EU-RISK MANAGEMENT PLAN FOR VIMPAT® (LACOSAMIDE) AND LACOSAMIDE UCB® (LACOSAMIDE)

50MG, 100MG, 150MG, 200MG FILM-COATED TABLETS

10MG/ML SOLUTION FOR INFUSION

10MG/ML SYRUP

Version 17.0

Date: 17 May 2023 STN-2023-01725 (Vimpat)/STN-2023-01726 (Lacosamide UCB)

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) version number: 17.0

Data Lock Point for this RMP: 28 Feb 2023

Date of final sign-off: 17 May 2023

Rationale for submitting an updated RMP:

The milestone for submission of the study report for studies SP848 and EP0034 was reached.

Furthermore, the RMP is updated to include the following:

- Update of Part I to reflect the indication and dosage currently approved
- Incidence and prevalence have been updated to reflect the most recent data under module SI.
- Summary of completed in vitro patch clamp studies to assess Vimpat's inhibitory profile on cardiac sodium channel (NaV1.5), including establishing Vimpat's potency and Vaughan Williams antiarrhythmic drug classification (Food and Drug Administration postmarketing requirement) included under module SII and SVII.
- Clinical trial exposure (as updates to RMP Pool 2 and SPX-1 Pool) and postauthorization exposure (Data Lock Point: 28 Feb 2023) have been updated. Also, relevant sections have been updated in line with this Pool update.
  - SP0967 and SP0969 are to be counted in exposure as "adjunctive studies" and footnoted as pediatric studies; double counting avoided.
  - Completed studies: updated to include SP1042, SP848, EP0034, SP0967.
  - Ongoing studies: updated to note EP0151 (pediatrics) and SP0968 (neonates)
- Study EP0158 details have been removed due to study closure by lack of enrolment in several sections.
- Removal of studies SP848 and EP0034 from the additional pharmacovigilance activities as they were completed and study EP0012 details have been added as applicable in relevant sections
- Sections updated to "Lacosamide is excreted in human breast milk" in case it mentions "It is unknown whether lacosamide is excreted in human breast milk" (as applicable).

Other RMP version under evaluation (if applicable): Not applicable.

Details of the currently approved RMP

Version number: 16.2

Approved with procedure: EMEA/H/C/000863/WS2049/0091 (Vimpat); EMEA/H/C/005243/WS2049/0009 (Lacosamide UCB)

Date of approval (European Commission decision date): 04 Mar 2022 (Vimpat); 24 Feb 2022 (Lacosamide UCB)

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

Please see the electronic signature of the European Economic Area QPPV or his deputy on the last page of this module.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AED	antiepileptic drug
CI	confidence interval
DDD	defined daily dose
DNP	diabetic neuropathic pain
EPAR	European Public Assessment Report
EURAP	European and International Registry of Antiepileptic Drugs in Pregnancy
IQ	intelligence quotient
LCM	lacosamide
NAAPR	North American Antiepileptic Drug Pregnancy Registry
PGTCS	primary generalized tonic-clonic seizure
POS	partial-onset seizure
TEAE	treatment-emergent adverse event
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
SmPC	summary of product characteristics

PART I: PRODUCT(S) OVERVIEW

Table 1–1: Product overview

Active substance(s)	Lacosamide (LCM)
Pharmacotherapeutic group(s)	Other antiepileptics (N03AX18)
Marketing Authorization Holder	UCB Pharma S.A.
Medicinal products to which this Risk Management Plan refers	Vimpat®/Lacosamide UCB®
Invented name(s) in the European Economic Area (EEA)	Vimpat/Lacosamide UCB
Marketing authorization procedure	Centralized procedure
Brief description of the product	The active substance, LCM, is a (R)-2-acetamido-N-benzyl-3-methoxypropionamide.
	The precise mechanism by which LCM exerts its antiepileptic effect in humans remains to be fully elucidated. In vitro electrophysiological studies have shown that LCM selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	**ema-combined-h863en-annotated** (Vimpat) **ema-combined-h5243en-annotated** (Lacosamide UCB)
Indication(s) in the EEA	Current: Vimpat is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy. Vimpat is indicated as adjunctive therapy in the following cases: • Treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy. • Treatment of primary generalized tonic-clonic seizures in adults, adolescents, and children from 4 years of age with idiopathic generalized epilepsy.
	Proposed: None
Dosage in the EEA	Current:

Table 1–1: Product overview

Adolescents and children weighing 50kg or more and adults

Starting dose	Titration (incremental steps)	Maximum recommended dose
Monotherapy: 50mg twice a day (100mg/day) or 100mg twice a day (200mg/day) Adjunctive therapy: 50mg twice a day (100mg/day)	50mg twice a day (100mg/day) at weekly intervals	Monotherapy: up to 300mg twice a day (600mg/day) Adjunctive therapy: up to 200mg twice a day (400mg/day)
Alternate initial dosage[a] (if applicable): 200mg single loading dose followed by 100mg twice a day (200mg/day)		

[a] Patients may be initiated on a loading dose 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 serious cardiac arrhythmia and central nervous system adverse reactions (see Section 4.8 of the Summary of Product Characteristics). Administration of a loading dose has not been studied in acute conditions such as status epilepticus.

Monotherapy (in the treatment of partial-onset seizures)

The recommended starting dose is 50mg twice daily (100mg/day), which should be increased to an initial therapeutic dose of 100mg twice daily (200mg/day) after 1 week.

Lacosamide can also be initiated at the dose of 100mg twice a day (200mg/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 50mg twice a day (100mg/day), up to a maximum recommended daily dose of 300mg twice a day (600mg/day).

In patients having reached a dose greater than 200mg twice a day (400mg/day) and who need an additional antiepileptic medicinal product, the posology that is recommended for adjunctive therapy below should be followed.

Adjunctive therapy (in the treatment of partial-onset seizures or in the treatment of primary generalized tonic-clonic seizures)

The recommended starting dose is 50mg twice a day (100mg/day), which should be increased to an initial therapeutic dose of 100mg twice a day (200mg/day) after 1 week.

Table 1–1: Product overview

Depending on response and tolerability, the maintenance dose can be further increased at weekly intervals by 50mg twice a day (100mg/day), up to a maximum recommended daily dose of 200mg twice a day (400mg/day).

Children from 2 years of age and adolescents weighing less than 50kg

Starting dose	Titration (incremental steps)	Maximum recommended dose
Monotherapy and Adjunctive therapy: 1mg/kg twice a day (2mg/kg/day)	1mg/kg twice a day (2mg/kg/day) at weekly intervals	Monotherapy: • up to 6mg/kg twice a day (12mg/kg/day) in patients weighing ≥10kg to <40kg • up to 5mg/kg twice a day (10mg/kg/day) in patients weighing ≥40kg to <50kg
		Adjunctive therapy: • up to 6mg/kg twice a day (12mg/kg/day) in patients weighing ≥10kg to <20kg • up to 5mg/kg twice a day (10mg/kg/day) in patients weighing ≥20kg to <30kg • up to 4mg/kg twice a day (8mg/kg/day) in patients weighing ≥30kg to <50kg

Note: Children weighing less than 50kg should preferably start treatment with Vimpat 10mg/mL syrup.

The dose is determined based on body weight. It is therefore recommended to initiate treatment with the syrup and switch to tablets, if desired. When prescribing the syrup the dose should be expressed in volume (mL) rather than weight (mg).

Monotherapy (in the treatment of partial-onset seizures)

The recommended starting dose is 1mg/kg twice a day (2mg/kg/day) which should be increased to an initial therapeutic dose of 2mg/kg twice a day (4mg/kg/day) after 1 week.

In children weighing from 10kg to less than 40kg, a maximum dose of up to 6mg/kg twice a day (12mg/kg/day) is recommended. In children

Table 1–1: Product overview

	weighing from 40 to under 50kg, a maximum dose of 5mg/kg twice a day (10mg/kg/day) is recommended. *Adjunctive therapy (in the treatment of primary generalized tonic-clonic seizures from 4 years of age or in the treatment of partial-onset seizures from 2 years of age)* The recommended starting dose is 1mg/kg twice a day (2mg/kg/day) which should be increased to an initial therapeutic dose of 2mg/kg twice a day (4mg/kg/day) after 1 week. Due to an increased clearance compared to adults, in children weighing from 10kg to less than 20kg, a maximum dose of up to 6mg/kg twice a day (12mg/kg/day) is recommended. In children weighing from 20 to under 30kg, a maximum dose of 5mg/kg twice a day (10mg/kg/day) is recommended, and in children weighing from 30 to under 50kg, a maximum dose of 4mg/kg twice a day (8mg/kg/day) is recommended, although in open-label studies (see Sections 4.8 and 5.2), a dose up to 6mg/kg twice a day (12mg/kg/day) has been used by a small number of these children. *Initiation of LCM treatment with a loading dose (initial monotherapy or conversion to monotherapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of partial-onset seizures or adjunctive therapy in the treatment of primary generalized tonic-clonic seizures)* In adolescents and children weighing 50kg or more and adults, LCM treatment may also be initiated with a single loading dose of 200mg, followed approximately 12 hours later by a 100mg twice a day (200mg/day) maintenance dose regimen. A loading dose is not recommended in children weighing less than 50kg. 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 LCM 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 serious cardiac arrhythmia and 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. Proposed: None
Pharmaceutical form(s) and strength(s)	Current Film-coated tablets: 50mg/100mg/150mg/200mg Syrup: 10mg/mL Solution for infusion: 10mg/mL
	Proposed Not applicable

Table 1–1: Product overview

Is/will the product be subject to additional monitoring in the EU?	No

EEA=European Economic Area; LCM=lacosamide

PART II: SAFETY SPECIFICATION

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1 INCIDENCE

The International League Against Epilepsy (ILAE) task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher et al, 2014).

Every year, an estimated 5 million people are newly diagnosed with epilepsy (https://www.who.int/news-room/fact-sheets/detail/epilepsy). According to a recent worldwide systematic review and meta-analysis, the annual cumulative incidence of epilepsy was 67.77 per 100,000 persons (95% confidence interval [CI] 56.69-81.03), while the incidence rate was 61.44 per 100,000 person-years (95% CI 50.75-74.38) (Fiest et al, 2017).

According to a review summarizing incidence studies of epilepsy, the incidence rate of epilepsy in Europe ranges from 29 to 47 per 100,000 person-years (Banerjee et al, 2009). The estimated number of new cases per year amongst European children and adolescents is 130,000 (incidence rate 70 per 100,000 person-years); 96,000 in adults 20 to 64 years (incidence rate 30 per 100,000 person-years); and 85,000 in the elderly 65 years and older (incidence rate 100 per 100,000 person-years). Approximately 20% to 30% of the epilepsy population has more than 1 seizure per month (Forsgren et al, 2005a).

In the recent literature review of European population based studies, 5 studies reported the incidence rates per 100,000 person years, which ranged from 77.1 (95% CI 53.8-100.4) in Sweden to 144 (95% CI: 122-168) in Norway in infants aged <1 year (Aaberg et al, 2017, Saarinen et al 2016, Casetta et al 2012, Adelow et al 2009, Olafsson et al 2005), 51.7 (95% CI 42.4-61.0) in Sweden to 61 (95% CI: 54-68) in Norway in children aged 1-4 years (Aaberg et al, 2017, Casetta et al 2012, Adelow et al 2009, Olafsson et al 2005), from 67.76 (95% CI 53.4-84.7) in Italy to 77.7 (95% CI 64.4–91.0) in Sweden in children aged 5-9 years (Casetta et al 2012, Adelow et al 2009), 33.8 (95% CI 23.9-52.1) in Italy to 49.4 (95% CI 39.2–59.6) in Sweden in children aged 10-14 years (Casetta et al 2012, Adelow et al 2009).

Based on estimates from population-based incidence studies from Europe, partial/focal epilepsies account for 32% to 88% of new cases of epilepsy, generalized epilepsies account for 9% to 69% of new cases of epilepsy, and unclassified represent 0 to 10% of new cases of epilepsy (reviewed by Cesnic et al, 2013 and Banerjee et al, 2009). The incidence of focal epilepsy has increased over last 40 years (Sillanpää et al, 2016).

2 PREVALENCE

In 2016, there were 45.9 million (95% uncertainty interval [UI] 39.9-54.6) patients with active epilepsy (both idiopathic and secondary epilepsy globally; age-standardized prevalence 621.5 per 100,000 population; 95% UI 540.1-737.0) (GBD 2016 Epilepsy Collaborators, 2019). In Europe, the prevalence of active epilepsy ranges from 320 to 780 per 100,000 population (Forsgren et al,

2005a). In 2023, according to World Health Organization, more than 50 million people worldwide have epilepsy, and nearly 80% live in low- and middle-income countries (https://www.who.int/news-room/fact-sheets/detail/epilepsy).

In a recently published meta-analysis, the point prevalence of active epilepsy was 638 per 100,000 persons (95% CI 557-730) and the lifetime prevalence was 760 per 100,000 persons (95% CI 617-938) (Fiest et al, 2017). In that meta-analysis (Fiest et al, 2017), active generalized epilepsy prevalence was 433 (95% CI: 255-832) per 100,000 persons and the prevalence of focal epilepsy was 299 (139-642) per 100,000 persons.

Generalized epilepsies were found in 190 per 100,000 children (35% of children with epilepsy). Children with epilepsy with onset during the first 2 years of life had an even distribution of focal and generalized epilepsies, whereas focal epilepsies became dominant at later ages of onset (Aaberg et al, 2017).

In a Norwegian nationwide pediatric study, the prevalence per 100,000 population of active epilepsy (ie, seizures in last 5 years and/or ongoing antiepileptic treatment) was 450 (95% CI: 410-490) and 620 (95% CI: 500-740) at 5 years and 10 years of children's age, respectively (Aaberg et al, 2017).

3 DEMOGRAPHICS OF THE POPULATION IN THE AUTHORIZED INDICATION AND RISK FACTORS FOR THE DISEASE

Most studies on prevalence by age show a general trend toward an increase in epilepsy prevalence during adolescence or early adulthood, decreases after age 30, and remains fairly constant for the remainder of life (Fiest et al 2017). In developed countries, most studies show the prevalence of epilepsy to be stable in the adult age groups and to increase with age after 50 years (Banerjee et al, 2009).

The burden of epilepsy is higher in developing countries than in developed countries. The median lifetime prevalence of epilepsy in developed countries is 5.8 per 1000 population (5th to 95th percentile range 2.7 to 12.4) whilst in developing countries it is 15.4 per 1000 persons (5th to 95th percentile range 4.8 to 49.6) and 10.3 (2.8–37.7) in urban and rural populations, respectively (Ngugi et al, 2010). The median prevalence of active epilepsy is 4.9 per 1000 (2.3-10.3) for developed countries and 12.7 per 1000 (3.5-45.5) and 5.9 (3.4-10.2) in rural and urban studies, respectively, in developing countries (Ngugi et al, 2010).

For most cases of epilepsy including children and adults (approximately 55% to 75%), the cause is unknown (Cowan, 2002). For patients with epilepsy with known etiology, factors that have been attributed to cause epilepsy include cerebrovascular disease (11% to 21%), trauma (2% to 6%), tumors (4% to 7%), and infection (0 to 3%) (Olafsson et al, 2005; Oun et al, 2003; Forsgren et al, 1996).

For cases where the cause is identifiable, the etiology varies by age. In children, the most common causes of epilepsy include congenital malformations, metabolic disorders, trauma, and central nervous system infections (Olafsson et al, 2005; Oun et al, 2003; Forsgren et al, 1996). Head trauma, central nervous system infections, and tumors may occur at any age and may lead to epilepsy, but tumors are more common after the age of 40 years. Cerebrovascular disease is the most common risk factor for epilepsy in people older than 60 years (Hitiris et al, 2007). The

distribution of the etiological factors for epilepsy varies by geographic location (Banerjee et al, 2009). In some parts of developing countries, endemic infections such as malaria, neurocysticercosis, paragonimiasis, and toxocariasis significantly contribute to the development of epilepsy compared to other etiological factors (Singh et al, 2006; Carter et al, 2004; Senanayake and Román, 1993).

There are several factors that have been associated with an increased risk of epilepsy in children. A family history of epilepsy has been associated with an increased risk for epilepsy that ranges from 2.5- to 3-fold (Annegers et al, 1996). Children with a history of febrile and neonatal seizures have an increased risk of epilepsy compared with those without seizures (rate ratio 5.43, 95% CI 5.19-5.69) (Vestergaard et al, 2007). Approximately 22% to 33.8% of children who have seizures in the newborn period develop epilepsy (Ronen et al, 2007; Garcias Da Silva et al, 2004) and 3% to 10% of children with central nervous system infection or brain trauma develop epilepsy (Guerrini, 2006).

4 THE MAIN EXISTING TREATMENT OPTIONS

The main goal of the treatment of epilepsy in children and adults is seizure freedom. The primary treatment for epilepsy is using antiepileptic drugs (AEDs). The choice of AEDs is dependent on the age of the patient, type of seizures, presence of comorbidities, efficacy, tolerability, and ease of use of the drug; the choice in women is also dependent on the possibility of pregnancy, lactation, and potential teratogenic effects (Perucca and Tomson, 2011). Patients are initially started on AED monotherapy, and if they are nonresponsive, they are changed to an alternative monotherapy regimen or adjunctive therapy. The duration of each treatment trial before deciding on continuing or changing to an alternative drug depends on the occurrence of side effects and seizure frequency. According to the International League against Epilepsy task force, patients are defined as having drug-resistant epilepsy when there is failure of adequate trials of 2 tolerated, appropriately chosen, and administered AEDs (whether as monotherapy or in combination) to achieve seizure freedom (Kwan et al, 2010). If AEDs are not successful in controlling seizures, nonpharmacological treatments such as surgery, a ketogenic diet, or vagus nerve stimulation may be tried. Surgery is usually performed in patients with refractory epilepsy that is associated with a localized focal lesion that can be resected. The ketogenic diet is a special high-fat, low-carbohydrate diet that helps to control seizures in some people with epilepsy. The vagus nerve stimulator is an internalized implantable device that is implanted in the left upper chest under the skin and connected via electrodes to the left vagus nerve in the neck. The device is programmed to deliver intermittent stimulation every 3 to 5 minutes. It is used, for example, in pediatric patients to manage Lennox-Gastaut syndrome.

5 NATURAL HISTORY OF THE INDICATED CONDITION IN THE EPILEPSY POPULATION, INCLUDING MORTALITY AND MORBIDITY

Estimates indicate that 10 years of life are lost for people whose epilepsy has a known cause, and 2 years are lost for people with epilepsy from an unknown cause (Gaitatzis et al, 2004a). Studies have consistently reported higher mortality rates in epilepsy compared with the general population (Neligan et al, 2011; Sillanpää and Shinnar, 2010; Shackleton et al, 2002; Callenbach et al, 2001; Lindsten et al, 2000).

With respect to the 2013 European Standard Population, the mean age-adjusted mortality rate from year 2001-2015 for epilepsy in Ireland was 1.9 (95% CI: 1.73-2.07) per 100,000 person-years over the 15-year period. For status epilepticus, the mean age-adjusted mortality rate was 2.1 (95% CI: 0.15-0.27) per 100,000 person-years over the 15-year period. The deaths were related to epilepsy or status epilepticus in the death certificates. Authors admitted that there was an underestimation of deaths due to status epilepticus (Kinney et al, 2019).

In a population-based study in the UK children with epilepsy (age ≥1 and <18 years), all-cause mortality rate was 88.1 per 100,000 patient-years (95% CI: 44-158). Higher seizure frequency was associated with higher mortality rates. No deaths were recorded in the lowest category of <1 seizure per year, whereas mortality rate was 487.8 per 100,000 patient-years (95% CI: 196.1-1005.1) in the highest category of seizure at least daily. The deaths may or may not be related to epilepsy (Myland et al 2019). In children who experience a first unprovoked focal or generalized tonic-clonic seizure, the cumulative risk of recurrence is 42% at 8 years follow-up, with only 3% of all recurrences occurring after 5 years (Shinnar et al, 1996). About 63% to 70% of individuals with epilepsy achieve long-term remission, most within 5 years of diagnosis (Kwan and Sander, 2004; MacDonald et al, 2000).

The ability to achieve remission of seizures or to discontinue antiepileptic medication varies by type of epilepsy, etiology, the presence of other neurological disorders, and initial response to treatment. The higher the number of years before entering 5-year remission, the higher was the annual risk of relapse. Those with cryptogenic or symptomatic generalized epilepsy, West syndrome, and Lennox-Gastaut syndrome had the lowest proportions of terminal remission (Sillanpää and Schmidt, 2006).

The highest mortality rates occur during the first years after seizure onset, mainly due to the underlying conditions causing the epilepsy (Neligan et al, 2010; Forsgen et al, 2005b). However, a significant excess mortality has also been recorded, even many years after the diagnosis of epilepsy (Neligan et al, 2011). Studies of cause-specific mortality rates in patients with epilepsy have shown excess mortality from cerebrovascular disease, heart disease, neoplasms, and pneumonia (Neligan et al, 2011; Forsgren et al, 2005b). One of the factors contributing to the increased mortality is the occurrence of sudden unexpected death in epilepsy with an estimated incidence of 2 per 10,000 person-years in children with epilepsy (Donner et al, 2001). Frequency of generalized tonic-clonic seizures is a well-established risk factor for sudden unexpected death in epilepsy (Harden et al, 2017).

6 IMPORTANT COMORBIDITIES

Compared to subjects without epilepsy, patients with epilepsy have significantly higher rates of comorbidities including almost all health-related comorbidities (Jennum et al, 2017).

Children and adults with epilepsy have a significantly higher prevalence of some psychiatric disorders, behavioral and development disabilities, and somatic conditions compared with the general population (Lin et al, 2012; Gaitatzis et al, 2004b; Gaitatzis et al, 2004c; Pellock, 2004).

One study found that children with epilepsy had increased prevalence of depression (8% versus 2%), anxiety (17% versus 3%), attention-deficit/hyperactivity disorder (23% versus 6%), conduct disorder (16% versus 3%), developmental delay (51% versus 3%), autism spectrum disorder (16% versus 1%), social problems (relative risk 2.16, 95% CI 1.61-2.90), and parental

aggravation (2.19, 95% CI 1.44-3.32) compared with children without epilepsy (Russ et al, 2012). Studies have also found that children with uncomplicated epilepsy had lower verbal intelligence quotient (IQ) and full-scale IQ than healthy control individuals (Rantanen et al, 2010). Serious psychiatric disturbances are less common in children with epilepsy compared with adults with epilepsy (Pellock, 2004). A pediatric study showed that 25% of children (3-17 years) with epilepsy had migraine, whereas the prevalence in adolescents (12-17 years) was 32% (Jancic et al, 2018; Kelley et al, 2012).

Comorbid conditions in adults with epilepsy have been broadly studied and are similar to those observed in children. Comorbidities occurring at a particularly high prevalence include depression, anxiety, sleep disturbances, fractures, migraine, and stroke (Swinkles et al, 2005). The prevalence of depression in epilepsy has been reported to range from 20% to 55% (Tellez-Zenteno et al, 2007; Victoroff et al, 1994). Other psychiatric conditions that have been reportedly high in epilepsy patients include anxiety (11%) and psychoses (9%) (Hesdorffer et al, 2012; Rai et al, 2012; Gaitatzis et al, 2004c). Studies have also reported a higher prevalence of attention-deficit/hyperactivity disorder in adults with epilepsy (30% to 40%) compared to 15% in the general population (Hamed, 2011). Additional studies have reported a high incidence of cognitive impairment including learning disability and academic underachievement (van Blarikom et al, 2006) and autoimmune diseases, ie, type 1 diabetes mellitus, hypothyroidism, myasthenia gravis, and multiple sclerosis (Wie Borsheim et al, 2020).

A meta-analysis of 74 studies reported a standardized mortality ratio of 3.3 (95% CI: 2.8-3.7) comparing the mortality rate due to suicide in patients with epilepsy to the general population (Bell et al, 2009).

The most common somatic comorbid conditions that have been reported among adults with prevalent epilepsy include fractures, ischemic heart disease, and heart failure. Studies have shown that the standardized mortality ratios for cardiovascular disease are 1.5 to 2.5 times higher in people with epilepsy than in the general population (Neligan et al, 2011). The risk of fractures in epileptic patients is elevated approximately 2-fold compared with the general population; the fractures result directly from seizure-induced injury or predisposed by drug-induced reduction in bone mineral density (Wirrell, 2006). Among older adults, the occurrence of stroke is associated with an increased risk of epilepsy and vice versa (Cleary et al, 2004; Hauser et al, 1993). Studies involving adults at least 18 years of age with epilepsy have also reported sleep disturbance conditions including increased latency to sleep onset, increased number and duration of awakenings, and increased duration of sleep stages 1 and 2 (van Golde et al, 2011).

Patients with cancer have an increased risk of developing epileptic seizures in the course of their disease. The lifetime risk of patients with brain tumors to have epileptic seizures is 20% to 80% (van Breemen et al, 2007). The risk of having epileptic seizures is higher in patients with primary brain tumors than in those with brain metastasis. Seizures can occur in patients with cancer in the absence of central nervous system involvement. Even when a brain lesion is present, it may not be the cause of seizures. Other factors that cause seizures in these patients include medications, metabolic disturbances, stroke, and infection (Singh et al, 2007). Patients with Alzheimer's disease are at increased risk for developing seizures and epilepsy. The reported lifetime prevalence rates of seizures in patients with Alzheimer's disease ranges from 1.5% to 64% (Friedman et al, 2012).

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PART II: MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage are detailed in Table 1–1.

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
General safety pharmacology	
Cardiovascular findings (including potential for QT interval prolongation) In vitro studies In isolated canine Purkinje fibers stimulated at normal and slow rates, lacosamide (LCM) significantly decreased action potential duration and tended to decrease the maximal rate of depolarization at concentrations of 50 and 150µmol/L (study 20000377P). These effects can be attributed to LCM's inhibitory effect on the cardiac sodium channel which has been demonstrated in recombinant human cardiac sodium channels (studies 011119.TDA, E-01-014-001). Lacosamide produced a concentration-dependent inhibition of sodium current with half maximum inhibitory concentration (IC50) values of 293µmol/L (study 011119.TDA) and 112µmol/L (study E-01-014-001). In both studies, block was incomplete, leveling off at about 70% at 1000µmol/L (study 011119.TDA) and 5000µmol/L (study E-01-014-001) and showed a use-dependent additional block. Lacosamide demonstrated weak blocking effects of less than 10% on Na^+ and L-type Ca^{2+} currents in voltage-clamped atrial myocytes from human atrial appendage tissue (study SB01D01). Under conditions in which the myocardial cell membrane is depolarized to 70mV, the inhibitory effect of LCM on sodium current was more pronounced. Lacosamide concentration dependently inhibited sodium current with an IC50 of about 68µmol/L. In guinea pig ventricular myocytes (study LPT 15066/01), LCM did not have any influence on the L-type calcium channel up to the maximum concentration tested of 500µmol/L.	The inhibitory effect of LCM on the cardiac Na^+ current in nonclinical studies as well as the results of clinical studies should be taken into account when treating patients with other relevant concomitant myocardial conditions. These issues are explored in further depth in the identified risks sections (see EU Risk Management Plan Part II, Module SVII) and are also addressed in the Summary of Product Characteristics (SmPC).

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
At a concentration of 3000µM, LCM inhibited only about 7% of the human ether-à-go-go-related gene (hERG)-mediated potassium current in recombinant human hERG channels (study 020316.TDA, 2002). In vitro study was performed following the US Food and Drug Administration (FDA) postmarketing requirement. In this in vitro patch-clamp study (NCD3699), the kinetics of $Na_V1.5$ peak current blockade (off-rate time constant) of LCM and 3 other reference antiarrhythmic drugs (AADs; quinidine: Class 1A AAD, mexiletine: Class 1B AAD, and flecainide: Class 1C AAD) were evaluated in order to determine the LCM Vaughan Williams' AAD classification. When tested at 8.5mM (ie, at its $Na_V1.5$ IC50), LCM showed recovery from block (at -15mV for 200s) similar to that of mexiletine. Therefore, LCM can be classified as a Class 1B AAD. Note that the LCM concentration used for this AAD classification (8.5mM) corresponds to over 200-fold the free therapeutic plasma concentration (37µM) at the maximum recommended human dose (400mg/day). Therefore, these data are not considered to be clinically relevant. <u>In vivo studies</u> A safety pharmacology study with intravenous (iv) administration of LCM in anesthetized dogs showed transient increases in PR interval and QRS complex duration and decreases in blood pressure most likely due to a cardiodepressant action. These transient changes started in the same concentration range as after maximum recommended clinical dosing. In general, female dogs were more susceptible than male dogs in this study (study 20000376P). After iv administration of higher doses (15-60mg/kg) of LCM to anesthetized dogs and monkeys, more severe conduction disturbances like atrioventricular (AV) block, slowing of atrial and ventricular conductivity, and AV dissociation were reported (studies 0247DH15.001, 0247DH15.002, 0247DH15.003). These changes were accompanied by marked reductions in blood pressure and cardiac output. No relevant effects have been found on the QT interval in animal studies. Lacosamide has also been shown to have effects on cardiac sodium channels across different test systems	The conditions under which the in vivo studies were conducted in animals (anesthetized and given surgery) are not comparable to the normal clinical conditions. The issue of PR prolongation will be explored in further depth in the clinical potential risks sections below and is also addressed in the SmPC.

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
(human cloned sodium channels, guinea pig action potential recordings, and electrocardiogram in anesthetized dogs). These studies showed that at concentrations corresponding to the maximum plasma level of LCM achieved in humans, a small effect on cardiac sodium channels is evident. In summary, in vitro LCM partially inhibited the cardiac sodium current that is associated with a decrease in upstroke velocity and duration of the action potential, whereas in vivo, LCM exerted a cardiodepressant action in anesthetized dogs and monkeys including decreases in blood pressure, slowing of intra-atrial conductivity, AV block, and AV dissociation. These findings started at plasma concentrations that were also achieved at the maximum recommended human dose (MRHD).	
Repeated toxicity studies	
Nervous system findings Central Nervous System effects including convulsions: In repeated-dose toxicity studies with mice, rats, rabbits, and dogs, exaggerated pharmacodynamics effects of LCM on the CNS at high doses resulting in severe clinical signs, such as ataxia, abdominal and/or lateral position, tremors, or convulsions, were considered dose limiting in all species. Convulsions (which are considered to be related to peak plasma levels) were observed starting at oral doses of 180, ≥160, ≥25, and ≥20mg/kg in mice (study LPT 13124/00), rats (study LPT 13295/00), pregnant rabbits (study 1108-002P), and dogs (study LPT 13196/00), respectively. At these doses, exposure compared to the MRHD of 600mg/day was about 2.6, 3.3, 1.3, and 1.3 times higher based on C_{max} for mice, rats, rabbits, and dogs, respectively.	Proconvulsant activity at supratherapeutic doses has also been observed with other antiepileptic drugs (AEDs). Therefore, it is considered of possible relevance to human use. This issue is addressed in the SmPC and in the pharmacovigilance plan.
Liver changes In repeated-dose studies in rats, elevated liver parameters were noted starting at 80mg/kg/day orally, corresponding to approximately 3 times the exposure at the MRHD. Liver weights increased (up to +44%) along with serum alkaline phosphatase (up to +88%), cholesterol (up to +56%), triglycerides (up to +95%), and alanine aminotransferase (ALT) (up to +86%), so the liver might be considered a target organ in rats.	Mild liver changes occurred in only one species with absence of structural damage and with complete reversibility. Abnormal liver function test with LCM use have been reported in postmarketing setting. This adverse reaction is listed in the SmPC (Section 4.8).

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
However, all changes were completely reversible within a 4-week recovery period (study 148-235). Further, electron microscopic examinations revealed hypertrophy of hepatocytes with an increase of the rough endoplasmic reticulum and mitochondria in the cytoplasm, but no degenerative changes in hepatocytes or their cellular organelles were observed (report no. 148-235; Drommer, 2002). No macroscopic or other histopathological changes were noted. Furthermore, in the 2-year carcinogenicity study in rats, ALT activities recovered from test Week 52 onward, ie, the elevation was transient (study LPT 13295/00). Overall, the effects in rat livers are therefore regarded as physiological adaptive mechanisms. There were no effects on liver parameters in studies with mice and dogs up to the highest doses tested. Although maximum systemic exposure in mice (C_{max} and AUC) and dogs (C_{max} only) was within the range of that yielding first effects in rats, it was slightly lower in mice and about half (C_{max}) or approximately one third (AUC) lower in dogs when compared to the highest exposure tested in rats, ie, rats are the most sensitive species but a trans-species effect at high doses cannot be ruled out completely.	
Reproductive and developmental toxicity Lacosamide was tested for effects on all stages of reproduction, ie, on fertility, early and embryo-fetal development, and pre-/postnatal development including maternal function, by oral administration to rats (combined fertility embryo-fetal toxicity, study 1108-003 and study 1108-004) and oral administration to rabbits (study 1108 002). In animal reproductive and developmental toxicity studies, LCM did not affect male or female fertility in rats and was not teratogenic in either rats or rabbits, but was embryotoxic at maternal toxic doses. In a standard pre-/postnatal development study in rats (dosage levels: 25, 70, and 200mg/kg/day) (study 1108-004), the mean duration of gestation was significantly prolonged in all LCM groups (22.8, 22.9, and 23.0 days, respectively) compared with the control group (22.4 days) and a tendency toward increased numbers of	The relevance to human usage is unknown, but there is no suggestion of any effects on fertility or any teratogenic effect. Embryotoxicity was only observed at maternally toxic doses. However, LCM has not been studied in pregnant woman. This issue is addressed in the SmPC and in the pharmacovigilance plan.

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
stillborn pups and pup deaths in the peripartum period and slightly reduced live litter sizes and pup body weights was observed at a maternally toxic dose of 200mg/kg/day, ie, at systemic exposure levels similar to the expected clinical exposure (based on the AUC). All adverse effects on the delivered litters were considered secondary to the adverse effects and reduced maternal care that occurred in the dams. No effects were noted on the F2 generation up to weaning. On request from the FDA, the effects of LCM on brain development were investigated using more sensitive techniques for assessing CNS structure and function than those employed in the standard pre- and postnatal development study. In addition, in this study, twice daily dosing (10 hours apart) was used as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern (dosage levels: 50, 100, and 200mg/kg/day [studies NCD2103, WIL549017]). This postmarketing commitment was considered by FDA as fulfilled on 18 Apr 2014. **Developmental toxicity** The no observable adverse effect level (NOAEL) for F0 maternal systemic effects was considered to be 50mg/kg/day based on F0 clinical signs, body weight losses and lower body weight gains and food consumption at 100 and 200mg/kg/day and increased F0 mortality/moribundity at 200mg/kg/day. Following treatment of the dams at 200mg/kg/day, the F1 generation presented lower postnatal survival (including total litter loss), lower birth and pup body weights, and a transient decrease in learning performance for females only during postnatal day (PND) 22 Biel maze testing. This latter effect was no longer observed on PND62.There were no test item-related macroscopic or microscopic changes in the F1 animals, including no changes in brain structure as investigated by sensitive techniques (brain weights and macroscopic and microscopic evaluations) at any dose level. The NOAEL for neurobehavioral and developmental toxicity was considered to be 100mg/kg/day, similar to the exposure at the MRHD of 600mg/day based on the	

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
AUC. The exposure of the F1 pups was 6% to 8% of the exposure of the lactating F0 females, irrespective of the dose.	
Genotoxicity Lacosamide gave equivocal results without and weak positive results with metabolic activation in the in vitro mouse lymphoma assay (study G97BR23.704), but it was negative in the in vitro Ames test (study G97BR23.502 and study IPL-R 000603), in vivo bone marrow mouse micronucleus test (study G97BR23.123), and in vivo rat liver unscheduled DNA synthesis test (study IPL-R 000801). For the in vivo studies, relevant systemic exposure was demonstrated by toxicokinetic and tissue distribution studies. In the mouse lymphoma assay, the effects observed at the highest concentration without metabolic activation were considered equivocal as the increase in mutant frequency was only marginal. There was no clear dose relationship and interfering cytotoxicity was noted, potentially causing an artifact. In the S9-activated cultures, a weak dose-related positive response was only observed at excessively high concentrations (ie, above the maximum recommended limit of 10mM [currently even lowered to 1mM]).Based on these studies, an independent expert report concludes that LCM is devoid of genotoxic potential in vivo and that it presents no genotoxic risk for human in the planned clinical use.	A "weight of evidence" analysis allows the conclusion that LCM does not present a genotoxic risk under clinical exposure conditions.
Carcinogenicity Lacosamide did not possess any carcinogenic potential in the 2-year carcinogenicity studies in mice (study LPT 13124/00) and rats (study LPT 13295/00), tested up to maximum tolerated doses of 180 and 160mg/kg per os, respectively. This corresponds to 2.3 times the exposure at the MRHD of 600mg/day (based on the AUC).	There is no suggestion of a potential tumorigenic risk for humans.
Other toxicity-related information or data	
Studies in juvenile animals: In a juvenile toxicity study in rats, animals were treated with LCM (dosage levels: 30, 90 and 180mg/kg/day) for 6 weeks starting on PND7 (study LPT 18602/04). There were no functional or histopathological findings	The relevance to human usage is unknown, but in contrast to other AEDs, there is no suggestion of age-specific toxicity. However, LCM is currently under investigation in pediatric patients <4 years

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
indicating any age-specific toxicity despite an initially markedly higher systemic exposure to LCM in the juvenile animals as compared to adults at identical doses. Reduced body weight gain was dose-limiting. As a secondary effect to this, a slightly delayed physical development of the high dose groups in general was observed as reflected by a slight delay in vaginal opening and a slight, reversible decrease in absolute brain weights but this remained without any functional consequences. A slight anxiolytic-like effect (ie, slightly decreased latency time to move from the center sector) was noted in the open field test in the intermediate and high dose group 8 days after cessation of dosing but this is not considered adverse. The NOAEL for juvenile toxicity and development was 90mg/kg/day, ie, comparable to that in adult rats and similar to the exposure observed at the MRHD based on the AUC, at PND7 (equivalent to late gestational status in human) and PND48 (equivalent to 12-year-old children), respectively. In juvenile Beagle dogs, no specific effect of LCM on growth and developmental parameters was seen at oral dosage levels up to 35mg/kg given once and twice daily. Dosing started post-weaning at an age of 7 to 8 weeks and lasted for 33 weeks. In this study, no treatment-related effects were observed on bone mineral content, bone area, or bone mineral density in either male or female dogs at either the lumbar vertebrae or any of the 4 regions-of-interest in the tibia. At 35 and 2× 35mg/kg/day, dose-limiting clinical signs including tonic convulsions and emesis were observed. Based on these findings, the NOAEL for the juvenile dogs was set at 10mg/kg, whereas the NOAEL for developmental parameters was 35mg/kg bid (ie, 70mg/kg/day). At these dosage levels, systemic exposure levels in dog were in the range of the MRHD based on the AUC.	of age. The absence of pediatric data is addressed in the SmPC.
Other toxicity-related information or data Abuse and dependence liability: At concentrations considerably in excess of those observed therapeutically, no specific binding of LCM or its major human metabolite was detected in radioligand binding	The absence of signs for abuse or dependence potential in targeted nonclinical studies supports the overall conclusion that LCM is unlikely to have abuse liability in man.

Table 1–1: Key safety findings from nonclinical studies and their relevance to human usage

Key safety findings (from nonclinical studies)	Relevance to human usage
experiments to 20 abuse- or dependence-related molecular targets (study 10263). There was no evidence for abuse potential of LCM in a drug discrimination study (study 05.237/5), in a place-preference test (study 05.122/6), or in an iv self-administration procedure (study 05.673/4) in rats. After prolonged administration to rats and dogs, there was no tolerance to LCM's pharmacological actions and abrupt cessation of treatment did not produce psychological and/or physical dependence (study RS211).	
Mechanisms for drug interactions In vitro studies indicate that the enzyme activity of drug metabolizing cytochrome (CYP 1A2, 2B6, 2C9, 2C19, 3A4) is not induced by LCM at concentrations observed in clinical studies (50µmol/L, ie, 12.5µg/mL). An increase in CYP3A4 activity in a single donor at a 10-fold higher LCM concentration is not considered as relevant since it accounts for only 20% of the activity determined in the positive control. No or low inhibitory interactions were detected with the CYP isoforms 1A2, 2A6, 2B6, 2C8, 2D6, and 2E1. The inhibitory concentrations of CYP1A1, 2C9, 2C19, 3A4, and 3A5 were at least 30-fold higher than human LCM plasma concentrations (14.5µg/mL, SP588). In vitro study (NCD2005) with specific inhibitors on human liver microsomes as well as recombinant human CYP isoforms, showed that the major CYP isoforms involved in the formation of SPM 12809 are CYP3A4, 2C9, and 2C19. In caco-2 cell transport assay, LCM was not a substrate for P-glycoprotein and did not modulate the transport of digoxin at concentrations up to 3mmol/L (750µg/mL) (study 651).	In vitro studies suggest a low risk for drug-drug interactions with coadministered drugs which are substrates of CYP isoforms in vivo. The pharmacokinetics of digoxin was not influenced in the clinical interaction study SP644. Caution is recommended in concomitant treatment with strong inhibitors of CYP2C9 (eg, fluconazole) and CYP3A4 (eg, itraconazole, ketoconazole, ritonavir, clarithromycin), which may lead to increased systemic exposure of LCM. Such interactions have not been established in vivo but are possible based on in vitro data (Section 4.5, Interaction with other medicinal products and other forms of interaction, of the SmPC).

AAD=antiarrhythmic drug; AED=antiepileptic drug; ALT=alanine aminotransferase; AV=atrioventricular; CNS=central nervous system; CYP=cytochrome; FDA=Food and Drug Administration; hERG=human ether-à-go-go-related gene; IC50=half maximum inhibitory concentration; iv=intravenous; LCM=lacosamide; MRHD=maximum recommended human dose; NOAEL=no observable adverse effect level; PND=postnatal day; SmPC=summary of product characteristics

PART II: MODULE SIII: CLINICAL TRIAL EXPOSURE

1 CLINICAL STUDY EXPOSURE

Exposure in this RMP encompasses exposure data through a data cutoff date of 29 May 2020 (RMP Pool 1-final data), 28 Feb 2023 (RMP Pool 2), and 27 May 2022 (Pool SPX-1-final data) as shown in Table 1–1.

Table 1–1: Overview of exposure pools

Pool	Pool definition	Studies included
Risk Management Plan (RMP) Pool 1	All completed Phase 2/3 randomized, double-blind, controlled studies in all approved indications	SP755, SP754, SP667, EP0008, SP902, SP0993, SP0969[a], SP0982
RMP Pool 2	All Phase 1-Phase 4 clinical studies (except noninterventional studies or studies using commercial VIMPAT® [lacosamide])	**Adjunctive treatment partial-onset seizures (POS) (completed studies)** SP586, SP598, SP607, SP615, SP616, SP667, SP754, SP755, SP756, SP757, SP774, SP925, SP926, SP954, EP0024, EP0008, EP0009, SP0978, SP0980, SP0969[a], SP0967[a] **Monotherapy treatment POS (completed studies)** SP902, SP904, SP0993, SP0994, SP1042, EP0057 **Primary generalized tonic-clonic seizures (PGTCS) (completed studies)** SP0961, SP0962, SP0982 **Pediatrics (completed studies)** SP847, SP848, SP0966, SP0967[a], SP0969[a], EP0034, EP0060 **Pediatrics (ongoing studies)** EP0151 **Neonates (ongoing studies)** SP0968 **PGTCS (ongoing studies)** EP0012 **Indications no longer pursued (completed studies)** SP614, SP665, SP742, SP743, SP745, SP746, SP746 (open label), SP768, SP830, SP874, SP611, SP647, SP655, SP690, SP887, SP905, SP906 **Phase 1 (completed studies)** EP0013, EP0036, EP0059, SP587, SP588, SP599, SP600, SP601, SP602, SP603, SP618, SP619, SP620, SP640, SP641, SP642, SP643, SP644, SP645, SP657, SP658, SP660, SP661, SP834 (FRC 101), SP835 (FRC 102), SP836 (FRC 103), SP863, SP903, SP940, SP952, SP955, SP1031, SP1039, SP1046, SP0983, SP0998, SP1001, SP1043

Table 1–1: Overview of exposure pools

Pool	Pool definition	Studies included
Pool SPX-1	The analysis pool to support the pediatric submission in study participants ≥1 month to <4 years of age and ≥4 to <16 years of age.	SP847, SP848 [b] EP0034

PGTCS=primary generalized tonic-clonic seizure; POS=partial-onset seizure; RMP=risk management plan
[a] SP0967 and SP0969 are completed adjunctive treatment POS pediatric studies
[b] Study participants enrolled in SP848 from SP0966 (generalized seizures) are excluded from Pool SPX-1

Total exposure to lacosamide (LCM) during the development program was summarized by indication using data from completed studies in addition to data from ongoing studies as of 28 Feb 2023. Table 1–2 summarizes the LCM exposures and includes breakdowns by indication.

Table 1–2: Overview of exposure as of data cutoff (28 Feb 2023)

Indication	Number of LCM exposures
Partial-onset seizures	
Adjunctive therapy[a]	2861
Monotherapy	888
Pediatric[b]	969
Primary generalized tonic-clonic seizures[c]	312
Phase 1 (healthy study participants and study participants with hepatic or renal impairment)	1028
Neonates	8
Indications not currently pursued[d]	
Diabetic neuropathic pain, mixed neuropathic pain, and postherpetic neuralgia	2139
Other indications (migraine prophylaxis, fibromyalgia, osteoarthritis)	296

LCM=lacosamide
[a]Includes completed pediatric studies SP0967 and SP0969.
[b]Includes pediatric studies SP847, SP848, SP0966, EP0034, and EP0060. Excludes completed pediatric studies SP0967 and SP0969 as both are counted under adjunctive therapy; however, it includes study participants from SP0969 and SP0967 who rolled over into EP0034.
[c]Includes ongoing study EP0012.
[d]The number of study participants in indications not currently pursued are adapted from previous version of Risk Management Plan.

As of the data cutoff of 28 Feb 2023, overall, 8501 study participants have been exposed to LCM in the clinical development program, and of these, 2861 adult and pediatric study participants

received adjunctive LCM therapy and 888 adult study participants received monotherapy for treatment of partial-onset seizures (POS).

Cumulative study participant exposure from ongoing and completed clinical studies is presented by duration of exposure, by age group and gender, by dose, and by racial group in the sections below.

1.1 RMP Pool 1 (completed, double-blind, randomized, controlled studies in approved indications)

Risk Management Plan Pool 1 is comprised of completed (as of 29 May 2020), double-blind, controlled studies in approved indications.

Exposure data from RMP Pool 1 are presented by duration of exposure overall and indication (Table 1–3); dose overall and indication (Table 1–4); age group, gender overall, and indication (Table 1–5); and ethnic/racial origin overall and indication (Table 1–6).

Table 1–3: Duration of exposure to LCM overall and by indication for completed, double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Duration of exposure	Number of study participants	Participant-years of exposure
Partial-onset seizures-total exposed population		
>0 month	2347	1009.9
≥3 months	1954	969.7
≥5 months	1166	699.7
Partial-onset seizures-adjunctive therapy		
>0 month	1478	474.7
≥3 months	1231	449.5
≥5 months	536	208.6
Partial-onset seizures-monotherapy		
>0 month	869	538.5
≥3 months	724	523.5
≥5 months	631	494.4
Primary generalized tonic-clonic seizures-all approved indications		
>0 month	121	45.4
≥3 months	78	38.4
≥5 months	67	35.2

LCM=Lacosamide; RMP=risk management plan

Table 1–4: Exposure to LCM by dose overall and by indication for completed double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Partial-onset seizures–total exposed population		
Dose of exposure	**Number of study participants**	**Participant-years of exposure**
Lacosamide (LCM) 200mg/day	453	148.6
LCM 300mg/day	106	33.8
LCM 400mg/day	970	304.7
LCM 600mg/day	203	58.6
Partial-onset seizures-adjunctive therapy		
Randomized dose of exposure	**Number of study participants**	**Participant-years of exposure**
LCM 200mg/day	453	148.6
LCM 400mg/day	651	205.4
LCM 600mg/day	203	58.6
Partial-onset seizures-monotherapy		
Randomized dose of exposure	**Number of study participants**	**Participant-years of exposure**
LCM 300mg/day	106	33.8
LCM 400mg/day	319	99.3

LCM=lacosamide; RMP=risk management plan
Note: Study participants from SP0969, SP0993, and SP0982 are not included since study participants in these studies were assigned to LCM as treatment and not a specific dose of LCM.

Table 1–5: Exposure to LCM by age group and by gender, overall and by indication for completed double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Age group	**Number of study participants**		**Participant-years of exposure**	
	Male	**Female**	**Male**	**Female**
Partial-onset seizures–total exposed population				
24 months to <12 years	47	44	16.7	16.5
12 to <18 years	71	57	27.2	26.5
18 to <65 years	1024	1010	458.5	403.9
65 to <85 years	49	43	35.0	25.4
≥85 years	1	1	0.1	0.1

Table 1–5: Exposure to LCM by age group and by gender, overall and by indication for completed double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Age group	Number of study participants		Participant-years of exposure	
	Male	Female	Male	Female
Partial-onset seizures-adjunctive therapy				
24 months to <12 years	47	44	16.7	16.5
12 to <18 years	64	46	22.2	16.3
18 to <65 years	623	635	204.7	192.9
65 to <85 years	9	10	2.8	2.6
Partial-onset seizures–monotherapy				
24 months to <12 years	0	0	0	0
12 to <18 years	7	11	5.0	13.5
18 to <65 years	401	375	253.8	211.1
65 to <85 years	40	33	32.2	22.7
≥85 years	1	1	0.1	0.1
Primary generalized tonic-clonic seizures-all approved indications				
24 months to <12 years	5	33	2.3	1.3
12 to <18 years	5	11	2.0	44.8
18 to <65 years	45	51	18.3	16.6
65 to <85 years	0	1	0.0	0.1
≥85 years	0	0	0.0	0.0

LCM=lacosamide

Table 1–6: Exposure to LCM by ethnic/racial origin overall and by indication for completed, double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Ethnic/racial origin	Number of study participants	Participant-years of exposure
Partial-onset seizures–total exposed population		
American Indian/Alaskan native	3	0.5
Asian	445	177.2
Black	108	37.2

Table 1–6: Exposure to LCM by ethnic/racial origin overall and by indication for completed, double-blind, randomized, controlled studies (all approved indications) (RMP Pool 1)

Ethnic/racial origin	Number of study participants	Participant-years of exposure
Native Hawaiian or Pacific Islander	1	1.5
White	1717	769.2
Other/mixed	69	23.1
Partial-onset seizures-adjunctive therapy		
American Indian/Alaskan native	1	0.3
Asian	396	129.5
Black	40	13.0
Native Hawaiian or Pacific Islander	0	0
White	1002	320.7
Other/mixed	39	11.3
Partial-onset seizures-monotherapy		
American Indian/Alaskan native	2	0.3
Asian	49	47.8
Black	68	24.2
Native Hawaiian or Pacific Islander	1	1.5
White	715	451.8
Other/mixed	30	11.8
Primary generalized tonic-clonic seizures–all approved indications		
American Indian/Alaskan native	1	0.6
Asian	18	8.1
Black	2	0.7
Native Hawaiian or Pacific Islander	0	0.0
White	97	35.0
Other/mixed	3	1.0

LCM=lacosamide; RMP=risk management plan

1.2 RMP Pool 2 (all Phase 1-4 clinical studies on approved indications)

The studies in RMP Pool 2 were given in Table 1–1. For this section, these comprise completed and ongoing studies (as of 28 Feb 2023) in approved indications.

Exposure data from RMP Pool 2 are presented by duration of exposure overall and indication (Table 1–7); age group and gender overall and indication (Table 1–8); and ethnic/racial origin overall and indication (Table 1–9).

Table 1–7: Duration of exposure to LCM overall and by indication for all studies (all approved indications) (RMP Pool 2)

Duration of exposure (at least)	Number of study participants	Participant-years of exposure
Partial-onset seizures–total exposed population		
>0 months	3749	7153.8
≥3 months	3063	7084.5
≥6 months	2568	6905.6
≥12 months	1934	6510.2
≥18 months	1683	6225.8
≥24 months	1526	5973.9
≥36 months	1030	4820.4
≥48 months	778	4010.8
≥60 months	494	2826.6
Partial-onset seizures-adjunctive therapy[a]		
>0 months	2861	5330.3
≥3 months	2292	5271.0
≥6 months	1869	5117.1
≥12 months	1311	4771.5
≥18 months	1144	4580.8
≥24 months	1030	4398.8
≥36 months	844	3974.6
≥48 months	657	3374.2
≥60 months	423	2395.0
Partial-onset seizures–monotherapy		
>0 months	888	1823.5
≥3 months	771	1813.4

Table 1–7: Duration of exposure to LCM overall and by indication for all studies (all approved indications) (RMP Pool 2)

Duration of exposure (at least)	Number of study participants	Participant-years of exposure
≥6 months	699	1788.5
≥12 months	623	1738.8
≥18 months	539	1645.0
≥24 months	496	1575.1
≥36 months	186	845.7
≥48 months	121	636.6
≥60 months	71	431.6
Primary generalized tonic-clonic seizures–all approved indications		
>0 months	312	806.0
≥3 months	276	801.6
≥6 months	266	798.2
≥12 months	245	785.6
≥18 months	205	735.8
≥24 months	187	707.0
≥36 months	156	634.6
≥48 months	106	474.6
≥60 months	49	240.9

LCM=lacosamide; RMP=risk management plan
[a] SP0967 and SP0969 are included as partial-onset seizure adjunctive studies.

Table 1–8: Exposure to LCM by age group and by gender, overall and by indication for all studies (all approved indications) (RMP Pool 2)

Age group	Number of study participants		Participant-years of exposure	
	Male	Female	Male	Female
Partial-onset seizures-total exposed population				
28 days to <24 months	32	31	3.6	3.3
24 months to <12 years	86	70	21.2	19.4
12 to <18 years	80	66	101.6	101.5
18 to <65 years	1644	1624	3589.4	3105.0

Table 1–8: Exposure to LCM by age group and by gender, overall and by indication for all studies (all approved indications) (RMP Pool 2)

Age group	Number of study participants		Participant-years of exposure	
	Male	Female	Male	Female
65 to <85 years	61	53	117.1	91.5
≥85 years	1	1	0.1	0.1
Partial-onset seizures-adjunctive therapy[a]				
28 days to <24 months	32	31	3.6	3.3
24 months to <12 years	86	70	21.2	19.4
12 to <18 years	73	55	86.3	67.0
18 to <65 years	1234	1241	2705.8	2384.3
65 to <85 years	19	20	20.8	18.7
Partial-onset seizures-monotherapy				
28 days to <24 months	0	0	0.0	0.0
24 months to <12 years	0	0	0.0	0.0
12 to <18 years	7	11	15.3	34.5
18 to <65 years	410	383	883.7	720.7
65 to <85 years	42	33	96.3	72.8
≥85 years	1	1	0.1	0.1
Primary generalized tonic-clonic seizures–all approved indications				
28 days to <24 months	0	0	0.0	0.0
24 months to <12 years	8	9	24.7	23.4
12 to <18 years	11	30	33.5	85.5
18 to <65 years	106	146	298.8	339.3
65 to <85 years	0	2	0.0	0.7

LCM=lacosamide; RMP=risk management plan
[a] SP0967 and SP0969 are included as partial-onset seizure adjunctive studies.

Table 1–9: Exposure to LCM by ethnic/racial origin overall and by indication for all studies (all approved indications) (RMP Pool 2)

Ethnic/racial origin	Number of study participants	Participant-years of exposure
Partial-onset seizures-total exposed population		

Table 1–9: Exposure to LCM by ethnic/racial origin overall and by indication for all studies (all approved indications) (RMP Pool 2)

Ethnic/racial origin	Number of study participants	Participant-years of exposure
American Indian/Alaskan native	36	12.6
Asian	663	1799.2
Black	173	266.3
Native Hawaiian or Pacific Islander	1	1.5
White	2724	4895.3
Other/mixed	148	177.7
Partial-onset seizures-adjunctive therapy[a]		
American Indian/Alaskan native	34	12.3
Asian	595	1625.0
Black	105	158.1
Native Hawaiian or Pacific Islander	0	0
White	2009	3401.4
Other/mixed	118	133.5
Partial-onset seizures-monotherapy		
American Indian/Alaskan native	2	0.3
Asian	68	174.2
Black	68	108.2
Native Hawaiian or Pacific Islander	1	1.5
White	715	1493.9
Other/mixed	30	44.2
Primary generalized tonic-clonic seizures–all approved indications		
American Indian/Alaskan native	1	3.0
Asian	49	168.2
Black	13	20.6
Native Hawaiian or Pacific Islander	0	0.0
White	239	585.8
Other/mixed	10	28.5

[a] SP0967 and SP0969 are included as partial-onset seizure adjunctive studies.

1.3 Pool SPX-1

The studies included in Pool SPX-1 were given in Table 1–1. Exposure data from Pool SPX-1 is presented by duration of exposure (Table 1–10), age group and gender (Table 1–11), and ethnic/racial origin (Table 1–12).

Table 1–10: Overall duration of exposure to LCM for pediatric study participants in Pool SPX-1

Duration of exposure (at least)	Number of study participants	Participant-years of exposure
>0 months	870	1411.4
≥3 months	811	1403.6
≥6 months	759	1386.6
≥9 months	721	1365.7
≥12 months	700	1348.4
≥15 months	672	1320.1
≥18 months	658	1302.5
≥21 months	642	1278.5
≥24 months	583	1172.0
≥27 months	47	149.8
≥30 months	33	119.9
≥33 months	32	117.5
≥36 months	31	114.8
≥39 months	31	114.8
≥42 months	31	114.8
≥45 months	27	101.4
≥48 months	16	62.1
≥51 months	8	31.8
≥54 months	1	4.2
≥57 months	0	0.0
≥60 months	0	0.0

LCM=lacosamide

Table 1–11: Exposure to LCM by age group and by gender for pediatric study participants in Pool SPX-1

Age group	Number of study participants		Participant-years of exposure	
	Male	Female	Male	Female
28 days to <24 months	70	68	110.3	95.4
24 months to <12 years	273	213	429.7	344.5
12 to <18 years	134	112	228.4	203.0

LCM=lacosamide

Table 1–12: Exposure to LCM by ethnic/racial origin for pediatric study participants in Pool SPX-1

Ethnic/racial origin	Number of study participants	Participant-years of exposure
American Indian/Alaskan native	18	31.9
Asian	195	343.1
Black	28	39.3
Native Hawaiian or Pacific Islander	0	0.0
White	593	934.7
Other/mixed	36	62.4

LCM=lacosamide

PART II: MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 1–1 provides an overview of important exclusion criteria in the pivotal clinical studies across the development program.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Hypersensitivity to the active substance or to any of the excipients	
Reason for exclusion	Hypersensitivity reactions have been reported in patients treated with lacosamide (LCM). These reactions are variable in expression and can be associated with involvement of different organ systems. As preventive measure, hypersensitivity is a standard exclusion criterion for any investigational medicinal product in a UCB clinical trial.
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity to the active substance or to any of the excipients is a contraindication.
Known second and third atrioventricular (AV) block	
Reason for exclusion	Dose-related prolongations in PR interval with LCM have been observed in clinical studies. Second degree or higher AV block has been reported in postmarketing experience. In the placebo-controlled trials of LCM in epilepsy patients, atrial fibrillation or flutter were not reported; however, both have been reported in open-label epilepsy trials and in postmarketing experience.
Is it considered to be included as missing information?	No
Rationale	Cardiac adverse events (AEs) that may be potentially associated with PR interval prolongation or sodium channel modulation are an important identified risk (refer to EU Risk Management Plan [RMP] Part II Module SVII). In addition, known second and third AV block is a contraindication.
Pregnancy	
Reason for exclusion	Investigational drugs are not routinely given to pregnant women in clinical studies as there are no adequate data to support their use. There is no adequate data from the use of LCM in pregnant women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses. The potential risk for humans is unknown.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Is it considered to be included as missing information?	Yes
Lactation	
Reason for exclusion	At the time of the development program, it was unknown whether LCM was excreted in human breast milk. Animal studies had shown excretion of LCM in breast milk. Although there has been no evidence of harm in pregnancies or lactation reported during the clinical program, the data are currently insufficient to justify advocating the use of LCM in this population.
Is it considered to be included as missing information?	Yes
Hepatic impairment	
Reason for exclusion	This exclusion criterion was specific to study designs to maintain dosing within a typical therapeutic range.
Is it considered to be included as missing information?	No
Rationale	Lacosamide has been studied in patients with moderate hepatic impairment but not severe hepatic impairment. The Summary of Product Characteristics (SmPC) reflects this limitation.
Study participant with a known history of serious blood dyscrasias	
Reason for exclusion	Investigational drugs are not routinely given to study participants with a known history of serious blood dyscrasias in clinical studies as there are no adequate data to support their use.
Is it considered to be included as missing information?	No
Rationale	Agranulocytosis is listed in the SmPC as an adverse drug reaction.
Renal impairment	
Reason for exclusion	This exclusion criterion was specific to study designs to maintain dosing within a typical therapeutic range.
Is it considered to be included as missing information?	No
Rationale	Data suggest that LCM does not cause renal toxicity. Lacosamide has been studied in patients with mild, moderate, and severe renal impairment. The SmPC reflects this experience and implications for dosing.
Suicidality	

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Criterion	
Reason for exclusion	A meta-analysis of randomized, placebo-controlled studies of antiepileptic drugs (AEDs) as a drug class (performed by the US Food and Drug Administration [FDA]) (FDA, 2008) has shown a small increased risk of suicidal ideation and behavior. Subsequently, the European Medicines Agency conducted an independent review and also issued warnings about AEDs and suicidality (National Prescribing Centre, 2014).
Is it considered to be included as missing information?	No
Rationale	Suicidality is a warning that appears as class labeling among all AEDs.
Severe cardiac disease	
Reason for exclusion	Prolongations in PR interval with LCM have been observed in clinical studies. In clinical studies with patients with diabetic neuropathic pain, cases of syncope have been reported. Therefore, exclusion criteria related to the patients with severe cardiac disease have been added in all LCM clinical studies as risk minimization.
Is it considered to be included as missing information?	No
Rationale	Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation are an important identified risk (refer to EU-RMP Part II Module SVII). Syncope is listed in the SmPC as an adverse drug reaction. In addition, caution is recommended for use of LCM in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (eg, myocardial ischemia/infarction, heart failure, structural heart disease, or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blockers.

AE=adverse event; AED=antiepileptic drug; AV=atrioventricular; RMP=risk management plan; FDA=Food and Drug Administration; LCM=lacosamide; SmPc=Summary of Product Characteristics.

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions (occurring ≥0.01% to <0.1%), adverse reactions due to prolonged exposure, or those caused by cumulative effects and those which have a prolonged latency period. Details of these limitations and their implications for the target population are noted in Table 2–1.

Table 2–1: Limitations of adverse drug reaction detection

Ability to detect adverse reactions	Limitation of study program	Discussion of implications for target population
Which are rare (≥0.01% to <0.1%)	A sample size of 30,000 is needed to detect rare events (Keech et al, 2004). As this number of observations has not been achieved in the lacosamide (LCM) study program, the ability to detect rare events is limited.	As with the rare identified adverse drug reaction of second-degree atrioventricular block, if a rare event is observed and is considered to be an adverse drug reaction, it will be considered for inclusion in Summary of Product Characteristics (SmPC) Section 4.8 if it is deemed medically significant. Vigilance will be maintained to identify medically significant rare reactions.
Due to prolonged exposure	The LCM clinical database includes a limited number of study participants exposed for up to 8 years; thus, the ability to detect adverse reactions due to prolonged exposure is limited.	No risks have been identified that are due to prolonged exposure. Concerns over decreased bone mineral density have been identified for some antiepileptic drugs in particular enzyme-inducing antiepileptic drugs after prolonged exposure (Ensrud et al, 2008; Stephen et al, 1999). A signal has not been observed with LCM. Preclinical toxicological studies revealed that daily LCM treatment in juvenile dogs for 33 weeks at doses up to 70mg/kg/day did not alter bone mass parameters assessed at various skeletal sites (Simko et al, 2015). Vigilance will be maintained to identify events due to prolonged exposure.
Due to cumulative effects	The LCM clinical database includes a limited number of study participants exposed for up to 8 years; thus, the ability to detect adverse reactions due to the cumulative effects of LCM is limited.	No identified or potential risks due to cumulative effects have been observed for LCM. Vigilance will be maintained to identify potential cumulative effects.

Table 2–1: Limitations of adverse drug reaction detection

Ability to detect adverse reactions	Limitation of study program	Discussion of implications for target population
Which have a long latency	The LCM clinical database includes study participants exposed for up to 8 years; thus, the ability to detect adverse reactions with a long latency is limited.	After exposure of up to 8 years in ongoing studies, no signals relevant to long-latency reactions have been observed. Vigilance will be maintained to identify events which have a long latency via postmarketing data.

LCM=lacosamide; SmPC=summary of product characteristics

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 3–1 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant and lactating women (not included in preauthorization clinical development program)	Pregnant or lactating women have not been included in lacosamide (LCM) clinical studies. As per protocols, if a woman became pregnant during a clinical study, the study drug was stopped, and the study participant was discontinued. There are 2 pregnancy registries, the European Register of Antiepileptic Drugs and Pregnancy and the North American Antiepileptic Drug Pregnancy Registry that assess pregnancy outcomes of women being treated with LCM. This data cannot be used to estimate the overall exposure to LCM during pregnancy.
Patients with relevant comorbidities: Patients with hepatic impairment (included in preauthorization clinical development program)	**Patients with hepatic impairment:** A study (SP642) comparing healthy study participants (6 male and 2 female study participants) with study participants with moderate hepatic impairment (6 male and 2 female study participants; Child-Pugh stage B) has been conducted. In this study, study participants with hepatic impairment showed approximately 50% to 60% higher plasma concentrations of LCM and about 40% to 50% lower plasma concentrations of the major metabolite of LCM (SPM 12809). Half-life was slightly prolonged and the amount excreted into urine was reduced for LCM and SPM 12809. However, detailed analyses have shown a major impact of renal impairment in the observed group. The hepatic clearance of LCM is regarded as of minor relevance. The effect of hepatic impairment was not evaluated in the pediatric studies; however, based on the currently approved labeling for adults with hepatic impairment, no dose adjustment is needed for patients with mild-to-moderate hepatic impairment. The dose titration in these patients should be performed with caution considering coexisting renal impairment. A loading dose of 200mg may be considered, but further dose titration (>200mg daily) should be performed with caution. The pharmacokinetics (PK) of LCM has not been evaluated in severely hepatic impaired patients (Summary of Product Characteristics [SmPC] Section 5.2).
Patients with renal impairment (included in preauthorization clinical	**Patients with renal impairment:** The influence of renal impairment on the PK of LCM and

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
development program)	SPM 12809 was investigated in study SP641 (40 study participants). The exposure of LCM and SPM 12809 increased with increasing degree of renal impairment. Exposure (measured as $AUC_{(0-\tau)ss}$) in study participants with mild or moderate renal impairment is expected to be increased by approximately 30% compared with healthy study participants. In study participants with severe renal impairment, an approximately 60% increased exposure compared with healthy study participants is expected. In addition, the results from SP641 showed that a standard 4-hour hemodialysis procedure cleared LCM and SPM 12809 from the systemic body circulation and reduced the exposure to LCM and SPM 12809 by approximately 50%. This has to be taken into consideration if stable plasma concentrations are mandatory (eg, in epilepsy patients). Dose supplementation of up to 50% of the divided daily dose may need to be considered on hemodialysis days. Based on the dose adjustments recommended for adults with renal impairment, similar dose adjustments are recommended for pediatric study participants with renal impairment. No dose adjustment is necessary for pediatric patients with mild and moderate renal impairment (CL_{CR} >30mL/min). In pediatric patients with severe renal impairment (CL_{CR} ≤30mL/min) and those with end-stage renal disease, a reduction of 25% of the maximum dose is recommended. These data suggest that caution should be used when using LCM in study participants with severe renal impairment and/or undergoing hemodialysis. This issue is addressed in the pharmacovigilance plan and in the SmPC Section 4.2, with respect to study participants with renal impairment.
Patients with cardiovascular impairment (not included in preauthorization clinical development program)	**Patients with cardiovascular impairment:** In the Phase 2/3 studies in adult study participants (≥16 years of age), patients with a clinically significant abnormality in electrocardiogram (ECG), in certain protocols including prolonged QTc (Bazett's machine-read) interval defined as ≥450ms for males and ≥470ms for females, were excluded. No correlation between LCM and prolongation of QTc has been demonstrated. In pediatric studies, study participants with a clinically relevant ECG abnormality, in the opinion of the investigator (eg, second or third degree heart block at rest or a corrected QT interval [QTc] greater than 450ms) were excluded. As with the adult study participants, no correlation between LCM and prolongation of QTc has been demonstrated.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	Status epilepticus is a severe manifestation of epilepsy. Lacosamide has not been studied in status epilepticus; therefore, there are limited data regarding its use in this population (SmPC Section 4.2).
Population with relevant different ethnic origin	No LCM clinical studies exclude study participants based on race or ethnic origin. In EP Pool S1, 110 (8.4%) study participants were non-white (4.3% were black, 0.8% were Asian, and 3.4% were "Other"). In DNP Pool S1, 179 (13.6%) study participants were non-white (7.1% were black, 0.5% were Asian, and 6.0% were "Other"). This potential limitation has been addressed by a Phase 1 study of LCM to study the PK and safety in white, black, and Asian study participants (SP661, CTD Module 5.3.3.1.7). The results of this study indicate that the PK of LCM are the same in Asian, black, and white study participants. No clinically relevant differences were observed between the 3 ethnic groups with regard to exposure (measured as AUCτ,ss,norm), Cmax,ss, and t1/2 of LCM. An additional study, SP952, investigated the influence of race and ethnicity in Korean study participants. The PK of LCM in healthy male Koreans showed similar results to what has been seen in various other studies with white study participants.
	The effect of race and ethnicity on the PK of LCM was evaluated in SP1046, which investigated the PK of LCM in healthy, young (between 18 and 45 years of age, inclusive), male study participants from 2 different ethnic groups (Japanese and Chinese). The PK of LCM was similar between Japanese and Chinese healthy male study participants. Results indicated that LCM PK findings in Japanese and Chinese study participants were consistent with the known PK profile in Caucasian study participants. A total of 548 Japanese and Chinese study participants were included in EP0008. Non-white ethnic groups other than Asian study participants are underrepresented in the database. It is anticipated that LCM may be used in study participants of all ethnic origins. No further action is required.
Subpopulations carrying relevant genetic polymorphisms	**Poor metabolizers (PMs; CYP2C19):** In SP643, PK data were gained from PMs and extensive metabolizers (EMs) of CYP2C19. Plasma concentrations of LCM were similar in PMs and EMs, but plasma concentrations of SPM 12809 were about 70% reduced in

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
	PMs compared with EMs. The data indicate that CYP2C19 is involved in the metabolism of LCM and the formation of the main metabolite SPM 12809. Nevertheless, variants of CYP2C19 have shown no relevant effect on LCM plasma concentrations (see SmPC Section 5.2). The effect of genetic polymorphisms was not evaluated in the pediatric studies. However, based on results of PK in studies in healthy adults, no dose adjustment is expected to be needed in pediatric study participants who are PMs of CYP2C19 or pediatric study participants who receive a CYP2C19-inhibiting drug in parallel to LCM.
Other relevant comorbidities: Depression, anxiety, sleep disturbances, fractures, migraine, stroke, psychoses, and cognitive impairment	In clinical studies with LCM, study participants were excluded at the Investigator's discretion if it was considered they were at risk of not understanding the study requirements sufficiently to give informed consent and follow through with study procedures and visits. Additionally, inclusion/exclusion criteria excluded study participants who had severe uncontrolled psychiatric conditions. Among pediatric study participants (4 to <16 years), those with a medical condition that could be expected in the opinion of the investigator to interfere with drug absorption, distribution, metabolism, and excretion were excluded. Upon the introduction of the Columbia-Suicide Severity Rating Scale through protocol amendments (designed to help the investigator determine suicidal ideation/behavior), those study participants with a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) or those who had suicidal ideation in the past 6 months were excluded from studies. Study participants already enrolled in clinical studies who presented a lifetime history (prior to study entry or since study start) of suicide attempt or who had active suicidal ideation at the time of the assessment or recalled active suicidal ideation/behaviors were withdrawn. In the majority of studies within the program, LCM has been used as adjunctive therapy; therefore, attributing causality of the symptoms of these comorbid conditions to LCM is difficult.
Pediatric patients (included in preauthorization clinical development program)	A Pediatric Investigation Plan (PIP) was submitted; a final Pediatric Committee (PDCO) positive opinion on the initial PIP application was obtained on 12 Apr 2013 and the decision was adopted by EMA on 31 May 2013. This initial PIP was split into 2 PIPs: POS PIP and Syndromes PIP. The POS PIP

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
	is completed and a positive PDCO compliance opinion was received on 27 Jul 2018. The Syndromes PIP is still open and studies SP0982 and EP0012 are part of this PIP. A total of 9 clinical studies have been or are currently being conducted in pediatric study participants from 1 month to 18 years of age to support the LCM pediatric program. Exposure data in the pediatric population in the clinical development program are presented in EU Risk Management (RMP) Part II Module SIII.
Pediatric patients (Postauthorization safety study)	EP0147 Real World Evidence study was conducted to examine the safety and tolerability of a loading dose in pediatric patients <17 years of age. This retrospective cohort study was conducted using data from the Pediatric Learning Health System (PEDSnet) database. Electronic health record data was collected from 01 Jan 2009 to 29 Feb 2020. The duration of follow-up was for a maximum of 37 days after receipt of first intravenous LCM dose. After applying selection criteria and subsequent chart reviewing, 686 patients aged ≥1 month to <17 years and 28 neonates aged <30 days were eligible for the study. The median duration of follow-up in the recommended and loading dose cohorts was 8 days (range 2-23) and 7 days (range 2-27), respectively. In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall adverse events (AEs) in the recommended and loading dose cohorts were 64.44 (95% confidence interval [CI]: 55.88, 73.95) vs 50.00 (95% CI: 39.82, 61.98). In patients aged <30 days, the crude incidence rates per 1000 person-days of overall AEs in the recommended and loading dose cohorts were 36.04 (95% CI: 15.56, 71.01) vs 8.85 (95% CI: 1.07, 31.97). In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days of overall AEs that physicians attributed to LCM in the recommended and loading dose cohorts were 0.98 (95% CI: 0.36, 2.12) vs 1.37 (95% CI: 0.37, 3.51). In patients aged <30 days, no AEs were reported that physicians could attribute to LCM. In patients aged <30 days, no incidence rate ratios were calculated due to small sample size. No relevant statistically significant differences were observed between the recommended and loading dose cohorts for the AE diagnostic categories and most of the specific AE diagnoses in patients aged ≥1 month to <17 years. In ≥1 month to <17 years, there was a 2-fold increased risk of rash in the loading dose cohort

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
	compared with the recommended dose cohort. Overall, the current study findings were in line with the previously established LCM safety profile.
Elderly (included in preauthorization clinical development program)	Including unblinded data from SP0993, a total of 114 epilepsy study participants that were between 65 and 84 years of age (inclusive) have received LCM in all approved indications. Two study participants in the age category ≥85 years received LCM in SP0993. Exposure data in study participants by years of age are provided in the EU-RMP Part II, Module SIII for RMP Pool 1 and RMP Pool 2. In a study in elderly men and women including 4 study participants >75 years of age, the AUC was about 30% and 50% increased compared to young men, respectively (SP620). This was partly related to lower body weight. The body weight normalized difference was 26% and 23%, respectively. Based on the results of SP620, elimination of LCM (characterized by $t_{1/2}$) was not different in elderly and young study participants. Lacosamide was generally well-tolerated in elderly male and female healthy study participants. In conclusion, although there has been no evidence of harm in elderly population reported during the clinical program, the clinical experience in study participants ≥65 years is limited. Therefore, elderly patients will be monitored through routine pharmacovigilance activities.

AE=adverse event; AED=antiepileptic drug; CI=confidence interval; ECG=electrocardiogram; EM=extensive metabolizer; RMP=risk management plan; LCM=lacosamide; PK=pharmacokinetic; PM=poor metabolizer; PIP=pediatric investigation plan; PDCO=Pediatric Committee; SmPC=summary of product characteristics

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PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

1 POSTAUTHORIZATION EXPOSURE

1.1 Method used to calculate exposure

The cumulative exposure data were estimated using sales data for the period 01 Sep 2008 to 28 Feb 2023. The defined daily dose (DDD) for LCM is assumed to be 300mg/day according to the World Health Organization. It was also assumed that 1 year corresponds to 365.25 days. The patient exposure time is calculated using the following formula:

$$\text{Patient-years} = \frac{\text{(total milligrams of product distributed)/DDD}}{\text{365.25 days in year}}$$

0.25 is added to account for leap years

1.2 Exposure

A conservative view was adopted by assuming that all patients receive complete dosage regimens at the time of treatment. Patient exposure is estimated using the available UCB sales data from 01 Sep 2008 to 28 Feb 2023 for the cumulative time interval. Note that sales data are only available to UCB on a month-to-month basis.

The total amount of product distributed during the cumulative time interval is 384,677,105,450mg and is derived from the UCB sales data reported, while the DDD is assumed to be 300mg according to the World Health Organization.

The patient exposure to LCM during the cumulative time interval from 01 Sep 2008 to 28 Feb 2023 is estimated at approximately 3,510,628 patient-years using the following formula:

$$\text{Patient-years} = \frac{\text{(total amount of product distributed)/DDD}}{\text{365.25 days in year}}$$

0.25 is added to account for leap years.

Cumulatively, 384,677,105,450mg of product has been distributed worldwide from 01 Sep 2008 to 28 Feb 2023, contributing to approximately 3,510,628 patient-years.

Data on cumulative exposure by region is presented in Table 1–1.

Table 1–1: Cumulative patient exposure by region till 28 Feb 2023

Region	Country	Patient-years for the cumulative interval
European Economic Area (EEA)	Austria	[redacted]
	Belgium	[redacted]
	Bulgaria	[redacted]
	Cyprus	[redacted]
	Czech Republic	[redacted]

Table 1–1: Cumulative patient exposure by region till 28 Feb 2023

Region	Country	Patient-years for the cumulative interval
	Denmark	[redacted]
	Finland	[redacted]
	France Departments	[redacted]
	Germany	[redacted]
	Greece	[redacted]
	Hungary	[redacted]
	Iceland	[redacted]
	Ireland	[redacted]
	Italy	[redacted]
	Netherlands	[redacted]
	Norway	[redacted]
	Poland	[redacted]
	Portugal	[redacted]
	Romania	[redacted]
	Slovakia	[redacted]
	Slovenia	[redacted]
	Spain	[redacted]
	Sweden	[redacted]
Asia Pacific	Asia Pacific	333,600
Europe/non-EEA[a]	Europe/non-EEA	200,899
	Switzerland	[redacted]
	United Kingdom	[redacted]
Latin America	Latin America	115,459
Middle East and Africa	Middle East and Africa	63,581
US and Canada	US and Canada	[redacted]
Other	Other	761
Total		3,510,628

EEA=European Economic Area

Table 1–1: Cumulative patient exposure by region till 28 Feb 2023

Region	Country	Patient-years for the cumulative interval

[a] The UK withdrew from the EU and EEA on 31 Jan 2020. As of 14 Apr 2021, UK exposure data are presented in the Europe/non-EEA category instead of the Europe/EEA category. Therefore, cumulative exposure data for Europe/EEA may be different from prior versions of this report

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Lacosamide is not an immediate precursor of any known controlled substance, nor does it have physico-chemical properties similar to any controlled substance. Hence, this class of drug is not generally associated with abuse or diversion. In the US, LCM is classified under Schedule V.

Lacosamide is known to exert at least part of its effect through action at the sodium channel. Other established AEDs that operate through sodium channel actions include phenytoin, carbamazepine, and lamotrigine. None of these drugs is scheduled under the US Controlled Substances Act, nor have any of them demonstrated abuse potential after years in the marketplace.

There was no evidence for abuse liability of LCM in in vitro radioligand binding experiments, animal studies in rats, or in human abuse liability studies (SP903). After prolonged administration, there were no tolerance or abrupt cessation symptoms in rats or humans (see EU-RMP Part II, Module SII).

Results of a randomized, placebo-controlled human abuse liability study (SP903) in recreational drug users demonstrated minimal abuse potential with LCM. Review of adverse events reported during other Phase 1-3 clinical studies also demonstrated minimal evidence of abuse potential. Further review of adverse events collected during Taper and Discontinuation Phases showed no increase in withdrawal syndrome-related adverse events in LCM-treated patients compared with placebo.

Lacosamide is a prescription drug and will be distributed by regionally established and controlled distribution lines. Therefore, the potential for diversion is minimized.

In summary, there is minimal potential for abuse of LCM and events are monitored through routine pharmacovigilance.

PART II: MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable since this is not an initial RMP.

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

There is no new safety concern or reclassification.

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

For adverse event (AE) data provided in this section, pooled data are available from study participants with partial-onset seizures (POS; Epilepsy [EP] Pool S1 and EP Pool S2), study participants with diabetic neuropathic pain (DNP; DNP Pool S1 and DNP Pool S2), and pediatric study participants with POS (Pool SPX-1). The safety data pools are defined in Table 3–1.

Table 3–1: Overview of safety pools

Pool	Definition	Studies included
Study participants with partial-onset seizures (POS)		
Epilepsy (EP) Pool S1 (original submission)	Study participants receiving at least 1 dose of placebo or lacosamide (LCM) from the double-blind, placebo-controlled studies (N=924)	SP667, SP754, SP755
EP Pool S2 (original submission)	Study participants receiving at least 1 dose of LCM from the double-blind, placebo-controlled studies and study participants who received at least 1 dose of LCM in open-label studies (N=1327)	SP607, SP615, SP667, SP754, SP755, SP756, SP774
Study participants with diabetic neuropathic pain (DNP)		
DNP Pool S1 (original submission)	Study participants with DNP receiving at least 1 dose of placebo or LCM from the double-blind, placebo-controlled studies (N=1023)	SP614, SP742, SP743, SP768
DNP Pool S2 (original submission)	Study participants with DNP receiving at least 1 dose of LCM from the double-blind, placebo-controlled studies and study participants who received at least 1 dose of LCM in open-label studies (N=1566)	SP614, SP665, SP742, SP743, SP745, SP746, SP768, SP830

Table 3–1: Overview of safety pools

Pool	Definition	Studies included
Pediatric study participants with POS		
Pool SPX-1 (final data, data cutoff 27 May 2022)	The analysis pool to support the pediatric submissions in study participants ≥1 month to <4 years of age and ≥4 to <16 years of age. Pediatric study participants with POS who received at least 1 dose of LCM (N=870)	SP847, SP848,[a] EP0034

DNP=diabetic neuropathy; EP=epilepsy; LCM=lacosamide; POS=partial-onset seizure
[a] Patients enrolled in SP848 from SP0966 (generalized seizure) are not included in Pool SPX-1

Other AE data for controlled, uncontrolled, and long-term follow-up studies in study participants with POS and primary generalized tonic clonic seizures have become available and are presented on study basis in Table 3–2 and Table 3–3, respectively.

Table 3–2: Overview of individual studies in study participants with POS

Study number/ Status	Study name
Controlled studies	
EP0008/ Completed	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of lacosamide as adjunctive therapy in Japanese and Chinese adults with uncontrolled partial-onset seizures with or without secondary generalization
SP0969/ Completed	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥4 years to <17 years of age with partial-onset seizures.
Adjunctive therapy study SP0967/ Completed	A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of lacosamide as adjunctive therapy in subjects with epilepsy ≥1 month to <4 years of age with partial-onset seizures.
Conversion to monotherapy study SP902/ Completed	A historical-controlled, multicenter, double-blind, randomized trial to assess the efficacy and safety of conversion to lacosamide 400mg/day monotherapy in subjects with partial-onset seizures
Monotherapy study SP0993/ Completed	A multicenter, double-blind, double-dummy, randomized, positive controlled study comparing the efficacy and safety of lacosamide (200 to 600mg/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

Table 3–2: Overview of individual studies in study participants with POS

Study number/ Status	Study name
Long-term, follow-up studies	
EP0009/ Completed	A multicenter, open-label, uncontrolled, long-term, extension study to evaluate the safety and efficacy of lacosamide as adjunctive therapy in Japanese and Chinese adults with partial-onset seizures with or without secondary generalization coming from EP0008
SP942/ Completed	Post-authorization safety study to evaluate the long-term safety and tolerability of VIMPAT (lacosamide) as add-on therapy in epilepsy patients with partial-onset seizures who are uncontrolled on current therapy
SP1007/ Completed	A multicenter, open-label study to evaluate the tolerability, safety and efficacy of lacosamide (200-400mg/day) as add-on therapy for patients with partial-onset epilepsy using a flexible dose-escalation schedule and individualized maintenance doses
Conversion to monotherapy study SP904/ Completed	A multicenter, open-label extension trial to assess the long-term use of lacosamide monotherapy and safety of lacosamide monotherapy and adjunctive therapy in subjects with partial-onset seizures
Monotherapy study SP0994/ Completed	A multicenter, double-blind, double-dummy, follow-up study evaluating the long-term safety of lacosamide (200 to 600mg/day) in comparison with controlled release carbamazepine (400 to 1200mg/day), used as monotherapy in subjects with partial-onset or generalized tonic-clonic seizures ≥16 years of age coming from SP0993

Table 3–3: Overview of individual studies in study participants with primary generalized tonic clonic seizures

Study number/ Status	Study name
Controlled studies	
SP0982/ Completed	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy
Uncontrolled studies	

Table 3–3: Overview of individual studies in study participants with primary generalized tonic clonic seizures

Study number/ Status	Study name
SP0961/ Completed	An open-label pilot study to assess the safety of oral lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy
Long-term, follow-up studies	
SP0962/ Completed	An open-label extension study to assess the safety and seizure frequency associated with long-term oral lacosamide for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy
EP0012/ Ongoing (database lock 03 May 2023)[a]	An open-label, multicenter extension study to evaluate the long-term safety and efficacy of lacosamide as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy

[a] EP0012 was ongoing at the time of the data cutoff for this EU Risk Management Plan update (28 Feb 2023). Database lock occurred on 03 May 2023.

Throughout this section for studies not included in data pools, the frequencies of AEs reported are presented by individual studies. Of note, in the Summary of Product Characteristics, the frequencies of AEs reported are based on placebo-controlled pooled data in epilepsy, and therefore, may be different from those presented below.

3.1 Presentation of important identified risks and important potential risks

When relevant and available, the clinical incidence data in Table 3–4 are presented in the following order: Controlled studies (EP Pool S1, DNP Pool S1, EP0008, pediatric study [SP0969], conversion to monotherapy study [SP902], monotherapy study [SP0993], adjunctive therapy study [SP0967], and PGTCS study [SP0982]), uncontrolled studies (SP0961 and SP0962), and long-term, follow-up studies (EP Pool S2, DNP Pool S2, EP0009, Pool SPX-1, SP942, SP1007, SP904, SP0994, and EP0012).

The term “incidence” in the below tables refers to the percentage of study participants with an event among study participants at risk.

3.1.1 Important identified risk

Important identified risk with LCM treatment is characterized in Table 3–4.

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

Medical Dictionary for Regulatory Activities terms (v22.0)	Preferred Terms: AV block first degree, AV block second degree, AV block, AV block complete, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Arrhythmia, Tachyarrhythmia, Bradycardia, Bradycardia neonatal, Sinus bradycardia, Atrial fibrillation, Atrial flutter, Syncope, Presyncope, Electrocardiogram PR prolongation, Electrocardiogram abnormal, Ventricular fibrillation, Ventricular flutter, Ventricular tachycardia, Bradyarrhythmia, Cardiac arrest, Heart rate decreased, Neonatal sinus bradycardia, Neonatal bradyarrhythmia, Sinus node dysfunction, Ventricular asystole, and Ventricular tachyarrythmia.
Potential mechanisms	The mechanism for lacosamide (LCM) effect on the PR interval is unknown. The inhibitory effect of LCM on the cardiac Na+ current in nonclinical studies could be a potential mechanism (Kellinghaus, 2009). In preclinical studies, LCM partially inhibited the cardiac Na+ current that is associated with a decrease in upstroke velocity and duration of the action potential in vitro and with slowing of cardiac impulse propagation which may appear as prolongation of PR interval in vivo. The potential mechanism for atrial fibrillation/flutter is linked to an underlying cardiac pathology/risk factors as outlined above. The mechanisms underlying atrial fibrillation are complex, involving both increased spontaneous ectopic firing of atrial cells and impulse reentry through atrial tissue. Gene variants impairing Na+ channel function promote atrial fibrillation, presumably via conduction slowing that favors re-entry (Wakili et al, 2011). However, none of these mutations selectively affect slow inactivation, as LCM does, and they also affect fast inactivation in different manners. Moreover, the effect of a mutation cannot be directly compared to a pharmacological modulation of Na+ channels. Ictal bradycardia and bradyarrhythmias are caused by an increase in parasympathetic activity or a disruption of sympathetic activity resulting from propagating ictal activity in the respective autonomic cortical or subcortical networks (Sevcencu and Struijk, 2010). Lacosamide interacts with cardiac sodium channels, and therefore, could potentially affect normal cardiac electrophysiology. Strong sodium channel inhibition can delay intraventricular conduction, which is observed on electrocardiogram (ECG) as QRS widening. QRS prolongation can predispose to ventricular arrhythmia by prolonging repolarization. This effect is expected to be more pronounced and potentially become clinically significant in patients with ongoing proarrhythmic conditions, especially in combination with concomitant sodium channel blocker or PR interval prolonging medications.

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

Evidence source(s) and strength of evidence	In in vitro preclinical studies, LCM exerted a concentration-dependent inhibition of sodium currents in mammalian cells expressing human cardiac sodium channels as well as in human atrial myocytes. In an in vitro patch-clamp study (NCD3699), the kinetics of $Na_V1.5$ peak current blockade (off-rate time constant) of LCM and 3 other reference antiarrhythmic drugs (AADs; quinidine: Class 1A AAD, mexiletine: Class 1B AAD, and flecainide: Class 1C AAD) were evaluated in order to determine the LCM Vaughan Williams' AAD classification. When tested at 8.5mM (ie, at its $Na_V1.5$ half maximum inhibitory concentration), LCM showed a recovery from block (at -15mV for 200s) similar to that of mexiletine. Therefore, LCM can be classified as a Class 1B AAD. Note that the LCM concentration used for this AAD classification (8.5mM) corresponds to over 200-fold the free therapeutic plasma concentration (37µM) at the maximum recommended human dose (400mg/day). Therefore, these data are not considered to be clinically relevant. In halothane-anesthetized dogs, LCM showed transient increases in PR interval and QRS complex duration. These transient changes observed in anesthetized dogs started in the same concentration range as that observed with maximum recommended clinical dosing and well correlated with the sodium channel blockade observed in vitro. In addition, in anesthetized dogs, intravenous administration of LCM dose-dependently decreased arterial blood pressure, left ventricular pressure, contractility, and cardiac output, starting at plasma concentrations slightly above those in healthy human volunteers after oral doses of 300mg twice daily. At higher doses, atrioventricular (AV) block and AV dissociation were also seen in anesthetized dogs and monkeys. Although the conditions under which these tests were conducted (anesthetized animals) are not completely comparable to the normal clinical conditions, similar findings were observed in clinical studies (PR interval prolongation and AV blocks). In the Phase 1 clinical pharmacology studies SP587 and SP640, an apparent dose-related increase of PR interval was observed. In the double-blind, placebo-controlled studies (EP Pool S1), a small, dose-related increase in the mean PR interval change from baseline was observed among the LCM treatment groups. This risk was upgraded by UCB from important potential risk to important identified risk based on a cumulative analysis of postmarketing data which indicated a causal relationship with LCM.
Characterization of risk	**Incidence (percentage of study participants with event among study participants at risk)** **Clinical development** **Controlled studies** The incidence in clinical studies of study participants with partial-onset seizure (POS), study participants with diabetic neuropathic pain (DNP), and study participants with primary generalized tonic-clonic seizures (PGTCS) is

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	summarized by individual treatment-emergent changes in PR interval and treatment-emergent adverse events (TEAEs) potentially related to PR interval prolongation and sodium channel modulation. Of note, study participants with POS or PGTCS were generally healthy from a cardiovascular standpoint, while study participants with DNP characteristically have underlying macro- and microvascular disease processes associated with longstanding diabetes. In controlled studies, individual treatment-emergent changes in PR interval were classified as observed values >200ms, >220ms, or >250ms. EP Pool S1 In the double-blind, placebo-controlled studies in study participants with POS (EP Pool S1), the incidences of treatment-emergent PR prolongation >200ms within the individual LCM treatment groups was higher than that in the placebo group (11.2%, 9.0%, 7.1%, and 4.5% for the LCM 200mg/day, LCM 400mg/day, LCM 600mg/day, and placebo treatment groups, respectively); the higher incidences do not show a relationship to LCM dose. Placebo-treated study participants were slightly more likely to have a treatment-emergent PR interval >220ms than the LCM treated study participants (0.8%, 2.2%, 0.5%, and 2.8% of study participants in the LCM 200mg/day, 400mg/day, 600mg/day, and placebo treatment groups, respectively). There were 4 study participants who had a treatment-emergent PR interval >250ms (3 study participants in the LCM 400mg/day treatment group and 1 study participant in the LCM 600mg/day treatment group). The frequency of TEAEs potentially related to PR interval prolongation was low in both the LCM and placebo groups. Eight occurred in study participants randomized to LCM (AV block first degree and sinus bradycardia in 3 [0.3%] LCM-treated study participants each [no events in placebo-treated study participants], and syncope and ECG PR prolongation in 1 [0.1%] LCM-treated study participant each [no events of ECG PR prolongation and 1 event of syncope (0.3%) were reported in placebo-treated study participants]). DNP Pool S1[b] Overall, in the double-blind, placebo-controlled studies in study participants with DNP (DNP Pool S1), there was a higher proportion of study participants in the active treatment groups who had treatment-emergent PR prolongation of >200ms (11.2%, 14.8%, and 16.3% of study participants in the LCM 200mg/day, 400mg/day, and 600mg/day treatment groups, respectively) than in the placebo group (6.8%). The incidence of study participants with treatment-emergent increases in PR interval of >220ms also seemed to be related to the dose of LCM (4.1%, 6.1%, and 8.3% for study participants in the LCM 200mg/day, LCM 400mg/day, and LCM 600mg/day treatment groups, respectively [the incidence in placebo-treated study participants was 3.9%]). Though slightly higher in the active treatment groups than in the placebo group, the number of study participants with PR intervals of >250ms was nonetheless relatively low in all treatment groups, and there was no evidence of a dose related increase (2.7%, 1.7%, and 2.3% for study participants in the LCM 200mg/day, LCM 400mg/day,

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	and LCM 600mg/day treatment groups, respectively [the incidence in placebo-treated study participants was 0.4%]). The frequency of TEAEs potentially related to PR interval prolongation was similar between LCM and placebo. Twenty-three events occurred in study participants randomized to LCM: AV block first degree (5 LCM-treated study participants [0.5%], no events in placebo-treated study participants), bradycardia and ECG PR prolongation (4 LCM-treated study participants [0.4%] each), bradycardia (1 placebo-treated study participant [0.3%] and no ECG PR prolongation in placebo-treated study participants), AV block second degree (1 LCM-treated study participant [<0.1%] and no AV block second degree in placebo-treated study participants), and ventricular fibrillation (1 LCM-treated study participant [<0.1%] and none in placebo-treated study participants). In addition, syncope was reported in 8 LCM-treated study participants (0.8%), and no events of syncope were reported in placebo-treated study participants. EP0008 A total of 18 study participants (3.5%) experienced a treatment-emergent PR interval of >200ms, the incidence of which was higher in the LCM 400mg/day group (5.2%) compared with the LCM 200mg/day group (2.4%) and the placebo group (2.8%). In addition, a total of 5 study participants (0.9%) experienced a treatment-emergent PR interval of >220ms, the incidence of which was also higher in the LCM 400mg/day group (2.2%) compared with the LCM 200mg/day group (0 study participants) and the placebo group (0.5%). One study participant in the LCM 400mg/day group (0.6%) and no study participants in the placebo group experienced a treatment-emergent PR interval of >250ms. This study participant had a PR interval of 295ms at Week 4 during the Titration Period; PR intervals for this study participant at all prior and subsequent visits were <200ms (EP0008 clinical study report [CSR] Listing 21). At Week 4, this study participant had a documented ECG abnormality of first degree AV block (EP0008 CSR Listing 22), although no ECG-related TEAEs were reported (EP0008 CSR Listing 17.4). Overall, a total of 10 study participants in the LCM treatment group reported 10 cardiac-related TEAEs of interest for this cardiac risk. The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM and placebo treatment groups during the Treatment Period in EP0008: AV block first degree (LCM: 4 study participants, 1.1%, 4 events; placebo: 0 study participants), bradycardia (LCM: 2 study participants, 0.6%, 2 events; placebo: 0 study participants), bundle branch block left, sinus bradycardia, and defect conduction intraventricular (LCM: 1 study participant, 0.3%, and 1 event each; placebo: 0 study participants), and syncope (LCM: 1 study participant, 0.3%, 1 event; placebo: 1 study participant, 0.5%, 1 event) (EP0008 CSR Table 10.3.1.3). Pediatric study SP0969

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	In SP0969, 8 study participants in the LCM treatment group reported 8 cardiac-related TEAEs of interest and 3 study participants in the placebo treatment group reported 3 cardiac-related TEAEs of interest for this cardiac risk during the Treatment Period (defined as the Titration Period plus Maintenance Period) (SP0969 Labeling Update Table 1.2.1.1). The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM treatment group during the Treatment Period by 1 study participant (0.6%) each: arrhythmia supraventricular, AV block first degree, bradycardia, and left ventricular hypertrophy. All cardiac-related TEAEs of interest for this cardiac risk in the LCM treatment group were reported in the ≥4 to <12 years age group (SP0969 Labeling Update Table 1.2.1.1 and Table 1.2.1.2). No ventricular TEAEs of interest were reported. In the Investigations System Organ Class (SOC), ECG QT prolonged was reported by 2 study participants (1.2%) in the LCM treatment group and 3 study participants (1.7%) in the placebo treatment group. One study participant in the LCM treatment group and 2 study participants in the placebo treatment group were in the ≥4 to <12 years age group, and 1 study participant in the LCM treatment group and 1 study participant in the placebo treatment group were in the ≥12 to <17 years age group (SP0969 Labeling Update Table 1.2.1.1 and Table 1.2.1.2). Electrocardiogram QRS complex prolonged was reported by 1 study participant (0.6%) in the LCM treatment group (≥12 to <17 years age group) and 0 study participants in the placebo treatment group. In addition, 1 study participant (0.6%) in the LCM treatment group (≥12 to <17 years age group) and 0 study participants in the placebo treatment group reported syncope (SP0969 Labeling Update Table 1.2.1.1 and Table 1.2.1.2). The same study participant in the LCM group also reported syncope 6 days after stopping LCM during the Safety Follow-up period. <u>Adjunctive therapy SP0967</u> In the LCM-treated group, 1 study participant reported a cardiac-related TEAE of interest (0.8%, 1 event): the cardiac-related TEAE of interest was sinus bradycardia (SP0967 final CSR, Table 11.2.1). The event was not serious, not related to LCM, mild in intensity, had not recovered, and did not lead to study discontinuation (SP0967 final CSR Listing 7.3). <u>Conversion to monotherapy study SP902</u> In SP902, a total of 14 study participants (3.6%) experienced a treatment-emergent PR interval of >200ms, the incidence of which was higher in the LCM 300mg/day group (6.3%) compared with the LCM 400mg/day group (2.7%). Only 2 study participants, both in the LCM 400mg/day group (0.6%), experienced a PR interval of >220ms. One of these study participants (0.3%) experienced a PR interval of >250ms. Overall, a total of 5 study participants in the LCM treatment group reported 6 cardiac-related TEAEs of interest for this cardiac risk.

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	The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM-treated study participants during the Treatment Period in SP902: AV block first degree (2 study participants, 0.5%, 3 events) and sinus bradycardia, tachycardia, and ECG abnormal (1 study participant, 0.2%, and 1 event each). No TEAEs of syncope were reported (SP902 CSR Table 11.2.2). Monotherapy study SP0993 In SP0993, 40 study participants (9.6%) in the LCM treatment group and 37 study participants (8.9%) in the carbamazepine controlled release (CBZ-CR) treatment group experienced a treatment-emergent PR interval of >200ms. Sixteen study participants (3.7%) in the LCM treatment group and 13 study participants (3.0%) in the CBZ-CR treatment group experienced a treatment-emergent PR interval of >220ms. Three study participants in each treatment group (0.7% in each treatment group) experienced a PR interval of >250ms. These 3 study participants with a PR interval of >250ms did not report any ECG-related TEAEs during the study. Overall, a total of 40 study participants in the LCM treatment group reported 41 cardiac-related TEAEs of interest for this cardiac risk and a total of 26 study participants in the CBZ-CR treatment group reported 29 cardiac-related TEAEs of interest for this cardiac risk. The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM and CBZ-CR treatment group during the Treatment Period in SP0993: AV block first degree (LCM: 9 study participants, 2.0%, 9 events; CBZ-CR: 8 study participants, 1.8%, 10 events), sinus bradycardia (LCM: 7 study participants, 1.6%, 7 events; CBZ-CR: 9 study participants, 2.0%, 10 events), bradycardia (LCM: 4 study participants, 0.9%, 5 events; CBZ-CR: 4 study participants, 0.9%, 4 events), sinus tachycardia (LCM: 4 study participants, 0.9%, 4 events; CBZ-CR: 0 study participants), defect conduction intraventricular (LCM: 2 study participants, 0.5%, 2 events; CBZ-CR: 0 study participants), tachycardia (LCM: 2 study participants, 0.5%, 2 events; CBZ-CR: 1 study participant, 0.2%, 1 event), atrial fibrillation (1 study participant, 0.2%, 1 event in each treatment group), heart rate decreased, sinoatrial block, heart rate increased, and tachycardia paroxysmal (1 study participant, 0.2%, 1 event; CBZ-CR: 0 study participants), and AV block (LCM: 0 study participants; CBZ-CR: 2 study participants, 0.5%, 2 events). No ventricular TEAEs of interest were reported. In addition, syncope was observed during SP0993 (LCM: 7 study participants, 1.6%, 7 events; CBZ-CR: 1 study participant, 0.2%, 1 event) (SP0993 CSR Table 10.3.8). The events of syncope observed with LCM were primarily related to orthostatic hypotension or a vagal reaction. The EU Summary of Product Characteristics (SmPC) has been updated to reflect the data on syncope from SP0993. PGTCS study SP0982 Overall, mean and median changes from Baseline to Last Visit for all 12-lead ECG parameters were small, with the exception of mean change in PR interval,

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	which was 9.96ms in the LCM treatment group compared with -0.79ms in the placebo treatment group. This effect is consistent with the known safety profile of LCM. No clinically relevant mean or median changes from Baseline to Last Visit were observed for any 12-lead ECG parameter. No TEMA 12 lead ECG results were reported in the 3 years to <12 years age categories. In the ≥12 years to <17 years age category for the Last Visit, PR interval >200ms was reported in 1/10 study participants (10.0%) in the Placebo group and ≥25% increase from Baseline was reported in 1/10 study participants (10.0%) in the LCM group. In the ≥17 years age category for the Last Visit, PR interval >200ms was reported in 3/101 study participants (3.0%) in the LCM group and 1/102 study participants (1.0%) in the Placebo group. Four (3.3%) study participants in the LCM treatment group reported 4 cardiac-related TEAEs of interest and 3 (2.5%) study participants in the placebo treatment group reported 4 cardiac-related TEAEs of interest for this cardiac risk during the Treatment Period (SP0982 CSR Table 11.2.1.1). The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM treatment group during the Treatment Period: bundle branch block right (2 study participants with 1 event each; 1.7%), arrhythmia (1 study participant with 1 event; 0.8%), and AV block first degree (1 study participant with 1 event; 0.8%). One event of right bundle branch block was reported in the ≥4 to <12 years age group and the event of AV block first degree was reported in the ≥12 to <18 years age group (SP0982 CSR Table 11.2.1.2). **Uncontrolled studies** PGTCS study SP0961 In SP0961, no study participants reported a TEAE potentially associated with cardiac-related TEAEs of interest for this cardiac risk. PGTCS study SP0962 In SP0962, no study participants reported a TEAE potentially associated with cardiac-related TEAEs of interest for this cardiac risk. **Long-term follow-up studies** EP Pool S2 In total in EP Pool S2, there were 59 (4.4%) treatment-emergent “other significant AEs” in the Cardiac disorders SOC related to cardiac and ECG abnormalities (Integrated Summary of Safety [ISS] POS/DNP Section 6.13.3.1.2). In the General disorders and administration site conditions SOC, there were 48 (3.6%) treatment-emergent “other significant AEs” related to cardiac and ECG abnormalities. In the Investigations SOC, there were 17 (1.3%) treatment-emergent “other significant AEs” related to cardiac and ECG abnormalities. Additional cardiovascular terms not included as an “other significant AE” are myocardial infarction, acute myocardial infarction, and cardio-respiratory arrest. In EP Pool S2, there were 2 events of myocardial infarction, 1 of acute myocardial

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	infarction, and 1 of cardio-respiratory arrest. No ventricular TEAEs of interest were reported. DNP Pool S2 One hundred sixteen study participants (7.4%) experienced an "other significant AE" in the Cardiac disorders SOC; all other significant events in the Cardiac disorders SOC were experienced by <1% of study participants and were distributed over a large number of events. The most common events were angina pectoris (16 study participants, 1.0%), palpitations (15 study participants, 1.0%), and bundle branch block right (13 study participants, 0.8%). There were 45 (2.9%) study participants who had ECG results that were considered to be "other significant AEs"; all other significant events in the ECG results were experienced by less than 1% of study participants. Most individual cardiac- and ECG-related AEs occurred at frequencies <1% and were scattered over a large number of events similar to those reported in DNP Pool S1. EP0009 In EP0009, 29 LCM-treated study participants (6.4%) experienced a treatment-emergent PR interval of >200ms during the Treatment Period. Seven study participants (1.5%) experienced a treatment-emergent PR duration of >220ms during the Treatment Period, and no study participant experienced a PR interval of >250ms (EP0009 CSR Table 10.5.1). A total of 5 LCM-treated study participants reported 5 cardiac-related TEAEs of interest for this cardiac risk. The following cardiac-related TEAEs of interest for this cardiac risk were reported during the Treatment Period in EP0009: arrhythmia (3 study participants, 0.6%, 3 events), AV block first degree (4 study participants, 0.8%, 4 events), bradycardia (1 study participant, 0.2%, 1 event), bundle branch block left (2 study participants, 0.4%, 2 events), bundle branch block right (1 study participant, 0.2%, 1 event), sinus arrhythmia (1 study participant, 0.2%, 1 event), sinus bradycardia (8 study participants, 1.7%, 9 event) (EP0009 final CSR Table 7.2.1.1). No events of syncope were reported. No TEAEs potentially related to ECG findings were serious (EP0009 final CSR Table 8–19). Three TEAEs related to ECG findings (ECG QT prolonged, defect conduction intraventricular, and arrhythmia) led to study discontinuation (EP0009 final CSR Table 8–251). Pool SPX-1 In Pool SPX-1, while an increase in PR interval was observed, a similar increase was observed across weight bands. As increase in PR interval has also been observed with LCM usage in epilepsy patients ≥16 years, the current data suggest no new safety signal for LCM treatment in pediatric patients with epilepsy ≥1 month (SCS Section 4.2.4). In study participants ≥1 month to <4 years of age, a total of 11 study participants in the LCM treatment group reported 16 cardiac-related TEAEs. In study

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	participants ≥1 month to <4 years of age, the following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM treatment group during the Treatment Period in Pool SPX-1: AV block first degree (3 study participants, 1.1%, 8 events); sinus bradycardia (2 study participants, 0.7%, 2 events); and bradycardia, defect conduction intraventricular, and Brugada syndrome (1 study participant, 0.4%, 1 event each). In study participants ≥4 to <12 years of age, a total of 11 study participants in the LCM treatment group reported 15 cardiac-related TEAEs. In study participants ≥4 to <12 years of age, the following cardiac-related TEAEs of interest for this cardiac risk were reported during LCM exposure in Pool SPX-1: AV block first degree (3 study participants, 0.9%, 4 events), bradycardia (2 study participants, 0.6%, 2 events), cardiac arrest (1 study participant, 0.3%, 1 event), sinus tachycardia (1 study participant 0.3%, 1 event), and bundle branch block (1 study participant, 0.3%, 1 event). In pediatric study participants >12 to <18 years of age, a total of 6 study participant in the LCM treatment group reported 8 cardiac-related TEAEs. In study participants >12 to <18 years of age, the following cardiac-related TEAEs of interest for this cardiac risk were reported during LCM exposure in Pool SPX-1: AV block first degree (2 study participants, 0.8%, 2 events); bradycardia (1 study participant, 0.4%, 1 event); sinus tachycardia (1 study participant 0.3%, 2 events); and defect conduction intraventricular, nodal arrythmia, and ventricular extrasystoles (1 study participant, 0.4%, 1 event each). SP942 In this postauthorization safety study, in 5 patients in the VIMPAT group, ECG abnormalities not present at Baseline (related to the identified cardiovascular risks) were reported after initiating treatment with VIMPAT (1 patient with AV block first degree, 1 patient with atrial fibrillation, 2 patients with atrial flutter, and 1 patient with sinus bradycardia). For 4 of these patients, an AE was reported (the patient with observed sinus bradycardia was not considered clinically significant). No TEAEs of syncope were reported in a patient receiving VIMPAT. No ventricular TEAEs of interest were reported. SP1007 No cardiac-related TEAEs of interest for this cardiac risk were reported. Conversion to monotherapy study SP904 In SP904, 27 LCM-treated study participants (8.7%) experienced a treatment-emergent PR interval of >200ms during the Treatment Period. Nine study participants (2.9%) experienced a treatment-emergent PR duration of >220ms during the Treatment Period. Two study participants (0.6%) experienced a PR interval of >250ms (SP904 CSR Table 11.5.1). A total of 29 study participants in the Overall LCM treatment group reported 31 cardiac-related TEAEs of interest for this cardiac risk. The following cardiac-

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	related TEAEs of interest for this cardiac risk were reported in the LCM treatment group during the Treatment Period in SP904: bradycardia (5 study participants, 1.6%, 5 events), sinus tachycardia (3 study participants, 0.9%, 3 events), AV block first degree, sinus bradycardia, bundle branch block right, heart rate decreased, heart rate increased, tachycardia (2 study participants, 0.6%, 2 events each), and defect conduction intraventricular, supraventricular tachycardia, and ECG PR prolongation (1 study participant [0.3%] each). No ventricular TEAEs of interest were reported. Treatment-emergent AEs of syncope (6 study participants, 1.9%, 6 events) and TEAEs of presyncope (2 study participants, 0.6%, 2 events) were reported; however, there is no evidence these were cardiac-related events (SP904 CSR Table 8.2.1). Of the 29 study participants with TEAEs of interest provided above, 19 study participants had cardiac-related TEAEs of interest for this cardiac risk while on LCM monotherapy and 10 study participants had cardiac-related TEAEs of interest for this cardiac risk while not on LCM monotherapy (SP904 CSR Table 8.2.1; SP904 CSR Table 8.2.2). Taking into account the limited number of study participants included in SP904 and the long duration of the study, the characterization of risk is not considered to have changed compared to the EP Pool S1 studies. <u>Monotherapy study SP0994</u> In SP0994, 27 LCM-treated study participants (11.9%) and 21 CBZ-CR-treated study participants (9.4%) experienced treatment-emergent PR intervals of >200ms during the Treatment Period. Nine LCM-treated study participants (3.8%) and 9 CBZ-CR-treated study participants (4.0%) experienced treatment-emergent PR intervals of >220ms during the Treatment Period. Two LCM-treated study participants (0.8%) and 1 CBZ-CR-treated study participant (0.4%) experienced treatment-emergent PR intervals of >250ms during the Treatment Period (SP0994 CSR Table 12.5.2). A total of 14 study participants in the LCM treatment group reported 20 cardiac-related TEAEs of interest for this cardiac risk and a total of 10 study participants in the CBZ-CR treatment group reported 11 cardiac-related TEAEs of interest for this cardiac risk. The following cardiac-related TEAEs of interest for this cardiac risk were reported in the LCM and CBZ-CR treatment groups during the Treatment Period in SP0994: AV block first degree (LCM: 3 study participants, 1.1%, 4 events; CBZ-CR: 2 study participants, 0.8%, 2 events), bradycardia (LCM: 2 study participants, 0.8%, 6 events; CBZ-CR: 2 study participants, 0.8%, 2 events), sinus bradycardia (LCM: 2 study participants, 0.8%, 3 events; CBZ-CR: 2 study participants, 0.8%, 2 events), atrial fibrillation (LCM: 2 study participants, 0.8%, 2 events; CBZ-CR: 0 study participants), bundle branch block left (LCM: 1 study participant [0.4%]; CBZ-CR: 1 study participant [0.4%]), AV block second degree (LCM: 0 study participants; CBZ-CR: 1 study participant [0.4%]), defect conduction intraventricular (LCM: 0 study participants; CBZ-CR: 1 study participant [0.4%]), ECG abnormal (LCM: 1 study participant [0.4%];

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	CBZ: 0 study participants), and ECG PR prolongation (LCM: 0 study participants; CBZ-CR: 1 study participant [0.4%]). No ventricular TEAEs of interest were reported. Treatment-emergent AEs of syncope (LCM: 4 study participants, 1.5%, 4 events; CBZ-CR: 1 study participant [0.4%]) and TEAEs of presyncope (LCM: 1 study participant [0.4%]; CBZ-CR: 0 study participants) were reported; however, there is no evidence these were cardiac-related events (SP0994 CSR Table 10.3.1). PGTCS study EP0012 As of the clinical cutoff date for this interim CSR (28 Aug 2019), overall, TEMA 12-lead ECG results were reported as follows: 10/35 study participants (28.6%) at Visit 1 (Week 0), 42/126 study participants (33.3%) at Visit 8 (Week 46), 23/67 study participants (34.3%) at Visit 11 (Week 94), and 65/208 study participants (32.8%) at the Last Visit (Table 16.3). As of the clinical cutoff date of 28 Nov 2019, 7 LCM-treated study participants reported 9 cardiac-related TEAEs of interest for this cardiac risk in EP0012: sinus tachycardia (2 study participants, 0.9%, 3 events), bradycardia (1 study participant, 0.5%, 2 events), AV block first degree (1 study participant, 0.5%, 1 event), bundle branch block right (1 study participant, 0.5%, 1 event), and syncope (1 study participant, 0.5%, 1 event) (EP0012 Interim CSR Table 10.2). **Postmarketing** A safety signal assessment for cardiac arrhythmias with serious outcomes was performed based on an overall review of data from the UCB Global Safety database, additional cases identified by the US Food and Drug Administration (FDA), nonclinical data, clinical data, epidemiological data, and expert opinion from a cardiologist. The signal for ventricular tachyarrhythmias and AV block, which occur very rarely and are potentially fatal, in patients with underlying proarrhythmic conditions (ie, severe cardiac disease, cardiac conduction disorders, sodium channelopathies, structural heart disease) was confirmed. Concomitant medications affecting cardiac conduction, including antiarrhythmics and sodium channel blocker drugs (including antiepileptics), are confirmed to be a contributing risk factor for these events in these patients. The signal is refuted in patients who do not have underlying proarrhythmic conditions. Ventricular tachycardia was added to Section 4.8 of the EU SmPC dated 26 Aug 2019. The US FDA approved the label change on 11 Nov 2018. A positive opinion was received from the EMA on 14 Jun 2019 and the European Commission Decision related to Var II/0073/G this label change (variation II/0073/G) was received on 31 Jul 2019; the EU SmPC was amended to include the addition of serious cardiac arrhythmia under the Posology (loading dose) Section 4.2 as follows: “It should be administered under medical supervision with consideration of the potential for increased incidence of serious cardiac arrhythmia and central nervous system adverse reactions.”
	Severity

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	Controlled studies EP Pool S1[a] Within the Cardiac disorders SOC, in the LCM-treated group, 1 event was serious (sinus bradycardia) and 3 events led to premature discontinuation from the study (1 sinus bradycardia, 2 extrasystoles). All cardiac TEAEs were considered mild to moderate in intensity. In the General disorders and administration site conditions SOC, 1 event (chest pain) in the LCM-treated group was serious and 3 events led to premature discontinuation from the study (all events leading to discontinuation were chest pain). In the Investigations SOC, within the LCM group, 2 events were serious (ie, ECG PR prolongation, ECG abnormal) and 2 events led to early discontinuation from the study (ie, ECG PR prolongation, ECG abnormal). These events did not relate to QRS prolongation. DNP Pool S1[b] Twenty-three events occurred in study participants randomized to LCM (AV block first degree, bradycardia, ECG PR prolongation, AV block second degree, ventricular fibrillation, and syncope). Three cardiac-related events were serious TEAEs (sinus bradycardia, ECG PR prolongation, and ventricular fibrillation), and 1 of these events (sinus bradycardia) resulted in study discontinuation for this study participant. The event of ventricular fibrillation resulted in death assessed as not related to LCM by the investigator. Additionally, 2 nonserious TEAEs of syncope, 1 moderate and 1 severe in intensity, both led to study discontinuation. None of these events resulted in death. EP0008 Cardiac-related TEAEs of interest for this cardiac risk in LCM treated study participants were AV block first degree, bradycardia, bundle branch block left, sinus bradycardia, defect conduction intraventricular, and syncope. All 4 TEAEs of AV block first degree were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. The TEAE of bundle branch block left was nonserious, moderate in intensity, did not lead to study discontinuation, and was considered resolved. The TEAEs of sinus bradycardia and defect conduction intraventricular were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. None of these cardiac-related TEAEs resulted in death (EP0008 CSR Listing 17.4). None of these study participants had an increase in PR intervals >200ms throughout the study. The TEAE of syncope was nonserious, mild in intensity, did not lead to study discontinuation, and was considered resolved. Pediatric study SP0969 In SP0969, no study participants reported a TEAE potentially associated with cardiac-related TEAEs of interest for this cardiac risk that had an intensity of severe (SP0969 Labeling Update Table 1.2.2). Adjunctive therapy study SP0967

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	In SP0967, the cardiac-related TEAEs of interest were AV block second degree, AV block third degree, bradyarrhythmia, bradycardia, atrial fibrillation, atrial flutter, sinus bradycardia, ventricular tachycardia, ventricular fibrillation, and ventricular tachyarrhythmia. In the LCM-treated group, 1 event of sinus bradycardia was reported (SP0967 final CSR, Table 11.2.1). The event was not serious, not related to LCM, mild in intensity, had not recovered, and did not lead to study discontinuation (SP0967 final CSR Listing 7.3). Conversion to monotherapy study SP902 In SP902, cardiac-related TEAEs of interest for this cardiac risk were AV block first degree, sinus bradycardia, tachycardia, and ECG abnormal. Both TEAEs of AV block first degree occurred during the Titration Phase, were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. The TEAEs of sinus bradycardia, tachycardia, and ECG abnormal were considered nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved (SP902 CSR Listing 11.1.1). Monotherapy study SP0993 In SP0993, cardiac-related TEAEs of interest for this cardiac risk were AV block first degree, sinus bradycardia, bradycardia, sinus tachycardia, defect conduction intraventricular, atrial fibrillation, tachycardia, heart rate decreased, sinoatrial block, heart rate increased, tachycardia paroxysmal, and AV block. One TEAE of sinus tachycardia was serious, moderate in intensity, did not lead to study discontinuation, and was considered resolved. The 3 remaining TEAEs of sinus tachycardia were nonserious, mild in intensity, did not lead to study discontinuation, and 2 of the 3 TEAEs were considered resolved. The TEAE of atrial fibrillation was serious, moderate in intensity, did not lead to study discontinuation, and was considered resolved with sequelae. The TEAE of heart rate increased was nonserious, severe in intensity, did not lead to study discontinuation, and was considered resolved. The TEAEs of AV block first degree were nonserious, mild or moderate in intensity, 2 events led to study discontinuation, and the majority were considered resolved. The TEAEs of sinus bradycardia were nonserious, mild to moderate in severity, 1 event led to study discontinuation, and the majority were considered resolved. The TEAEs of bradycardia, defect conduction intraventricular, sinoatrial block, tachycardia, tachycardia paroxysmal, and heart rate decreased were nonserious, mild to moderate in intensity, did not lead to study discontinuation, and the majority of the TEAEs were considered resolved or resolving. Of the 7 TEAEs of syncope, 1 TEAE was serious, severe in intensity, did not lead to study discontinuation, and was considered resolved. The 6 remaining TEAEs of syncope were nonserious, mild to moderate in intensity, did not lead to study discontinuation, and all were considered resolved (SP0993 CSR Table 10.3.7;

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	SP0993 CSR Listing 7.1.1). The majority of TEAEs of syncope observed with LCM were primarily related to orthostatic hypotension or a vagal reaction. In LCM-treated study participants, the only cardiac-related TEAE of interest was 1 event of sinus bradycardia (SP0967 final CSR, Table 11.2.1). The event was not serious, not related to LCM, mild in intensity, had not recovered, and did not lead to study discontinuation (SP0967 final CSR Listing 7.3). PGTCS study SP0982 In SP0982 in LCM-treated study participants, cardiac-related TEAEs of interest for this cardiac risk were 2 events of bundle branch block right and 1 event each of arrhythmia and AV block first degree. Both TEAEs of bundle branch block right and the 1 event of arrhythmia were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. The TEAE of AV block first degree was nonserious, moderate in intensity, did not lead to study discontinuation, and was considered not resolved (SP0982 CSR Listing 7.2). **Uncontrolled studies** PGTCS study SP0961 In SP0961, no study participants reported a TEAE potentially associated with cardiac-related TEAEs of interest for this cardiac risk. PGTCS study SP0962 In SP0962, no study participants reported a TEAE potentially associated with cardiac-related TEAEs of interest for this cardiac risk. **Long-term, follow-up studies** EP Pool S2 Of the 59 treatment-emergent "other significant AEs" in the Cardiac disorders SOC related to cardiac and ECG abnormalities, 8 of these TEAEs were serious (ie, bundle branch block right, angina pectoris, sinus bradycardia [3 events], tachycardia, atrial fibrillation, and cardiac arrest) and 5 events led to premature discontinuation from the study (ie, bundle branch block right, sinus bradycardia, tachycardia, and extrasystoles [2 events] ISS POS/DNP Section 6.13.3.1.2). In the General disorders and administration site conditions SOC, 8 TEAEs were serious (ie, 7 chest pain events and 1 chest discomfort event) and 3 events led to premature discontinuation from the study (ie, 2 chest pain events and 1 chest discomfort event). In the Investigations SOC, 4 TEAEs were serious (ie, ECG QRS complex prolonged [2 events], ECG change, and ECG PR prolongation) and 3 events led to premature discontinuation from the study (ie, ECG QTc interval prolonged, ECG QRS complex prolonged, and ECG PR prolongation). Of the additional cardiovascular terms not included as an "other significant AE" (ie, myocardial infarction, acute myocardial infarction, and cardio-respiratory arrest), all events, with the exception of 1 myocardial infarction, were reported as serious. DNP Pool S2

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	Sixty-one events in the Cardiac disorders SOC were considered by the investigator to be related to study medication, 31 were serious adverse events, and 27 study participants discontinued because of an "other significant AE" in the Cardiac disorders SOC. Thirty-four events of ECG abnormalities were considered by the investigator to be related to study medication, 2 were SAEs, and 17 study participants discontinued because of ECG abnormalities that were considered to be "other significant AEs." The majority of Cardiac disorders SOC and ECG-related events were not serious. <u>EP0009</u> In EP0009, cardiac-related TEAEs of interest for this cardiac risk were arrhythmia, sinus bradycardia, and defect conduction intraventricular. Three events of arrhythmia were reported during the Treatment Period. One cardiac-related TEAE of arrhythmia was nonserious, mild in intensity, did not lead to study discontinuation, and considered resolved. One TEAE of arrhythmia was nonserious, moderate in intensity, did not lead to study discontinuation, and considered resolved. One TEAE of arrhythmia was nonserious, moderate in intensity, led to study discontinuation, and considered resolved. Eight participants reported 9 events of sinus bradycardia during the Treatment Period (1 study participant reported 2 events). One TEAE of sinus bradycardia was serious, mild in intensity, not related to study medication, and resolved. All others events of TEAE sinus bradycardia were not serious. All TEAE sinus bradycardia events were mild in intensity, except 1 case that was moderate. Five events were considered by the investigator to be related to study medication, and none of the events led to study discontinuation. Four participants reported 4 events of defect conduction intraventricular during the Treatment Period. The TEAE of defect conduction intraventricular was considered nonserious, mild (2 events), or moderate (2 events) in intensity. Two events were considered related to study medication and led to study discontinuation; the other 2 events were not related to study medication and did not lead to study discontinuation. All events were considered resolved (EP0009 final CSR Listing 12.2). <u>Pool SPX-1 (cutoff date: 27 May 2022)</u> In study participants ≥1 month to <4 years of age, a total of 3 study participants (1.1%) experienced AV block first degree; 2 study participants (0.7%) experienced sinus bradycardia; and 1 study participant (0.1%) each experienced bradycardia, defect conduction intraventricular, and Brugada syndrome. Eight events of AV block first degree; 2 events of sinus bradycardia; and 1 event each of bradycardia, defect conduction intraventricular, and Brugada syndrome were reported. All 8 events of AV block first degree were not serious and mild in intensity, 5 events were related to LCM, and none led to study discontinuation. The event of bradycardia was not serious, mild in intensity, did not lead to study discontinuation, and was not related to LCM. Both events of sinus bradycardia

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	were not serious, 1 event was moderate in intensity and 1 event was mild in intensity, 1 event led to discontinuation from the study, and both events were considered related to LCM. The events of defect conduction intraventricular and Brugada syndrome were not serious, mild in intensity, did not lead to discontinuation from the study, and were not related to LCM. In study participants ≥4 to <12 years of age, 4 events of AV block first degree, 2 events of bradycardia, 1 event of cardiac arrest, 1 event of sinus tachycardia, and 1 event of bundle branch block were reported. The 4 events of AV block first degree were not serious, mild in intensity, did not lead to study discontinuation, and were all related to LCM. One event of bradycardia was serious and not related to LCM; the other one was not serious and related to LCM. They were both mild in intensity and none lead to study discontinuation. The event of cardiac arrest was fatal. The event was serious, severe in intensity, and not related to LCM. The events of sinus tachycardia and bundle branch block were not serious, mild in intensity, not related to LCM, did not lead to study discontinuation, and had resolved. The TEAEs of tachycardia, sinus tachycardia, bundle branch block, ECG abnormal, syncope, and presyncope were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. In study participants ≥12 to ≤18 years of age, the following cardiac-related TEAEs of interest for this cardiac risk were reported during LCM exposure in Pool SPX-1: 2 events of AV block first degree; 1 event of bradycardia; 2 events of sinus tachycardia; 1 event each of defect conduction intraventricular, nodal arrhythmia, and ventricular extrasystoles. The 2 events of AV block first degree were not serious, 1 event was considered related to LCM and 1 event was considered not related to LCM, both events were mild in intensity, and both events did not lead to study discontinuation. The events of bradycardia and sinus tachycardia were not serious, mild in intensity, did not lead to study discontinuation, and was not related to LCM. The event of defect conduction intraventricular was not serious, moderate in intensity, did not lead to study discontinuation, and was related to LCM. The events of nodal arrythmia and ventricular extrasystoles were not serious, mild in intensity, did not lead to study discontinuation, and were related to LCM. <u>SP942</u> All of the cardiovascular-related TEAEs were mild or moderate in severity, and the only TEAEs judged to be related to study medication by the Investigator were sinus bradycardia and AV block first degree (0.2% of patients each in the VIMPAT group). One cardiac-related TEAE (atrial flutter) had a maximum intensity of severe. None of the predefined cardiovascular-related TEAEs were considered serious, and none led to discontinuation of any patients. <u>SP1007</u> No TEAEs associated with cardiac and ECG-related terms were reported.

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	Conversion to monotherapy study SP904 In SP904, the cardiac-related TEAEs of interest for this cardiac risk were bradycardia, sinus tachycardia, AV block first degree, sinus bradycardia, bundle branch block right, heart rate decreased, heart rate increased, tachycardia, defect conduction intraventricular, supraventricular tachycardia, ECG PR prolongation, syncope, and presyncope. One TEAE each of bradycardia and heart rate decreased were serious, severe in intensity, did not lead to study discontinuation, and were considered resolved. The remaining 4 TEAEs of bradycardia and 1 TEAE of heart rate decreased were nonserious, mild to moderate in intensity, did not lead to study discontinuation, and were considered resolved. The TEAEs of AV block first degree, bundle branch block right, heart rate increased, sinus bradycardia, defect conduction intraventricular, tachycardia, supraventricular tachycardia, and ECG PR prolongation were nonserious, mild in intensity, did not lead to study discontinuation, and the majority were considered resolved. One TEAE of sinus tachycardia was nonserious, severe in intensity, did not lead to study discontinuation, and had not resolved. Two TEAEs of sinus tachycardia were nonserious, mild to moderate in intensity, did not lead to study discontinuation, and 1 was considered resolved and the other study participant's outcome was unknown. Three TEAEs of syncope were considered serious, severe in intensity, did not lead to study discontinuation, and were considered resolved. The remaining 3 TEAEs of syncope and the 2 TEAEs of presyncope were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved (SP904 CSR Table 8.2.1; SP904 CSR Listing 9.2.1). Monotherapy study SP0994 In SP0994, in LCM-treated study participants, the cardiac-related TEAEs of interest for this cardiac risk were AV block first degree, bradycardia, sinus bradycardia, atrial fibrillation, and bundle branch block left. One TEAE of sinus bradycardia was serious, mild in intensity, did not lead to study discontinuation, and the TEAEs of sinus bradycardia first degree were nonserious, mild to moderate in intensity, did not lead to study discontinuation, and 2 of the 3 events had resolved. Two cardiac-related TEAEs of bradycardia, 1 TEAE of sinus bradycardia were nonserious, mild in intensity, did not lead to study discontinuation, and were considered resolved. One cardiac-related TEAE of bundle branch block left was nonserious, mild in intensity, did not lead to study discontinuation, and the outcome was unknown. The 4 TEAEs of syncope were nonserious, 2 events were mild in intensity, 1 event was moderate in intensity, and 1 event was severe in intensity, none led to study discontinuation, and the majority were considered resolved (SP0994 CSR). PGTCS study EP0012 In EP0012, cardiac-related TEAEs of interest for this cardiac risk were 3 events of sinus tachycardia, 2 events of bradycardia, 1 event each of AV block first degree,

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	bundle branch block right, and syncope. The 3 events of sinus tachycardia were not serious, mild in intensity, not related to study medication, and had resolved. Both TEAEs of bradycardia were nonserious, mild in intensity, did not lead to study discontinuation, and had resolved. The TEAE of AV block first degree was nonserious, mild in intensity, did not lead to study discontinuation, and was considered resolving. The TEAE of bundle branch block right was nonserious, mild in intensity, did not lead to study discontinuation, and was considered resolved. The TEAE of syncope was nonserious, mild in intensity, did not lead to study discontinuation, and was considered resolved (EP0012 Interim CSR Listing 7.2). EP0147 Real World Evidence study This study was conducted to examine the safety and tolerability of a loading dose in pediatric patients of <17 years of age. In the present study, 686 patients aged ≥1 month to <17 years and 28 patients aged <30 days were identified from large specialized pediatric centers, who received off-label iv LCM. Of 686 patients aged ≥1 month to <17 years, 68.7% vs 31.3% were administered iv LCM at the recommended dose or a loading dose as initial doses, respectively. In patients aged ≥1 month to <17 years, the crude incidence rates per 1000 person-days were 0.16 (95% CI: 0.00, 0.89) for atrioventricular (AV) block, bradyarrhythmia, ventricular tachyarrhythmia and 4.91 (95% CI: 3.29, 7.05) for bradycardia in the recommended dose cohort. No AE's from the cardiac SOC was reported in the loading dose cohort. No AE's were attributed to the use of LCM Overall, the current study findings were in line with the previously established LCM safety profile. **Long-term outcomes** First degree AV block is usually nonserious and can be asymptomatic. However, significant delay in cardiac conduction (second or third degree AV block) or significantly abnormal cardiac rhythm (bradycardia, atrial fibrillation, and atrial flutter) can be serious and/or lead to other serious complications /outcomes. In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been rarely reported. In rare cases, these events have led to asystole, cardiac arrest, and death in patients with underlying proarrhythmic conditions. Cardiac AEs can lead to syncope and can require treatment with cardioversion or a pacemaker. **Impact on quality of life** PR prolongation and first degree AV block are usually asymptomatic ECG findings, without any anticipated clinical signs or symptoms. Higher degrees of AV block are likely to be associated with irregular pulse or bradycardia and need medical evaluation. Patients with drug-induced atrial flutter often present with tachycardia and an irregular pulse, but some may be asymptomatic which usually resolve as soon as the patient stops taking the drug. Atrial fibrillation has a heterogeneous clinical presentation. Approximately one third of the patients are

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	asymptomatic (Tamargo et al, 2012). However, in other patients, the initial presentation of atrial fibrillation may be an embolic complication. Most patients however present with palpitations, chest pain, dyspnea, and fatigue (Fuster et al, 2006). In some cases, an electrical and/or pharmacological cardioversion is required to restore the sinus rhythm.
Risk factors and risk groups	The risk factors for developing AEs related to PR prolongation include a presence of pre-existing heart failure or a recent myocardial infarction or known conduction abnormalities (Ryvlin et al, 2013; Strzelczyk et al, 2008; Rocamora et al, 2003). Studies on the risk factors for AEs related to PR prolongation have been done in the general population. The incidence of atrial fibrillation increases with age (Friberg et al, 2010). Other risk factors for atrial fibrillation include a history of hypertension and cardiac diseases including valvular, ischemic, and congestive heart failure (Krahn et al, 1995). The frequency of cardiac syncope also increases with age from approximately 1.1% in people less than 40 years to 16% in individuals more than 75 years of age (Ryvlin et al, 2013; Olde et al, 2009; Ungar et al, 2006). Ictal bradycardia is most prevalent in individuals with temporal lobe epilepsy (Monté et al, 2007; Reeves et al, 1996). There is no data available on the risk factors specific to antiepileptic drugs. Lacosamide should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (eg, myocardial ischemia/infarction, heart failure, structural heart disease, or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blockers. Older age (>65 years) and/or intravenous therapy were not identified as independent risk factors.
Preventability	By excluding patients with known second degree or higher AV blocks, potentially severe cardiac adverse events can potentially be prevented (see Section 4.3, Contraindications of the LCM SmPC). The substantial diurnal variation in PR interval in relation to the small increase of the PR interval by LCM, the low predictive value of a pretreatment ECG to detect changes resulting from treatment, and the very rare frequency of detecting second degree AV block on a pretreatment screening ECG do not support use of a pretreatment ECG as a preventive measure in patients with no known conduction problems or severe cardiac diseases (Kellinghaus, 2009). By using LCM with caution in patients with known conduction problems or severe cardiac disease (eg, a history of myocardial infarction or heart failure), severe cardiac adverse events can potentially be detected and/or prevented. This is especially true for elderly patients as they may be at an increased risk of cardiac disorders. Making patients aware of the symptoms of second degree or higher AV block (eg, slow or irregular pulse, feeling of lightheaded, and fainting) and of the symptoms of atrial fibrillation and atrial flutter (eg, palpitations, rapid or irregular pulse, and shortness of breath) and asking them to seek medical advice should

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

	reduce or prevent the occurrence of severe cardiac events (see Section 4.4, Special warnings and precautions for use of the LCM SmPC). Currently, there is limited data on the effect of epilepsy on cardiac conduction abnormalities (Sevcencu and Struijk, 2010). More research is required in order to understand the cardiovascular effects of epilepsy. This information would help to develop better strategies to prevent them.
Impact on the risk-benefit balance of the product	Risk of cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation has been incorporated in the benefit-risk assessment with overall benefit-risk balance remaining positive. Current pharmacovigilance activities are considered sufficient to monitor this particular risk. Information relating to cardiac AEs is described in the Contraindications, Special warnings and precautions for use, and Undesirable effects sections of the SmPC.
Public health impact	The prognosis of conditions associated with PR interval prolongation and sodium channel modulation including AV block, bradycardia, atrial fibrillation, atrial flutter, and syncope in the general population depends on the patient's underlying medical condition. In most cases, the conditions are acute and resolve after the underlying condition has been treated. However, when severe, there is an impact on the quality of life in individuals suffering from these conditions. Patients with syncope have reduced health-related quality of life in many aspects of their lives, including limitations in daily activities, apprehension about the future, and impact on emotions such as depression and anxiety (Rose et al, 2000). Recurrent syncope is associated with fractures and soft tissue injury in 12% of patients. In patients with syncope presenting to an emergency department, 29.1% reported minor trauma and 4.7% reported major trauma (Bartoletti et al, 2008). There is a paucity of data on the natural history of atrial flutter, which often coexists with atrial fibrillation (Tunick et al, 1992). The prognosis of atrial flutter depends greatly on the clinical presentation and degree of the underlying cardiac disease. Atrial fibrillation is associated with substantial morbidity, including a 5-fold increased risk of ischemic stroke, which in turn confers increased mortality and greater disability compared to nonatrial fibrillation causes of stroke, including longer hospital stays and lower rates of functional independence after discharge (Lin et al, 1996). Atrial fibrillation has also been shown to be an independent predictor of mortality (Krahn et al, 1995), and patients with atrial fibrillation have a higher risk of all-cause dementia (Dublin et al, 2011). In patients with proarrhythmic conditions, ventricular tachyarrhythmia has been rarely reported in association with LCM. In rare cases, AV block and ventricular tachyarrhythmias have led to asystole, cardiac arrest, and death in patients with underlying proarrhythmic conditions.

AAD=antiarrhythmic drug; AE=adverse event; AV=atrioventricular; CBZ-CR=carbamazepine controlled release; CSR=clinical study report; DNP=diabetic neuropathic pain; ECG=electrocardiogram; FDA=Food and Drug Administration; ISS=integrated summary of safety; LCM=lacosamide; PGTCS=primary generalized

Table 3–4: Important identified risk: Cardiac AEs that may be potentially associated with PR interval prolongation or sodium channel modulation

tonic-clonic seizure; POS=partial-onset seizure; SAE=serious adverse event; SmPC=summary of product characteristics; SOC=system organ class; TEAE=treatment-emergent adverse event

[a] EP Pool S1 (safety pool) consists of study participants with POS receiving at least 1 dose of study medication (LCM and placebo) from the double-blind placebo-controlled studies SP667, SP754, and SP755.

[b] DNP Pool S1 consists of study participants with DNP receiving at least 1 dose of study medication (LCM and placebo) from the double-blind placebo-controlled studies SP614, SP742, SP743, SP768, and SP874.

3.1.2 Important potential risks

None.

3.2 Presentation of the missing information

3.2.1 Pregnant or lactating women

Evidence source:

There are no adequate data from the use of LCM in pregnant or lactating women. Studies in animals did not indicate any teratogenic effects in rats or rabbits, but embryotoxicity was observed in rats and rabbits at maternal toxic doses. The potential risk for humans is unknown.

Population in need of further characterization:

The safety and efficacy in pregnant or breastfeeding women have not been established. Lacosamide should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus). If women decide to become pregnant, the use of this product should be carefully re-evaluated.

Lacosamide is excreted in human breast milk. A risk to the newborns/infants cannot be excluded. Animal studies have shown excretion of LCM in breast milk. For precautionary measures, breastfeeding should be discontinued during treatment with LCM.

3.2.2 Impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population

Evidence source:

There is limited clinical experience with LCM on long-term growth, neurodevelopment, and puberty in pediatric patients. In study SP969, 171 LCM treated study participants aged ≥4 up to <17 years received LCM for a mean duration of 106.8 days during the treatment period. The median duration of treatment for both LCM and placebo groups during the Treatment Period was 43.0 days and 70.0 days, respectively. Current available data do not provide enough information on the impact of LCM on long-term growth, long-term neurodevelopment, and puberty in the pediatric population.

Population in need of further characterization:

Pediatric patients will be further characterized for the following safety concerns: growth, neurodevelopment, and puberty.

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PART II: MODULE SVIII: SUMMARY OF SAFETY CONCERNS

Table 1: Summary of safety concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION STUDIES)

1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaire for cardiac adverse events that may be potentially associated with PR interval prolongation or sodium channel modulation to facilitate prompt follow-up of relevant information.

The specific follow-up questionnaire is enclosed in EU-RMP Part VII Annex 4.

- Other forms of routine pharmacovigilance activities:
  - Independent teratologist review will be performed for all nonregistry cases of congenital anomaly received since Dec 2018 for all UCB-marketed products.

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities include the following:

- Registry studies to monitor pregnancy outcomes: participation in and sponsorship of European and International Registry of Antiepileptic Drugs (AEDs) in Pregnancy (EURAP) and in the North American AED Pregnancy Registry (NAAPR).

Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries. The protocols for EURAP and NAAPR include possible activities to follow-up on the children.

Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AEDs into the EURAP and NAAPR. References to registries are included on the pregnancy follow-up letter, US Call Center script, and information for Medical Science Liaisons.

- Study EP0012 is an ongoing clinical trial including pediatric patients who are followed for up to 5 years (according to the actual protocol):
  - Endocrinology, body weight, height, and calculated body mass index will be measured per protocol.
  - Neurodevelopmental maturation will be assessed in the pediatric studies as per protocol by the investigator using physical examination and neurodevelopmental validated scales including Achenbach Child Behavior Checklist, Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function®-preschool version, and Tanner staging.

Tabulated summary of ongoing and completed pharmacovigilance activities is provided in EU-RMP Part VII Annex 2.

Protocols for ongoing studies in the pharmacovigilance plan are provided in EU-RMP Part VII Annex 3.

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table 3–1.

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Participation in and sponsorship of European and International Registry of Antiepileptic Drugs in Pregnancy Ongoing	To collect data on pregnancy	Missing information on use of lacosamide (LCM) in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in Periodic Safety Update Reports (PSURs).
Participation in and sponsorship of North American Antiepileptic Drug Pregnancy Registry Ongoing	To collect data on pregnancy	Missing information on use of LCM in pregnant or lactating women	Start of data collection Completion of data collection Interim study report (semiannual)	Cumulative data appearing in these registries are discussed in PSURs.

Table 3–1: Ongoing and planned additional pharmacovigilance activities

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
EP0012 Open-label, multicenter extension study to evaluate the long-term safety and efficacy of LCM as adjunctive therapy for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy (IGE). Ongoing	To document the long-term safety, tolerability, and efficacy of LCM in study participants 4 years and older with IGE	Missing information on impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population.	Final study report submission	Aug 2023

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

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

There are no planned or ongoing imposed postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations for lacosamide.

RMP PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK

Risk minimization plan

The safety information in the proposed product information is aligned to the reference medicinal product.

1 ROUTINE RISK MINIMIZATION MEASURES

Description of routine risk minimization measures by safety concern is presented in Table 1–1.

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Cardiac adverse events that may be potentially associated with PR interval prolongation or sodium channel modulation	Routine risk communication: Summary of Product Characteristics (SmPC) Section 4.2 (Posology and method of administration – intravenous formulation), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction), SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Routine risk minimization activities recommending specific clinical measures to address the risk: caution statement is included in SmPC Section 4.4 (Special warnings and precautions for use) Other routine risk minimization measure beyond the Product Information: available by prescription only
Important potential risks: None	
Missing information	
Pregnant or lactating women	Routine risk communication: SmPC Section 4.6 (Fertility, pregnancy and lactation), SmPC Section 5.3 (Preclinical safety data) Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.6 (Fertility, pregnancy and lactation) Other routine risk minimization measure beyond the Product Information: available by prescription only; lacosamide should not be used during pregnancy unless clearly necessary.
Impact on long-term growth, long-term neurodevelopment, and	Routine risk communication: No additional wording in SmPC Routine risk minimization activities recommending specific clinical measures to address the risk: None

Table 1–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
puberty in pediatric population	Other routine risk minimization measure beyond the Product Information: available by prescription only

SmPC=summary of product characteristics

2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. Additional risk minimization measures are not considered necessary.

3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 3–1 provides a summary of pharmacovigilance activities and risk minimization activities by safety concern.

Table 3–1: Summary of pharmacovigilance activities and risk minimization activities

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

Table 3–1: Summary of pharmacovigilance activities and risk minimization activities

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

PhV=pharmacovigilance; SmPC=summary of product characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for lacosamide

This is a summary of the Risk Management Plan (RMP) for lacosamide (LCM). The RMP details important risks of LCM, how these risks can be minimized, and how more information will be obtained about LCM risks and uncertainties (missing information).

Lacosamide Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LCM should be used.

This summary of the RMP for LCM should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is a part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the LCM RMP.

1 THE MEDICINE AND WHAT IT IS USED FOR

Lacosamide is authorized as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients aged 2 years and above with epilepsy (see SmPC for the full indication). Lacosamide is also indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults, adolescents, and children from 4 years of age with idiopathic generalized epilepsy. It contains LCM as the active substance and it is given by oral tablet in the following strengths: 50mg, 100mg, 150mg, and 200mg film-coated tablets; by 10mg/mL syrup; or by injection of 10mg/mL solution for infusion.

Further information about the evaluation of LCM benefits can be found in the LCM EPAR, including its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/vimpat; For UCB Lacosamide EPAR, the link is : https://www.ema.europa.eu/en/medicines/human/EPAR/lacosamide-ucb

2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of LCM, together with measures to minimize such risks and the proposed studies for learning more about LCM risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be as follows:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that prompt action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of LCM is not yet available, it is listed under "missing information" in Table 2–1 below.

2.1 List of important risks and missing information

Important risks of LCM are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LCM. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 2–1: List of important risks and missing information

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

2.2 Summary of important risks

Table 2–2: Summary of important risks

Important identified risk: Cardiac adverse events (AEs) that may be potentially associated with PR interval prolongation or sodium channel modulation	
Evidence for linking the risk to the medicine	Prolongations in PR interval with lacosamide (LCM) have been observed in clinical studies. A phase 1 study revealed a small dose-related increase in the mean PR interval with LCM-treated subjects. Nonclinical studies revealed an interaction with LCM and cardiac sodium channels which could potentially affect normal cardiac electrophysiology. This risk was upgraded by UCB from important potential risk to important identified risk based on a cumulative analysis of postmarketing data which indicated a causal relationship with LCM.
Risk factors and risk groups	The risk factors for developing AEs related to PR prolongation include a presence of pre-existing heart failure or a recent myocardial infarction or known conduction abnormalities (Ryvlin et al, 2013; Strzelczyk et al, 2008; Rocamora et al, 2003).

Table 2–2: Summary of important risks

	Studies on the risk factors for AEs related to PR prolongation have been done in the general population. The incidence of atrial fibrillation increases with age (Friberg et al, 2010). Other risk factors for atrial fibrillation include a history of hypertension and cardiac diseases including valvular, ischemic, and congestive heart failure (Krahn et al, 1995).The frequency of cardiac syncope also increases with age from approximately 1.1% in people less than 40 years to 16% in individuals more than 75 years of age (Rvylin et al, 2013; Olde et al, 2009; Ungar et al, 2006). Ictal bradycardia is most prevalent in individuals with temporal lobe epilepsy (Monté et al, 2007; Reeves et al, 1996). There is no data available on the risk factors specific to antiepileptic drugs (AEDs). Lacosamide should be used with caution in patients with underlying proarrhythmic conditions such as patients with known cardiac conduction problems or severe cardiac disease (eg, myocardial ischemia/infarction, heart failure, structural heart disease, or cardiac sodium channelopathies) or patients treated with medicinal products affecting cardiac conduction, including antiarrhythmics and sodium channel blockers. Older age (>65 years) and/or intravenous therapy were not identified as independent risk factors.
Risk minimization measures	Routine risk minimization measures: Summary of Product Characteristics (SmPC) Section 4.2 (Posology and method of administration - intravenous formulation), SmPC Section 4.3 (Contraindications), SmPC Section 4.4 (Special warnings and precautions for use), SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction), SmPC Section 4.8 (Undesirable effects), SmPC Section 5.3 (Preclinical safety data) Available by prescription only Additional risk minimization measures: None
Missing information: Pregnant or lactating women	
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.6 (Fertility, pregnancy and lactation), SmPC Section 5.3 (Preclinical safety data) Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: participation in and sponsorship of pregnancy registries (European and International Registry of AEDs in Pregnancy and North American AED Pregnancy Registry) See Section 2.3.2 of this summary for an overview of the postauthorization development plan.
Missing information: Impact on long-term growth, long-term neurodevelopment, and puberty in pediatric population	
Risk minimization measures	Routine risk minimization measures: No additional wording in SmPC Available by prescription only. Additional risk minimization measures: None

Table 2–2: Summary of important risks

Additional pharmacovigilance activities	Additional pharmacovigilance activities: ongoing pediatric study with a follow-up of up to 5 years in EP0012 (according to the actual study protocol). See Section 2.3.2 of this summary for an overview of the postauthorization development plan.

AE=adverse event; AED=antiepileptic drug; LCM=lacosamide; SmPC=summary of product characteristics

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of LCM.

2.3.2 Other studies in postauthorization development plan

Additional pharmacovigilance activities include the following:

- Registry studies to monitor pregnancy outcomes: participation in and sponsorship of European and International Registry of Antiepileptic Drugs (AEDs) in Pregnancy (EURAP) and in the North American AED Pregnancy Registry (NAAPR).

Activities include provision of requested data from UCB to the registries and regular review of interim outputs from the registries. The protocols for EURAP and NAAPR include possible activities to follow-up on the children.

Prescribers and reporters of pregnancy cases are encouraged to register pregnant women exposed to AEDs into the EURAP and NAAPR. References to registries are included on the pregnancy follow-up letter, US Call Center script, and information for Medical Science Liaisons.

- Study EP0012 is an ongoing clinical trial including pediatric patients who are followed for up to 5 years (according to the actual study protocol):
  - Endocrinology, body weight, height, and calculated body mass index will be measured in the studies per protocol.
  - Neurodevelopmental maturation will be assessed in the pediatric studies as per protocol by the investigator using physical examination and neurodevelopmental validated scales including the Achenbach Child Behavior Checklist, Behavior Rating Inventory of Executive Function®/Behavior Rating Inventory of Executive Function®-preschool version, and Tanner staging.

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RMP PART VII: ANNEXES

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The cardiac follow-up form is included below.

	VIMPAT® - Lacosamide UCB® **Cardiac Follow-up Form**	Doc number: sop-af-009221 Version: 5.0 Ref. sop-009247

Product: **LACOSAMIDE**	**Contact information:** **Reporter/Investigator:** **Email :** **FAX :** **CRO :** **Email :** **FAX :**		**Patient Safety Case ID:** **Query N°:**
Adverse Event type: **CARDIAC**			
Patient initials:	**Patient DOB:**	**Country:**	***If study*:** **Study N°:** **CRF N°:** **Treatment N°:**
Patient gender:	**Patient age:**		
Patient race/ethnicity: ☐ **White** ☐ **Black** ☐ **Hispanic** ☐ **Asian** ☐ **Australian Aboriginal/Torres Strait Islander** ☐ **Other (specify)**			

You reported that your patient presented a cardiac event (e.g. "*Prolongation of the PR interval")* while exposed to lacosamide. In order for UCB to better assess this case, could you kindly provide us with the following information?

Question	**Reply (Reporter / Investigator)**
Patient date of birth and initials (if not previously provided)	
Clinical symptoms which led to the diagnosis	
Onset date (DD-MMM-YYYY)	
Physical examination findings (e.g. weight, blood pressure, heart rate)	
Medical history, especially risk factors: -family history of premature ischemic heart disease or arrhythmia -obesity -sleep apnea syndrome -hypertension -hyperlipidemia -nicotine use -diabetes mellitus -cardiac disorder: eg valvular heart disease, heart failure, coronary artery disease -acute temporary cause: eg alcohol intake, cardiac or thoracic surgery, electrocution, myocardial infarction, pericarditis, myocarditis, pulmonary embolism, hyperthyroidism	

Other non-cardiac relevant medical history	
Lacosamide dose and indication	
Lacosamide start date	
Lacosamide stop date (if applicable)	
Lacosamide route of administration: If intravenous, please provide rate of infusion:	
Other suspect drug(s). Please include dose and start/stop date if applicable.	
Concomitant drug(s). Please include dose and start/stop date if applicable.	
Was a baseline ECG performed? If so, please provide ECG date and tracings.	
Was an ECG done at the time of the event? If so, please provide ECG tracings.	
Was an echocardiography done? Please provide results.	
Was a Holter done? Please provide results.	
Was a specific atrial enlargement searched?	
Could you exclude any thromboembolic event?	
Were lab tests performed? If so, please specify the tests performed. In particular, were the following tests performed: serum potassium, serum magnesium, serum ionized calcium, TSH and T4 levels? Please attach the lab reports with baseline values (if available) and with normal ranges, through the time of the patient's recovery.	

Other Tests/Investigations performed		
Treatment of the event.		
Action taken with lacosamide (stop date if applicable).		
Outcome of the event.		
Relationship to lacosamide (Related/Not related).		
Other Comments:		
Completed by :	Date :	Signature :

Your personal data is treated in line with applicable data privacy regulations. For more information, see the UCB Pharmacovigilance Privacy Policy, available at https://www.ucb.com/Pharmacovigilance-privacy-policy

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Not applicable