24-week Treatment Period.

For pediatric study participants, the 50% responder rates for reduction in days with absence seizures for the LCM and placebo groups were each 6.7% (1 of 15) and 20.0% (2 of 10), respectively, during the Titration Period, first 12 weeks of the Treatment Period, and 24-week Treatment Period.

For adult study participants, the 50% responder rates for reduction in days with absence seizures for the LCM and placebo groups were 19.4% and 15.6%, respectively, during the Titration Period; 25.0% and 12.5%, respectively, during the first 12 weeks of the Treatment Period; and 25.0% and 15.6%, respectively, for the 24-week Treatment Period.

Responder status for reduction in days with myoclonic seizures

The 50% responder rates for reduction in days with myoclonic seizures for the LCM and placebo groups were 21.3% and 26.5%, respectively, during the Titration Period, 23.4% and 26.5%, respectively, during the first 12 weeks of the Treatment Period, and 27.7% and 28.6%, respectively, during the 24-week Treatment Period.

For pediatric study participants, the 50% responder rates for reduction in days with myoclonic seizures for the LCM and Placebo groups were each 20.0% (1 of 5) and 14.3% (1 of 7), respectively, during each time period.

For adult study participants, the 50% responder rates for reduction in days with myoclonic seizures for the LCM and Placebo groups were 21.4% and 28.6%, respectively, during the Titration Period; 23.8% and 28.6%, respectively, during the first 12 weeks of the Treatment Period; and 28.6% and 31.0%, respectively, for the 24-week Treatment Period.

50% responder rate for reduction of days with PGTCS was higher in LCM treated patients compared to placebo during Titration, 12-weeks Treatment and 24-week Treatment periods. Meanwhile, both 50% responder rates for reduction of absences and myoclonic seizures were similar between treatment groups at all timepoints assessed. It seems that only one out of 15 paediatric patients was 50% responder for reduction of days with absence seizures.

PGTCS worsening

Overall, the percentage of study participants with 50% seizure worsening for PGTCS for the LCM and placebo groups were 10.1% and 14.9%, respectively, during the Titration Period; 10.1% and 15.7%, respectively, during the first 12 weeks of the Treatment Period; and 10.1% and 16.5%, respectively, during the 24-week Treatment Period.

For pediatric study participants, the percentage of study participants with 50% seizure worsening for PGTCS for the LCM and placebo groups were each 4.2% and 20.0%, respectively, during the Titration Period, the first 12 weeks of the Treatment Period, and the 24-week Treatment Period.

For adult study participants, the percentage of study participants with 50% seizure worsening for PGTCS was 11.6% during each time period for the LCM group, and 13.5%, 14.6%, and 15.6%, respectively, during the Titration Period, the first 12 weeks of the Treatment Period, and the 24-week Treatment Period for the placebo group.

It is acknowledged that it seems there were no obvious PGTCS worsening in patients treated with LCM compared to placebo as described by the MAH.

However, 6 out of 47 patients with myoclonic seizures treated with LCM experienced an increase in number of days with myoclonic seizures during the treatment period compared to prospective baseline in contrast to 3 out of 49 patients treated with placebo (Table 8.7.3, CSR). Increase in myoclonic seizure frequency compared to prospective baseline was also more common in patients treated with LCM (8 out of 47) compared to placebo (5 out of 49) (Table 8.7.3.2, CSR).

In order to have clearer picture how many patients experienced improvement/worsening of myoclonic and absence seicures and magnitude of these changes the MAH is requested to present the waterfall figures depicting both change of days and seizure frequency for myoclonic and absence seizures in patients treated with LCM and placebo (LoQ).

Health quality related outcomes

QOLIE-31-P

The QOLIE-31-P Version 2 was used to evaluate the health-related quality of life of study participants ≥18 years of age.

Mean scores at Baseline for QOLIE 31 P total and subscale score, QOLIE 31 P distress item score, and QOLIE 31 P prioritization items score were generally similar between the LCM and placebo groups.

Small changes in QOLIE 31 P total and subscale scores were observed from Baseline to the Last Visit in both the LCM and placebo groups (all changes were <10 points on a 100 point scale). The mean changes observed in the LCM group were generally similar to those observed for the placebo group.

PedsQL

The PedsQL was used in pediatric study participants <18 years of age.

Overall, the mean total PedsQL score at Baseline was 76.0 in the LCM group and 80.9 in the placebo group. Mean changes in total PedsQL scores from Baseline to Last Visit were 3.0 in the LCM group and -2.9 in the placebo group. In general, mean changes from Baseline overall and for individual subscale scores were small and variable in both the LCM and placebo groups. No worsening in the mean value for any score was observed for participants in the LCM group.

EQ-5D-3L quality of life

The EQ-5D-3L was only assessed for study participants ≥12 years of age. The scale is scored from 0 (worst imaginable health state) to 100 (best imaginable health state).

Overall, the mean EQ-5B-3L VAS score at Baseline was 74.6 in the LCM group and 74.3 in the placebo group. The mean changes in EQ-5B-3L VAS scores at the Last Visit were 3.6 in the LCM group and 0.9 in the placebo group. No worsening was observed.

No clear effects on improvement of quality of life of patients in treated with LCM were observed. It is reassuring that no worsening of quality of life was neither reported.

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of Efficacy for trial SP0982

Title: A double-blind, randomized, placebo controlled, parallel group, multicenter study to evaluate the efficacy and safety of LCM as adjunctive therapy for PGTCS in study participants with IGE			
Study identifier	SP0982		
Design	A double-blind, randomized, placebo controlled, parallel group, multicenter study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks (time to event study) 4 weeks 4 weeks taper + 30 days safety follow up	
Hypothesis	Superiority		
Treatments groups	Lacosamide	Lacosamide. 24 weeks, n=118	
	Placebo	Placebo. 24 weeks, n=121	
Endpoints and definitions	Primary endpoint	Time to second PGTCS	Time to second PGTCS during 24-week Treatment period
	Key Secondary endpoint	Seizure freedom for PGTCS	Seizure freedom for PGTCS during the 24-week Treatment Period, estimated using Kaplan-Meier (KM) analysis
	Secondary endpoint	Time to first seizure	Time to first seizure during the 24-week Treatment Period
Database lock	20 June 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The Full Analysis Set		
Descriptive statistics and estimate variability	Treatment group	Lacosamide	Placebo
	Number of subjects	N=118	n=121
	KM survival estimate at the end of the treatment period (%), Time to event, (median, days)	55.27% - (days)	33.37% 77.0 (days)
	Time to event (days) 95% CI	144, 0	49.0, 128.0

	Seizure freedom for PGTCS (KM seizure free (%))	31.0%	17.3%
	95% CI	22.4, 39.6	10.3, 24.3
	Time to first seizure (number of events (events), KM survival estimate at the end of the treatment period (%), Time to event, (median, days)) Time to event (days) 95% CI	79 (events) 30.97% 36.0 (days) 25.0, 78.0	97 (events) 17.27% 20.0 13.0, 34.0

Effect estimate per comparison	Primary endpoint	Comparison groups	LCM vs Placebo
		HR	0.540
		95% CI of HR	0.377, 0.774
		P-value	<0.001
	Key Secondary endpoint	Comparison groups	LCM vs Placebo
		KM seizure free %	14.1%
		95% CI	3.2, 25.1
		P-value	0.011
	Secondary endpoint	Comparison groups	LCM vs Placebo
		HR	0.683
		95% CI of HR	0.507, 0.921
		P-value	0.012

Supportive study(ies)

EP0012

EP0012 is a Phase 3, multicenter, open-label extension study designed to assess the long-term safety and efficacy of LCM as adjunctive therapy for PGTCS in study participants 4 years of age and older with IGE. This study enrolls study participants who are Baseline failures as well as those who completed a protocol-defined endpoint in the SP0982 study. Approximately 250 study participants will be enrolled in EP0012 and only LCM will be administered in addition to background AEDs.

EP0012 is an ongoing study. At the time of clinical cut-off, study participants were still enrolling and participating in SP0982.

Pediatric study participants weighing <30kg and ≥30kg to <50kg will start EP0012 on a dose of LCM 10mg/kg/day and 8mg/kg/day respectively. Adult study participants ≥18 years old and pediatric study participants ≥50kg will start the study taking a dose of LCM 400mg/day. Pediatric study participants weighing <50kg who are baseline failures from SP0982 will start the study taking a dose of LCM 2mg/kg/day while the adult study participants ≥18 years of age or pediatric study participants weighing ≥ 50kg who are baseline failures will start the study taking a dose of LCM 100mg/day.

Study participants will be eligible to participate in EP0012 for 5 years with at least a minimum of 2 years. The study consists of a Treatment Period, an up to 4-week Taper Period, and a 30-day Safety Follow-Up Period. The maximum duration of study drug administration is 242 weeks.

The primary variables in this study are safety variables only.

The secondary efficacy variable is the percent change in PGTC seizure frequency (SF) per 28 days from Combined Baseline Period.

Results

As of the clinical cut-off date, a total of 211 study participants were enrolled and started the study. Overall, 167 study participants (79.1%), 128 study participants (60.7%), and 66 study participants (31.3%) were in the 22 Weeks, 46 Weeks, and 94 Weeks completer cohorts, respectively.

Table 12. Summary of study participant disposition and discontinuation reasons by Baseline age in SP0982 (SS)

	Baseline age in SP0982 (years)				
Disposition	≥4 to <12 N=12 n (%)	≥12 to <18 N=30 n (%)	≥18 to <65 N=168 n (%)	≥65 N=1 n (%)	All study participants N=211 n (%)
Started study	12 (100)	30 (100)	168 (100)	1 (100)	211 (100)
Ongoing within 94 weeks of treatment	8 (66.7)	11 (36.7)	73 (43.5)	0	92 (43.6)
Completed >94 weeks of treatment	4 (33.3)	14 (46.7)	69 (41.1)	0	87 (41.2)
Discontinued within 94 weeks of treatment	0	5 (16.7)	26 (15.5)	1 (100)	32 (15.2)
Primary reason for discontinuation within 94 weeks of treatment					
Adverse event	0	1 (3.3)	2 (1.2)	1 (100)	4 (1.9)
Lack of efficacy	0	2 (6.7)	8 (4.8)	0	10 (4.7)
Protocol violation	0	0	1 (0.6)	0	1 (0.5)
Lost to follow up	0	0	2 (1.2)	0	2 (0.9)
Consent withdrawn	0	2 (6.7)	10 (6.0)	0	12 (5.7)
Other	0	0	3 (1.8)	0	3 (1.4)
Ongoing[a]	12 (100)	24 (80.0)	139 (82.7)	0	175 (82.9)
Completed study	0	0	0	0	0
Discontinued	0	6 (20.0)	29 (17.3)	1 (100)	36 (17.1)
Primary reason for discontinuation					
Adverse event	0	1 (3.3)	2 (1.2)	1 (100)	4 (1.9)
Lack of efficacy	0	2 (6.7)	9 (5.4)	0	11 (5.2)
Protocol violation	0	0	2 (1.2)	0	2 (0.9)
Lost to follow up	0	0	2 (1.2)	0	2 (0.9)
Consent withdrawn	0	3 (10.0)	11 (6.5)	0	14 (6.6)
Other	0	0	3 (1.8)	0	3 (1.4)

Baseline characteristics

As of the clinical cut-off date for this interim CSR, based on the ILAE seizure classification history from SP0982, overall the majority of study participants (210 [99.5%]) had a history of tonic-clonic seizures, and 79 study participants (37.4%) and 72 study participants (34.1%) had histories of myoclonic and absence seizures, respectively.

Overall, the mean time since first diagnosis at SP0982 entry was 15.287 years (range: 0.49 to 60.74 years) and the mean age at epilepsy diagnosis was 13.044 years (range: 0 to 39.76 years). As expected, the mean time since first diagnosis and the mean age at epilepsy diagnosis generally increased with increasing age cohort.

Table 14. Baseline characteristics by Baseline age in SP0982 (SS)

Variable Statistic	Baseline age in SP0982 (years) ≥4 to <12 N=12 n (%)	≥12 to <18 N=30 n (%)	≥18 to <65 N=168 n (%)	≥65 N=1 n (%)	All study participants N=211 n (%)
Combined Baseline PGTCS frequency from SP0982					
Mean (SD)	3.502 (5.411)	1.014 (0.441)	1.711 (1.811)	5.895[c]	1.734 (2.122)
Min, max	0.75, 19.40	0.50, 2.75	0.25, 15.02	5.89, 5.89	0.25, 19.40
Combined Baseline PGTCS categories from SP0982 (from CRF)					
≤2 per 28 days	8 (66.7)	23 (76.7)	120 (71.4)	0	151 (71.6)
>2 per 28 days	3 (25.0)	2 (6.7)	26 (15.5)	1 (100)	32 (15.2)
Missing	1 (8.3)	5 (16.7)	22 (13.1)	0	28 (13.3)

At EP0012 entry, the majority of study participants were using concomitant AEDs: 68 study participants (32.2%) were using 1 concomitant AED, 103 study participants (48.8%) were using 2 concomitant AEDs, and 35 study participants (16.5%) were using 3 concomitant AEDs. Study participants were permitted to withdraw concomitant AEDs. A total of 5 study participants (2.4%) were not using concomitant AEDs at EP0012 entry. The majority of study participants (168 [79.6%]) were not using concomitant benzodiazepines at EP0012 entry.

Percent change from Combined Baseline in PGTCS frequency per 28 days by completed cohort and Treatment Period (FAS)

Completer cohort Statistic	All study participants N=210
0 to 22 Weeks, n	167
Mean (SD)	-67.607 (60.205)
Median (min, max)	-87.030 (-100.000, 473.826)
0 to 46 Weeks, n	128
Mean (SD)	-70.944 (43.734)
Median (min, max)	-83.376 (-100.000, 211.119)
0 to 94 Weeks, n	66
Mean (SD)	-73.999 (42.451)
Median (min, max)	-84.695 (-100.000, 203.179)
Treatment Period, n	210
Mean (SD)	-63.331 (67.590)
Median (min, max)	-84.996 (-100.000, 465.353)

As of the clinical cut-off date for this interim report, overall a median percent change of -84.996% (range: -100.000 to 465.353) from Combined Baseline in PGTCS frequency per 28 days was observed during the Treatment Period.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH applied for the new indication for use of LCM as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients with idiopathic generalized epilepsy (IGE) aged 4 years and older. The basis for demonstration of efficacy for the indication extension is the pivotal study SP0982 and is in line with the CHMP scientific advice issued on 20 Sep 2012 (EMEA/H/SA/1570/4/2012/II).

SP0982 is a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study designed to assess the efficacy of oral LCM versus placebo as adjunctive therapy for PGTCS in study participants ≥4 years of age with IGE, taking 1 to 3 concomitant AEDs independent of the number of prior failed AEDs over 24 week treatment period. The pivotal study SP0982 is a measure of the PIP EMEA-000402-PIP03-17-M03 and the number of events was agreed to be at least 17.6% of the events from the paediatric age group from 4 to less than 18 years of age.

The time to event as a primary efficacy endpoint (second PGTCS during the 24-week Treatment period) is recommended as one of the possible primary endpoints in the "Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders" (CHMP/EWP/566/98 Rev.3 2) and is acceptable. The key secondary efficacy variables - seizure freedom for PGTCS during the 24-week Treatment Period - and the other secondary efficacy variable - the time to the first PGTCS during the Treatment Period - are considered support the primary efficacy variable and are acceptable.

Other seizure related endpoints (PGTCS frequency per 28-days, number of days with seizures per 28 days, seizure free status, 50% and 75% responders) were considered as exploratory and were used in assessment of all generalized seizures - PGTCS, absence and myoclonic seizures.

The study included a 12-week Historical Baseline and a 4-week prospective baseline period (that altogether form the Combined baseline), followed by a 6-week (minimum) to 24-week (maximum) Treatment Period, which included a 6-week Titration Period and an 18-week (maximum) Maintenance Period. Of the 3 PGTCS minimum required for subjects to enroll, 1 or 2 PGTCS must have occurred in the first 8 weeks or the second 4 weeks of Historical baseline, and not more than 1 PGTCS must have occurred during the prospective baseline, to ensure adequate baseline seizure assessment.

It is noted that while primary and secondary endpoints as well other efficacy variables assessing PGTCS used Combined Baseline (Historical + Prospective Baseline) for comparison of treatment effect, all other seizure related endpoints refer to Prospective Baseline for comparison of treatment effects. Having in mind that recognition of absence seizures is more challenging compared to PGTCS, the validity of retrospective data on absence seizures could be questionable and the choice of different baselines could be acceptable. The MAH stated that myoclonic seizures were anticipated to be more difficult to be remembered back from the 12-week Historical Baseline Period. Due to the potential for under-reporting of myoclonic seizures with the use of the Historical Baseline, the Prospective Baseline was chosen for myoclonic seizures. This potential risk of under reporting is acknowledged. Potentially under-reporting of myoclonic seizures during the historical baseline period would result in even higher apparent worsening of them during the treatment period. Since worsening of myoclonic seizures is agreed by the MAH and proposed to be considered as an adverse event with the relevant information reflected in the Product Information, this is acceptable.

The patient population as defined by inclusion and exclusion criteria is considered acceptable. Both LCM and placebo groups were balanced regarding age, sex and ethnicity. Patients with Lennox-Gastaut Syndrome (typically presenting with seizures including tonic seizures), some other related syndromes

like Doose's syndrome (typically presenting with myoclonic-atonic seizures), or evidence of both focal and generalized epilepsy were excluded. The study participants were allowed to have treatment with 1 to 3 concomitant AEDs. What drugs were mostly used as combinations of 2 or 3 AED were not presented and not discussed since it was agreed that the groups would have been very small and therefore not relevant for conclusions.

Patients which received at least 1 dose of study medication are included in the Safety Set analysis. The Full Analysis Set (FAS) included patients who had at least one seizure diary assessment during the treatment period. The primary efficacy variable was analyzed based on FAS data set. It is noted that 3 patients treated with LCM were not included in the FAS data set. The MAH clarified that the reason for not including 3 subjects in the FAS data set is due to lack of post-baseline seizure diary, and this was considered as an acceptable explanation.

The statistical methods are considered adequate to the study design. Being a time-to-event study, no imputation for missing data was performed. Since PGTCS counts reported as 'not done' in the patient diary on a specific day were assumed to be zero, there is the need to understand if this has impacted on the primary and key secondary endpoint. The MAH has subsequently provided a reassuring low incidence of PGTCS counts reported as 'not done' on the diaries, which were surprisingly low as compared to the number of evaluable days, as well as evenly distributed among treatment groups.

Of note, the final stratum pooling algorithm used in the primary and secondary efficacy analyses, was defined only with SAP amendment 4, implemented close to the date of LPLV (5 Jul 2019). The defined three pooled strata were the following: Strata 1: Baseline PGTCS frequency ≤2 per 28 days and paediatric; Strata 2: Baseline PGTCS frequency ≤2 per 28 days and adult; Strata 3: Baseline PGTCS frequency >2 per 28 days and All (paediatric and adult). A stratum pooling algorithm was defined in all versions of the SAPs, from the original through SAP Amendment 4, and it was clarified that pooling would have been implemented in the case that almost no study participants in any single stratum would experience an event. Since the number of subjects in the >2 baseline PGTCS per 28 days stratum was only 1 pediatric participant with no events (i.e. 2 PGTCS), it was decided to combine paediatric with adult pools.

Regarding the temporal proximity of SAP amendment 4 implementation to the LPLV date, it has been stated that, as already known, it was triggered by an FDA request of a Type C meeting.

The MAH reaffirmed that the protocol included the use of the randomization strata as covariates in the primary and secondary analyses and that, according to CHMP Guidelines randomization, strata were attempted to be used as covariates.

The maintenance of LCM treatment effect over long term period is investigated in the EP0012 study. EP0012 is a Phase 3, multi-centre, open-label extension study designed to assess the long-term safety and efficacy of LCM as adjunctive therapy for PGTCS in study participants 4 years of age and older with IGE. This study enrols study participants who are Baseline failures as well as those who completed a protocol-defined endpoint in the SP0982 study. Approximately 250 study participants will be enrolled in EP0012 and only LCM will be administered in addition to background AEDs. This study is ongoing.

No primary efficacy variables are defined for EP0012. The secondary efficacy variable is the percent change in PGTC seizure frequency (SF) per 28 days from Combined Baseline Period.

Efficacy data and additional analyses

The primary endpoint was achieved, and LCM treatment had statistically significantly lower risk for the development of the second PGTCS during the 24-week Treatment period compared to placebo.

It is agreed that subgroup analysis (age, sex, region, baseline PGTCS frequency, number of AEDs) did not reveal any major differences in treatment effect, what could most likely be explained by small numbers of patients in each subgroup. A very limited number of patients treated with LCM was aged <18 years: 8 patients in the ≥4 to <12 years age group (vs 9 in the PBO group), and 16 patients in the >12 to <18 years range (same as PBO). These numbers are too small to understand the consequences of LCM treatment in paediatric patients with IGEs, considering that most syndromes include also myoclonic jerks and absence seizures that peak at different ages compared to GTC seizures and can be worsened by a drug acting on Na+ currents.

Of the 125 total events analysed for the primary efficacy variable analysis, 102 (81.6%) were observed in the adult group (62 in PBO and 40 in LCM group) and 23 events (18.4%) were observed in paediatric group (9 in LCM group and 14 in PBO group). Although numbers are too low to draw sound conclusions, it is of note that when looking at treatment effect across the 3 age groups (the 3 paediatric groups and the adult one) the risk to develop a second PGTCS was highest in the $\geq$ 12 to 18 age group when, according to natural history, PGTCS are more likely to peak.

Patients with the most common IGE syndromes (i.e. childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal seizures on awakening) may experience generalized tonic-clonic seizures. The MAH provided the information regarding different epilepsy diagnosis included into the SP0982 study, however, results in these subgroups were not presented. Although the sample sizes for many of the epileptic syndromes subtypes by which the subgroup analyses were requested turned out to be small to draw conclusions, it is acknowledged that they were directionally consistent with the primary analysis with hazard ratios generally favoring LCM over placebo, and ranging from 0.106 (childhood absence epilepsy) to 0.904 (juvenile absence epilepsy).

The MAH provided the information regarding different epilepsy syndromes included into the SP0982 study. Rather unexpectedly, the majority of paediatric participants (63.3% overall) were classified as 'Other generalized idiopathic epilepsies not defined', with a predominance in the LCM group compared with PBO group (17 [70.8%] vs 14 [56.0%], respectively). The MAH explained the difficulty that can be encountered trying to categorize the type of IGE into a specific epileptic syndrome, as demonstrated by the evolution of the natural history of Juvenile Absence Epilepsy potentially evolving into PGTCS, or JME that evolve into an almost myoclonic-free picture later on in adulthood.

However, as the sought extended indication includes the treatment of PGTCS in drug-resistant subjects with IGE from 4 years of age, per definition this category includes generalized idiopatic epilepsies which cannot be regarded as none among Benign neonatal familial convulsions/Benign neonatal convulsions/Benign myoclonic epilepsy in infancy/Childhood absence epilepsy/Juvenile absence epilepsy/Juvenile myoclonic epilepsy. For this reason, a smaller proportion of subjects falling into this category was expected in the adult subject population, for which a clearer categorization could be ruled out. The reasons for the uncertainties described by the MAH can be more satisfactorily acknowledged for the paediatric population compared with the adults. In study SP0982 the most commonly classified syndrome was 'Other generalized idiopathic epilepsies not defined' in adult study participants (40.3% overall), as well as in paediatric participants (63.3% overall).

The key secondary efficacy endpoint seizure freedom for PGTCS during 24-week period supported the favourable effect of LCM treatment compared to placebo. The stratified KM estimate of the proportion of study participants who were seizure free at Day 166 was 31.3% (95% CI: 22.8%, 39.9%) in the LCM group

and 17.2% (95% CI: 10.4%, 24.0%) in the placebo group. The difference was even more obvious in strata with baseline PGTCS frequency >2 seizures per 28 days (30.0% for the LCM group and 4.9% for the placebo group). The MAH specified that 7 paediatric study participants were included in stratum 3 (< 2 seizures), none whom was seizure-free by Day 166, whereas only adult participants in this stratum met seizure freedom. The similar difference was observed also following stratification of paediatric and adult patients in the strata with Baseline PGTCS frequency $\leq$2 per 28 days.

The secondary efficacy variable of time to first PGTCS was also in favour of LCM compared to placebo supporting the positive effect on PGTCS. The median time to first PGTCS was 36.0 days (95% CI: 25.0, 78.0) for the LCM group and 20.0 days (95% CI: 13.0, 34.0) for the placebo group.

The median PGTCS frequency per 28 days was rather low at the combined baseline period. The reduction of median PGTCS frequency from Combined Baseline per 28 days was highest at 24-week Treatment Period and similar between children and adults. Of note, the median PGTCS frequency per 28 days was rather low at the combined baseline period, for both LCM and PBO groups (1.25 and 1.24, respectively) and significantly lower than the corresponding mean value (1.88 and 2.02, respectively). The distribution is thus skewed to the right indicating that the scores fall toward the lower side of the frequency scale. Moreover, baseline LCM values are lower compared to PBO and differences are observed between SD values (1.76 vs 2.42). It is thus questionable if the assumption that the probability to develop a second seizure is similar in the two arms is soundly demonstrated by data. The magnitude of treatment effect on the primary endpoint could have been thus overestimated.

Number of patients with juvenile absence seizures was rather high in LCM group (40.5%) and in placebo group (33.9%). However, the number of days with absence seizures was relatively low during the Prospective Baseline period in both treatment groups. The LCM treatment reduced frequency of days with absence seizures at higher degree compared to placebo, especially in paediatric population.

The median number of days with myoclonic seizures during Prospective Baseline was slightly higher in LCM group compared to placebo. As regards myoclonic seizures, 9 subjects of whom 6 in LCM showed worsening in days with seizures, whereas 13 subjects of whom 8 in LCM had an increase in seizure frequency. Conversely, as regards absence seizure worsening, of the 12 subjects who reported increase in days with seizures 9 were in placebo, whereas of the 15 subjects with increased absence seizure frequency 6 were in LCM. The incidence of myoclonic seizure emergence or worsening was higher in the titration period, however, it was more clustered within the first 4 weeks since randomization in placebo group (10/13 events) and was more interspersed over time in LCM group (13/27 in the first 4-week period since randomization then 4/27 in the two following 4-week blocks, 2/27 in both the >12 to ≤16 and >16 to ≤20 and 2 in the >24 week period. Although the MAH has reiterated how fickle and unstable the occurrence of myoclonic seizures can be (also through the 4 subjects illustrated by way of example), it is undeniable that the design of the study and the randomization applied is expected to evenly distribute variables among treatment groups. Therefore, the overall interpretation of these data is that there is a clear trend towards worsening of myoclonic seizures with LCM (see also Clinical safety section).

The 50% responder rate for reduction of days with PGTCS was higher in LCM treated patients compared to placebo during Titration, 12-weeks Treatment and 24-week Treatment periods. Meanwhile, both 50% responder rates for reduction of absences and myoclonic seizures were similar between treatment groups at all timepoints assessed.

It is acknowledged that it appears there were no obvious PGTCS worsening in patients treated with LCM compared to placebo as described by the MAH. However, 6 out of 47 patients with myoclonic seizures treated with LCM experienced an increase in number of days with myoclonic seizures during the treatment period compared to prospective baseline in contrast to 3 out of 49 patients treated with

placebo. Increase in myoclonic seizure frequency compared to prospective baseline was also more common in patients treated with LCM (8 out of 47) compared to placebo (5 out of 49).

No clear effects on improvement of quality of life of patients treated with LCM were observed. Since positive effect on PGTCS was not followed by the same trend for myoclonic seizures, it is reassuring that no worsening of quality of life was neither reported.

The long-term effects of LCM treatment on PGTCS was assessed in the EP0012 study. The total discontinuation rate (17.1%) in EP0012 study was rather similar to the one in the SP0982 study (14,9% LCM group). However, the main reason for discontinuation in the LCM group in the SP0982 study were adverse events (8.3%) while lack of efficacy was reported only by one patient (0.8%). This observation is contrasting to the EP0012 study where lack of efficacy as one of reasons for discontinuation was reported by 5.2% percent of patients (n=11). Possibly this might reflect longer study duration. On the other hand, it also indicates that long term efficacy will be reported in preselected population responding to the treatment.

The median percent changes from Combined Baseline in PGTCS frequency per 28 days observed in the LCM group during the Titration Period (-66.37%), first 12 weeks (-71.33%), and 24-week Treatment Period (-77.92%) in the SP0982 study. Similar changes in percent change from Combined Baseline in PGTCS frequency per 28 days were reported at least until week 94 in EP0012 study - median percent changes from Combined Baseline in PGTCS frequency in the 0 to 22 Weeks, 0 to 46 Weeks, and 0 to 94 Weeks completer cohorts were -87.0, -83.3, and -84.6, respectively. Taking all these considerations into account, it appears that in the open-label EP0012 study LCM treatment has similar long-term effect on the frequency of the PGTCS as reported in the 24-week controlled trial, but definite conclusions is difficult to draw due to the open-label nature of the trial and potential selection bias.

Assessment of paediatric data on clinical efficacy

Only 49 paediatric patients were included into the SP0982 study, including 24 of them on LCM treatment. However, the number of events registered during study was higher compared to the one agreed with the PDCO (at least 17.6% of the events from the paediatric age group from 4 to less than 18 years of age). There were only 8 patients younger than 12 years old exposed to LCM treatment. It is noted that the 2nd substantial amendment allowed inclusion of paediatric study participants (≥4 to 12 years of age).

In general, the effect of LCM treatment in paediatric patients was similar to the one described in adults. Furthermore, the risk for second PGTCS was lower in the youngest children group (2 out of 8, 75%) compared to adults (40 out of 94, 54%). In general, the LCM treatment effect in paediatric patients seems to have similar effect as in adults as assessed by other endpoints like PGTCS frequency and 50% responders' rate. On the other hand, the PGTCS free status was achieved by substantially smaller proportion of paediatric patients and compared to adults (13.0% vs 31.4%, respectively).

2.4.4. Conclusions on the clinical efficacy

Based on the review of all information provided, the CHMP concluded that the efficacy of the use of Lacosamide as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients with idiopathic generalized epilepsy (IGE) aged 4 years and older is proven.

2.5. Clinical safety

Introduction

The safety profile of LCM has previously been investigated in adult and paediatric (adolescents and children from 4 years of age) patients with POS. Based on data with LCM as adjunctive therapy, the most common adverse drug reactions (ADRs) in adults were related to the CNS and gastrointestinal system and included dizziness, headache, nausea and diplopia. In monotherapy studies in adult patients with POS, the most frequently reported adverse reactions observed with LCM were headache and dizziness. Dizziness was the most common reason for LCM treatment discontinuation. The paediatric safety profile of LCM was generally found to be consistent, with ADRs mainly related to the CNS (e.g. dizziness, and somnolence) and gastrointestinal system (e.g. vomiting).

The main safety data for the current application originates from the pivotal study SP0982, together with interim results from the ongoing open-label extension study EP0012. Safety data from the completed Phase 2 open-label pilot study (SP0961) and its extension (SP0962) were also provided. In addition, 2 safety pools were defined:

- Pool SGTC-1: all participants receiving at least one dose of LCM in either the SP0982 or EP0012 studies.

- Pool SGTC-2: all participants receiving at least one dose of LCM in either the SP0961 or SP0962 studies.

To evaluate differences in the LCM safety profile between paediatric and adult study participants in the PGTCS and POS populations, the incidence of the most common treatment-emergent adverse events (TEAEs) (occurring in ≥2% of patients) from Pool SGTC-1 were presented side-by-side with previously pooled data from adult and paediatric patients with POS (Pool S2 and Pool SPX-1, respectively).

Pool S2 (completed studies SP667, SP754, SP755, SP607, SP615, SP756, and SP774) was previously submitted to support the initial LCM adjunctive therapy submission in adults with POS and Pool SPX-1 (SP847 [completed], SP848 and EP0034 [then ongoing with a cut-off date of 01 Nov 2016]) was previously submitted to support the LCM paediatric submission in study participants 4 to <16 years of age with POS.

Patient exposure

Overall, the safety set included 242 study participants, including 121 each in the LCM and Placebo groups, respectively. A total of 213 study participants (88.0%) completed the study (103 [85.1%] in the LCM group and 110 [90.9%] in the placebo group). Of the paediatric study participants (<18 years of age), a total of 8 (6.6%) in the LCM group and 9 (7.4%) in the placebo group were ≥4 to <12 years of age, and 16 study participants (13.2%) in each group were ≥12 to <18 years of age. In total, there were 2 study participants (0.8%) who were ≥65 years of age, 1 in the LCM group and 1 in the placebo group.

In the pivotal study SP0982, LCM (N=121) and Placebo (N=121) patients were exposed for a total of 37.2 and 31.1 study participant-years, respectively. During the 6-week Titration Period, median study medication duration was similar between the LCM and Placebo groups (42.0 days each). During the Maintenance Period, median duration of exposure was also similar, 126.0 days (range: 13.0 to 135.0 days) in the LCM group and 120.5 days (range: 3.0 to 134.0 days) in the Placebo group.

Overall, median study medication duration was 143.0 days (range: 1.0 to 176.0 days) in the LCM group and 65.0 days (range: 7.0 to 176.0 days) in the Placebo group.

In the Titration Period and Maintenance Period, median duration of exposure was similar between the respective LCM and Placebo groups. However, only 70 of 121 patients in the Placebo group continued to the Maintenance Period as compared to 82 in the LCM group, resulting in lower overall median exposure in the Placebo group (65.0 days) compared to LCM (143.0 days) when both periods were combined. The applicant provided some supplemental safety tables that adjust for exposure.

For the open-label extension study EP0012, as of the clinical cut-off date (28 Nov 2018) for the interim CSR, 211 study participants (100%) were exposed to LCM, for a total of 277.86 study participant-years.

In Pool SGTC-1 (studies SP0982 and EP0012 combined up to the cut-off date), 255 study participants were exposed to LCM for a total of 330.51 study participant-years (see table below).

Table 13: Pool SGTC-1 exposure to LCM over time

LCM exposure	Number of study participants N=255 n (%)	Participant-years exposed Total
>0 months	255 (100)	330.51
≥6 months	202 (79.2)	320.51
≥12 months	147 (57.6)	286.30
≥18 months	114 (44.7)	248.94
≥24 months	81 (31.8)	195.66
≥30 months	47 (18.4)	124.64
≥36 months	12 (4.7)	34.80

LCM=lacosamide
Note: LCM exposure=(date of last LCM dose-date of first LCM dose)+1 for completed studies or (date of clinical cut-off date-date of first LCM dose)+1 for ongoing study participants.
Note: A month is defined as 28 days.
Note: Participant-years of exposure is the total treatment duration in days divided by 365.25.
Note: Percentages are relative to the number of study participants in Pool SGTC-1.
Data source: Table 4.1.1

A summary of exposure by dose is provided in the table below. In all study participants, the median modal dose (mg/day) was 400 mg (range: 100 mg to 800 mg), and the median maximum dose (mg/day) was 400 mg/day (range: 100 mg to 800 mg).

In Pool SGTC-1, as of the clinical cut-off date, a total of 255 subjects were exposed to LCM for a total of 330.51 subject-years, of whom 50 were in the paediatric age and 205 in the adult age category, with 64.97 and 265.54 subject-years exposure, respectively. A total of 147 subjects (57.6%) were exposed for ≥12 months of whom only 28 subjects (56%) were in the paediatric age for a total exposure of 53.83 subject-years, compared with 119 adult subjects (58%) who were exposed to LCM for 232.46 subject-years.

In comparison, in Pool SPX-1, including safety data of the paediatric patient population with POS exposed to LCM in the open-label studies SP847, SP848, or EP0034, 120 subjects (39.6%) were exposed to LCM for at least 12 months, with a total exposure of 194.1 subject-years.

The number and exposure of the paediatric population with PGTCS is thus limited. The MAH was requested to provide tabulated data on exposure and disposition by age and weight band. In particular, given the reported differences in the literature, in the predominant seizure pattern and age of onset of IGE syndromes, with almost doubled onset in the 12-17 years age group compared to 5-11 years group.

The ≥4 to <12 years age group had lower percentages of study participants exposed to LCM for ≥18, ≥24, and ≥30 months compared with the ≥12 to <16 years age group (33.3%, 13.3%, and 6.7% vs. 60.0, 53.3%, and 33.3%, respectively). No study participants in the ≥4 to <12 years age group were exposed to LCM for ≥36 months compared with 2 study participants in the ≥12 to <16 years age group (13.3%). Similarly, the <30kg weight band group had a lower percentage of study participants exposed to LCM for ≥18 months compared with the ≥30 to <50kg weight band (16.7% vs. 54.5%). No study participants in the <30kg weight band group were exposed to LCM for ≥24 months compared with 4 study participants in the ≥30 to <50kg weight band group (36.4%).

Table 14: Pool SGTC-1 exposure to LCM

Variable Statistic	Pediatric N=50	Adult N=205	All study participants N=255
Exposure (years)			
n	50	205	255
Mean (SD)	1.3 (0.851)	1.3 (0.918)	1.3 (0.903)
Q1, Q3	0.515, 1.979	0.501, 2.094	0.507, 2.094
Median	1.012	1.177	1.155
Min, max	0.17, 2.83	0.00, 3.13	0.00, 3.13
Maximum Daily Dose (mg/kg/day)			
n	16	0	16
Mean (SD)	10.1 (3.5)	-	10.1 (3.5)
Q1, Q3	8.0, 12.0	-	8.0, 12.0
Median	8.0	-	8.0
Min, max	6, 16	-	6, 16
Maximum Daily Dose (mg/day)			
n	40	205	245
Mean (SD)	431.3 (148.8)	502.2 (174.9)	490.6 (172.7)
Q1, Q3	400, 475	400, 600	400, 600
Median	400	400	400
Min, max	200, 800	100, 800	100, 800
Modal Dose (mg/kg/day)			
n	16	0	16
Mean (SD)	9.0 (3.4)	-	9.0 (3.4)
Q1, Q3	7.5, 10	-	7.5, 10
Median	8.0	-	8.0
Min, max	3, 16	-	3, 16
Modal Dose (mg/day)			
n	40	205	245
Mean (SD)	358.8 (89.8)	372.9 (109.2)	370.6 (106.2)
Q1, Q3	300, 400	300, 400	300, 400
Median	400	400	400
Min, max	200, 600	100, 800	100, 800

LCM=lacosamide; max=maximum; min=minimum; Q1=lower quartile; Q3=upper quartile; SD=standard deviation
Note: LCM exposure=(date of last LCM dose-date of first LCM dose)+1 for completed studies or (date of clinical cutoff date-date of first LCM dose)+1 for ongoing study participants.

Note: Modal dose was defined as the daily LCM dose the study participant received for the longest duration during the LCM Exposure Period.
Note: Participant-years of exposure is the total treatment duration in days divided by 365.25.
Data source: Table 4.1.2

Table 15: Pool SGTC-1 exposure to LCM over time by age group

	≥4 to <16 years						≥16 years		All pediatric participants	
	≥4 to <12 yrs		≥12 to <16 yrs		Total					
LCM exposure	N=15 n (%)	P-Y exposed	N=15 n (%)	P-Y exposed	N=30 n (%)	P-Y exposed	N=20 n (%)	P-Y exposed	N=50 n (%)	P-Y exposed
>0 months	15 (100)	16.78	15(100)	25.10	30 (100)	41.88	20 (100)	23.08	50 (100)	64.97
≥6 months	13 (86.7)	15.92	13 (86.7)	24.34	26 (86.7)	40.26	17 (85.0)	22.45	43 (86.0)	62.71
≥12 months	9 (60.0)	13.52	10 (66.7)	22.61	19 (63.3)	36.13	9 (45.0)	17.71	28 (56.0)	53.83
≥18 months	5 (33.3)	9.41	9 (60.0)	21.37	14 (46.7)	30.78	7 (35.0)	15.40	21 (42.0)	46.18
≥24 months	2 (13.3)	4.53	8 (53.3)	19.71	10 (33.3)	24.25	6 (30.0)	13.63	16 (32.0)	37.88
≥30 months	1 (6.7)	2.55	5 (33.3)	13.06	6 (20.0)	15.61	3 (15.0)	7.92	9 (18.0)	23.53
≥36 months	0	0	2 (13.3)	5.54	2 (6.7)	5.54	1 (5.0)	2.83	3 (6.0)	8.38

LCM=lacosamide; P-Y=participant-years; yrs=years
Note: LCM exposure=(date of last LCM dose-date of first LCM dose)+1 for completed studies or (date of clinical cut-off date-date of first LCM dose)+1 for ongoing study participants.
Note: A month is defined as 28 days.
Note: Participant-years of exposure is the total treatment duration in days divided by 365.25.
Note: Percentages are relative to the number of study participants in Pool SGTC-1.
Data source: Pool SGTC-1 Table 4.1.1.1

Table 16: Pool SGTC-1 exposure to LCM over time by weight band

	<50kg						≥50kg		All pediatric participants	
	<30kg		≥30 to <50kg		Total					
LCM exposure	N=6 n (%)	P-Y exposed	N=11 n (%)	P-Y exposed	N=17 n (%)	P-Y exposed	N=33 n (%)	P-Y exposed	N=50 n (%)	P-Y exposed
>0 months	6 (100)	5.31	11 (100)	15.86	17 (100)	21.17	33 (100)	43.79	50 (100)	64.97
≥6 months	5 (83.3)	4.85	9 (81.8)	15.06	14 (82.4)	19.92	29 (87.9)	42.79	43 (86.0)	62.71
≥12 months	3 (50.0)	3.76	6 (54.5)	13.26	9 (52.9)	17.01	19 (57.6)	36.82	28 (56.0)	53.83
≥18 months	1 (16.7)	1.59	6 (54.5)	13.26	7 (41.2)	14.85	14 (42.4)	31.33	21 (42.0)	46.18
≥24 months	0	0	4 (36.4)	9.97	4 (23.5)	9.97	12 (36.4)	27.91	16 (32.0)	37.88
≥30 months	0	0	3 (27.3)	7.71	3 (17.6)	7.71	6 (18.2)	15.82	9 (18.0)	23.53
≥36 months	0	0	1 (9.1)	2.78	1 (5.9)	2.78	2 (6.1)	5.60	3 (6.0)	8.38

LCM=lacosamide; P-Y=participant-years
Note: LCM exposure=(date of last LCM dose-date of first LCM dose)+1 for completed studies or (date of clinical cut-off date-date of first LCM dose)+1 for ongoing study participants.
Note: A month is defined as 28 days.
Note: Participant-years of exposure is the total treatment duration in days divided by 365.25.
Note: Percentages are relative to the number of study participants in Pool SGTC-1.
Data source: Pool SGTC-1 Table 4.1.1.2

In study EP0012, investigators were allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction. As of the clinical cut-off date, 9 adult study participants were exposed to LCM≥800mg/day at least once during the Treatment Period. And 3 paediatric study participants were exposed to LCM≥600mg/day (tablet formulation) during the Treatment Period, as shown by the maximum ranges in this table.

In Pool SGTC-2, a total of 49 study participants were exposed to LCM for a total of 45.94 study participant-years. A total of 37 study participants (75.5%) were exposed for ≥6 months, 33 (67.3%) were exposed for ≥12 months, and 1 (2.0%) was exposed for ≥18 months. Overall, the median duration

of LCM exposure was 1.248 years (range:0 to 1.38 years). The median modal dose (mg/day) was 400 mg (range: 50 mg to 800 mg), and the median maximum dose was 500 mg/day (range: 50 mg to 800 mg).

Adverse events

Common adverse events

Study SP0982

The most common TEAEs (≥3% of study participants in the LCM or Placebo group) are summarized in the following table:

Table 17: Most common TEAEs (≥3% of pts) in study SP0982 (safety set)

MedDRA v16.1 SOC PT	Placebo N=121 n (%) [#]	LCM N=121 n (%) [#]	All study participants N=242 n (%) [#]
Any TEAEs	79 (65.3) [231]	96 (79.3) [320]	175 (72.3) [551]
Ear and labyrinth disorders	2 (1.7) [3]	9 (7.4) [9]	11 (4.5) [12]
Vertigo	2 (1.7) [2]	8 (6.6) [8]	10 (4.1) [10]
Eye disorders	3 (2.5) [3]	9 (7.4) [11]	12 (5.0) [14]
Vision blurred	1 (0.8) [1]	4 (3.3) [6]	5 (2.1) [7]
Gastrointestinal disorders	19 (15.7) [28]	25 (20.7) [47]	44 (18.2) [75]
Nausea	7 (5.8) [7]	12 (9.9) [13]	19 (7.9) [20]
Vomiting	1 (0.8) [3]	7 (5.8) [11]	8 (3.3) [14]
Diarrhoea	2 (1.7) [2]	4 (3.3) [5]	6 (2.5) [7]
General disorders and administration site conditions	14 (11.6) [15]	15 (12.4) [18]	29 (12.0) [33]
Fatigue	6 (5.0) [6]	8 (6.6) [8]	14 (5.8) [14]
Infections and infestations	23 (19.0) [32]	25 (20.7) [34]	48 (19.8) [66]
Nasopharyngitis	4 (3.3) [4]	8 (6.6) [12]	12 (5.0) [16]
Upper respiratory tract infection	6 (5.0) [9]	3 (2.5) [3]	9 (3.7) [12]
Injury, poisoning and procedural complications	16 (13.2) [21]	11 (9.1) [18]	27 (11.2) [39]
Contusion	5 (4.1) [6]	4 (3.3) [5]	9 (3.7) [11]
Investigations	11 (9.1) [21]	9 (7.4) [12]	20 (8.3) [33]
Alanine aminotransferase increased	4 (3.3) [4]	4 (3.3) [4]	8 (3.3) [8]
Aspartate aminotransferase increased	5 (4.1) [5]	2 (1.7) [2]	7 (2.9) [7]
Nervous system disorders	36 (29.8) [51]	58 (47.9) [108]	94 (38.8) [159]
Somnolence	17 (14.0) [17]	20 (16.5) [21]	37 (15.3) [38]
Dizziness	7 (5.8) [7]	28 (23.1) [36]	35 (14.5) [43]
Headache	12 (9.9) [13]	17 (14.0) [19]	29 (12.0) [32]
Ataxia	0	4 (3.3) [5]	4 (1.7) [5]
Disturbance in attention	0	4 (3.3) [5]	4 (1.7) [5]

MedDRA v16.1 SOC PT	Placebo N=121 n (%) [#]	LCM N=121 n (%) [#]	All study participants N=242 n (%) [#]
Respiratory, thoracic and mediastinal disorders	4 (3.3) [4]	8 (6.6) [11]	12 (5.0) [15]
Cough	1 (0.8) [1]	4 (3.3) [4]	5 (2.1) [5]

LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: Percentages were based on the number of study participants in the SS.
Note: [#] is the number of individual occurrences of the TEAE.
Data source: SP0982 CSR Table 11.2.1.1

In the LCM group, TEAEs were most commonly reported in the SOCs of Nervous system disorders (58 study participants [47.9%]), and Infections and infestations and Gastrointestinal disorders (25 study participants [20.7%] each). By PT, the most common TEAEs were dizziness (28 study participants [23.1%]), somnolence (20 [16.5%]), and headache (17 [14.0%]).

In the Placebo group, TEAEs were also most commonly reported in the SOCs of Nervous system disorders (36 study participants [29.8%]), Infections and infestations (23 study participants [19.0%]), and Gastrointestinal disorders (19 [15.7%]). By PT, the most common TEAEs were somnolence (17 [14.0%]), headache (12 [9.9%]), and nausea and dizziness (7 [5.8%] each).

For the LCM group, TEAEs were reported more frequently in the Titration Period as compared with the Maintenance Period (79 of 121 study participants [65.3%] vs. 44 of 82 [53.7%], respectively) but were reported with similar frequency in these periods for the Placebo group (67 of 121 study participants [55.4%] vs 39 of 70 [55.7%], respectively).

The most common TEAEs (≥3% of study participants in the LCM or Placebo group) adjusted for exposure are summarized for the paediatric and adult patient groups, respectively, in the table below.

Table 18: Most common TEAEs (≥3% of pts) per 100 pt-months in study SP0982 (safety set)

MedDRA v16.1 SOC PT	Pediatric		Adult		All study participants	
	Placebo rate (sum of PM=117.57)	LCM rate (sum of PM=134.79)	Placebo rate (sum of PM=402.75)	LCM rate (sum of PM=457.07)	Placebo rate (sum of PM=520.32)	LCM rate (sum of PM=591.86)
Ear and labyrinth disorders						
Vertigo	0.85	0	1.24	1.97	1.15	1.52
Eye disorders						
Vision blurred	0	0	0.50	1.31	0.38	1.01
Gastrointestinal disorders						
Nausea	0.85	2.23	2.23	2.41	1.92	2.37
Vomiting	1.70	0.74	1.49	2.19	1.54	1.86
Diarrhoea	0.85	0	0.25	1.31	0.38	1.01
General disorders and administration site conditions						
Fatigue	0.85	0.74	1.74	1.53	1.54	1.35
Infections and infestations						
Nasopharyngitis	1.70	2.97	0.99	1.97	1.15	2.20
Upper respiratory tract infection	5.10	1.48	1.74	0.22	2.50	0.51
Injury, poisoning and procedural complications						
Contusion	2.55	0	0.74	1.09	1.15	0.84
Investigations						
Alanine aminotransferase increased	0	0.74	0.99	0.66	0.77	0.68
Aspartate aminotransferase increased	0	0	1.24	0.44	0.96	0.34
Nervous system disorders						
Somnolence	1.70	5.94	5.46	2.84	4.61	3.55
Dizziness	2.55	5.19	3.48	7.22	3.27	6.76
Headache	2.55	2.23	3.72	3.50	3.46	3.21
Ataxia	0	0.74	0	0.88	0	0.84
Disturbance in attention	0	0	0	1.09	0	0.84
Respiratory, thoracic and mediastinal disorders						
Cough	0	1.48	0.25	0.44	0.19	0.68

AE=adverse event; LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PM=participant-months; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Rates are calculated using the total number of AEs (unique and non-unique) divided by the sum of the duration of each dosing period, in months (sum of participant-months), experienced by each study participant, multiplied by 100.
Data source: Supplemental Statistical Output Table 1.1

Irrespective of age, a notably different incidence rate (>2.00 per 100 person-months difference) between the LCM and placebo groups was observed for the TEAE of dizziness (6.76 vs 3.27, respectively).

In the LCM group, notably different incidence rates (>2.00 difference) between paediatric and adult study participants were observed for the TEAEs of somnolence (5.94 vs 2.84, respectively) and dizziness (5.19 vs 7.22, respectively).

In the placebo group, notably different incidence rates (>2.00 difference) between paediatric and adult study participants were observed for the TEAEs of upper respiratory tract infection (5.10 vs 1.74) and somnolence (1.70 vs 5.46).

Exposure-duration adjusted incidence rate for dizziness was higher for adult than for paediatric patients although the comparative differences to placebo were similar. Paediatric patients in the LCM group showed higher rates of somnolence over placebo (5.94 vs. 1.70) as compared to adult patients (2.84 vs. 5.46, respectively).

Severity and relatedness of TEAEs

The majority of TEAEs in both groups were mild (62.8% and 61.2%, respectively) or moderate (34.7% and 19.0%, respectively). Severe TEAEs were reported for 6 study participants (5.0%) in the LCM group compared with 3 study participants (2.5%) in the Placebo group. Most severe events were non-serious. Severe TEAEs in the SOCs of Nervous system disorders and Gastrointestinal disorders were exclusively reported in the LCM group (4 patients [3.3%] and 2 patients [1.7%], respectively).

The incidence of study participants reporting related TEAEs as per the investigator was higher in the LCM group (56 study participants [46.3%]) compared with the Placebo group (42 [34.7%]). In the LCM group, the most common related TEAEs were dizziness (21 study participants [17.4%]), somnolence (16 [13.2%]), and nausea (9 [7.4%]). In the Placebo group, the most common related TEAEs were somnolence (14 study participants [11.6%]), aspartate aminotransferase (AST) increased and dizziness (4 [3.3%] each), and alanine aminotransferase (ALT) increased, fatigue, and nausea (3 [2.5%] each).

The incidence of related TEAEs was higher in the LCM group compared with the Placebo group in both the paediatric (45.8% vs 16.0%, respectively) and adult (46.4% vs 39.6%, respectively) categories.

TEAEs by age

In the ≥4 to <12 years (n=17), ≥12 to <18 years (n=32), and ≥18 to <65 years (n=191) age categories, 52.9%, 87.5%, and 71.7% of study participants, respectively, reported any TEAEs during the study.

In the ≥4 to <12 years (n=17) age category, the most common TEAEs by SOC were Infections and infestations (6 study participants [35.3%]) and Injury, poisoning and procedural complications, Nervous System Disorders, and Psychiatric Disorders (2 [11.8%] each). By PT, the most common TEAE was influenza (2 study participants [11.8%]); no other TEAE was reported by >1 study participant.

In the ≥12 to <18 years (n=32) age category, the most common TEAEs by SOC were Nervous system disorders (16 study participants [50.0%]), Infections and infestations (11 [34.4%]), and Gastrointestinal disorders (9 study participants [28.1%]). By PT, the most common TEAEs were dizziness and somnolence (7 study participants [21.9%] each) and headache and upper respiratory tract infection (4 [12.5%] each).

In the ≥18 to <65 years (n=191) age category, the most common TEAEs by SOC were Nervous System Disorders (75 study participants [39.3%]), Gastrointestinal disorders (35 study participants [18.3%]), and Infections and infestations (31 study participants [16.2%]). By PT, the most common TEAEs were somnolence (29 study participants [15.2%]), dizziness (26 study participants [13.6%]), and headache (24 study participants [12.6%]).

In the ≥65 years age category (n=2), no TEAEs (by SOC or PT) were reported by >1 study participant.

Serious TEAEs were reported by 0%, 6.3%, and 5.2% of study participants in the ≥4 to <12 years, ≥12 to <18 years, and ≥18 to <65 years age categories, respectively. Treatment-emergent AEs leading to discontinuation were reported by 0%, 3.1%, and 7.3% of study participants in the ≥4 to <12 years, ≥12 to <18 years, and ≥18 to <65 years age categories, respectively. There were no SAEs in the ≥65 years age category.

Severe TEAEs were reported by 0%, 6.3%, and 3.1% of study participants in the ≥4 to <12 years, ≥12 to <18 years, and ≥18 to <65 years age categories, respectively. There were 2 study participants in the ≥65 years age category (n=1 each in the LCM and Placebo groups).

In the paediatric category, related TEAEs reported by ≥5% of study participants in either the LCM (n=24) or placebo (n=25) group included dizziness (25.0% and 0%, respectively), somnolence (20.8% and 4.0%, respectively), and headache and nausea (8.3% and 0%, respectively, each). In the adult category, related TEAEs reported by ≥5% of study participants in either the LCM (n=97) or placebo

(n=96) group included dizziness (15.5% and 4.2%, respectively), somnolence (11.3% and 13.5%, respectively), vertigo (7.2% and 2.1%, respectively), nausea (7.2% and 3.1%, respectively), vomiting (5.2% and 0%, respectively), and fatigue (5.2% and 2.1%, respectively).

Incidence of TEAEs by actual dose at TEAE onset

Overall, 111 study participants each in the LCM and Placebo groups took tablets at any dose. For tablets, the incidence of TEAEs among study participants taking Placebo (n=111), LCM>0 to <200mg/day (n=111), LCM ≥200 to <400mg/day (n=106), and LCM ≥400 to <600mg/day (n=97) at TEAE onset was 66.7%, 31.5%, 42.5%, and 56.7%, respectively. Ten study participants each in the LCM and Placebo groups took oral solution at any dose. For oral solution, the incidences of TEAEs among study participants taking Placebo (n=10), LCM >0 to <4mg/kg/day (n=7), LCM ≥4 to <8mg/kg/day (n=10), and LCM ≥8mg/kg/day (n=9) at TEAE onset were 50.0%, 14.3%, 60.0%, and 44.4%, respectively.

As expected, slight dose-related trends could be observed for TEAEs related to nervous system disorders (dizziness, somnolence) and vertigo.

Study EP0012

A summary of TEAEs by baseline age in the feeder study, SP0982, is shown in the table below.

Table 19: Overview of TEAEs in study EP0012 (safety set)

Category	Baseline age in SP0982 (years)				All study participants
	≥4 to <12 N=12	≥12 to <18 N=30	≥18 to <65 N=168	≥65 N=1	N=211
	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]
Any TEAEs	7 (58.3) [39]	24 (80.0) [104]	135 (80.4) [670]	1 (100) [3]	167 (79.1) [816]
Serious TEAEs	2 (16.7) [4]	7 (23.3) [10]	23 (13.7) [35]	0	32 (15.2) [49]
Study participant discontinuations due to TEAEs	0	1 (3.3) [1]	3 (1.8) [10]	1 (100) [1]	5 (2.4) [12]
Drug-related TEAEs	3 (25.0) [5]	9 (30.0) [21]	59 (35.1) [144]	1 (100) [2]	72 (34.1) [172]
Severe TEAEs	0	2 (6.7) [4]	16 (9.5) [24]	1 (100) [1]	19 (9.0) [29]
All Deaths	0	0	0	0	0
Deaths (TEAEs leading to Death)	0	0	0	0	0

AE=adverse event; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least one TEAE in that category.
Note: Percentages were based on the number of study participants in the SS.
Note: [#] was the number of individual occurrences of the TEAE in that category.
Note: An AE with missing intensity was treated as severe; an AE with missing drug relationship was treated as related.
Data source: EP0012 interim CSR Table 10.1

As of the clinical cut-off date for the interim CSR, the most frequently reported TEAEs (PT) per 100 person-months were: nasopharyngitis (35 study participants [16.6%]), with a rate of 0.97 person-months; headache (34 study participants [16.1%]), 0.94 person-months; dizziness (32 [15.2%]), 0.88 person-months; somnolence (22 [10.4%]), 0.61 person-months; upper respiratory tract infection (14 [6.6%]), 0.39 person-months; and contusion and nausea (13 [6.2%] each), 0.36 person-months each.

Comparison of TEAEs for PGTCS vs. POS populations

A side-by-side presentation of common TEAEs between Pool SGTC-1 as compared to two previously submitted data pools for the adult and paediatric POS populations, respectively, is shown below.

Table 20: Most common TEAEs (≥2% of pts in Pool SGTC-1) in paediatric and adult PGTCS and POS studies

	Pediatric study participants[a]		Adult study participants[b]	
	PGTCS	POS	PGTCS	POS
MedDRA v16.1 SOC PT	Pool SGTC-1[c] N=50 n (%)	Pool SPX-1[d] N=408 n (%)	Pool SGTC-1[c] N=205 n (%)	Pool S2[e] N=1327 n (%)
Any TEAEs	41 (82.0)	300 (73.5)	178 (86.8)	1224 (92.2)
Ear and labyrinth disorders	2 (4.0)	10 (2.5)	23 (11.2)	153 (11.5)
Vertigo	2 (4.0)	6 (1.5)	21 (10.2)	89 (6.7)
Eye disorders	2 (4.0)	40 (9.8)	21 (10.2)	440 (33.2)
Diplopia	1 (2.0)	13 (3.2)	8 (3.9)	254 (19.1)
Vision blurred	0	10 (2.5)	7 (3.4)	160 (12.1)
Gastrointestinal disorders	19 (38.0)	127 (31.1)	47 (22.9)	565 (42.6)
Nausea	6 (12.0)	19 (4.7)	18 (8.8)	220 (16.6)
Vomiting	5 (10.0)	60 (14.7)	13 (6.3)	199 (15.0)
Diarrhea	3 (6.0)	32 (7.8)	11 (5.4)	99 (7.5)
Abdominal pain	1 (2.0)	19 (4.7)	6 (2.9)	39 (2.9)
General disorders and administration site conditions	9 (18.0)	92 (22.5)	40 (19.5)	476 (35.9)
Fatigue	3 (6.0)	21 (5.1)	13 (6.3)	195 (14.7)
Pyrexia	3 (6.0)	53 (13.0)	7 (3.4)	50 (3.8)
Irritability	1 (2.0)	11 (2.7)	5 (2.4)	49 (3.7)
Infections and infestations	26 (52.0)	176 (43.1)	79 (38.5)	599 (45.1)
Nasopharyngitis	14 (28.0)	64 (15.7)	29 (14.1)	201 (15.1)
Upper respiratory tract infection	5 (10.0)	41 (10.0)	12 (5.9)	135 (10.2)
Influenza	4 (8.0)	20 (4.9)	7 (3.4)	90 (6.8)
Urinary tract infection	2 (4.0)	8 (2.0)	6 (2.9)	76 (5.7)
Gastroenteritis	1 (2.0)	12 (2.9)	6 (2.9)	23 (1.7)
Injury, poisoning and procedural complications	9 (18.0)	62 (15.2)	52 (25.4)	479 (36.1)
Contusion	6 (12.0)	11 (2.7)	11 (5.4)	151 (11.4)
Head injury	3 (6.0)	5 (1.2)	7 (3.4)	49 (3.7)
Laceration	1 (2.0)	12 (2.9)	6 (2.9)	123 (9.3)
Fall	2 (4.0)	7 (1.7)	4 (2.0)	91 (6.9)
Ligament sprain	0	3 (0.7)	6 (2.9)	57 (4.3)
Investigations	5 (10.0)	38 (9.3)	25 (12.2)	339 (25.5)
Alanine aminotransferase increased	2 (4.0)	1 (0.2)	5 (2.4)	20 (1.5)
Musculoskeletal and connective tissue disorders	2 (4.0)	22 (5.4)	26 (12.7)	359 (27.1)
Back pain	0	2 (0.5)	10 (4.9)	133 (10.0)
Arthralgia	0	4 (1.0)	6 (2.9)	67 (5.0)
Nervous system disorders	27 (54.0)	162 (39.7)	119 (58.0)	964 (72.6)

	Pediatric study participants[a]		Adult study participants[b]	
	PGTCS	POS	PGTCS	POS
MedDRA v16.1 SOC PT	Pool SGTC-1[c] N=50 n (%)	Pool SPX-1[d] N=408 n (%)	Pool SGTC-1[c] N=205 n (%)	Pool S2[e] N=1327 n (%)
Dizziness	11 (22.0)	55 (13.5)	53 (25.9)	609 (45.9)
Headache	9 (18.0)	38 (9.3)	43 (21.0)	291 (21.9)
Somnolence	13 (26.0)	40 (9.8)	32 (15.6)	151 (11.4)
Grand mal convulsion	2 (4.0)	0	11 (5.4)	11 (0.8)
Migraine	0	5 (1.2)	10 (4.9)	21 (1.6)
Myoclonic epilepsy	0	0	8 (3.9)	1 (<.1)
Paresthesia	0	2 (0.5)	8 (3.9)	52 (3.9)
Tremor	0	18 (4.4)	8 (3.9)	152 (11.5)
Balance disorder	1 (2.0)	10 (2.5)	6 (2.9)	126 (9.5)
Amnesia	0	1 (0.2)	6 (2.9)	29 (2.2)
Ataxia	1 (2.0)	2 (0.5)	5 (2.4)	141 (10.6)
Disturbance in attention	0	2 (0.5)	6 (2.9)	31 (2.3)
Psychiatric disorders	6 (12.0)	57 (14.0)	30 (14.6)	390 (29.4)
Anxiety	1 (2.0)	3 (0.7)	6 (2.9)	64 (4.8)
Insomnia	1 (2.0)	8 (2.0)	6 (2.9)	86 (6.5)
Respiratory, thoracic and mediastinal disorders	6 (12.0)	68 (16.7)	17 (8.3)	290 (21.9)
Oropharyngeal pain	0	11 (2.7)	7 (3.4)	79 (6.0)
Vascular disorders	1 (2.0)	3 (0.7)	11 (5.4)	126 (9.5)
Hypertension	0	0	7 (3.4)	54 (4.1)

LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PGTCS=primary generalized tonic-clonic seizure; POS=partial-onset seizure; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: Percentages were based on the number of study participants with LCM exposure during TEAE onset.
[a] Pediatric was defined as study participants from ≥4 to <18 years of age for Pool SGTC-1 and ≥4 years to <16 years of age for Pool SPX-1.
[b] Adult was defined as study participants from ≥18 years of age for Pool SGTC-1 and ≥16 years of age for Pool S2.
[c] Pool SGTC-1 included all study participants receiving at least 1 dose of LCM in the double-blind, placebo-controlled study SP0982 or the open-label study EP0012.
[d] Pool SPX-1 included all study participants receiving at least 1 dose of LCM in the open-label studies SP847, SP848, or EP0034. Study participants from EP0034 were limited to those who participated in SP0969. Study participants in SP848 who participated in SP0966 were excluded.
[e] Pool S2 included all study participants receiving at least 1 dose of LCM from the double-blind, placebo-controlled studies SP667, SP754, and SP755, and all study participants who received at least 1 dose of LCM in open-label studies SP607, SP615, SP756, and SP774.
Data source: Table 5.1.1, Nov 2016 Pool SPX-1 Table 7.2.1, and Pool S2 Table EP.6.1.2

To further contextualize the safety profile for the PGTCS population, the MAH provided a side-by-side presentation of common TEAEs between Pool SGTC-1 as compared to two data pools for the adult and paediatric POS populations, respectively. Overall, given the differences in underlying epileptic conditions (PGTCS vs. POS) and considering differences in dataset sizes that may explain some of the fluctuations, the common TEAE pattern seems to be broadly similar between the indications and for both populations. However, some differences in the frequencies of TEAEs were observed; a slightly higher incidence of TEAEs were observed in PGTCS compared with POS (82.0 vs 73.5%, respectively).

A summary table with further division by age is shown below. Generally, the incidence of somnolence was higher for all age groups in PGTCS compared with POS. This difference is not explained by concomitant intake of other AEDs in PCTCS patients; paediatric patients in the LCM group showed higher rates of

somnolence over placebo (5.94 vs. 1.70 per 100 pt-months), which was not observed in adult patient. Thus, this may indicate that especially paediatric patients with PGTCS are more at risk for this ADR.

Also, paediatric patients with PGTCS experienced contusions, head injury, and falls much more frequently than both paediatric patients with POS and adult with PGTCS (12% vs 2.7% vs 5.4%; 6% vs 1.2% vs 3.4%, and 4% vs 1.7% vs 2%, respectively). The difference cannot be ascribed to the occurrence of dizziness, as this TEAE was more common in adults compared to paediatric patients (7.22/100 participants-month vs 5.19/100 participants-month, respectively). Rather, it may indicate differences in the predominant seizure pattern of epileptic syndromes between children and adults with primary generalized epilepsy. However, quite unexpectedly, given the high prevalence in children with primary generalized epilepsy, no myoclonic epilepsy has been listed among TEAEs in the paediatric population, while a frequency of 3.9% was recorded in adult patients. More in general, as discussed below in this AR, the MAH was requested to provide more information on the adjudication of epilepsy events as TEAEs.

The issue of worsening of seizures is further discussed below.

Table 21: Incidence of the most common TEAEs (≥2% of all study participants in Pool SGTC-1) in PGTCS and POS studies by age category

	Pediatric study participants				Adult study participants	
	PGTCS ≥4 to <12 years	POS ≥4 to <12 years	PGTCS ≥12 to <16 years	POS ≥12 to <16 years	PGTCS ≥16 years	POS ≥16 years
MedDRA v16.1 SOC PT	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=253 n (%)	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=155 n (%)	Pool SGTC-1[a] N=205 n (%)	Pool S2[c] N=1327 n (%)
Any TEAEs	11 (73.3)	186 (73.5)	13 (86.7)	114 (73.5)	178 (86.8)	1224 (92.2)
Ear and labyrinth disorders	1 (6.7)	6 (2.4)	1 (6.7)	4 (2.6)	23 (11.2)	153 (11.5)
Vertigo	1 (6.7)	4 (1.6)	1 (6.7)	2 (1.3)	21 (10.2)	89 (6.7)
Eye disorders	0	21 (8.3)	1 (6.7)	19 (12.3)	21 (10.2)	440 (33.2)
Diplopia	0	7 (2.8)	0	6 (3.9)	8 (3.9)	254 (19.1)
Vision blurred	0	5 (2.0)	0	5 (3.2)	7 (3.4)	160 (12.1)
Gastrointestinal disorders	2 (13.3)	77 (30.4)	7 (46.7)	50 (32.3)	47 (22.9)	565 (42.6)
Nausea	0	12 (4.7)	3 (20.0)	7 (4.5)	18 (8.8)	220 (16.6)
Vomiting	0	41 (16.2)	1 (6.7)	19 (12.3)	13 (6.3)	199 (15.0)
Diarrhea	2 (13.3)	19 (7.5)	1 (6.7)	13 (8.4)	11 (5.4)	99 (7.5)
Abdominal pain	0	15 (5.9)	1 (6.7)	4 (2.6)	6 (2.9)	39 (2.9)
General disorders and administration site conditions	2 (13.3)	60 (23.7)	4 (26.7)	32 (20.6)	40 (19.5)	476 (35.9)
Fatigue	1 (6.7)	12 (4.7)	1 (6.7)	9 (5.8)	13 (6.3)	195 (14.7)
Pyrexia	1 (6.7)	39 (15.4)	2 (13.3)	14 (9.0)	7 (3.4)	50 (3.8)
Irritability	0	10 (4.0)	1 (6.7)	1 (0.6)	5 (2.4)	49 (3.7)
Infections and infestations	7 (46.7)	123 (48.6)	9 (60.0)	53 (34.2)	79 (38.5)	599 (45.1)
Nasopharyngitis	4 (26.7)	48 (19.0)	2 (13.3)	16 (10.3)	29 (14.1)	201 (15.1)

MedDRA v16.1 SOC PT	Pediatric study participants				Adult study participants	
	PGTCS ≥4 to <12 years	POS ≥4 to <12 years	PGTCS ≥12 to <16 years	POS ≥12 to <16 years	PGTCS ≥16 years	POS ≥16 years
	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=253 n (%)	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=155 n (%)	Pool SGTC-1[a] N=205 n (%)	Pool S2[c] N=1327 n (%)
Upper respiratory tract infection	1 (6.7)	27 (10.7)	4 (26.7)	14 (9.0)	12 (5.9)	135 (10.2)
Influenza	3 (20.0)	11 (4.3)	1 (6.7)	9 (5.8)	7 (3.4)	90 (6.8)
Urinary tract infection	0	6 (2.4)	0	2 (1.3)	6 (2.9)	76 (5.7)
Gastroenteritis	0	10 (4.0)	1 (6.7)	2 (1.3)	6 (2.9)	23 (1.7)
Injury, poisoning and procedural complications	1 (6.7)	38 (15.0)	1 (6.7)	24 (15.5)	52 (25.4)	479 (36.1)
Contusion	1 (6.7)	7 (2.8)	0	4 (2.6)	11 (5.4)	151 (11.4)
Head injury	1 (6.7)	3 (1.2)	1 (6.7)	2 (1.3)	7 (3.4)	49 (3.7)
Laceration	1 (6.7)	8 (3.2)	0	4 (2.6)	6 (2.9)	123 (9.3)
Fall	1 (6.7)	4 (1.6)	0	3 (1.9)	4 (2.0)	91 (6.9)
Ligament sprain	0	1 (0.4)	0	2 (1.3)	6 (2.9)	57 (4.3)
Investigations	2 (13.3)	25 (9.9)	2 (13.3)	13 (8.4)	25 (12.2)	339 (25.5)
Alanine aminotransferase increased	0	1 (0.4)	1 (6.7)	0	5 (2.4)	20 (1.5)
Musculoskeletal and connective tissue disorders	1 (6.7)	12 (4.7)	0	10 (6.5)	26 (12.7)	359 (27.1)
Back pain	0	1 (0.4)	0	1 (0.6)	10 (4.9)	133 (10.0)
Arthralgia	0	1 (0.4)	0	3 (1.9)	6 (2.9)	67 (5.0)

MedDRA v16.1 SOC PT	Pediatric study participants				Adult study participants	
	PGTCS ≥4 to <12 years	POS ≥4 to <12 years	PGTCS ≥12 to <16 years	POS ≥12 to <16 years	PGTCS ≥16 years	POS ≥16 years
	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=253 n (%)	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=155 n (%)	Pool SGTC-1[a] N=205 n (%)	Pool S2[c] N=1327 n (%)
Nervous system disorders	5 (33.3)	105 (41.5)	9 (60.0)	57 (36.8)	119 (58.0)	964 (72.6)
Dizziness	2 (13.3)	29 (11.5)	3 (20.0)	26 (16.8)	53 (25.9)	609 (45.9)
Headache	2 (13.3)	23 (9.1)	1 (6.7)	15 (9.7)	43 (21.0)	291 (21.9)
Somnolence	4 (26.7)	35 (13.8)	3 (20.0)	5 (3.2)	32 (15.6)	151 (11.4)
Grand mal convulsion	0	0	0	0	11 (5.4)	11 (0.8)
Migraine	0	3 (1.2)	0	2 (1.3)	10 (4.9)	21 (1.6)
Myoclonic epilepsy	0	0	0	0	8 (3.9)	1 (<.1)
Paresthesia	0	0	0	2 (1.3)	8 (3.9)	52 (3.9)
Tremor	0	14 (5.5)	0	4 (2.6)	8 (3.9)	152 (11.5)
Balance disorder	0	7 (2.8)	0	3 (1.9)	6 (2.9)	126 (9.5)
Amnesia	0	1 (0.4)	0	0	6 (2.9)	29 (2.2)
Ataxia	0	2 (0.8)	1 (6.7)	0	5 (2.4)	141 (10.6)
Disturbance in attention	0	2 (0.8)	0	0	6 (2.9)	31 (2.3)
Psychiatric disorders	2 (13.3)	41 (16.2)	3 (20.0)	16 (10.3)	30 (14.6)	390 (29.4)
Anxiety	0	3 (1.2)	1 (6.7)	0	6 (2.9)	64 (4.8)
Insomnia	0	8 (3.2)	0	0	6 (2.9)	86 (6.5)
Respiratory, thoracic and mediastinal disorders	1 (6.7)	48 (19.0)	0	20 (12.9)	17 (8.3)	290 (21.9)

MedDRA v16.1 SOC PT	Pediatric study participants				Adult study participants	
	PGTCS ≥4 to <12 years	POS ≥4 to <12 years	PGTCS ≥12 to <16 years	POS ≥12 to <16 years	PGTCS ≥16 years	POS ≥16 years
	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=253 n (%)	Pool SGTC-1[a] N=15 n (%)	Pool SPX-1[b] N=155 n (%)	Pool SGTC-1[a] N=205 n (%)	Pool S2[c] N=1327 n (%)
Oropharyngeal pain	0	7 (2.8)	0	4 (2.6)	7 (3.4)	79 (6.0)
Vascular disorders	1 (6.7)	2 (0.8)	0	1 (0.6)	11 (5.4)	126 (9.5)
Hypertension	0	0	0	0	7 (3.4)	54 (4.1)

LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PGTCS=primary generalized tonic-clonic seizure; POS=partial-onset seizure; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: Percentages were based on the number of study participants with LCM exposure during TEAE onset.
[a] Pool SGTC-1 included all study participants receiving at least 1 dose of LCM in the double-blind, placebo-controlled study SP0982 or the open-label study EP0012.
[b] Pool SPX-1 included all study participants receiving at least 1 dose of LCM in the open-label studies SP847, SP848, or EP0034. Study participants from EP0034 were limited to those who participated in SP0969. Study participants in SP848 who participated in SP0966 were excluded.
[c] Pool S2 included all study participants receiving at least 1 dose of LCM from the double-blind, placebo-controlled studies SP667, SP754, and SP755, and all study participants who received at least 1 dose of LCM in open-label studies SP607, SP615, SP756, and SP774.
Data source: Pool SGTC-1 Table 5.1.1.4, Nov 2016 Pool SPX-1 Table 7.2.1, and Pool S2 Table EP.6.1.2

Pool SGTC-2

Overall, TEAEs were reported by 47 study participants (95.9%) in Pool SGTC-2. The most common TEAEs were dizziness (22 study participants [44.9%]), nausea (15 study participants [30.6%]), upper respiratory tract infection (12 study participants [24.5%]), and headache (12 study participants [24.5%]).

AEs of special interest

Data related to seizures

Study SP0982

As compared to the 16-week Combined Baseline period (i.e., the 12-week Historical Baseline plus the 4-week Prospective Baseline), new seizure types that were reported during the Treatment Period included *absence seizures* (1 study participant [0.8%] in the LCM group and 0 in the placebo group), *myoclonic seizures* (6 study participants [5.0%] in the LCM group and 4 [3.3%] in the placebo group), and unclassified epileptic seizures (2 study participants [1.7%] in the LCM group and 0 in the placebo group).

When considering both Combined Baseline as well as seizure history, new seizure types reported during the Treatment Period included *myoclonic seizures* (1 study participant [0.8%] in the LCM group and 1 [0.8%] in the placebo group), and unclassified epileptic seizures (1 study participant [0.8%] in the LCM group and 0 in the placebo group).

Absence seizures

A total of 93 study participants (LCM, n=51; placebo, n=42) experienced absence seizures during the Prospective Baseline. Greater percent changes from Prospective Baseline in median days with absence seizures were observed in the LCM group compared with the placebo group during the Titration Period (-24.6% and-11.1%, respectively), first 12 weeks of the Treatment Period (-30.4% and -13.3%, respectively), and 24-week Treatment Period (-30.1% and -15.3%, respectively).

This was the case for both the adult and paediatric populations. For paediatric participants, the median percent change in days with absence seizures from Prospective Baseline during the 24-week Treatment Period was -51.8% for paediatric study participants in the LCM group and -44.6% in the Placebo group.

Myoclonic seizures

A total of 96 study participants (LCM, n=47; placebo, n=49) experienced myoclonic seizures during the Prospective Baseline.

The percent changes from Prospective Baseline in median number of days with myoclonic seizures for the LCM and placebo groups were -32.5% and -51.8%, respectively, during the Titration period; -43.8% and -65.7%, respectively, during the first 12 weeks of the Treatment Period; and -54.6% and -65.7%, respectively, during the 24-week Treatment Period.

Summaries of seizure worsening (defined as a study participant experiencing ≥50% increase in the number of days with absence or myoclonic seizures per 28 days from Prospective Baseline) for absence seizures and myoclonic seizures are provided in the table below.

Table 2 Seizure worsening for days with absence seizures and myoclonic seizures as compared to Prospective Baseline in study SP0982 (safety set)

Time Period Variable	Placebo	LCM
Absence seizures	**N=42**	**N=51**
Titration Period		
n	42	49
50% seizure worsening, n (%)	3/42 (7.1)	1/51 (2.0)
First 12 weeks of the Treatment Period		
n	42	49
50% seizure worsening, n (%)	3/42 (7.1)	1/51 (2.0)
24-week Treatment Period		
n	42	49
50% seizure worsening, n (%)	3/42 (7.1)	1/51 (2.0)
Myoclonic seizures	**N=49**	**N=47**
Titration Period		
n	49	46
50% seizure worsening, n (%)	2/49 (4.1)	4/47 (8.5)
First 12 weeks of the Treatment Period		
n	49	46
50% seizure worsening, n (%)	2/49 (4.1)	4/47 (8.5)
24-week Treatment Period		
n	49	46
50% seizure worsening, n (%)	2/49 (4.1)	4/47 (8.5)

LCM=lacosamide; SS=Safety Set
Note: Percentages were based on the number of subjects in the SS who reported a history of absence/myoclonic seizures or an occurrence of absence/myoclonic seizures in the Combined Baseline or in the Treatment Period.
Note: Seizure worsening was defined as a study participant experiencing ≥50% increase in the number of days with seizures per 28 days from Prospective Baseline.
Data sources: Table 8.6.4 and Table 8.7.4

For myoclonic seizures, the percentage of study participants with 50% seizure worsening for days with myoclonic seizures for the LCM and Placebo groups was 8.5% (4 of 47) and 4.1% (2 of 49), respectively, each during the Titration Period, first 12 weeks of the Treatment Period, and 24-week Treatment Period.

For paediatric study participants, the percentage of study participants in the LCM group with 50% worsening was 20% (1 of 5) each during the Titration Period, first 12 weeks of the Treatment Period, and during the 24-week Treatment Period. No paediatric study participants in the Placebo group had 50%

worsening during the Titration Period, first 12 weeks of the Treatment Period, or 24-week Treatment Period.

Onset of myoclonic seizures or worsening in days of myoclonic seizures

A total of 21 study participants experienced onset of myoclonic seizure or ≥50% worsening in days of myoclonic seizures, of which 14 study participants were in the LCM group and 7 were in the Placebo group. Study participants in the LCM group included 8 males and 6 females of 13 to 53 years of age.

Six study participants out of the 14 had a medical history of absence and myoclonic seizures, 7 study participants reported a medical history of myoclonic seizure only, and one study participant had no history of absence or myoclonic seizure. Among the 13 study participants with a medical history of myoclonic seizure at baseline, 8 reported ≥50% worsening in days of myoclonic seizures compared to the Baseline Period in at least one Treatment Period and 5 study participants had an occurrence of a new myoclonic seizure in the treatment period that was not reported in the Combined Baseline Period of SP0982. The remaining study participant, who reported no myoclonic seizure history, experienced an emergent myoclonic epilepsy.

TEAEs related to epilepsy

Treatment-emergent adverse events of relevance to the PGTCS population (per medical review) were: status epilepticus (1 adult study participant taking 50mg LCM), grand mal convulsion (4 adult study participants; 3 taking LCM [200mg, 250mg, and 400mg] and 1 taking placebo), and myoclonus (1 adult study participant taking 300mg LCM).

Brief narratives of these cases follow below.

One event of status epilepticus was reported during the Treatment Period:

- A ≥30 to <40-year-old study participant in the LCM group reported a serious TEAE of generalized status epilepticus during the Titration Period. The LCM dose at onset was 50 mg/day, and the study participant received this dose for 1 day prior to the event onset. The event began on Day 10, was severe in intensity, was considered related per the investigator, and led to discontinuation of IMP. The event resolved after 3 days. The study participant was hospitalized and received intubation, arterial blood gas sampling, computed tomography scan, chest x-ray, ECG, drug monitoring, and other laboratory tests as needed. The study participant was treated with ceftriaxone, sodium chloride, suxamethonium chloride, and vecuronium during the time of the event. Concomitant AEDs used by the study participant included lamotrigine, levetiracetam, etomidate, lorazepam, midazolam hydrochloride, propofol, and phenytoin.

Three events of grand mal convulsion were reported during the Treatment Period, and 1 event was reported during the Post-Treatment Period:

- An ≥18 to <30-year-old study participant in the LCM group reported a serious TEAE of grand mal convulsion during the Titration Period. The LCM dose at onset was 250 mg/day, and the study participant received this dose for 1 day prior to the event onset. The event began on Day 30, was mild in intensity, was considered not related per the investigator, and did not lead to discontinuation of IMP. The event was intermittent and resolved after 2 days. Concomitant AEDs used by the study participant included lamotrigine and levetiracetam.
- A ≥18 to <30-year-old study participant in the Placebo group reported a nonserious TEAE of grand mal convulsion during the Treatment Period. The LCM dose at onset was 400 mg/day, and the study participant received this dose for 90 days prior to the event onset. The event began on Day 111, was moderate in intensity, was considered related per the investigator, and did not lead to discontinuation of IMP. The event was continuous and did not resolve during the study. Concomitant AEDs used by the study participant included levetiracetam.
- An ≥18 to <30-year-old study participant in the LCM group reported a serious TEAE of grand mal convulsion during the Taper Period. In the days prior to the event the study participant had received LCM at a dose of 400 mg/day.

The event began on Day 45, was severe in intensity, and was considered not related per the investigator. The event was intermittent and resolved after 11 days. Concomitant AEDs used by the study participant included valproic acid.

- An ≥18 to <30-year-old study participant in the LCM group reported a nonserious TEAE of grand mal convulsion during the Post-Treatment (Taper) Period. The LCM dose at onset was 200 mg/day, and the study participant received this dose for 23 days prior to the event onset. The event began on Day +8, was severe in intensity and was considered related per the investigator. The event was intermittent and resolved after 1 day. Concomitant AEDs used by the study participant included levetiracetam, lamotrigine, and gabapentin.

One event coded as *myoclonus* was reported during the Treatment Period:

- A ≥30 to <40-year-old study participant in the Placebo group reported a nonserious TEAE of myoclonus during the Maintenance Period. The LCM dose at onset was 300mg/day, and the study participant received this dose for 22 days prior to the event onset. The event began on Day 62, was mild in intensity, was considered related per the investigator, and did not lead to discontinuation of IMP. The event was intermittent and did not resolve during the study. Concomitant AEDs used by the study participant included valproate sodium and clonazepam

Also, 3 study participants (2.5%) in the LCM group reported 3 TEAEs of *myoclonic epilepsy* during treatment (the Titration Period) as compared with 0 study participants in the Placebo group. None of the TEAEs were serious.

- A ≥30 to <40-year-old study participant reported a TEAE of myoclonic epilepsy (verbatim: increase seizures [myoclonic]) during the Titration Period. The LCM dose at onset was 400 mg/day, and the study participant received this dose for 14 days prior to the event onset. The event began on Day 35, was moderate in intensity, and was considered related per the investigator. The event was intermittent, did not lead to discontinuation of IMP, and had resolved after 3 days. Concomitant AEDs used by the study participant included clonazepam, levetiracetam, and topiramate.
- An ≥18 to <30-year-old study participant reported a TEAE of myoclonic epilepsy (verbatim: worsening of myoclonic seizure) during the Titration Period. The LCM dose at onset was 100 mg/day, and the study participant received this dose for 15 days prior to the event onset. The event began on Day 15, was moderate in intensity, and was considered related per the investigator. The event was intermittent, led to discontinuation of IMP, and had not resolved at the end of the study. Concomitant AEDs used by the study participant included perampanel.
- An ≥18 to <30-year-old study participant reported a TEAE of myoclonic epilepsy (verbatim: myoclonic seizure) during the Titration Period. The LCM dose at onset was 200 mg/day, and the study participant received this dose for 4 days prior to the event onset. The event began on Day 11, was mild in intensity, and was not considered related per the investigator. The event was intermittent, did not lead to discontinuation of IMP, and had not resolved at the end of the study. Concomitant AEDs used by the study participant included lamotrigine and retigabine.

In addition, 1 study participant in the LCM group reported a TEAE of *myoclonic epilepsy* during the Post-Treatment (Transition) Period:

- An ≥18 to <30-year-old study participant reported a TEAE of myoclonic epilepsy (verbatim: worsening of myoclonic seizures). The LCM dose at onset was 400 mg/day, and the study participant received this dose for 8 days prior to the event onset. The event began on Day 69, was nonserious, was mild in intensity, and was not considered related per the investigator. The event was intermittent, did not lead to discontinuation of IMP, and had not resolved at the end of the study. Concomitant AEDs used by the study participant included levetiracetam.
    - The above events are briefly schematized in the table below:
    - Treatment-emergent adverse events considered relevant to the PGTCS and myoclonic epilepsy population

(Treatment group)	Adverse event category	MedDRA preferred term	Date of event onset/ Days to onset [a] Period (phase)	Dose at onset/ Duration of event	Intensity/ Relationship	Outcome/ Action taken with study drug
(LCM)	DISC, SAE	Status epilepticus	/ 10 days Treatment (Titration)	LCM 50mg/day/ 3 days	Severe/ Related	Resolved / Withdrawn
(LCM)	SAE	Grand mal convulsion	/ 30 days Treatment (Titration)	LCM 250mg/day/ 2 days	Mild/ Not related	Resolved/ Dose not changed
(PBO)	DISC, SAE	Femur fracture *(due to GM convulsion)*	/ 111 days Maintenance	PBO 400mg 90 days	Severe/ Related	Not resolved/ Withdrawn
(LCM)	SAE	Grand mal convulsion	/ 45 days Post-treatment (Transition)	LCM 0mg/day/ 11 days *[LCM 400mg/day 2 days]*	Severe/Not related	Resolved/ Dose not changed
(LCM)	Other	Grand mal convulsion	8 days Post-Treatment (Taper)	LCM 200 mg/day/ 23 Days	Severe/ Related	Resolved
(LCM)	Other	Myoclonic epilepsy	/ 69 days Post-Treatment (Transition)	LCM 400mg/day/ Ongoing	Mild/ Not related	Not resolved/ Dose not changed
(LCM)	Other	Myoclonic epilepsy	/ 11 days Treatment (Titration)	LCM 200mg/day/ Ongoing	Mild/ Not related	Not resolved/ Dose not changed
(LCM)	Other	Myoclonic epilepsy	/ 35 days Treatment (Titration)	LCM 400mg/day/ 3 days	Moderate/ Related	Resolved/ Dose not changed
(LCM)	DISC, Other	Myoclonic epilepsy	/ 15 days Treatment (Titration)	LCM 100mg/day/ Ongoing	Moderate/ Related	Not resolved/ Withdrawn
(PBO)	Other	Myoclonus	/ 62 days Treatment (Maintenance)	PBO/ Ongoing	Mild/ Related	Not resolved/ Dose not changed
(PBO)	SAE	Clonic convulsion	/ 214 days Post-treatment (Safety follow-up)	N/A/ 11 days	Mild/ Related	Resolved/ N/A

- DISC=discontinuation due to adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PGNBE=pediatric growth-, neurodevelopment behavioral-, and endocrine-related adverse event; SAE=serious adverse event Source: Listing 7.2; 7.3; SP0982 Narratives

Even in cases considered not causally related by the investigator, a causal relationship cannot be excluded. For example, subject had no documented medical history of myoclonic seizures according to the demographic data listing. Also, there may have been a degree of underreporting of TEAEs; as is stated earlier, among the 13 LCM study participants in this study with a medical history of myoclonic seizure at baseline, 8 reported ≥50% worsening in days of myoclonic seizures compared to the Baseline Period in at least one Treatment Period. In this regard, although the investigator was to review any self-assessment procedures (eg, the seizure diary) employed in the study, the number of cases that resulted in TEAEs being reported seems to be low.

Myoclonic epilepsy was proposed as a new ADR for LCM in patients with PGTCS by the MAH and this is endorsed. However, it was considered that a warning also needed to be included in section 4.4 of the SmPC, stating that new onset or worsening of myoclonic seizures has been reported in patients with PGTCS.

Study EP0012

Absence seizures

A total of 11 study participants (5.2%) reported new absence seizures during the Treatment Period as compared with Combined Baseline, compared with 164 study participants (77.7%) who did not report new seizures.

One study participant (0.5%) reported new absence seizures during the Treatment Period (as compared with seizure history and/or Combined Baseline), compared with 137 study participants (64.9%) who did not report new absence seizures.

Myoclonic seizures

A total of 12 study participants (5.7%) reported new myoclonic seizures during the Treatment Period as compared with Combined Baseline, compared with 161 study participants (76.3%) who did not report new seizures.

A total of 5 study participants (2.4%) reported new myoclonic seizures during the Treatment Period (compared with seizure history and/or Combined Baseline), compared with 128 study participants (60.7%) who did not report new myoclonic seizures.

TEAEs related to epilepsy

As of the clinical cut-off date for the interim CSR, overall, the most frequently reported TEAE of relevance to the PGTCS population was grand mal convulsion (11 study participants [5.2%]); followed by myoclonic epilepsy, petit mal epilepsy and convulsions (5 study participants [2.4%] each); depression (4 study participants [1.9%]); and status epilepticus (3 study participants [1.4%]).

Table 23: Summary of selected TEAEs in study EP0012 (safety set)

MedDRA v16.1 SOC PT	Total N=211 Overall TEAE incidence n (%) [#]	Severe[a] n (%)	Related[b] n (%) [#]	Serious n (%) [#]	Discontinuation due to TEAE n (%) [#]
Nervous system disorders					
Grand mal convulsion	11 (5.2) [12]	2 (0.9)	0	8 (3.8) [9]	0
Myoclonic epilepsy	5 (2.4) [5]	1 (0.5)	1 (0.5) [1]	1 (0.5) [1]	2 (0.9) [2]
Petit mal epilepsy	5 (2.4) [9]	0	2 (0.9) [2]	0	0
Tonic convulsion	1 (0.5) [1]	0	0	1 (0.5) [1]	0
Convulsion	5 (2.4) [6]	0	1 (0.5) [1]	2 (0.9) [2]	1 (0.5) [1]
Status epilepticus	3 (1.4) [7]	2 (0.9)	0	3 (1.4) [5]	0
Psychiatric disorders					
Depression	4 (1.9) [4]	0	1 (0.5) [1]	0	1 (0.5) [1]

MedDRA=Medical Dictionary for Regulatory Activities; PGTCS=primary generalized tonic-clonic seizure; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: [#] was the number of individual occurrences of the TEAE.
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: Percentages were based on the number of study participants in the SS.
Note: Each study participant was counted once within each SOC/PT according to the severity and relationship for all TEAEs within that SOC or PT.
[a] A TEAE with missing intensity was treated as severe.
[b] A TEAE with missing drug relationship was treated as related.
Data sources: EP0012 interim CSR Table 10.2, EP0012 interim CSR Table 10.3, EP0012 interim CSR Table 10.4, EP0012 interim CSR Table 10.5.1, and EP0012 interim CSR Table 10.6.1

Other significant TEAEs

Ataxia

In SP0982, 4 (3.3%) study participants on LCM and 0 on Placebo reported TEAEs of ataxia. All were considered related to IMP per the Investigator. The events were mild to moderate in intensity, were not considered serious, and did not lead to withdrawal of LCM.

Based on these findings, the PT of Ataxia is proposed as a new ADR for LCM in patients with PGTCS. Of note, ADRs of Balance disorder, Coordination abnormal, Gait disturbance, Dizziness, Vertigo, and Nystagmus are already listed for LCM in the EU-SmPC.

It is agreed that this PT should be included as ADR in the product information. The events were mild or moderate and considered related to study drug by the investigator. Three of the cases were reported in adults and one in a 13-year-old paediatric patient. All events were reported during the titration phase.

Overall in study SP0982, differences in the incidence of TEAEs between the LCM and Placebo groups were observed for PTs of dizziness (23.1% vs 5.8%, respectively), somnolence (16.5% vs 14.0%, respectively), headache (14.0% vs 9.9%, respectively), nausea (9.9% vs 5.8%, respectively), vomiting (5.8% vs 0.8%, respectively), ataxia (3.3% vs 0%, respectively), disturbance in attention (3.3% vs 0%, respectively), myoclonic epilepsy (2.5% vs 0%, respectively), vertigo (6.6% vs 1.7%, respectively), and vision blurred (3.3% vs 0.8%, respectively). These ADR terms (except ataxia) are already included in section 4.8 of the SmPC.

There were no reports of ataxia in the interim EP0012 study.

Hepatic

In the controlled study SP0982, the incidence of study participants meeting criteria for potential drug-induced liver injury (PDILI) at any visit on treatment was similar between the LCM (1.7%; 2 of 119 study participants) and Placebo (2.5%; 3 of 121 study participants) groups. Two study participants (1.7%) in the Placebo group reported 2 TEAEs of blood bilirubin increased. Overall, 8 study participants (3.3%) reported 8 TEAEs of ALT increased during the Treatment Period, including 4 study participants (3.3%) each in the LCM and Placebo groups. Seven study participants (2.9%) reported 7 TEAEs of AST increased, including 2 study participants (1.7%) in the LCM group and 5 study participants (4.1%) in the Placebo group. All of the TEAEs were mild or moderate in intensity.

A total of 4 study participants in study EP0012 reported AEs related to PDILI, 3 of which were TEAEs. None of these were considered related to LCM by the investigator. No study participants reported TEAEs meeting the criteria for Hy's law. A brief description of these cases is provided below.

- A subject in the ≥46 Weeks completer cohort who reported an AE of liver disorder during the Pre-Treatment Period. The event began on Day -98, was nonserious, mild in intensity, and was considered not related to LCM by the Investigator. The event was continuous and was resolving at the time of clinical cut-off. No further details were available at the time of interim reporting. Concomitant AEDs used by the study participant during the study included lamotrigine and levetiracetam.
- A subject in the ≥94 Weeks completer cohort who reported a TEAE of alanine aminotransferase increased during the Treatment Period. The event began on Day 17; the LCM dose at onset was 400mg and the study participant received this dose for 16 days prior to the event onset. At Visit 2 (Week 2, Day 17), the study participant had a markedly abnormal high ALT value of 319U/L (normal range: 0 to 33U/L), which was classified as NCI CTC Grade 3. This value was a change from Baseline of 285U/L, with minimum and maximum post-Baseline values of 14U/L and 319U/L, respectively. The event resulted in an interruption of LCM. A PDILI test panel was performed using the local laboratory and a hepatologist was consulted. The study participant's ALT value had returned to within normal limits by Visit 5 (Week 22); no sign of drug-induced liver injury was present, and the study participant's LCM dose was continued. The study participant's ALT value remained normal for the remainder of the reporting period. The TEAE was nonserious, moderate in intensity, and was considered not related to LCM by the Investigator. The event was continuous and resolved 15 days after onset. Concomitant AEDs and benzodiazepines used by the study participant during the study included levetiracetam, lamotrigine, and clobazam.
- A subject in the ≥94 Weeks completer cohort who reported a TEAE of hepatic steatosis during the Treatment Period. The event began on Day 287; the LCM dose at onset was 400mg and the study participant received this dose for 286 days prior to the event onset. The TEAE was nonserious, mild in intensity, and was considered not related to LCM by the Investigator. No action was taken with LCM. The event was continuous and was resolving at the time of clinical cut-off. Concomitant AEDs used by the study participant during the study included lamotrigine, phenytoin, and brivaracetam.
- A subject in the ≥46 Weeks completer cohort who reported a TEAE of hepatic steatosis during the Treatment Period. The event began on Day 1; the LCM dose at onset was 400mg and the study participant received this dose for 1 day prior to the event onset. The TEAE was nonserious, mild in intensity, and was considered not related to LCM by the Investigator. No action was taken with LCM. The event was continuous and was resolving at the time of clinical cut-off. Concomitant AEDs and benzodiazepines used by the study participant during the study included clonazepam and carbamazepine.

Overall, the data do not evoke new safety concerns about hepatic toxicity.

Suicidality

In study SP0982, no study participants in the LCM group reported positive responses Columbia-Suicide Severity Rating Scale (C-SSRS) Question 4 or 5 during the Treatment Period. Two study participants in the LCM group reported TEAEs of suicidal ideation during the Treatment Period. As of the clinical cut-off date for the interim CSR, 3 study participants had positive suicide ideation responses to C-SSRS Questions 4 and 5 at Baseline, and 1 study participant each had a positive response at the ET Visit and at the Week 118 Visit. In addition, 1 study participant reported a TEAE of suicide ideation. No actual suicide attempts were reported in the C-SSRS assessment.

Suicidal ideation and behaviour are sufficiently covered by section 4.4 of the current product information.

Cardiac events and ECG-related observations

In study SP0982, overall and by development subgroups, mean and median changes from Baseline to Last Visit for all 12-lead ECG parameters were small, with the exception of mean change in PR interval, which was 9.96ms in the LCM group compared with -0.79ms in the Placebo group. This effect is consistent with the known safety profile of LCM.

A summary of TEAEs related to abnormal ECG findings is presented in the table below. Overall, the most common TEAEs related to ECG findings values were sinus bradycardia and bundle branch block right (2 study participants [0.8%] each).

Table 24: Incidence of TEAEs related to abnormal ECG findings in study SP0982 (safety set)

MedDRA v16.1 SOC PT	Placebo N=121 n (%) [#]	LCM N=121 n (%) [#]	All study participants N=242 n (%) [#]
Cardiac disorders	3 (2.5) [4]	4 (3.3) [4]	7 (2.9) [8]
Sinus bradycardia	2 (1.7) [3]	0	2 (0.8) [3]
Bundle branch block right	0	2 (1.7) [2]	2 (0.8) [2]
Arrhythmia	0	1 (0.8) [1]	1 (0.4) [1]
Atrioventricular block first degree	0	1 (0.8) [1]	1 (0.4) [1]
Tachycardia	1 (0.8) [1]	0	1 (0.4) [1]

LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE within the SOC/PT.
Note: Percentages were based on the number of study participants in the SS.
Note: [#] is the number of individual occurrences of the TEAE.
Note: Treatment-emergent AEs shown in the table were selected based on the topic of concern and do not necessarily include all PTs within an SOC.
Data source: Table 11.2.1.1

No trends related to age category were observed for these adverse events. The mean change in PR interval seems to be consistent with prior data in paediatric patients with POS (procedure II-65-G).

In study SP0982, one patient in the placebo group reported a TEAEs of sinus bradycardia. In study EP0012, one patient reported sinus bradycardia and one 2 events of bradycardia, respectively. In both patients, the events were of mild severity and not related to study drug according to the investigator.

Cardiac rhythm and conduction AEs including sinus bradycardia are known ADRs for LCM and covered in the product information.

Serious adverse event/deaths/other significant events

No deaths occurred in the completed clinical studies, or as of the cut-off date of study EP0012.

Other SAEs

Study SP0982

A summary of serious TEAEs is provided in the table below.

Table 25: Serious TEAEs in study SP0982 (safety set)

MedDRA v16.1 PT	Placebo N=121 n (%) [#]	LCM N=121 n (%) [#]	All study participants N=242 n (%) [#]
Any serious TEAEs	4 (3.3) [4]	8 (6.6) [14]	12 (5.0) [18]
Dizziness	0	2 (1.7) [2]	2 (0.8) [2]
Somnolence	0	2 (1.7) [2]	2 (0.8) [2]
Abdominal pain	0	1 (0.8) [1]	1 (0.4) [1]
Nausea	0	1 (0.8) [1]	1 (0.4) [1]
Vomiting	0	1 (0.8) [1]	1 (0.4) [1]
Asthenia	0	1 (0.8) [1]	1 (0.4) [1]
Upper respiratory tract infection	1 (0.8) [1]	0	1 (0.4) [1]
Contusion	0	1 (0.8) [1]	1 (0.4) [1]
Femur fracture	1 (0.8) [1]	0	1 (0.4) [1]
Road traffic accident	1 (0.8) [1]	0	1 (0.4) [1]
Transaminases increased	0	1 (0.8) [1]	1 (0.4) [1]
Liver function test abnormal	1 (0.8) [1]	0	1 (0.4) [1]
Pain in extremity	0	1 (0.8) [1]	1 (0.4) [1]
Grand mal convulsion	0	1 (0.8) [1]	1 (0.4) [1]
Headache	0	1 (0.8) [1]	1 (0.4) [1]
Status epilepticus	0	1 (0.8) [1]	1 (0.4) [1]

LCM=lacosamide; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 serious TEAE within the PT.
Note: Percentages were based on the number of study participants in the SS.
Note: [#] is the number of individual occurrences of the serious TEAE.
Data source: Table 11.6.1

Serious TEAEs were reported for 8 study participants (6.6%) in the LCM group compared with 4 study participants (3.3%) in the Placebo group.

Serious TEAEs considered related to study medication by the investigator included nausea, vomiting, transaminases increased, status epilepticus, and dizziness, reported by 1 study participant (0.8%) each; one study participant (0.8%) in the placebo group reported a related serious TEAE of femur fracture.

The reported PT terms appear to be mostly consistent with the previously reported safety profile of LCM. There were 3 LCM patients with reported SAEs of dizziness according to the narrative list, as opposed to 2 in the summary table above. However, the event for one patient started during the transition phase to study EP0012. The patient was also listed with an SAE of nausea.

Of note, one patient in the LCM group experienced an SAE of status epilepticus and one experienced grand mal convulsion. A brief description of these cases (condensed from the narratives) follows below.

- A subject, assigned to LCM, was first diagnosed with epilepsy in 1990. He developed serious and severe status epilepticus during the Titration Period, 10 days after study drug initiation. Prior to the event, the patient had received LCM 100 mg/day. Concomitant antiepileptic medication(s) and benzodiazepines included lamotrigine and

levetiracetam. After several seizures, the patient was admitted to the ER. The participant's condition was diagnosed as status epilepticus, acidosis, aspiration pneumonitis, diabetic ketoacidosis, acute urinary tract infection (UTI), renal insufficiency, and vomiting. Following hospitalization and treatment, the event resolved after 3 days. The SAE was considered related to study drug and the patient was discontinued from the study.

- A subject, assigned to LCM, was first diagnosed with epilepsy in 2016. He developed a mild grand mal convulsion during the Titration Period and was presented to the ER. The event occurred 30 days after study drug initiation. At the time of the tonic-clonic seizure aggravation, the study participant was taking LCM 250 mg/day and had been at this dose for 1 day in this study. During the 7 days prior to the event, he had received LCM 200 mg/day. Concomitant antiepileptic medication(s) and benzodiazepines at the time of the event included lamotrigine and levetiracetam. There were no other concomitant medications at the time of the event. The relationship of study drug to the event was reported as not related. The event resolved 2 days after onset. As stated in the narrative, approximately one month later, the patient again experienced episodes of tonic-clonic seizures and was re-hospitalized due to suspected head trauma (mild). The patient completed the study.

Of note, an additional patient in the LCM group developed severe grand mal convulsion during post-treatment (transition to study EP0012). The patient was not taking LCM at the time of the event.

In general, from the table of narratives provided by the MAH to list each study participant with a serious TEAE, it is noted that the number of subjects for whom at least one event of relevant TEAE was reported as SAE is 16 and not 12 as displayed above in the table. However, for two subjects the events occurred in the post-treatment period: a subject randomized to PBO experienced an SAE of clonic convulsion after 17 days off-study medication, and a subject randomized to LCM who experienced induced abortion during 211 days after study drug initiation and when off study drug for 15 days. The missing data are expected to pertain to these subjects and the MAH was requested to further discuss any possible discrepancies, check the incidence and numbers of all SAEs and provide updated summary tables and lists of SAE narrative cases as appropriate.

The only SAE of nausea listed is assumed to refer to a subject with BMI 34.7kg/m2, with a 1-year known history of epilepsy and on concomitant levetiracetam and brivaracetam who experienced moderate SAEs of dizziness, nausea, somnolence, and vomiting 16 days after study drug initiation, during the Titration Period, while on LCM 250mg/day for 1 day. A first episode of PGTCS, on the same day as the events, was also reported. The event was reported as related to LCM. The subject was hospitalized for one day. Per definition, hospitalization configures a TEAE to be of severe intensity, not moderate, as depicted.

In addition, a subject with BMI 18.6kg/m2, with approximately 8-months history of epilepsy and on concomitant lamotrigine, experienced SAEs of dizziness and nausea, 194 days after study drug initiation and while on LCM 400mg/day for 4 days. Both events were considered mild in intensity, were reported as related to study drug and started during the transition/taper period before entering EP0012.

One SAE of head injury was reported (and is missing from the table) for a subject with BMI 24.1kg/m2, with approximately 2-year history of epilepsy as of the time of enrolment, on concomitant lamotrigine and levetiracetam, who experienced SAEs of contusion, headache, grand mal convulsion and head injury across a two-month period. The event of Head injury was reported as mild in intensity, occurred during the Transition Period, 69 days after study drug initiation and while on LCM 400mg/day for 33 days in this study. The event was reported as not related to study drug.

One more SAE of grand mal convulsion was reported for a subject randomized to LCM, who experienced an episode of Epilepsy aggravated (IIE) while on concomitant valproic acid, only two days after taking LCM 400 mg, and during the Transition/Taper Period.

One patient developed an SAE of increased transaminases which also resulted in discontinuation from the study treatment (and study):

A subject, assigned to LCM) was diagnosed with epilepsy in 2010. The patient developed an SAE of moderate increased transaminases during the Maintenance Period of the study, 90 days after drug initiation. At the time of the SAE, the patient was treated with 400 mg LCM. The patient had been at this dose for 69 days. Concomitant antiepileptic medication(s) and benzodiazepines at the time of the event included valproic acid and levetiracetam. There were no other concomitant medications. According to the narrative, her ALT and AST levels had also been slightly increased (~2 X ULN) prior to LCM initiation. The patient developed a 3-fold increase in the level of ALT and AST. Additional diagnostic tests for e.g. viral hepatitis, Cytomegalovirus and infectious mononucleosis were negative. The event was considered related to study medication and resolved 265 days after onset and following discontinuation of LCM and dose reduction in valproate.

Liver function test abnormalities is covered by section 4.8 of the SmPC. Overall, no new safety concerns were identified.

Study EP0012

The most frequently reported SAEs (≥1%) were in the SOCs of Nervous system disorders (19 study participants [9.0%]), followed by Injury, poisoning and procedural complications (6 [2.8%]); Gastrointestinal disorders (4 [1.9%]); and Infections and infestations (3 [1.4%]).

In the SOC of Nervous system disorders, the only SAE reported by ≥5 study participants was grand mal convulsion (8 study participants [3.8%] reported 9 SAEs). Of these 9 SAEs, 4 were mild, 3 were moderate, and 2 were severe; none of the events were considered related to LCM by the Investigator.

Table 3: Serious TEAEs in study EP0012 (safety set)

MedDRA v16.1 SOC PT	Baseline age in SP0982 (years) ≥4 to <12 N=12 n (%)	≥12 to <18 N=30 n (%)	≥18 to <65 N=168 n (%)	≥65 N=1 n (%)	All study participants N=211 n (%)
Any serious TEAEs	2 (16.7) [4]	7 (23.3) [10]	23 (13.7) [35]	0	32 (15.2) [49]
Nervous system disorders	2 (16.7) [4]	5 (16.7) [5]	12 (7.1) [13]	0	19 (9.0) [22]
Grand mal convulsion	0	2 (6.7) [2]	6 (3.6) [7]	0	8 (3.8) [9]
Status epilepticus	1 (8.3) [3]	0	2 (1.2) [2]	0	3 (1.4) [5]
Convulsion	0	2 (6.7) [2]	0	0	2 (0.9) [2]
Tonic convulsion	1 (8.3) [1]	0	0	0	1 (0.5) [1]
Gastrointestinal disorders	0	2 (6.7) [2]	2 (1.2) [3]	0	4 (1.9) [5]
Vomiting	0	2 (6.7) [2]	0	0	2 (0.9) [2]
Respiratory, thoracic and mediastinal disorders	0	0	2 (1.2) [3]	0	2 (0.9) [3]
Pneumonia aspiration	0	0	2 (1.2) [2]	0	2 (0.9) [2]

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SAE=serious adverse event; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least one TEAE within the SOC/PT.
Note: Percentages were based on the number of study participants in the SS.
Note: [#] was the number of individual occurrences of the SAE.
Note: For the ≥4 to <12 years category, all serious TEAEs were included; for all other age categories, serious TEAEs by PT that occurred in ≥2 study participants were included.
Data source: EP0012 interim CSR Table 10.5.1

As explained in the footnote of the table, for the ≥4 to <12 years category, all serious TEAEs were included; for all other age categories, serious TEAEs by PT that occurred in ≥2 study participants were included. One patient had an SAE of myoclonic epilepsy that also resulted in discontinuation from the study:

A subject entered the open-label study and received the first dose of LCM 400 mg/day in Apr 2017. The patient was assigned to the LCM group in the feeder study. She had been diagnosed with epilepsy at the age of 15 but her medical history was otherwise unremarkable. Concomitant antiepileptic medication(s) and benzodiazepines at the time of the myoclonic epilepsy included the following: zonisamide and ethosuximide. Other concomitant medication(s) at the time

of the event included: ibuprofen, hydroxyzine, ergocalciferol, folic acid and multivitamins. The study participant experienced a nonserious adverse event (AE) of petit mal epilepsy (worsening absence seizures) on 07 Nov 2017. The event resolved on 14 Jan 2019. The relationship of the study drug to the event was reported as related.

The study participant experienced a SAE of myoclonic epilepsy on 01 Mar 2018, during the Treatment Period. The event occurred 325 days after study drug initiation. The event was considered moderate in intensity. The relationship of the study drug to the event was reported as not related. At the time of the myoclonic epilepsy, the study participant was taking LCM 500 mg/day tablets and had been at this dose for 52 days in this study. The event resolved on 29 November 2018, 274 days after onset. The patient discontinued from the study due to the myoclonic seizures. The final dose of study drug was taken on 13 January 2019. The final visit was not reported.

A causal relationship to LCM cannot be excluded.

Also, the incidence of SAEs was significantly higher in the paediatric PGTCS-population compared to adults with PGTCSs.

In pool SGTC-2 (Studies SP0961 and SP0962), overall, a total of 4 study participants (8.2%) experienced serious TEAEs (pneumonia, convulsion, migraine, petit mal epilepsy, and abnormal behaviour), all of whom were adults. No serious TEAEs were reported in >1 study participant.

Laboratory findings

Study SP0982

Overall, no consistent or clinically relevant treatment-related changes in mean or median haematology values were observed. The incidence of TEAEs related to abnormal haematology values was generally low and similar between the LCM and the Placebo groups. The incidences of TEAEs related to haematology abnormalities were low across age categories. No haematology-related TEAEs were reported in pediatric study participants.

Similarly, no consistent or clinically relevant treatment-related changes in mean or median clinical chemistry and endocrinology values were observed. The incidence of TEAEs related to abnormal clinical chemistry values was generally low and similar between the LCM and Placebo groups. Overall, the most common TEAEs related to abnormal clinical chemistry values were ALT increased (8 study participants [3.3%]), AST increased (7 study participants [2.9%]), and gamma glutamyl transferase increased (4 study participants [1.7%]). All other TEAEs were reported by ≤2 study participants.

Overall, 4 patients (3.3%) each in the placebo and LCM groups reported ALT increased.

Study EP0012

In EP0012, as of the clinical cut-off date for the interim CSR, mean values for the majority of haematology and clinical chemistry parameters remained within normal ranges. Overall, the incidences of TEAEs related to haematology abnormalities were low across age categories. No haematology-related TEAEs were reported in pediatric study participants. the incidence of TEAEs related to clinical chemistry abnormalities was low across age categories.

Studies SP0961 and SP0962

In these studies, in general, median values for haematology and clinical chemistry parameters remained within the normal range and the changes from Baseline were not of clinical relevance. In study SP0961 the clinical chemistry abnormalities reported as a TEAE were ALT increased (1 [2.0%]) and hypokalaemia (1 [2.0%]). In study SP0962, clinical chemistry abnormalities reported as TEAEs were ALT, AST, and GGT increased (2 study participants each [5.1%]) and blood alkaline phosphatase increased and blood calcium decreased (1 study participant each [2.6%]).

Safety in special populations

The MAH was requested to conduct an analysis of safety with respect to Race, Gender, Renal and hepatic impairment or Geographical region.

As regards gender, dizziness an somnolence were more frequently reported in female than male subjects in the LCM group (30.3% vs. 14.5% and 22.7% vs. 9.1%, respectively), whereas the mismatch for headache was lower and slightly prevailing in male compared with female subjects in the LCM group (16.4% vs 12.1, respectively).

In Pool SGTC-1 the overall incidence of most commonly reported TEAEs (in ≥2% of all subjects) by gender were similar in pediatric vs adult study participants (82.0% vs 86.8%, respectively), with somnolence more prevalent in pediatric than adult subjects (26.0 vs 15.6%), and dizziness almost equally reported (25.9 and 22.0% for adults and pediatrics, respectively). However, female subjects reported higher incidences of TEAEs as compared to males, either in adult or pediatric subjects regarding the following relevant TEAEs:

- dizziness was more frequently reported in either female pediatric compared with male pediatric subjects (31.3% and 5.6%, respectively), or female adult compared with male adult subjects (33.6% and 15.7%, respectively);

- headache was more frequently reported in either female pediatric compared with male pediatric subjects (21.9 and 11.1%, respectively), or in female adult compared with male adult subjects (24.1 vs 16.9%).

- somnolence was more frequently reported in female pediatric compared with male pediatric subjects (31.3 and 16.7%, respectively), whereas the incidence in female adult compared with male adult subjects was comparable (15.5 and 15.7%, respectively).

- nausea was reported only in female pediatric subjects (18.8%) and was slightly more reported in female adult compared with male adult subjects (9.5 vs. 7.9%, respectively).

No clinically relevant differences were observed in SP0982 and Pool SGTC-1 with respect to Region.

Safety related to drug-drug interactions and other interactions

The LCM drug interactions are presented in the current SmPC. No new safety concerns were identified.

No pregnancies were reported in EP0012 or SP0961. In study SP0982, one study participant had a positive urine pregnancy test on the Transition Period Final Clinic Visit. The study participant reported an SAE of abortion induced, and the subsequent urine pregnancy test at the Safety Follow-up Visit was negative. In SP0962, pregnancies were reported for 2 study participants, in both cases resulting in the delivery of a baby. In one case, nonserious AEs of pre-eclampsia and premature labour were reported, however, there were no AEs during the postpartum period.

No new safety concerns were identified.

Discontinuation due to adverse events

Study SP0982

The incidence of TEAEs leading to discontinuation was low overall (16 study participants [6.6%]), including 11 (9.1%) in the LCM group and 5 study participants (4.1%) in the placebo group.

The most common TEAEs leading to discontinuation overall (by PT) were rash (3 study participants [1.2%]) and ALT increased, AST increased, and dizziness (2 [0.8%] each). Dizziness and suicidal ideation were more commonly reported in the LCM group (1.7% each) compared with the placebo group (0% each).

The listing of narratives of Study SP0982 as well as listing 7.4 of the CSR list a total of 17 patients with TEAEs resulting in discontinuation, 17 in the LCM group and 5 in the placebo group. The additional LCM patient was reported with suicidal thoughts (non-serious, moderate) during the post-treatment phase of the study.

Overall, there were 3 patients with TEAEs leading to discontinuation that were also serious; two of these were in the LCM group:

- A subject, first diagnosed with epilepsy in 1990. He developed serious and severe status epilepticus during the Titration Period, 10 days after study drug initiation. At the time of the event, the patient was taking LCM 50 mg/day. Concomitant antiepileptic medication(s) and benzodiazepines included lamotrigine and levetiracetam. Following hospitalization and treatment, the event was considered resolved after 3 days.

- A subject, was diagnosed with epilepsy in 2010. The patient developed an SAE of moderate increased transaminases during the Maintenance Period of the study, 90 after drug initiation. At the time of the SAE, the patient was treated with 400 mg LCM. Concomitant antiepileptic medication(s) and benzodiazepines at the time of the event included the following: valproic acid and levetiracetam. According to the narrative, her ALT and AST levels had been slightly increased also prior to LCM initiation. There were no other concomitant medications. The patient developed a 3-fold increase in the level of ALT and AST. The event resolved 265 days after onset and following discontinuation of LCM and dose reduction in valproate.

Study EP0012

As of the clinical cut-off date for the interim CSR, overall, a total of 5 study participants (2.4%) reported 12 TEAEs leading to discontinuation of study drug. These were most frequently reported in the Nervous system disorders SOC: 5 study participants (2.4%) reported 9 TEAEs leading to discontinuation of study drug; 1 event of myoclonic epilepsy was severe, not serious, and considered related to LCM by the Investigator, 1 event of myoclonic epilepsy was moderate, serious, and considered not related to LCM by the Investigator, and 1 event of convulsion was mild, serious, and considered not related to LCM by the Investigator. All other TEAEs leading to discontinuation of study drug were mild or moderate in intensity and were nonserious.

In Pool SGTC-2, TEAEs leading to discontinuation were reported by 7 (14.3%) study participants. With the exception of petit mal epilepsy (2 study participants [4.1%]), none of the TEAEs leading to discontinuation (vertigo, diplopia, vision blurred, nausea, gait disturbance, dizziness, grand mal convulsion, sedation, abnormal behaviour, confusional state, and hallucination) occurred in >1 study participant.

Post marketing experience

Since 2008, LCM has been approved worldwide in over 70 countries. Patient exposure (all known LCM exposures) was estimated using the available UCB sales data from 01 Sep 2008 to 28 Feb 2019 for the cumulative time interval. The total amount of product sold during the cumulative reporting interval is 194,732,060,200 mg, as derived from the UCB sales data reported. The defined daily dose was assumed to be 300 mg. Accordingly, the patient exposure to LCM during the cumulative reporting interval from 01 Sep 2008 to 28 Feb 2019 is estimated to be approximately 1,777,158 patient-years.

Cumulatively, 578 safety case reports associated with the post-marketing use of LCM in patients with potential PGTCS were identified worldwide in the UCB Global Safety database. Among these 578 case reports, 281 case reports were considered relevant to PGTCS and 297 were considered non-PGTCS cases. The majority were received from US (45.8%) and Germany (18.86%). From the 216 cases for which gender was reported, 135 cases (48.04%) involved female and 81 cases (28.82%) involved male patients. From the 154 cases that reported age, 14 cases involved paediatric patients (4.98%), 128 involved adults (45.55%), and 12 involved elderly patients (4.27%).

In the 281 cases, 826 PTs were reported. The most frequently reported SOC as classified under the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 in patients who received LCM were Nervous system disorders (237 AEs; 28.69%) and General disorders and administration site conditions (195 AEs; 23.6%).

A comprehensive review of the fatal cases (including sudden unexpected death in epilepsy [SUDEP]) and cases reported with significant AEs related to cardiac, syncope/loss of consciousness, suicidality, hepatotoxicity, multiorgan hypersensitivity reactions/serious cutaneous adverse reactions (SCARs), dizziness/ataxia, other significant AEs including blood and lymphatic disorders, anaphylaxis, rhabdomyolysis, renal failure and impairment, pancreatitis, and AEs reported under the SOC Injury, poisoning, and procedural complication did not display concerns specific to the use of LCM in patients with PGTCS.

A review of LCM use in PGTCS patients from the special populations of pregnancy and lactation, elderly, and paediatric did not exhibit concerns as compared to the known safety profile of LCM reported in VIMPAT SmPC.

Based on review of cases related to drug abuse, lack of efficacy, intravenous (IV) and oral use of LCM, and worsening of seizure or new onset of seizures, no specific safety concerns were identified for use of LCM in PGTCS patients.

A review of relevant publications describing the use of LCM in PGTCS patients did not identify specific safety concerns and were confounded by presence of other antiepileptic drugs (AEDs).

In conclusion, the cumulative post-marketing LCM analysis in PGTCS patients did not identify new safety concerns and supports the use of LCM as adjunctive therapy (or monotherapy) in PGTCS patients. The safety profile is consistent with the known safety profile of LCM.

2.5.1. Discussion on clinical safety

The safety analysis results from the EP0012 interim CSR and SP0982 final CSR, and SP0961 and SP0962 final CSRs were submitted, as well as pooled safety summaries, were submitted from this extension of indication.

The clinical safety data from adjunctive LCM use for the treatment of PGTCS in adults and paediatric study participants with IGE down to 4 years of age in study SP0982 included a total of 242 study participants. Of these, 49 study participants were <18 years of age (17 were 4 to <12 years of age and 32 were ≥12 to <18 years of age) at the time of enrolment in SP0982. In total, 147 study participants in Pool SGTC-1 (the combined SP092 and interim EP0012 studies) have been exposed to adjunctive LCM treatment for PGTCS for at least 1 year. In all study participants, the median modal dose (mg/day) was 400 mg (range: 100 mg to 800 mg), and the median maximum dose (mg/day) was 400 mg/day (range: 100 mg to 800 mg).

In the LCM group, TEAEs were most commonly reported in the SOCs of Nervous system disorders (58 study participants [47.9%]), and Infections and infestations and Gastrointestinal disorders (25 study

participants [20.7%] each). By PT, the most common TEAEs were dizziness (28 study participants [23.1%]), somnolence (20 [16.5%]), and headache (17 [14.0%]).

In the Placebo group, TEAEs were most commonly reported in the SOCs of Nervous system disorders (36 study participants [29.8%]), Infections and infestations (23 study participants [19.0%]), and Gastrointestinal disorders (19 study participants [15.7%]). By PT, the most common TEAEs in the Placebo group were somnolence (17study participants [14.0%]), headache (12 study participants [9.9%]), and nausea and dizziness (7 study participants [5.8%] each.

The most common related TEAEs for the LCM group were dizziness (21 study participants [17.4%]), somnolence (16 [13.2%]), and nausea (9 [7.4%]). The incidence of study participants reporting serious TEAEs was low overall (5.0%) and was 6.6% and 3.3% in the LCM and Placebo groups, respectively. The most commonly reported SAEs in the LCM were dizziness (1.7%) and somnolence (1.7%). No deaths were reported in the study.

Paediatric patients in the LCM group showed higher exposure-duration adjusted rates of somnolence over placebo (5.94 vs. 1.70 per 100 pt-months) as compared to adult patients (2.84 vs. 5.46, respectively). This is reflected in the current product information (section 4.8 of the SmPC).

As of the clinical cut-off date for the interim EP0012 study, the most frequently reported TEAEs (PT) per 100 person-months were: nasopharyngitis (35 study participants [16.6%]), with a rate of 0.97 person-months; headache (34 study participants [16.1%]), 0.94 person-months; dizziness (32 [15.2%]), 0.88 person-months; somnolence (22 [10.4%]), 0.61 person-months; upper respiratory tract infection (14 [6.6%]), 0.39 person-months; and contusion and nausea (13 [6.2%] each), 0.36 person-months each.

The applicant provided a side-by-side presentation of common TEAEs between Pool SGTC-1 (studies SP0982 and the interim study EP0012 combined) as compared to two previously submitted data pools for the adult and paediatric POS populations (Pool S2 and Pool SPX-1), respectively. Overall, and considering differences in dataset sizes that may explain some of the fluctuations, the common TEAE pattern was broadly similar between the indications and for both populations.

However, for further analyses, the MAH provided additional summary tables of exposure to LCM by age group and by weight band and also a side-by-side comparison of doses/exposure data between Pool SGTC-1 vs. Pool SPX-1 and Pool S2 from the POS populations. Overall, the median duration of exposure for pediatric study participants with PGTCS (≥4 to <18 years of age) and pediatric study participants with POS (≥4 to <16 years of age) were 369.5 days (range: 61 to 1035 days) and 300.0 days (range: 1 to 860 days), respectively. Median duration of exposure for adult study participants with PGTCS (≥18 years of age) and adult study participants with POS (≥16 years of age) were 430.0 days (range: 1 to 1143 days) and 726.0 days (range: 1.0 to 2913.0 days), respectively. Also, for this side-by-side comparison, the MAH provided tabulated TEAE data by age and weight band, for both PGTCS and POS using appropriate age cut-offs. The incidence of somnolence was higher for all age groups in PGTCS compared with POS. In study SP0982, paediatric patients in the LCM group showed higher rates of somnolence over placebo (5.94 vs. 1.70 per 100 pt-months), which was not observed in adult patient. Thus, this may indicate that paediatric patients with PGTCS are more at risk for this ADR. The relevant information is reflected in section 4.8 of the SmPC.

The applicant investigated the aggravation of absence seizures and myoclonic seizures by LCM. There was no clear evidence of worsening for days with absence seizures in the LCM group compared with Placebo.

However, regarding myoclonic seizures, in SP0982, 3 study participants (2.5%) in the LCM group reported 3 TEAEs of myoclonic epilepsy during the Treatment Period compared with 0 in the placebo group. Two TEAEs of myoclonic epilepsy were considered as related, all 3 were mild to moderate in intensity, and none were considered as serious. In addition, 1 study participant in the LCM group reported a mild TEAE of myoclonic epilepsy during the Post-Treatment (Transition) Period. Myoclonus was reported

by 1 study participant (0.8%) in the placebo group. Although these are few events, there could be an underreporting of myoclonic seizures as TEAEs in this study.

A total of 96 study participants (LCM, n=47; placebo, n=49) in study SP0982 experienced myoclonic seizures during the Prospective Baseline. The percent changes from Prospective Baseline in median number of days with myoclonic seizures for the LCM and placebo groups were -32.5% and -51.8%, respectively, during the Titration period; -43.8% and -65.7%, respectively, during the first 12 weeks of the Treatment Period; and -54.6% and -65.7%, respectively, during the 24-week Treatment Period.

Also, a total of 21 study participants experienced onset of myoclonic seizure or ≥50% worsening in days of myoclonic seizures, of which 14 study participants were in the LCM group and 7 were in the Placebo group. Of the 13 LCM study participants in this study with a medical history of myoclonic seizure at baseline, 8 reported ≥50% worsening in days of myoclonic seizures compared to the Baseline Period in at least one Treatment Period. However, only 2 cases of worsening of myoclonic seizures (during titration) were reported as TEAEs. The MAH was requested to discuss this issue of potential underreporting. According to the MAH, such reporting differences (using 28-day blocks) may not always qualify as an AE in the view of the investigator in light of the prior knowledge of the patient's history. In this regard, a longer baseline period would have been a more objective way to assess whether significant fluctuations in seizure patterns were truly treatment emergent or not.

There were 4 patients in the LCM group (8.5%) who experienced >75% increase in myoclonic seizures during the treatment period as compared to the prospective baseline (as compared to one patient in the placebo groups). Even if not all of these shifts were considered to constitute AEs by the investigator, there remains an imbalance between the groups.

The risk of myoclonic seizures or worsening of myoclonic seizures also appeared to be increased during titration of LCM. There were 3 patients with TEAEs of myoclonic epilepsy during the 6-week titration period as compared with 1 (myoclonus) during the 18-week maintenance phase and 1 (myoclonic epilepsy) post-treatment. Also, for the 4 patients who reported 50% seizure worsening for days with myoclonic seizures in the study as compared to prospective baseline, this occurred during the titration period (4/47 patients for LCM as compared with 2/49 for placebo).

Myoclonic epilepsy is therefore added as a new ADR for LCM in patients with PGTCS (section 4.8 of SmPC). In addition, a warning stating that new onset or worsening of myoclonic seizures has been reported in patients with PGTCS is added in section 4.4 of the SmPC.

In SP0982, 4 (3.3%) study participants on LCM and 0 on Placebo reported TEAEs of ataxia. All were considered related to study drug per the Investigator. The events were mild to moderate in intensity and did not lead to withdrawal of LCM. Three of the cases were reported in adults and one in a 13-year-old paediatric patient. All events were reported during the titration phase. The PT of ataxia is therefore added as ADR in section 4.8. in the SmPC.

Two study participants (1.7%) in the Placebo group reported 2 TEAEs of blood bilirubin increased. Overall, 8 study participants (3.3%) reported 8 TEAEs of ALT increased during the Treatment Period, including 4 study participants (3.3%) each in the LCM and Placebo groups. Seven study participants (2.9%) reported 7 TEAEs of AST increased, including 2 study participants (1.7%) in the LCM group and 5 study participants (4.1%) in the Placebo group. All of the TEAEs were mild or moderate in intensity. Overall, TEAEs related to hepatic toxicity are consistent with the existing product information and known safety profile of LCM in the POS population.

Two study participants in the LCM group in study SP0982 reported TEAEs of suicidal ideation during the Treatment Period. In addition, 1 study participant reported a TEAE of suicide ideation. Two study participants in the LCM group in study SP0982 reported TEAEs of suicidal ideation during the Treatment

Period. Information on Suicidal ideation and behaviour is already included in section 4.4 of the current PI as class effect.

Present data are too scarce to allow to assess the potential impact of LCM on behaviour and executive functioning in children with primary generalized epilepsy.

Overall, in study SP0982, the most common abnormalities related to ECG findings values were sinus bradycardia and bundle branch block right (2 study participants [0.8%] each) but there were no AEs of cardiac disorders in the LCM group. ECG-related observations included a mean change in PR interval, which was 9.96 ms in the LCM group compared with -0.79ms in the Placebo group. This effect is consistent with the known safety profile of LCM.

A total of 2 study participants in EP0012 reported AEs with cardiac and electrocardiogram (ECG) related PTs, 1 of which was a TEAE (sinus bradycardia and 2 events of bradycardia, respectively). These events were not considered related to LCM by the investigator although this cannot be excluded given the known safety profile of LCM.

No new safety concerns were identified in the interim data from study EP0012. The safety profile from the open-label studies SP0961 and SP0962 (Pool SGTC-2) was also consistent with the above safety findings. However, further data from this study are pending; this study is included in the pharmacovigilance plan as a Category 3 study with a due date of August 2024.

Assessment of paediatric data on clinical safety

Of the 49 paediatric study participants (<18 years of age) in study SP0982, a total of 8 (6.6%) in the LCM group and 9 (7.4%) in the placebo group were ≥4 to <12 years of age, and 16 study participants (13.2%) in each group were ≥12 to <18 years of age.

Paediatric patients in the LCM group showed higher rates of somnolence vs. placebo as compared to adult patients. This is appropriately addressed in the product information. In general, the current safety data in the paediatric patients was consistent with the data seen in adults and prior safety data of LCM in paediatric patients with POS.

However, myoclonic seizure worsening was more frequent in children compared to adults.

For paediatric study participants, the percentage of study participants in the LCM group with 50% worsening of myoclonic seizures was 20% (1 of 5) each during the Titration Period, first 12 weeks of the Treatment Period, and during the 24-week Treatment Period. No paediatric study participants in the Placebo group had 50% worsening during the Titration Period, first 12 weeks of the Treatment Period, or 24-week Treatment Period. As discussed above, section 4.4 and 4.8 of the SmPC is updated to reflect the relevant data regarding myoclonic epilepsy.

2.5.2. Conclusions on clinical safety

The CHMP concluded that, based on the available safety data, the safety profile of LCM in the treatment of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy is acceptable.

The Product Information have been updated to reflect the relevant safety information, including onset or worsening of myoclonic seizures.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The Work-sharing Applicant (WSA) submitted an updated Risk Management Plan (RMP) version with this application.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 15.1 (dated 12 May 2020) is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

- To retain the potential risk of hepatoxicity in the PSUR list of safety concerns and closely monitor, present, and discuss this risk in future PSURs;
- To ensure the final, up to date SmPC text is reflected in the RMP at the next regulatory opportunity.

The CHMP endorsed this advice without changes.

The CHMP endorsed the RMP version 15.1 with the following content:

Safety concerns

Summary table of safety concerns

Important identified risks	• Cardiac AEs 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 on puberty in pediatric population aged 4 to <16 years

AE=adverse event

Pharmacovigilance plan

Table 27: Table of Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Participation in and sponsorship of European and International Registry of AEDs in Pregnancy (EURAP) Ongoing **Category 3**	To collect data on pregnancy	Missing information on use of laocosamide (LCM) in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semi-annual)	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs).
Participation in and sponsorship of North American AED Pregnancy Registry (NAAPR) Ongoing **Category 3**	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 (semi-annual)	Cumulative data appearing in these registries are discussed in PSURs.
SP848 Open-label study to determine safety, tolerability, and efficacy of long-term oral LCM as adjunctive therapy in children with epilepsy Ongoing **Category 3**	To document the long-term safety, tolerability, and pharmacokinetics (PK) of LCM in study participants from 1 month to less than 18 years with epilepsy	Missing information on impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years	Final study report submission	Dec 2021
EP0034 Open-label, multicenter, long-term extension study to investigate the efficacy and safety of LCM as adjunctive therapy in pediatric subjects with epilepsy with partial-onset seizures (POS). Ongoing **Category 3**	To document the long-term safety, tolerability, effects on behavior, cognition and quality of life in study participants from 1 month to less than 18 years with POS	Missing information on impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years	Final study report submission	Dec 2022

Table 27: Table of Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 (PGTCS) in subjects with idiopathic generalized epilepsy (IGE). Ongoing **Category 3**	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 on puberty in pediatric population aged 4 to <16 years	Final study report submission	Aug 2024

AED=antiepileptic drug; EURAP=European and International Registry of AEDs in Pregnancy; LCM=lacosamide; IGE=idiopathic generalized epilepsy; NAAPR=North American AED Pregnancy Registry; PGTCS=primary generalized tonic-clonic seizures; PK=pharmacokinetics; POS=partial-onset seizures; PSUR=periodic safety update report

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation	Routine risk minimization measures: Summary of Product Characteristics (SmPC) Section 4.2 (Posology and method of administration – intravenous (iv) formulation), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction), SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Available by prescription only Additional risk minimization measures: None	Routine pharmacovigilance (PhV) activities beyond adverse reactions reporting and signal detections: specific cardiac follow-up query. Additional PhV activities: None

Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pregnant or lactating women	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation), SmPC Section 5.3 (Preclinical safety data) Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities: participation in and sponsorship of pregnancy registries (European and International Registry of Antiepileptic Drugs [EURAP] and North American Antiepileptic Drug Pregnancy Registry (NAAPR)
Impact on long-term growth, long-term neurodevelopment, and on puberty in pediatric population aged 4 to < 16 years	Routine risk minimization measures: No additional wording in SmPC Available by prescription only. Additional risk minimization measures: None	Routine PhV activities beyond adverse reactions reporting and signal detection: None Additional PhV activities (according to the actual study protocols): Ongoing pediatric studies with a follow-up of up to 2 years in SP848/EP0034. Study EP0012 includes pediatric patients who are followed for up to 5 years.

AE=adverse event; CNS=central nervous system; EURAP=European and International Registry of Antiepileptic Drugs; NAAPR= North American Antiepileptic Drug Pregnancy Registry; PhV=pharmacovigilance; SmPC=summary of product characteristics

2.7. Update of the Product information

As a result of this variation, section(s) 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated to reflect the proposed extension of the Vimpat and Lacosamide UCB indication as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients with idiopathic generalized epilepsy (IGE) aged 4 years and older. The Package Leaflet (PL) is updated accordingly.

The applicant takes this opportunity to align the Product Information of Lacosamide UCB with the Product Information of Vimpat, by implementing the latest editorial changes that have been approved for Vimpat.

In addition, the applicant takes this opportunity to align the Product Information of Vimpat and Lacosamide UCB with the QRD template version 10.1

Please refer to Attachment 1 for full details of agreed Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA. This is acceptable for the following reasons:

- The last user testing report was submitted in July 2016 for the Vimpat POS extension of indication in children down to 4 years of age (II/65).

- The pre-authorisation guidance states that a user consultation is always required for the first authorisation of a medicinal product with a new active substance, medicinal products which have undergone a change in legal status, medicinal products with a new presentation and medicinal products with particular critical safety issues. As this application object does not fall in one of the above-mentioned situation, it was agreed pre submission that no user consultation will be provided.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The most common seizure type in patients with epilepsy is partial seizures (57%), followed by tonic-clonic seizures (23%), absence seizures (6%), and myoclonic seizures (3%); the latter 3 seizure types comprise the majority of generalized seizures (convulsive and nonconvulsive) (Hauser et al, 1993).

Generalized seizures are those in which the first clinical changes indicate initial involvement of both brain hemispheres. Consciousness may be impaired, and this impairment may be the initial manifestation. Motor manifestations are bilateral. Generalized epilepsies can be further classified as primary/idiopathic and secondary/symptomatic epilepsies. In view of the purpose of this application, only idiopathic generalized epilepsy (IGE) is discussed.

IGE is a category of disorders defined by strict clinical and electroencephalogram (EEG) features proposed by the International League Against Epilepsy (ILAE) classification of epileptic syndromes (ILAE, 1989). Clinical experience has shown that IGEs represent a heterogeneous condition in which many factors interact (such as age at onset, external factors, role of medications, and sleep) (Jallon and Latour, 2005).

IGE are assumed to have a genetic etiology and onset almost always occurs during childhood or adolescence, although there are exceptions; some patients develop these kinds of epilepsies after the second decade of life or, rarely, even later.

Within the group of IGEs, there are a number of different epilepsy syndromes. Patients with the most common IGE syndromes (ie, childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal seizures on awakening) may experience generalized tonic-clonic seizures.

Typically, the onset of childhood absence epilepsy is between 4 to 8 years of age, with peak onset at ages 6 to 7 years. Approximately 40% develop generalized tonic-clonic seizures as they reach adolescence.

The onset of juvenile absence epilepsy is between 10 to 17 years of age, with peak onset between 10 and 12 years. These patients may have occasional tonic-clonic seizures.

The onset of juvenile myoclonic epilepsy varies from 8 to 26 years and peaks at 12 to 14 years. Juvenile myoclonic epilepsy is characterized by myoclonic seizures that appear with tonic-clonic seizures in most patients, and absence seizures in about one-third of patients.

The onset of epilepsy with grand mal seizures on awakening is usually in the second decade of life. This syndrome typically presents as a generalized tonic-clonic seizure within 2 hours after awakening but may include myoclonic and/or absence seizures.

IGE with PGTCS only is considered a syndrome in the new ILAE diagnostic scheme (Engel, 2006) and incorporates ‘epilepsy with PGTCS on awakening’ (ILAE, 1989; Janz, 2000). The terminology ‘IGE with

PGTCS only' implies that it includes only those patients with PGTCS alone (i.e. without absences and/or jerks) and that these may occur at any time. Overall, PGTCS are reported to occur on awakening (17% to 53% of patients), diffusely while awake (23% to 36%) or during sleep (27% to 44%), or randomly (13% to 26%) (Wolf, 2002). It is undetermined what proportion of these patients also has other generalized seizures (jerks or absences).

Age at onset varies from 6 to 47 years with a peak at 16 to 17 years; 80% have their first PGTCS in the second decade of life. Men (55%) slightly predominate over women, probably because of differences in alcohol exposure and sleep habits. Exact prevalence of 'IGE with PGTCS only' is unknown. If strict criteria apply (PGTCS only), this may be very small (0.9% of IGE), but others give a prevalence of 13% to 15% among IGE (Roger et al, 1994; Oller-Daurella and Oller, 1994).

3.1.2. Available therapies and unmet medical need

As the patient population with PGTCS is heterogeneous and as PGTCS can occur as an isolated seizure type or in association with other generalized seizure types, treatment of PGTCS is complex. The MAH shortly presented the available treatment options.

Table 4: Serious TEAEs in study EP0012 (safety set) AEDs for treatment of PGTCS

Drug	EU	US
Valproic acid	Epilepsy general, so primary generalized tonic-clonic seizures (PGTCS) would be included, all ages Not specific on mono- or adjunctive therapy	Valproic acid and valproic acid extended release not approved in PGTCS
Carbamazepine	Generalized tonic-clonic seizures (GTCS), all ages Adjunctive and monotherapy	Carbamazepine: GTCS (grand mal), all ages, adjunctive and monotherapy Carbamazepine extended release: GTCS, 6 years above, adjunctive and mono therapy
Lamotrigine	Adjunctive or monotherapy in patients aged ≥3 years Adjunctive therapy in patients aged 2 to 12 years	Adjunctive therapy in patients aged ≥2 years
Levetiracetam	Adjunctive therapy in patients aged ≥6 years	Adjunctive in patients aged ≥6 years
Perampanel	Adjunctive therapy in patients aged ≥12 years	Adjunctive therapy in patients aged ≥12 years
Topiramate	Monotherapy in patients aged >6 years Adjunctive therapy in patients aged ≥ 2 years	Monotherapy in patients aged ≥2 years Adjunctive therapy in patients aged 2 to 16 years

AED=antiepileptic drug; GTCS=generalized tonic-clonic seizure; PGTCS=primary generalized tonic-clonic seizure

In the past decade, several new options for the medical treatment of epilepsy have been introduced, including novel AEDs and vagus nerve stimulation. The newer AEDs differ from older agents in several

important ways, including mechanism of action, spectrum of activity, and PK characteristics (Herman and Pedley, 1998).

Between 15% and 40% of patients with generalized epilepsy remain refractory to therapy or do not tolerate the currently available AEDs (valproate, ethosuximide, phenytoin [PHT], lamotrigine [LTG], carbamazepine [CBZ], topiramate, and levetiracetam) (Bartolomei et al, 1997; Verrotti et al, 2007). Some of these AEDs can induce serious, life threatening AEs (e.g. aplastic anaemia, rash, hepatic failure). Generalized tonic-clonic seizures may respond to drugs that aggravate typical absences and/or myoclonic jerks (Genton, 2000; Verrotti et al, 2007). Two IGE seizure types, typical absences and myoclonic jerks, are particularly prone to aggravation by certain AEDs (CBZ, vigabatrin, tiagabine, PHT, phenobarbital [PB], and LTG). The pharmacodynamic aggravation is usually associated with a clear increase of interictal (and ictal) EEG changes.

Of patients with IGE experiencing PGTCS, clinical experience has shown that up to 30% of patients who are treated with currently available AEDs have insufficient seizure control or unacceptable drug tolerability. Thus, there is a significant unmet medical need for new treatment options in this patient population.

3.1.3. Main clinical studies

The main studies supporting the indication of LCM in the treatment of PGTCS with IGE in adults and children 4 years of age and older are listed the table below.

Study SP0982 provided data for efficacy assessment. The EP0012 study provided data for long-term LCM treatment assessment in the open-label setting. Studies SP0961 and SP0962 were used only for safety assessment.

Study number	Study description	Study Status
SP0961	A Phase 2, open-label pilot study to assess the safety of oral LCM as adjunctive therapy for uncontrolled PGTCS in study participants with IGE	Completed
SP0962	A Phase 2 OLE study to assess the safety and seizure frequency associated with long-term oral LCM for uncontrolled PGTCS in study participants with IGE	Completed
SP0982	A Phase 3, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of oral LCM as adjunctive therapy for uncontrolled PGTCS in study participants ≥4 years of age with IGE	Completed
EP0012	A Phase 3, multicenter, OLE study designed to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled PGTCS in study participants with IGE, previously enrolled in SP0982	Ongoing

3.2. Favourable effects

The risk of developing a second PGTCS during the 24-week Treatment Period was statistically significantly lower in the LCM group compared with the placebo group; the survival estimates at the end of the Treatment Period were 55.27% in the LCM group and 33.37% in the placebo group (HR: 0.540 [95% CI: 0.377, 0.774]; p<0.001).

Results on the primary analysis were confirmed by all sensitivity analyses.

The stratified KM estimate of the proportion of study participants who were seizure free at Day 166 was 31.3% (95% CI: 22.8%, 39.9%) in the LCM group and 17.2% (95% CI: 10.4%, 24.0%) in the placebo group. The difference in seizure freedom rate at Day 166 between the LCM and placebo groups was 14.1% (95% CI: 3.2%, 25.1%); this difference was statistically significant (p=0.011).

The risk of developing a first PGTCS during the 24-week Treatment Period was lower in the LCM group compared with the placebo group; the survival estimates at the end of the Treatment Period were 30.97% in the LCM group and 17.27% in the placebo group (HR: 0.683 [95% CI: 0.507, 0.921]; p=0.012).

3.3. Uncertainties and limitations about favourable effects

Even though the primary endpoint as well secondary endpoints supported the favourable effects of LCM treatment compared to placebo in patients with PGTCS in IGE during 24-weeks treatment period, some uncertainties remain.

Subgroup analysis (age, sex, region, baseline PGTCS frequency, number of AEDs) did not reveal any obvious differences in terms to response to LCM treatment of PGTCS seizures. However, for the subgroup Western/Central Europe comprising 77 subjects, the KM survival estimates were numerically somewhat lower in the LCM compared to the placebo group (46.22 % and 48.30 %, respectively). A very limited number of patients treated with LCM was aged <18 years: 8 patients in the ≥4 to <12 years age group and 16 patients in the >12 to <18 years range. However, from these very limited data, it appears that LCM treatment in paediatric patients is similar to the one observed in adults regarding the appearance of 2nd PGTC seizure or PGTCS seizure frequency with the exception on PGTCS free status where adults seems to have better response compared to paediatric patients.

The data regarding treatment beyond 24 weeks is difficult to interpret since the long-term open label study EP00012 is not finished and the interim results indicate that among patients who discontinued treatment substantial number of patients did so due to lack of effect. There was no clear pattern in timing of discontinuation from this study due to lack of efficacy.

3.4. Unfavourable effects

The clinical safety data from LCM use for the treatment of PGTCS in adults and paediatric study participants with IGE down to 4 years of age in study SP0982 included a total of 242 study participants. Of these, 49 study participants were <18 years of age (17 were 4 to <12 years of age and 32 were ≥12 to <18 years of age) at the time of enrolment in SP0982.

In the LCM group, TEAEs were most commonly reported in the SOCs of Nervous system disorders (58 study participants [47.9%]), and Infections and infestations and Gastrointestinal disorders (25 study participants [20.7%] each). By PT, the most common TEAEs were dizziness (28 study participants [23.1%]), somnolence (20 [16.5%]), and headache (17 [14.0%]). In the Placebo group, TEAEs were also most commonly reported in the SOCs of Nervous system disorders (36 study participants [29.8%]), Infections and infestations (23 study participants [19.0%]), and Gastrointestinal disorders (19 [15.7%]). By PT, the most common TEAEs were somnolence (17 [14.0%]), headache (12 [9.9%]), and nausea and dizziness (7 [5.8%] each).

Paediatric patients in the LCM group showed higher exposure duration-adjusted rates of somnolence over placebo (5.94 vs. 1.70 per 100 person-months) as compared to adult patients (2.84 vs. 5.46, respectively).

The incidence of study participants reporting serious TEAEs was 6.6% and 3.3% in the LCM and Placebo groups, respectively. The most commonly reported SAEs in the LCM were dizziness (1.7%) and somnolence (1.7%). No deaths were reported in the study.

Four (3.3%) study participants on LCM and 0 on Placebo reported unlisted TEAEs of ataxia. All were considered related to study drug per the Investigator.

The applicant investigated the aggravation of absence seizures and myoclonic seizures by LCM. There was no clear evidence of worsening for days with absence seizures in the LCM group compared with Placebo.

Three study participants (2.5%) in the LCM group reported 3 TEAEs of myoclonic epilepsy during the Treatment Period compared with 0 in the placebo group. In addition, 1 study participant in the LCM group reported a mild TEAE of myoclonic epilepsy during the Post-Treatment (Transition) Period. Myoclonus was reported by 1 study participant (0.8%) in the placebo group. Also, a total of 21 study participants experienced onset of myoclonic seizure or ≥50% worsening in days of myoclonic seizures, of which 14 study participants were in the LCM group and 7 were in the Placebo group.

As of the clinical cut-off date for the interim EP0012 study, the most frequently reported TEAEs (PT) per 100 person-months were: nasopharyngitis (35 study participants [16.6%]), with a rate of 0.97 person-months; headache (34 study participants [16.1%]), 0.94 person-months; dizziness (32 [15.2%]), 0.88 person-months; somnolence (22 [10.4%]), 0.61 person-months; upper respiratory tract infection (14 [6.6%]), 0.39 person-months; and contusion and nausea (13 [6.2%] each), 0.36 person-months each.

The safety of LCM in the treatment of PGTCS in adults, adolescents and children from 4 years of age with IGE was in general consistent with the known safety profile of LCM in the POS population except for worsening of myoclonic seizures.

3.5. Uncertainties and limitations about unfavourable effects

The available data are too scarce to allow the assess the potential impact of LCM on behaviour and executive functioning in children with IGE.

The CHMP noted that additional safety data are pending as the open-label extension study EP0012 is still ongoing.

3.6. Effects Table

Table 29: Effects Table for [insert product name and indication] <(data cut-off: 28 Nov 2018)

Effect	Short description	Unit	LCM	Placebo	Strength of evidence / Uncertainties	References
Favourable Effects						
Time to 2nd PGTCS	KM survival estimate at the end of the treatment period	%	55.27	33.37	P<0.001/can vary in different IDE diagnosis	Study SP0982
Proportion of patients with seizure freedom at day 166	KM seizure free	%	31	17.3	P=0.011	SP0982

Effect	Short description	Unit	LCM	Placebo	Strength of evidence / Uncertainties	References
Time to 1st PGTCS during the 166-day treatment Period	Time to event (median)	Days	36	20	P=0.012	SP0982
Unfavourable Effects						
Dizziness		n (%)	28 (23.1)	7 (5.8)		
Somnolence		n (%)	20 (16.5)	17 (14.0)		
Headache		n (%)	17 (14.0)	12 (9.9)		
Myoclonic epilepsy		n (%)	3 (2.5)	0 (0)		
Ataxia		n (%)	4 (3.3)	0 (0)		

Abbreviations: PGTCS – primary generalized tonic-clonic seizures, KM – Kaplan-Meier

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Primary generalized tonic-clonic seizures (PGTCS) are considered to be the most debilitating seizure type within IGE, since repeated and uncontrolled seizures may result in irreversible damage to the brain. Treatment with LCM as demonstrated reduced risk of appearance of PGTCS during the treatment period (24 week) compared to placebo in the SP0982 study. Other generalized seizures, like absences and myoclonic seizures, apparently have not been improved by the LCM treatment.

The improvement in the most debilitating type of generalized seizures (PGTCS) is considered to be of major importance for patients with IGE. It is expected that positive effects on PGTCS are not achieved at the expense of worsening of other generalized seizures. Other AEDs (e.g. carbamazepine or lamotrigine) have reported negative effects on other types of generalized seizures such as absences or myoclonic seizures. It is recognised that these effects can however be handled with the relevant warnings in the SmPC.

A complete understanding of treatment benefit in paediatric patients is hampered by the small number of children recruited in the pivotal trial. The observed LCM-induced worsening of myoclonic seizures is a concern and could be more relevant for the paediatric population compared to adults.

Long-term sustained treatment effect is of key importance for patients with the PGTCS for patients with IGE. However, the data regarding treatment beyond 24 weeks is difficult to interpret since the long-term open label study EP00012 is not finished and the interim results indicate that among patients who discontinued treatment substantial number of patients did so due to lack of effect.

Safety data for LCM in the treatment of PGTCS in adults, adolescents and children from 4 years of age with IGE were in general consistent with the known safety profile of LCM in the POS population except for ADRs of myoclonic seizures and ataxia. These ADRs are correctly reflected in section 4.8 of the SmPC, completed by a warning for the risk of myoclonic seizures in section 4.4.

3.7.2. Balance of benefits and risks

The potential benefit of LCM treatment of PGTCS in the IGE should be weighed taking into account the effects on other generalized seizures such as absences and myoclonic seizures, as well as observed effects in the patients with specific diagnosis studied (e.g. Juvenile absence epilepsy, juvenile myoclonic epilepsy).

3.8. Conclusions

The overall B/R ratio of Vimpat/Lacosamide UCB as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment as adjunctive therapy of primary generalised tonic-clonic seizures in adults, adolescents and children from 4 years of age with idiopathic generalised epilepsy for Lacosamide UCB and Vimpat. Consequently sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 15.1 has also been submitted.
Furthermore, the PI is brought in line with the latest QRD template version 10.1. The MAH also takes the opportunity to align the PI of Lacosamide UCB with the PI of Vimpat.

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-000402-PIP03-17 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Vimpat-H-C-WS1782 and Lacosamide UCB-H-C-WS1782

Attachments

1. SmPC and Package Leaflet of Vimpat, as a relevant example with changes highlighted as adopted by the CHMP on 15 October 2020.