10 November 2016
EMA/132443/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vimpat

International non-proprietary name: lacosamide

Procedure No. EMEA/H/C/000863/II/0060/G

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

AE	Adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AS	active substance
AST	aspartate aminotransferase
BMI	body mass index
CBZ	carbamazepine
CBZ-CR	carbamazepine (controlled release)
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CT	computed tomography
CV	Cardiovascular
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
EU	European
FAS	Full Analysis Set
F_{pen}	market penetration factor
FDA	(US) Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GGT	gamma glutamyl transferase
ICH	International Conference on Harmonisation
ILAE	International League Against Epilepsy
ITT	intent-to-treat
KM	Kaplan-Meier
K_{OC}	adsorption coefficient
LCM	lacosamide
LFT	liver function test
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PEC	Predicted Environmental Concentration
PGIC	Patient's Global Impression of Change
PK	pharmacokinetic(s)
POS	Partial onset seizures
PPS	Per Protocol Set
PPSS	Per Protocol Set Subset
PT	preferred term
QRD	Quality Review of Documents
RMP	Risk management plan
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SS	Safety Set
SUDEP	Sudden Unexpected Death in Epilepsy
TBI	Traumatic Brain Injury
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 11 January 2016 an application for a group of variations.

The following variations were requested in the group:

Variations 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, II, IIIA and IIIB
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IA	None
B.I.b.2.a	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	Type IA	None

Extension of Indication to extend the indication to monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

As a consequence sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the Product Information (PI) in line with the latest QRD template.

In addition, the MAH grouped the variation with a number of type IA variations as follows:

B.I.b.1.b type IA – tightening of the specification limit for heavy metals in the lacosamide drug substance.
B.I.b.1.b type IA – tightening of the specification limit for bacterial endotoxins in the lacosamide drug substance.
B.II.d.1.a type IA - B.I.b.1 type IA – tightening of the specification limit for bacterial endotoxins in Vimpat 10mg/ml solution for infusion.
B.I.b.2.a type IA – Minor change to the test procedure for heavy metals in the lacosamide drug substance.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling 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 P/0183/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0183/2015 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 applicant 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 applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Filip Josephson Co-Rapporteur: Luca Pani

Timetable	Actual dates
Submission date	11 January 2016
Start of procedure:	30 January 2016
CHMP Rapporteur Assessment Report	23 March 2016
CHMP Co-Rapporteur Assessment Report	24 March 2016
PRAC Rapporteur Assessment Report	1 April 2016
PRAC Outcome	14 April 2016
CHMP members comments	15 April 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 April 2016
Request for supplementary information (RSI)	28 April 2016
CHMP Rapporteur Assessment Report	23 August 2016
CHMP members comments	5 September 2016
Updated CHMP Rapporteur Assessment Report	8 September 2016
Second Request for supplementary information (RSI)	15 September 2016
CHMP Rapporteur Assessment Report	27 October 2016
CHMP members comments	31 October 2016
Updated CHMP Rapporteur Assessment Report	4 November 2016
CHMP Opinion	10 November 2016

2. Scientific discussion

2.1. Introduction

Vimpat contains the active substance lacosamide (LCM), an amino acid derivative with anticonvulsive activity. While its precise mechanism of action has not been fully elucidated, LCM has been shown to enhance slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyper-excitable neuronal membranes. This effect is thought to help preventing neuronal seizure activity.

Vimpat has been authorised in the European Union (EU)/European Economic Area through the centralised procedure by Commission Decision in August 2008. It is approved as adjunctive therapy in the treatment of partial-onset seizures (POS) with or without secondary generalization in adult and adolescent (16 to 18 years) patients with epilepsy. LCM is available as tablets (50mg, 100mg, 150mg, and 200mg), solution for infusion (10mg/mL), and syrup (10mg/mL). Treatment is initiated at a starting dose of 50 mg twice a day which is titrated in weekly increments to a maintenance dose of 100 mg to 200 mg twice a day (maximum daily dose of 400 mg LCM).

With this application, the MAH proposed an extension of the indication from add-on treatment to monotherapy of POS in adults and adolescents with or without secondary generalisation. The MAH furthermore proposed to initiate treatment at a starting dose of 200mg/day LCM (100 mg twice a day) as well as a maximum daily maintenance dose of 600 mg LCM (300 mg twice a day) for monotherapy.

Epilepsy is a heterogeneous and serious brain disorder characterised by the occurrence of unprovoked recurrent seizures. Partial-onset seizures (POS) are initially confined to a discrete area of the cerebral cortex, but may spread to involve both cerebral hemispheres resulting in a secondary generalisation. Amongst the estimated 50 million people worldwide affected by epilepsy, more than 50% have POS. POS may present as simple or complex seizures, depending on whether consciousness is affected. They can manifest as motor, sensory, automatic or psychic symptoms and, in case of secondary generalisation, as absences, tonic, clonic, tonic-clonic, myoclonic or tonic seizures. According to the 1981 classification by the International League Against Epilepsy (ILAE), which is still widely used, POS can be divided in 3 different seizure subtypes, IA (simple partial seizures), IB (complex partial seizures) and IC (with secondary generalized tonic-clonic convulsions).

According to relevant treatment guidelines (e.g. ILAE and UK National Institute for Health and Care Excellence) first line treatment of patients with newly diagnosed POS consists of monotherapy with an anti-epileptic drug (AED). Approximately 70-80% of epilepsy patients become seizure-free on a single AED, but about 20-30% require adjunctive treatment, which is usually applied after two failed monotherapies. Traditionally, AEDs are first studied in add-on trials in refractory epilepsy patients. As a result, clinical testing and approval for treatment of newly diagnosed patients is delayed and additional treatment options for monotherapy are needed.

This application was supported by the results of the randomised controlled phase 3 trial, study SP0993, and interim data from its extension, study SP0994. An additional conversion to monotherapy study (SP902) has been conducted to provide the primary basis for the application for a LCM monotherapy indication in the United States (US), which was approved in August 2014. Data from study SP902 and its long-term extension SP904 have been previously reviewed by the CHMP in a variation procedure in November 2013 (EMEA/H/C/000863/II/0045), whereby the MAH did not apply for a monotherapy indication but changes to SmPC section 4.8 were agreed (addition of common adverse drug reactions paraesthesia, diarrhoea, feeling drunk and contusion).

2.2. Quality aspects

Further to the application for POS monotherapy with LCM doses up to 600 mg/day, i.e. an increased maximum maintenance dose compared to the current add-on treatment regimen (up to 400 mg/day), the MAH proposed tightened specifications limits for some of the quality attributes of the active substance and the finished product (for the solution for infusion), as follows:

B.I.b.1.b type IA – tightening of the specification limit for heavy metals in the lacosamide drug substance.

The MAH proposed to tighten the heavy metals limit for both the oral and the parenteral grade.

B.I.b.1.b type IA – tightening of the specification limit for bacterial endotoxins in the lacosamide drug substance.

The bacterial endotoxin limit of the parenteral grade of LCM was proposed to be tightened.

B.II.d.1.a type IA - B.I.b.1 type IA – tightening of the specification limit for bacterial endotoxins in Vimpat 10mg/ml solution for infusion.

The specification limit for bacterial endotoxins in Vimpat 10 mg/ml solution for infusion was proposed to be tightened.

B.I.b.2.a type IA – Minor change to the test procedure for heavy metals in the lacosamide drug substance.

As a consequence of the tightened limit for heavy metals, minor changes to the analytical method were proposed, including changes in the preparation of the standard and sample solutions to account for the tightened specification limit.

All proposed changes were considered acceptable by the CHMP. As regards limits for drug related impurities and solvents, no change has been proposed and none was considered needed by the CHMP.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. An updated environmental risk assessment (ERA) has been provided taking into account the increased exposure due to the extended target population and maximum daily dose of 600 mg/day.

2.3.1. Ecotoxicity/environmental risk assessment

For the purpose of this application, the potential environmental impact of the extension of indication from add-on to mono-therapy of POS in adults and adolescents (16 – 18 years) and the new maximum recommended dose of 600 mg/day LCM was assessed.

The market penetration factor (F_{pen}) was refined based on published prevalence data (World Health Organisation, 2007) and Forsgren et al (2005). Using the worst case estimates from Forsgren et al. (2005), F_{pen} was calculated at 0.015 (2019 forecast). Using this values, and assuming a maximum dose of 600 mg lacosamide/day and 100% excretion as unchanged substance, the Predicted Environmental Concentration in surface water ($PEC_{surfacewater}$) was estimated at 0.0045 mg/L. As LCM is not ready biodegradable and its mean adsorption coefficient (K_{OC}) of 9 L/kg is below the action limit of 10,000 L/kg, a revised $PEC_{groundwater}$ was calculated at 0.0011 mg/L.

As shown in Table 1, the risk characterisation using revised PEC/predicted no-effect concentration (PNEC) ratios resulted in values lower than the Tier B trigger values specified in the Guideline on the Environmental Risk Assessment of medicinal Products for Human Use (CPMP/SWP/4447/00).

Table 1 – Summary of ERA Fate and Effect Analysis

Risk Characterisation			
PEC (mg/L)	**PNEC (mg/L)**	**PEC/PNEC ratio**	**Criterion for Tier B Evaluation**
$PEC_{SURFACEWATER}$ = 0.0045	$PNEC_{WATER} \geq 1$	≤ 0.0045	PEC/PNEC Ratio ≥ 1
$PEC_{SURFACEWATER}$ = 0.0045	$PNEC_{MICROORGANISM} \geq 100$	$\leq 4.5 * 10^{-5}$	PEC/PNEC Ratio > 0.1
$PEC_{GROUNDWATER}$ = 0.0011	$PNEC_{GROUNDWATER}$ = 3.2	$3.4 * 10^{-4}$	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 raporteur, EMEA/CHMP/628025/2008)[5] (see Annex)			> 10%

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in support of this application. As summarized in section 5.3 of the SmPC, in animal studies, toxicity was observed for the cardiovascular (CV) system and liver whereby effects were seen at no or low margins of exposure. Effects on the CV system and on the liver were also seen in humans. In the Risk Management Plan (RMP), cardiac conduction and electrocardiogram (ECG)-related events are included as important identified risk and potential for hepatotoxicity is included as an important potential risk.

The non-clinical data submitted and assessed in the original Marketing Authorisation Application were considered by the CHMP adequate to also support the present application for an extension of the indication to POS monotherapy.

With regard to the updated ERA, the CHMP considered the approach of refining market penetration and environmental exposure using worst case assumptions acceptable. Even when accounting for the extended target population and proposal for a maximum daily dose of 600 mg/day LCM, risk characterisation based on revised PEC/PNEC ratios showed that LCM is unlikely to present a risk to the terrestrial and aquatic environments.

2.3.3. Conclusion on the non-clinical aspects

The CHMP agreed that no new non-clinical studies were necessary to support the present application.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of LCM. Considering the above data, LCM is not expected to pose a risk to the environment

2.4. Clinical aspects

2.4.1. Introduction

Good Clinical Practice (GCP)

The MAH claimed that the clinical trials were performed in accordance with GCP.

The MAH 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.

Table 2 – Tabular Overview of Clinical Studies

Study No./ Country or Region(s)	Objective(s) of Study	Study Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/ Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Study Status/ Type of Report
5.3.5 - Reports of Efficacy and Safety Studies							
5.3.5.1 - Study Reports of Clinical Studies							
SP0993/ Europe, Australia, Canada, Japan, Mexico, Philippines, South Korea, Thailand, US	To compare the efficacy and safety of LCM (200 to 600mg/day) to CBZ-CR (400 to 1200mg/day) used as monotherapy for at least 1 year, efficacy being measured as a primary endpoint by 6-month seizure freedom, in newly or recently diagnosed epilepsy subjects	Phase 3, multicenter, double-blind, double-dummy, randomized, positive-controlled noninferiority study comparing the efficacy and safety of LCM to CBZ-CR used as monotherapy	LCM/ 200 to 600mg/day CBZ-CR/ 400 to 1200mg/day Oral tablet (LCM) Overencapsu-lated oral tablet (CBZ-CR)	Up to 121 weeks	445 LCM 443 CBZ-CR 53.6% M/46.4% F	41.8 years/ (16 to 87)	Complete/ Full
SP0994/ Europe, Australia, Canada, Japan, Mexico, Philippines, South Korea, Thailand, US	To obtain information about the long term safety of LCM in comparison with CBZ-CR when used as monotherapy in subjects with recently diagnosed partial-onset or generalized tonic-clonic seizures and to allow subjects who completed the monotherapy study SP0993 to continue to receive LCM or CBZ-CR	Phase 3, double-blind, double-dummy extension study	LCM/ 200 to 600mg/day CBZ-CR/ 400 to 1200mg/day Oral tablet (LCM) Overencapsu-lated oral tablet (CBZ-CR)	>104 weeks	LCM: 266 enrolled CBZ-CR: 259 enrolled/ 55.2% M/44.8% F	43.1 years/ (17 to 84)	Ongoing/ Interim
SP902/ US, Canada, Europe, Australia	To demonstrate the efficacy and safety of conversion to LCM 400mg/day monotherapy for partial-onset seizures (with or without secondary generalization) in subjects 16 to 70 years of age who were withdrawn from 1 to 2 marketed AEDs	Phase 3, historical-controlled, multicenter, double-blind, randomized conversion to monotherapy	LCM/ 300 or 400mg/day (150 or 200mg bid)/ Oral tablet	Up to 20 weeks	106 LCM 300mg/day 320 LCM 400mg/day/ 48.5% M/51.5% F	40.6 years/ (16 to 69)	Complete/ Full

Study No./ Country or Region(s)	Objective(s) of Study	Study Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/ Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Study Status/ Type of Report
5.3.5.2 - Study Reports of Uncontrolled Clinical Studies							
SP904/ US, Canada, Europe, Australia	To obtain information about the percentage of subjects who remain on LCM monotherapy and the duration of LCM monotherapy treatment; to obtain information about the long-term safety of LCM when used as monotherapy or adjunctive therapy in subjects with partial-onset seizures	Phase 3, open-label, long-term extension	LCM/ 100 to 800mg/day (50 to 400mg bid)/ Oral tablet	Up to 2 years	323 enrolled/ 50.0% M/50.0% F	40.7 years/ (16 to 69)	Complete/ Full

AED=antiepileptic drug; BA=bioanalytical; bid=twice daily; CBZ-CR=carbamazepine controlled release; F=female; LCM=lacosamide; M=male; No.=Number

[a] Daily dose, unless otherwise specified.

2.4.2. Pharmacokinetics

Sparse pharmacokinetic (PK) data were collected in study SP0993. Blood samples were collected during the stabilisation phase, escalation and evaluation phases in order to determine plasma concentrations of LCM and carbamazepine (CBZ). The time the subject took the most recent dose of study medication and the time of blood sampling were recorded.

Table 3 - LCM plasma concentration (µg/mL) by visit and actual dose

Visit	Actual dose (mg)	n/nLOQ[a]	Mean (SD)	CV (%)	Median (Min, Max)
Dose level 1					
SV1	100	409/399	4.26 (2.13)	49.90	4.12 (0.00, 14.05)
EV2-1	100	235/225	4.45 (2.37)	53.19	4.18 (0.00, 16.09)
MV2-1	100	202/189	4.15 (2.18)	52.60	3.95 (0.00, 11.54)
Dose level 2					
EV2-2	200	54/51	8.43 (3.64)	43.15	8.64 (0.00, 17.38)
MV2-2	200	39/37	8.18 (4.06)	49.68	8.11 (0.00, 17.75)
Dose level 3					
EV2-3	300	18/18	12.05 (6.12)	50.82	11.77 (1.96, 24.96)
MV2-3	300	14/14	13.51 (6.17)	45.66	12.63 (2.14, 26.92)

CV=coefficient of variation; EV=Evaluation Visit; LCM=lacosamide; LOQ=lower limit of quantification; Max=maximum; Min=Minimum; MV=Maintenance Visit; PK=pharmacokinetic; SD=standard deviation; SS=Safety Set; SV=Stabilization Visit

Note: Actual dose was the dose of the most recent administration prior to PK sampling. Summary statistics were presented for visits with at least two-thirds of the data above the LOQ.

[a] nLOQ=number of measurements above the LOQ (0.05 µg/mL). Values below the LOQ were set to 0 for the calculation of the summary statistics.

Table 4 - CBZ plasma concentration (µg/mL) by visit and actual dose

Visit	Actual dose (mg)	n/nLOQ[a]	Mean (SD)	CV (%)	Median (Min, Max)
Dose level 1					
SV1	200	399/388	6.25 (2.29)	36.56	6.23 (0.00, 20.84)
EV2-1	200	224/213	5.55 (2.11)	37.96	5.68 (0.00, 12.12)
MV2-1	200	200/191	5.52 (2.09)	37.88	5.49 (0.00, 13.10)
Dose level 2					
EV2-2	400	58/55	7.32 (2.76)	37.76	7.47 (0.00, 12.71)
MV2-2	400	45/43	7.02 (2.56)	36.46	7.20 (0.00, 12.34)
Dose level 3					
EV2-3	600	13/13	11.16 (2.18)	19.54	11.15 (7.70, 14.35)
MV2-3	600	6/6	10.24 (2.65)	25.87	9.83 (7.12, 13.55)

CBZ=carbamazepine; CV=coefficient of variation; EV=Evaluation Visit; LOQ=lower limit of quantification; Max=maximum; Min=Minimum; MV=Maintenance Visit; PK=pharmacokinetic; SD=standard deviation; SS=Safety Set; SV=Stabilization Visit

Note: Actual dose was the dose of the most recent administration prior to PK sampling. Summary statistics were presented for visits with at least two-thirds of the data above the LOQ.

[a] nLOQ=number of measurements above the LOQ (0.25 µg/mL). Values below the LOQ were set to 0 for the calculation of the summary statistics.

Upon a request by the CHMP, the MAH furthermore presented comparative data for systemic exposure to LCM at a daily dose of 600 mg in the pivotal add-on trials SP754 and SP667 and for monotherapy. Small differences were observed with slightly lower values of exposure parameters including $c_{max,ss}$ and $AUC_{tau,ss}$ in the add-on trials. The coefficients for variation (CV) were large with values between 30-70%.

Discussion and conclusions on clinical pharmacology

Data from sparse PK sampling in study SP0993 supported that subjects were treated with active drug. The MAH stated that LCM and CBZ-CR plasma concentrations were within the expected ranges. However, the CHMP noted that concomitant use of enzyme inducing medicines are known to decrease the systemic exposure of LCM and therefore LCM exposure in the mono-therapy trial SP0993 might have been higher at the same dose level as in the previously conducted add-on trials. To address this concern, the MAH presented comparative exposure data for SP0993 and two pivotal add-on trials a daily dose of 600 mg LCM. While small differences for the monotherapy and add-on data were observed, given the large CVs, these were not considered to be of clinical relevance.

The CHMP was of the view that no additional clinical pharmacology data were needed to support this application.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose-response studies have been conducted in support of this application.

The MAH stated that the target dose of 400 mg/day for LCM monotherapy was chosen based on the results from previous Phase 2 and Phase 3 studies using LCM 200 mg/day, 400 mg/day, and 600 mg/day as adjunctive therapy for subjects with POS. The MAH furthermore stated that the dose levels of LCM for SP0993 (200, 400, and 600 mg/day) were selected in order to include potentially minimum effective doses in a monotherapy situation, as well as higher doses that may further optimize treatment for some patients. LCM 600 mg/day dose has previously been investigated in the add-on setting but was less well tolerated compared to the 400 mg/day dose and was consequently not recommended for use in clinical practice.

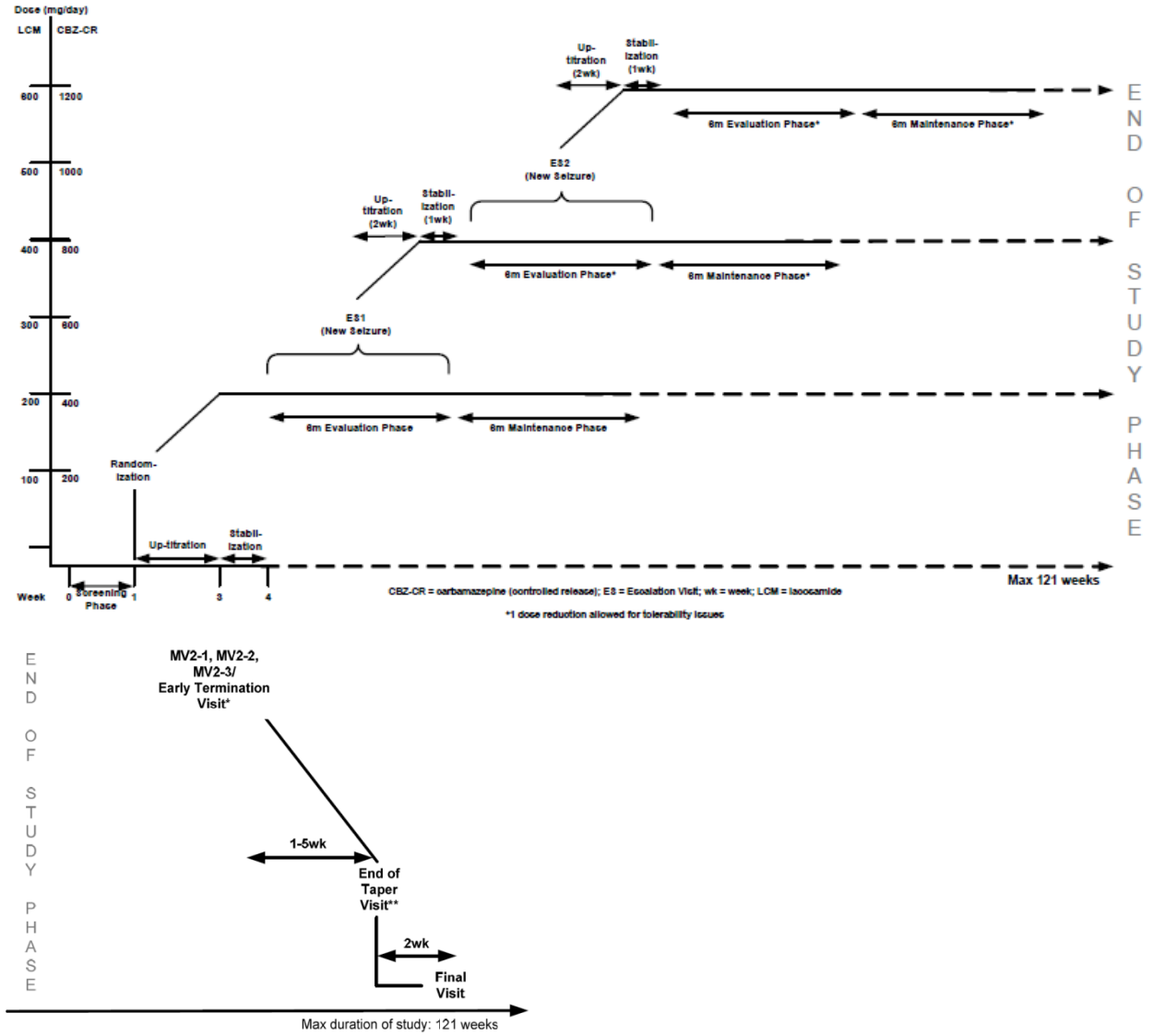
2.5.2. Main study(ies)

Study SP0993: Multicentre, double-blind, double-dummy, randomized, positive-controlled study comparing the efficacy and safety of Lacosamide (200 to 600 mg/day) to controlled release Carbamazepine (400 to 1200mg/day), used as monotherapy in subjects (≥16 years) newly or recently diagnosed with epilepsy and experiencing partial-onset or generalized tonic-clonic seizures.

Methods

Study SP0993 was designed as a non-inferiority study to show at least a similar efficacy and safety profile for LCM and the comparator controlled-release carbamazepine (CBZ-CR). The study consisted of the following phases, with a maximum duration of 121 weeks (maximum duration of investigational medicinal product administration was 118 weeks) for an individual subject:

- Screening Phase: 1 week
- Up-titration and Stabilization Phase: 3 weeks
- Evaluation Phase: 26 weeks
- Maintenance Phase: 26 weeks
- End of Study Phase: up to 7 week



CBZ-CR=carbamazepine (controlled release); LCM=lacosamide; MV=Maintenance Visit; wk=week
* Subjects who did not participate in SP0994 entered the SP0993 End of Study Phase. Subjects who will participate in SP0994 will not taper their dose of study medication.
** Not to scale. Subjects were taking LCM 0mg/day or CBZ-CR 200mg/day.

Figure 1 - Study SP0993 Schematic Design (top) and Diagram of the End of Study Phase (bottom)

A step-wise study design was used employing 3 pre-defined dose levels for both LCM and the active comparator CBZ-CR. All subjects started from the first target dose level. Dose escalation to the next target dose level was done if a seizure occurred during an Evaluation Phase until further dose increase was no longer possible (highest dose level reached). Considering the step-wise design, clinic visits and study duration were related to the highest target dose reached by a subject. Generally, the duration of the study was longer in subjects who needed higher target doses.

Following completion of the Stabilization Phase, subjects were to begin the Evaluation Phase that included two study visits occurring every 13 week. Completion of the second visit had to allow a full 6-month (26-week) Evaluation Phase.

Study participants

The main ***inclusion criteria*** were as follows:

- Subject was male or female and ≥16 years of age. Minors were included in some countries only if legally permitted.
- Subject had newly or recently diagnosed epilepsy having experienced unprovoked partial-onset seizures (IA, IB, IC with clear focal origin) or generalized tonic-clonic seizures (without clear focal origin) that were classifiable according to the ILAE Classification of Epileptic Seizures, 1981. The discrimination between IC and IIE was not requested for inclusion.
- Subject had experienced at least 2 unprovoked seizures (separated by a minimum of 48 hours) in the 12 months preceding Visit 1 (Screening Visit) out of which at least 1 unprovoked seizure occurred in the 3 months preceding Visit 1.
- Subject had an electroencephalogram (EEG) and a brain computed tomography (CT) scan or magnetic resonance imaging (MRI) exam of the brain within the past 12 months. If the EEG and brain CT scan or MRI exam were not performed prior to Visit 1, they needed to be completed and results must have been available prior to randomization at Visit 2.

Subjects were not permitted to enrol in the study if any of the following (main) ***exclusion criteria*** were met:

- Subject had a history or presence of seizures of other types than partial-onset (IA, IB, IC with clear focal origin) and generalized tonic-clonic (without clear focal origin) seizures (eg, myoclonic, absence).
- Subject had a history or presence of seizures occurring in clustered patterns.
- Subject had a history, clinical, or EEG finding suggestive of idiopathic generalized epilepsy (IGE) at randomization (according to the ILAE Classification of Epilepsies and Epileptic Syndromes, 1989).
- Subject had current or previous diagnosis of pseudoseizures, conversion disorders, or other non-epileptic ictal events that could have been confused with seizures based on expert opinion and/or EEG evidence.
- Subject had ever been treated (for any indication) with LCM or CBZ in the past.
- Subject had a medical condition that could reasonably be expected to interfere with drug absorption, distribution, metabolism, or excretion.
- Subject had a history of alcohol or drug abuse within the previous 2 years.
- Subject had sick sinus syndrome without a pacemaker, or second- or third-degree atrioventricular (AV) block, or subject had any other clinically significant ECG abnormalities.
- Subject had experienced a myocardial infarction in the last 3 months.
- Subject had New York Heart Association Class III or Class IV heart failure.
- Subject had a history of status epilepticus.

Treatments

Study medication was administered orally twice daily (bid; at approximately 12 hour intervals in the morning and in the evening) in 2 equally divided doses.

LCM was administered as tablets and CBZ-CR as capsules. In order to maintain the blind, each treatment kit included both tablets (active LCM or placebo) and capsules (active CBZ-CR or placebo).

The proposed dose levels of LCM in study SP0993 were 200, 400, and 600 mg/day.

The proposed dose levels of the comparator CBZ-CR were 400, 800, and 1200 mg/day.

Table 5 - Dosing schedule of Study SP0993 for Up-titration and Stabilization Phase, Evaluation Phase, and Maintenance Phase

Daily target dose	Up-titration and Stabilization Phase			Evaluation Phase and Maintenance Phase
	First week (up-titration)	Second week (up-titration)	Third week (stabilization)	
First target dose				
LCM 200mg/day	LCM 100mg/day	LCM 200mg/day	LCM 200mg/day	LCM 200mg/day
CBZ-CR 400mg/day	CBZ-CR 200mg/day	CBZ-CR 400mg/day	CBZ-CR 400mg/day	CBZ-CR 400mg/day
Second target dose (if optimization was required)				
LCM 400mg/day	LCM 300mg/day	LCM 400mg/day	LCM 400mg/day	LCM 400mg/day
CBZ-CR 800mg/day	CBZ-CR 600mg/day	CBZ-CR 800mg/day	CBZ-CR 800mg/day	CBZ-CR 800mg/day
Third target dose (if optimization was required)				
LCM 600mg/day	LCM 500mg/day	LCM 600mg/day	LCM 600mg/day	LCM 600mg/day
CBZ-CR 1200mg/day	CBZ-CR 1000mg/day	CBZ-CR 1200mg/day	CBZ-CR 1200mg/day	CBZ-CR 1200mg/day

CBZ-CR=carbamazepine (controlled release); LCM=lacosamide.

In case of a tolerability issues at the second or third target dose level, the subject was allowed to decrease the dose by 100mg/day for LCM or 200mg/day for CBZ-CR if medically justified (i.e. LCM 300mg/day, LCM 500mg/day, CBZ-CR 600mg/day, CBZ-CR 1000mg/day). The dose reduction option was allowed only once per subject during the evaluation or maintenance phase for the second or third target dose.

Subjects who were treated for epilepsy with any AED (including benzodiazepines) in the 6 months prior to Visit 1 were not eligible for the study. However, acute and subacute seizure treatment was accepted with a maximum of 2 weeks duration and was allowed if treatment was stopped at least 3 days prior to randomization. The use of benzodiazepines as rescue therapy for epilepsy was allowed if taken at a maximum frequency of once per week prior to Visit 1 and during study participation; more frequent use precluded subjects from study participation.

Addition or use of any concomitant AED during the study period was not allowed except if circumstances obliged the investigator for safety reasons. Any additions of concomitant AED medication during the study period constituted a protocol deviation. Concomitant AEDs were allowed during the end of study period.

Objectives

The objective was to compare the efficacy and safety of LCM (200 to 600 mg/day) to CBZ-CR (400 to 1200 mg/day) used as monotherapy for at least 1 year in newly or recently diagnosed epilepsy subjects.

Outcomes / endpoints

The ***primary efficacy variable*** was the proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject.

Other efficacy variables included the following:

- Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject.
- Time to first seizure or discontinuation due to adverse event (AE) or lack of efficacy during 12 months of treatment following stabilization at the last evaluated dose for each subject.
- Time to first seizure or discontinuation during 12 months of treatment following stabilization at the last evaluated dose for each subject.
- Time to first seizure during 12 months of treatment from the first dose of study medication.
- Time to first seizure or discontinuation due to AE or lack of efficacy during 12 months of treatment from the first dose of study medication.
- Time to first seizure or discontinuation during 12 months of treatment from the first dose of study medication.
- Time to discontinuation due to AE or lack of efficacy during 12 months of treatment from the first dose of study medication.

The primary and other efficacy parameters were measured using data obtained from a diary kept by the subjects to record the daily seizure activity from the beginning of the Up-titration and Stabilization Phase until the last visit. The seizure records were checked by the investigator with regards to correct and thorough daily completion by the subject, and to determine if a dose escalation was required.

Exploratory variables were as follows:

- Clinical Global Impression of Change (CGIC)
- Patient's Global Impression of Change (PGIC)
- Health care resource use: additional health care provider visits unforeseen by the protocol, and hospitalizations

Sample size

At the planning stage it was expected that approximately 1000 subjects were to be enrolled in order to randomise 878 subjects at 200 sites. A sample size of 439 randomised subjects per treatment arm would provide approximately 0.90 power for the comparison of the Kaplan Meier (KM) estimates for the difference in proportion of subjects seizure free for the 26-week Evaluation Phase following stabilization at the last evaluated dose for LCM versus CBZ-CR. This sample size was based on a 2-group test for equivalence of proportions with a 0.05 significance level (2-sided), an assumed seizure-free rate for CBZ-CR of 0.60, and a non-inferiority margin of -0.12 absolute difference. Other assumptions included a 20% rate of important protocol deviations resulting in removal from the PPS.

Subgroup analyses based on subjects with confirmed partial-onset epilepsy were planned. It was expected that approximately 10% of subjects randomized would have unclassified epilepsy and would be excluded from the subgroup analyses because of a diagnosis of generalized epilepsy during the course of the study or because of unclassified epilepsy at the end of the study.

Randomisation

An Interactive Voice Response System was used for treatment assignment based on a pre-determined randomisation schedule. At clinic visit 2 (Week 1), eligible subjects were randomised to receive treatment with LCM or CBZ-CR in a 1:1 ratio. The randomisation was stratified by number of seizures in the 3-month period prior to Visit 1 (≤2 seizures and >2 seizures).

Blinding (masking)

This was a double-blind study. Masking of treatments was achieved through the use of a double-dummy approach (see also treatment section above). All presentations of LCM, CBZ-CR, and matching placebos and accompanying packaging were identical in appearance (size and colour) and packaging so that neither the investigator nor the subject was able to tell whether the subject was receiving LCM or CBZ-CR.

Except for emergency or safety reasons, subjects' study drug treatments were to remain blinded (also if subjects went on to participate in SP0994) until the study was completed and the SP0993 database was locked. Study SP0994 was to be unblinded following database lock and unblinding of SP0993.

Statistical methods

Analysis sets

The primary efficacy assessment was based on the Per Protocol Analysis Set (PPS) and the Full Analysis Set (FAS).

The FAS was defined as all randomised subjects who took at least 1 dose of study medication. The definition was the same as for the Safety Set (SS), hence both sets included the same subjects.

The PPS was defined to include all subjects in the FAS who did not have any important protocol deviations determined to impact the interpretation of primary efficacy.

In addition, a Per Protocol Analysis Set Subset (PPSS) was defined as all subjects in the PPS further excluding subjects who discontinued during the 6 month seizure freedom evaluation period due to reasons unrelated to efficacy. To investigate the robustness of the results, a separate sensitivity analysis of the primary efficacy variable was conducted using the PPSS. An additional 5 sensitivity analyses were performed; treating subjects who discontinued due to reasons other than AE as not seizure free, treating subjects who discontinued due to any reason as not seizure free, treating a day with seizure data missing as a day with seizures, censor for unblinding, and, excluding subjects at one study site (due to findings of non-compliance with applicable regulations, GCPs, and ICH guidelines) from the FAS.

Efficacy analyses

The primary efficacy analysis was a non-inferiority assessment of LCM versus CBZ-CR for the proportion of subjects remaining seizure free for 6 months at the last evaluated dose estimated by the survivor function using KM methods and a non-inferiority margin of -0.12 based on absolute difference. Additionally, it was required that the lower confidence limit for the difference between LCM and CBZ-CR relative to the KM estimate of CBZ-CR 6-month seizure freedom rate was >-20%. Subjects who did not experience a seizure during the 6-month seizure freedom evaluation period were censored at the date of the last dose of study medication during the Treatment Period or Day 182, whichever was earliest. Subjects who discontinued during an Up-titration and Stabilization Phase were censored in the KM analysis with a censoring time as 1 day. The proportion of subjects remaining seizure free during the 12 month seizure freedom evaluation period was estimated in a similar manner as described for the primary endpoint, using the survivor function at Day 364 relative to the start day of the Last Evaluation Period.

All seizure-related efficacy analyses were stratified by past 3-month seizure count (≤2 or >2). The stratified proportion and the estimate for the stratified difference in proportion of subjects seizure free on LCM versus CBZ-CR and a corresponding 95% 2-sided confidence interval (CI) for LCM versus CBZ-CR was produced using Mantel Haenszel methods.

If a subject stopped reporting seizure data prior to the date of last dose of study medication during the Treatment Period, the date of last available seizure count data was considered as the end of the efficacy evaluation period for seizure-related efficacy variables. An intermediate day prior to the end of the efficacy evaluation period with seizure data missing was considered as a day with no seizure in the efficacy analyses unless otherwise specified.

No multiplicity adjustment was employed.

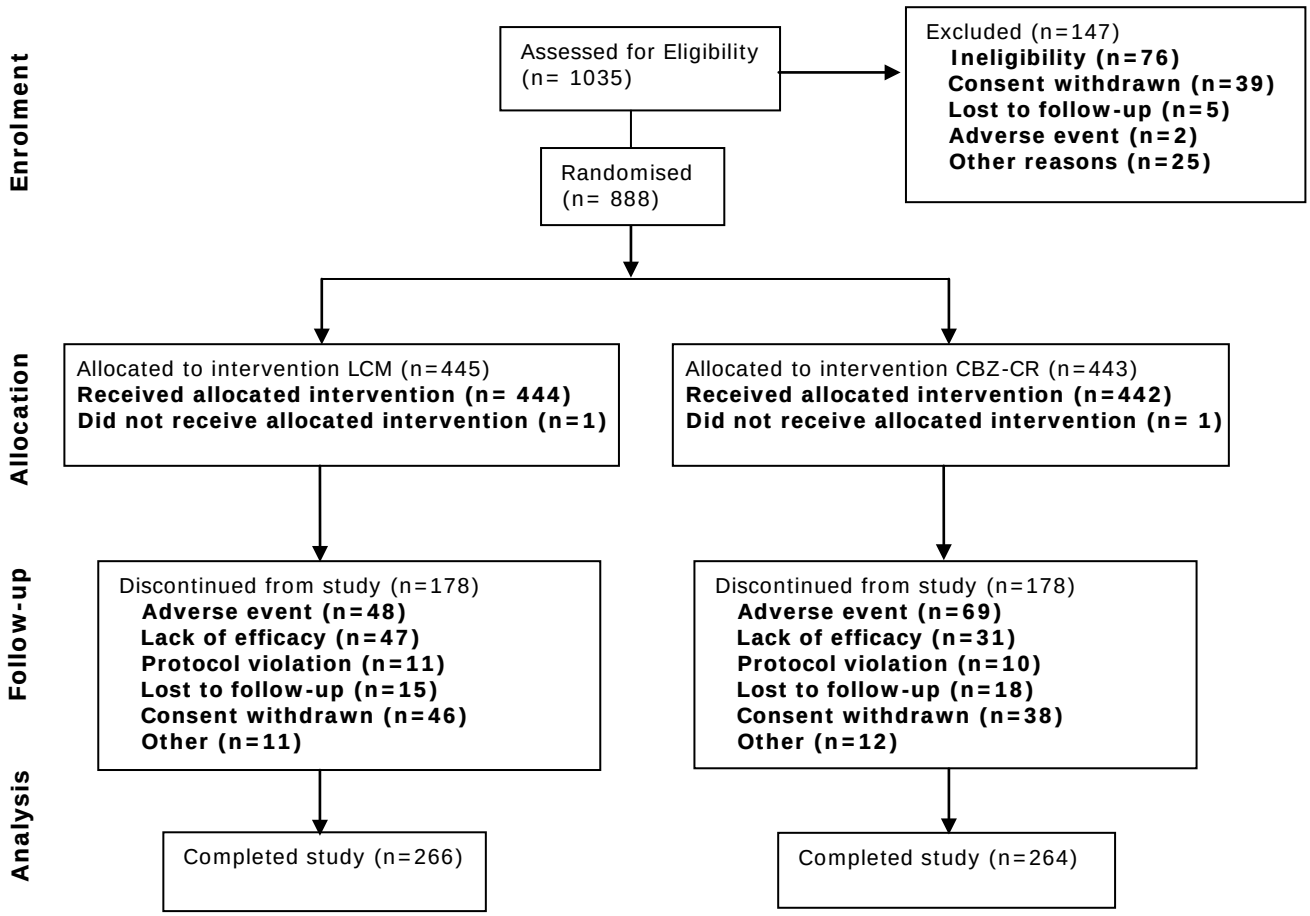
Additional covariates that could be predictive of the time to first seizure during the 6-month seizure freedom evaluation period were explored for selected efficacy variables and considered for exploratory analyses. A Cox proportional hazard model was used to explore these variables after controlling for the stratification factor and treatment effect. The base model included treatment as a covariate and past 3-month seizure count (≤2 and >2) as strata. Additional covariates were added using a stepwise procedure (significant at 0.1 to enter and significant at 0.05 to stay). Any additional covariates included in the final model were considered as predictive. The exploratory covariates examined were Geographic region (Europe vs rest of the world), Focal epileptiform abnormality (Yes vs No) and Neurological disorder (Yes vs No).

The same methods and presentation as for the primary endpoint were to be repeated for the FAS and PPS in the following subgroups: Diagnosed partial-onset or unclassified epilepsy, Diagnosed partial-onset epilepsy, History of Type IC seizure(s), History of Type IC or IIE seizure(s), History of Type IIE seizure(s) only and Elderly. The statistical evaluation of non-inferiority, LCM versus CBZ-CR, was only to be performed for diagnosed partial-onset or unclassified epilepsy subgroup and diagnosed partial-onset epilepsy subgroups as only these two subgroups were expected to be sufficiently powered.

Regarding changes to the planned analyses (see results section, conduct of the study), a further sensitivity analysis was added after database unblinding in which the primary efficacy analysis was repeated for the PPS excluding 5 subjects, 4 in the LCM arm and 1 in the CBZ-CR arm, identified as having measurable LCM and CBZ concentrations in multiple or all plasma samples taken during the study.

Results

Participant flow



Overall, 1035 subjects were screened. The most common reason for screen failure was ineligibility (76 subjects [7.3%]) followed by consent withdrawn (39 subjects [3.8%]) and other reasons (25 subjects [2.4%]). A total of 888 subjects were randomised, 445 to the LCM and 443 to the CBZ-CR treatment arm, respectively, whereof 530 subjects (59.8%) completed the study and 356 subjects (40.2%) discontinued with the most common reasons for discontinuation being AEs (13.2%), consent withdrawn (9.5%), and lack of efficacy (8.8%). Of the total number of subjects randomised 75% (666/888) were recruited at European centres.

In the LCM and CBZ-CR treatment groups, 266 subjects (59.9%) and 264 subjects (59.7%), respectively, completed the study, and 178 subjects (40.1%) and 178 subjects (40.3%), respectively, discontinued prematurely. The most common reasons for discontinuation were the same in both treatment groups: AE (10.8% and 15.6%), lack of efficacy (10.6% and 7.0%), and consent withdrawn (10.4% and 8.6%) in the LCM and CBZ-CR treatment groups, respectively.

The distribution of subjects across dose levels was very similar between the treatments with 70.7% (314/444), 19.6% (87/444) and 9.7% (43/444) in the LCM arm and, 73.3% (324/442), 19.2% (85/442) and 7.5% (33/442) in the CBZ-CR arm at dose level 1, 2 and 3, respectively.

The most common reasons during the entire study for discontinuation at Dose level 1 for the LCM group (200 mg/day) and the CBZ-CR group (400 mg/day) were AEs (9.9% and 17.0%, respectively), consent withdrawn (10.2% and 7.7%, respectively), and lack of efficacy (6.7% and 3.4%, respectively). Discontinuations rates in the LCM treatment group were comparable between the Last Evaluation period

(LEP) and the Maintenance Period for the LCM group (13.4% and 12.7%), whereas for the CBZ-CR group 17.3% occurred during the LEP and 8.3% during the Maintenance Period. At this dose level, all of the above-mentioned discontinuations due to lack of efficacy occurred during the Maintenance Period.

Dose level 2 was maintained by 87 (19.6%) subjects in the LCM group (400 mg/day) and 85 subjects (19.2%) in the CBZ-CR group (800 mg/day). The most common reasons during the entire study for discontinuation at dose level 2 for the LCM and CBZ-CR treatment groups were AE (17.2% and 11.8%, respectively), consent withdrawn (11.5% and 12.9%, respectively), and lack of efficacy (10.3% and 3.5%, respectively). The discontinuation rates in the LCM treatment group were comparable between the LEP and the Maintenance Period (19.5% and 20.7%, respectively), whereas for the CBZ-CR group, 21.2% (n=18) of discontinuations occurred during the LEP and 12.9% (n=17) occurred during the the Maintenance Period. At this dose level, all of the above-mentioned discontinuations due to lack of efficacy occurred during the Maintenance Period.

Forty three subjects (9.7%) and 33 subjects (7.5%) in the LCM and CBZ-CR groups, respectively, remained at Dose level 3 (600 mg/day LCM and 1200 mg/day CBZ-CR). The most common reason during the entire study for discontinuation at dose level 3 for the LCM and CBZ-CR treatment groups was lack of efficacy (39.5% and 51.5%, respectively), adverse event (4.7% and 12.1%), 'other' (9.3% and 9.1%) and consent withdrawn (9.3% and 6.1%). At this dose level, the discontinuation rates for the LCM group between LEP and Maintenance Period were 51.2% (n=22) and 9.3% (n=4), respectively, and for the CBZ-CR group they were 48.5% (n=16) and 21.2% (n=7), respectively. The proportion of subjects who discontinued for lack of efficacy during the LEP for the LCM and CBZ-CR group was 34.9% (n=15) and 36.4% (n=12), respectively, whereas during the Maintenance Period 2.3% (n=1) and 12.1% (n=4) of subjects discontinued because of LOE.

Protocol deviation regarding inclusion and exclusion criteria were evenly distributed in both treatment groups, both overall and for those with potential impact on the primary endpoint, with only slightly higher occurrence in the CBZ-CR group (9.5%) compared to the LCM group (7.9%).

Recruitment

A total of 185 sites in Australia, Canada, Europe, Japan, Mexico, Philippines, South Korea, Thailand, and United States participated (i.e. enrolled subjects) in the study. The study period was approximately 4 years and 3 months. The first subject was enrolled on 27 April 2011 and the last subject completed at 07 August 2015.

Conduct of the study

The original SP0993 study protocol was dated 07 July 2010. Subsequently, 6 global protocol amendments were issued:

- Global protocol amendment 1 (13 Dec 2010) primarly to add an exclusion criterion for known sodium channelopathy and revise withdrawal criteria and follow-up recommendations for abnormal liver function tests (LFTs), following a recommendation from the US Food and Drug Administration (FDA) due to a theoretical concern that enhanced slow inactivation of sodium channels by LCM may be proarrhythmic in subjects with sodium channelopathies. The decision to re-insert additional withdrawal criteria and follow-up recommendations for abnormal LFTs was based on a newly adopted FDA Guidance on Drug-Induced Liver Injury (July 2009), and the fact that LFT abnormal has been added as a postmarketing adverse drug reaction in the EU SmPC.
- Global Protocol amendment 2 (18 Nov 2011), primarily to revise the exclusion criteria related to a history of suicidality and to add withdrawal criteria related to suicidality.

- Global Protocol Amendment 3 (01 Aug 2012), primarily to provide clarification for the efficacy variables, withdrawal criteria (eg, following a seizure that occurred after dose reduction), and the use of concomitant medications that may have interacted with study medication.
- Global protocol amendment 4 (27 Nov 2012) to modify exclusion criterion 11 (regarding prior treatment of epilepsy with any AED) to indicate that acute and subacute seizure treatment was accepted with a maximum of 2 weeks duration and if treatment was stopped "at least 3 days prior to randomization" (formerly "at least 1 week before Visit 1"). This change decreased the duration of time during which subjects could potentially go untreated before initiating study medication in SP0993, with the aim to increase subject safety. Most withdrawal seizures were expected to occur within 72 hours of AED withdrawal, and most AEDs (including benzodiazepines) were expected to be cleared within this time period with little potential for drug interactions. Furthermore, a withdrawal criterion was clarified for situations in which a subject experienced a seizure during the Evaluation Phase at the maximum dosage of study medication. Finally, the protocol (permitted agents whose plasma levels may be affected by CBZ) was updated with the addition of alprazolam to and the deletion of amitriptyline from the list of permitted agents whose plasma levels may be affected by CBZ (amitriptyline use as an antidepressant was disallowed in another section of the protocol).
- Global Protocol Amendment 5 (14 Mar 2013) ws only submitted to local ethic committees in Spain and was not implemented by any site; therefore, no subjects were randomized under this amendment. The protocol was updated based on a recommendation from the Japanese regulatory authorities to exclude subjects of Asian ancestry who tested positive for the HLA-A*3101 allele in addition to those who tested positive for the HLA-B*1502 allele. Contraceptive measures for male were deleted because preclinical studies did not find any LCM-related findings at any dose level on male reproductive function. Female contraception requirements were adjusted based on WHO guidance on highly effective methods of contraception for women of childbearing potential taking enzyme-inducing AEDs (2010). Text regarding antidepressant and neuroleptic use was modified to permit the introduction of antidepressants (eg, serotonin-selective reuptake inhibitors) that do not cause drug interaction issues and do not interfere with epilepsy therapy as concomitant non-AED treatments. Furthermore, alprazolam was removed as a permitted medication whose plasma levels may be affected by CBZ. This change was made in order to be consistent with other sections of the protocol that limit the use of benzodiazepines.
- Global Protocol Amendment 6 (20 May 2013) included all of the changes in Protocol Amendment 5 and also provided the following revisions: The following sentence was deleted from the protocol (section Concomitant non-AED treatments): "Oral contraceptive use is allowed if ethinylestradiol dosage is at least 50µg per intake." This correction was made to be consistent with the exclusion criteria. With the implementation of Protocol Amendment 6.2, 27 Feb 2015 (applying to: Bulgaria, Canada, Germany, Japan, Latvia, Lithuania, Mexico, Philippines, Romania, Russia, Slovakia, South Korea, Sweden, Ukraine, United States) and Protocol Amendment 6.3 (Czech Republic), UCB considered SP0993 to be complete as of 31 Jul 2015 and committed to classifying any subject ongoing at the time of study closure as a treatment failure in efficacy analyses. SP0993 was fully recruited and had been ongoing for a significantly longer time than originally planned due to the subject response step-wise study design. The limited number of ongoing SP0993 subjects in July 2015, an end of treatment visist was planned to be conducted by 31 July 2015 and these subjects were then to be transferred to the extension study, SP0994. As a result of Protocol Amendment 6.2/6.3, 11 subjects, 5 subjects in the LCM treatment group and 6 subjects in the CBZ-CR treatment group were discontinued from the study.

Baseline data

Demographics

A summary of subject demographics is presented in Table 6.

Table 6 - Summary of demographics for the FAS of Study SP0993

Variable	Overall		Total
	LCM N=444	CBZ-CR N=442	N=886
Age (years), n	444	442	886
Mean (SD)	41.9 (17.9)	41.8 (17.2)	41.8 (17.6)
Median	40.0	41.0	40.0
Min, max	16, 87	16, 85	16, 87
Age group [a], n (%)			
12 to <18 years	14 (3.2)	11 (2.5)	25 (2.8)
18 to <65 years	368 (82.9)	374 (84.6)	742 (83.7)
65 to <85 years	60 (13.5)	56 (12.7)	116 (13.1)
≥85 years	2 (0.5)	1 (0.2)	3 (0.3)
Age group [b], n (%)			
≤18 years	27 (6.1)	19 (4.3)	46 (5.2)
>18 to <65 years	355 (80.0)	366 (82.8)	721 (81.4)
≥65 years	62 (14.0)	57 (12.9)	119 (13.4)
Gender, n (%)			
Male	243 (54.7)	232 (52.5)	475 (53.6)
Female	201 (45.3)	210 (47.5)	411 (46.4)
Racial group, n (%)			
American Indian/Alaskan native	1 (0.2)	3 (0.7)	4 (0.5)
Asian	48 (10.8)	58 (13.1)	106 (12.0)
Black	6 (1.4)	2 (0.5)	8 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.1)
White	378 (85.1)	366 (82.8)	744 (84.0)
Other/mixed	6 (1.4)	10 (2.3)	16 (1.8)
Missing	4 (0.9)	3 (0.7)	7 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	27 (6.1)	26 (5.9)	53 (6.0)
Not Hispanic or Latino	413 (93.0)	413 (93.4)	826 (93.2)
Missing	4 (0.9)	3 (0.7)	7 (0.8)
Weight (kg), n	444	442	886
Mean (SD)	72.52 (16.08)	73.24 (15.84)	72.88 (15.96)
Median	71.00	71.00	71.00
Min, max	35.6, 130.0	37.2, 136.1	35.6, 136.1
Height (cm), n	441	441	882
Mean (SD)	169.65 (9.90)	168.83 (10.22)	169.24 (10.06)
Median	170.00	168.00	169.00
Min, max	140.0, 193.0	111.5, 200.0	111.5, 200.0
BMI (kg/m^2), n	441	441	882
Mean (SD)	25.10 (4.88)	25.70 (5.29)	25.40 (5.09)
Median	24.50	25.00	24.70
Min, max	14.3, 44.4	16.0, 67.8	14.3, 67.8
BMI category (kg/m^2), n (%)			
<18.5	27 (6.1)	10 (2.3)	37 (4.2)
≥18.5 to <25	210 (47.3)	210 (47.5)	420 (47.4)
≥25 to <30	147 (33.1)	157 (35.5)	304 (34.3)
≥30	57 (12.8)	64 (14.5)	121 (13.7)
Missing	3 (0.7)	1 (0.2)	4 (0.5)

BMI=body mass index; CBZ-CR=carbamazepine (controlled release); FAS=Full Analysis Set; LCM=lacosamide; Max=maximum; Min=minimum; SD=standard deviation

[a] EudraCT age categories

[b] ClinicalTrials.gov age categories

Aetiology of epilepsy

The most common aetiology for the LCM treatment group, was aetiology unknown (71.4%) followed by cranial trauma (9.9%), cerebrovascular accident (6.1%), and congenital (5.9%). The most common aetiology for the CBZ-CR treatment group was aetiology unknown (71.9%) followed by cerebrovascular accident (7.7%) and cranial trauma and congenital (6.8% each). Other aetiologies at lower percentatges included genetic origin, perinatal events, cerebral neoplasm, brain surgery, cerebral infection and other.

The proportion of subjects with 'cortical dysplasia', an aetiology with higher incidence in medically refractory forms of dymptomatic epilepsy, was higher in the CBZ-CR group than in the LCM-treated group (15 subjects [3.4%] vs. 9 subjects [2.0%], respectively). The difference was more evident between the LCM and CBZ-CR treatment groups as per the last evaluated dose levels: At dose level 1, 8 subjects (2.5%) in the CBZ-CR 400 mg/day group vs. 6 subjects (1.9%) in the LCM 200 mg/day group had cortical dysplasia. At dose level 2, 6 subjects (7.1%) in the CBZ-CR 800 mg/day group vs. only 1 subject (1.1%) in the LCM 400 mg/day group had cortical dysplasia. At dose level 3, 1 subject (3.0%) in the CBZ-CR 1200 mg/day group vs. 2 subjects (4.7%) in the LCM 600 mg/day group had cortical dysplasia.

With regards to the aetiology 'cranial trauma', to which epilepsy is more heterogeneously linked, either as pathophysiology and prognosis, no major differences in distribution were observed among the two treatment groups overall, occurring in 44 (9.9%) LCM-treated subjects and 30 (6.8%) CBZ-CR subjects. With regards to the proportions by dose, the distribution at dose level 1 was 8.9% (n=28) for LCM 200 mg/day vs. 5.6% (n=18) for CBZ-CR 400 mg/day, at dose level 2 it was 14.9% (n=13) for LCM 400 mg/day and 10.6% (n=9) for CBZ-CR 800 mg/day and at dose level 3 it was 7% (n=3) for LCM 600 mg/day and 9.1% (n=3) for CBZ-CR 1200 mg/day. Unless otherwise specified, it was presumed that the term 'cranial trauma' refers to Traumatic Brain Injury (TBI) which is a condition potentially associated to further development of symptomatic epilepsy, even weeks or years after the event. The relative risk for epilepsy after TBI is strongly related to the severity of head injury, i.e., 4-fold increased risk after moderate TBI and only a 1.5-fold increased risk after mild TBI (Lowenstein DH, 2009).

Classification of epileptic syndrome

The majority of epileptic syndromes for both the LCM and CBZ-CR treatment groups were classified at screening as localization related (91.0% and 91.9%, respectively) and of these, most were classified as cryptogenic (51.8% and 48.0%, respectively) or symptomatic (31.3% and 34.6%, respectively) and less as idipathic (7.9% and 9.3%). Epilepsies and syndromes undetermined whether focal or generalised were 8.8% and 8.1 % in the LCM and CBZ groups, respectively.

Prior and concomitant AEDs

In the LCM treatment group, 45 subjects (10.1%) reported the use of at least 1 prior AED; the most common prior AED was diazepam (16 subjects [3.6%]), followed by clobazam (8 subjects [1.8%]), levetiracetam (7 subjects [1.6%]), and valproate (6 subjects [1.4%]).

In the CBZ-CR treatment group, 37 subjects (8.4%) reported the use of at least 1 prior AED; the most common prior AEDs were diazepam (11 subjects [2.5%]), levetiracetam (10 subjects [2.3%]), and valproate (6 subjects [1.4%]).

In the LCM treatment group, 53 subjects (11.9%) reported the use of at least 1 concomitant AED throughout the study; the most common concomitant AED was levetiracetam (26 subjects [5.9%]), followed by valproate and lamotrigine (6 subjects [1.4%], each). In the CBZ-CR treatment group, 52 subjects (11.8%) reported the use of at least 1 concomitant AED; the most common concomitant AED was levetiracetam (21 subjects [4.8%]), followed by valproate (9 subjects [2.0%]), and lamotrigine (7 subjects [1.6%]). During the treatment period 12 subjects (2.7%) in the LCM treatment group and

6 subjects (1.4%) in the CBZ-CR treatment group reported the use of at least 1 concomitant AED. The majority of concomitant AEDs in both treatment groups were benzodiazepines taken no more than once per week which was permitted by the protocol. In the LCM and CBZ-CR treatment groups, 5 subjects and 1 subject, respectively, took non-benzodiazepine AEDs during the Treatment Period and were reported as important protocol deviations.

Prior and concomitant diseases

- Medical history

In the LCM and CBZ-CR treatment groups, 377 and 384 subjects (84.9% and 86.9%), respectively, had at least 1 medical history finding. The most common MedDRA system organ class (SOC) in which medical history findings were noted was Nervous system disorders (LCM: 159 subjects [35.8%] and CBZ-CR: 143 subjects [32.4%]).

- Concomitant diseases

In the LCM and CBZ-CR treatment groups, 322 and 319 subjects (72.5% and 72.2%), respectively, had at least 1 concomitant disease. The most common SOCs in which concomitant disease findings were noted for the LCM group were Nervous system disorders (122 subjects [27.5%]) followed by Vascular disorders (100 subjects [22.5%]) and Metabolism and nutrition disorders (94 subjects [21.2%]). For CBZ-CR these were Vascular disorders (123 subjects [27.8%]) followed by Nervous system disorders (103 subjects [23.3%]) and Metabolism and nutrition disorders (96 subjects [21.7%]).

Numbers analysed

Of the total number of 888 subjects randomised 886 subjects received at least 1 dose of study medication and were included in the SS and FAS. Five analysis populations were defined: the randomised set (RS), SS, FAS, PPS, and the PPS subset (PPSS).

Table 7 – Analysis Population

Population	LCM	CBZ-CR	Total
RS	445	443	888
SS (FAS)	444	442	886
PPS	408	397	805
PPSS	338	309	647

CBZ-CR=carbamazepine (controlled release); FAS=Full Analysis Set, LCM=lacosamide; RS=Randomized Set, SS=Safety Set, PPS=Per-Protocol Set, PPSS=Per-Protocol Set Subset

Seventy-seven subjects were excluded from the PPS due to important protocol deviations related to primary efficacy including four subjects at a study site due to findings of noncompliance with applicable regulations, GCPs, and ICH guidelines. In addition, four subjects from sites in the Ukraine and Crimea region were excluded from the PPS due to missing data as a result of political and civil unrest, which prohibited study-related activities. Overall, aapproximately 10% of subjects included in the FAS were excluded in the PPS to be compared with the 20% that was expected at the planning stage. The proportion of subjects included in the PPS was similar between the two treatment arms; 91.7% (408/445) LCM and 89.6% (397/443) CBZ-CR. Among the 805 subjects from the PPS, 647 subjects were included in the PPSS (which excluded discontinuations unrelated to efficacy that occurred during the 6-month seizure freedom evaluation period). The proportion of subjects in PPSS was slightly higher in the LCM arm, 76.0% (338/445) compared to 69.8% (309/443) in the CBZ-CR arm.

Outcomes and estimation

Primary efficacy variable: Proportion of subjects remaining seizure free for 6 consecutive months (26 weeks) of treatment following stabilization at the last evaluated dose for each subject.

The results for the KM proportion of seizure free subjects are presented in Table 8.

Table 8 - Kaplan-Meier proportion of subjects seizure free for 6 months at the last evaluated dose (FAS and PPS)

Parameter	FAS		PPS	
	LCM N=444	CBZ-CR N=442	LCM N=408	CBZ-CR N=397
Stratum 1: Past 3-month seizure count ≤2				
Number of subjects	224	224	204	202
Number of subjects with a seizure, n (%)	11 (4.9)	11 (4.9)	8 (3.9)	8 (4.0)
Number of subjects censored, n (%) [a]	38 (17.0)	47 (21.0)	34 (16.7)	40 (19.8)
KM seizure free (%) (95% CI)	94.3 (91.0, 97.6)	94.1 (90.8, 97.5)	95.4 (92.3, 98.5)	95.3 (92.1, 98.5)
Stratum 2: Past 3-month seizure count >2				
Number of subjects	220	218	204	195
Number of subjects with a seizure, n (%)	29 (13.2)	22 (10.1)	23 (11.3)	16 (8.2)
Number of subjects censored, n (%) [a]	39 (17.7)	54 (24.8)	36 (17.6)	48 (24.6)
KM seizure free (%) (95% CI)	85.2 (80.2, 90.2)	88.0 (83.3, 92.8)	87.4 (82.6, 92.2)	90.2 (85.6, 94.8)
Stratified [b]				
KM seizure free (%) (95% CI)	89.8 (86.8, 92.8)	91.1 (88.2, 94.0)	91.5 (88.6, 94.3)	92.8 (90.0, 95.5)
LCM–CBZ-CR:				
KM seizure free (%) (95% CI)	-1.3 (-5.5, 2.8)		-1.3 (-5.3, 2.7)	
Relative ratio (%) [c]	-6.0		-5.7	
Noninferiority of LCM vs CBZ-CR	Yes		Yes	

CBZ-CR=carbamazepine (controlled release); CI=confidence interval; FAS=Full Analysis Set; KM=Kaplan-Meier; LCM=lacosamide; PPS=Per Protocol Set

[a] Subjects censored prior to Day 182.

[b] Estimated by Mantel Haenszel methods.

[c] Relative ratio=Lower limit of 2-sided 95% CI of the stratified difference between LCM and CBZ-CR in seizure-free rates divided by CBZ-CR seizure-free rate.

The lower limit of the CI was within the pre-specified non-inferiority margin of -12% in both the PPS (-5.3%) and FAS (-5.5%) analysis respectively. Additionally, the lower confidence limit for the difference between LCM and CBZ-CR relative to the KM estimate of CBZ-CR 6-month seizure freedom rate (PPS: -5.7% and FAS: -6.0%) was >-20%. Since both of the predefined non-inferiority criteria were achieved in the FAS and the PPS, LCM was considered non-inferior to CBZ-CR based on the proportion of subjects seizure free for 6 months at the last evaluated dose level.

The KM estimates of the proportion of subjects seizure free for 6 months were similar for the LCM and CBZ-CR treatment groups within each stratum; however, the proportion of subjects seizure free was higher in stratum 1 (past 3-month seizure count ≤2) for both treatment groups (94.3% and 94.1% for the LCM and CBZ-CR treatment groups, respectively) compared with stratum 2 (past 3-month seizure count >2) for both treatment groups (85.2% and 88.0% for the LCM and CBZ-CR treatment groups, respectively).

Table 9 summarises the results of analyses in which subjects who discontinued due to reasons unrelated to seizure were treated as failures (i.e. not seizure fee).

Table 9 - Subjects completed 6 months and seizure free at the last evaluated dose (FAS and PPS)

Last evaluated dose level	FAS		PPS	
Parameter	LCM	CBZ-CR	LCM	CBZ-CR
Overall, n	444	442	408	397
Seizure free for 6 months [a], n (%)	327 (73.6)	308 (69.7)	307 (75.2)	285 (71.8)
Dose level 1, n	314	324	288	291
Seizure free for 6 months [a], n (%)	249 (79.3)	235 (72.5)	235 (81.6)	219 (75.3)
Dose level 2, n	87	85	80	74
Seizure free for 6 months [a], n (%)	59 (67.8)	60 (70.6)	55 (68.8)	54 (73.0)
Dose level 3, n	43	33	40	32
Seizure free for 6 months [a], n (%)	19 (44.2)	13 (39.4)	17 (42.5)	12 (37.5)

CBZ-CR=carbamazepine (controlled release); FAS=Full Analysis Set; LCM=lacosamide; PPS=Per Protocol Set
Note: Percentages were based on the number of subjects in the FAS or PPS at the corresponding last evaluated dose level.
Note: Dose level 1=LCM 200mg/day or CBZ-CR 400mg/day; Dose level 2=LCM 400mg/day or CBZ-CR 800mg/day; Dose level 3=LCM 600mg/day or CBZ-CR 1200mg/day.
[a] Subjects who completed the 6-month seizure freedom evaluation period and were seizure free.

With regards to the last evaluated dose levels, in the FAS, the proportions of subjects who completed the 6 months and were seizure free at the last evaluated dose level were comparable between the two groups at dose level 1, 2 and 3 respectively: 79.3% (249/314), 67.8% (59/87) and 44.2% (19/43) for the LCM group and 72.5% (235/324), 70.6% (60/85) and 39.4% (13/33) for the CBZ-CR group. Comparable results between the two groups at each of the three levels were also achieved in the PPS analyses. In general, the numbers regarding subjects who achieved 6 months seizure freedom at dose level 3 are small and only descriptive.

Time to first seizure during 12 months at the last evaluated dose was a secondary endpoint (see results and Figure 2 below). Analogous analyses for the time period of 6 months were also conducted. For the FAS, the KM curves for LCM and CBZ-CR were very similar within each stratum. The KM curves were consistently higher in stratum 1 as compared with stratum 2, corresponding to a higher probability of remaining seizure free for subjects in stratum 1. For the subjects who reported seizures, the median duration (days) from Day 0 (Last Evaluation Period) to the date of first seizure was 76.0 days (n=11) for the LCM treatment group and 30.0 days (n=11) for the CBZ-CR treatment group in stratum 1 and 12.0 days (n=29) and 14.5 days (n=22) for the LCM and CBZ-CR treatment groups, respectively, in stratum 2.

Sensitivity analyses of the primary efficacy variable

Several sensitivity analyses of the primary efficacy variable were conducted to assess the impact of premature discontinuations, missing data, and noncompliance on the primary efficacy evaluation. The sensitivity analyses were based on the following:

- Sensitivity analysis 1: Subjects in the PPSS.
- Sensitivity analysis 2: Subjects who discontinued during the 6-month seizure freedom evaluation period due to reasons other than AE were treated as not seizure free.
- Sensitivity analysis 3: Subjects who discontinued due to any reason were treated as not seizure free.
- Sensitivity analysis 4: Subjects with missing seizure diary data were treated as not seizure free (i.e, an intermediate day with seizure data missing was treated as a day with seizure).
- Sensitivity analysis 5: Subjects censored at the date of un-blinding if no seizure occurred before then.
- Sensitivity analysis 6: Excluding from the FAS subjects from Site 876 due to significant study conduct deficiencies.
- Sensitivity analysis 7: Excluding from the PPS subjects who had measurable concentrations of both LCM and CBZ-CR in multiple or all plasma samples taken during the study.

In summary, all sensitivity analyses supported the primary non-inferiority conclusion.

In the PPSS (sensitivity analysis 1) the overall proportion of patients who were seizure free for 6 months was 90.8% and 92.2% for the LCM and CBZ-CR treatment group, respectively. The KM estimate (95% CI) was -1.2 (-5.5, 3.0) and the relative ratio was -6.0%. When considering the last evaluated dose levels, in this analysis set the proportions of subjects who completed the 6 months and were seizure free at the three last evaluated dose levels were 97.1% (235/242), 88.7% (55/62) and 50.0% (17/34) for the LCM group and 98.6% (219/22), 88.5% (54/61) and 46.2% (12/26) for the CBZ-CR group. No significant change emerged in respect with the results observed in the FAS and PPS.

For sensitivity analysis 2 and 3, and considering the similar patterns seen in both arms of discontinued subjects with regard to number and reason, it is not surprising that the estimates of treatment differences and corresponding CIs were similar to the primary outcome.

In sensitivity analysis 4, when comparing the number of events with those in the primary analysis the difference was +1 event in the LCM group and +2 events in the CBZ-CR group. This implies that diary compliance was very high. It is further assumed that subjects who stopped reporting seizure data eventually discontinued and were therefore most likely accounted for in e.g. sensitivity analysis 3.

With regards to sensitivity analysis 5, treatment assignment was unblinded for 15 subjects during the course of the study; 6 subjects in the LCM treatment group and 9 subjects in the CBZ-CR treatment group. Comparing sensitivity analysis 5 with the primary analysis the difference was seemingly only data from one subject (in the CBZ-CR-arm).

The small differences seen between analyses 6 and 7 and the primary analysis, respectively, are explained by the limited number of excluded subjects. In analysis 6, 1 and 3 subjects and, in analysis 7, 4 and 1 subject were excluded in the LCM and CBZ-CR arm respectively.

Other efficacy variables

- *12-months (52 consecutive weeks) seizure freedom*

The Kaplan-Meier proportion of subjects being seizure free for 12 months at the last evaluated dose is presented for the FAS in

Table 10.

The stratified KM estimate of the proportion of subjects seizure free for 12 months was 77.8% (95% CI: 73.4%, 82.2%) and 82.7% (95% CI: 78.5%, 86.8%) in the LCM and the CBZ-CR treatment group, respectively. The difference in stratified seizure-freedom rate (and 2-sided 95% CI) between the LCM and CBZ-CR treatment groups at Day 364 was -4.9% (95% CI: -10.9%, 1.1%).

Table 10 - Kaplan-Meier proportion of subjects seizure free for 12 months at the last evaluated dose (FAS)

Parameter	LCM N=444	CBZ-CR N=442
Stratum 1: Past 3-month seizure count ≤2		
Number of subjects	224	224
Number of subjects with a seizure, n (%)	37 (16.5)	23 (10.3)
Number of subjects censored, n (%) [a]	135 (60.3)	141 (62.9)
KM seizure free (%) (95% CI)	79.8 (74.0, 85.6)	86.3 (80.8, 91.8)
Stratum 2: Past 3-month seizure count >2		
Number of subjects	220	218
Number of subjects with a seizure, n (%)	44 (20.0)	36 (16.5)
Number of subjects censored, n (%) [a]	122 (55.5)	139 (63.8)
KM seizure free (%) (95% CI)	75.7 (69.2, 82.3)	78.9 (72.8, 85.1)
Stratified [b]		
KM Seizure Free (%) (95% CI)	77.8 (73.4, 82.2)	82.7 (78.5, 86.8)
LCM–CBZ-CR:		
KM seizure free (%) (95% CI)	-4.9 (-10.9, 1.1)	
Relative ratio (%)	-13.2	

CBZ-CR=carbamazepine (controlled release); CI=confidence interval; FAS=Full Analysis Set; KM=Kaplan-Meier; LCM=lacosamide
[a] Subjects censored prior to Day 364.
[b] Estimated by Mantel Haenszel methods.

In the FAS, the overall proportion of subjects who completed 12 months and remained seizure free at the last evaluated dose level was similar between the LCM (59.5%, n=264/444) and CBZ-CR (59.3%, n= 262/442) treatment groups. At the last evaluated dose level 1, 2, and 3, the subjects in the LCM treatment group who completed 12 months and were seizure free were 47.1% (209/444), 9.0% (40/444), and 3.4% (15/444), respectively, whereas in the CBZ treatment group the proportions were 47.1% (208/442), 10.9% (48/442), and 1.4% (6/442), respectively.

In subjects treated with LCM, 209 out of 314 subjects (66.6%) completed 12 months and were seizure free at the first dose level, 40 out of 87 subjects (46.0%) at dose level 2, and 15 out of 43 subjects (34.9%) at dose level 3. In subjects treated with CBZ-CR, 208 out of 324 subjects (64.2%) completed 12 months and were seizure free at dose level 1, 48 out of 85 subjects (56.5%) at dose level 2, and 6 out of 33 subjects (18.2%) at dose level 3. Although the numbers were small, at dose level 3 a lower proportion of subjects in the CBZ-CR group as compared to the LCM group remained seizure free at the combined Last Evaluation and Maintenance Period (18.2% vs. 34.9%).

- *Time to first seizure during the 12-month seizure freedom at the Last Evaluated Dose*

The Kaplan-Meier plot of time to first seizure during the 12-month seizure freedom evaluation period are provided for the FAS and presented by stratum the following figure.

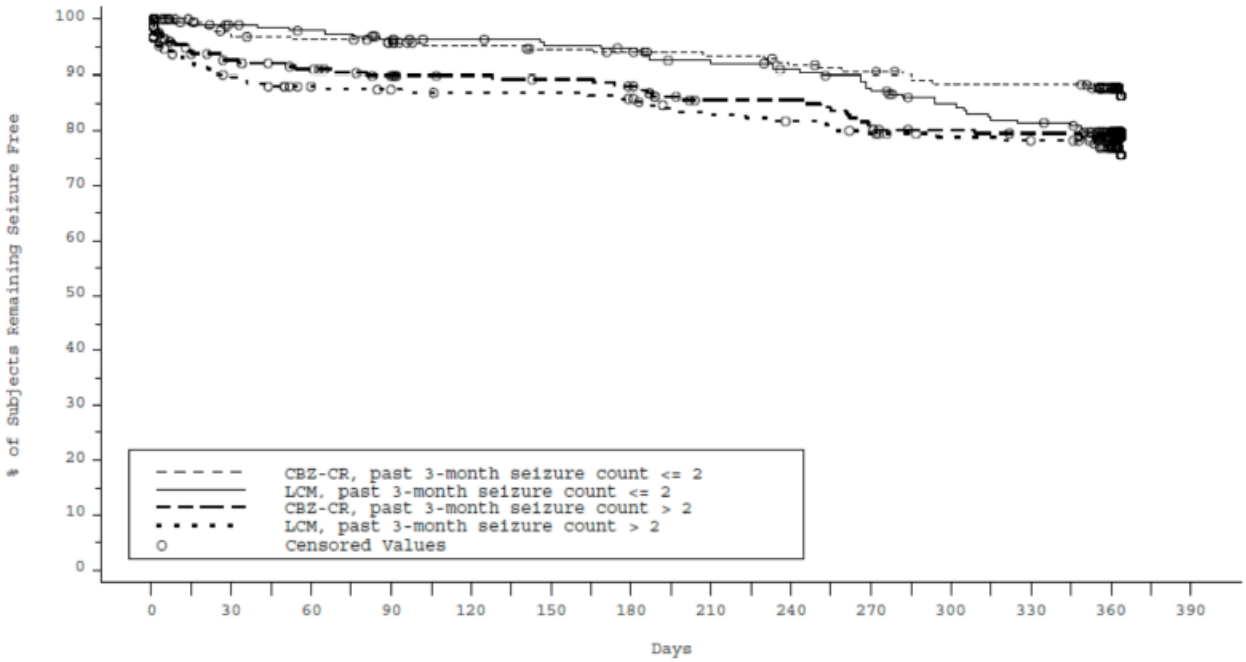


Figure 2 - Kaplan-Meier plot of time to first seizure during the 12 months at the last evaluated dose by stratum (FAS)

CBZ-CR=carbamazepine (controlled release); FAS=Full Analysis Set; LCM=lacosamide
Note: For descriptive purposes, past 3-month seizure count ≤2 is referred to as Stratum 1 in text and past 3-month seizure count >2 is referred to as Stratum 2 in text for both treatment groups.

The results for the KM estimates are presented in Table 11.

Table 11 - Time to First Seizure during the 12 Months at the Last Evaluated Dose

Parameter	FAS	
	LCM N=444	CBZ-CR N=442
Overall		
Time to 1st seizure (days) [a]		
n (%)	81	59
mean (SD)	161.0 (124.6)	141.4 (118.1)
median (min, max)	184.0 (1, 364)	141.0 (1, 364)
KM Estimate for Time to First Seizure (days)		
25th Percentile (95% CI)	NE	NE
Median (95% CI)	NE	NE
Stratum 1: Past 3-month seizure count ≤2		
Time to 1st seizure (days) [a]		
n (%)	37	23
mean (SD)	219.2 (100.0)	172.6 (118.5)
median (min, max)	252.0 (8, 350)	207.0 (16, 364)
KM Estimate for Time to First Seizure (days)		
25th Percentile (95% CI)	NE	NE
Median (95% CI)	NE	NE
Stratum 2: Past 3-month seizure count >2		
Time to 1st seizure (days) [a]		
n (%)	44	36
mean (SD)	112.0 (123.2)	121.5 (115.1)
median (min, max)	35.5 (1,364)	75.0 (1,349)
KM Estimate for Time to First Seizure (days)		
25th Percentile (95% CI)	NE	NE
Median (95% CI)	NE	NE

[a] Only for subject who experienced a seizure during the 12-month seizure freedom evaluation period.

The KM curves for time to first seizure during the 12-month seizure freedom evaluation period are generally similar for LCM and CBZ-CR in both strata. Of note, a greater decrease was observed in the KM curve for the LCM treatment group as compared with the CBZ-CR treatment group in stratum 1 at around Day 260 as more subjects experienced seizures in the LCM treatment group on Day 260 or later.

The KM methods could not be applied to estimate the median and 25th percentile for the time to first seizure because for both treatment groups in both strata more than 75% of subjects remained seizure-free by Day 364. The median duration in days from start day of the Last Evaluation Period to the date of first seizure was consistently different between the two strata: 252 days (n=37) for the LCM treatment group vs. 207 days (n=23) for the CBZ-CR group in stratum 1 and 35.5 days (n=44) for the LCM group vs. 75.0 days (n=36) for the CBZ-CR group in stratum 2.

With regards to the Cox proportional hazard model to explore baseline variables, the base model included treatment as a covariate and time to first seizure during the 12 months at the last evaluated dose. The hazard ratio for LCM to CBZ-CR (95% CI) was 1.32 (0.95, 1.85) (p=0.102). None of the additional covariates, geographic region [Europe vs rest of the world], the focal epileptiform abnormality [Yes vs No], and neurological disorder [Yes vs No], met the criteria for inclusion in the final model and, therefore, were not considered predictive of time to first seizure. The final model was the same as the base model.

- *Time to first seizure or discontinuation due to AE or lack of efficacy during 12 months at the last evaluated dose (FAS)*

The stratified KM estimate of the proportion of subjects who were seizure free and did not discontinue due to AE or lack of efficacy at Day 364 (12 months) was comparable between the LCM and CBZ-CR treatment groups [73.6% (95% CI: 69.1%, 78.1%) and 74.8% (95% CI: 70.4%, 79.3%), respectively].

The difference in stratified KM survival rate (and 2-sided 95% CI) between the LCM and CBZ-CR groups at Day 364 at the last evaluated dose was -1.3% (-7.6%, 5.1%) with a relative ratio of -10.2% to the survival rate in the CBZ-CR treatment group.

The KM curve (not displayed) showed that the overall difference in stratified survival rate (and 2-sided 95% CI) was comparable among the two treatment groups at Day 364, without considering the last evaluated dose level. At last evaluated dose levels 2 and 3 the proportion of subjects who were seizure free and did not discontinue due to AE or lack of efficacy at Day 364 was higher for CBZ-CR at level 2 compared to the LCM group and out of 33 and 43 subjects treated with CBZ-CR and LCM, respectively, at level 3, none presented seizures at day 364. Notably, the number of subjects at these dose levels were limited. Presentation by stratum resulted in a trend similar to what has been illustrated above at around day 260.

- *Time to first seizure during 12 months of treatment from the first dose of study medication*

The Kaplan-Meier curves (not displayed) for time to first seizure during the 12-month following first dose of study medication were remarkably higher in stratum 1 than in stratum 2, because a greater proportion of subjects in stratum 1 remained seizure free. For subjects who had an event, the median duration of time to the first seizure during the 12 months following the first dose of study medication in stratum 1 was 61.0 days (n=70) for the LCM treatment group and 57.5 days (n=54) for the CBZ-CR treatment group. The median duration of time to the first seizure in stratum 2 was 6.0 days (n=138) and 7.0 days (n=130) for the LCM and CBZ-CR treatment groups, respectively.

The stratified KM estimate of the proportion of subjects seizure free at Day 364 (12 months) for the LCM treatment group and the CBZ-CR treatment group was 50.8% (95% CI: 46.2%, 55.4%) and 54.9% (95% CI: 50.3%, 59.6%), respectively. The difference in stratified KM survival rate (and 2-sided 95% CI) between the LCM and CBZ-CR groups at Day 364 at the last evaluated dose was -4.1% (-10.7%, 2.4%) with a relative ratio of -19.4% to the seizure freedom rate in the CBZ-CR treatment group.

Exploratory variables

- *Clinical Global Impression of Change (CGIC)*

The proportions of subjects within each response category for the CGIC, based on the clinician-rated assessment results for the CBZ-CR group and the LCM group were: improved status at Evaluation Visit 2 (84.3% and 83.2%, respectively) and at Maintenance Visit 2 (86.7% and 84.4%, respectively). At the last visit, which accounted for the last assessment during the Treatment Period, 29.8% (n=124) of CBZ-CR treated subjects vs. 25.3% (n=107) of LCM treated subjects responded to feel "very much improved". The overall proportion of subjects who were judged to be worsened in this phase of the study was 8.9% (n=37) and 10.4% (n=44) in the CBZ-CR and LCM groups, respectively.

- *Patient's Global Impression of Change (PGIC)*

The proportions of subjects within each response category for the PGIC, based on the patient-rated assessment in CBZ-CR treatment groups and the LCM groups were: an improved status at Evaluation Visit 2 was in fact reported by 82.6% (n=252) and 81.2% (n=263), respectively; at Maintenance Visit 2 85.8% (n=224) and 82.1% (n=215), respectively. At the last visit, an improved status was reported by 72.0% (n=296) and 68.2% (n=288) in the CBZ-CR and LCM groups, respectively.

- *Health care resource use*

During the Treatment Period, the proportion of subjects in the LCM and CBZ-CR treatment groups without health care provider consultations not foreseen by the protocol was 67.6% and 61.1%, respectively. Among the consultations taken place, the most frequently reported types of provider consultations in the LCM and CBZ-CR groups were general practitioner (44.3% and 37.3%, respectively) and specialist physician (43.0% and 49.6%). No emergency room visits were necessary for 91.9% and 92.1% of subjects in the LCM and CBZ-CR treatment groups, no hospitalizations (86.5% and 86.0%, respectively), and no concomitant medical procedures (73.9% and 72.9%, respectively). The median duration of hospitalization for the LCM and CBZ-CR treatment groups was 2.0 days and 4.0 days, respectively.

Ancillary analyses

The MAH performed subgroup analyses of the primary efficacy variable. The primary efficacy variable was evaluated in the following subgroups for the FAS and the PPS:

- diagnosed partial-onset or unclassified epilepsy,
- diagnosed partial-onset epilepsy,
- history of Type IC seizure(s),
- history of Type IC or Type IIE seizure(s),
- history of Type IIE seizure(s) only, and
- elderly (subjects ≥65 years old at study entry).

Results of subgroup analyses of the KM stratified proportion of subjects' seizure free for 6 months are presented in Table 12.

Table 12 - Subgroup analyses of the KM stratified proportion of subjects seizure free for 6 months (FAS and PPS)

Subgroup Analysis set	LCM N KM seizure free (%) (95% CI)	CBZ-CR N KM seizure free (%) (95% CI)	LCM–CBZ-CR Stratified [a] KM seizure free (%) (95% CI)	Relative ratio (%) [b]	Noninferiority
Diagnosed partial-onset or unclassified epilepsy					
FAS	443 89.8 (86.8, 92.8)	441 91.1 (88.2, 94.0)	-1.3 (-5.5, 2.8)	-6.0	Yes
PPS	407 91.5 (88.6, 94.3)	396 92.8 (90.0, 95.5)	-1.3 (-5.3, 2.7)	-5.7	Yes
Diagnosed partial-onset epilepsy					
FAS	405 89.5 (86.3, 92.6)	405 91.2 (88.2, 94.2)	-1.8 (-6.1, 2.6)	-6.7	Yes
PPS	374 91.0 (88.0, 94.1)	364 92.5 (89.5, 95.4)	-1.4 (-5.7, 2.8)	-6.1	Yes
History of Type IC seizure(s)					
FAS	254 89.9 (86.0, 93.9)	261 93.3 (90.0, 96.5)	-3.3 (-8.4, 1.8)	-9.0	Not assessed
PPS	235 92.0 (88.4, 95.7)	236 93.5 (90.1, 96.9)	-1.5 (-6.5, 3.5)	-6.9	Not assessed
History of Type IC or Type IIE seizure(s)					
FAS	298 90.6 (87.1, 94.1)	302 93.0 (89.9, 96.1)	-2.4 (-7.1, 2.3)	-7.6	Not assessed
PPS	274 92.7 (89.5, 96.0)	272 93.9 (90.9, 97.0)	-1.2 (-5.6, 3.3)	-6.0	Not assessed
History of Type IIE seizure(s) only					
FAS	40 95.0 (86.5, 100.0)	39 90.9 (81.0, 100.0)	4.1 (-9.0, 17.1)	-9.9	Not assessed
PPS	36 95.4 (87.7, 100.0)	35 96.7 (90.4, 100.0)	-1.3 (-11.2, 8.7)	-11.6	Not assessed
Elderly (≥65 years old)					
FAS	62 93.6 (87.8, 99.5)	57 92.3 (83.9, 100.0)	1.4 (-8.9, 11.6)	-9.6	Not assessed
PPS	57 96.3 (91.5, 100.0)	48 96.4 (89.7, 100.0)	-0.1 (-8.4, 8.2)	-8.7	Not assessed

CBZ-CR=carbamazepine (controlled release); CI=confidence interval; FAS=Full Analysis Set; KM=Kaplan-Meier; LCM=lacosamide; PPS=Per Protocol Set

[a] Note: Stratified proportion estimated by Mantel Haenszel methods.

[b] Relative Ratio=Lower limit of 2-sided 95% CI of the stratified difference between LCM and CBZ-CR in seizure-free rates divided by CBZ-CR seizure-free rate.

The results for the subgroup analyses were generally in line with the primary efficacy analysis, showing consistently similar outcomes for the LCM and the CBZ-CR treatment groups. Non-inferiority was not formally assessed due to limited sample size.

For the subgroup of elderly subjects the stratified KM estimate of subjects who were seizure free for 6 months was similar between the two groups (93.6% [95% CI: 87.8%, 99.5%] and 92.3% [95% CI: 83.9%, 100.0%], respectively), without major differences in respect with the PPS. The following table shows the proportions of the distribution of elderly subjects who completed the 6 months evaluation phase and were seizure free at the last evaluated dose, in the FAS and PPS:

Table 13 - Elderly Subjects (≥65 years) Completed 6 Months and Seizure Free at the Last Evaluated Dose

Last evaluated dose level Parameter	FAS		PPS	
	LCM N=444 n(%)	CBZ-CR N=442 n(%)	LCM N=408 n(%)	CBZ-CR N=397 n(%)
Overall, n	62	57	57	48
Seizure free for 6 months[a], n (%)	45 (72.6)	34 (59.6)	43 (75.4)	31 (64.6)
Dose level 1, n	55	42	51	33
Seizure free for 6 months[a], n (%)	43 (78.2)	24 (57.1)	41 (80.4)	21 (63.6)
Dose level 2, n	6	11	6	11
Seizure free for 6 months[a], n (%)	2 (33.3)	9 (81.8)	2 (33.3)	9 (81.8)
Dose level 3, n	1	4	0	4
Seizure free for 6 months[a], n (%)	0	1 (25.0)	0	1 (25.0)

[a]Subjects who completed the 6-month seizure freedom evaluation period and were seizure free. Percentages are based on the number of subjects in the FAS at the corresponding last evaluated dose level

The overall proportion of elderly subjects who completed the 6-month evaluation period and were seizure free at the last evaluated dose level was higher in the LCM treatment group compared to the CBZ-CR group (72.6% and 59.6%, respectively). A higher percentage of subjects in the CBZ-CR treatment group (35.1%, n=20) discontinued prior to the end of 6 month evaluation period due to reasons unrelated to seizures compared to the LCM treatment group (21.0%, n=13). Similar proportions were found for the PPS population with 33.3% (n=16) and 21.1% (n=12) discontinuations due to reasons unrelated to seizures in the CBZ-CR and LCM groups, respectively.

With regards to the distribution of the subjects among the three dose levels, at dose level 1 forty-three (43) subjects in the LCM group (78.2%) and 24 subjects in the CBZ-CR group (57.1%) were seizure free for six months, indicating that most of elderly LCM treated subjects responded at this dose.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 - Summary of Efficacy for Trial SP0993

Title: A Multicentre, Double-blind, Double-dummy, Randomized, Positive-controlled Study Comparing the Efficacy and Safety of Lacosamide (200 to 600 mg/day) to Controlled Release Carbamazepine (400 to 1200mg/day), Used as Monotherapy in Subjects (≥16 years) Newly or Recently Diagnosed with Epilepsy and Experiencing Partial-onset or Generalized Tonic-clonic Seizures		
Study identifier	SP0993	
Design	Multicentre, double-blind, double-dummy, randomized, positive-controlled study	
	Duration of main phase:	26 weeks evaluation phase 26 weeks maintenance phase
	Duration of run-in phase:	Screening Phase: 1 week Up-titration and Stabilization Phase: 3 weeks
	Duration of extension phase:	3 years (follow-up study SP0994)

Hypothesis	Non-inferiority		
Treatment groups	LCM		Lacosamide 200 mg/day or 400 mg/day or 600 mg/day, maximum duration of treatment: 118 weeks, 445 patients randomised
	CBZ-CR		Carbamazepine (controlled release) 400mg/day or 800 mg/day or 1200mg/day, maximum duration of treatment: 118 weeks, 443 patients randomised
Endpoints and definitions	Primary endpoint	% seizure free 6 months	Proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject, adjusted by past 3-month seizure count (≤2 and >2) (PPS, FAS)
	Other endpoint	% seizure free 12 months	Proportion of subjects remaining seizure free for 12 consecutive months (52 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject, adjusted by past 3-month seizure count (≤2 and >2) (FAS)
	Other endpoint	% seizure free and completed 12 months	Subjects completed 12 months and were seizure free at the last evaluated dose (FAS)
	Other endpoint	Time to 1st seizure or discontinuation 12 months	Time to first seizure or discontinuation due to AE or lack of efficacy during 12 months of treatment following stabilization at the last evaluated dose (FAS)
	Other endpoint	Time to 1st seizure 12 months	Time to first seizure during 12 months of treatment from the first dose of study medication (FAS)
Database lock	Last subject completed: 7 August 2015		

Results and analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Full analysis set (FAS): all randomized subjects who took at least 1 dose of study medication [a)] Per protocol set (PPS): all subjects in the FAS who did not have any important protocol deviations determined to impact the interpretation of primary efficacy. Time point: 26 (primary analysis) or 52 weeks		
Descriptive statistics and estimate variability	**Treatment group**	**LCM**	**CBZ-CR**
	Number of subjects	**PPS: 408** **FAS: 444**	**PPS: 397** **FAS: 442**
	% seizure free 6 months (stratified KM estimate, %)	PPS: 91.5 FAS: 89.8	PPS: 92.8 FAS: 91.1
	95% CI	PPS: 88.6, 94.3 FAS: 86.8, 92.8	PPS: 90.0, 95.5 FAS: 88.2, 94.0

	% seizure free 12 months (stratified KM estimate, %)	77.8	82.7
	95% CI	73.4, 82.2	78.5, 86.8
	% seizure free and completed 12 months	59.5	59.3
	Time to 1st seizure or discontinuation 12 months (median, mean, days)	N=100 [c)] median: 171.5 mean: 150.3	N=93 [c)] median: 69.0 mean: 115.2
	Standard Deviation (SD)	121.9	110.9
	Time to 1st seizure 12 months (median, mean, days)	N=208 [c)] median: 14.0 mean: 55.8	N=184 [c)] median: 12.0 mean: 56.5
	SD	86.6	79.4
Effect estimate per comparison	Primary endpoint: % seizure free 6 months [b)]	Comparison groups	LCM vs. CBZ-CR
		Absolute difference in KM estimate	PPS/FAS: -1.3%
		95% CI	PPS: -5.3, 2.7 FAS: -5.5%, 2.8%
		Relative ratio (%)	*PPS: -5.7%* *FAS: -6.0%*
	Other endpoint: % seizure free 12 months	Comparison groups	LCM vs. CBZ-CR
		Absolute difference in KM estimate	-4.9%
		95% CI	-10.9, 1.1%
		Relative ratio (%)	*-13.2%*
	Other endpoint: % seizure free and completed 12 months	n/a	n/a
	Other endpoints: Time to 1st seizure or discontinuation 12 months	n/a	n/a
	Other endpoint: Time to 1st seizure 12 months	n/a	n/a
Notes	[a)] The primary efficacy endpoint was assessed based on the PPS and the FAS. [b)] Statistical evaluation of non-inferiority was only carried out for the primary endpoint. Non-inferiority was assumed when the lower limit of the CI was within the pre-specified non-inferiority confidence limit of -12%. [c)] Number of subjects who had an event.		
Analysis description	**Subgroup analyses on primary endpoint (FAS, 26 weeks):** **- Patients diagnosed with POS** **- Elderly patients (subjects ≥65 years old at study entry)**		
Descriptive statistics and estimate variability	**Treatment group**	**LCM**	**CBZ-CR**
	Number of POS subjects	**405**	**405**
	stratified KM estimate (%)	89.5	91.2
	95% CI	86.3, 92.6	88.2, 94.2
	Number of elderly subjects	**62**	**57**
	stratified KM estimate (%)	93.6	92.3

	95% CI	87.8, 99.5	83.9, 100.0
Effect estimate per comparison	Subgroup: POS patients	Comparison groups	LCM vs. CBZ-CR
		Absolute difference in KM estimate	-1.8%
		95% CI	-6.1, 2.6
		Relative ratio (%)	*-6.7%*
	Subgroup: Elderly [c)]	Comparison groups	LCM vs. CBZ-CR
		Absolute difference in KM estimate	1.4%
		95% CI	-8.9, 11.6
		Relative ratio (%)	*-9.6%*
Notes	[c)] A higher proportion of elderly in the LCM treatment group (72.6%) compared with the CBZ-CR treatment group (59.6%) completed the 6-month seizure freedom evaluation period and were seizure free at the last evaluated dose level.		

Clinical studies in special populations

See ancillary analyses.

Supportive study(ies)

Study SP0994

Study SP0994 was a double-blind, double-dummy extension study for subjects who completed SP0993 or for subjects who experienced a seizure at the first or second target dose in the maintenance phase of SP0993. Following the database lock and un-blinding of SP0993, SP0994 was un-blinded. To support the regulatory submission of LCM monotherapy, the MAH performed an interim analysis of this study. The data for the interim analysis is based on a clinical cut-off of 22 May 2015. Only selected subject information (disposition and demographics) and safety information (based on AE reporting and ECG data) was summarised. No efficacy results are presented. The safety results for SP0994 are summarised in the safety sections of this report.

Study SP902

Albeit already reviewed in a previous procedure (EMEA/H/C/000863/II/0045), the MAH also provided the two studies SP902 and its open-label extension SP904 as supportive studies.

SP902 was a Phase 3, historical-controlled, multicenter, double-blind, randomised, conversion to monotherapy study designed to assess the efficacy and safety of LCM 400mg/day (200mg twice daily) monotherapy in subjects 16 to 70 years of age with partial-onset seizures, including secondary generalised seizures. A LCM 300mg/day (150mg twice daily) arm was added to blind the treatment group and to ensure a study design consistent with the historical-control studies on which SP902 was based. The maximum duration of study participation was to be 30 weeks with a maximum duration of blinded study medication administration of up to 20 weeks. Following a 56-day (8-week) Baseline Phase, during which subjects had to be taking stable doses of 1 or 2 other AEDs, subjects were randomized and began a 3-week Titration Phase with 100 mg/week steps up to the final maintenance dose of either 300 mg/day or 400 mg/day. Once the subject reached the end of a 3-week Titration Phase, the subject began the Maintenance Phase of the study, which was composed of a 6-week period for withdrawal of background AEDs, followed by a 10-week Monotherapy Period at the targeted LCM dose. One dose reduction was

allowed during the 16-week Maintenance Phase if the subject was unable to tolerate the randomised target dose (ie, from LCM 400mg/day to LCM 300mg/day or from LCM 300mg/day to LCM 200mg/day). A subject must have taken at least 1 dose of Maintenance Phase study medication in order to qualify for the dose reduction.

The historic control used for study SP902 was based on a meta-analysis by French et al, 2010, of eight similarly designed studies that included drugs that demonstrated efficacy in conversion to monotherapy, whereby the active investigational AED had been compared to a pseudo-placebo control group. From the studies included in this met-analysis, a historical-control exit rate of 0.653 was deducted.

The primary efficacy endpoint in SP902 was the cumulative exit rate by Day 112 relative to the start of the withdrawal of background AEDs (ie, at the end of the maintenance phase) for subjects meeting at least 1 of the following exit criteria:

- A 2-fold or greater increase in average monthly (28-day) partial-onset seizure frequency (motor and non-motor) compared to average monthly partial-onset seizure frequency (motor and non-motor) during the Baseline Phase.
- A 2-fold or greater increase in consecutive 2-day partial-onset seizure frequency (motor and non-motor) versus the highest consecutive 2-day partial-onset seizure frequency (motor and non-motor) that occurred during the Baseline Phase. If the highest consecutive 2-day partial-onset seizure frequency during the Baseline Phase was 1, a 2-day partial-onset seizure frequency of ≥ 3 was required to meet this exit criterion.
- Occurrence of a single generalised tonic-clonic seizure if none had occurred in the 6 months prior to randomization.
- A prolongation or worsening of overall seizure duration, frequency, type or pattern considered by the investigator as serious enough to warrant study discontinuation.
- Status epilepticus or new onset of serial/cluster seizures.

A total of 425 subjects were randomised at 120 sites in North America, Australia, and Europe with the majority of the sites being in the US. Subjects were randomized in a 3:1 ratio to the LCM 400mg/day and the LCM 300mg/day arms.

In the LCM 400 mg/day group, 28.9% of the subjects met at least 1 exit criterion. Based on the primary efficacy analysis, the KM estimate of the percentage of subjects meeting at least 1 exit criterion by Day 112 for the LCM 400mg/day group was 0.300 (95% CI: 0.246, 0.355). The upper limit of the 2-sided 95% CI for this estimate was 0.355, indicating that the predicted exit rate was statistically significantly lower than the historical control exit rate (0.653) and thus, superiority of LCM 400mg/day over the historical control was demonstrated.

Amongst those patients who completed titration and started withdrawing other AEDs (284 and 99 in the LCM 400mg/day and the LCM 300mg/day arms, respectively), monotherapy was maintained in 71.5 % and 70.7 % of patients at a dose of LCM 400mg/day and 300mg/day, respectively for 57-105 days (median 71 days), over the targeted observation period of 70 days.

Study SP904

SP904 was a multicentre, open-label extension study to assess the long-term use of LCM monotherapy and safety of LCM monotherapy and adjunctive therapy in subjects with POS (with and without secondary generalization) who were previously enrolled in the conversion to monotherapy study SP902. Long-term safety was evaluated across a range of LCM doses. For subjects receiving LCM monotherapy at the time of study entry, the addition of up to 2 concomitant AEDs was allowed to optimize tolerability and seizure reduction. Concomitant AEDs should be added only when the subject had not responded optimally or

adequately to a maximum tolerated dose of LCM monotherapy.

At the termination of the previous study, SP902, subjects received a dose of LCM 300 mg/day or LCM 400 mg/day. During SP904, investigators were allowed to increase or decrease the dose of LCM to optimize tolerability and seizure reduction for each subject. The dose could be increased no faster than LCM 100 mg/day per week up to LCM 800 mg/day.

An objective of SP904 was to obtain information about the percentage of subjects from SP902 who remained on LCM monotherapy and the duration of LCM monotherapy treatment.

The total subject-years of exposure to LCM were 525.5 years (322 subjects). The majority of subjects (296 subjects [91.9%]) had at least 6 months of exposure to LCM, 258 subjects (80.1%) had at least 12 months of exposure to LCM, 240 subjects (74.5%) had at least 18 months of exposure to LCM, and 216 subjects (67.1%) had at least 24 months of exposure to LCM. For all subjects, the mean treatment duration was 596.1 days (SD: 227.0). The mean maximum daily dose was 551.2mg/day, the mean modal dose was 496.7mg/day, and the median modal dose was 500mg/day.

A summary of the longest period of LCM monotherapy treatment during the Treatment Phase by monotherapy status at SP904 entry is presented in Table 15.

Table 15 – LCM monotherapy (longest period) during the Treatment Phase by monotherapy status at SP904 entry (SS)

LCM monotherapy	Monotherapy at SP904 entry N=282 n/N (%)	Non-monotherapy at SP904 entry N=40 n/N (%)
>0 months	282/282 (100)	10/40 (25.0)
≥3 months	254/271 (93.7)	6/36 (16.7)
≥6 months	228/262 (87.0)	5/34 (14.7)
≥12 months	177/230 (77.0)	2/28 (7.1)
≥18 months	152/214 (71.0)	2/26 (7.7)
≥24 months	126/196 (64.3)	0

LCM=lacosamide; SS=Safety Set
Note: Monotherapy status was determined for subjects who were exposed to LCM and whose concomitant medications were known. LCM monotherapy was based on the longest period of continuous monotherapy usage.
Note: Percentages were based on the number of subjects, N, exposed for the given time period.
Note: Monotherapy at SP904 entry were those subjects who were taking LCM only for at least 2 consecutive days starting with their first dose of SP904 study medication.

2.5.3. Discussion on clinical efficacy

To support this application for an extension of the indication of Vimpat to monotherapy of POS with or without secondary generalisation in adult and adolescent (16 to 18 years), the MAH performed one pivotal phase 3 study SP0993. In addition, interim results are provided for the long-term extension study SP0994 and the MAH re-submitted the results from the conversion to monotherapy study SP902 and its long-term extension SP904.

Design and conduct of clinical studies

Study SP0993 was designed as a non-inferiority trial in line with the recommendation in the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98

Rev.2/Corr, hereafter referred to as epilepsy guideline). The objective was to compare the efficacy and safety of LCM at doses of 200 to 600 mg/day to CBZ-CR at dose of 400 to 1200 mg/day used as monotherapy for at least 1 year in newly or recently diagnosed subjects with epilepsy and experiencing POS or generalized tonic-clonic seizures. The inclusion/exclusion criteria selected for this study were generally considered by the CHMP adequate to select a patient population representative of the proposed extended target population. Duration of the trial (evaluation phase of 26 weeks and maintenance phase of 26 weeks) of 1 year was also considered adequate and in accordance with the guideline.

The choice of CBZ-CR as comparator in study SP0993 was considered acceptable. CBZ-CR is widely used as first choice treatment for POS and the controlled-release formulation of CBZ allows more stable plasma levels of the drug, avoiding peaks in plasma concentration and resulting in an overall better tolerability. CBZ-CR is currently considered the most commonly used reference treatment in study for monotherapy of POS (Perucca, 2008), and is regarded as the active comparator of choice.

Study SP0993 used a step-wise design that allowed the enrolled subjects to scale up to three different, increasing pre-defined target dose levels of either LCM (200, 400 and 600mg/day) or CBZ-CR (400, 800 and 1200 mg/day). With regard to the dosing schedule selected, the CHMP noted that the highest dose of CBZ-CR (1200 mg/day) reflected the most commonly used dose in clinical practice, but was far below the maximum permitted dose of 2400 mg/day, whereas the maximum dose of LCM (600 mg/day) was higher than the maximum permitted dose in the add-on setting (400 mg/day). The selection of the CBZ-CR dose range was justified by the MAH on the basis of previous data from a non-inferiority study comparing levetiracetam to CBZ-CR, in which the majority of subjects remained at the 400 mg/day dose although doses from 400 to 1200 mg/day were allowed. This was considered acceptable by the CHMP. Less compelling evidence was provided to support the selection of the LCM dose range, given that data from previous studies (SP667 and SP754) showed no clinically relevant incremental benefit in terms of the primary endpoint of the 600 mg/day dose compared to the 400 mg/day dose, and only a trend towards increased efficacy in terms of secondary endpoints, in a small number of patients, whereas a worsening of the tolerability profile (gastrointestinal and CNS-related AEs) was observed. It thus appears that the selection of the maximum LCM dose was based on limited evidence generated in a small number of patients and in trials with different design than SP0993. Nevertheless, the CHMP acknowledged that the benefit-risk balance of the 600 mg/day dose may be different when LCM is used in monotherapy and is cautiously up-titrated, which justified the dose selection in this study.

The primary efficacy endpoint was the proportion of subjects remaining seizure free for 6 consecutive months (26 consecutive weeks) of treatment following stabilization at the last evaluated dose for each subject. In line with the epilepsy guideline, this is considered the appropriate primary efficacy measure in the monotherapy setting. Secondary efficacy variables for the whole 12 months duration of the trial were also acceptable. Efficacy analyses were based on diary data. Diary compliance has not been explicitly discussed but can be assumed to have been high, which was confirmed in sensitivity analyses of the primary endpoint.

The choice of non-inferiority margin has previously been discussed within a scientific advice procedure in 2010. According to the MAH, specification of a non-inferiority margin based on statistical reasoning according to the CHMP Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99, 2005) was not possible because the effect of CBZ-CR over placebo has not been well established for a sufficiently similar patient population. However, CBZ-CR is currently considered the active comparator of choice and efficacy has been demonstrated through clinical practice and superiority over placebo is assumed clinically, although this has not been explicitly demonstrated statistically. Rather, the absolute margin of -12% was determined by the MAH under the expectation of a seizure-free rate of 60% for CBZ-CR and the understanding that a relative difference of more than 20% was clinically important (ILAE, Glauser et al., 2006). A second criterion, a non-inferiority margin of -0.20 for the relative difference, in case the seizure-free rate in the control arm was lower than expected, had therefore also been proposed.

The CHMP concluded that although the proposed margin could be acceptable, it appeared large and a tighter margin would have been preferable. The issue was not further discussed given the study results whereby the lower bound of the CI for the difference between treatment groups was well within the -12% margin (see also discussion of results below).

Overall, the statistical methods were acceptable including the decision to perform the primary analysis on both the FAS and the PPS. Moreover, the sensitivity analyses were considered useful including the PPSS which allowed to directly compare those subjects who completed the treatment evaluation period seizure free (not informative censoring) with those who presented an 'event' of seizure. Efficacy analyses were performed taking into account the restriction implied by the stratified randomisation, which was agreed.

Overall, 1035 subjects were screened and a total of 888 subjects were randomised. At the planning stage it was expected that the withdrawal rate would be higher with the reference treatment. However, the proportions of subjects who completed and discontinued the study, respectively, were almost identical in the two treatment arms. Some differences were observed within dose level 2 and 3, but the number of subjects reaching dose level 2 and 3 was limited since most subjects remained at dose level 1 and no firm conclusions could be drawn. Stratification by number of seizures during 3 months prior to baseline was reasonable (stratum 1: ≤2 seizures and stratum 2: >2 seizures) given the association with the risk of seizure recurrence and thus the influence on the primary efficacy outcome.

No concern arose from the conduct of the study.

The demographic data were balanced between the LCM and CBZ groups, and the various aetiologies of epilepsy were evenly distributed between the two treatments. Medical history and concomitant diseases were similar for the LCM and CBZ-CR treatment groups.

Efficacy data and additional analyses

The primary efficacy variable in SP0993 was the proportion of subjects remaining seizure free for 6 consecutive months of treatment following stabilisation at the last evaluated dose for each subject. In the PPS, the stratified KM estimate of the primary efficacy variable was 91.5% (95% CI: 88.6%, 94.3%) in the LCM treatment group and 92.8% (95% CI: 90.0%, 95.5%) in the CBZ-CR treatment group. In the FAS the corresponding estimates were 89.8% (95% CI: 86.8%, 92.8%) and 91.1% (95% CI: 88.2%, 94.0%) in the LCM and CBZ-CR treatment groups, respectively. In both cases (FAS and PPS), the rates in the two treatment groups were of similar magnitude, whereby the crude proportions of subjects with a seizure were overall slightly higher with LCM than with CBZ-CR. The difference in stratified seizure freedom rate (and 2-sided 95% CI) between the LCM and CBZ-CR groups was -1.3% (-5.3%, 2.7%) in the PPS analysis and -1.3% (-5.5%, 2.8%) in the FAS analysis. Given that the lower limit of the CI was well within than the pre-specified non-inferiority margin of -12%, non-inferiority between LCM and CBZ-CR was concluded. All sensitivity analyses supported the primary non-inferiority conclusion, supporting robustness of the findings.

While the primary analysis may have overestimated the success rates considering the censoring of patients who discontinued, estimates of the proportion of subjects being seizure-free for 6 months considering discontinuation as failures were 73.6% and 75.2% in the LCM group and 69.7% and 72.8% and CBZ-CR treatment group for the FAS and PPS, respectively. The observed proportion of subjects who completed the study and were seizure free at month 6 was thus still higher than initially expected (60% response rate for CBZ-CR) for the purpose of the statistical analysis. The rates remained of comparable magnitude in the two treatment groups.

The differences between the PPS and the FAS analyses, respectively, were small as could be expected considering that approximately 90% of the subjects included in the FAS were also included in the PPS.

A higher seizure count during the past 3 months indicates a more difficult to treat form of epilepsy. It was

therefore to be expected that subjects in stratum 1 (lower past 3-month seizure count of ≤2) have a higher probability of remaining seizure free. Indeed, more subjects in stratum 2 (seizure count of >2) than stratum 1 experienced a seizure during the study, the estimates within treatment groups being similar with the lowest seizure free rate among subjects in stratum 2 in the LCM arm. While no treatment comparisons have been performed within each stratum, the results were considered sufficiently consistent to support the primary outcome.

For the assessment of maintenance of efficacy, the 12 months seizure freedom rate was measured. The KM seizure free rate at month 12 (95% CI) was 77.8% (73.4, 82.2) in the LCM arm and 82.7% (78.5, 86.8) in the CBZ-CR arm. The difference between the two treatments was -4.9 (-10.9, 1.1). All analyses of 12 months data were based on the FAS only. Considering the primary objective being non-inferiority, analyses should also have been based on the PPS. However, considering the small difference observed at least in the primary analysis between the FAS and the PPS, the issue was not further pursued by the CHMP.

While the lower limit of the CI was within the non-inferiority margin, the crude proportions of subjects with seizures during the 12 months were higher, in both strata, with LCM compared to CBZ-CR. Overall, the KM estimates of proportion of subjects being seizure free were high although many subjects were censored and that to a greater extent in the control arm compared to the LCM arm. In comparing estimates of proportion of subjects who were seizure free for 12 months treating those who discontinued as failures, the outcome was very similar with 59.5% for LCM and 59.3% for CBZ-CR.

The results of patient- and clinician-rated scales assessing the impression of change were only descriptive and no test for statistical significance of the differences was carried out or weighted for the sample size. From the results it could be seen that the proportion of subjects who reported improvements after or at the end of treatment period were generally slightly higher for CBZ-CR compared to LCM, although the differences were small. No particular differences were evident among the two groups with regards to health care resource use.

The results of the subgroup analyses on the primary endpoint including patients with diagnosed POS and diagnosed POS or unclassified epilepsy, respectively, supported non-inferiority of LCM to CBZ-CR, whereby these subgroups overlapped to a large extent. While non-inferiority was not formally assessed for the subgroups by history of Type IC seizures, Type IC or Type IIE seizures, Type IIE seizures only and elderly subjects due to limited sample size, the results were generally consistent with the overall primary efficacy outcome.

With regards to the conversion to monotherapy study SP902, the CHMP had previously reviewed the study (EMEA/H/C/000863/II/0045) and identified weaknesses in the study design related to the choice of two treatment arms with effective LCM doses and use of an historic control which raised doubts with regards to selection bias and adequate blinding. Nevertheless, in line with the epilepsy guideline, the CHMP agreed that the availability of conversion to monotherapy data is informative for patient management and therefore considered an update of SmPC section 5.1 acceptable to include information on SP902 in a balanced manner.

Posology

The MAH proposed a maximum recommended dose for POS monotherapy of 600 mg/day, which was the same dose as used at dose level 3 in the pivotal clinical trial SP0993. The MAH justified the choice of dose levels for study SP0993 by referring to the main add-on trials. In these studies, although the effect size was found to be similar for the primary efficacy endpoints, there were numerical trends in some secondary endpoints suggesting a possible additional benefit of LCM 600 mg/day over LCM 400 mg/day. However, at the time of the initial marketing authorisation application, the CHMP did not accept 600 mg/day for add-on POS treatment given that no clinically relevant improvement in efficacy had been

observed and since the safety profile of this dose was worse than for LCM 400 mg/day (see also section 2.6.). The proposed maximum maintenance dose for POS monotherapy (600 mg/day) was thus higher than the maximum dose recommended for add-on use (400 mg/day).

Due to the limited number of subjects at dose level 3 in study SP0993, it was difficult to draw firm conclusions about the efficacy of LCM 600 mg/day in POS monotherapy. The MAH argued that in SP0993, the proportion of subjects escalating to the 600 mg/day dose level (9.7%), as well as the proportion of subjects achieving seizure freedom at this dose (4.3%) were similar to the results observed for CBZ-CR 1200 mg/day (7.5% and 2.9%, respectively). There were thus a limited number of patients in the study who appeared to benefit from the highest permitted dose level of LCM. Relevant treatment guidelines and expert recommendations advise use of the maximum tolerated dose of a given AED in epilepsy monotherapy before switching to another AED or adding a second treatment (Elger and Schmidt, 2008; NICE, 2012). Availability of LCM 600 mg/day would increase flexibility in order to optimise treatment at an individual patient level and in particular for the small subset of patients that are not controlled with lower doses of LCM monotherapy. The CHMP therefore agreed that, from an efficacy point of view, titration of LCM up to a dose of 600 mg/day could be acceptable for POS monotherapy.

2.5.4. Conclusions on the clinical efficacy

The pivotal study for this application was conducted in line with the epilepsy guideline and previous CHMP scientific advice. The results showed similar proportions of patients achieving seizure freedom when treated with LCM or CBR-CR. Non-inferiority of LCM to CBZ-CR in monotherapy of POS with or without secondary generalisation was thus demonstrated. The data furthermore suggested that some patients could benefit from doses up to 600 mg/day.

In conclusion, the available evidence for clinical efficacy was considered acceptable to support the present application.

2.6. Clinical safety

Introduction

The most common adverse reactions with LCM as adjunctive therapy of POS are related to the CNS and gastrointestinal (GI) system and include dizziness, headache, nausea and diplopia. Some of these events are dose-related. Incidence and severity of CNS and GI adverse reactions usually decrease over time. In all of the controlled studies with LCM as adjunctive therapy, the discontinuation rate due to adverse reactions was 12.2% for patients randomized to LCM and 1.6% for patients randomized to placebo. The most common adverse reaction resulting in discontinuation of LCM therapy was dizziness.

The use of LCM is furthermore associated with dose-related increase in the PR interval. Associated adverse reactions (e.g. atrioventricular [AV] block, syncope, and bradycardia) may occur. The incidence of first degree AV block (PR prolongation beyond 200ms) is uncommon. Cases with second and third degree AV block associated with LCM treatment have been reported in post-marketing experience. In pooled adjunctive therapy clinical trials, the incidence rate for syncope was uncommon. Furthermore, abnormalities in liver function tests have been observed in controlled trials with LCM in adult patients with POS who were taking 1 to 3 concomitant AEDs.

The safety evaluation of the present application was based on the data derived from the pivotal trial SP0993 and its extension SP0994 as well as the supportive studies SP902 and SP904.

Patient exposure

Study SP0993

In SP0993, 444 subjects received LCM and 442 subjects received CBZ-CR. The majority of subjects had a duration of exposure to LCM (63.5%) and to CBZ-CR (60.4%) of >364 to ≤546 days. The mean durations of LCM and CBZ-CR exposure during the Treatment Period were 328.6 and 318.6 days, respectively. The total subject-years of exposure to LCM and CBZ-CR during the Treatment Period were 399.5 and 385.5 subject-years, respectively.

Overall, 70.7% (314/444), 19.6% (87/444) and 9.7% (43/444) of the patients in the LCM arm and, 73.3% (324/442), 19.2% (85/442) and 7.5% (33/442) in the CBZ-CR arm maintained dose level 1, 2 and 3, respectively. The median study medication duration of LCM was 355.5 days at >100 to 200mg/day (dose level 1), 176.0 days at >300 to 400mg/day (dose level 2), and 111.5 days at >500 to 600mg/day (dose level 3). Subject-years exposed for LCM were 288.9, 69.8, and 21.0 at dose level 1, dose level 2, and dose level 3, respectively. The median study medication duration of CBZ-CR was 291.0 days at >200 to 400mg/day (dose level 1), 209.0 days at >600 to 800mg/day (dose level 2), and 104.5 days at >1000 to 1200mg/day (dose level 3). Subject-years exposed for CBZ-CR were 281.0, 70.4, and 14.2 at dose level 1, dose level 2, and dose level 3, respectively.

The Safety Set (SS) was defined in the same way as the FAS, i.e. all randomised subjects who took at least 1 dose of study medication (see section 2.5.2. for details on the analysis set and demographics).

Supportive studies

As of the SP0994 cut-off date of 22 May 2015, 81 subjects (30.5%) and 71 subjects (27.4%) had a duration of exposure to LCM and CBZ-CR of >182 to ≤364 days, respectively; 30 subjects each (11.3% and 11.6%) had a duration of exposure to LCM and CBZ-CR of >728 days, respectively. The mean duration of exposure and subject-years of exposure was comparable in the LCM and CBZ-CR treatment groups (378.8 days in the LCM treatment group compared with 359.4 days in the CBZ-CR treatment group and 275.9 and 254.8 subject-years of exposure in the LCM and CBZ-CR treatment groups respectively). In SP0994, by the cut-off date, 197 subjects had received LCM at >100 to 200mg/day

(dose level 1), 57 subjects had received LCM at >300 to 400mg/day (dose level 2), and 25 subjects had received LCM at >500 to 600mg/day (dose level 3) for at least 1 day during the Treatment Period. A total of 192 subjects received CBZ-CR at >200 to 400mg/day (dose level 1), 64 subjects received CBZ-CR at >600 to 800mg/day (dose level 2), and 11 subjects received CBZ-CR at >1000 to 1200mg/day (dose level 3) for at least 1 day during the Treatment Period.

For the combined treatment periods of SP0993 and SP0994, a total of 59 subjects (13.3%) were exposed to LCM >500 to 600mg/day. A total of 26 subjects (5.9%) had at least 6 months exposure to LCM >500 to 600mg/day, and 16 subjects (3.6%) had at least 12 months exposure to LCM >500 to 600mg/day.

In SP902, overall, subjects had a mean of 21.2 days of exposure during the Titration Phase, 97.1 days of exposure during the Maintenance Phase, and 108.4 days of exposure during the Treatment Phase. Over one-half of all subjects in the LCM 400mg/day and LCM 300mg/day groups (51.7% and 56.6%) had durations of >126 to ≤140 days of exposure during the Treatment Phase.

In SP904, the total subject-years of exposure to LCM for 322 subjects was 525.5 years. The majority of subjects (296 subjects [91.9%]) had at least 6 months of exposure to LCM, 258 subjects (80.1%) had at least 12 months of exposure to LCM, 240 subjects (74.5%) had at least 18 months of exposure to LCM, and 216 subjects (67.1%) had at least 24 months of exposure to LCM. The most common LCM modal dose was 300 to <400mg/day (107 subjects [33.2%]). The number of patients exposed to the >500 to 600 mg/day dose range for at last 6 months were 71 and for at least 12 months 44. Overall, 43 subjects had at least 6 months exposure to LCM >600 mg and 35 subjects had at least 12 months exposure to LCM >600 mg.

Adverse events (AEs)

- Study SP0993

In SP0993, treatment emergent AEs (TEAEs) were defined as AEs that started on or after the date of first dose of study medication and within 30 days following the date of final study medication administration, or AEs whose intensity worsened on or after the date of first dose of study medication and within 30 days following the date of last dose. Signs or symptoms of the condition/disease for which the investigational product was being studied were recorded as AEs only if their nature changed considerably or their frequency or intensity increased in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline assessment

The most common TEAEs reported in at least 3% of subjects in the LCM treatment group in SP0993 were headache (13.7%), followed by dizziness (11.7%), fatigue (7.2%), nasopharyngitis (6.3%), and somnolence (5.4%). The most common TEAEs (reported in at least 3% of subjects) in the CBZ-CR treatment group were headache (12.9%) followed by fatigue (10.4%), somnolence (9.3%), dizziness (8.6%), gamma glutamyl transferase (GGT) increased (8.1%), nasopharyngitis (6.6%), nausea (5.0%), hypercholesterolemia (4.8%), constipation (4.3%), diarrhoea (3.8%), urinary tract infection, alanine aminotransferase (ALT) increased (3.4% for each), and rash (3.2%). Among the most commonly reported TEAEs (≥3%), dizziness occurred with a higher incidence (≥2% difference) in the LCM treatment group compared with the CBZ-CR treatment group. Among the most commonly reported TEAEs (≥3%), GGT increased (8.1% vs 1.6%), somnolence (9.3% vs 5.4%), constipation (4.3% vs 0.7%), fatigue (10.4% vs 7.2%), and hypercholesterolemia (4.8% vs 2.5%) occurred with a higher incidence (≥2% difference) in the CBZ-CR treatment group compared with the LCM treatment group.

Most subjects in the LCM and CBZ-CR treatment groups reported TEAEs with a maximum intensity of mild (177 subjects [39.9%] and 162 subjects [36.7%], respectively) or moderate (121 subjects [27.3%] and 128 subjects [29.0%], respectively). Thirty subjects (6.8%) and 42 subjects (9.5%) in the LCM and CBZ-CR treatment groups reported TEAEs with a maximum intensity of severe. Severe TEAEs for the LCM and

CBZ-CR treatment groups were most frequently reported in the SOC of Nervous system disorders (14 subjects [3.2%] and 10 subjects [2.3%], respectively).

A summary of the most common TEAEs (reported in at least 3% of subjects in any treatment group) with onset during the Treatment Period for study SP0993 is presented in Table 16.

Table 16 - Incidence of the most commonly reported TEAEs (≥ 3% in either treatment group) in Study SP0993 with onset during the Treatment Period (SS)

MedDRA SOC PT	LCM N=444 n (%) [#]	CBZ-CR N=442 n (%) [#]
Any TEAEs	**328 (73.9) [1212]**	**332 (75.1) [1374]**
Gastrointestinal disorders		
Nausea	26 (5.9) [32]	22 (5.0) [28]
Diarrhoea	9 (2.0) [11]	17 (3.8) [20]
Constipation	3 (0.7) [3]	19 (4.3) [20]
General disorders and administration site conditions		
Fatigue	32 (7.2) [36]	46 (10.4) [52]
Infections and infestations		
Nasopharyngitis	28 (6.3) [40]	29 (6.6) [36]
Urinary tract infection	13 (2.9) [16]	15 (3.4) [19]
Investigations		
ALT increased	8 (1.8) [9]	15 (3.4) [16]
GGT increased	7 (1.6) [8]	36 (8.1) [37]
Metabolism and nutrition disorders		
Hypercholesterolaemia	11 (2.5) [11]	21 (4.8) [21]
Nervous system disorders		
Headache	61 (13.7) [81]	57 (12.9) [75]
Dizziness	52 (11.7) [60]	38 (8.6) [47]
Somnolence	24 (5.4) [25]	41 (9.3) [46]
Skin and subcutaneous tissue disorders		
Rash	7 (1.6) [11]	14 (3.2) [16]

ALT=alanine aminotransferase; CBZ-CR=carbamazepine (controlled release); GGT=gamma-glutamyl transferase; 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 subjects reporting at least 1 TEAE within SOC/PT. (%)=Percentage with respect to the number of subjects in the SS. [#] was the number of individual occurrences of the TEAE.
Note: Any TEAE is provided for context and is not subjected to any data cut-off.

The incidence of the most commonly reported TEAEs by LCM dose at onset in study SP0993 are presented in Table 17.

Table 17 - Incidence of the most commonly reported TEAEs with onset during the Treatment Period by LCM dose at onset in study SP0993 (Safety Set)

MedDRA SOC PT	LCM dose at onset (N=444)					
	≤100mg/day N=443 n (%)	>100 to 200mg/day N=438 n (%)	>200 to 300mg/day N=130 n (%)	>300 to 400mg/day N=127 n (%)	>400 to 500mg/day N=44 n (%)	>500 to 600mg/day N=44 n (%)
Any TEAE	**100 (22.6)**	**260 (59.4)**	**32 (24.6)**	**59 (46.5)**	**8 (18.2)**	**24 (54.5)**
Gastrointestinal disorders						
Nausea	6 (1.4)	16 (3.7)	3 (2.3)	2 (1.6)	0	1 (2.3)
Diarrhoea	0	7 (1.6)	0	2 (1.6)	0	0
Constipation	1 (0.2)	2 (0.5)	0	0	0	0
General disorders and administration site conditions						
Fatigue	11 (2.5)	13 (3.0)	3 (2.3)	4 (3.1)	0	3 (6.8)
Infections and infestations						
Nasopharyngitis	2 (0.5)	18 (4.1)	1 (0.8)	5 (3.9)	1 (2.3)	3 (6.8)
Urinary tract infection	0	7 (1.6)	1 (0.8)	3 (2.4)	0	1 (2.3)
Investigations						
ALT increased	0	6 (1.4)	1 (0.8)	1 (0.8)	0	0
GGT increased	0	4 (0.9)	1 (0.8)	1 (0.8)	1 (2.3)	0
Metabolism and nutrition disorders						
Hypercholesterolaemia	3 (0.7)	8 (1.8)	0	0	0	0
Nervous system disorders						
Headache	14 (3.2)	38 (8.7)	5 (3.8)	11 (8.7)	1 (2.3)	3 (6.8)
Dizziness	14 (3.2)	25 (5.7)	2 (1.5)	10 (7.9)	1 (2.3)	3 (6.8)
Somnolence	11 (2.5)	9 (2.1)	2 (1.5)	1 (0.8)	1 (2.3)	1 (2.3)
Skin and subcutaneous tissue disorders						
Rash	2 (0.5)	6 (1.4)	1 (0.8)	0	0	0

AE=adverse event; ALT=alanine aminotransferase; GGT=gamma-glutamyltransferase; 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 subjects reporting at least 1 TEAE within SOC/PT. (%)=Percentage with respect to the number of subjects for whom the dose was administered during the period.
Note: If a subject had >1 occurrence of the same AE at different doses at onset, the AE was summarized under each applicable dose at onset.
Note: AEs starting prior to the first dose or after the last dose of study medication were not included in this summary.
Note: The most commonly reported TEAEs are defined as those reported by ≥3% of subjects in either treatment arm.

The incidences of any TEAEs for subjects in the LCM treatment group with onset during the treatment period were 59.4% at >100 to 2 00mg/day (dose level 1), 46.5% at >300 to 400mg/day (dose level 2) and 54.5% at>500 to 600mg/day (dose level 3). Fatigue and nasopharyngitis were reported by a slightly higher percentage (≥2% difference) of subjects (3 subjects [6.8%] for each) at dose level 3 (LCM >500 to 600mg/day) compared with the lower dose levels. A trend for a higher incidence in the highest dose group >500 to 600 mg/day was seen for the common TEAEs fatigue and nasopharyngitis, but for most other commonly reported TEAEs the incidence was not higher and no unexpected TEAEs were observed as compared with the lower doses. It should be noted, however, that relatively few subjects reached the highest dose of 600 mg/day (N = 44). For selected less common TEAEs in SP0993, there was a dose-related increase in incidence rate (defined as a doubling of incidence between target dose level 1 and 3 and increasing in a dose-dependent manner) for some TEAEs. These TEAEs included visual impairment, fatigue, gait disturbance, bronchitis, sinusitis, myalgia, balance disorder, disturbance in attention, hypoaesthesia, memory impairment, syncope, metrorrhagia, and pruritus.

TEAEs with a significant increase in event rate between target dose level 1 and 3 in the CBZ-CR treatment group included sinus bradycardia, vertigo, constipation, sinusitis, creatinine renal clearance increased, disturbance in attention, tremor, affect lability, cough, and oropharyngeal pain.

In the CBZ-CR treatment group, the incidences of TEAEs for subjects with onset during the treatment period were 59.4% at >200 to 400mg/day (dose level 1), 68.1% at >600 to 800mg/day (dose level 2), and 43.8% at >1000 to 1200mg/day (dose level 3). Constipation and nasopharyngitis were reported by a higher percentage (≥2% difference) of subjects (3 subjects [9.4%] and 4 subjects [12.5%], respectively) at the highest dose level (CBZ-CR >1000 to 1200mg/day) and dizziness was reported by a higher percentage of subjects (4 subjects [12.1%]) at the >800 to 1000mg/day dose level compared with the lower dose levels.

Dose reductions for tolerability issues occurred with higher frequency in the higher dose groups, compared to the dose level 2 groups. The frequency of dose reductions due to tolerability issues at each dose level was similar between LCM and CBZ-CR (LCM 600 mg group, 5/43, 11.6%; CBZ CR 1200 group 5/33, 15.2%; LCM 400 mg: 3/87, 3.4%; CBZ CR 800 mg: 3/85, 3.5%). Dose reductions in the LCM group were mostly due to dizziness, vertigo, diplopia, headache, memory impairment.

A lower percentage of subjects in the LCM treatment group reported TEAEs considered related to study medication by the investigator during the Treatment Period (165 subjects [37.2%]) compared with the CBZ-CR treatment group (203 subjects [45.9%]). The incidences of TEAEs considered related to study medication per the investigator for the LCM and CBZ-CR treatment groups were most frequently reported in the SOC of Nervous system disorders (84 subjects [18.9%] and 90 subjects [20.4%], respectively).

In the LCM treatment group, TEAEs considered to be related to study medication by the investigator occurring in ≥5 subjects during the Treatment Period were dizziness (35 subjects [7.9%]); fatigue (25 subjects [5.6%]); somnolence (20 subjects [4.5%]); headache (18 subjects [4.1%]); nausea (17 subjects [3.8%]); vertigo (11 subjects [2.5%]); irritability, disturbance in attention, and memory impairment (8 subjects [1.8%] for each); and ALT increased, AST increased, hypercholesterolemia, and syncope (5 subjects [1.1%] for each).

In the CBZ-CR treatment group, TEAEs considered to be related to study medication by the investigator occurring in ≥5 subjects during the Treatment Period were somnolence (39 subjects [8.8%]), fatigue (31 subjects [7.0%]), GGT increased (27 subjects [6.1%]), headache (22 subjects [5.0%]), dizziness (20 subjects [4.5%]), nausea (18 subjects [4.1%]), ALT increased (13 subjects [2.9%]), constipation and hypercholesterolemia (12 subjects [2.7%] for each), vertigo (10 subjects [2.3%]), rash (9 subjects [2.0%]), increased appetite (7 subjects [1.6%]), AST increased (8 subjects [1.8%]), disturbance in attention (6 subjects [1.4%]), and urine albumin/creatinine ratio increased (5 subjects [1.1%]).

In study SP0993, 8 subjects (1.8%) reported TEAEs of weight decreased in the LCM treatment group compared to 2 subjects (0.5%) in the CBZ-CR treatment group. Three (3) of the 8 events that occurred in the LCM treatment group were considered drug related by the investigator and both events in the CBZ-CR treatment group were considered drug related by the investigator. None of the events of weight decrease were serious AEs (SAEs) or led to discontinuation. Furthermore, three subjects (0.7%) reported TEAEs of weight increased in the LCM treatment group compared to 6 subjects (1.4%) in the CBZ-CR treatment group.

- Supportive studies

The most common TEAEs in SP0994 (reported in at least 2% of subjects in the LCM treatment group) were nasopharyngitis (4.9%) and headache (3.0%). The most common TEAEs (reported in at least 3% of subjects in the CBZ-CR treatment group) were nasopharyngitis (5.0%), headache (3.5%), and GGT increased and dizziness (3.1% for each). The incidences of the most common TEAEs (by MedDRA preferred term [PT]) were similar between the LCM and CBZ-CR treatment groups. In study SP0994,

there were no TEAEs related to body weight change reported in the LCM treatment group, while in the CBZ-CR treatment group 2 subjects (0.8%) reported weight decreased.

In SP902, a total of 84.5% of subjects experienced TEAEs with onset during the Treatment Phase. Dizziness was the most frequently reported common TEAE (24.0% of subjects), followed by headache (14.4%), nausea (13.4%), convulsion (11.5%), somnolence (10.4%), and fatigue (10.1%).

In SP904, dizziness (27.3%) was the most commonly reported TEAE, followed by headache (17.1%), nausea (14.3%), upper respiratory tract infection (13.7%), convulsion (13.4%), fatigue (12.4%), and nasopharyngitis (11.8%). In study SP904 the incidences of any TEAEs during the Treatment Phase increased with increasing doses both overall (11.6%, 59.6% and 66.7%, for the >100 to 200, >300 to 400 and >500 to 600 mg/day respectively) and while on LCM monotherapy (6.8%, 52.9% and 58.6%) and not on LCM monotherapy (11.3%, 28.4% and 38.3%). In general, the incidences of any TEAEs during the Treatment Phase increased with increasing doses ranging from 11.6% and 19.4% at the lowest doses (>100 to 200mg/day and 0 to 100mg/day) to 81.1% at the highest dose (>600mg/day). The incidences of dizziness and headache were highest in subjects who were receiving LCM >600mg/day. Of note, the proportions of subjects reporting the most commonly reported TEAEs were, in general, equally distributed among the subjects who were receiving LCM 0 to 100mg/day, LCM >100 to 200mg/day, and LCM >200 to 300mg/day. The incidence of TEAEs during the Treatment Phase by dose at onset was generally similar for subjects on LCM monotherapy compared with subjects not on monotherapy. In study SP904, twelve subjects (3.7%) reported weight increased, and 9 subjects (2.8%) reported weight decreased. None of these events were serious or led to study medication discontinuation.

- Post-hoc analysis of TEAEs during treatment initiation to support LCM 200 mg/day starting dose

The MAH proposed a starting dose in POS monotherapy of 100 mg twice a day (200 mg/day). In adjunctive POS therapy, the recommended starting dose is 50 mg twice a day (100 mg/day), which should be increased to an initial therapeutic dose of 100 mg twice a day after one week. In the historically controlled conversion to monotherapy study SP902, LCM was administered at an initial dose of 200 mg/day, whereas in study SP0993 LCM treatment was initiated at 100 mg/day. TEAEs occurring in the first 10 days of treatment in study SP902 (subjects with 1 concomitant AED) where compared to those occurring during the first 14 days of treatment in study SP0993. SP902 data were furthermore compared with a pool of phase 2/3 adjunctive LCM therapy studies, where LCM was initiated at a dose of 100 mg/day and increased to 200 mg/day during the second week (Werhahn et al., 2005).

Table 18 – Incidence of TEAEs and TEAEs leading to discontinuation in adults with focal seizures following initiation of LCM 200 mg/day versus 100 mg/day

Study	SP0993		SP902			Data pooled from SP667, SP754, and SP755[a]	
Study description	Phase 3, double-blind, positive-controlled study comparing LCM to CBZ-CR used as monotherapy		Phase 3, historical-controlled, double-blind, conversion to LCM monotherapy study			Phase 2/3, placebo-controlled, double-blind, adjunctive LCM therapy studies	
Period evaluated	Up to 14 days		Up to 10 days			Up to 14 days	
LCM initial dose	100mg/day Week 1, 200mg/day Week 2		200mg/day			100mg/day Week 1, 200mg/day Week 2	
				Number of background AEDs			
Population	LCM N=444 n (%)	CBZ-CR N=442 n (%)	Overall LCM N=425 n (%)	1 AED N=312 n (%)	2 AEDs N=113 n (%)	LCM N=142 n (%)	Placebo N=62 n (%)
TEAEs							
At least 1 TEAE	138 (31.1)	164 (37.1)	175 (41.2)	128 (41.0)	47 (41.6)	53 (37.3)	24 (38.7)
TEAEs occurring in ≥3% of subjects in any LCM group							
Dizziness	25 (5.6)	17 (3.8)	35 (8.2)	25 (8.0)	10 (8.8)	15 (10.6)	3 (4.8)
Nausea	9 (2.0)	14 (3.2)	24 (5.6)	20 (6.4)	4 (3.5)	4 (2.8)	2 (3.2)
Fatigue	17 (3.8)	27 (6.1)	19 (4.5)	17 (5.4)	2 (1.8)	4 (2.8)	2 (3.2)
Somnolence	14 (3.2)	27 (6.1)	17 (4.0)	13 (4.2)	4 (3.5)	4 (2.8)	2 (3.2)
Headache	20 (4.5)	34 (7.7)	16 (3.8)	15 (4.8)	1 (0.9)	6 (4.2)	2 (3.2)
Dry mouth	1 (0.2)	0	11 (2.6)	11 (3.5)	0	1 (0.7)	1 (1.6)
TEAEs leading to discontinuation							
At least 1 TEAE leading to discontinuation	10 (2.3)	22 (5.0)	13 (3.1)	11 (3.5)	2 (1.8)	3 (2.1)	1 (1.6)
TEAEs leading to discontinuation in ≥1% of subjects in any LCM group							
Vomiting	0	0	4 (0.9)	4 (1.3)	0	1 (0.7)	0
Dizziness	2 (0.5)	0	3 (0.7)	2 (0.6)	1 (0.9)	3 (2.1)	0
Nausea	0	2 (0.5)	3 (0.7)	3 (1.0)	0	1 (0.7)	0
Coordination abnormal	0	0	1 (0.2)	1 (0.3)	0	2 (1.4)	0
Flatulence	0	0	0	0	0	2 (1.4)	0

AEDs=antiepileptic drugs; CBZ-CR=carbamazepine-continuous release; LCM=lacosamide; TEAEs=treatment-emergent adverse events
[a] Limited to subjects taking 1 concomitant AED.

In study SP902, the incidence of any TEAEs in the first 10 days following LCM initiation was slightly higher than in the first 14 days of treatment in a pool of adjunctive therapy studies and in study SP0993 with 41.2%, 31.1% and 37.3%, respectively. Also the incidence of the most common TEAEs was higher in the first 10 days of study SP902 compared to the first 14 days of study SP0993 (dizziness 8.2% vs 5.6%; nausea 6.4% vs 2.0%, fatigue 5.4% vs 3.8%, somnolence 4.2% vs 3.2%, dry mouth 3.5% vs 0.2%).

Serious adverse event/deaths/other significant events

Death

Two subjects died in study SP0993; 1 due to subarachnoid haemorrhage in the LCM treatment group and 1 due to ischemic stroke in the CBZ-CR treatment group. Both events were not considered related to study medication by the investigator. In SP0994, 1 subject taking LCM 200 mg/day died as of the clinical cut-off date of 22 May 2015. The investigator considered the death due to renal failure and adenocarcinoma to be not related to study medication.

There were 3 deaths during SP902, which were all considered unlikely or unrelated to LCM. Two of the deaths were considered to be Sudden Unexpected Death in Epilepsy (SUDEP), both of which occurred in subjects with only IC seizures. Three subjects died during study SP904 (1 due to cardiac arrest, 1 due to metastatic squamous cell carcinoma, and 1 due to SUDEP). The event of cardiac arrest was considered by the investigator to be unlikely related, and the events of metastatic squamous cell carcinoma and SUDEP were considered to be not related to study medication.

Other serious adverse events (SAE)

- SP0993

In SP0993, a total of 32 subjects (7.2%) reported 46 SAEs during the Treatment Period in the LCM treatment group and 43 subjects (9.7%) reported 59 SAEs in the CBZ-CR treatment group. In the LCM treatment group, the most frequently reported SAE was convulsion (3 subjects [0.7%]). Additional SAEs reported by ≥2 subjects in the LCM treatment group included gait disturbance, tendon rupture, and epilepsy (2 subjects [0.5%] for each). In the CBZ-CR treatment group, the most frequently reported SAE was partial seizures with secondary generalization (3 subjects [0.7%]). Additional SAEs reported by ≥2 subjects in the CBZ-CR treatment group included convulsion, cerebrovascular accident, and ischemic stroke (2 subjects [0.5%] for each).

The incidences of SAEs for subjects in the LCM treatment group with onset during the Treatment Period were 5.9% at >100 to 200mg/day (dose level 1), 1.6% at >300 to 400mg/day (dose level 2) and 6.8% at >500 to 600mg/day (dose level 3). The incidences of SAEs for subjects in the CBZ-CR treatment group with onset during the Treatment Period were 6.0% at >200 to 400mg/day (dose level 1) 12.9% at >600 to 800mg/day (dose level 2), and 6.4% at >1000 to 1200mg/day (dose level 3).

SAEs that were severe, related to study medication per the investigator, and led to discontinuation were as follows: 2 subjects in the LCM treatment group reported 2 SAEs (rash macular and suicidal ideation); 4 subjects in the CBZ-CR treatment group reported 4 SAEs (aplastic anaemia, hypersensitivity, rash generalized, and dermatitis allergic); and 1 subject reported 3 SAEs (aspartate aminotransferase [AST] increased, ALT increased, and GGT increased).

- Supportive studies

In SP0994, a total of 21 subjects (7.9%) reported 37 SAEs during the Treatment Period in the LCM treatment group compared with 19 subjects (7.3%) who reported 36 SAEs in the CBZ-CR treatment group. The most frequently reported SAEs were gastroenteritis (no subjects in the LCM treatment group and 3 subjects [1.2%] in the CBZ-CR treatment group reported 4 SAEs) and suicidal ideation (1 subject [0.4%] in the LCM treatment group reported 1 SAE and 2 subjects [0.8%] in the CBZ-CR treatment group reported 2 SAEs). Suicide attempt (no subjects in the LCM treatment group and 2 subjects [0.8%] in the CBZ-CR treatment group) was the only other SAE reported by ≥2 subjects in either treatment group.

Fourteen subjects (7.1%) reported SAEs at the LCM >100 to 200mg/day dose level, 6 subjects (10.5%) reported SAEs at the LCM >300 to 400mg/day dose level, and 1 subject (4.0%) reported an SAE at the LCM >500 to 600mg/day dose level. Fourteen subjects (7.3%) reported SAEs at the CBZ-CR >200 to 400mg/day dose level, 3 subjects (4.7%) reported SAEs at the CBZ-CR >600 to 800mg/day dose level, and 1 subject (9.1%) reported an SAE at the CBZ-CR >1000 to 1200mg/day dose level.

In SP902, during the Treatment Phase, 17 subjects (4.0%), all of whom were randomized to LCM 400 mg/day, reported treatment-emergent SAEs. Events coded to convulsion were the most frequently reported treatment-emergent SAEs with onset during the Treatment Phase, reported by 5 subjects (1.2%). No other treatment-emergent SAE was reported by more than 1 subject in SP902.

In SP904, a total of 54 subjects (16.8%) reported 97 treatment-emergent SAEs during the Treatment

Phase. The most commonly reported SAEs were coded to convulsion (5.3%), syncope (0.9%), status epilepticus (0.9%), and postictal state (0.6%). The incidence of SAEs was 12.0% in subjects while on LCM monotherapy and 14.6% in subjects while not on LCM monotherapy.

One event of dyskinesia occurred in a 27 year old male on LCM 600 mg/day. The subject experienced involuntary movements and was hospitalized. He had difficulty in pronouncing words and was having a hard time communicating with the family. The subject was conscious the entire time, but had vertigo, involuntary movements, and ataxia. The EEG and magnetic resonance imaging results were reported as nonsignificant. The event lasted for 1.5 hours. The subject was discharged from the hospital and study drug dose was reduced to LCM 400 mg/day. There were no concomitant AEDs or other concomitant medications at the time of the dyskinesia. The relationship of the study drug to the dyskinesia was reported as probably related.

Other significant TEAEs

Based on safety data from clinical studies with LCM and general safety considerations, certain TEAEs were given special consideration. These TEAEs were termed 'other significant TEAEs' and included hepatotoxicity related terms (hepatitis toxic and hepatotoxicity), cardiac and ECG-related terms (atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular tachycardia, AV block second degree, AV block third degree, bradycardia, bradyarrhythmia, sinus bradycardia, HR decreased, sick sinus syndrome, and cardiac pacemaker insertion), suicidality-related terms (completed suicide, depression suicidal, suicidal behaviour, suicidal ideation, suicide attempt, intentional self-injury, self-injurious behaviour, self-injurious ideation, intentional overdose, multiple drug overdose intentional, and poisoning deliberate), and syncope and loss of consciousness.

- Hepatotoxicity

No events of hepatotoxicity were reported during the study.

- Cardiac-related TEAEs

In study SP0993 the frequency of cardiac-related TEAEs (2.3% and 2.0% in the LCM and CBZ-CR treatment group, respectively) and of treatment emergent SAEs (0.2% in both groups) was similar in both treatment groups. In study SP0994 the frequency of cardiac-related TEAEs (1.9% vs 0.8%) and of treatment emergent SAEs (1.1% vs 0.4%) was higher in the LCM treatment group compared to CBZ-CR. In both study SP0993 and SP0994 the types of events observed were bradycardia and atrial fibrillation plus one event of second degree atrioventricular (AV) block (that occurred in the CBZ-CR treatment group).

In study SP904, seven cardiac-related TEAEs of bradycardia and related terms (bradycardia, sinus bradycardia and heart rate decreased) were reported; two of these events were SAEs. Furthermore, a fatal event of cardiac arrest in a 46 year old subject occurred. The frequency of cardiac-related TEAEs and of treatment emergent SAEs were 2.5% and 0.8%.

- Suicidality

In study SP0993 the frequency of TEAEs related to suicidality (1.1% and 0.9%) and of treatment emergent SAEs (0.2% ad 0) was similar in both treatment groups (LCM and CBZ-CR, respectively). In study SP0994 the frequency of TEAEs related to suicidality (0.7% and 2.7%) and of treatment emergent SAEs (0.4% and 0.8) was lower in the LCM treatment group, compared to CBZ-CR.

In study SP904 10 subjects (3.1%) reported suicidal ideation; one of these events was serious (not on LCM monotherapy) and 2 events led to study drug discontinuation (one while on LCM monotherapy and one not). Among the events that occurred while on LCM monotherapy, 5/8 events occurred in subjects receiving a dose ≥500 mg.

- Syncope

Seven subjects (1.6%) reported 7 TEAEs of syncope in the LCM treatment group compared only 1 subject (0.2%) in the CBZ-CR treatment group during the Treatment Period. Two subjects in the LCM treatment group reported mild, non-serious events, one of which was considered to be related to study medication according to the investigator while the other was not. Four subjects in the LCM treatment group reported moderate events: 2 of these events were non-serious and related to study medication according to the investigator; 1 of these events was serious and related to study medication according to the investigator; and the last event was non-serious and considered related to study medication by the investigator. One subject in the LCM treatment group reported a severe, non-serious event that was related to study medication per the investigator. One subject in the CBZ-CR treatment group reported a mild, non-serious event that was not considered related to study medication by the investigator.

One of the events in the LCM treatment group led to study discontinuation. The majority of subjects had predisposing factors for syncope (i.e., cardiovascular disease or history of syncope).

Laboratory findings

In SP0993, no trend was observed with regards to changes from baseline for the LCM treatment groups for haematology or clinical chemistry parameters. No trend was observed in changes from baseline for the LCM treatment group for the thyroid and sex hormones and lipid parameters.

Clinically relevant trends in changes from baseline were observed for the CBZ-CR treatment group for the following parameters: decreases from baseline for thyroxine and increases from baseline in sex hormone binding globulin. In addition, increases from baseline were observed for the lipid parameters of cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol calculated and non-high-density lipoprotein cholesterol. Notable increases from baseline were observed for ALT and GGT in the CBZ-CR treatment group.

Overall, no consistent changes after the onset of treatment from baseline in urinalysis values were observed. With the exception of monocytes/leukocytes, changes in haematology parameters for which shifts occurred in ≥10% of subjects from normal values at baseline to a maximum high or minimum low value post-baseline, these changes occurred at higher incidences in the CBZ-CR treatment group compared with the LCM treatment group. In general, changes in clinical chemistry parameters for which shifts occurred in ≥10% of subjects from normal values at baseline to a maximum high value post-baseline for liver enzymes, these changes occurred at higher incidences in the CBZ-CR treatment group compared with the LCM treatment group.

Overall, the incidence of treatment-emergent markedly abnormal values for haematology parameters during the treatment period was low (<5.7% for either treatment group). Likewise, the incidence of treatment-emergent markedly abnormal values for clinical chemistry parameters during the treatment period was low (≤3% for the LCM treatment group and ≤10.0% for the CBZ-CR treatment group), with the exception of cholesterol (10.6% and 20.1% in the LCM and CBZ-CR treatment groups, respectively) .

In study SP0994, no particular deviations were evident compared to study SP0993. The incidence of treatment-emergent markedly abnormal values were generally similar in the CBZ-CR treatment group compared with the LCM treatment group, with the biggest differences (≥2%) observed for high cholesterol (12/167 subjects [7.2%] in the LCM treatment group compared with 34/165 subjects [20.6%] in the CBZ-CR treatment group), high GGT (6/238 subjects [2.5%] in the LCM treatment group compared with 17/228 subjects [7.5%] in the CBZ-CR treatment group), and low thyroxine (1/241 subjects [0.4%] in the LCM treatment group compared with 8/230 subjects [3.5%] in the CBZ-CR treatment group).

In SP902 and SP904, the incidence of treatment-emergent marked abnormalities in laboratory parameters was low (<2% for most parameters).

Vital signs, physical findings, and other observations related to safety

In study SP0993, the incidences of TEAEs related to abnormal vital sign values were low and similar between treatment groups. Four TEAEs related to abnormalities in blood pressure and heart/pulse rate were reported: hypertension (9 subjects [2.0%] in LCM group vs 8 subjects [1.8%] in CBZ-CR group), hypotension (3 [0.7%] vs. 0), hypertensive crisis (1 [0.2%] vs. 0), and orthostatic hypotension (no subjects in the LCM treatment group and 1 subject [0.2%] in the CBZ-CR treatment group). One SAE of hypertension was reported during the study in the CBZ-CR group. One subject with a history of hypertension treated with LCM discontinued the study due to a TEAE of moderate hypertensive crisis considered as related to study drug.

In study SP904, TEAEs related to vital signs included hypertension (15 subjects, 4.7%), bradycardia (5, 1.6%); blood pressure increased, hypotension, and sinus tachycardia (for all, 3 subjects, 0.9%); sinus bradycardia, heart rate increased, heart rate decreased, tachycardia (for all, 2 subjects, 0.6%), and supraventricular tachycardia (1 subject, 0.3%). Three SAEs related to vital signs but not considered related to study medication were reported: bradycardia and hypotension on the same day by the same subject, and heart rate decreased. No TEAEs related to vital signs led to discontinuation from the study.

Regarding ECG findings, overall, in the pivotal study SP0993, a mean increase from baseline of PR interval duration was observed for both treatment groups at most time points, but it was slightly higher for LCM compared with CBZ-CR and showed a dose-relationship particularly for LCM: PR interval >220 ms was found in 2.4%, 3.1%, 4.7% and 0 patients in the LCM dose categories ≤200 mg/day, >200-400 mg/ day and >400-600 mg/ day, 600 mg/ day respectively. Mean increases from baseline of QRS interval (1 to 5 ms) were observed at most post-baseline time points in both the LCM and CBZ-CR treatment groups with no difference between the two treatment groups. Regarding QT interval, there was a tendency towards an increase in LCM patients compared with CBZ-CR. Moreover, there was a great variability with high standard deviations for both treatment groups. Regarding QTcB and QTcF intervals, although the numbers were small, a tendency towards an increase only at the 3rd target dose level of LCM could be observed.

In study SP0994, there were no marked differences in ECG parameters between the LCM and CBZ-CR treatment groups. Small mean increases in PR interval from baseline were observed in both treatment groups. In study SP904, small increases from baseline in the mean PR (range from 5.7 to 7.9) were observed at post-baseline time points.

Safety in special populations

Safety data for special populations in study SP0993 is summarised below.

Age

An overview of TEAEs with onset during the treatment period of study SP0993 by age groups is provided in Table 19.

Table 19 – Overview of TEAEs with onset during Treatment Period of Study SP0993 by Age (Safety Set)

AE category	<65 years		65 to <75 years		75 to <85 years		≥85 years	
	LCM N=382 n (%)	CBZ-CR N=385 n (%)	LCM N=41 n (%)	CBZ-CR N=45 n (%)	LCM N=19 n (%)	CBZ-CR N=11 n (%)	LCM N=2 n (%)	CBZ-CR N=1 n (%)
Any TEAEs	277 (72.5)	284 (73.8)	36 (87.8)	36 (80.0)	14 (73.7)	11 (100)	1 (50.0)	1 (100)
Deaths	0	0	1 (2.4)	0	0	1 (9.1)	0	0
Serious TEAEs	24 (6.3)	31 (8.1)	7 (17.1)	8 (17.8)	1 (5.3)	3 (27.3)	0	1 (100)
Discontinuations due to TEAEs	34 (8.9)	54 (14.0)	9 (22.0)	10 (22.2)	3 (15.8)	4 (36.4)	1 (50.0)	1 (100)
CNS-related TEAEs (confusion, extrapyramidal)	17 (4.5)	24 (6.2)	2 (4.9)	5 (11.1)	4 (21.1)	0	0	1 (100)
AEs related to falling	30 (7.9)	27 (7.0)	6 (14.6)	4 (8.9)	4 (21.1)	0	0	1 (100)
Cardiovascular events	39 (10.2)	28 (7.3)	9 (22.0)	8 (17.8)	2 (10.5)	1 (9.1)	1 (50.0)	1 (100)
Cerebrovascular events	0	1 (0.3)	2 (4.9)	2 (4.4)	0	1 (9.1)	0	1 (100)
Infections	92 (24.1)	108 (28.1)	12 (29.3)	6 (13.3)	2 (10.5)	1 (9.1)	0	1 (100)

AE=adverse event; CBZ-CR=carbamazepine (controlled release); LCM=lacosamide; TEAE=treatment-emergent adverse event.
Note: n=Number of subjects reporting at least 1 TEAE in that category. (%)=Percentage with respect to the number of subjects in the age category.

In the LCM treatment group, a total of 72.5% of subjects <65 years of age reported at least 1 TEAE during the Treatment Period compared with 82.3% of subjects ≥65 years of age. In subjects ≥65 years of age, the only events which occurred at higher incidences (≥5% difference) compared with subjects <65 years of age were fall (9.7% vs 0.8%, respectively), diarrhoea (6.5%vs 1.3%, respectively), and tremor (6.5% vs 0.3%, respectively). Of the 6 subjects ≥65 years of age in the LCM treatment group who reported TEAEs of fall, 4 subjects reported falls that were considered to be not related to study medication by the investigator. One subject reported 3 TEAEs of fall and 1 subject reported 1 TEAE of fall; all of these TEAEs were considered to be related to study medication by the investigator. All 6 TEAEs were non-serious.

In the CBZ-CR treatment group, a total of 73.8% of subjects <65 years of age reported at least 1 TEAE during the Treatment Period compared with 84.2% of subjects ≥65 years of age. In subjects ≥65 years of age, the only event which occurred at a higher incidence (≥5% difference) compared with subjects <65 years of age was constipation (8.8% vs 3.6%, respectively).

Among the subjects ≥65 years of age, TEAEs occurring in ≥5% of subjects in either treatment group with a higher (≥5% difference) incidence in the LCM treatment group compared with the CBZ-CR treatment group included fall (9.7% vs 1.8%, respectively). For the CBZ-CR treatment group, reporting rates of headache (14.0% vs 6.5%, respectively), somnolence (12.3% vs 4.8%, respectively), GGT increased (10.5% vs 0, respectively), constipation (8.8% vs 1.6%, respectively), and eosinophilia (5.3% vs 0, respectively), were higher (≥5% difference) compared with the incidences in the LCM treatment group.

Gender

The incidences of TEAEs in the LCM treatment group were generally similar between males and females

with the exception of dizziness, nausea, and urinary tract infection, which were reported at lower percentages (≥2% difference) in male subjects (7.4%, 4.9%, and 1.6%, respectively) compared with female subjects (16.9%, 7.0%, and 4.5%, respectively). Furthermore, ALT increased was reported at a higher incidence in males (2.9%) compared with females (0.5%).

Within the CBZ-CR treatment group, the incidences of TEAEs were generally similar between genders with the exceptions of nausea (2.6% vs 7.6%), fatigue (8.6% vs 12.4%), urinary tract infection (1.3% vs 5.7%), headache (9.5% vs 16.7%), and somnolence (7.8% vs 11.0%), which were reported at lower percentages (≥2% difference) in male subjects compared with female subjects.

Race

There were no clinically relevant differences observed in the incidence of TEAEs by race for the LCM or CBZ-CR treatment groups.

Discontinuation due to adverse events

A total of 47 subjects (10.6%) in SP0993 in the LCM treatment group reported TEAEs leading to discontinuation during the Treatment Period. Dizziness was the most common TEAE leading to discontinuation (6 subjects [1.4%]) during the Treatment Period followed by rash (4 subjects [0.9%]), vertigo and AST increased (3 subjects [0.7%] each). All other TEAEs leading to discontinuation were reported by ≤2 subjects in the LCM treatment group.

A total of 69 subjects (15.6%) in SP0993 in the CBZ-CR treatment group reported TEAEs leading to discontinuation during the Treatment Period. This incidence was thus slightly higher than in the LCM treatment group. The most common causes for discontinuation were cutaneous allergic reactions and increases in liver transaminases. Rash was the most common TEAE leading to discontinuation (7 subjects [1.6%]) for subjects in the CBZ-CR treatment group during the Treatment Period followed by GGT increased (6 subjects [1.4%]); ALT increased and somnolence (5 subjects [1.1%] each); drug hypersensitivity, AST increased, and headache (4 subjects [0.9%] each); and fatigue, hypersensitivity, and dermatitis allergic (3 subjects [0.7%] each). All other TEAEs leading to discontinuation were reported by ≤2 subjects in the CBZ-CR treatment group.

In SP0994, a total of 11 subjects (4.1%) reported 13 TEAEs leading to discontinuation during the Treatment Period for the LCM treatment group compared with 13 subjects (5.0%) who reported 22 TEAEs leading to discontinuation in the CBZ-CR treatment group. The only TEAEs leading to discontinuation reported in ≥2 subjects in either treatment group were suicidal ideation (1 subject [0.4%] in the LCM treatment group and 2 subjects [0.8%] in the CBZ-CR treatment group) and suicide attempt (no subjects in the LCM treatment group and 2 subjects [0.8%] in the CBZ-CR treatment group).

Five subjects (2.5%) reported TEAEs leading to discontinuation at the LCM >100 to 200mg/day dose level, 4 subjects (7.0%) reported TEAEs leading to discontinuation at the LCM >300 to 400mg/day dose level, and 1 subject (4.0%) reported a TEAE leading to discontinuation at the LCM >500 to 600mg/day dose level. Eight subjects (4.2%) reported TEAEs leading to discontinuation at the CBZ-CR >200 to 400mg/day dose level, 2 subjects (3.1%) reported TEAEs leading to discontinuation at the CBZ-CR >600 to 800mg/day dose level, and 1 subject (9.1%) reported a TEAE leading to discontinuation at the CBZ-CR >1000 to 1200mg/day dose level. No apparent dose-related trends were observed in TEAE event rate per 100 subject-months in either treatment group; however, too few events were available to make meaningful comparisons.

Post marketing experience

The MAH has searched their Global Safety database cumulatively for all post-marketing cases (excluding UCB-sponsored interventional clinical trial reports) compatible with the use of LCM (any dose and

formulation) as monotherapy from 29 August 2008 to 31 August 2015. Cumulatively, 5614 cases compatible with the use of LCM as monotherapy were identified in the UCB Global Safety database. From the 2829 cases where gender was reported, 1614 cases (58%) involved female and 1215 cases (42%) involved male patients. A short summary of this cumulative analysis is provided below.

In the overall monotherapy dataset, the most frequently reported events were (N≥80): seizure (511), drug ineffective (462), dizziness (347), fatigue (202), nausea (198), headache (155), somnolence (155), off-label use (132), rash (106), vomiting (97), malaise (88), and depression (83). The most frequently reported adverse drug reactions in cases compatible with an exposure to LCM as monotherapy were all listed in the Vimpat EU SmPC.

2.6.1. Discussion on clinical safety

To support the present application, the MAH provided safety data from the pivotal phase 3 trial SP0993 and from the three supportive studies SP0994, SP902 and SP904 as well as post-marketing data. In the supportive study SP902 (conversion to monotherapy) most patients were taking concomitant AEDs and the maximum LCM dose was 400 mg/day. For these reasons the safety assessment of this application focused on the pivotal study (SP0993) and its long term extension SP0994 as well as SP904, the long term extension of the conversion to monotherapy study SP902 in which dose increases up to 800 mg/day were allowed.

The most common adverse reactions of LCM as adjunctive therapy of POS are related to the CNS and GI tract and include dizziness, headache, nausea and diplopia. A dose-related increase for some of these side effects has been observed. The safety observations in the POS monotherapy study SP0993 and its long term extension SP0994, as well as study SP904 indicated a generally similar safety profile of LCM as previously been reported in the POS add-on studies.

In study SP0993, TEAEs occurred with similar frequency in both treatment groups (73.9% vs 75.1% in the LCM and CBZ-CR group, respectively). The safety profile appeared slightly more favourable in the LCM arm compared to the CBZ-CR arm, with a lower frequency of SAEs (7.2% vs 9.7%), TEAEs leading to discontinuation (10.6% vs 15.6%), TEAEs considered drug related (37.2% vs 45.9%), and severe TEAEs (6.8% vs 9.5%). One death occurred in each treatment group, but none of these cases was considered related to study medication. Few treatment-emergent laboratory abnormalities and TEAEs related to laboratory abnormalities occurred including events of abnormal liver function test and hypercholesterinaemia, which were reported at a higher frequency in the CBZ-CR group compared to the LCM group.

Eight subjects (1.8%) reported TEAEs of weight decreased in the LCM treatment group in study SP0993 compared to 2 subjects (0.5%) in the CBZ-CR treatment group. Three of the eight events that occurred in the LCM treatment group were considered drug related by the investigator. In SP904, 9 subjects (2.8%) reported 9 TEAEs of weight decreased. All these events of weight decreased were considered mild to moderate in intensity, and none of the events were serious or led to study discontinuation. In most of the cases the subject recovered from the event, although LCM treatment dose continued unchanged. The MAH furthermore clarified that all cases were confounded either by a comorbidity of overweight [body mass index (BMI) of 25 to 29.9 kg/m^2] or obesity (BMI ≥30 kg/m^2) at Baseline, or relevant medical history. For these reasons, the CHMP was of the view that no signal emerged from the available data requiring an update of the safety information.

One SAE of dyskinesia occurred and was considered by the investigator as probably related to LCM. Overall, in study SP0993 and SP904, 4 TEAEs of dyskinesia were reported, but apart from the serious case, the other 3 events had cofounding factors or possible alternative explanations for the occurrence of movement disorders. The CHMP therefore concluded that, at the time of this report, the available data

were too limited to confirm a causal relationship of this adverse event with LCM.

All TEAEs leading to discontinuation in at least 3 subjects in the LCM treatment group with onset during the Treatment Period in study SP0993 (dizziness, rash, vertigo, AST increased) were known adverse reactions for Vimpat, apart from anxiety, which led to study drug discontinuation in two subjects (0.5%). One of these events was classified as drug related by the investigator and the other was considered not related. Overall, 14 events of anxiety occurred in 11 subjects (2.5%) in study SP0993. In study SP904, TEAEs of anxiety were observed in 5.5% of subjects while on LCM monotherapy (n=16). However, no clear causal relationship could be established due to confounding by medical history, resolution of the events while LCM continued or a negative de-challenge. Furthermore, anxiety is a frequent co-morbidity in epilepsy (Rai et al., 2012).

The incidence of syncope was higher in the monotherapy study SP0993 (1.6%) than in previous adjunctive therapy studies (0.1 %). Most syncope cases (n=3) occurred on doses of 200 mg/day and 400 mg/day (n=2). The remaining two cases occurred in patients on 100 mg/day (n=1) and 600 mg/day (n=1) LCM doses, respectively. In order to clarify if syncope episodes had a clear cardiac origin, available ECG data from subjects with syncopal episodes were reviewed. Only in two cases was an ECG performed on the same day when the syncope occurred. Of the 7 cases, only in one instance was a cardiac syncope suspected, based on ECG findings of first degree AV block and left anterior hemi-block emerging during the treatment period. For most cases there was no evidence of an underlying cardiac conduction disorder. No clear explanation as to why syncope was more frequent in SP0993 than in previous POS add-on studies was identified and there was no clear pattern in the subjects' demographics or medical history that could represent a distinctive risk. However, a longer exposure in SP0993 may have contributed to the difference, since 4 out of 7 cases occurred after day 126.

Cardiac adverse events that may be potentially associated with PR interval prolongation and sodium channel modulation are known to occur with LCM use and are already listed as an important identified risk in the RMP of Vimpat. Furthermore, Vimpat is contraindicated in patients with second- or third-degree AV block and a warning statement is included in section 4.4 of the SmPC. SmPC section 4.8 already describes syncope as an example of adverse reactions associated with PR prolongation. However, it had not been included in the table of adverse reactions. The CHMP agreed that, based on the available cumulative data, an update of the tabulated list of adverse reactions to include syncope was adequate. The incidence rate was determined as uncommon based on the results of pooled adjunctive therapy clinical trials with LCM, which is in line with the SmPC guideline. Further information on the observed incidence of syncope in the monotherapy trial was included in the section 'Description of selected adverse reactions' in SmPC section 4.8.

Overall, the cases of PR interval prolongation observed in the pivotal study SP0993 and supporting studies appeared to be of limited clinical concern. The data in the monotherapy setting suggest a dose-dependent increase in ECG abnormalities including PR prolongation, as has previously been observed under add-on treatment (see also discussion on posology, maximum daily dose below). Furthermore, post-marketing data showed that among 323 cardiac AEs potentially associated with PR interval prolongation, 246 (76%) were reported as serious and six (1.8%) had a fatal outcome. A cumulative review of post-marketing cases compatible with LCM monotherapy use suggested that a considerable amount of cardiac-related TEAEs occurred in patients with pre-existing cardiac disorders. Furthermore, one third of the reports occurred in elderly patients (>65 years of age). In most cases, decrease of LCM dose or LCM discontinuation coincided with an improvement or a complete recovery of the cardiac-related TEAEs. Based on these data, the CHMP was of the view that the current warning in SmPC section 4.4 should be updated to clarify that the incidence of PR prolongation increased with dose and that monitoring is advised in patients at risk of developing cardiac-related AEs under treatment with LCM. These include patients with known conduction problems, severe cardiac disease, elderly patients, or patients using concomitant medicinal products known to be associated with PR prolongation. In these

patients, it should be considered to perform an ECG before LCM dose increase above 400 mg/day and after LCM is titrated to steady-state.

With regards to elderly patients, the MAH provided data on ECG abnormalities and treatment emergent abnormal ECG findings by age category (<65 vs ≥65 years). As expected, in all studies (SP0993, SP0994 and SP904) higher percentages of subjects ≥65 years presented treatment emergent abnormalities in PR and QRS interval as well as heart rate compared to subjects < 65 years of age, both in the LCM and CBZ-CR treatment groups. The warning statement in SmPC section 4.4 on PR prolongation already advises caution for the treatment of elderly patients due to an increased risk of cardiac complication (see also discussion above on the need for monitoring). In addition, the CHMP requested that information should be provided in SmPC section 4.8 to describe relevant safety findings in the elderly, including adverse reactions occurring at an increased frequency in patients aged ≥65 years compared to younger adult patients. In addition to the cardiac-related adverse reaction of first degree AV block, these included fall, diarrhoea and tremor. Also, discontinuations due to TEAEs were observed more frequently in the elderly.

Posology

In order to support a LCM starting dose of 100 mg twice a day (200 mg/day) for POS monotherapy, the MAH performed additional analyses comparing rates of TEAEs during and immediately after titration of LCM starting at 200 mg/day (study SP902) versus 100 mg/day (study SP0993 and add-on study pool). The incidence of TEAEs was slightly higher when treatment was initiated at 200 mg twice a day (41.2% in study SP902) compared to patients receiving a starting dose of 100mg/day (31.1% in study SP0993 and 37.3%, in the add-on study pool). The same was true for the incidence of the most common TEAEs in study SP902 and SP0993 (dizziness 8.2% vs 5.6%; nausea 6.4% vs 2.0%, fatigue 5.4% vs 3.8%, somnolence 4.2% vs 3.2%, dry mouth 3.5% vs 0.2%).

The CHMP acknowledged that the differences in tolerability were small and that patients in study SP902 and the add-on trials also received other AEDs, which may explain the increased TEAE rates at least to some extent. However, based on the available data at the time of this report and in line with common clinical practice in epilepsy therapy, the CHMP was of the view that it was preferable to maintain the currently recommended starting dose of 50 mg LCM twice a day (100mg/day) which should be increased to an initial therapeutic dose of 100 mg LCM twice a day (200 mg/day) after one week. A higher starting dose of 100 mg LCM twice a day (200mg/day) could be considered at the possible expense of a worse safety profile in case of a clinical need to quickly reach optimum control of seizures. The choice of the starting dose should be based on the physician's assessment of required seizure reduction versus potential side effects thus taking into account the individual patient's needs. The possibility to use a loading dose (i.e. 200 mg LCM single dose followed by 100 mg LCM after 12 hours) in selected cases has already been agreed in the adjunctive therapy setting and the CHMP considered the approach to be also valid for monotherapy.

With regards to the proposed maximum daily dose of 600 mg LCM, the CHMP noted that this dose had been refused during the initial approval of Vimpat in the EU for POS add-on therapy as a dose-dependent increase in the incidence of some side effects has been observed. Furthermore, the results of the clinical pharmacology trials provided with the initial marketing authorisation application showed a dose-related increase in mean PR interval. In a QT study, the time of the maximum observed mean PR interval correlated to Tmax. The placebo-subtracted increase at 1 hour post-dose was 7.3 ms for the Vimpat 400 mg/day group and 11.9 ms for the Vimpat 800 mg/day group. The frequency of first degree AV block was 5.6 % in the placebo group and 3.6 % in the Vimpat 400 mg/day group but increased considerably in the Vimpat 800 mg/day group (21.2 %).

Data in the monotherapy setting also suggest a dose-dependent increase in ECG abnormalities including PR prolongation (see also previous discussion in this regard). In addition, a dose-related increase was observed for other side effects, including the common TEAEs fatigue and nasopharyngitis. For some less

common TEAEs in SP0993, there was also a dose-related increase in the reporting rates (defined as a doubling of incidence between target dose level 1 and 3 and increase in a dose-dependent manner). These TEAEs included visual impairment, fatigue, gait disturbance, bronchitis, sinusitis, myalgia, balance disorder, disturbance in attention, hypoaesthesia, memory impairment, syncope, metrorrhagia, and pruritus. However, only approximately 10% of patients in study SP0993 increased the dose to 600 mg/day and consequently the safety data were difficult to evaluate in terms of dose-relationship. Furthermore, in study SP0993, only 2/43 (4.7%) of subjects in the LCM 600 mg/ day group discontinued due to AEs, compared to 4/33 (12.1%) in the CBZ-CR 1200 mg/day group, and a dose reduction at dose level 3 was only required by 5/43 (11.6%) of subjects at LCM 600 mg/ day, compared to 5/33 (15.2%) of subjects at CBZ-CR 1200 mg/ day. These findings suggest that LCM at the highest dose level was generally tolerated. Finally, the design of study SP0993 was different from previous force titration in the add-on trials: in study SP0993 subjects escalated only when required, i.e. when seizure occurred, similarly to clinical practice, where dose escalation is decided upon clinical need/response and tolerability.

Overall, a maximum maintenance dose of 600mg/day for monotherapy was considered acceptable by the CHMP. However, as previously discussed, given the observed dose-dependent increase in ECG abnormalities, the CHMP was of the view that it should be considered to perform an ECG before dose increases above LCM 400 mg/day in patients at risk of developing cardiac AEs. In addition, reference to the need for monitoring in case of doses above 400 mg/day should be made in SmPC section 4.2 for the solution for infusion. This is in light of the fact that, while bioequivalence has previously been shown between the tablet formulation and 30 or 60 minutes intravenous infusion, a 20% higher mean c_{max} was obtained when the infusion was administered more rapidly, i.e. over 15 minutes. While data presented previously with the initial marketing authorisation application had not shown an increase in cardiac events when LCM was administrated intravenously at doses of 200 to 800 mg/day over 30, 15 and 10 minutes, considering the limited amount of safety data for single infusions >200 mg LCM and since up to 300 mg LCM per single infusion will be possible in monotherapy, an infusion duration of at least 30 minutes in such cases is preferred.

2.6.2. Conclusions on clinical safety

Overall, the safety data obtained from the monotherapy study SP0993 and its long-term extension SP0994 indicate a similar safety profile of LCM as has previously been reported for use in POS add-on treatment. Based on updates of the safety information in the SmPC including a recommendation to consider ECG monitoring before a LCM dose increase above 400 mg/day and after LCM is titrated to steady-state, the CHMP was of the view that the available data were adequate to support the extension of the indication of Vimpat to monotherapy in the treatment of POS with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy. Monotherapy should be initiated with a starting dose of 50 mg LCM twice a day (100 mg/day) and may be increased up to a maximum maintenance dose of 600 mg/day. A higher starting dose of 100 mg LCM twice a day (200mg/day) may be considered based on the physician's assessment of individual patient's needs.

2.6.3. PSUR cycle

The PSUR cycle remains unchanged.

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

The CHMP endorsed RMP version 11.1 with the following content:

Safety concerns

No new safety concerns have been identified within this extension of indication. Ongoing safety concerns based on cumulative non-clinical and clinical data, during the conduct of the LCM clinical development program and post-marketing experience are presented below.

Table 20 – Summary of Safety Concerns

Important identified risks	• Cardiac AEs that may be potentially associated with PR interval prolongation and sodium channel modulation • Suicidality • Dizziness
Important potential risks	• Potential for hepatoxicity • Potential for worsening of seizures • Potential for abuse as a CNS-active product • Potential for off-label use of a loading dose in acute conditions such as status epilepticus
Missing information	• Pregnant or lactating women • Pediatric patients

Pharmacovigilance plan

No new pharmacovigilance activity was requested in the context of this extension of indication.

Risk minimisation measures

The changes made within the procedure are highlighted in bold:

Table 21 - Summary table of risk minimization measures

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Cardiac AEs that may be potentially associated with PR interval prolongation and sodium channel modulation	**Available by prescription only.** **SmPC Section 4.2, Posology and method of administration (iv formulation)** SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use informs of conduction and rhythm related data from clinical studies and postmarketing. 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.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Suicidality	**Available by prescription only.** **Packaging** SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects	None
Dizziness	**Available by prescription only.** **SmPC Section 4.2, Posology and method of administration** SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.7, Effects on ability to drive and use machines SmPC Section 4.8, Undesirable effects A Type II variation about loading dose has received a positive opinion and contains a statement in Section 4.2, Posology and method of administration, of the SmPC that loading dose should be administered under medical supervision for increased incidence of CNS adverse reactions such as dizziness. Furthermore, Section 4.8, Undesirable effects, of the SmPC states that the incidence of CNS adverse reactions such as dizziness may be higher after a loading dose.	None
Potential for hepatotoxicity	**Available by prescription only.** SmPC Section 4.8, Undesirable effects SmPC Section 5.3, Preclinical safety data	None
Potential for worsening of seizures	Available by prescription only	None
Potential for abuse as a CNS-active product	**Available by prescription only.** **Packaging** SmPC Section 4.8, Undesirable effects:	None
Potential for off-label use of a loading dose in acute conditions such as status epilepticus	**Available by prescription only.** SmPC Section 4.2, Posology and method of administration:	None
Pregnant or lactating women	**Available by prescription only.** SmPC Section 4.6, Fertility, pregnancy and lactation SmPC Section 5.3, Preclinical safety data	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Pediatric patients	**Available by prescription only.** SmPC Section 4.2, Posology and method of administration	None

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC have been updated for all Vimpat presentations. The warning statement in SmPC section 4.4 in relation to cardiac rhythm and conduction was updated to clarify that there was a dose-relationship in the observed cases of PR prolongation and that monitoring is advised in patients at risk of developing cardiac-related AEs under treatment with LCM.

The full product information is available in Attachment 1.

(i) Vimpat tablets and syrup

Changes to SmPC sections 4.1, 4.2 and 4.4 of the tablets and syrup presentations are shown below (additions in **bold and underlined**, deletions in ~~strike-through~~):

- SmPC section 4.1 - Therapeutic indications

Vimpat is indicated as **monotherapy and** adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

- SmPC section 4.2 – Posology and method of administration

Posology

Lacosamide must be taken twice a day (usually once in the morning and once in the evening). Lacosamide may be taken with or without food.

Monotherapy

The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).

In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy

~~Lacosamide must be taken twice a day (usually once in the morning and once in the evening).~~ The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

~~Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.~~

Depending on response and tolerability, the maintenance dose can be further increased **at weekly intervals by 50 mg twice a day (100 mg/day)** ~~by 50 mg twice a day every week~~, **up** to a maximum recommended daily dose of 400 mg (200 mg twice a day). ~~Lacosamide may be taken with or without food.~~

Initiation of lacosamide treatment with a loading dose

Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation

In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly ~~*Older people*~~ *(over 65 years of age)*

No dose reduction is necessary in elderly patients. ~~The experience with lacosamide in elderly patients with epilepsy is limited.~~ Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). **There is limited clinical epilepsy data in the elderly, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8 and 5.1).**

(…)

- SmPC section 4.4 - Special warnings and precautions for use

Cardiac rhythm and conduction

Dose-related p~~P~~rolongations in PR interval with lacosamide have been observed in clinical studies. Lacosamide should be used with caution in patients with known conduction problems**,** ~~or~~ severe cardiac disease ~~such as a~~**(e.g.** history of myocardial infarction or heart failure**)**. ~~Caution should especially be exerted when treating~~**, in** elderly patients, ~~as they may be at an increased risk of cardiac disorders~~ or when lacosamide is used in combination with products known to be associated with PR prolongation.

In these patients it should be considered to perform an ECG before a lacosamide dose increase above 400mg/day and after lacosamide is titrated to steady-state.

(ii) Vimpat solution for infusion

The SmPC of the solution for injection was updated accordingly, but the wording in section 4.2 of the SmPC was slightly different from the tablets and the syrup. Changes to SmPC section 4.2 of the solution for injection are summarised below (additions in **bold and underlined**, deletions in ~~strike-through~~):

- SmPC section 4.2 – Posology and method of administration

Posology

Lacosamide therapy can be initiated with either oral or i.v. administration. Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with i.v. lacosamide is at the physician's discretion; there is experience from clinical trials with twice daily infusions of lacosamide for up to 5 days in adjunctive therapy. Monitor closely patients with known cardiac conduction problems, on concomitant medications that prolong PR interval, or with severe cardiac disease (e.g. myocardial ischemia, heart failure) when lacosamide dose is higher than 400 mg/day (see Method of administration below and section 4.4).

Lacosamide must be taken twice a day (usually once in the morning and once in the evening).

Monotherapy

The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

Lacosamide can also be initiated at the dose of 100 mg twice a day based on the physician's assessment of required seizure reduction versus potential side effects.

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50 mg twice a day (100 mg/day), up to a maximum recommended maintenance daily dose of 300 mg twice a day (600 mg/day).

In patients having reached a dose greater than 400mg/day and who need an additional antiepileptic drug, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy

~~Lacosamide therapy can be initiated with either oral or i.v. administration. Solution for infusion is an alternative for patients when oral administration is temporarily not feasible. The overall duration of treatment with i.v. lacosamide is at the physician's discretion; there is experience from clinical trials with twice daily infusions of lacosamide for up to 5 days~~

~~Lacosamide must be administered twice a day (usually once in the morning and once in the evening).~~ The recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after one week.

~~Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.~~

Depending on response and tolerability, the maintenance dose can be further increased **at weekly**

intervals by 50 mg twice a day (100 mg/day)~~by 50 mg twice a day every week~~, **up** to a maximum recommended daily dose of 400 mg (200 mg twice a day).

Initiation of lacosamide treatment with a loading dose

Lacosamide treatment may also be initiated with a single loading dose of 200 mg, followed approximately 12 hours later by a 100 mg twice daily (200 mg/day) maintenance dose regimen. Subsequent dose adjustments should be performed according to individual response and tolerability as described above. A loading dose may be initiated in patients in situations when the physician determines that rapid attainment of lacosamide steady state plasma concentration and therapeutic effect is warranted. It should be administered under medical supervision with consideration of the potential for increased incidence of central nervous system adverse reactions (see section 4.8). Administration of a loading dose has not been studied in acute conditions such as status epilepticus

Discontinuation

In accordance with current clinical practice, if lacosamide has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week).

Special populations

Elderly ~~*Older people*~~ *(over 65 years of age)*

No dose reduction is necessary in elderly patients. ~~The experience with lacosamide in elderly patients with epilepsy is limited.~~ Age associated decreased renal clearance with an increase in AUC levels should be considered in elderly patients (see following paragraph 'renal impairment' and section 5.2). **There is limited clinical epilepsy data in the elderly, particularly at doses greater than 400 mg/day (see sections 4.4, 4.8 and 5.1).**

(…)

Method of administration

Product with particulate matter or discolouration should not be used.

The solution for infusion is infused over a period of 15 to 60 minutes twice daily. **An infusion duration of at least 30 minutes for administration >200 mg per infusion (i.e. >400 mg/day) is preferred.**

Changes were also made to the PI including Annex II and Annex IIIA to bring it in line with the current Agency/QRD template, and the SmPC guideline, which were reviewed and accepted by the CHMP. There were also some editorial changes made.

The Package Leaflet has been updated accordingly. The Package Leaflet of Vimpat solution for infusion has been updated with information specific to the medical or healthcare professionals in line with approved information on shelf-life and handling of the solution for infusion in section 6 of the SmPC.

3. Benefit-Risk Balance

Benefits

Beneficial effects

With this application, the MAH proposed an extension of the indication for Vimpat from POS add-on treatment to monotherapy of POS in adults and adolescents (16-18 years) with or without secondary generalisation. Despite the approval of several AEDs for use in the adjuvant therapy of POS in recent years, there is still a need for additional monotherapy options to optimise individual epilepsy treatment. This reflects the fact that usually new AEDs are first studied in add-on trials in refractory epilepsy patients, so that development for monotherapy in newly diagnosed patients is often delayed.

To support the application, one pivotal efficacy and safety study SP0993 was conducted. In this study LCM was compared with CBZ-CR at three dose levels using a non-inferiority design, in line with the CHMP epilepsy guideline. The primary efficacy variable in SP0993 was the proportion of subjects remaining seizure fee for 6 consecutive months of treatment following stabilisation at the last evaluated dose. The results for LCM and CBZ-CR were similar with 89.8% (86.8%, 92.8%) and 91.1% (88.2%, 94.0%) of seizure free patients (PPS, stratified KM estimate, 95% CI), respectively. The difference between treatment groups was -1.3% and the lower limit of the 95% CI (-5.3%, 2.7%) was within the pre-specified non-inferiority margin of -12%. Analysis on the FAS as well as all sensitivity analyses supported non-inferiority of LCM compared to CBZ-CR. Subgroup analyses for subjects with history of Type IC seizures, history of Type IC or Type IIE seizures, and Type IIE seizures only also showed similar results, supporting robustness of the primary study outcome, although non-inferiority was not assessed due to the small subgroup sample sizes.

Maintenance of efficacy was assessed by evaluating 12 month seizure freedom rates. The stratified KM estimate (95% CI) of the proportion of subjects who were seizure free for 12 months was 77.8% (73.4%, 82.2%) and 82.7% (78.5%, 86.8%) in the LCM and the CBZ-CR treatment group, respectively. The difference in stratified seizure-freedom rate between the LCM and CBZ-CR treatment groups was -4.9% and the lower limit of the CI (-10.9%, 1.1%) was within the non-inferiority margin.

In study SP0993, patients were allowed to receive daily LCM doses up to 600 mg. Approximately 10% of the patients in the LCM study arm were escalated to the 600 mg dose level (9.7%), and 44.2% (19/43) of these achieved seizure freedom for a period of 6 months, which was a similar result compared to the maximum CBZ-CR dose level1200 mg/day (39.4%, 13/33). This suggests that there were a limited number of patients who benefitted from higher doses of LCM to achieve optimum control of seizures. Based on the study results and in line with clinical practice, whereby any given AED for epilepsy monotherapy should first be up-titrated to the maximum tolerated dose before switching to another AED or adding a second AED, LCM doses up to a maximum maintenance dose of 600 mg/day were considered acceptable by the CHMP.

Uncertainty in the knowledge about the beneficial effects

The non-inferiority margin was large and although eventually accepted by the CHMP given the study results and the justification by the MAH considering a relative difference of more than 20% to be clinically important, a tighter margin would have been preferred. At the same time, the seizure freedom rates in the primary efficacy analyses were high and the CHMP considered that the primary analysis may have overestimated the success rates due to censoring of patients. Estimates of the proportion of subjects being seizure-free for 6 months considering discontinuation as failures were however still high with approximately 70-75% of patients in either treatment group for both the FAS and the PPS and still higher than initially expected (60%) for the purpose of the statistical analysis. Nevertheless, reassurance on the

non-inferiority conclusion was obtained from the fact that generally similar proportions of seizure free patients were observed for both treatment arms, the lower bound of the CI for the difference between treatment groups for the primary endpoint was well within the -12% margin, and since sensitivity and subgroup analyses supported robustness of the primary efficacy analysis.

With regards to long-term efficacy data, while again the study results supported non-inferiority of LCM compared to CBZ-CR, the CHMP noted that the crude proportions of subjects with seizures were higher, in both strata (past 3-month seizure count of ≤2 and >2) with LCM than with CBZ-CR. However, when accounting for censoring, which occurred to a greater extent in the control arm, by treating study subjects who discontinued as failures, the estimates of proportion of subjects who were seizure free for 12 months were very similar with 59.5% for LCM and 59.3% for CBZ-CR.

Risks

Unfavourable effects

At the time of this application, the most common known adverse reactions with LCM as adjunctive treatment of POS were related to the CNS and the GI tract. They include dizziness, headache, nausea and diplopia and a dose-related increase for some of these events has been observed. The use of LCM is furthermore associated with dose-related increase in the PR interval and related adverse reactions including AV block, syncope, and bradycardia. This has been reflected as an important identified risk in the RMP of Vimpat. Other important identified risks are suicidality and dizziness. Furthermore, abnormalities in liver function tests have been observed in controlled trials with LCM in adult patients with POS who were taking 1 to 3 concomitant AEDs and the RMP lists the potential for hepatotoxicity as an important potential risk.

Overall, the safety results of the monotherapy study SP0993 and its extension SP0994 as well as study SP904 were consistent with the safety profile of LCM previously observed in the adjuvant setting. With regards to the comparator CBZ-CR in the pivotal trial, the safety profile of LCM appeared slightly more favourable with a lower frequency of SAEs (7.2% vs 9.7%), TEAEs leading to discontinuation (10.6% vs 15.6%), TEAEs considered drug related (37.2% vs 45.9%), and severe TEAEs (6.8% vs 9.5%).

The incidence of syncope was higher in the monotherapy study SP0993 (1.6%) than in previous adjunctive therapy studies (0.1 %). There was no unequivocal explanation for this finding, but a longer exposure in the monotherapy setting was proposed to have contributed to the difference.

Cardiac adverse events that may be potentially associated with PR interval prolongation and sodium channel modulation are known to occur with LCM use and this is reflected as an important identified risk in the RMP of Vimpat. Furthermore, Vimpat is contraindicated in patients with second- or third-degree AV block and the SmPC includes a warning statement in relation to cardiac rhythm and conduction in section 4.4. The CHMP noted that syncope was already listed as an example of adverse reactions associated with PR prolongation in SmPC section 4.8. The CHMP consequently agreed that an update of the tabulated list of adverse reactions to include syncope was adequate.

Overall, the cases of PR interval prolongation observed in the pivotal study SP0993 and supporting studies appeared to be of limited clinical concern. However, as previously observed in the add-on setting, data from the pivotal monotherapy trial showed a dose-dependent increase in ECG abnormalities including PR prolongation. Furthermore, post-marketing data suggested that a considerable amount of cardiac-related TEAEs occurred in patients with pre-existing cardiac disorders and the vast majority of the reported cardiac AEs were serious in nature. Based on these data, the CHMP was of the view that SmPC section 4.4 should be updated to clarify that there was a dose-depended increase in cases of PR prolongation and that it should be considered to perform an ECG before dose increase above 400 mg/day and after LCM is titrated to steady-state in patients at risk of developing cardiac-related AEs.

As for the starting dose, the available data suggested a higher incidence of TEAEs during the first 2 weeks after treatment initiation with LCM 200 mg/day compared to LCM 100 mg/day. Although the differences in tolerability were small, the CHMP was of the view that a starting dose of 50 mg LCM twice a day (100 mg/day) was preferable, which is also in line with common clinical practice in epilepsy therapy. A higher initial dose of 100 mg LCM twice a day (200 mg/day) could be considered if there is a clinical need to rapidly achieve optimum seizure control. The choice of the starting dose should be based on the physician's assessment of required seizure reduction versus potential side effects taking into account the individual patient's needs. The possibility to use a loading dose (i.e. 200 mg LCM single dose followed by 100 mg LCM after 12 hours) in selected cases and under medical supervision has already been agreed in the adjunctive therapy setting and the CHMP considered that this approach was also valid for monotherapy.

The CHMP was furthermore of the view that additional information should be added to SmPC section 4.8 to describe findings of adverse reactions in the elderly, including those occurring at an increased frequency compared to younger adults. In addition to the cardiac-related adverse reaction first degree AV block, adverse reactions reported at a higher incidence (≥5% difference) in patients aged ≥ 65 years compared to younger adult patients included fall, diarrhoea and tremor. Also, discontinuations due to TEAEs were observed more frequently in the elderly.

Uncertainty in the knowledge about the unfavourable effects

Among the common TEAEs, fatigue and nasopharyngitis showed a dose-related increase. Other TEAEs with a significant increase [defined as a doubling of incidence between dose level 1 (100 mg/day) and 3 (600 mg/day) and increasing in a dose-dependent manner] in incident rate in the LCM group included visual impairment, fatigue, gait disturbance, bronchitis, sinusitis, myalgia, balance disorder, disturbance in attention, hypoaesthesia, memory impairment, syncope, metrorrhagia and pruritus. A dose-dependent increase for PR prolongation was also observed. The CHMP therefore questioned the safety of the proposed highest daily maintenance dose of 600 mg LCM. However, the number of patients in the pivotal study SP0993 and in its extension exposed to LCM 600 mg/day for longer periods of time was limited (44 patients in study SP0993 with a median LCM exposure of slightly less than 4 months; 25 patients in study SP0994 with a median LCM exposure of 6 months), and did not allow for a reliable estimate of the incidence of side effects at this dose level. Furthermore, only few patients who were escalated to the LCM 600 mg/day dose level in study SP0993 discontinued due to AEs (2/43, 4.7%) or required dose reduction (5/43, 11.6%) and the rates were lower compared to CBZ-CR 1200 mg/day. These findings suggested that LCM at the highest dose level was tolerated.

For these reasons the CHMP agreed that maximum daily dose of 600 g/day acceptable, but the Committee was of the view that ECG monitoring should be considered in certain cases. Reference to the possible need for monitoring in before dose increases above 400 mg/day should be made in SmPC section 4.2 for the solution for infusion. This is in light of the fact that a 20% higher mean c_{max} was observed in previous studies when the infusion was administered over a period of 15 minutes, the most rapid approved period for infusion. Considering the limited amount of safety data for single infusions >200 mg LCM and since up to 300 mg LCM per single infusion will be possible in monotherapy, an infusion duration of at least 30 minutes in such cases is preferred. The product information was updated accordingly.

Effects Table

Table 21 - Effects Table for Vimpat (LCM) for monotherapy of POS with or without secondary generalisation in adults and adolescents (16-18 years)

Effect	Short Description	Unit	LCM	CBZ-CR	Uncertainties / Strength of evidence	Ref.

Effect	Short Description	Unit	LCM	CBZ-CR	Uncertainties/ Strength of evidence	Ref.
Favourable Effects						
Seizure freedom	Proportion of subjects remaining seizure free following stabilisation at the last evaluated dose	% (CI) 6 months 12 months	 PPS: 91.5 (88.6, 94.3) FAS: 89.8 (86.8, 92.8) FAS: 77.8 (73.4, 82.2)	 PPS: 92.8 (90.0, 95.5) FAS: 91.1 (88.2, 94.0) FAS: 82.7 (78.5, 86.8)	Lower limit of the CI was within the pre-specified limit of -12%. Robustness of results was supported by sensitivity analyses.	Study SP0993
Unfavourable Effects						
CNS AEs	Dizziness		11.7	8.6		Study SP0993
	Fatigue		7.2	10.4		
Cardiac AEs	PR prolongation >200 ms >220 ms		 9.6 3.7	 8.9 3.0		Study SP0993
	Syncope		1.6	0.2		
Suicidality [(1)]			1.1	0.9		Study SP0993
Abnormal liver function test	ALT increased		1.8	3.4		Study SP0993
	GGT increased		1.6	8.1		

AE: adverse event, ALT: alanine aminotransferase, CBZ-CR: carbamazepine controlled release, CI: 95% confidence interval, FAS: Full analysis set, GGT: gamma glutamyl transferase, LCM: lacosamide, PPS: Per protocol set, Ref.: reference.

[(1)] Suicidality related terms were: completed suicide, depression suicidal, suicidal behaviour, suicidal ideation, suicide attempt, intentional self-injury, self-injurious behaviour, self-injurious ideation, intentional overdose, multiple drug overdose intentional, and poisoning deliberate.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

At the time of this report, LCM had already been approved for adjunctive therapy of POS. With the present application, the MAH sought approval of LCM for POS monotherapy. The clinical development plan is thus in line with the CHMP epilepsy guideline (CHMP/EWP/566/Rev.2/Corr), which states that once efficacy of an AED in combination with other AEDs has been determined, it is important to evaluate the efficacy of the product in the monotherapy setting. Monotherapy of epilepsy can give certain advantages for patients when compared with adjunctive therapy including improved patient compliance as well as a decreased risk for drug interactions and better tolerability.

Use of LCM in POS monotherapy was supported by a single pivotal clinical trial in newly/recently diagnosed patients, which was conducted in line with the epilepsy guideline. The study showed that LCM monotherapy up to a maximum maintenance dose of 600 mg/day was non-inferior to CBZ-CR with regards to achieving seizure freedom for a period of 6 months. Both treatments prevented seizures in approximately 90% of the patients. The difference between treatments was -1.3% and the lower limit of the 95% CI was within the pre-specified non-inferiority margin of -12%. Sensitivity and subgroup analyses supported the robustness of the primary efficacy analysis. Long-term data and the results for secondary efficacy variables were generally in line with the primary study outcome. Given that prevention of seizures is the ultimate objective of any anti-seizure treatments and taking into account that CBZ represents the standard-of care for POS being widely used as first-line treatment option in clinical

practice, demonstration of non-inferiority of LCM to CBZ in achieving 6 months seizure freedom is of clinical relevance.

The safety data from the POS monotherapy studies were generally consistent with the known safety profile as previously reported in studies in epilepsy patients with refractory POS where LCM was used in combination with other AEDs. The safety profile of LCM appeared slightly more favourable compared to CBZ-CR. Important identified risks of LCM (cardiac AEs, suicidality and dizziness) as well as important potential risks including hepatotoxicity, as currently described in the RMP, remain unchanged. A dose dependent increase in some AEs was observed including PR prolongation, but overall the data suggested that doses up to 600 mg/day were generally tolerated. Nevertheless, in patients at risk of developing cardiac adverse reactions, it should be considered to perform an ECG before dose increases above LCM 400 mg/day and after LCM is titrated to steady-state. Furthermore, due to increased peak plasma concentration previously observed for the solution for injection when the infusion duration was short (i.e. 15 minutes), an infusion duration of at least 30 minutes for administration of doses >200 mg LCM per infusion (i.e. >400 mg/day) is preferred.

Initial dose titration starting at 100 mg/day appeared to be slightly better tolerated compared to a starting dose of 200 mg/day, and was thus recommended by the CHMP for treatment initiation. A higher initial dose of 200 mg/day could be considered at the expense of a possibly worse safety profile, based on the physician's assessment of individual patient's needs if there is a clinical need to rapidly achieve optimum seizure control.

Benefit-risk balance

There is a clear need for additional effective monotherapy options in epilepsy in order to allow optimised treatment at an individual patient level. Given that a clinically relevant effect of LCM has been shown by demonstrating non-inferiority to CBZ-CR in achieving seizure freedom in recently diagnosed epilepsy patients, and since LCM treatment was overall well tolerated in this population up to a maximum maintenance dose of 600 mg/day, the CHMP considered that the benefits of LCM monotherapy in the treatment of POS with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy outweighed its risks.

Subject to updates of the product information, including a recommendation to consider an ECG before LCM dose increases above 400 mg/day and after LCM is titrated to steady-state, the CHMP concluded that the benefit-risk balance was positive.

Additional considerations on the benefit-risk balance

Not applicable.

4. Recommendations

Outcome

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

Variations 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	Type II	I, II, IIIA and IIIB

	approved one		
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None
B.I.b.2.a	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	Type IA	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IA	None
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None

Extension of Indication to extend the indication of Vimpat to monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy.

As a consequence sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated. The warning in SmPC section 4.4 in relation to cardiac rhythm and conduction was updated to clarify that a dose-relationship in the observed cases of PR prolongation has been observed and that monitoring is advised in patients at risk of developing cardiac-related adverse reactions under treatment with LCM.

The Package Leaflet is updated in accordance. The Package Leaflet of Vimpat solution for infusion has furthermore been updated with information specific to the medical or healthcare professionals in line with approved information on shelf-life and handling of the solution for infusion in section 6 of the SmPC.

In addition, the MAH took the opportunity to update the PI in line with the latest QRD template. Furthermore, the MAH made a few editorial amendments throughout the PI.

The group of variations leads to amendments to the SmPC, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

The MAH grouped the variation with a number of type IA variations which were acceptable.

5. EPAR changes

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

Scope

Extension of Indication to extend the indication of Vimpat to monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent (16-18 years) patients with epilepsy. As a consequence sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated. The warning in SmPC section 4.4 in relation to cardiac rhythm and conduction was updated to clarify that a dose-relationship in PR prolongation has been observed and that it may be appropriate to perform an ECG in patients at risk of developing cardiac-related adverse reactions under treatment with LCM.

The Package Leaflet is updated in accordance. The Package Leaflet of Vimpat solution for infusion has furthermore been updated with information specific to the medical or healthcare professionals in line with approved information on shelf-life and handling of the solution for infusion in section 6 of the SmPC.

In addition, the MAH took the opportunity to update the PI in line with the latest QRD template. Furthermore, the MAH made a few editorial amendments throughout the PI.

Summary

For further information, please refer to the scientific discussion Vimpat EMEA/H/C/00863/II/0060/G.