EVALUATING THE OCCURRENCE OF ADVERSE EVENTS AMONG PEDIATRIC PATIENTS EXPOSED TO INTRAVENOUS LACOSAMIDE (VIMPAT®) USING REAL WORLD DATA

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Non-interventional Study Protocol EP0147	FINAL VERSION 18/09/19
Protocol amendment	10/02/20

PASS INFORMATION:

Title: Evaluating the occurrence of ADVERSE events among pediatric patients exposed to intravenous lacosamide (Vimpat®) using real world data

Protocol version: Final approved

Date of last version of protocol:18th September 2019

EU PAS register number: EUPAS32597.

Active Substance: Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide)

Medicinal Product: Vimpat

Product reference: EU/1/08/470/001 to 035

Procedure Number: Not applicable

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Joint Pass: No

Research Question and objectives: To estimate the incidence of the selected medical events for 8 System Organ Classes (SOC) and 3 Standardized MedDRA Queries (SMQs) in pediatric patients after treatment with higher IV LCM doses, compared to pediatric patients treated with recommended initial/maintenance IV LCM dose.

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DECLARATIONS AND SIGNATURES /SPONSORS DECLARATION

I confirm that I have carefully read and understand this Retrospective Study protocol and agree to conduct this retrospective study as outlined in this protocol and according to current Good Pharmacoepidemiology Practice.

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STUDY PHYSICIAN: e-signed

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drug
AESI	Adverse events of special interest
BRV	Brivaracetam
CDM	Common data model
CRN	Clinical Research Network
CIOMS	Council for International Organizations of Medical Sciences
CPT	Current procedural terminology
HER	Electronic health record
HCPs	Healthcare providers
HCPCS	Healthcare common procedure coding system
HIPAA	Health Insurance Portability and Accountability Act
ICD	International classification of disease
IEC	Institutional ethics committee
IRB	Institution review board
IV	Intravenous
LCM	Lacosamide
LEV	Levetiracetam
LOINC	Logistical observation identifier names and codes
NDC	National drug code
OMOP	Observational medical outcomes partnership
PCORnet	Patient-Centered Clinical Research Network
SADR	Severe adverse drug reaction
SAE	Serious adverse event
SNOMED-CT	Systematized nomenclature of medicine-clinical terms
US	United States
WHO	World Health Organization

1 EXECUTIVE SUMMARY

- **Rationale and background**

An estimated 6.8 per 1,000 insured children are affected by epilepsy (Kim et al., 2016). Off-label use of newly introduced antiepileptic drugs (AEDs) in pediatric patients provides an opportunity to assess their real world use and safety. Vimpat® (lacosamide, LCM) is indicated for the treatment of partial-onset seizures in patients 4 years of age and older. This indication is currently limited to Vimpat® oral dosage forms (Film-Coated Tablets and Oral Solution) in the USA. IV use of lacosamide in children four years and over is however authorized in EU; its benefit risk is assessed as favorable by UCB and by the EU Health Authorities. Vimpat® injection is only indicated in USA for the treatment of partial-onset seizures in adults (17 years of age and older). Vimpat® dosage in adult patients can be started with the recommended initial dosage (as monotherapy 100 mg twice daily; as adjunctive therapy 50 mg twice daily) followed by a titration regimen (increase by 50 mg twice daily every week). Alternatively, it may be initiated with a single loading dose of 200 mg. The use of a loading dose in pediatric patients has not been studied yet. The purpose of the present study is to characterize further the safety of IV LCM in a pediatric population by using available data from electronic healthcare databases.

- **Research question and objectives**

Primary Objective

To estimate the incidence of the selected medical events for 8 System Organ Classes (SOC) (i.e. Cardiac disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, Metabolism and nutrition disorders, Psychiatric disorders, Injury, poisoning and procedural complications, General disorders and administration site conditions, Investigations) and 3 Standardized MedDRA Queries (SMQs) (i.e. Drug reaction with eosinophilia and systemic symptoms syndrome, Severe cutaneous adverse reactions, Hypersensitivity) in pediatric patients after treatment with higher IV LCM doses, compared to pediatric patients treated with recommended initial/maintenance IV LCM dose.

Secondary Objectives

1) To estimate the incidence of specific medical events included in the above mentioned 8 System Organ Classes (SOC) and 3 Standardized MedDRA Queries (SMQs) in pediatric patients aged ≥1 month < 17 years, after treatment with higher IV LCM doses, compared to pediatric patients treated with recommended initial/maintenance IV LCM dose.

2) To estimate the effect of increasing IV LCM loading dose on the incidence of select medical events for the 8 SOCs and 3 SMQ terms, and to compare the incidence of these medical events in pediatric patients treated with recommended initial/maintenance IV LCM dose.

- **Study design, including data sources**

Study Design

A retrospective cohort study will be conducted using data from the PEDSnet database to achieve the study objectives. Electronic health record (EHR) data will be collected from January 2009 to December 2018. Two mutually exclusive cohorts will be identified, the first

cohort consisting of pediatric patients treated with higher than the recommended IV LCM doses, and the second (comparator) cohort comprising pediatric patients treated with recommended initial/maintenance IV LCM dose. The index date will be defined as the initiation of a new IV LCM treatment episode/receipt of a higher IV LCM dose than known maintenance dose. The exposure period will be the period between the index date (as defined above) and discontinuation of LCM. Subjects will be followed from the index date up to 30 days after discontinuing treatment with LCM or censoring, and during this time will be assessed for occurrence of described study outcomes. All subjects require a baseline period prior to the index date free of either oral or IV LCM. In the stratified assessment of increasing LCM loading dose, follow up will be from the index date up to 24 hours and 7 days after discontinuing treatment with IV LCM. Outcome ascertainment will be done in two ways, 1) data elements within the PEDSnet common data model (CDM) will be examined to identify select medical events of interest; and 2) a chart review of the EHRs for all eligible study patients will be conducted to examine unstructured, text data not captured in the CDM to identify the select medical events of interest.

Patients with status epilepticus diagnostic codes in their record will be identified from the cohort and will have their results presented separately in sub tables. They will also contribute to the main study populations.This is to fulfill commitment to examine outcomes in SE patients when exposed to lacosamide.

- **Data analysis**

  For both the higher IV LCM dose cohort and recommended initial/maintenance IV LCM dose comparator cohort, counts and frequencies of AEs will be reported, also the incidence rates of the AEs and associated 95% confidence intervals (CI) will be calculated. The numerator will be the total number of patients with the outcomes identified during the follow-up period. The denominator will be patient-days. Incidence rate ratios and associated 95% confidence intervals will be calculated for each outcome to compare the incidence rates of the AEs for the higher IV LCM cohort to those for the comparator cohort. To examine the safety and tolerability of increasing intravenous LCM loading dose a stratified analysis of the incidence of the primary and secondary variables will be conducted by increasing loading dose. Stratification will be centered around UCBs proposed recommended IV LCM loading dose.

  If study numbers permit, all analyses will also be stratified by 1) exposure to additional AEDs, 2) IV LCM treatment indication, 3) preexisting medical events of interest, 4) use in the intensive care unit or other hospital departments, and 5) first time IV loading dose exposure vs multiple exposures. A number of sensitivity analyses will be conducted, these will include, 1) shortening the baseline period to 6 weeks, 2) excluding patients with preexisting medical events of interest, and 3) assessment of outcome definitions to assess the impact of the case definitions on the effect estimates.

2 MILESTONES*

Milestone (MCR)	Expected Planned date
Start of data collection[1]	January 2020
End of data collection[2]	April 2020
Final report of study result	June 30th 2020
Milestone (DB)	**Expected Planned date**
Start of database analysis	November 2019
End of database analysis	April 2020
Final report of study result	June 30th 2020

[1] Date from which data extraction starts.
[2] Date from which the analytical dataset is completely available. *
The final timeline will be decided based on the final approval date of the protocol

3 RATIONALE AND BACKGROUND

Epilepsy affects the pediatric population with an estimated prevalence of 6.8 per 1,000 insured children (Kim et al., 2016). Newly introduced antiepileptic drugs (AEDs) may be used off-label in children with epilepsy before completion of pediatric regulatory studies, creating an opportunity to evaluate the real-world use and safety of these drugs in children to support the pediatric clinical trial program (McGinnis & Kessler, Osokogu et al., 2016).

Vimpat® (lacosamide, LCM) is an AED that selectively enhances the slow inactivation of voltage-gated sodium channels without affecting rapid inactivation (Casas-Fernandez et al., 2012). It is available as oral solution, oral tablet, and intravenous (IV) solution. It is currently approved in USA for use as oral solution, oral tablet in patients over 4 years of age and as IV solution in patients over 16 years of age as an alternative to oral administration (FDA, 2017). Vimpat® was approved on Oct 2008 and first introduced to the market in 2009. IV use of lacosamide in children over four years is however authorized in the EU; its benefit risk profile is assessed as favorable by UCB and by the EU Health Authorities. Vimpat® injection is only indicated in USA for the treatment of partial-onset seizures in adults (17 years of age and older). Vimpat® dosage in adult patients can be started with the recommended initial dosage (as monotherapy 100 mg twice daily; as adjunctive therapy 50 mg twice daily) followed by a titration regimen (increase by 50 mg twice daily every week). Alternatively, it may be initiated with a single loading dose of 200 mg. The use of a loading dose in pediatric patients has not been studied yet. The purpose of the present study is to characterize further the safety of IV LCM in a pediatric population by using available data from electronic healthcare databases.

4 RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to estimate the incidence of the select medical events of interest, those being the 8 System Organ Classes (SOCs) and 3 Standardized MedDRA Queries (SMQs) listed below, in pediatric patients after treatment with higher IV LCM doses, compared to pediatric patients treated with recommended initial/maintenance IV LCM dose:

- Cardiac disorders

- Skin and subcutaneous tissue disorders
- Nervous system disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Injury, poisoning and procedural complications
- General disorders and administration site conditions
- Investigations of ECG indicating long PR
- Drug reaction with eosinophilia and systemic symptoms syndrome
- Severe cutaneous adverse reactions
- Hypersensitivity

The secondary objectives of this study are:

1. To estimate the incidence of the selected medical events included in the 8 System Organ Classes (SOC) and 3 Standardized MedDRA Queries (SMQs) as indicated below, in pediatric patients after treatment with higher than the recommended IV LCM doses, compared to pediatric patients treated with recommended initial/maintenance IV LCM dose.

- Cardiac disorders
    - Atrioventricular block
    - Atrioventricular block complete
    - Atrioventricular block first degree
    - Atrioventricular block second degree
    - Arrhythmia
    - Bradyarrhythmia
    - Bradycardia
    - Cardiac fibrillation
    - Cardiac flutter
    - Tachyarrhythmia
    - Atrial fibrillation
    - Atrial flutter
    - Cardiac arrest
    - Torsade de pointes
    - Ventricular arrhythmia
    - Ventricular fibrillation
    - Ventricular tachyarrhythmia
    - Palpitations

- Skin and subcutaneous tissue disorders
    - Stevens-Johnson syndrome
    - Toxic epidermal necrolysis
    - Angioedema
    - Urticaria

  - Pruritus
  - Rash

- Nervous system disorders
  - Dizziness
  - Somnolence
  - Paresthesias
  - Loss of consciousness
  - Syncope

- Metabolism and nutrition disorders
  - Appetite disorder
  - Decreased appetite
  - Diet refusal
  - Hypophagia
  - Food aversion

- General disorders and administration site conditions
  - Chest pain
  - Gait disturbances

- Injury, poisoning and procedural complicationInjection site discomfort
  - Injection site erythema
  - Injection site irritation
  - Injection site pain

2. To estimate the effect of increasing IV LCM loading dose on the incidence of select medical events for 8 SOCs and 3 SMQ terms (listed in the primary objective), compared to pediatric patients treated with recommended initial/maintenance IV LCM dose.

5 METHODOLOGY

5.1 Study design

This will be a retrospective cohort study that will use data from the PEDSnet database to estimate the incidence of select medical events for 8 SOCs and 3 SMQ terms and specific medical events included in these broad categories, and examine the effect of increasing IV LCM loading dose on the incidence of these select medical events. The study will also compare the incidence of the selected medical events in pediatric patient (aged ≥ 1 month <17 years) treated with higher IV LCM doses (including UCB's defined loading dose) to the incidence of these events in pediatric patients treated with a recommended initial/maintenance IV LCM dose.

The study will use electronic healthcare records (EHR) data from the PEDSnet data network, collected from the earliest (2009) through the latest date that data are available (~2018) for each included patient. The cohort design will allow the identification of pediatric patients treated with higher IV LCM doses or a recommended initial/maintenance IV LCM dose, and the ability to follow them to identify the occurrence of outcomes of interest.

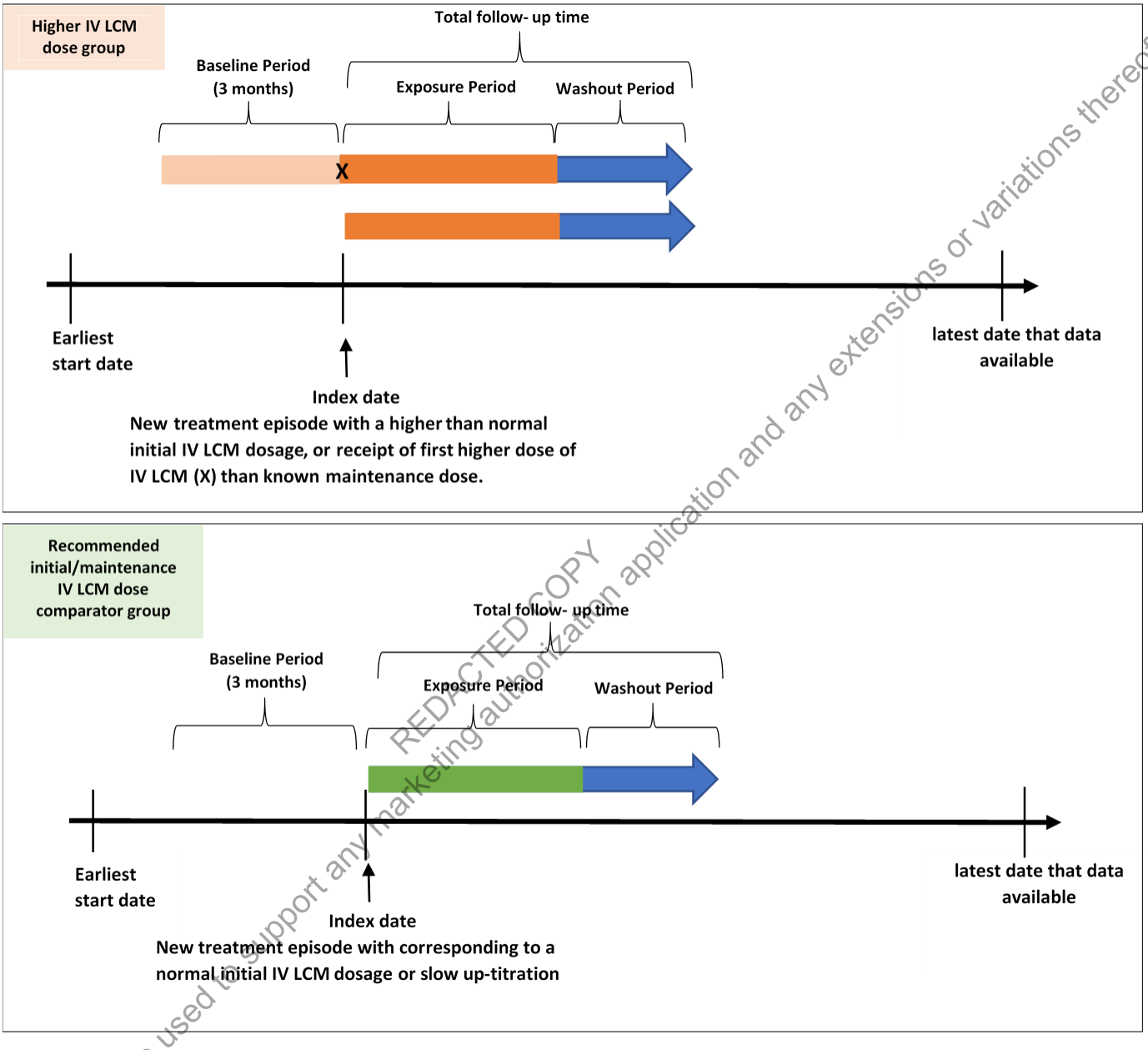
The study will consist of two mutually exclusive cohorts. The first cohort will consist of pediatric patients treated with higher IV LCM doses (including UCB's defined loading dose).

The second, the comparator cohort will comprise of pediatric patients treated with recommended initial/maintenance IV LCM dose. The index date will be defined as the initiation of a new IV LCM treatment episode/receipt of a higher IV LCM dose than known maintenance dose (described in detail in Section 5.3.1). The exposure period will be defined as the time between the index date (as defined above) and discontinuation of IV LCM (described in more detail in Section 5.5.4). Demographic characteristics will be defined at the index date. Baseline data will be used to define clinical characteristics, LCM exposure indications and identify prevalent cases of the selected medical events of interest. Each subject will be followed from the index date up to 30 days after discontinuing treatment with IV LCM. During the follow-up period, data will be assessed for occurrence of the select medical events, defined in Section 5.5.5.

Outcome ascertainment will be performed in two ways. First, data elements within the PEDSnet common data model (CDM), which comprises structured data extracted from EHRs will be examined to identify the select medical events of interest. Each event will be defined using algorithms that will include diagnostic codes and if needed procedure and medication codes, recorded in the EHR. Second, because not all symptoms, signs, and health problems are included in the structured data as diagnosis codes, a chart review of the EHRs for all eligible study patients will be conducted to examine unstructured text data not captured in the CDM to identify additional patients with the select medical events of interest.

Patients with status epilepticus diagnostic codes in their record will be identified from the cohort and will have their results presented separately in sub tables. They will also contribute to the main study populations.This is to fulfill commitment to examine outcomes in SE patients when exposed to lacosamide. It is assumed that any patients treated with a loading dose of LCM will be more likely to be in SE and proving refractory to treatment than the usual seizure presentation in children.

Figure 1 Schematic of the study design



The index date will vary for each patient and will depend on when the patients fulfils the study criteria

5.2 Study population

The study population will consist of the following two mutually exclusive cohorts:

- Pediatric patients treated with higher IV LCM doses (including UCB's defined loading dose), regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.
- Pediatric patients treated with recommended initial/maintenance IV LCM dose regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.

These two groups are defined by the proposed alternative higher initial dosage (first dose, first treatment in observed episode) and the recommended initial dosage (first dose, first treatment in observed episode) and patients remain in that group thereafter. Switching is not allowed at any time.

Patients will be initially identified using the following study criteria.

5.2.1 Inclusion Criteria

- Patients with at least one iv LCM administration (earliest administration defines index date)
- At least 1 encounter with iv LCM administered between ages of ≥1 month and ≤17 years

5.2.2 Exclusion Criteria

- No exposure to either oral or iv LCM within the 3 months prior to the index date
    - In the case of patients < 90 days of age, no prior LCM ever in the record

A separate cohort for patients < 30 days old is established with the following criteria.

5.2.3 Neonates Inclusion Critera

- Patients with at least one iv LCM administration (earliest administration defines index date)
- At least 1 encounter with iv LCM administered before 30 days of age.

5.2.4 Neonates exclusion criteria

- No exposure to either oral or iv LCM prior to the index date

5.2.5 Dosing criteria for groups

Once the LCM population is identified dose thresholds are applied to define the "Recommended Dose Group" and the "Loading Dose Group"). The following thresholds apply:
The recommended loading dose groups are as follows:

- < 4 mg/kg for patients less than 30 kg and less than 6 months of age
- < 6 mg/kg for patients less than 30 kg and greater than or equal to 6 months of age
- < 4 mg/kg for patients between 30 and 50 kg
- < 200 mg for patients
- greater than 50 kg

Note: Whilst babies are allowed higher mg/kg dosing than older children, due to issues of metabolism and weight, babies under 6 months of age have immature organs and a loading dose should be lower than older babies under 1 year.
High dose group have doses greater than the recommended group cut limits, applicable for age and weight.

- ≥ 4 mg/kg for patients less than 30 kg and less than 6 months of age
- ≥ 6 mg/kg for patients less than 30 kg and greater than or equal to 6 months of age
- ≥ 4 mg/kg for patients between 30 and 50 kg
- ≥ 200 mg for patients greater than 50 kg

5.3 Methodological techniques for patient selection

The selection criteria will be applied using the PEDSnet CDM data. First, the higher IV LCM cohort will be selected. Thereafter, the recommended initial/maintenance IV LCM cohort will be selected. The cohorts will be mutually exclusive, therefore a patient can only be included in one cohort. The medical chart review will only include eligible patients who fulfill the selection criteria and are identified using the PEDSnet CDM data.

5.3.1 Patient selection period

The study period will be from the earliest data availability to the latest data availability based on the eligible patients identified. The PEDSnet CDM includes any person with at least one encounter with the member health system after December 31, 2008 which included a visit with a clinician; and one or more coded diagnoses were recorded in the person's record after December 31, 2008. For persons meeting these criteria, any available data is included in the PEDSnet CDM, including data earlier than 2009.

The study period will not be restricted by the FDA approval date for LCM, as it occurred in 2008 before the earliest date of data availability in the PEDSnet database.

The exposure to IV LCM will be defined by the presence of RxNorm codes for generic or brand name of IV formulations of LCM as indicated below in Section 5.5.4.

The index date for the higher IV LCM cohort will be the earliest of either of the following identified during the study period and with the required 3-month baseline period:

- a new treatment episode for an IV LCM dose (as described in Section 5.2); or
- receipt of a first higher IV LCM dose than known maintenance dose (as described in Section 5.2 .

The index date for the recommended initial dosage/maintenance IV LCM cohort will be the earliest of the following identified during the study period and with the required 3-month baseline period:

- a new treatment episode corresponding to an recommended initial dosage or a slow up-titration (as described in Section 5.2)

IV LCM is usually administered in an inpatient setting for treatment of severe seizure conditions. We therefore anticipate the level of detail recorded for clinical information for the patients treated with IV LCM will be comprehensive as most of the patients will be treated in an inpatient setting.

5.3.2 Baseline (pre-index) period

The baseline period for this study will be the 3 months prior to either the first newly initated qualifying treatment episode of a higher IV LCM dose or a recommended initial IV LCM dose; for patients less than 3 months of age at index event, the baseline period will be birth through index event.

Data from the baseline period will be used to determine the indications for LCM and to define a new treatment episode. All available data prior to the index date will be used to evaluate the patient characteristics, diagnosis, procedures, and medications administered, dispensed or prescribed (AEDs, benzodiazepines and non-AEDs) medications, and identify preexisting

conditions of interest, if any. Preexisting medical events of interest are not exclusion criteria in this study; instead, they will be used to characterize the patient population. Section 5.5.6 details pre-existing medical events of interest that will be evaluated during the baseline period.

Potential indications for IV LCM include but are not limited to epilepsy, febrile seizures, and status epilepticus. The indications in both the higher and recommended IV LCM cohorts will be classified as follows:

- Patients with only one of the listed potential indications in the baseline period will be assigned the identified indication
- Patients with none of the listed potential indications in the baseline period will be classified as having other indications
- Patients with more than 1 of the listed potential indications in the baseline period will be classified as having multiple indications.

5.3.3 Follow-up (post-index) period

The duration of follow-up is for a maximum of 37 days from index date.

IV LCM treatment may span several days; treatment will be considered continuous if subsequent IV LCM treatment is noted to occur within 7 days of a previous treatment. If 7 days pass without a documented iv or LCM treatment, the index exposure has ended. Follow then continues until end of follow up or until the following censoring conditions apply:

Censoring: Patients will be followed for either 37 days OR until the patient is lost to follow-up[transfer out]; OR the patient is discharged from the in-patient setting [events that occur at home are not easy to track and are not included here; outpatient setting events are also excluded as we do not know what the patient has being doing at home during routine care]; OR the patient dies; OR the patient switches to another AED instead of/or adjunct to LCM; whichever comes first.

Clarification of follow up: The purpose of the study is to evaluate iv loading dose and higher subsequent dosing risk. Some patients may receive only one iv loading dose and then transfer to oral dosing which may last some weeks in the hospital setting. In the case where a patient has just one dose of iv LCM and switches to continuous oral LCM therapy, the follow up for AE evaluation will cease after a maximum of seven days of oral therapy or until censoring occurs as above. The same applies for those exposed to one dose of iv LCM and no further LCM exposure (either oral or iv).

Patients who have more than one dose of iv LCM and then switch to oral therapy will have a maximum follow up of 37 days of follow up index date or until censoring.

Patient time is contributed until either end of follow up or censor point (in days).

Patients are only included once in this study, so if we find evidence of a further iv loading dose of LCM given 6 months later say, they do not contribute to the study.

5.4 Study procedures

The medical chart reviews will only include patients who fulfill the eligibility criteria and are identified using the PEDSnet CDM data. Experienced healthcare personnel (e.g.neurologist or nurse) at each site will conduct any chart reviews.

Prior to study start, the CRF content (for use with extracted medical information) will be agreed by vendor and UCB.

5.4.1 Plan for data collection

The PEDSnet database consists of electronic medical records and is not an administrative claims database. It consists of both structured and unstructured data that is recorded by physicians during all health encounters that patients have in the healthcare network.

The study primary outcomes will be ascertained in two steps; i) review of coded events in the common data model (CDM) and ii) medical chart extraction which will include both coded data and free text. PEDSnet uses Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT)to represent the diagnoses; SNOMED-CT, ICD-9, ICD-10, CPT-4 and HCPCS codes to map procedures; RxNorm for dispensed and prescribed medications; and LOINC to represent laboratory results observations. The medical charts are considered the gold standard as they contain the original source of information for the medical encounters and include free hand information that is recorded by the physician during a health encounter. Therefore, including the medical chart review in addition to using data from the CDM will ensure that all available clinical information is utilized to validate the database findings and answer any queries.

First step: The PEDSnet network uses SNOMED-CT to enable standardization and pooling of diagnoses data across the across the 8 health systems included in the network. Initially, data will be evaluated relating to the study outcomes using the SNOMED-CT codes in the common dataset. The data in the CDM are coded using SNOMED-CT, an international logic-based, controlled vocabulary used in clinical care that enables meaning-based retrieval of clinical information from electronic health records. SNOMED CT is the most comprehensive, multilingual clinical terminology in the world, containing more than 300,000 medical concepts (diagnoses or findings), divided into hierarchies as diverse as body structure, clinical findings, geographic location and pharmaceutical/biological product. Each concept is represented by an individual code number and several concepts can be used simultaneously to describe a complex condition, for example presenting symptoms arising from a disease. This allows for separation of symptoms of drug exposure versus a comorbid chronic condition e.g. cardiac arrythmia. Consequently, it is expected that the data in the CDM will include detailed information on the study outcomes.

Second step: Medical charts include the physician notes, laboratory results, EEG recordings and any other original and detailed information that will be used to evaluate or validate the study outcomes. To improve the validity of medical chart review results, at each site these chart reviews will be conducted by experienced healthcare personnel (e.g. nurse clinician) who will be given standardized training before starting the review and a manual of procedures and code set index for assistance. In the case of any queries, an experienced neurologist will be consulted.

The quality control process used to set up the common dataset is described in section 5.7.

The hierarchical level of final reporting of the adverse event outcomes will be agreed with the UCB safety physicians attached to each UCB product, but initially will be reported to include all events. Those not listed (as being specific to LCM) will be included under Section 5.5.1.1 – other diagnoses. In this way all events are captured.

A selection of patients (approximately 10%) will have their charts reviewed (proportion to be agreed post evaluation of final patient numbers and quality of data). As these are retrospective deidentified data, no patient or family consent is required. UCB will not be party to any personal information regarding patients such as name, address or any other identifying variable. Only pertinent medical and treatment data will be collected.

The medical chart reviewers will not be blinded to IV LCM dosage contained within the patient notes as they need to assess dose so that patients can ultimately be categorised into treatment groups at the time of analysis. However, to avoid observation bias, they will be blinded to the full study protocol including title, objectives, and to how study group assignment criteria are applied. Instead, they will be provided instructions as to how to perform data extraction and provided with a case report form to complete. It is assumed based on clinical practice that the information in the medical charts will only indicate the dosage that was prescribed to the patients and will not include language relating to "loading dose/higher dose or recommended dose" per se. Therefore, blinding the medical chart reviewers to the full protocol, will minimize the risk for ascertainment bias.

5.5 Variables

5.5.1 Primary outcome measure

The following primary variables will be measured to meet the study objectives:

- The incidence rate and incidence rate ratio of cardiac disorders (selected prefered terms (PTs) as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of general disorders and administration site conditions (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of injury, poisoning and procedural complications (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of investigations (i.e. the incidence rate of ECG PR prolongation)
- The incidence rate and incidence rate ratio of skin and subcutaneous tissue disorders (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of drug reactions with eosinophilia and systemic symptoms syndrome (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of severe cutaneous adverse reactions (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of hypersensitivity (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of nervous system disorders (selected PTs as described in Section 5.5.5)
- The incidence rate and incidence rate ratio of metabolism and nutrition disorders (selected PTs as described in Section 5.5.5)

- The incidence rate and incidence rate ratio of psychiatric disorders (i.e. abnormal behavior)

5.5.2 Secondary outcome measure

The secondary variables that will be evaluated in this study include:

- Incidence rate and incidence rate ratio of atrioventricular block
- incidence rate and incidence rate ratio of atrioventricular block complete
- incidence rate and incidence rate ratio of atrioventricular block first degree
- incidence rate and incidence rate ratio of atrioventricular block second degree
- incidence rate and incidence rate ratio of arrhythmia
- incidence rate and incidence rate ratio of bradyarrhythmia
- incidence rate and incidence rate ratio of bradycardia
- incidence rate and incidence rate ratio of cardiac fibrillation
- incidence rate and incidence rate ratio of cardiac flutter
- incidence rate and incidence rate ratio of tachyarrhythmia
- incidence rate and incidence rate ratio of atrial fibrillation
- incidence rate and incidence rate ratio of atrial flutter
- incidence rate and incidence rate ratio of cardiac arrest
- incidence rate and incidence rate ratio of torsade de pointes
- incidence rate and incidence rate ratio of ventricular arrhythmia
- incidence rate and incidence rate ratio of ventricular fibrillation
- incidence rate and incidence rate ratio of ventricular tachyarrhythmia
- incidence rate and incidence rate ratio of palpitations
- incidence rate and incidence rate ratio of chest pain
- incidence rate and incidence rate ratio of gait disturbances
- incidence rate and incidence rate ratio of injection site discomfort
- incidence rate and incidence rate ratio of injection site erythema
- incidence rate and incidence rate ratio of injection site irritation
- incidence rate and incidence rate ratio of injection site pain
- incidence rate and incidence rate ratio of stevens-johnson syndrome
- incidence rate and incidence rate ratio of toxic epidermal necrolysis
- incidence rate and incidence rate ratio of angioedema
- incidence rate and incidence rate ratio of urticaria

- incidence rate and incidence rate ratio of pruritus
- incidence rate and incidence rate ratio of rash
- incidence rate and incidence rate ratio of dizziness
- incidence rate and incidence rate ratio of somnolence
- incidence rate and incidence rate ratio of paresthesias
- incidence rate and incidence rate ratio of loss of consciousness
- incidence rate and incidence rate ratio of syncope
- incidence rate and incidence rate ratio of appetite disorder
- incidence rate and incidence rate ratio of decreased appetite
- incidence rate and incidence rate ratio of diet refusal
- incidence rate and incidence rate ratio of hypophagia
- incidence rate and incidence rate ratio of food aversion

5.5.3 Other variables - baseline characteristics

During the baseline period, patient characteristics (e.g. age at index date, gender, ethnicity, PEDSnet health system site, weight), clinicial characteristics (i.e. number of previous AEDs and concomitant medications prescribed prior to the index date [AEDs, benzodiazepines and non-AEDs], prevalence of comorbidities, medical procedures such as EEG) will be evaluated. Baseline data will be assessed for IV LCM exposure indications, dosage of IV LCM and preexisting medical events of interest (i.e. cardiac conditions, dermatologic conditions, vascular conditions, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations, drug reaction with eosinophilia and systemic symptoms syndrome, severe cutaneous adverse reactions, hypersensitivity events).

5.5.4 Exposure Definition and Measurement

The study population for this study is pediatric patients treated with higher IV LCM doses and recommended initial/maintenance IV LCM dose. Lacosamide will be identified based on prescription or dispensing data from the medications table in the PEDSnet CDM using RxNorm codes (Table 1 RxNorm codes for Lacosamide), and if needed the free text will be reviewed for further details about the LCM dosage. The equivalent NDC codes have been provided in Table 2 NDC codes for Lacosamide.

Table 1 RxNorm codes for Lacosamide

RxNorm CUI	Term	Term Type
1734186	lacosamide injection [Vimpat]	Branded Drug Form
1734189	lacosamide 10 mg/ml injection [Vimpat]	Branded Drug
809984	20 ml lacosamide 10 mg/ml injection [Vimpat]	Quant Branded Drug
809974	20 ml lacosamide 10 mg/ml injection	Quant Clinical Drug

RxNorm CUI	Term	Term Type
1734184	lacosamide injection	Clinical Drug Form
1734188	lacosamide 10 mg/ml injection	Clinical Drug
1186608	Vimpat Injectable Product	Branded Dose Group
1161965	lacosamide Injectable Product	Clinical Dose Group

These subsume exposures that would be described by the following National Drug Codes (NDC) (current and prior) in other data sources as indicated below in Table 2.

Table 2 NDC codes for Lacosamide

NDC	Description
00131181067	lacosamide 10 mg/ml injectable solution [Vimpat]
001311810	lacosamide 10mg/ml intravenous injection [Vimpat]
68842081067	lacosamide 10 mg/ml injectable solution [Vimpat]
00091181067	lacosamide 10 mg/ml injectable solution [Vimpat]

The treatment episode for IV LCM will be defined based on the prescription/dispensing information including dosage, formulation, date and time (as available in the database).

The IV LCM loading dose will be defined, where possible, as the single, initial high IV LCM dose which is followed within approximately 12 hours by a subsequent lower maintenance dose.

As we are evaluating IV LCM, which is usually administered in a hospital (inpatient) setting, it is anticipated that in most cases detailed dosage information will be recorded in the patients' medical chart with detailed information on individual IV LCM doses administered, including exact dosage data and time stamps indicating time of administration. This will enable the capture of IV LCM loading dose and the identification of subsequent episodes of IV LCM loading dose exposure.

5.5.5 Outcome Definitions and Measurement

The study outcomes will first be defined by querying the PEDSnet CDM for clinically relevant terms associated with these outcomes including signs, symptoms, diagnoses and procedures. These data are coded using Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT). SNOMED-CT is an international logic-based, controlled vocabulary used in clinical care that enables meaning-based retrieval of clinical information from electronic health records. SNOMED-CT is based on three types of components: (i) concepts which represent a clinical meaning and have a unique identifier, (ii) descriptions which represent labels of these concepts and (iii) relationships which are binary links between concepts that help define the meaning of each concept. SNOMED-CT has over 300,000 concepts organized according to a hierarchy rooted by 19 high-level classes or axes. Each top-level hierarchy contains sub-hierarchies that further specify a concept.

Currently, there are no available validated algorithms to identify the study outcomes using the SNOMED-CT vocabulary. The SNOMED-CT concepts (listed in Table 3 will be reviewed and cased definitions for each outcome will be developed using appropriate algorithms that will

be developed in consultation with clinicians. Second, additional information for these outcomes will be ascertained by medical records review as indicated in Section 5.4. Additionally, the laboratory results may be included during the chart review to confirm any diagnoses. **Sensitivity analyses will be conducted to assess the impact of the case definitions on the effect estimates.**

A number of broad outcomes will be examined in this study and will include:

- Cardiac disorders
- Skin and subcutaneous tissue disorders
- Nervous system disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Injury, poisoning and procedural complications
- General disorders and administration site conditions
- Investigations – prolonged PR on ECG
- Drug reaction with eosinophilia and systemic symptoms syndrome
- Severe cutaneous adverse reactions
- Hypersensitivity

Additionally, specific medical events under each broad category will be evaluated as listed below:

- Cardiac Disorders
    - Atrioventricular block
    - Atrioventricular block complete
    - Atrioventricular block first degree
    - Atrioventricular block second degree
    - Arrhythmia
    - Bradyarrhythmia
    - Bradycardia
    - Cardiac fibrillation
    - Cardiac flutter
    - Tachyarrhythmia
    - Atrial fibrillation
    - Atrial flutter
    - Cardiac arrest

  - Torsade de pointes
  - Ventricular arrhythmia
  - Ventricular fibrillation
  - Ventricular tachyarrhythmia
  - Palpitations
- Skin and subcutaneous tissue disorders
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Angioedema
  - Urticaria
  - Pruritus
  - Rash
- Nervous system disorders
  - Dizziness
  - Somnolence
  - Paresthesias
  - Loss of consciousness
  - Syncope
- Metabolism and nutrition disorders
  - Appetite disorder
  - Decreased appetite
  - Diet refusal
  - Hypophagia
  - Food aversion
- General disorders and administration site conditions
  - Chest pain
  - Gait disturbances
- Injury, poisoning and procedural complicationInjection site discomfort
  - Injection site erythema
  - Injection site irritation
  - Injection site pain

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Cardiac Disorders	
Atrioventricular block	SCTID: 233917008
Atrioventricular block complete	SCTID: 27885002
Atrioventricular block first degree	SCTID: 270492004
Atrioventricular block second degree	SCTID: 195042002
Cardiac Arrhythmia (disorder)	SCTID: 698247007
Nodal rhythm disorder (disorder)	SCTID: 71792006
Atrial arrhythmia (disorder)	SCTID: 17366009
Cardiac arrhythmia (disorder)	SCTID: 698247007
Atrio-ventricular node arrhythmia (disorder)	SCTID: 88412007
Neonatal dysrhythmia (disorder)	SCTID: 276513001
Electrocardiogram: sinus arrhythmia (finding)	SCTID: 427393009
Ventricular arrhythmia (disorder)	SCTID: 44103008
Premature beats (disorder)	SCTID: 29717002
Electrocardiographic ventricular arrhythmia (finding)	SCTID: 164893009
Supraventricular arrhythmia (disorder)	SCTID: 72654001
Electrocardiographic supraventricular arrhythmia (finding)	SCTID: 164887001
Bradyarrhythmia	SCTID: 421869004
Supraventricular bradyarrhythmia (disorder)	SCTID: 762534000
Bradycardia	
Electrocardiogram: bradycardia (finding)	SCTID: 426627000
Bradycardia (finding)	SCTID: 48867003
Cardiac fibrillation (disorder)	SCTID: 40593004
Ventricular fibrillation (disorder)	SCTID: 71908006
Atrial fibrillation (disorder)	SCTID: 49436004
Rapid atrial fibrillation (disorder	SCTID: 314208002
Electrocardiographic atrial fibrillation (finding)	SCTID: 164889003
Electrocardiographic ventricular fibrillation (finding)	SCTID: 164896001
Chronic atrial fibrillation (disorder)	SCTID: 426749004
Paroxysmal atrial fibrillation (disorder)	SCTID: 282825002
Persistent atrial fibrillation (disorder)	SCTID: 440059007
Preexcited atrial fibrillation (disorder)	SCTID: 762247006
Atrial fibrillation and flutter (disorder)	SCTID: 195080001
Non-rheumatic atrial fibrillation (disorder)	SCTID: 233911009
Sustained ventricular fibrillation (disorder)	SCTID: 429243003
Lone atrial fibrillation (disorder)	SCTID: 233910005
Ventricular fibrillation and flutter (disorder)	SCTID: 195083004
Permanent atrial fibrillation (disorder)	SCTID: 440028005

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Cardiac flutter	
Fluttering heart (finding) *	SCTID: 161969004
Ventricular fibrillation and flutter (disorder)	SCTID: 195083004
Atrial fibrillation and flutter (disorder)	SCTID: 195080001
Tachyarrhythmia (disorder)	SCTID: 6285003
Atrial fibrillation	SCTID: 49436004
Atrial fibrillation and flutter (disorder)	SCTID: 195080001
Paroxysmal atrial fibrillation (disorder)	SCTID: 282825002
Rapid atrial fibrillation (disorder	SCTID: 314208002
Electrocardiographic atrial fibrillation (finding)	SCTID: 164889003
Chronic atrial fibrillation (disorder)	SCTID: 426749004
Persistent atrial fibrillation (disorder)	SCTID: 440059007
Preexcited atrial fibrillation (disorder)	SCTID: 762247006
Atrial fibrillation and flutter (disorder)	SCTID: 195080001
Non-rheumatic atrial fibrillation (disorder)	SCTID: 233911009
Lone atrial fibrillation (disorder)	SCTID: 233910005
Ventricular fibrillation and flutter (disorder)	SCTID: 195083004
Permanent atrial fibrillation (disorder)	SCTID: 440028005
Atrial flutter	SCTID: 5370000
Electrocardiographic atrial flutter (finding)	SCTID: 164890007
Typical atrial flutter (disorder)	SCTID: 720448006
Atypical atrial flutter (disorder)	SCTID: 15964901000119107
Cardiac arrest	SCTID: 410429000
Neonatal cardiac arrest (disorder)	SCTID: 180906006
Bradycardic cardiac arrest (disorder)	SCTID: 703162001
Cardiac arrest due to cardiac disorder (disorder)	SCTID: 423191000
Torsade de pointes	SCTID: 31722008
Electrocardiographic torsades de pointes (finding)	SCTID: 426882006
Ventricular arrhythmia	SCTID: 44103008
Electrocardiographic ventricular arrhythmia (finding)	SCTID: 164893009
Ventricular fibrillation	SCTID: 71908006
Electrocardiographic ventricular fibrillation (finding)	SCTID: 164896001
Sustained ventricular fibrillation (disorder)	SCTID: 429243003
History of ventricular fibrillation (situation)	SCTID: 161513002
Ventricular tachyarrhythmia (disorder)	SCTID: 6624005
Palpitations (finding)	SCTID: 80313002
Palpitations - rapid (finding)	SCTID: 248648003
Bumping heart (finding)	SCTID: 161968007

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Pounding heart (finding)	SCTID: 248657009
Fluttering heart (finding) *	SCTID: 161969004
Palpitations with regular rhythm (finding)	SCTID: 428919002
Intermittent palpitations (finding)	SCTID: 102590007
History of palpitations (situation)	SCTID: 473122004
Skin and subcutaneous tissue disorders	
Stevens-Johnson syndrome (disorder)	SCTID: 73442001
Stevens-Johnson syndrome caused by drug (disorder)	SCTID: 403609001
Stevens-Johnson syndrome, toxic epidermal necrolysis spectrum (disorder)	SCTID: 768946000
Stevens Johnson syndrome AND toxic epidermal necrolysis overlap (disorder)	SCTID: 124911000119100
Stevens-Johnson and toxic epidermal necrolysis overlap syndrome caused by drug (disorder)	SCTID: 724833000
Toxic epidermal necrolysis	
Lyell syndrome (disorder)	SCTID: 768962006
Toxic epidermal necrolysis caused by drug (disorder)	SCTID: 402744003
Stevens-Johnson syndrome, toxic epidermal necrolysis spectrum (disorder)	SCTID: 768946000
Stevens Johnson syndrome AND toxic epidermal necrolysis overlap (disorder)	SCTID: 124911000119100
Stevens-Johnson and toxic epidermal necrolysis overlap syndrome caused by drug (disorder)	SCTID: 724833000
Angioedema	SCTID: 41291007
Giant urticaria (disorder)	SCTID: 400075008
Drug-aggravated angioedema-urticaria (disorder)*	SCTID: 241958006
Angioedema and/or urticaria (disorder)*	SCTID: 404177007
Urticaria	SCTID: 126485001
Acute urticaria (disorder)	SCTID: 402408009
Chronic urticaria (disorder)	SCTID: 51611005
Allergic urticaria (disorder)	SCTID: 40178009
Immunologic urticaria (disorder)	SCTID: 40370006
Contact urticaria (disorder)	SCTID: 19364004
Allergic contact urticaria (disorder)	SCTID: 402304007
Urticaria medicamentosa (disorder)	SCTID: 11012891000119106
Urticaria caused by serum (disorder)	SCTID: 89322006
Drug-aggravated angioedema-urticaria (disorder)*	SCTID: 241958006
Angioedema and/or urticaria (disorder)*	SCTID: 404177007

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
History of urticaria (situation) (Prevalent code)	SCTID: 213325008
Dermatographic urticaria (disorder)	SCTID: 7632005
Pruritus	
Pruritic disorders (disorder)	SCTID: 279333002
Itching of skin (finding)	SCTID: 418363000
Generalized pruritus (finding)	SCTID: 276444007
Pruritus caused by drug (disorder)	SCTID: 724843002
Generalized pruritus of unknown etiology (disorder)	SCTID: 403576004
Pruritic rash (disorder)	SCTID: 64144002
Pruritus due to systemic disorder (disorder)	SCTID: 403575000
Pruritus due to neurological disorder (disorder)	SCTID: 724844008
Rash	
Eruption of skin (disorder)	SCTID: 271807003
Eruption (morphologic abnormality)	SCTID: 1806006
Eruption caused by drug (disorder)	SCTID: 28926001
Serum rash (disorder)	SCTID: 213323001
Generalized rash (disorder)	SCTID: 725119006
Localized eruption of skin (disorder)	SCTID: 724877007
On examination - rash present (situation)	SCTID: 268911002
Localized skin eruption caused by drug and medicament (disorder)	SCTID: 200893007
Pseudolymphomatous eruption caused by drug (disorder)	SCTID: 402748000
Generalized skin eruption caused by drug and medicament (disorder)	SCTID: 200892002
On examination - discoid rash (disorder)	SCTID: 164427005
On examination - mouth rash (disorder)	SCTID: 163148009
On examination - itchy rash (disorder)	SCTID: 304386008
On examination - scalp rash (disorder)	SCTID: 395122007
On examination - allergic rash (disorder)	SCTID: 275955005
On examination - erythematous rash (disorder)	SCTID: 135888007
Macular eruption (disorder)	SCTID: 271756005
Bullous eruption (disorder)	SCTID: 271759003
Macular rash (morphologic abnormality)	SCTID: 89757007
Papular rash (morphologic abnormality)	SCTID: 70831001
Pruritic rash (disorder)	SCTID: 64144002
Pustular rash (morphologic abnormality)	SCTID: 48055004
Purpuric rash (disorder)	SCTID: 284078000
Vesicular rash (morphologic abnormality)	SCTID: 53788007

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Blistering eruption (disorder)	SCTID: 247464001
Vasculitic rash (morphologic abnormality)	SCTID: 27006004
Premycotic eruption (disorder)	SCTID: 404102002
Weal (disorder)	SCTID: 247472004
Synchronous rash (finding)	SCTID: 409642009
Morbilliform rash (morphologic abnormality)	SCTID: 50495000
Multimorphic rash (disorder)	SCTID: 301447009
Morbilliform eruption (disorder)	SCTID: 247470007
Maculopapular rash (morphologic abnormality)	SCTID: 47725002
Grade of skin rash (observable entity)	SCTID: 424223007
Maculopapular eruption (disorder)	SCTID: 247471006
Vesiculobullous rash (morphologic abnormality)	SCTID: 14912003
Papulovesicular rash (morphologic abnormality)	SCTID: 4538007
Complaining of a rash (finding)	SCTID: 162415008
Application site rash (disorder)	SCTID: 95371007
Cutaneous hypersensitivity (disorder)	SCTID: 21626009
Nervous System disorders	
Dizziness (finding)	SCTID: 404640003
Dizziness present (situation)	SCTID: 162260006
Dizziness of unknown cause (finding)	SCTID: 429530004
Dizziness due to drug (disorder)	SCTID: 473188002
Dizziness on standing up (finding)	SCTID: 407645004
Postural dizziness (finding)	SCTID: 103017008
Dizziness and giddiness (finding)	SCTID: 271789005
Somnolence	
Drowsiness, function (observable entity)	SCTID: 79519003
Drowsy (finding)	SCTID: 271782001
Complaining of somnolence (finding)	SCTID: 272026007
Daytime somnolence (finding)	SCTID: 141000119100
Excessive somnolence (finding)	SCTID: 372947007
Disorders of excessive somnolence (disorder)	SCTID: 194439006
Somnolence syndrome (disorder)	SCTID: 370971007
Paresthesia (finding)	SCTID: 91019004
Paresthesia of upper limb (finding)	SCTID: 95673003
Facial paresthesia (finding)	SCTID: 95665007
Paresthesia of foot (finding)	SCTID: 309087008
Paresthesia of hand (finding)	SCTID: 309086004
Paresthesia of finger (finding)	SCTID: 762374005

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Transient paresthesia (finding)	SCTID: 135873002
Circumoral paresthesia (finding)	SCTID: 1141007
Paresthesia of lower extremity (finding)	SCTID: 429783005
Paresthesia of right upper limb (finding)	SCTID: 15973701000119104
Paresthesia of right lower limb (finding)	SCTID: 15634791000119106
On examination - paresthesia present (finding)	SCTID: 163707002
Injection site paresthesia (disorder)	SCTID: 95399003
Paresthesia of left lower limb (finding)	SCTID: 15634841000119109
Paresthesia of left upper limb (finding)	SCTID: 15973661000119106
Oral paresthesia (disorder)	SCTID: 95524000
Paresthesia of mucous membrane (finding)	SCTID: 95358009
Paresthesia of tongue (disorder)	SCTID: 95527007
Numbness of skin (finding)	SCTID: 102603008
Burning sensation of skin (finding)	SCTID: 762397008
Prickling sensation of skin (finding)	SCTID: 162248005
Numbness and tingling sensation of skin (finding)	SCTID: 101000119102
Finding of sensation of skin (finding)	SCTID: 297971001
Altered sensation of skin (finding)	SCTID: 247325003
Skin sensation disturbance (finding)	SCTID: 80910005
Complaining of paresthesia (finding)	SCTID: 31048100
Loss of consciousness	
Loss of consciousness (finding)	SCTID: 419045004
Brief loss of consciousness (finding)	SCTID: 32834005
Moderate duration loss of consciousness (finding)	SCTID: 40863000
Prolonged loss of consciousness (finding)	SCTID: 7862002
Syncope	SCTID: 271594007
Syncope and collapse (disorder)	SCTID: 309585006
Metabolism and nutrition disorders	
Appetite disorder	
Non-organic loss of appetite (disorder)	SCTID: 192017004
Appetite problem (finding)	SCTID: 289163007
Appetite symptom (finding)	SCTID: 161824009
Centrally acting appetite suppressant adverse reaction (disorder)	SCTID: 292259006
Altered appetite (finding)	SCTID: 249473004
Eating disorders management (procedure)	SCTID: 386264009
Decrease in appetite (finding)	SCTID: 64379006
Non-organic loss of appetite (disorder)	SCTID: 192017004

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Decreased appetite	
Decrease in appetite (finding)	SCTID: 64379006
Diet refusal	
Refusing food (finding)	SCTID: 105481005
Does not eat (finding)	SCTID: 288887001
Unable to eat (finding)	SCTID: 288885009
Hypophagia	
Decrease in appetite (finding)	SCTID: 64379006
Non-organic loss of appetite (disorder)	SCTID: 192017004
Food aversion	
Aversion to food or drink (finding)	SCTID: 248134002
Finding of food aversion and cravings (finding)	SCTID: 289143000
Sensory aversion to particular foods (finding)	SCTID: 16230791000119104
Aversion to particular food (finding)	SCTID: 248135001
General disorders and administration site conditions	
Chest pain	SCTID: 29857009
Acute chest pain (finding)	SCTID: 102587001
Atypical chest pain (finding)	SCTID: 102589003
Cardiac chest pain (finding)	SCTID: 426396005
Central chest pain (finding)	SCTID: 161972006
Chest pain at rest (finding)	SCTID: 9267009
Chest pain due to pericarditis (finding)	SCTID: 34791000119103
Chest pain on breathing (finding)	SCTID: 274664007
Chest pain on exertion (finding)	SCTID: 81953000
Chest wall pain (finding)	SCTID: 102588006
Crushing chest pain (finding)	SCTID: 59139008
Dull chest pain (finding)	SCTID: 3368006
Ischemic chest pain (finding)	SCTID: 225566008
Left sided chest pain (finding)	SCTID: 285385002
Localized chest pain (finding)	SCTID: 97001000119106
Musculoskeletal chest pain (finding)	SCTID: 281245003
Noncardiac chest pain (finding)	SCTID: 274668005
Parasternal pain (finding)	SCTID: 161974007
Pleuritic pain (finding)	SCTID: 2237002
Pleuropericardial chest pain (finding)	SCTID: 13057000
Precordial pain (finding)	SCTID: 71884009
Radiating chest pain (finding)	SCTID: 10000006
Retrosternal pain (finding)	SCTID: 4568003

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Right sided chest pain (finding)	SCTID: 285386001
Squeezing chest pain (finding)	SCTID: 371030007
Upper chest pain (finding)	SCTID: 285389008
Angina decubitus (disorder)	SCTID: 59021001
Angina (disorder)	SCTID: 194828000
(Prevalent) History of angina pectoris (situation)	SCTID: 161504004
Gait disturbances	
Abnormal gait (finding)	SCTID: 22325002
Tandem gait test - abnormal (finding)	SCTID: 401211005
Functional gait abnormality (finding)	SCTID: 69161000119103
Abnormal gait due to muscle weakness (finding)	SCTID: 432559006
Abnormal gait due to impairment of balance (finding)	SCTID: 431524008
Frontal gait disorder (disorder)	SCTID: 250054005
Peripheral sensory gait disorder (finding)	SCTID: 250027007
High level sensorimotor gait disorder (finding)	SCTID: 250043000
Low level sensorimotor gait disorder (finding)	SCTID: 250003005
Middle level sensorimotor gait disorder (finding)	SCTID: 250034009
Peripheral skeletomuscular gait disorder (finding)	SCTID: 250004004
Ataxic gait (finding)	SCTID: 25136009
On examination - gait ataxic (finding)	SCTID: 163686004
Visual ataxic gait (finding)	SCTID: 250033003
Sensory ataxic gait (finding)	SCTID: 250029005
Staggering gait (finding)	SCTID: 78691002
Vestibular ataxic gait (finding)	SCTID: 250032008
Spastic gait (finding)	SCTID: 9447003
Paraplegic gait (finding)	SCTID: 250035005
On examination - gait spastic (finding)	SCTID: 163685000
On examination - limping gait (finding)	SCTID: 163691003
Investigations	
ECG PR Prolonged	
Electrocardiogram: partial atrioventricular block - long PR (finding)	SCTID: 164902006
Prolonged PR interval (finding)	SCTID: 164947007
Injury, poisoning and procedural complications	
Injection site discomfort	
Injection site burning (disorder)	SCTID: 95389008
Injection site reaction (disorder)	SCTID: 95377006
Injection site disorder (disorder)	SCTID: 95376002

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Injection site dermatitis (disorder)	SCTID: 95393002
Injection site urticaria (disorder)	SCTID: 95394008
Injection site edema (disorder)	SCTID: 95392007
Swelling at injection site (disorder)	SCTID: 213340005
Injection site inflammation (disorder)	SCTID: 95391000
Injection site induration (disorder)	SCTID: 95402002
Induration at injection site (disorder)	SCTID: 213337005
Injection site hypersensitivity (disorder)	SCTID: 95378001
Injection site cyst (disorder)	SCTID: 95396005
Injection site mass (disorder)	SCTID: 95395009
Injection site ulcer (disorder)	SCTID: 95400005
Injection site abscess (disorder)	SCTID: 95382004
Injection site atrophy (disorder)	SCTID: 95404001
Injection site necrosis (disorder)	SCTID: 95397001
Injection site fibrosis (disorder)	SCTID: 95403007
Injection site bruising (disorder)	SCTID: 95401009
Injection site infection (disorder)	SCTID: 95381006
Injection site granuloma (morphologic abnormality)	SCTID: 24389009
Injection site thrombosis (disorder)	SCTID: 95386001
Injection site hemorrhage (disorder)	SCTID: 95385002
Injection site paresthesia (disorder)	SCTID: 95399003
Injection site nerve damage (disorder)	SCTID: 95390004
Injection site malabsorption (disorder)	SCTID: 95387005
Injection site extravasation (disorder)	SCTID: 95384003
On examination - Injection sites abnormal (disorder)	SCTID: 308092004
Injection site sterile abscess (disorder)	SCTID: 95383009
Injection site pigmentation change (disorder)	SCTID: 95380007
Application AND/OR injection site disorder	SCTID: 95363008
Application site rash (disorder)	SCTID: 95371007
Injection site pain (disorder)	SCTID: 95388000
Erythema at injection site (disorder)	SCTID: 213338000
Injection site irritation (disorder)	SCTID: 95379009
Injection site erythema	
Erythema at injection site (disorder)	SCTID: 213338000
Injection site irritation	
Injection site irritation (disorder)	SCTID: 95379009
Injection site pain	
Injection site pain (disorder)	SCTID: 95388000

Table 3 SNOMED-CT concepts for the study

Study outcome	SNOMED code
Psychiatric disorders	
Abnormal behavior (finding)	SCTID: 25786006
Mildly abnormal behavior (finding)	SCTID: 165311008
Severely abnormal behavior (finding)	SCTID: 165312001
Drug reaction with eosinophilia and systemic symptoms Syndrome	
Drug reaction with eosinophilia and systemic symptoms Syndrome (disorder)	SCTID: 702809001
Acute generalized exanthematous pustulosis (disorder)	SCTID: 702617007
Severe cutaneous adverse reactions	
Drug reaction with eosinophilia and systemic symptoms Syndrome (disorder)	SCTID: 702809001
Acute generalized exanthematous pustulosis (disorder)	SCTID: 702617007
Lyell syndrome (disorder)	SCTID: 768962006
Toxic epidermal necrolysis caused by drug (disorder)	SCTID: 402744003
Stevens-Johnson syndrome, toxic epidermal necrolysis spectrum (disorder)	SCTID: 768946000
Stevens Johnson syndrome AND toxic epidermal necrolysis overlap (disorder)	SCTID: 124911000119100
Stevens-Johnson and toxic epidermal necrolysis overlap syndrome caused by drug (disorder)	SCTID: 724833000
Stevens-Johnson syndrome (disorder)	SCTID: 73442001
Stevens-Johnson syndrome caused by drug (disorder)	SCTID: 403609001
Cutaneous hypersensitivity (disorder)	SCTID: 21626009
Hypersensitivity	
Non-allergic drug hypersensitivity disorder (disorder)	SCTID: 427640001
Hypersensitivity disease of liver caused by drug (disorder)	SCTID: 735456000
Renal hypersensitivity caused by drug (disorder)	
Allergic reaction, caused by correct medicinal substance properly administered (disorder)	SCTID: 762531008
	SCTID: 57302007
Drug reaction with symptoms (eosinophilia and systemic disorder)	SCTID: 702809001

5.5.6 Baseline Characteristics

Baseline characteristics that will be evaluated include patient characteristics, as well as diagnosis (including IV LCM exposure indications and preexisting conditions of interest as described in Section 5.5.3), procedures, and medications administered, dispensed or prescribed (AEDs, benzodiazepines and non-AEDs) (including AED line of therapy) will be evaluated. Diagnostic and procedural data will be identified using International Classification of Disease (ICD)-9, ICD-

10-Procedures, Current Procedural Terminology (CPT)-4, Healthcare Common Procedure Coding System (HCPCS), and Logistical Observation Identifier Names and Codes (LOINC) vocabularies which provide a systematic nomenclature for medical laboratory observations.

5.6 Data source and data management

5.6.1 Description of database

PEDSnet (pedsnet.org) is a clinical research network (CRN) that was launched in 2014 and is currently a Clinical Data Research Network (CDRN) inmember of the Patient-Centered Clinical Research Network (PCORnet, pcornet.org). PEDSnet includes 8 pediatric health systems across the United States including Boston Children's hospital, Children's Hospital Colorado, Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, Nationwide Children's Hospital, Nemours Children's Health System, St Louis Children's Hospital and Seattle Children's Hospital. The PEDSnet core data includes information on 6.2 million children, seen since 2009. The regional catchment area for the network extends across 22 states in the US, currently providing care annually for 2.5 million patients, or 2.8% of all children in the USA, from diverse demographic, geographic, and socioeconomic backgrounds. The historical database from 2009-present includes 6.5 million children inclusive of all their inpatient and outpatient care that occurs in member institutions.

The PEDSnet database consists of data from electronic healthcare records (EHRs) generated during a health encounter at any of the health institutions included in the network. The data includes demographic characteristics, encounter data for primary care, specialty care, emergency department and inpatient visits, procedures, prescribed or dispensed medications, laboratory results, diagnoses, anthropometrics and vital signs collected during routine care or management of complex illnesses, Table 4 Measures available in the PEDSnet database.

Table 4 Measures available in the PEDSnet database

Domain	Type of Data
Demographics	Age, date of birth, gestational age, sex, ethnicity, race, zip code, PEDSnet health system site, primary care provider, death and cause of death (if available)
Outpatient encounters (~75 visit specialty types available)	Primary care visits, specialty care clinics (e.g., cardiology, endocrinology, nephrology, oncology, etc.), physical therapy, occupational therapy, speech language pathology, medical genetics/genomics, etc.
Inpatient admissions	Length of stay, discharge status; diagnoses, procedures, medications, and lab results associated with inpatient stay
Emergency department encounters	Diagnoses, procedures, medications, and lab results associated with emergency department visit; emergency department visits resulting in inpatient admission
Anthropometrics	Height (cm) and weight (kg), body mass index, head circumference
Vital signs	Temperature, blood pressure
Providers	Specialty, health care facility
Diagnoses	Final diagnoses are recorded at each encounter and are mapped to a standardized codes (typically SNOMED-CT)

Domain	Type of Data
Procedures	Procedures are recorded at each encounter and are mapped to standardized SNOMED-CT, ICD-9 Procedure, ICD-10 Procedure, CPT-4, and HCPCS codes
Prescribed medications	Medications ordered are recorded at each encounter and mapped to a standardized RxNorm code
Dispensed medications	Medications dispensed, when available, are recorded and mapped to a standardized RxNorm code
Laboratory test results	Contains the orders and results for more than 400 laboratory tests. Examples include key components of lipid panel, complete metabolic panel, complete blood counts, microbiologic cultures, liver function tests, urinalysis, viral panels, etc.
Visit payer	Plan class (private/commercial, medicaid/sCHIP, Medicare, other public, self-pay, other/unknown), plan type (HMO, PPO, POS, fee for service, other/unknown) for every unique visit. Enrollment information unavailable.

The EHR contain data in a structured format from predefined categories based on the EHR systems and data in unstructured (free text) format generated from physician and nurses notes. It is anticipated that there may be variation in the amount of clinical data recorded based on the healthcare setting i.e. inpatient, emergency department versus outpatient. It is anticipated that inpatient data will be highly detailed, as complete data capture on all signs and symptoms over the time period spent in hospital is often the practice.

Each of the partner site creates a local dataset. The PEDSnet database is updated on a quarterly basis by extracting data from the member institutions and transforming the data into a CDM. Data are extracted from the EHR and entered into the Research Electronic Data Capture (REDCap) system which enables integration with the structured data captured in a pediatric-specific CDM. The PEDSnet CDM is an extension of the Observational Health Data Sciences and Informatics Collaborative's Observational Medical Outcomes Partnership (OMOP) CDM. It was developed to facilite the use of data generated from multiple facilities with different EHR structures. PEDSnet uses SNOMED-CT to represent the diagnoses; SNOMED-CT, ICD-9, ICD-10, CPT-4 and HCPCS codes to map procedures; RxNorm for dispensed and prescribed medications; and LOINC to represent laboratory results observations. Each patient is assigned a study code that is used in place of direct identifiers to facilitate longitudinal research with reduced risk of violating privacy. Additionally, each member site operates under the guidance of their Institutional Review Board, which is charged with protecting the safety and privacy of patients and families that participate in research.

5.7 Data management and Quality control

5.7.1 Data Quality

The completeness and validity of the EHRs at the partner sites is dependent upon the physician recording the information during the health encounter. Each PEDSnet institution employs rules relating to how EHR data should be documented to ensure the validity and consistentency of the data entered. Quality control of the PEDSnet CDM is ensured by means of an extensive data quality assessment program (DQA) which examines data submitted by each organization and

across all PEDSnet data partners. This program maximizes the validity of the EHR-derived datasets and data quality by means of quarterly extensive data quality testing, which evaluates errors in the collection or standardization of data (i.e. to ensure data is in a "workable" state for research purposes). The process begins with approximately 850 tests done on data from each PEDSnet site in each quarterly data cycle. The errors evaluated by the data coordinating center include programming pipeline errors, data entry errors, administrative errors, or source data incompleteness. The quality assessment includes review of individual data elements for consistency with the CDM specification and with clinical plausibility, for trends over time, and for expected correlations between data elements. The DQA process assesses the description of the operating characteristics of the data in several dimensions which includes data reliability, consistency, accuracy and completeness. Test results are reviewed by data scientists at Data Coordinating Center and discussed with each site. Issues that arise from errors in data extraction or transmission are corrected and the data reloaded. Any identified issues (e.g. errors in data extraction/transmission) can then be resolved. In addition to this, PCORnet conducts a data characterisation process based on the Mini-Sentinel data quality review process. As a PCORnet network partner, PEDSnet must also meet PCORnets coordinating center quality assessments, which further assesses the data model conformance, missing data in enrollment, encounters, demographics, vital findings, diagnoses, and procedures tables, and the plausibility of date and vital measures data.

Quality assurance: For the overall data network, data quality assessment (DQA) occurs on several levels. There is a published specification document (current version available at https://PEDSnet.org/documents/206/ETL_Conventions_for_use_with_PEDSnet_CDM_v3.1_OMOP_V5.2.pdf) that each site uses to develop ETL. The database uses a relational architecture, so the second step applies at data loading, and enforces base type constraints and referential integrity. A series of DQA tests are applied across the entirety of the data, which focus on value set compliance, consistency, missingness, and similar structural checks. The tools are available at https://github.com/PEDSnet/Data-Quality-Analysis. There is a summary of experience here:

Khare, R., Utidjian, L., Ruth, B.J., Kahn, M.G., Burrows, E., Marsolo, K., Patibandla, N.,Razzaghi, H., Colvin, R., Ranade, D., et al. (2017). A longitudinal analysis of data quality in a large pediatric data research network. J Am Med Inform Assoc 24, 1072-1079.

Relevant data quality issues are included as part of project reporting. During project execution, study-specific DQA may involve several techniques, depending on study design. Routine assessments include areas such as missing data and coding variation across data sources, as well as anomaly detection. Code set development addresses terminology structure, usage patterns, and where possible recovery of missing codes via source values. Cohort DQA includes assessment of variation across subsets, reliability over time, and where external data exist to set expectations, alignment of study data to those expectations. In appropriate studies construct composite measures of data quality across multiple covariates (e.g. different medication exposure variables), have been used as a tool to identify outliers among data sources. Specification for this type of study-specific DQA is part of the analysis planning that goes on between the requestor's study team and the data science team here. Finally, where external validation of classification is needed, medical records review is available, whether for a sample of the cohort to establish performance characteristics of an algorithm, or for study-specific data capture where needed. When review is done, a common abstraction tool is used, and post-review adjudication is centrally performed, and reviewers receive common training. We do not

routinely use multiple reviewers per record, though it is an option; routine QA would include inter-rater reliability.

Previous studies have applied these quality assessments to the standard to provide data for FDA submission, and deidentified datasets can be provided to the regulator.

5.7.2 Data Validity

The study will use both the PEDSnet CDM and EHR medical charts data. The validity of the data depends on the source data that was recorded by the physician during each specific encounter. As indicated in the Section 5.7.1, PEDSnet has put in place extensive measures to ensure high validity of the data that is transferred into the CDM. For the chart review, a random sample consisting of 10% of all the EHR medical charts included in the study will be reviewed by a second reviewer and assessed for inter-person variability.

5.7.3 Database entry and reconciliation

The data from the medical chart review will be entered into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review in order to check for discrepancies and to ensure consistency of the data. An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been electronically loaded. Regular backups of the electronic data will be performed.

5.8 Archiving and Data Retention

UCB requires the documents to be retained at least for 5 years after completion of the study. The documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB.

PEDSnet will contact UCB prior to the destruction of any study records or in the event of accidental loss or destruction of any study records.

5.9 Statistics

For the baseline characteristics, mean, standard deviation, median, and quartiles will be used to describe continuous variables, whereas frequencies and percentages will be used to describe categorical variables. The baseline characteristics will include demographic characteristics, number of previous and concomitant AEDs, and concomitant medications prescribed prior to the index date, prevalence of comorbidities, preexisting medical events of interest, medical procedures such as EEG, and dosage of IV LCM.

All analyses will be stratified as follows:

- Exposure to additional AEDs
- IV LCM treatment indication
- Preexisting medical events of interest
- Use in the intensive care unit or other hospital departments (e.g. emergency department, inpatient, and outpatient setting)

- First time IV loading dose exposure vs previous treatment with index medication

5.9.1 Planned analysis

A table of baseline characteritics comparing treatment groups will be presented along with a sub-table of those from each group with SE. Results will be presented stratified by ageband where appropriate.

5.9.1.1 Adjustment for baseline characteristics using propensity scores

We will use propensity score and inverse probability of treatment weights (IPTW) to control confounding (Brookhart 2013). The propensity score will be estimated using a logistic regression model, in which higher IV LCM dose (vs. recommended initial/maintenance IV LCM dose) will be regressed on the baseline characteristics. Covariates for inclusion in the propensity score model were selected based on their potential association with the outcomes, including patient characteristics, patient disease history, and treatment history, as indicated on page 35 of the study protocol under section 5.6.6, and on page 21 section 5.6.3 of the protocol, and as listed below:

- Weight
- Sex
- Age at time of seizure treated with loading dose
- Ethnicity (if available)
- PEDSNet site
- Diagnosed medical conditions
- Prior AED/benzodiazepine prescribing (home use) or administration in hospital
- Prior seizure number if available
- Treatment for said seizures (AED and/or benzodiazepine)
- Concomitant prescribing
- Pre-existing medical conditions of interest for the safety evaluation: cardiac conditions, dermatologic conditions, vascular conditions, injury, poisoning and procedural complications, general disorders and administration site conditions, investigations, drug reaction with eosinophilia and systemic symptoms syndrome, severe cutaneous adverse reactions, hypersensitivity events
- Prior EEG data at last seizure

After the propensity scores have been generated, we will assess for violations of underlying assumptions. Positivity violations will be assessed by plotting the propensity score distributions in an overlay plot for the comparator groups. To evaluate adequate overlap of the propensity scores, we will visually inspect the density distribution of the propensity scores (Rosenbaum and Rubin, 1984). The performance of the model will be evaluated by assessing the covariate balance across the treatment groups. Standardized differences will be used to compare the mean or prevalence of baseline covariates between the comparator treatment groups in the samples

weighted by the inverse probability of treatment. Additionally, continuous variables will be compared using graphical methods including boxplots and nonparametric density plots.

Then we will compute inverse probability of treatment weights, defined as the reciprocal of the probability of receiving the treatment that was actually received using the derived propensity score, to create a pseudo-population where the measured covariates are not associated with the outcome, and both cohorts are standardized to the overall population (Brookhart et al, 2013). Given IPTW is often hampered by extreme propensity scores, resulting in biased estimates and excessive variance, we will evaluate the distribution of the stabilized weights using graphical displays (e.g. boxplots) and descriptive statistics. The characteristics of the patients with outlier weights will be examined and if necessary, the model will be re-specified and the weights re-estimated, or if the outlier are not significant, symmetric trimming methods will be sued to exclude these patients using $\alpha = 0.1$ (cite Crump RK, Hotz VJ, Imbens GW, et al. Dealing with limited overlap in estimation of average treatment effects. Biometrika. 2009;96(1):187–199).

IPTW-weighted Poisson regression model with robust variance estimator (regressed on exposure status in the sample weighted by the IPTW) will be used to estimate adjusted incidence rate ratios and 95% CIs of each outcome. The advantages of IPTW weighting includes retention all study patients and estimation of an average exposure effect in the whole population of eligible patients as incidence rate ratio (IRR) the other propensity score methods require exclusion of patients who cannot be matched to a control. As this study is reliant on a relatively small population of pediatric patients, and where comparison is undertaken between groups, retaining all patients allows for greater power to investigate significant differences between groups. Use of an alternative matching method would also mean that the effect estimate obtained from the matching would only be generalizable to populations similar to the matched patients. Retention of all patients allows for greater generalizability to background populations.

5.9.1.2 Analysis of primary and secondary outcome measures

Only the first occurrence of the event after the index date will be counted in analyses. For both the IV LCM group and comparator group, counts and frequency of events will be recorded. For both the IV LCM high dose group and comparator group, several incidence rates will be calculated. First, the overall incidence rate of any event of interest will be calculated. Second, incidence rates for each of the following events will be calculated individually: Cardiac disorders, Skin and subcutaneous tissue disorders, Nervous system disorders, Metabolism and nutrition disorders, Psychiatric disorders, Injury, poisoning and procedural complications, General disorders and administration site conditions, and Investigations, Drug reaction with eosinophilia and systemic symptoms syndrome, Severe cutaneous adverse reactions and Hypersensitivity events. Third, incidence rates for each subcategory of the abovementioned events and associated 95% confidence intervals will be calculated. The incidence rate of each event with associated 95% confidence interval will be calculated for the IV LCM high dose group and comparator group.

The numerator will be the total number of patients with the outcomes identified during the follow-up period. The denominator will be in patient-days. That is, the total summation of individual patient-days at risk up to the first occurrence of the AE of interest for subjects with

that AE, and the total patient-days at risk calculated up to the censoring date i.e. discontinuation of IV LCM plus 30 days or loss to follow-up for those subjects not experiencing that AE. Incidence rates will be presented with a 95% exact confidence interval based upon the Poisson distribution or another relevant model if there is nonconvergence. It is important to note incidence rates per time at risk are based on a constancy assumption. That is, the rates per unit of time assume that the event occurs with a constant rate over time. Events that are more likely to occur early or late relative to the initial exposure or with an increasing or decreasing hazard rate over time would not meet the constancy assumption and these rates should be viewed with caution. The person time for each patient will be calculated as the total number of days of follow-up as described in Section 5.3.3 .

Incidence rate ratios associated 95% confidence intervals will be calculated for each outcome to compare the incidence rates of the AEs for the IV LCM high dose group to those for the comparator group.

Those with SE will have the same data presented in separate tables as well as contributing to the main results.

5.9.1.3 Analysis of loading dose / higher than recommended initial IV LCM dose

To examine safety and tolerability of iv LCM administration, the analysis of the key primary and secondary variables will be stratified by loading dose and recommended dose groups, stratified by ageband ie, separate tables per age band. Risk estimates will be provided with incidence rate ratios and 95% confidence limits.

5.9.1.4 Sensitivity Analysis

Sensitivity analyses will be conducted to assess parameters used for defining the selection criteria, exposure, outcomes, and the study period as indicated below:

- Shorten the baseline period to 6 weeks
- The follow-up time will not include the 30 days after discontinuation of IV LCM
- Exclude patients with preexisting medical events of interest
- Outcome definitions will include a code for an outcome related medication/procedure within the period following the diagnosis record (to be defined)

5.9.1.5 Statistical modelling

IPTW-weighted Poisson regression model with robust variance estimator (regressed on exposure status in the sample weighted by the IPTW) will be used to estimate adjusted incidence rate ratios and 95% CIs of each outcome.

5.9.2 Handling of Missing Data

Data is dependent on information that was recorded by physicians and nurses into the EHR. It is therefore assumed that the patient did not have the diagnosis of interest if it is not reported in the EHR. No missing data will be imputed. For demographic characteristics, the type of missingness will be evaluated.

5.9.3 Sample size

To date, the feasibility assessment included the total number of subjects between 1 month to 17 years who had at least one IV administration of LCM, which totaled 875 patients. To obtain count data on the two comparator groups i.e. .loading dose or initial maintenance dose, requires complex programming to evaluate dose data, patient weight, age and so forth. Some of these data may be available in structured fields, but there might be need for additional information from the medical charts to calculate accurate dose information. As this protocol will be finalized post full review by the Division, at which time programming will commence, the feasibility analysis to date was thus limited to population count.

We acknowledge that the total population number will be reduced post application of the full study criteria but should nevertheless still retain several hundred patients, enough to allow adequate and accurate evaluation of safety data for LCM in this specific population.

5.9.4 Strength and Limitations

Unmeasured confounding: As the study is comparing the incidence rates of select medical events in patients who are treated with a high dose of IV lacosamide to patients who are treated with recommended dose of IV lacosamide, the major confounders are factors that impact the incidence rate of these medical events of interest. These factors include age, gender, comorbidities, and exposure to other medications which are measured. Unmeasured confounding would only occur if there was a major confounder which is not measured and thus missed from the adjusted model. However, the electronic medical records include demographic information, the medical history of the patients and any medications prescribed by the physicians. Therefore we anticipate that information on most of the confounders will be available. It is possible that there will be missing information on some comorbidities, if they are not recorded by the physicians and on medications that are either bought over counter or prescribed outside the PEDSnet healthcare network. Nevertheless, most hospitals in the PEDSNet healthcare network are large with epilepsy comprehensive care centers within the neurology departments, so we anticipate reliable background medical. We do not anticipate that there will be a disproportionate difference in the recording of the medical history data and prescription of medications in patients who are treated with high dose lacosamide and recommended lacosamide prior to the index date. Therefore, we anticipate that there will be minimal unmeasured confounding. Additionally, the analysis will be using new user design to minimize confounding by indication.

Reduced generalizability: The PEDSnet database is restricted to subjects seeking and receiving medical care within a facility affiliated with PEDSnet. Data is obtained from multiple care sites and type (e.g. in-patient, out-patient, emergency department). However, if a report of an event was made or a subject was treated for an event at a facility that is not affiliated PEDSnet, this information will not be captured in the PEDSnet data. However, as most events are anticipated to occur within 24 hours of receiving IV LCM, the impact of this is likely to be low.

Misclassification: Ascertainment of outcomes will be made using controlled vocabularies. Currently there are no validated algorithms for defining these outcomes in EHR data therefore there is a risk for misclassification. Misclassification will be minimized through chart reviews that will be conducted by experienced healthcare personnel. Additionally, sensitivity analyses will be conducted to assess the impact of the case definitions on the effect estimates. Information available from outpatient or ER reports is likely not to provide as complete information as that recorded during hospitalisation, however, despite this it is likely that any severe AEs will be recorded. As noted, available data from the chart review is expected to be

complete for patients in an inpatient setting. In particular nurses notes should comprise detailed information on patient responses and patient reported outcomes. As IV LCM is generally administered in an inpatient setting, we therefore expect recording of immediate AEs to be well documented, including those that may be less severe such as injection site irritation/pain.
Strengths: Despite these limitations, this assessment will provide a large sample pediatric of patients exposed to off-label IV LCM, facilitating timely characterization of the safety profile of these patients and informing the pediatric trial program.

6 PROTECTION OF HUMAN SUBJECTS

6.1 Patient consent for data usage and processing

The data will be completely anonymized and thus will not contain any identifiable patient data (eg, patient initials or date of birth). In accordance with the "International Ethical Guidelines for Epidemiological Studies" [Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 113 pp., Genova: 2008, pp 21] - cit. “records and specimens taken in the course of clinical care, or for an earlier study, may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed” - it is considered for this study that a data collection patient informed consent form is not required as the patients are unidentifiable.

6.2 Patient identification

Data will be analyzed by PEDSnet. UCB will only obtain aggregate data without identifiers. Each patient has already been assigned a de-identified Patient ID number by the database provider and therefore will be used for this study. A unique number will also be assigned to each patient and will be entered into the electronic/paper CRF.

7 REPORTING OF ADVERSE EVENTS

7.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

7.2 Adverse drug reaction

An ADR is a response to a medicinal product which is noxious and unintended. 'Response' in this context means that a causal relationship between a medicinal product and an AE shows at least a reasonable possibility. This includes ADRs that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors

• Occupational exposure (this refers to the exposure to a prescribed treatment as a result of one's professional or nonprofessional occupation)

7.3 Serious adverse event/serious adverse drug reaction

An AE or ADR is serious if one or more of the following criteria are met:
• Death.
• Life threatening: An event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
• Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization is planned prior to the patient receiving the first dose of medicinal product, it is not classified as serious. However, if a hospitalization is unplanned and is a result of an adverse experience, this is considered a serious adverse event (SAE).
• Persistent or significant disability/incapacity.
• Congenital anomaly or birth defect.
• An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

7.4 Reporting obligations

This study uses existing health care databases, in which it is generally not possible to link (i.e., identify a potential causal relationship between) a particular product and medical event for any individual.
This retrospective study (secondary data collection study) is characterized by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. We cannot know if ADR/AEs has been reported previously. Further, initial reporter will not be identifiable (i.e. the 4 elements (compound, AE, Patient, reporter) for a valid Individual Safety Case Report (ICSR) will not be fulfilled.
In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to "Vimpat" that appears in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite, explicit statement of causality by the original healthcare provider linking drug administration to the AE.
The requirements for reporting safety events on the non-interventional study (NIS) adverse event Report Form to UCB Safety are as follows:
• All serious and non-serious AEs with explicit attribution to "Vimpat" that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to UCB Safety using the NIS AE Report Form.
• In this study scenarios involving drug exposure that include Vimpat use during pregnancy, during breast feeding, medication error, overdose, misuse, extravasation associated with the use

of "Vimpat" must be reported, within 24 hours of awareness, to UCB Safety using the NIS AE Report Form.
For these safety events with an explicit attribution to or associated with use of, respectively, "Vimpat", the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

Where relatedness to Vimpat is explicitly stated, the cases will be stored in the UCB safety database and be part of the routine signal detection activities. ADRs will be presented and summarized in the final study report.

8 TERMINATION OF THE STUDY

UCB reserves the right to suspend temporarily or prematurely discontinue this study at any time for reasons including, but not limited to unsatisfactory data quality or quantity.
If the study is prematurely terminated or suspended, UCB (or its representative) will inform PEDSnet, and the FDA of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable laws and regulations. The independent ethics committee (IEC) should also be informed and provided with reason(s) for the termination or suspension by PEDSnet, as specified by the applicable laws and regulations.

9 GOOD PHARMACOEPIDEMIOLOGY PRACTICES

This study follows the Guidelines for Good Epidemiologic Practice (GEP) practices laid out in 2005 FDA GPP and the 2008 International Society of Pharmacoepidemiology (ISPE) GPP.

10 AUDIT AND INSPECTION

Not applicable.

11 ETHICS AND REGULATORY REQUIREMENTS

11.1 Data consent

The data will be completely anonymized and thus will not contain any identifiable patient data (eg, patient initials or date of birth). In accordance with the "International Ethical Guidelines for Epidemiological Studies" [Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 113 pp., Genova: 2008, pp 21] - cit. "*records and specimens taken in the course of clinical care, or for an earlier study, may be used for research without the consent of the patients/subjects only if an ethical review committee has determined that the research poses minimal risk, that the rights or interests of the patients will not be violated, that their privacy and confidentiality or anonymity are assured, and that the research is designed to answer an important question and would be impracticable if the requirement for informed consent were to be imposed*" - it is considered for this study that a data collection patient informed consent form is not required as the patients are unidentifiable.

11.2 Institutional Review Boards and Independent Ethics Committees

Each member of the PEDSnet CDRN site operates under the guidance of their Institutional Review Board, which is charged with protecting the safety and privacy of patients and families that participate in research.
UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active treating physicians in accordance with applicable regulatory requirements. The appropriate Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) will also be informed by UCB (or its representative), as specified by the applicable regulatory requirements

11.3 Patient privacy

PEDSnet data at member sites and at the data coordinating center are stored on computers that are outfitted and maintained to be secure from unauthorized access. These systems are integrated into the same security mechanisms that the hospitals use to protect patients' medical data. Datasets that contain individual information and are transferred between PEDSnet sites only use secure file transfer systems. The data are Health Insurance Portability and Accountability Act (HIPAA) of 1996 compliant. All patient data are de-identified.

11.4 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, PEDSnet, the IRB/IEC, the FDA, prior to being implemented.

12 FINANCE AND PUBLICATION

The study results will be disseminated at a scientific congress and will be submitted to a peer-reviewed journal for a publication after completion of the study report. The study report is submitted to the regulator (FDA) as per agreements.

Financial arrangements and publication rights will be addressed in the written study agreements between UCB and the physician and/or the institution of the physician, as applicable.

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14 APPENDIX 1

14.1 Table 1 List of AED drug names

Drug/generic name
Carbamazepine
Clobazam
Clonazepam
Ethosuximide
Felbamate
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital
Phenytoin
Pregabalin
Primidone
Rufinamide
Tiagabine
Topiramate
Valproic acid/Valproate sodium/ Divalproex Sodium
Vigabatrin
Zonisamide

14.2 ENCePP form

15 PROTOCOL AMENDMENTS

During the programming of this protocol various amendments had to be made to the study protocol as follows:

Section 5.2 Study population.

1. This section contains both study criteria and explanation of a loading dose versus a recommended dose. The dosing information was clarified, the population criteria were amended to allow for appropriate time in the database for babies and neonates were added the population. Therefore, all of 5.2 was amended as follows:
    a. The dosing definitions for the loading and recommended groups were adjusted for babies < 6 months of age to allow for immature renal development and excretion of drug, particularly in neonates and the grouping dose wording was thus amended down to 4mg/kg from 6mg/kg dose. Additionally, the tables caused some confusion, so a concise table was developed with easier clarification of group definitions. The dose table under 15.2 has also been removed.
    b. Population inclusion criteria had to be amended, to allow for babies between 1 to 6 months of age to be included, as the original wording erroneously subjected babies to the same criteria as older children and required at least one health encounter or medical history within 6 months prior to the index date (first dose of lacosamide (LCM)), which is not possible in a baby aged less than 6 months.
    c. The criteria also were adjusted to allow for seven days follow up post last administration of LCM plus a maximum of 30 days of further observation, as per wording on page 21 Section 5.4.3 Follow Up (post index) period. The wording did not originally allow for that within the study inclusion criteria.
    d. Post communication with the FDA regarding the need to obtain data in neonates for LCM, it was decided to include neonates into the study, as currently there are no safety data in neonates for any AED, and dosing regimens of LCM are unknown. The protocol therefore had an additional set of study criteria added to accommodate this inclusion.
    e. There is an inclusion criterion that requires evidence of 37 days activity post the index date, to allow for follow-up. However, this removes patients who have died (all cause) during LCM exposure prior to 37 days. This has the effect of biasing the cohort towards healthy survivors and this clause has now been dropped. Follow up now has a maximum of 37 days but allows for the following censoring: at death, at transfer out of system, at transfer out the inpatient setting and at the addition of another AED. The current wording allowed for another AED to be introduced after LCM, but this introduces confounding regarding signal

attribution and is incorrect for retrospective review of adverse events. Section 5.3.3 Follow UP is also re-worded to allow for the censoring clarification.

2. The original safety section (Section 7) was incorrectly worded for a retrospective study safety evaluation and has since been re-worded to appropriately assess and report historical adverse events and re-defines the reporting process.
3. Section 5.9.1.3 includes information on the expected layout of loading dose results stratification. However, due to the amendment to change the dosing group definitions which only allows for recommended or high dosing, the table in this section is now redundant. Text has been amended in relation to this.

The following sections have therefore been amended.

Item 1: Section 5.2 Study population

Text did read:

The study population will consist of the following two mutually exclusive cohorts:

- Pediatric patients treated with higher IV LCM doses (including UCB's defined loading dose), regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.
- Pediatric patients treated with recommended initial/maintenance IV LCM dose regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.

These two groups are centered around the proposed alternative higher initial dosage and the recommended initial dosage, up-titration and maintenance dose regime as shown in Table 5 Proposed Pediatric Dosing for Patients ≥1 month to <17 YOA.

Table 5 Proposed Pediatric Dosing for Patients ≥1 month to <17 YOA

Drug	**Brand**	**GPI**	**Classification**
Age and Body Weight	**Initial Dosage**	**Titration Regimen**	**Maintenance Dosage**
Pediatric patients weighing 50 kg or more	50 mg twice daily (100 mg per day) **Proposed Alternate Initial Dosage**: 200 mg single loading dose, followed 12 hours later by 100 mg twice daily	Increase by 50 mg twice daily (100 mg per day) every week	**Monotherapy:** 150 mg to 200 mg twice daily (300 mg to 400 mg per day) **Adjunctive Therapy:** 100 mg to 200 mg twice daily (200 mg to 400 mg per day)
Pediatric patients weighing 30 kg to less than 50 kg	1 mg/kg twice daily (2 mg/kg/day) **Proposed Alternate Initial Dosage**: 4mg/kg followed 12 hours later by 2 mg/kg/day twice daily	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	2 mg/kg to 4 mg/kg twice daily (4 mg/kg/day to 8 mg/kg/day)

Drug	Brand	GPI	Classification
Pediatric patients weighing 4 kg* to less than 30 kg	1 mg/kg twice daily (2 mg/kg/day) **Proposed Alternate Initial Dosage**: 6mg/kg followed 12 hours later by 3 mg/kg/day twice daily	Increase by 1 mg/kg twice daily (2 mg/kg/day) every week	3 mg/kg to 6 mg/kg twice daily (6 mg/kg/day to 12 mg/kg/day)
*Babies < 4kg	Will be treated as above		

Higher IV LCM doses (including UCB's defined loading dose)

This cohort will include all pediatric patients:

- Starting IV LCM (as defined in Section 5.5.4) with a higher dose than the recommended dose, depending on the patient's recorded weight (at or nearest recorded to index date) the dosage would be that shown in Table 6 Initiating IV LCM dosages that do not correspond to a slow up-titration.
- Receiving one or two IV doses of LCM above their known maintenance dose within 24 hours.

Table 6 Initiating IV LCM dosages that do not correspond to a slow up-titration

Age and Body Weight	Higher LCM dose
Pediatric patients weighing 50 kg or more	>50 mg twice daily / 100 mg per day as a first administration
Pediatric patients weighing 30 kg to less than 50 kg	>1 mg/kg twice daily / 2 mg/kg/day as a first administration
Pediatric patients weighing 4 kg* to less than 30 kg	>1 mg/kg twice daily / 2 mg/kg/day as a first administration
*babies <4kg, will be treated as above	>1 mg/kg twice daily / 2 mg/kg/day as a first administration

This group will include patients with or without concomitant AEDs at the index date. Only the first eligible treatment episode with a higher IV LCM dose identified during the study period will be included in the analysis. Patients will be required to fulfill the selection criteria indicated below to be eligible for inclusion in the study.

Inclusion criteria for loading dose group (high dose)

Patients will be required to fulfill ALL of the following criteria:

- Starting a new treatment episode (i.e. first ever IV LCM dose or a new treatment episode for patients with a history of LCM treatment) with a higher than recommended initial IV LCM dose (that does not correspond to a slow up-titration, as per Table 6Initiating IV LCM dosages that do not correspond to a slow up-titration) or receiving a one or two higher IV LCM dose than their known maintenance LCM dose within 24 hours
- Aged ≥1 month and <17 years at the index date
- Patient should have either the presence of at least one health encounter within 6 months prior to the index date, and at least one health encounter ≥30 days after discontinuation of IV LCM to indicate presence in the database OR the presence of an adequate medical history (including comorbidities, procedure and medications) of at least 6 months prior to the index date and at least one health encounter ≥30 days after discontinuation of IV LCM to indicate presence in the database

Exclusion criteria for loading dose group (high dose)

- Any prescription for either oral or IV LCM during the baseline period (to ensure that any LCM related AEs evaluated during the study are related to IV dosing).

Recommended initial/maintenance IV LCM dose (Comparator Group)

This cohort will consist of all other pediatric patients with a new treatment episode (i.e. first ever IV LCM dose or a new treatment episode for patients with a history of LCM treatment) of IV LCM (excluding those described in Section 5.2.1), i.e. those who received a recommended initial IV LCM dosage, up-titration and maintenance dose regime, as per Table 5 Proposed Pediatric Dosing for Patients ≥1 month to <17 YOA

This will include patients with or without concomitant AEDs at the index date. Only the first eligible treatment episode of IV LCM identified during the study period will be included in the analysis. Patients will be required to fulfill the selection criteria indicated below to be eligible for inclusion in the study

Inclusion criteria for Comparator Group

Patients will be required to fulfil ALL of the following criteria:

- Starting a new treatment episode (i.e. either as first ever dose or a new episode for patients with a history of LCM treatment) with a recommended initial IV LCM dose, as per Table 5 Proposed Pediatric Dosing for Patients ≥1 month to <17 YOA
- Aged ≥1 month and <17 years at the index date
- Patient should have either the presence of at least one health encounter within 6 months prior to the index date, and at least one health encounter ≥30 days after discontinuation of IV LCM to indicate presence in the database OR the presence of an adequate medical history (including comorbidities, procedure and medications) of at least 6 months prior to the index date and at least one health encounter ≥30 days after discontinuation of IV LCM to indicate presence in the database

Exclusion criteria for Comparator Group

- Any prescription for either oral or IV LCM during the baseline period (to ensure that any LCM related AEs evaluated during the study are related to IV dosing).

Text now reads:

The study population will consist of the following two mutually exclusive cohorts:

- Pediatric patients treated with higher IV LCM doses (including UCB's defined loading dose), regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.
- Pediatric patients treated with recommended initial/maintenance IV LCM dose regardless of diagnostic code i.e. patients do not have to have a formal diagnosis of specific types of epilepsy and they may include children with SE caused by other conditions.

These two groups are defined by the proposed alternative higher initial dosage (first dose, first treatment in observed episode) and the recommended initial dosage (first dose, first treatment in observed episode) and patients remain in that group thereafter. Switching is not allowed at any time.

Patients will be initially identified using the following study criteria.

5.2.1 Inclusion Criteria

- Patients with at least one iv LCM administration (earliest administration defines index date)
- At least 1 encounter with iv LCM administered between ages of ≥1 month and <17 years

5.2.2 Exclusion Criteria

- No exposure to either oral or iv LCM within the 3 months prior to the index date
    - In the case of patients < 90 days of age, no prior LCM ever in the record

A separate cohort for patients < 30 days old is established with the following criteria.

5.2.3 Neonates Inclusion Critera

- Patients with at least one iv LCM administration (earliest administration defines index date)
- At least 1 encounter with iv LCM administered before 30 days of age.

5.2.4 Neonates exclusion criteria

- No exposure to either oral or iv LCM prior to the index date

5.2.5 Dosing criteria for groups

Once the LCM population is identified dose thresholds are applied to define the "Recommended Dose Group" and the "Loading Dose Group"). The following thresholds apply:
The recommended loading dose groups are as follows:

- < 4 mg/kg for patients less than 30 kg and less than 6 months of age
- < 6 mg/kg for patients less than 30 kg and greater than or equal to 6 months of age
- < 4 mg/kg for patients between 30 and 50 kg
- < 200 mg for patients greater than 50 kg

Note: Whilst babies are allowed higher mg/kg dosing than older children, due to issues of metabolism and weight, babies under 6 months of age have immature organs and a loading dose should be lower than older babies under 1 year.

High dose group have doses greater than the recommended group cut limits, applicable for age and weight.

- ≥ 4 mg/kg for patients less than 30 kg and less than 6 months of age
- ≥ 6 mg/kg for patients less than 30 kg and greater than or equal to 6 months of age
- ≥ 4 mg/kg for patients between 30 and 50 kg
- ≥ 200 mg for patients greater than 50 kg

5.3.3 Follow-up (post index) period amendment.

Text did read:

Follow-up (post-index) period

The duration of follow-up will vary depending on the duration of exposure to the index treatment episode of IV LCM.

IV LCM treatment may span several days ; treatment will be considered continuous if subsequent IV LCM treatment is noted to occur within 7 days of a previous treatment. If 7 days pass without a documented IV LCM treatment, the index exposure has ended. Patients will be followed for an additional 30 days after the last treatment with IV LCM irrespective of whether they initiate another AED during that time to ascertain adverse events (AEs).

Text now reads:

The duration of follow-up is for a maximum of 37 days from index date.

IV LCM treatment may span several days; treatment will be considered continuous if subsequent IV LCM treatment is noted to occur within 7 days of a previous treatment. If 7 days pass without a documented iv or LCM treatment, the index exposure has ended. Follow then continues until end of follow up or until the following censoring conditions apply:

Censoring: Patients will be followed for either 37 days OR until the patient is lost to follow-up[transfer out]; OR the patient is discharged from the in-patient setting [events that occur at home are not easy to track and are not included here; outpatient setting events are also excluded as we do not know what the patient has being doing at home during routine care]; OR the patient dies; OR the patient switches to another AED instead of/or adjunct to LCM; whichever comes first.

Clarification of follow up: The purpose of the study is to evaluate iv loading dose and higher subsequent dosing risk. Some patients may receive only one iv loading dose and then transfer to oral dosing which may last some weeks in the hospital setting. In the case where a patient has just one dose of iv LCM and switches to continuous oral LCM therapy, the follow up for AE evaluation will cease after a maximum of seven days of oral therapy or until censoring occurs as above. The same applies for those exposed to one dose of iv LCM and no further LCM exposure (either oral or iv).

Patients who have more than one dose of iv LCM and then switch to oral therapy will have a maximum follow up of 37 days of follow up index date or until censoring.

Patient time is contributed until either end of follow up or censor point (in days).
Patients are only included once in this study, so if we find evidence of a further iv loading dose of LCM given 6 months later say, they do not contribute to the study
.

Item 2. Section 7.

The safety section wording was replaced with the appropriate text for a retrospective study using secondary data.

Text did read:

REPORTING OF ADVERSE EVENTS

The procedures for reporting of AEs including adverse events of special interest (AESI) and adverse drug reactions (ADRs) in this study are described in the following sections. In addition to utilizing de-identified structured data from the PEDSnet CDM, the current study includes a manual chart review of patient level unstructured medical data. To ensure fulfillment of expedited reporting requirements to the FDA, the reviewing physician is required to report any identified serious ADRs and AESI. Data of all AEs/ADRs documented will be summarized in a final table study report. In general, the regulatory safety reporting requirements of the respective participating country will apply. Identification, reporting, follow up on adverse events and detection of safety signals will follow UCB's standard procedures.

Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse drug reaction

An ADR is a response to a medicinal product which is noxious and unintended. 'Response' in this context means that a causal relationship between a medicinal product and an AE shows at least a reasonable possibility. This includes ADRs that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure (this refers to the exposure to a prescribed treatment as a result of one's professional or nonprofessional occupation)

Serious adverse event/serious adverse drug reaction

An AE or ADR is serious if one or more of the following criteria are met:

- Death.
- Life threatening: An event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization is planned prior to the patient receiving the first dose of medicinal product, it is not classified as

serious. However, if a hospitalization is unplanned and is a result of an adverse experience, this is considered a serious adverse event (SAE).

- Persistent or significant disability/incapacity.
- Congenital anomaly or birth defect.
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

Adverse event of special interest

An AESI is any AE that a regulatory authority has mandated to be reported on an expedited basis, regardless of seriousness, expectedness, or relatedness of the AE to the administration of a UCB product.

Identification and description of AEs/AESI/SADRs

Following standard procedures, reviewing physicians will receive training on the identification of AEs/ADRs/AESIs, completion of the Serious Adverse Event Report form (SAE report form), assessment of the causal relationship between the UCB compound and each AEs/ADRs and other safety relevant information, reporting, and follow up.

In order to ensure complete safety data collection, all AEs leading to death, AESI and SADRs including safety relevant information identified during the record review must be documented in the SAE report form. This includes all AEs leading to death, AESI for all UCB products, and SADRs not present prior to the index event date and all AEs leading to death, AESI and SADRs that recurred or worsened after the initial index event date (e.g. underlying or previous concomitant diseases).

Signs or symptoms of the condition/disease for which the prescribed treatment is being studied will be recorded as AEs if leading to death and SADRs only if their nature changed considerably or their frequency or intensity increased in a clinically significant manner as compared to the clinical profile known to the reviewing physician from the patient's recorded history.

When recording an AE leading to death/AESI/SADR and or any other safety relevant information relating to these, the reviewing physician should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms, signs, or medical procedures. The SAE report form, and patient's record should be consistent.

Details for completion of the SAE report form are included on the form. Because this is a retrospective data review, it is expected that there will be limited information available for reporting purposes without the ability to provide additional information upon query or request by UCB.

Day Zero

For retrospective studies, the day 0 is the date an agent of UCB becomes aware of the safety information from any source (e.g. database, medical chart review).

For reports received electronically by UCB, an agent of UCB (e.g. CRO), an affiliate, or a license partner, receipt/awareness/first knowledge is interpreted to mean the date that the report arrives on a server (e.g. ECRF, email …), the date on a facsimile transmission, or the date a voicemail is recorded. It is not the date a report is retrieved from a server, fax machine, or from voicemail. For mail received via the postal system, the date of awareness/receipt/first knowledge is the date that is "date stamped" on the letter as being initially received by UCB, an agent of UCB, an affiliate, or a license partner.

Procedures for reporting AEs leading to death/AESI/SADRs

Reporting of serious ADRs and AESI is required in the US. If a serious ADR or AESI is reported, information will be transferred to UCB within 1 day via the SAE report form by the chart reviewer. The chart reviewer must complete duly the SAE report form, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusions. Receipt of safety data, processing and follow-up will be managed by UCB's Patient Safety department. Information recorded on the SAE report form will be entered into the global safety database. Safety data from the SAE report form and from the safety database will be presented in summary tabulation format.

In case UCB upgrades a case to serious and/or assesses a causal relationship to the drug, the treating physician will not be asked for confirmation. Both assessments will then appear in the final study report.

Follow up on AEs leading to death/AESI/SADRs

If clarifications on AEs are necessary, local UCB Patient Safety department shall request additional information to the reviewing physician and the latter shall provide requested information as soon as possible to allow accurate and timely reporting to the concerned regulatory authorities
For certain AEs leading to death and SADRs, standardized follow-up forms may be provided by UCB. Every effort should be made to provide as much information as possible on the form, from the records available and return it to UCB.
Additional information (e.g. autopsy or laboratory reports) available in the patient records must be provided on request without delay. If additional information is requested and the patient's record doesn't provide additional information, a response stating that: "additional information is not available in this patient's retrospective record" will be sufficient.

Safety signal detection

Reported safety data from this study will be reviewed periodically, together with other safety information received at UCB, to detect as early as possible any safety concern(s) related to the treatment so that regulatory authorities will be informed appropriately and as early as possible.

Text now reads:

REPORTING OF ADVERSE EVENTS

7.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

7.2 Adverse drug reaction

An ADR is a response to a medicinal product which is noxious and unintended. 'Response' in this context means that a causal relationship between a medicinal product and an AE shows at least a reasonable possibility. This includes ADRs that arise from:

- The use of a medicinal product within the terms of the marketing authorization
- The use of a medicinal product outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse, and medication errors
- Occupational exposure (this refers to the exposure to a prescribed treatment as a result of one's professional or nonprofessional occupation)

7.3 Serious adverse event/serious adverse drug reaction

An AE or ADR is serious if one or more of the following criteria are met:

- Death.
- Life threatening: An event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization is planned prior to the patient receiving the first dose of medicinal product, it is not classified as serious. However, if a hospitalization is unplanned and is a result of an adverse experience, this is considered a serious adverse event (SAE).
- Persistent or significant disability/incapacity.
- Congenital anomaly or birth defect.
- An important medical event or an event requiring significant intervention: Medical and scientific judgment must be exercised in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition. These are usually considered serious.

7.4 Reporting obligations

This study uses existing health care databases, in which it is generally not possible to link (i.e., identify a potential causal relationship between) a particular product and medical event for any individual.

This retrospective study (secondary data collection study) is characterized by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. We cannot know if ADR/AEs has been reported previously. Further, initial reporter will not be identifiable (i.e. the 4 elements (compound, AE, Patient, reporter) for a valid Individual Safety Case Report (ICSR) will not be fulfilled.

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to "Vimpat" that appears in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite, explicit statement of causality by the original healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event Report Form to UCB Safety are as follows:

• All serious and non-serious AEs with explicit attribution to "Vimpat" that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to UCB Safety using the NIS AE Report Form.

• In this study scenarios involving drug exposure that include Vimpat use during pregnancy, during breast feeding, medication error, overdose, misuse, extravasation associated with the use of "Vimpat" must be reported, within 24 hours of awareness, to UCB Safety using the NIS AE Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, "Vimpat", the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

Where relatedness to Vimpat is explicitly stated, the cases will be stored in the UCB safety database and be part of the routine signal detection activities. ADRs will be presented and summarized in the final study report.

Item 3. Section 5.9.1.3 Analysis of loading dose / higher than recommended initial IV LCM dose

Text did read:

To examine safety and tolerability of intravenous loading dose, a stratified analysis of the primary and secondary variables will be conducted by increasing loading dose. Loading dose will be defined, where possible, as the single, initial high IV LCM dose which is followed within approximately 12 hours by a subsequent lower maintenance dose (as described in Section 5.5.4). The cut-off time period to assess loading dose AEs will be 24 hours and 7 days after the index date, to examine immediate (e.g. injection site related) and delayed AEs (e.g. SJS) respectively. As there is currently no recommended loading dosage in Patients ≥1 month to <17 YOA, UCB expects to see a wide variation in doses used on clinical practice. Hence, for this analysis adverse event incidence will be stratified by increasing dosage, above and below UCB's recommended loading dose as described in Table 5.

Stratification will be centered around UCB's proposed recommended loading dose as described in Table 5. Where a patient's weight at (or nearest recorded to) baseline will be used to determine their dosage level, and their recorded loading dose will be categorized into the following increasing strata (less than UCB's recommended level, loading dose within UCB's recommended dosage level, and higher than UCB's recommended level), as shown in Table 7.

Table 7 Anticipated Loading Dose Stratification

	Incidence of Adverse event	
Loading dose according to UCB's proposed pediatric recommendation (described in Table 5).	**AE occurring ≤ 24 hours after index date**	**AE occurring ≤ 7 days after index date**
Less than recommended dosage level		
Within recommended dosage level		
Higher than recommended dosage level		

Text now reads:

To examine safety and tolerability of iv LCM administration, the analysis of the key primary and secondary variables will be stratified by loading dose and recommended dose groups, stratified by ageband ie, separate tables per age band. Risk estimates will be provided with incidence rate ratios and 95% confidence limits.

Approval Signatures

Name:	FINAL Loading-dose-prea-rwe-study-protocol_amendment
Version:	1.0
Document Number:	CLIN-000149607
Title:	EVALUATING THE OCCURRENCE OF ADVERSE EVENTS AMONG PEDIATRIC PATIENTS EXPOSED TO INTRAVENOUS LACOSAMIDE (VIMPAT®) USING REAL WORLD DATA
Approved Date:	17 Feb 2020

Document Approvals

Approval Verdict: Approved	Name: [redacted] Capacity: Non-clinical Date of Signature: 17-Feb-2020 10:50:13 GMT+0000